Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation

Prepared for:  
Agency for Healthcare Research and Quality  
U.S. Department of Health and Human Services  
540 Gaither Road  
Rockville, MD 20850  
www.ahrq.gov


Prepared by:  
Pacific Northwest Evidence-based Practice Center  
Oregon Health & Science University  
Mail Code: BICC  
3181 SW Sam Jackson Park Road  
Portland, OR 97239  
www.ohsu.edu/epc

Investigators:  
Heidi D. Nelson, MD, MPH  
Rongwei Fu, PhD  
Katrina Goddard, PhD  
Jennifer Priest Mitchell, BA  
Leila Okinaka-Hu, MD  
Miranda Pappas, MA  
Bernadette Zakher, MBBS

AHRQ Publication No. 12-05164-EF-1  
December 2013
This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0024). The investigators involved have declared no conflicts of interest with objectively conducting this research. The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

This report may be used, in whole or in part, as the basis for the development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

This document is in the public domain and may be used and reprinted without permission except those copyrighted materials that are clearly noted in the document. Further reproduction of those copyrighted materials is prohibited without the specific permission of copyright holders.

Acknowledgements

The authors acknowledge Andrew Hamilton, MLS, MS, for conducting literature searches and Amanda Brunton, BS, for assistance at the Oregon Health & Science University. We also thank AHRQ Officers Jennifer Croswell, MD, MPH, Karen Lee, MD, MPH, and Tess Miller, DrPH, and USPSTF leads Linda Baumann, PhD, RN, Joy Melnikow, MD, MPH, Virginia Moyer, MD, MPH, and Doug Owens, MD, MS, for their contributions to this report.

Suggested Citation

Structured Abstract

**Purpose:** To review new evidence on the benefits and harms of risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women for the U.S. Preventive Services Task Force.

**Data Sources:** MEDLINE and PsycINFO (January 2002 to December 31, 2012), Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (4th Quarter 2012), Scopus, and reference lists were searched for English-language studies of benefits and harms of risk assessment, genetic counseling, genetic testing, and interventions to reduce BRCA-related cancer and mortality.

**Data Synthesis:** Thirteen general risk models, such as the Gail model, are modest predictors of individual risk for breast cancer (c-statistic, 0.55 to 0.65). Five familial risk models for nongenetics specialists to guide referrals to genetic counseling accurately predict individual risk for BRCA mutations (c-statistic, >0.80). No studies reported harms of risk assessment. Sixteen studies indicated that genetic counseling decreases cancer worry, anxiety, and depression; increases the accuracy of risk perception; and decreases intention for mutation testing.

Thirty-two new studies and 38 earlier studies provided data for meta-analysis estimates of the prevalence and penetrance of BRCA mutations. Prevalence varies by population: 0.2 to 0.3 percent in general populations, 3 percent in women with breast cancer, 6 percent in women with breast cancer onset before age 40 years, 10 percent in women with ovarian cancer, and 20 percent in high-risk families. Among Ashkenazi Jewish women, prevalence is 2 percent in unselected populations and 10 percent in high-risk families. The penetrance of BRCA mutations differs by test result. Breast cancer penetrance to age 70 years if the test is positive is 46 to 71 percent for BRCA1 or BRCA2; ovarian cancer penetrance is 41 to 46 percent for BRCA1 and 17 to 23 percent for BRCA2. No estimates were available for women with variants of uncertain significance. The standardized incidence rate for breast cancer is 3.81 (95% CI, 3.06 to 4.75) for uninformative negative test results and 1.13 (95% CI, 0.81 to 1.58) for true negative results. Estimates for ovarian cancer were highly heterogeneous. Breast cancer worry and anxiety increased after testing in women with positive results and decreased in others, although results differed across studies. Risk perception improved after receiving test results.

No trials of the effectiveness of intensive screening for breast or ovarian cancer in women who are mutation carriers have been published. False-positive rates, unnecessary imaging, and unneeded surgery were higher in women undergoing intensive screening. Most women experienced no anxiety after screening with magnetic resonance imaging, mammography, or clinical breast examination, although women recalled for additional testing had transient anxiety. There are no trials of risk-reducing medications specifically in women who are mutation carriers. Tamoxifen and raloxifene reduced invasive breast cancer by 30 to 68 percent in placebo-controlled trials enrolling women with various levels of risk; tamoxifen had a greater effect than raloxifene in a head-to-head trial. Results suggested that reduction was greater in women with more relatives with breast cancer, but confidence intervals overlapped and results were not specific for women who are mutation carriers. Tamoxifen and raloxifene increased thromboembolic events and tamoxifen increased endometrial cancer and cataracts. In high-risk
women and women who are mutation carriers, risk-reducing mastectomy reduced breast cancer by 85 to 100 percent and breast cancer mortality by 81 to 100 percent; risk-reducing salpingo-oophorectomy reduced breast cancer by 37 to 100 percent, ovarian cancer by 69 to 100 percent, and all-cause mortality by 55 to 100 percent. Some women experienced physical complications of surgery, postsurgical symptoms, or changes in body image; some had improved anxiety.

Limitations: Including only English-language articles and studies applicable to the United States; varying number, quality, and applicability of studies.

Conclusions: Risk assessment using familial risk models to guide referrals is accurate. Genetic counseling reduces distress, improves risk perception, and reduces intention for testing. Genetic testing provides risk estimates for specific populations depending on test results. A true negative test indicates no increased risk for breast cancer. The effectiveness of intensive screening is not known, but it increases false-positive results and procedures. Tamoxifen and raloxifene reduce risk for breast cancer, but have adverse effects. Risk-reducing mastectomy and salpingo-oophorectomy are effective in reducing breast and ovarian cancer. Several evidence gaps remain and additional studies are necessary to better inform practice.
# Table of Contents

## Chapter 1. Introduction

- Purpose of Review and Prior USPSTF Recommendation .................................................... 1
- Condition Definition ............................................................................................................. 3
- Prevalence and Burden of Disease ...................................................................................... 4
- Rationale for Screening/Screening Strategies ..................................................................... 4
- Risk Assessment and Genetic Counseling ......................................................................... 4
- Mutation Testing ................................................................................................................ 5
- Interventions ....................................................................................................................... 6
- Current Clinical Practice .................................................................................................... 6
- Recommendations of Other Groups ................................................................................... 8

## Chapter 2. Methods

- Analytic Framework and Key Questions ............................................................................ 9
- Search Strategies ................................................................................................................ 9
- Study Selection ................................................................................................................... 9
- Data Abstraction and Quality Rating .................................................................................. 10
- Data Synthesis .................................................................................................................... 11
- Statistical Meta-Analysis .................................................................................................... 11
- External Review ................................................................................................................ 12
- Response to Comments Received During the Public Comment Period ............................ 12

## Chapter 3. Results

- Key Question 1. Does Risk Assessment, Genetic Counseling, and Genetic Testing Lead to Reduced Incidence of BRCA-Related Cancer and Reduced Cause-Specific and All-Cause Mortality? ................................................................................................................ 13
- Key Question 2a. What Is the Accuracy of Methods to Assess Familial Cancer Risk for BRCA-Related Cancer When Performed by a Nongenetics Specialist in a Clinical Setting? ........................................................................................................ 13
- Key Question 3a. What Are the Potential Adverse Effects of Risk Assessment? ............... 13
  - Summary ...................................................................................................................... 13
  - Evidence ....................................................................................................................... 14
- Key Questions 2b, 3b. What Are the Benefits and Potential Adverse Effects of Genetic Counseling in Determining Eligibility for Genetic Testing for BRCA-Related Cancer? .............................................................. 17
  - Summary ...................................................................................................................... 17
  - Evidence ....................................................................................................................... 17
- Key Question 2c. What Is the Clinical Validity of Genetic Testing for Deleterious Mutations in Women With Increased Risk for BRCA-Related Cancer? .......................................................... 21
  - Summary ...................................................................................................................... 21
  - Evidence ....................................................................................................................... 22
- Key Question 3c. What Are the Potential Adverse Effects of Genetic Testing? ............... 28
  - Summary ...................................................................................................................... 28
  - Evidence ....................................................................................................................... 28
- Supplemental Information on the Impact of Genetic Testing on Family Members ....31
Table 11. Penetrance of BRCA-Related Cancer in BRCA-Positive Women: Single Individual Tested
Table 12. Penetrance of BRCA-Related Cancer in BRCA-Positive Women: Multiple Individuals Tested
Table 13. Summary of Meta-Analysis of Studies of Breast and Ovarian Cancer Penetrance in BRCA-Positive Women in High-Risk Populations
Table 14. Penetrance of BRCA-Related Cancer in Women With Uninformative Negative Results
Table 15. Penetrance of BRCA-Related Cancer in Women With True Negative Results
Table 16. Studies of Distress After Genetic Testing
Table 17. Studies of Test Characteristics of Mammography vs. MRI for Breast Cancer Screening
Table 18. Results of Trials of Risk-Reducing Medications: Cancer and Mortality Benefits
Table 19. Studies of Risk-Reducing Surgery
Table 20. Harms of Intensive Screening for Breast Cancer Using Mammography vs. MRI in High-Risk Women
Table 21. Distress Due to Intensive Screening for Breast Cancer in Women Who Are Mutation Carriers
Table 22. Results of Trials of Risk-Reducing Medications: Adverse Effects
Table 23. Distress Due to Risk-Reducing Surgery
Table 24. Summary of Evidence

Appendixes
Appendix A1. Referral Criteria
Appendix A2. Definitions of Terms Used in Systematic Review

Appendix B. Detailed Methods
Appendix B1. Search Strategies
Appendix B2. Inclusion and Exclusion Criteria
Appendix B3. USPSTF Quality Rating Criteria
Appendix B4. List of Reviewers
Appendix B5. Literature Flow Diagram
Appendix B6. Excluded Studies List

Appendix C. Evidence Tables and Quality Tables
Appendix C1. Quality Ratings for Randomized, Controlled Trials
Appendix C2. Quality Ratings for Cohort Studies
Appendix C3. Quality Ratings for Case-Control Studies
Appendix C4. Quality Rating for Systematic Review
Appendix C5. Familial Risk Assessment Models
Appendix C6. Evidence Table of Genetic Counseling
Appendix C7. Evidence Table of Prevalence of BRCA1 and BRCA2 Mutations
Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer
Appendix C9. Evidence Table of Distress After Genetic Testing
Appendix C10. Evidence Table of Intensive Screening Interventions
Appendix C11. Evidence Table of Risk-Reducing Medications
Appendix C12. Evidence Table of Risk-Reducing Surgery
Appendix C13. Evidence Table of Harms of Intensive Screening
Appendix C14. Evidence Table of Psychological and Sexual Functioning Harms of Interventions
CHAPTER 1. INTRODUCTION

Purpose of Review and Prior USPSTF Recommendation

This systematic review is an update of the evidence for the U.S. Preventive Services Task Force (USPSTF) on the effectiveness and adverse effects of risk assessment, genetic counseling, and genetic testing for breast cancer susceptibility gene (BRCA)–related cancer in women who do not have cancer but are potentially at increased risk. Its purpose is to evaluate and summarize evidence addressing specific key questions important to the USPSTF as it considers new recommendations for primary care practice.

In 2005, based on results of a previous review,¹ ² the USPSTF recommended against routine referral for genetic counseling or routine BRCA testing for women whose family histories are not associated with increased risks for deleterious mutations in breast cancer susceptibility gene 1 (BRCA1) or breast cancer susceptibility gene 2 (BRCA2) (D recommendation).³ The USPSTF also recommended that women whose family histories are associated with increased risks for mutations in the BRCA1 or BRCA2 genes be referred for genetic counseling and evaluation for BRCA testing (B recommendation).

The USPSTF concluded that the potential harms of routine referral for genetic counseling or BRCA mutation testing in women without family history risk outweigh the benefits, and that the benefits of referring women with family history risk to suitably trained health care providers outweigh the harms. Benefits included improved accuracy of risk assessment and pretest probability for testing and improved patient knowledge, risk perception, and psychological and health outcomes. Potential harms included inaccurate risk assessment; inappropriate testing; misinterpretation of test results; and ethical, legal, and social implications; among others.

The 2005 USPSTF recommendation was intended for the primary prevention of cancer and applied to women without previous diagnoses of breast or ovarian cancer, consistent with the USPSTF scope of preventive care for the general population. Recommendations for men and women with cancer were not included. The 2005 USPSTF recommendation is included in the Affordable Care Act for covered preventive services,⁴ and provided the basis for a Healthy People 2020 objective to increase the proportion of women with family histories of breast or ovarian cancer who receive genetic counseling.⁵

The previous systematic review¹ ² identified several research limitations and evidence gaps. The review concluded that a primary care approach to genetic risk assessment and BRCA mutation testing had not been evaluated, and evidence was lacking to determine the benefits and harms of this approach for women without cancer. Risk assessment, genetic counseling, and mutation testing did not cause adverse psychological outcomes, and counseling improved distress and risk perception in the highly-selected populations studied. Studies of intensive cancer screening approaches, such as earlier and more frequent mammography, were inconclusive. Trials of risk-reducing medications, such as tamoxifen and raloxifene, reported reduced breast cancer incidence in women with varying baseline levels of risk compared with placebo, but also increased adverse effects. Observational studies of risk-reducing mastectomy and salpingo-
oophorectomy reported reduced breast and ovarian cancer outcomes in women who were mutation carriers.

Limitations identified by the previous review included:

- The quality and generalizability of studies varied.
- Although several risk assessment tools were available, most were designed for use by genetics specialists rather than primary care providers.
- Methods of risk stratification were subject to misclassification, and data to guide clinicians in the best approach were lacking.
- Studies of the effectiveness of genetic counseling on patient decisions and outcomes were lacking.
- Most studies of BRCA mutation testing were conducted in highly-selected samples of women, many with preexisting breast or ovarian cancer or from previously identified kindreds.
- Family history risk was often based on self-reported information; thus, the accuracy of risk stratification was limited by the accuracy of reported family history.
- In some cases, data to determine penetrance came exclusively from one study, and when multiple studies were available, they were heterogeneous and likely unreliable. (Penetrance is the probability of developing breast or ovarian cancer in women who have a known \textit{BRCA1} or \textit{BRCA2} mutation.)
- Most studies used research laboratory techniques to detect clinically significant mutations that differed from the DNA sequencing available clinically.
- The clinical significance of mutations was determined by each study.
- The applicability of studies based on highly-selected women in research settings to the general screening population was questionable.
- Data were not available to determine the optimal age at which to test and how age at testing influenced estimates of benefits and adverse effects.
- The long-term impact of testing was unknown, and most studies followed patients for less than 1 year.
- Studies did not evaluate psychological aspects of medical outcomes.
- Few data were available about the impact of testing on family members.
- Treatment effects were influenced by several variables that were not available and not easily factored into estimates of clinical outcomes.

Evidence gaps identified by the previous review included:

- Impact of screening in the general population.
- Patient-centered issues, such as access to testing; effectiveness of screening approaches, including risk stratification; use of system supports; and patient acceptance and education.
- Studies about who should perform risk assessment and genetic counseling services, and what skills are needed.
- Studies about what happens after patients are identified as high-risk in clinical settings.
• The consequences of genetic testing for individuals and their relatives.
• Well-designed investigations using standardized measures and enrolling subjects who reflect the general population, including minority women.
• Information about predictors of cancer, response to interventions, and other modifying factors from an expanded database or registry of patients who are counseled and tested for BRCA mutations.
• Additional research on interventions, including trials of risk-reducing medications that enroll women who are mutation carriers, evaluations of the effect of age at intervention, measurement of long-term outcomes, and factors related to acceptance of risk-reducing interventions.

Condition Definition

Clinically significant, or deleterious, mutations in the BRCA1 and BRCA2 genes are associated with increased risks for breast, ovarian, fallopian tube, and peritoneal cancer in women. Often referred to as the Hereditary Breast and Ovarian Cancer syndrome, this condition is described as BRCA-related cancer in this review to explicitly include fallopian tube and peritoneal cancer. Research indicates that BRCA-related fallopian tube cancer has probably been misdiagnosed as ovarian cancer in the past. These mutations are also associated with male breast cancer and, to a lesser degree, pancreatic and early-onset prostate cancer; BRCA2 mutations are associated with melanoma. Although all of these types of cancer are considered during familial risk assessment, studies with these cancer outcomes are outside the scope of this review. BRCA mutations cluster in families exhibiting an autosomal dominant pattern of transmission in either the maternal or paternal lineage.

Recent estimates indicate that clinically significant mutations in either of the BRCA genes increase a woman’s risk of breast cancer by age 70 years to 45 to 65 percent. BRCA1 mutations increase ovarian, fallopian tube, or peritoneal cancer risk to 39 percent, and BRCA2 mutations to 10 to 17 percent. These mutations are estimated to occur in 1 in 300 to 500 women in the general population and account for 5 to 10 percent of breast cancer overall.

Specific BRCA mutations, known as founder mutations, are clustered among certain ethnic groups, including Ashkenazi Jews, blacks, and Hispanics and among families in the Netherlands, Iceland, and Sweden. Several additional genes not included in this review are also associated with hereditary susceptibility to breast and ovarian cancer, but are not commonly tested.

Specific cancer phenotypes are also associated with BRCA mutations even in the absence of family history, including triple-negative breast cancer and high-grade serous ovarian or fallopian tube cancer. Pathologic and clinical characteristics of tumors also differ by the type of mutation. In a series of 3,797 cases of breast cancer in women who were BRCA1 mutation carriers, 78 percent were estrogen receptor (ER)–negative, 79 percent progesterone receptor (PR)–negative, 90 percent human epidermal growth factor receptor 2 (HER2)–negative, and 69 percent triple-negative. The proportion of ER-negative cases decreased with increasing age. In
a series of 2,392 cases of breast cancer in women who were *BRCA2* mutation carriers, 23 percent were ER-negative, 36 percent PR-negative, 87 percent HER2-negative, and 16 percent triple-negative. These characteristics are important in determining cancer treatment and prognosis.

**Prevalence and Burden of Disease**

Breast cancer is the second most common cancer in women in the United States after nonmelanoma skin cancer, and is the second leading cause of cancer death after lung cancer. In 2013, an estimated 232,340 women in the United States will be diagnosed with breast cancer and 39,620 women will die from it. According to lifetime risk estimates for the general population, 12.3 percent (95% confidence interval [CI], 12.2 to 12.4) of women will develop breast cancer sometime during their lives, and 2.8 percent (95% CI, 2.76 to 2.80) will die from it. The 5-year relative survival rate for all stages of breast cancer in the United States is 89 percent, but improves to 99 percent with localized disease. Five-year relative survival rates for women with regional and distant disease are 84 and 23 percent, respectively.

Ovarian cancer is the fifth leading cause of cancer death in women in the United States, accounting for an estimated 22,240 new cases and 14,030 deaths in 2013. According to lifetime risk estimates for the general population, 1.40 percent (95% CI, 1.38 to 1.43) of women will develop ovarian cancer sometime during their lives and 1.02 percent (95% CI, 1.01 to 1.03) will die from it. The 5-year relative survival rate for all stages of ovarian cancer in the United States is 44 percent, but may improve to 92 percent for women whose disease is detected and treated in early stages. However, up to 75 percent of women with ovarian cancer have nonlocalized disease at the time of diagnosis because early stages are often asymptomatic. Five-year relative survival rates for women with regional and distant disease are 72 and 27 percent, respectively.

**Rationale for Screening/Screening Strategies**

BRCA-related cancers are associated with family histories of these cancer types. Approximately 5 to 10 percent of women with breast cancer have a mother or sister with breast cancer, and up to 20 percent have either a first- or second-degree relative with breast cancer. Although most of these women do not have BRCA mutations, some women report family history patterns that suggest their presence. Genetic risk assessment and BRCA mutation testing involve determining individual risk for clinically significant BRCA mutations followed by mutation testing of high-risk individuals. Mutation testing of appropriate candidates could lead to increased awareness of cancer risk and effective use of interventions to reduce BRCA-related cancer incidence and mortality.

**Risk Assessment and Genetic Counseling**

Several characteristics are associated with an increased likelihood of deleterious BRCA mutations, including breast cancer diagnosed at an early age (before age 40 or 50 years), bilateral breast cancer, triple-negative breast cancer diagnosed before age 50 years, history of both breast and ovarian cancer, breast cancer in male relatives, multiple cases of breast cancer in
the family, both breast and ovarian cancer in the family, family members with two primary breast cancers, and Ashkenazi Jewish ancestry. These and other individual and family characteristics can be used to assess personal cancer risk and the need for referral for additional evaluation and testing. Approaches to assessing personal risk for BRCA mutation status range from simple checklists of criteria to comprehensive kindred analysis requiring expertise in cancer genetics. Practice and coverage standards in the United States generally follow the National Comprehensive Cancer Network (NCCN) referral criteria for genetic counseling (described in Appendix A1).50

Gene
tic counseling is the process of identifying and counseling individuals who are at risk for familial or inherited cancer and is recommended prior to BRCA mutation testing.50-52 Services include comprehensive evaluations of familial risk for inherited disorders using kindred analysis and models to estimate risk. These include models based on logistic regression (e.g., Couch46), Bayesian analysis (e.g., BRCAPRO,12,51 BOADICEA54), and patient data (Myriad prevalence tables55), among others. Some models are more appropriate for specific patients, and model accuracy varies across different populations.56 In the course of an evaluation for BRCA-related cancer, other cancer syndromes are sometimes identified. Genetic counseling also includes identification of candidates for testing, patient education, discussion of the benefits and harms of genetic testing, interpretation of results after testing, and discussion of management options. Some genetic counseling programs offer their services by telephone.

Providers of genetic counseling may be genetic counselors,57-59 nurse educators,60,61 or other health professionals with comparable skills.62 Accreditation standards from specialty groups specifically outline essential training and skills for genetics professionals.63

Mutation Testing

The NCCN provides specific criteria for genetic testing.50 Guidelines recommend that mutation testing begin with a relative with known BRCA-related cancer, including male relatives, to determine if a clinically significant mutation is segregating in the family before testing individuals without cancer.50 If an affected family member is not available, then the relative with the highest probability of mutation should be tested. Ideally, results of the initial test will guide testing decisions of other family members. However, the optimal candidate may not be available for testing, limiting the interpretation of results. Individuals without cancer meeting NCCN criteria for testing include those from families with known \textit{BRCA1} or \textit{BRCA2} mutations or from families with extensive cancer history (further described in Appendix A1).

The type of mutation analysis required also depends on family history (Table 1). A small number of clinically significant \textit{BRCA1} and \textit{BRCA2} mutations have been found repeatedly in different families, including the three founder mutations common in the Ashkenazi Jewish population. However, most identified mutations have been found in only a few families.64 Individuals from families with known mutations or from ethnic groups with common mutations can be tested specifically for them. Several clinical laboratories in the United States test for specific mutations or sequence specific exons. The sensitivity and specificity of analytic techniques are determined by the laboratories and are not generally available.
Individuals without linkages to known mutations can determine their mutation status by direct DNA sequencing. A commercial laboratory, Myriad Genetic Laboratories, previously held a patent on this procedure and provided most of the testing in the United States. Myriad reports analytic sensitivity and specificity as both greater than 99 percent. Approximately 12 percent of high-risk families without a BRCA1 or BRCA2 coding-region mutation may have other clinically significant genomic rearrangements. Many of these mutations can be tested using the BRCA Rearrangement Test, now available as a subsequent step in testing.

Tests may indicate positive (i.e., BRCA mutation detected), variant of uncertain clinical significance (i.e., an abnormality of the BRCA gene, but unknown if it is associated with an increased risk for cancer), uninformative negative, or true negative results. A true negative result represents the absence of a mutation in an individual who has relatives with cancer and known BRCA mutations. An uninformative negative also indicates the absence of a mutation in an individual; however, information about her relatives is not definitive because either a mutation was not detected by their tests or they have not been tested.

**Interventions**

Interventions to reduce risk for cancer in women who are BRCA mutation carriers include earlier, more frequent, or intensive cancer screening; risk-reducing medications; and risk-reducing surgery. Cancer screening recommendations specifically for women who are BRCA mutation carriers are outside the scope of the USPSTF. The NCCN recommends that women who are BRCA mutation carriers conduct monthly breast self-examinations beginning by age 18 years, annual or semiannual clinician breast examinations beginning at age 25 years, and annual mammography and breast magnetic resonance imaging (MRI) beginning at age 25 years or individualized based on the earliest age of onset in the family. The NCCN also recommends that women consider risk-reducing mastectomy and salpingo-oophorectomy, monitoring with transvaginal ultrasound (TVUS) and cancer antigen-125 (CA-125) levels every 6 months for women not undergoing salpingo-oophorectomy, and risk-reducing medications.

Tamoxifen, a selective estrogen receptor modulator (SERM), is considered a candidate for breast cancer risk reduction based on its effectiveness in preventing recurrences in women with breast cancer. Placebo-controlled randomized, controlled trials (RCTs) of tamoxifen indicate reduced primary ER-positive breast cancer in women with family histories of breast cancer. Raloxifene, another SERM used primarily for treating osteoporosis, also reduced risk for breast cancer in trials of women with various levels of breast cancer risk. SERMs also have important adverse effects, including thromboembolism, endometrial cancer (tamoxifen), and vasomotor and other symptoms. Exemestane, an aromatase inhibitor, also reduces risk for primary breast cancer in women with increased risk and is in clinical use, but is not approved by the U.S. Food and Drug Administration for this indication. The USPSTF currently recommends consideration of risk-reducing medications for women who are at increased risk for breast cancer and low risk for complications, and discourages its use in average-risk women.

Risk-reducing mastectomy and salpingo-oophorectomy are also options for women who are BRCA mutation carriers. Bilateral total simple mastectomy with or without reconstruction is
currently the most common approach.\textsuperscript{83,84} This procedure provides more complete removal of breast tissue than the previously used subcutaneous mastectomy. However, no procedure completely removes all breast tissue\textsuperscript{85} and breast cancer can still occur postmastectomy.\textsuperscript{86} Surgical reports indicating the potential for cancer occurrence after bilateral oophorectomy have led to more extensive procedures to remove potential tumor sites, such as bilateral salpingo-oophorectomy with or without hysterectomy.\textsuperscript{87,88} Despite this approach, the occurrence of peritoneal carcinomatosis remains a possibility.\textsuperscript{89-91}

**Current Clinical Practice**

Guidelines recommend testing for mutations only when an individual has personal or family history of cancer suggestive of inherited cancer susceptibility, the test can be adequately interpreted, and results will aid in management.\textsuperscript{51,92}

Actual practices in the United States are unclear. The lack of effectiveness trials, differing interpretations of existing research among specialties, variability of insurance coverage, and direct-to-consumer advertising targeting patients, physicians, and health systems have resulted in highly variable clinical practices. The initial focus of mutation testing has been on patients with cancer. For women without cancer or relatives with known BRCA mutations, an integrated clinical pathway generally involves a series of sequential steps, including: 1) risk stratification and referral for genetic counseling, 2) genetic counseling for women identified with increased risk based on family history information, 3) BRCA mutation testing for women or their relatives with significant familial risk, and 4) interventions to reduce risk based on benefits, harms, and patient preferences.

In practice, these steps may not be sequential or clearly defined. In the United States, genetic testing is marketed directly to consumers, who may bypass preceding steps. In surveys, many clinicians were unfamiliar with genetic tests and criteria for referral or testing.\textsuperscript{93,94} Some clinicians provide risk assessment, testing, and risk-reducing surgery without using comprehensive risk assessment methods or involving genetic counselors. Screening MRI is often performed based on risk criteria or other considerations that have not been evaluated for effectiveness, while risk-reducing medications are rarely used.\textsuperscript{95}

Relevant data describing current clinical practice was collected through the Michigan Department of Community Health Cancer Genomics Program using statewide telephone surveys and a clinical genetic counseling database. Results indicated that approximately 8 percent of women without breast or ovarian cancer had two or more first- or second-degree relatives with breast or ovarian cancer.\textsuperscript{96} Among women without cancer who had family histories indicating that they would probably benefit from genetic counseling, 35.7 percent received genetic counseling and 9.8 percent had genetic testing during 2009. Most referrals of women without cancer were made by obstetricians/gynecologists, primary care physicians, or patients themselves, comprising 44.3 percent of patients counseled. Among women without cancer who saw genetic counselors, 55.2 percent underwent genetic testing. Of these, results indicated 91.6 percent were negative, 3.9 percent were positive, and 4.5 percent were variants of unknown significance. Respondents described their top three reasons for declining testing after receiving
genetic counseling as: 1) not being the best candidate, 2) the test was not clinically indicated, and 3) inadequate insurance coverage.

The uptake of specialized services after genetic testing is generally high among women with positive test results that indicate the presence of clinically significant BRCA mutations.97,98 In a recent study of women who had genetic testing in a U.S. university-based cancer risk program, women with positive results were significantly more likely to have risk-reducing salpingo-oophorectomy and screening with TVUS and serum CA-125 testing, while those with true negative results were less likely to have these procedures.99 Among women with variants of uncertain significance and uninformative negative results, 12 percent had risk-reducing salpingo-oophorectomy, 37 percent had TVUS, and 34 percent had serum CA-125 testing.

**Recommendations of Other Groups**

Current recommendations of other professional groups are described in Table 2.
CHAPTER 2. METHODS

Analytic Framework and Key Questions

Based on evidence gaps identified from the previous review, the USPSTF and Agency for Healthcare Research and Quality (AHRQ) determined the key questions for this update using the methods of the USPSTF. Investigators created an analytic framework incorporating the key questions and outlining the patient populations, interventions, outcomes, and potential adverse effects (Figure 1). Definitions are described in Appendix A2 and key questions are outlined in Figure 1. A draft research plan describing the analytic framework, key questions, scope, and systematic review approach was posted on the USPSTF Web site for public comment for 30 days in March and April 2012. A total of 213 comments from 54 respondents were received and reviewed, and the research plan was modified after discussion with investigators, the AHRQ Medical Officer, and USPSTF members. In addition, the USPSTF requested information about the impact of genetic testing on family members and the effects of direct-to-consumer marketing of BRCA genetic tests. These are described in supplementary sections of the review.

The target population included women without cancer or known deleterious BRCA mutations who are seen in clinical settings applicable to U.S. primary care practice, although the ideal candidate for mutation testing could be a male or female relative with cancer. The conditions of interest were BRCA mutation carrier status and BRCA-related cancer (predominantly breast, ovarian, fallopian tube, and peritoneal).

Search Strategies

In conjunction with a research librarian, investigators used the National Library of Medicine’s Medical Subject Headings keyword nomenclature to search the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (2005 through the 4th Quarter 2012), Health Technology Assessment, National Health Sciences Economic Evaluation Database, Database of Abstracts of Reviews of Effects (4th Quarter 2012), and MEDLINE and PsycINFO (2004 to December 31, 2012) for relevant English-language studies, systematic reviews, and meta-analyses. Search strategies are listed in Appendix B1. Secondary referencing involved manually reviewing reference lists of papers and reviewing citations of key studies using Scopus.

Study Selection

Investigators developed inclusion and exclusion criteria for abstracts and articles based on the target population, key questions, and outcome measures (Appendix B2). New research conducted in the United States or in similar populations that receive services and interventions applicable to U.S. medical practice published in 2003 or later was considered. After an initial review of abstracts, full-text articles were reviewed using additional inclusion criteria. In addition, studies from the previous review that met inclusion criteria for this update were
included in summary tables and meta-analysis in order to build on prior relevant research.

RCTs, systematic reviews, prospective and retrospective cohort studies, case-control studies, and diagnostic accuracy evaluations that addressed key questions 1, 2, and 4 were included. These include studies of the accuracy of risk assessment methods, outcomes of genetic counseling and testing, and effectiveness studies of interventions to reduce risk of BRCA-related cancer in women who are mutation carriers. Risk assessment methods were included only if they were designed for use by non-genetics specialists to guide referrals and were feasible for clinical settings (i.e., brief, nontechnical, did not require special training to administer or interpret). Evaluation of complex models used in genetic counseling was outside the scope of this review. Interventions include intensive screening (e.g., earlier and more frequent mammography, breast MRI), risk-reducing medications (e.g., tamoxifen, raloxifene), and risk-reducing surgery (e.g., mastectomy, salpingo-oophorectomy). For intensive screening interventions, when effectiveness studies were not available, studies that reported test characteristics of screening modalities, such as sensitivity and specificity, were included. Only medications approved by the U.S. Food and Drug Administration for cancer risk reduction were considered, consistent with the scope of the USPSTF.

Studies of any design were included to describe potential adverse effects of risk assessment, genetic counseling, mutation testing, and risk-reducing interventions (key questions 3 and 5). Potential adverse effects include inaccurate risk assessment; inappropriate testing; false-positive and false-negative results; false reassurance; incomplete testing; misinterpretation of the test result; anxiety; cancer worry; immediate and long-term harms associated with breast imaging, risk-reducing medications, and risk-reducing surgery; and ethical, legal, and social implications.

**Data Abstraction and Quality Rating**

An investigator abstracted data about the study design and setting; participant characteristics; data collection procedures; numbers enrolled and lost to followup; methods of exposure and outcome ascertainment; analytic methods, including adjustment for confounders; and outcomes. A second investigator confirmed the accuracy of key data. By using predefined criteria for RCTs, systematic reviews, cohort, case-control, and diagnostic accuracy studies developed by the USPSTF, two investigators rated the quality of studies (good, fair, poor) and resolved discrepancies by consensus (Appendix B3).

Quality could not be assessed for many studies with designs that did not have predefined quality criteria, such as descriptive, cross-sectional, before-after, and case-series. For studies of penetrance (i.e., the probability of developing breast or ovarian cancer in women who have known *BRCA1* or *BRCA2* mutations) that computed a standardized incidence ratio (SIR) as the summary measure, we considered several factors to determine study quality in the absence of predefined criteria. Studies were considered high-quality if: 1) genotypes were known by direct measurement or inference from genotypes of relatives rather than probabilistically assigned; 2) breast and ovarian cancer outcomes were determined prospectively after ascertainment of the family genetic profile; 3) important covariates were measured for all individuals and accounted for in the analysis, including use of risk-reducing surgery and medications, age, Ashkenazi
Jewish ancestry, race or ethnicity, and vital status; and 4) reported family history was validated by review of medical records of family members.

The applicability of studies was determined using the population, intervention, comparator, outcomes, timing of outcomes measurement, and setting format adapted to this topic.\textsuperscript{102}

**Data Synthesis**

We assessed the aggregate quality of the body of evidence for each key question (good, fair, poor) by using methods developed by the USPSTF based on the number, quality, and size of studies and consistency of results between studies.\textsuperscript{100} Studies were considered consistent if outcomes were generally in the same direction of effect and ranges of effect sizes were narrow.

**Statistical Meta-Analysis**

To determine clinical outcomes related to various mutation testing results, we combined data in several meta-analyses to obtain estimates of mutation prevalence, penetrance, and relative risk for developing breast or ovarian cancer. These include estimates for women from unselected populations, high-risk cohorts, and Ashkenazi Jewish populations with tests indicating BRCA-positive (i.e., detected \textit{BRCA1} or \textit{BRCA2} mutations), variant of uncertain significance, uninformative negative, and true negative results using data from studies meeting inclusion criteria. Relevant studies from the previous review as well as those identified for this update were included in the meta-analyses.

To determine the appropriateness of meta-analysis, we considered clinical and methodological diversity and assessed statistical heterogeneity. We abstracted or calculated estimates of prevalence, penetrance, and relative risk (risk ratio [RR] or SIR) and their standard errors (SEs) from each study and used them in the meta-analysis. When the SIR was not reported, but the studies reported data for observed and expected numbers of cancer cases, or the study only reported the observed number of cancer cases and we could calculate the expected number of cancer cases from Surveillance Epidemiology and End Results data,\textsuperscript{39} we calculated the SIR and its CI based on observed and expected numbers of cancer cases using the relationship between the Poisson distribution and the chi-square distribution.\textsuperscript{103}

We assessed the presence of statistical heterogeneity among the studies by using standard chi-square tests, and the magnitude of heterogeneity by using the $I^2$ statistic.\textsuperscript{104} We used a random-effects model to combine data for prevalence, penetrance, and relative risk while accounting for variation among studies. In general, when there is no variation among studies, the random-effects model yields the same results as a fixed-effects model without a study effect.\textsuperscript{105} To account for clinical heterogeneity, we stratified analyses by clinical characteristics (e.g., breast vs. ovarian cancer, levels of risk, or methods used to select probands for BRCA-positive women) when necessary. We conducted sensitivity analyses to assess the robustness of results that considered variation from outlying studies. The results of the sensitivity analyses indicated no major differences from the main analysis. All analyses were performed using Stata/IC 12.1 (StataCorp, College Station, TX) and SAS 9.3 (SAS Institute, Cary, NC).

BRCA-Related Cancer
External Review

The draft report was reviewed by content experts, USPSTF members, AHRQ Project Officers, and collaborative partners and revised prior to finalization (Appendix B4).

Response to Comments Received During the Public Comment Period

A draft version of this evidence report was posted for public comment on the USPSTF Web site from April 2 to April 29, 2013. Comments were contributed by seven individuals and primarily concerned the scope of the review (i.e., include women with existing cancer, men, other types of mutations); issues that were already addressed by the systematic review, but were missed by the respondent (e.g., effect of risk-reducing salpingo-oophorectomy before and after menopause); studies or topics of interest that had no publications meeting inclusion criteria (e.g., testosterone supplements to reduce breast cancer risk); and comments about the recommendation statement. These comments did not lead to important changes in the systematic review.
CHAPTER 3. RESULTS

We reviewed 5,268 references from electronic searches, reference lists, and manual searches of recently published studies. After applying inclusion and exclusion criteria, we reviewed 1,600 full-text papers. Of these, 140 provided data addressing one or more of the key questions and were included in the systematic review. Appendix B5 shows the results of our literature search and selection process and Appendix B6 lists the excluded full-text papers. Included studies and quality ratings are in Appendixes C1 to C4.

Key Question 1. Does Risk Assessment, Genetic Counseling, and Genetic Testing Lead to Reduced Incidence of BRCA-Related Cancer and Reduced Cause-Specific and All-Cause Mortality?

No studies addressed the overarching issues of key question 1.

Key Question 2a. What Is the Accuracy of Methods to Assess Familial Cancer Risk for BRCA-Related Cancer When Performed by a Nongenetics Specialist in a Clinical Setting?

Key Question 3a. What Are the Potential Adverse Effects of Risk Assessment?

Summary

Several studies of risk stratification methods for nongenetics specialists met inclusion criteria for key question 2a, but no studies met criteria for key question 3a regarding potential adverse effects. The sensitivity of self-reported family cancer history in first-degree relatives varied between 65 and 82 percent for breast cancer and was 50 percent for ovarian cancer in validation studies, although specificity was greater than 90 percent. Referral criteria have been developed by several groups, but their accuracy has not been evaluated. A published systematic review of studies of 13 general breast cancer risk models and 11 studies of five familial risk models provided accuracy measures. Reference standards varied across studies, limiting comparisons between methods. General breast cancer risk models, such as the Gail model, are modest predictors for individuals (c-statistic, 0.55 to 0.65). Familial risk models, including the Ontario Family History Assessment Tool (FHAT), Manchester Scoring System, Referral Screening Tool (RST), Pedigree Assessment Tool (PAT), and FHS-7, predict risk specifically for BRCA mutations and are intended to guide referrals to genetic counseling. Studies indicated high accuracy for these models (c-statistic, >0.80), although some models have only been evaluated in single studies.
Evidence

This key question focuses on the evaluation of a patient’s individual familial risk for BRCA-related cancer in a clinical setting by a nongenetics specialist for the purpose of initiating appropriate referrals for more comprehensive evaluations by genetic counselors and other specialists. These methods of risk stratification and referral differ from those intended for comprehensive evaluations. Risk models have been developed that predict the probability of developing breast cancer or the likelihood of having a mutation. Although the mutation probability is linked to family history, BRCA mutations explain only a small proportion of the familial aggregation of breast cancer, and even less of the hereditable variance in risk in a population.

Determination of Family History

Family history of BRCA-related cancer is important in estimating individual risk for a BRCA1 or BRCA2 mutation in women without cancer or known family mutations. Among women with first-degree relatives with cancer, the relative risk for cancer has been estimated in meta-analyses as 2.1 (95% CI, 2.0 to 2.2) for breast cancer43 and 3.1 (95% CI, 2.6 to 3.7) for ovarian cancer.106 Decisions about referral, testing, and risk-reducing interventions are often based on self-reports of family histories that include type of cancer, relationship within the family, and age of onset. Appropriate decisions rely on family histories that are accurately reported by women and correctly obtained by clinicians.

The accuracy of family cancer history information was determined in studies that validated self-reported family histories with medical records. In one study, a report of breast cancer in a first-degree relative of a healthy individual had a sensitivity of 82 percent, specificity of 91 percent, positive likelihood ratio of 8.9 (95% CI, 5.4 to 15.0), and negative likelihood ratio of 0.20 (95% CI, 0.08 to 0.49).107 A more recent population-based study in the United States indicated the accuracy of self-reported breast cancer history in a first-degree relative as 64.9 percent sensitivity and 99.0 percent specificity.108 In this study, the accuracy for first-degree relatives was higher than for second-degree relatives. For ovarian cancer, a report of ovarian cancer in a first-degree relative was less reliable than for breast cancer, and had a sensitivity of 50 percent, specificity of 99 percent, positive likelihood ratio of 34.0 (95% CI, 5.7 to 202.0), and negative likelihood ratio of 0.51 (95% CI, 0.13 to 2.10).107

Referral Guidelines

Referral guidelines have been developed by health maintenance organizations,109 professional organizations,51,92 cancer programs,50,110 State and national health programs,111-113 and investigators114 to assist nongenetics specialists in identifying women who are at potentially increased risk for BRCA mutations. Although specific items vary among the guidelines, most include questions about personal and family history of BRCA mutations, breast and ovarian cancer, age at diagnosis, bilateral breast cancer, and Ashkenazi Jewish ancestry. Most guidelines are intended to lead to a referral for more extensive genetic evaluations and counseling, not directly to testing. Although guidelines vary, practice and coverage standards in the United States generally follow the NCCN referral criteria for genetic counseling (described in Appendix...
The effectiveness of this approach in improving breast cancer outcomes has not been evaluated.

**General Risk Stratification Models to Predict Individual Risk for Breast Cancer in Primary Care Settings**

Although used in clinical settings, general risk stratification models predicting individual risk for breast cancer were not developed to identify women with increased probabilities of BRCA mutations.

A recent systematic review included 19 studies evaluating 13 risk stratification models to identify women with increased risk for breast cancer (Table 3). Models specifically evaluating risk for BRCA1 and BRCA2 mutations were outside the scope of this review and were not included.

Most general risk models are based on the Breast Cancer Risk Assessment Tool, also referred to as the Gail model. This model was derived from multivariate logistic regression analysis of identified risk factors for breast cancer, and subsequently modified with Surveillance Epidemiology and End Results data. Subsequent models use a similar approach, but vary in their use of reference standards and included variables. The original Gail model included age, age at menarche, age at first birth, family history of breast cancer in first-degree relatives, number of prior breast biopsies, and history of atypical hyperplasia. Subsequent models include one or more of these variables in addition to other factors (Table 3).

Most models accurately predict breast cancer incidence in populations of women. For most models in the studies, the expected numbers of cases of breast cancer closely matched the observed numbers (calibration: estimated/observed [E/O], 0.90 to 1.10). However, they are only modestly accurate in predicting breast cancer risk for individuals. In studies, discriminatory accuracy was expressed as concordance statistics, determined by the area under the receiver-operating characteristic curve (c-statistic). Values ranged from 0.55 to 0.65 across the studies, which is comparable to age alone as a predictor.

**Familial Risk Stratification Models to Predict Individual Risk for BRCA Mutations in Primary Care Settings**

Familial risk stratification models for BRCA-related cancer are primarily intended for use by nongenetics specialists to guide patient referrals to genetic counselors for more definitive evaluations. Several models have been developed and evaluated, including the FHAT, Manchester Scoring System, RST, PAT, and FHS-7. Ten studies describing performance characteristics of these models met inclusion criteria for this review (Table 4, Appendix C5). Included studies met criteria for fair or good quality and compared the referral models to validated risk assessment models, including BRCAPRO, Claus, Myriad, BOADICEA, Tyrer-Cuzick, and Penn II. Studies of the RST, PAT, and FHS-7 were published after the previous USPSTF systematic review.

*FHAT*. The FHAT is a 17-question instrument developed to assist Canadian clinicians in
selecting patients for referral to genetic counseling. The referral threshold is equivalent to doubling the general population lifetime risk for breast or ovarian cancer (22%). In the FHAT, points are assigned according to the number of relatives, third-degree or closer, who are diagnosed with breast, ovarian, colon, or prostate cancer; age at diagnosis; and type of primary cancer and number of primary cancer cases. Patients with scores of 10 or more points warrant referral. FHAT results were compared with Claus and BRCAPRO estimates for 184 women with incident familial and nonfamilial breast cancer. The sensitivity and specificity of the FHAT for a clinically significant \textit{BRCA1} or \textit{BRCA2} mutation were 94 and 51 percent, respectively. This compares with sensitivity and specificity of 74 and 79 percent for a 20 percent threshold for having a clinically significant \textit{BRCA1} or \textit{BRCA2} mutation using BRCAPRO, and 74 and 54 percent using Claus methods. Additional validation studies of the FHAT have replicated its accuracy, and its concordance statistics range from 0.68 to 0.83 across a wide variety of conditions.

\textit{Manchester Scoring System.} The Manchester Scoring System was developed in the United Kingdom to predict \textit{BRCA1} or \textit{BRCA2} mutations at the 10 percent likelihood level. Points are assigned depending on type of cancer (breast, ovarian, pancreatic, or prostate), affected family members, and age at diagnosis. The model provides scores for \textit{BRCA1} and \textit{BRCA2} mutations separately. The scoring system was validated in three sample sets in other regions of the United Kingdom and compared with other existing models. In validation studies, the Manchester model (combined \textit{BRCA1} and \textit{BRCA2}) had 58 to 93 percent sensitivity, 33 to 71 percent specificity, and concordance statistics of 0.75 to 0.80, comparing well with the other models tested.

\textit{RST.} The RST was developed to help primary care clinicians make appropriate referrals for genetic counseling in response to the USPSTF 2005 recommendation. The RST is a clinical scoring tool that uses a checklist of risk information, including breast cancer at age 50 years or younger in self or relatives, ovarian cancer at any age in self or relatives, two or more breast cancer cases after age 50 years on the same side of the family, male breast cancer, and Jewish ancestry. The referral threshold is reached with two or more positive responses. It was designed for simplicity, and is the least complicated model to administer for screening purposes. In an evaluation study, the RST was administered to 2,464 unselected women undergoing screening mammography in a U.S. health care system. Results were compared against validated risk assessment models, including BRCAPRO, Myriad II, BOADICEA, and FHAT. The RST demonstrated a sensitivity of 81 percent, specificity of 92 percent, and concordance statistic of 0.87. A revised model is also available online.

\textit{PAT.} The PAT was also designed to identify women at increased risk for BRCA-related cancer in U.S. primary care settings. The PAT uses a point scoring system based on information from first-, second-, and third-degree relatives regarding breast cancer onset at ages younger or older than 50 years; ovarian cancer at any age; male breast cancer; and Ashkenazi Jewish ancestry. Performance characteristics were determined in a study of 3,906 women without cancer undergoing screening mammography at a U.S. community hospital. Results were compared against the Myriad II and Gail models. The PAT had optimal sensitivity of 100 percent and specificity of 93 percent at scores of 8 or more. The PAT had a concordance statistic of 0.96, which was much higher than results using the Gail 5-year (0.39) or lifetime estimate (0.59).
**FHS-7.** The FHS-7 is a seven-question instrument about family history of breast, ovarian, and colorectal cancer.\(^{138}\) It was developed as a simple instrument for primary care settings for screening and referral purposes. The questions include first-degree relatives with breast or ovarian cancer, any relatives age 50 years and younger with breast cancer, bilateral breast cancer, breast and ovarian cancer in the same person, male breast cancer, two or more relatives with breast and/or ovarian cancer, and two or more relatives with breast and/or colon cancer. A single positive response is the threshold for referral. In an evaluation study in Brazil, the FHS-7 was administered to 9,218 women during routine visits to primary care clinics. Results were compared with Claus, Gail, Tyrer-Cuzick, and Penn II models. The FHS-7 had a sensitivity of 88 percent, specificity of 56 percent, and concordance statistic of 0.96.\(^{138}\)

**Key Questions 2b, 3b. What Are the Benefits and Potential Adverse Effects of Genetic Counseling in Determining Eligibility for Genetic Testing for BRCA-Related Cancer?**

**Summary**

Sixteen new studies evaluated the benefits and harms of genetic counseling, including a systematic review; RCTs; and cohort, case-control, and before-after studies of distress, accuracy of risk perception, and intention for testing. Results indicated that counseling decreases cancer worry, anxiety, and depression; increases the accuracy of risk perception; and decreases intention for mutation testing. Face-to-face counseling was preferred in some studies. Limitations of studies included dissimilar comparison groups and small sizes.

**Evidence**

Twenty-seven studies met inclusion criteria, including 16 published since the prior review\(^{148-165}\) and 11 included previously\(^{57-60,62,166-171}\) (Table 5, Appendix C6). Studies provided data about distress due to genetic counseling for BRCA-related cancer measured as worry, anxiety, or depression. Additional outcomes included intention for genetic testing and accuracy of risk perception. Results for key questions 2b and 3b are both presented in this section of the review because studies generally provided measures for both benefits and harms.

Eleven studies included in the previous review indicated that breast cancer worry usually decreased after genetic counseling, and women preferred personal contact over computer software or telephone counseling.\(^{57-60,62,166-171}\) Also, studies showed that measures of anxiety and depression generally decreased or did not differ with counseling.\(^{59,62,166,167,169-171}\) Risk perception was not well reported in previous studies and results were inconclusive.\(^{57-59,166-171}\) Studies also showed that women’s intention to pursue genetic testing decreased after counseling.\(^{57,58,60}\)

The new studies include one fair-quality systematic review,\(^{165}\) seven RCTs (six fair-quality\(^{152,154,155,157,160,164}\) and one poor-quality\(^{151}\) ), one fair-quality prospective cohort study,\(^{161,162}\) one good-quality case-control study,\(^{148}\) and six studies with before-after designs for which quality rating criteria were not available.\(^{149,150,153,156,158,159,163}\) Limitations of studies included inadequate
Studies enrolled from 64 to 1,971 women with family histories of breast and ovarian cancer who were seeking genetic counseling and were potentially interested in receiving genetic testing for BRCA mutations. Several studies compared different types of genetic counseling and genetic counseling versus no counseling, while others compared outcomes before and after genetic counseling. The types of genetic counseling services provided are summarized in Table 6.

Breast Cancer Worry

No studies reported increases in measures of breast cancer worry after women received genetic counseling; eight studies reported decreases, while one study reported no changes.

A fair-quality RCT measuring worry with the CWS reported that women who received either in-person or telephone counseling had significant decreases in worry after counseling compared with the control group who did not receive counseling (mean decrease from baseline, 0.90 in-person vs. 0.82 telephone vs. 0.38 none; p=0.002). More women in the in-person counseling group felt they could discuss their concerns during counseling sessions compared with women who received telephone counseling (77.4% vs. 67.3%, respectively; p<0.05). Fewer women in the in-person counseling group said they would have preferred another type of counseling (14.9% vs. 37.0%, respectively; p<0.001).

A fair-quality RCT reported decreases in worry after both group and individual genetic counseling compared with a noncounseling control group (mean change from baseline, -0.7 group vs. -0.9 individual vs. +0.1 none; p<0.001). Another study comparing a computer intervention with an in-person counseling session reported significant decreases in both groups after counseling, with no differences between groups. Only one poor-quality RCT reported no significant difference in cancer worry after telephone counseling compared with a control group not receiving counseling, as measured on a three-item, 4-point Likert scale.

A fair-quality prospective cohort study reported that more women receiving counseling experienced decreases in cancer-specific distress, as measured by the IES. The cancer-specific distress of women with counseling decreased more from baseline to 1 year postcounseling (from 52% to 41%) compared with high-risk women referred for mammography with no genetic counseling (from 41% to 35%), or with a random sample from the general population (from 32% to 30%) with no counseling. Although more women who had genetic counseling experienced a decrease in cancer-specific distress, this difference was only statistically significant when
compared with women in the general population (p=0.006).

Similarly, two before-after studies, using a modified CWS, reported reductions in cancer worry after genetic counseling compared with baseline.\textsuperscript{153,158} One reported a reduction after 1 month, which became statistically significant after 1 year of followup (mean, 11.6 at baseline vs. 10.9 at 1 month vs. 10.8 at 1 year; p<0.001 for change from baseline to 1 year).\textsuperscript{158} While the other reported reductions after 9 months that remained after 6 years, they were not statistically significant (mean, 11.54 at baseline vs. 10.37 at 9 months vs. 10.35 at 6 years; p=0.29), and no statistically significant difference was observed in those who did not receive counseling (mean, 11.29 at baseline vs. 10.39 at 9 months vs. 10.65 at 6 years; p=0.44).\textsuperscript{153}

One before-after study (in two publications) using the IES reported that women’s levels of worry decreased over time from initial levels, particularly after they were informed of their risks.\textsuperscript{149,150} One fair-quality RCT reported significant reductions in cancer worry in women who were at moderate or high risk 6 months after genetic counseling compared with baseline, based on CWS scores.\textsuperscript{155} Reductions were also significant when compared with women who only attended initial in-person precounseling sessions.

### Anxiety and Depression

No studies reported significant increases in anxiety and depression after receiving genetic counseling; three studies reported significant decreases in anxiety and depression,\textsuperscript{154,163,164} while three studies reported no changes.\textsuperscript{150,158,162}

A good-quality RCT compared women receiving genetic counseling from a nurse specialist in addition to resources about informing at-risk relatives, a pamphlet, and a videotape versus women receiving the standard care given at the clinic, which was genetic counseling from a specialist nurse with no additional resources.\textsuperscript{164} Both groups reported significant decreases in mean anxiety and depression scores, as measured by the HADS, at 2 weeks and 8 months after counseling (p<0.01 over time). However, there were no significant differences between groups at any time point and none of the mean scores reached the clinical threshold (score of ≥8).

Another study reported significant decreases in mean anxiety scores, as measured by the STAI, from before genetic counseling, when scores indicated high anxiety (score >22), to immediately and 6 months after genetic counseling, when scores fell below the threshold for high anxiety (22.22 vs. 18.77 vs. 16.98, respectively; p<0.001).\textsuperscript{163} However, in a fair-quality RCT, anxiety scores at baseline indicated high anxiety and significantly increased from baseline to 3 months following counseling (Genetic Risk Assessment in the Clinical Environment [GRACE], 40.00 to 56.28 to 52.15 vs. counseling, 35.73 to 47.78 to 51.19; p<0.01 over time), as measured by the STAI.\textsuperscript{154} While participants’ scores in the GRACE group improved slightly at followup, they never returned to their baseline levels.

No significant differences in anxiety or depression scores were found in a fair-quality cohort study comparing women receiving genetic counseling with a high-risk reference sample and a random sample from the general population.\textsuperscript{162} The number of women meeting clinical thresholds for anxiety and depression, as measured by the HADS, was low (<12% anxiety and
<2% depression). However, slightly more women in the counseling group had moderate levels of distress, as measured by the IES (12% vs. 8%). A before-after study reporting anxiety outcomes from baseline to 1 year after genetic counseling also reported no significant differences, though all mean scores were above the clinical threshold for psychiatric disorders. In another before-after study, no significant changes in women’s anxiety or depression scores were detected over time, regardless of their levels of risk. In this study, only baseline scores indicated mild anxiety, and followup scores were below the clinical threshold for anxiety, as measured by the HADS.

Risk Perception

A fair-quality systematic review of 19 studies published before February 2007 reported results of studies of risk perception after genetic counseling. In these studies, risk perception was measured by changes in the proportion of women who accurately perceived their own risk, and by the degree of overestimation or underestimation of risk. Overall, the accuracy of risk perception increased from an average of 42 percent accuracy before counseling to 58 percent after counseling. Women who continued to overestimate their risks did so by approximately 18 percent (range, 6% to 40%), which was an improvement of approximately 8 percent after counseling. Seven studies indicated that counseling that delivered information about family history, heredity, and personal risk estimates positively influenced risk perception accuracy. Three of five studies showed significant improvement in risk accuracy when education about heredity was included, and three of six studies showed an improvement in risk accuracy when facilitating informed decisionmaking and adaptation to personal risk was part of counseling.

Eight studies published since 2004, including four cited in the 2007 published systematic review, were consistent in reporting improved accuracy of breast cancer risk perception after genetic counseling. One study reported less accuracy. These findings differ from the prior USPSTF review, in which results were inconclusive. The recent studies measured risk perception using subjects’ self-rated lifetime risk of breast cancer compared with the general population (0- to 100-point scale), lifetime likeliness of developing breast cancer on a 5-point Likert scale, and comparisons between risk estimates of subjects and counselors.

A fair-quality RCT measuring perceived breast cancer risk on a 5-point scale and rating chances of diagnosis from 0 to 100 percent reported that women overestimated their risks of breast cancer by an average of 25 percentage points. The proportion of women underestimating their risks was larger among women with perceived lower risks (40%) than in those who perceived it as the same (16%), higher (10%), or much higher (5%) than the risks of other women (p=0.009). Women with the highest overestimations were more likely to improve their accuracy with counseling (p<0.0001), although counseling was effective in improving accuracy only in women age 50 years or younger (p=0.0040).

A fair-quality RCT reported no differences in risk accuracy between telephone and in-person counseling. Accuracy significantly improved over time for both groups (p<0.001), and was better than in a control group that did not receive genetic counseling (p<0.001).
A before-after study measured risk perception using a 5-point scale ranging from 1 (chances of breast cancer much lower than the average woman) to 5 (chances much higher than the average woman). There was a significant decrease from baseline to 1 week (mean, 4.29 vs. 3.83; p=0.00) and at 1 week compared with a control group (mean, 3.83 vs. 3.97; p=0.01). However, perception of risk increased at 9 months (mean, 3.99) and after 6 years (mean, 4.08), without returning to baseline levels.\textsuperscript{153}

Only one before-after study assessed the accuracy of risk perception for developing ovarian cancer.\textsuperscript{159} In this study, all women underestimated their risks of developing ovarian cancer by 5 percent 6 months after counseling.

**Intent to Participate in Genetic Testing**

Two studies reported decreased intention to undergo genetic testing after genetic counseling.\textsuperscript{152, 157} A study comparing telephone counseling versus in-person counseling versus no counseling used a four-question measure to determine women’s intentions to pursue genetic testing.\textsuperscript{157} Participants’ combined baseline scores for their intention to pursue genetic testing was 2.22 and there were no significant differences between groups at baseline. After counseling, the control group had increased intention scores, while the two counseling groups had decreased scores (mean change from baseline, +0.51 control vs. -0.61 in-person vs. -0.52 telephone; p<0.001).

A fair-quality RCT reported decreased interests in genetic testing 6 months after group and individual counseling.\textsuperscript{152} Interests in testing for both counseling groups decreased significantly more than in the control group (mean decrease from baseline, 0.7 group vs. 0.6 individual vs. 0.2 control; p<0.01).

**Key Question 2c. What Is the Clinical Validity of Genetic Testing for Deleterious Mutations in Women With Increased Risk for BRCA-Related Cancer?**

**Summary**

In the context of this key question, clinical validity is how consistently and accurately BRCA mutation status predicts risk for BRCA-related cancer. This review describes clinical validity using the measures of prevalence and penetrance of BRCA mutations. Thirty-two new cohort, cross-sectional, and descriptive studies were combined with 38 earlier studies for meta-analysis estimates of the prevalence and penetrance of BRCA mutations in various groups of women. Limitations include heterogeneity of studies, differences between laboratory techniques for research and clinical care, lack of studies outside of high-risk populations, bias in estimates from women or families with cancer, and no studies of penetrance in women with test results indicating variants of uncertain significance.

Prevalence is the frequency of BRCA mutations in the population. Estimates of prevalence in high-risk populations overestimate assumptions of prevalence in unselected populations, but
inform an individual’s likelihood of carrying a BRCA mutation and candidacy for testing. Estimates of the prevalence of BRCA mutations vary by population: 0.2 to 0.3 percent in unselected women; 1.8 percent for BRCA1 and 1.3 percent for BRCA2 in women with breast cancer; 6 percent in women with breast cancer onset at age 40 years or younger; 4.4 percent for BRCA1 and 5.6 percent for BRCA2 in women with ovarian cancer; and 13.6 percent for BRCA1, 7.9 percent for BRCA2, and 19.8 percent for both combined in women with high-risk families. For Ashkenazi Jewish women, prevalence is 2.1 percent in unselected populations and 10.2 percent in those with high-risk families.

Penetrance is the likelihood of developing breast or ovarian cancer for a given BRCA genotype, and is age dependent. Estimates of the penetrance of BRCA mutations differ by test result. In high-risk women with positive test results, risks for breast cancer to age 70 years include 46 percent for BRCA1 and 50 percent for BRCA2 when a single family member is tested, and 70 percent for BRCA1 and 71 percent for BRCA2 when multiple family members are tested. Risks for ovarian cancer to age 70 years in high-risk women with positive test results are 41 percent for BRCA1 and 17 percent for BRCA2 when a single family member is tested, and 46 percent for BRCA1 and 23 percent for BRCA2 when multiple family members are tested. Risks for Ashkenazi Jewish women to age 75 years is 34 percent for breast cancer and 21 percent for ovarian cancer.

In women with uninformative negative test results, the SIR for breast cancer is 3.81 (95% CI, 3.06 to 4.75). In women with true negative test results, the SIR for breast cancer is 1.13 (95% CI, 0.81 to 1.58). Estimates for ovarian cancer are highly heterogeneous and cannot be combined in meta-analysis.

Evidence

A total of 32 studies of prevalence and penetrance not included in the prior review met inclusion criteria,21,172-202 in addition to 38 studies included in the prior review13,15,16,19,20,46,47,122,188,203-231 (Appendices C7 and C8). Studies estimated prevalence for high-risk and Ashkenazi Jewish populations and penetrance for BRCA-positive, uninformative negative, and true negative results (Figure 2). No studies provided risk estimates for women with variants of uncertain significance. Most studies used a variety of research laboratory techniques to detect clinically significant mutations that differ from the DNA sequencing that is clinically available.

Prevalence

Unselected Populations. No direct measures of the prevalence of clinically significant BRCA1 or BRCA2 mutations in the general, nonJewish U.S. population have been published. Models estimate it to be about 0.2 to 0.3 percent.13-16

High-Risk Populations. Studies provide prevalence estimates for three different types of high-risk groups: 1) women with early-onset breast or ovarian cancer (e.g., before age 45 years), 2) women with breast or ovarian cancer from selected high-risk cohorts (e.g., consecutive cases from cancer registries or surgical units), and 3) women from high-risk families based on family history of breast and/or ovarian cancer (Table 8). Prevalence estimates based on high-risk groups

BRCA-Related Cancer 22 Pacific Northwest EPC
overestimate prevalence in unselected or general populations. However, women from high-risk groups are the most likely candidates for BRCA testing and identifying them can guide testing decisions within a family.

**Early-Onset Breast or Ovarian Cancer.** Eleven studies reported prevalence estimates for women with early-onset breast or ovarian cancer:

For **BRCA1**, the meta-analysis indicated a prevalence of 4.26 percent (95% CI, 2.61 to 6.87; 10 studies) in women diagnosed with breast cancer at age 40 years or younger, and 5.17 percent (95% CI, 2.39 to 9.59; 2 studies) in those diagnosed with ovarian cancer at age 40 years or younger (Table 1). For **BRCA2**, prevalence was 2.90 percent (95% CI, 1.35 to 6.14; 5 studies) in women diagnosed with breast cancer at age 40 years or younger, and 0.64 percent (95% CI, 0.02 to 3.50) in those diagnosed with ovarian cancer at age 40 years or younger, based on only one study. For **BRCA1** or **BRCA2**, the combined prevalence estimate was 5.98 percent (95% CI, 1.87 to 17.47) in women diagnosed with breast cancer at age 40 years or younger. Additional estimates are described in Table 9 and suggest higher prevalence rates in women with younger ages of cancer onset. While subject selection for the youngest age group (≤35 years) in these studies was based primarily on age at diagnosis of breast or ovarian cancer, some studies used family history information to select subjects for the older age group (≤45 years).

**High-Risk Cohorts.** Results of a meta-analysis of four studies based on data from breast cancer case series indicated a combined prevalence estimate for **BRCA1** of 1.84 percent (95% CI, 0.72 to 4.63). The prevalence of **BRCA2** was 1.31 percent (95% CI, 0.67 to 1.95), based on one study.

Results of a meta-analysis of four studies based on data from ovarian cancer case series indicated a combined prevalence estimate for **BRCA1** of 4.41 percent (95% CI, 2.47 to 7.74), with substantial heterogeneity among studies ($I^2=70\%$; $p=0.006$). The prevalence of **BRCA2** was 5.61 percent (95% CI, 4.13 to 7.09), based on one study.

Prevalence was also reported for racial and ethnic minorities in three studies, however, the studies were small, few mutations were detected, and results were not conclusive.

**High-Risk Families.** Additional prevalence estimates for women from referral populations with various levels of family history range from 3.66 percent to 30.8 percent for **BRCA1** and from 6.1 percent to 15.4 percent for **BRCA2** in white, nonHispanic, nonAshkenazi Jewish women.

In 11 studies in which recruitment was based on family history of breast and/or ovarian cancer, results of the meta-analysis indicated **BRCA1** prevalence of 13.58 percent (95% CI, 10.09 to 17.07), with significant heterogeneity among studies ($I^2=86\%$; $p<0.001$). Heterogeneity remained high in a sensitivity analysis that excluded an outlier ($I^2=89\%$; $p<0.001$). Estimates were similar in sensitivity analyses that excluded two studies with mixed populations of race/ethnicity. One study reported a **BRCA1** prevalence of 35.71 percent (95% CI, 26.92 to 44.51) in families with two or more cases of ovarian cancer.
For **BRCA2**, meta-analysis results of eight studies in which recruitment was based on family history of breast and/or ovarian cancer indicated a prevalence of 7.90 percent (95% CI, 5.30 to 10.50). One study reported a prevalence estimate of 7.14 percent (95% CI, 2.13 to 12.15) in families with histories of two or more cases of ovarian cancer. For **BRCA1** and **BRCA2** combined, the prevalence was 19.78 percent (95% CI, 12.98 to 26.57).

Prevalence was also reported for racial and ethnic groups from referral populations with various levels of family history risk. One study reported a prevalence of 22.7 percent for **BRCA1** and 8.1 percent for **BRCA2** in 110 Hispanic individuals in a hereditary cancer registry. No **BRCA1** or **BRCA2** mutations were detected in three Hispanic individuals tested in another study. Black individuals presenting for BRCA testing in high-risk clinics had a prevalence of 16.3 percent for **BRCA1** and 11.6 percent for **BRCA2**.

**Ashkenazi Jewish.** Five studies provided estimates of **BRCA1** prevalence in Ashkenazi Jewish populations unselected by personal or family history of breast cancer, and six studies provided estimates for **BRCA2** prevalence (Table 10). These studies reported the prevalence of the three founder mutations, including mutations 5382insC and 185delAG in **BRCA1** and 6174delT in **BRCA2**.

Based on the meta-analysis, prevalence for **BRCA1** was 1.2 percent (95% CI, 0.98 to 1.42) and for **BRCA2** was 1.17 percent (95% CI, 0.95 to 1.38) (Table 11). For **BRCA1** and **BRCA2** combined, prevalence was 2.08 percent (95% CI, 1.28 to 2.88). There was significant heterogeneity among studies ($I^2=89\%$; $p<0.001$), with the most recent publication estimating prevalence at about half the rates of previous studies for both **BRCA1** and **BRCA2**. The new study included fewer women with family or personal histories of breast or ovarian cancer compared with other studies (e.g., personal history, 0.8% vs. 8%). Also, secular trends may have influenced prevalence estimates over time. For example, high-risk families who have already been tested may not have responded to advertisements recruiting participants to more recent studies. In a sensitivity analysis that excluded results from the most recent study, prevalence for the founder mutations was 2.46 percent (95% CI, 2.13 to 2.78) without significant heterogeneity among studies ($I^2=0\%$; $p=0.496$).

No new studies provided prevalence estimates for Ashkenazi Jews selected for personal or family histories of breast cancer. From the previous review, results of the meta-analysis indicated an estimated prevalence of founder mutations of 10.2 percent (95% CI, 4.2 to 22.9), including 6.4 percent (95% CI, 1.1 to 29) for **BRCA1** and 1.1 percent (95% CI, 0.6 to 2.0) for **BRCA2** in women with family histories of breast or ovarian cancer.
Penetrance

Penetrance is the probability of developing BRCA-related cancer in women who have a given \textit{BRCA1} or \textit{BRCA2} genotype, and is reported as the cumulative risk to a specified age. The meta-analysis results reflect the age parameters and cancer outcomes provided by the studies for positive, true negative, and uninformative negative test results. There were no studies of penetrance in women with variants of uncertain significance.

\textbf{BRCA-Positive Results in High-Risk Populations.} There were significant methodological differences across studies that reported penetrance in women who were \textit{BRCA1} or \textit{BRCA2} mutation carriers. Results are reported separately depending on whether a single person (Table 11) or multiple individuals (Table 12) in a family were tested.

Eight studies reported breast cancer penetrance based on testing a single individual per family.\cite{13, 15, 176, 187, 188, 190, 195, 225} For \textit{BRCA1} mutations, breast cancer penetrance was 46 percent (95% CI, 40 to 51) to age 70 years\cite{13, 15, 176, 188, 190} (Table 13); for \textit{BRCA2}, penetrance was 50 percent (95% CI, 40 to 60) to age 70 years.\cite{13, 15, 176, 188, 190}

Eight studies reported estimates based on testing multiple individuals per family.\cite{172, 173, 178, 185, 192, 201, 206, 210} For \textit{BRCA1} mutations, breast cancer penetrance was 70 percent (95% CI, 61 to 79) to age 70 years;\cite{173, 178, 185, 192, 201, 206} for \textit{BRCA2}, penetrance was 71 percent (95% CI, 59 to 83) to age 70 years.\cite{173, 178, 192, 201, 210} Between-study heterogeneity was significant.

Estimates were not combined across the two types of studies because of significant heterogeneity and large differences between estimates with nonoverlapping CIs. A published meta-analysis that combined all types of studies reported breast cancer penetrance in BRCA-positive women to age 70 years as 57 percent (95% CI, 47 to 66) for \textit{BRCA1} and 49 percent (95% CI, 40 to 57) for \textit{BRCA2}.\cite{12} A second meta-analysis that included 22 studies based on case-series unselected for family history reported estimates of 65 percent (95% CI, 44 to 78) for \textit{BRCA1} and 45 percent (95% CI, 31 to 56) for \textit{BRCA2}.\cite{11} This meta-analysis also reported significant between-study heterogeneity. The results of published meta-analyses differ from the results of this review because they included studies of women with Ashkenazi Jewish ancestry or studies in which only Ashkenazi Jewish founder mutations were tested. These populations were excluded from the meta-analysis reported in this review.

Seven studies reported ovarian cancer penetrance based on testing a single individual per family.\cite{13, 15, 176, 188, 190, 195, 225} For \textit{BRCA1} mutations, ovarian cancer penetrance was 41 percent (95% CI, 32 to 49) to age 70 years;\cite{13, 15, 176, 188, 190} for \textit{BRCA2}, penetrance was 17 percent (95% CI, 11 to 24) to age 70 years.\cite{13, 15, 176, 188} There was no significant heterogeneity between studies.

Six studies reported estimates based on testing multiple individuals per family.\cite{173, 178, 192, 201, 206, 210} For \textit{BRCA1} mutations, ovarian cancer penetrance was 46 percent (95% CI, 35 to 57) to age 70 years;\cite{173, 178, 192, 201, 206} for \textit{BRCA2}, penetrance was 23 percent (95% CI, 12 to 34) to age 70 years.\cite{173, 178, 192, 201, 210} There was significant heterogeneity between studies.

Estimates for ovarian cancer from studies of testing a single person or multiple individuals per
family were very similar and all studies were combined in additional meta-analyses. Combined measures for BRCA1 mutations include penetrance of 45 percent (95% CI, 37 to 52) to age 70 years and for BRCA2, 19 percent (95% CI, 13 to 25) to age 70 years. These estimates are similar to a published meta-analysis that reported penetrance in BRCA-positive women to age 70 years as 49 percent (95% CI, 40 to 57) for BRCA1 and 18 percent (95% CI, 13 to 23) for BRCA2.12 A second meta-analysis that included 22 studies based on case-series unselected for family history reported estimates of 39 percent (95% CI, 18 to 54) for BRCA1 and 11 percent (95% CI, 2.4 to 19) for BRCA2.11

Studies had several limitations and biases. Many studies selected families for analysis based on personal histories of breast or ovarian cancer (probands). Probands and their family members are more likely to have other risk factors for breast or ovarian cancer that may affect penetrance,233 and breast or ovarian cancer survivors may have a different spectrum of mutations compared with women with newly diagnosed cancer. Penetrance may also depend on the specific mutation within the gene, and only one study reported penetrance estimates stratified by exons.172

BRCA-Positive Results in Ashkenazi Jewish Populations. Several studies described in previous sections of this review provided estimates that included Ashkenazi Jewish along with non-Ashkenazi Jewish families. Only one new study reported penetrance in Ashkenazi Jewish families specifically, and these estimates combined women who were BRCA1 and BRCA2 mutation carriers.187 Estimates specifically for BRCA1 and BRCA2 were provided in the prior review1,2 and are similar to a published meta-analysis.234

In the previous meta-analysis of 10 studies,203,204,208,209,213,214,217,226,227,231 breast cancer penetrance was 33.7 percent (95% CI, 24.1 to 44.9) to age 75 years in Ashkenazi Jewish women without family histories of breast or ovarian cancer. In those with family histories, penetrance was 34.7 percent (95% CI, 17.6 to 57.0) to age 75 years, based on nine studies.47,203,208,209,213,214,217,224,226

From the previous meta-analysis of five studies,203,205,221,222,225 ovarian cancer penetrance was 21.4 percent (95% CI, 14.9 to 29.7) to age 75 years in Ashkenazi Jewish women without family histories of breast or ovarian cancer. In those with family histories, penetrance was 18.1 percent (95% CI, 7.6 to 37.3) to age 75 years, based on two studies.47,222

Uninformative Negative Results

An uninformative negative result can occur for several reasons, including other family members have not been tested; the family carries a BRCA mutation, but it was not detected because of limitations of the test; the family carries a high-risk mutation in another gene; or no high-risk mutation is segregating in the family.

Three studies provided data to estimate the SIR for the development of breast cancer in women with uninformative negative results compared with estimates for the general population (Table 15).182,189,230 Estimates across studies were very similar, ranging from 3.25 to 3.32. The overall estimate for the SIR for breast cancer was 3.81 (95% CI, 3.06 to 4.75) (Figure 3).

The same three studies provided data for SIRs for the development of ovarian cancer in women
with uninformative negative results compared with estimates for the general population (Figure 3, Table 14). However, these estimates varied widely across studies (0.85 to 11.6), and could not be combined because of significant heterogeneity ($I^2=77.4$%; $p=0.012$). This heterogeneity likely reflects the differing ascertainment criteria for study recruitment. The study with the lowest SIR (0.85 [95% CI, 0.23 to 3.12]) included only first-degree relatives of breast cancer cases. The other studies included families with breast cancer (SIR, 3.88 [95% CI, 0.05 to 21.6]) and families with at least two first-degree relatives with ovarian cancer (SIR, 11.6 [95% CI, 3.12 to 29.7]).

**True Negative Results**

A true negative result is possible for individuals who have relatives with cancer and a known BRCA mutation segregating in the family, but their own results are negative.

Ten studies provided data for the meta-analysis of SIRs for the development of breast cancer in women with true negative results compared with estimates for the general population (Table 15). Although SIR estimates ranged from 0.39 to 2.9 across studies, the CI for all studies included the value 1.0, indicating that the estimated risk was not statistically significantly different from that in the general population. The overall combined SIR estimate for breast cancer is 1.13 (95% CI, 0.81 to 1.58) (Figure 4).

Most studies included women as true negatives only if their genotype was known by direct testing or could be inferred from the known genotypes of their relatives (e.g., descendants of an individual who tested negative were inferred to also be mutation negative). However, two studies probabilistically assigned genotypes for a portion of women who were untested and whose genotypes were unknown. This approach would bias the results toward the null hypothesis of no difference between groups because of misassignment of genotypes. Also, all studies except one used a prospective design that included only newly diagnosed cancer cases after the identification of the family. A study design that includes cancer diagnoses known prior to the identification of the family could falsely increase the risk estimate in relatives because the family may be more likely to seek testing. Bias could also be introduced in studies that did not control for risk-reducing salpingo-oophorectomy in the analysis.

Two studies provided data for the SIR for the development of ovarian cancer in women with true negative results compared with estimates for the general population, although results differed (Figure 4, Table 15). One study reported an SIR of 0 (95% CI, 0 to 12) for BRCA1 and 0 (95% CI, 0 to 24) for BRCA2. A second study reported an increased risk of ovarian cancer with a SIR of 4.6 (95% CI, 1.2 to 11.7). However, this analysis was not conducted prospectively, and its ascertainment of families with strong family histories of breast and ovarian cancer could bias results. For this same study, the SIR estimate for breast cancer decreased from 5.3 (95% CI, 3.5 to 7.7) to 2.1 (95% CI, 0.4 to 6.2) after accounting for prospectively identified breast cancer cases only.
Key Question 3c. What Are the Potential Adverse Effects of Genetic Testing?

Summary

Thirteen cohort, case-control, and before-after studies reported distress measures and risk perception related to BRCA testing. Limitations of studies included high loss to followup and differences between comparison groups. In these studies, breast cancer worry and anxiety increased for women with positive results and decreased for others, although results differed across studies. Risk perception improved after receiving test results.

Evidence

Thirteen new observational studies met inclusion criteria, as well as one included previously. Studies provided data about distress due to BRCA testing measured as worry, anxiety, depression, or other psychosocial outcomes (Table 16, Appendix C9). No studies described other adverse effects of testing, such as false-positive or false-negative results or unnecessary risk-reducing interventions.

Of eight included cohort studies, five met criteria for good-quality, two for fair-quality, and one for poor-quality. The remaining studies included a fair-quality case-control study and five studies with before-after designs for which quality rating criteria were not available. Limitations of studies included unclear enrollment of the cohort, high loss to followup, and significant differences between groups at baseline or lack of reporting of baseline participant characteristics.

The studies varied in size from 17 to 10,244 women; however, the largest study was dominated by the control group (n=10,000). Studies enrolled women with family histories of breast and ovarian cancer seeking genetic testing for BRCA1 or BRCA2 mutations. Several studies reported outcomes by mutation status, while others compared outcomes before and after genetic testing.

Descriptions of the outcome measures are provided in Table 7. The studies used the IES, Cancer-Related Worry scale, and CWS-R to measure breast cancer worry; the STAI, IES, Post-Traumatic Growth Inventory, HADS, GHQ, Swedish Short-Form 36-Item Health Survey, Emotional Approach Coping Scale, Multidimensional Fatigue Symptom Inventory-Short Form, Beck Hopelessness Scale, Brief Symptom Inventory, Beck Depression Inventory, and Center for Epidemiologic Studies-Depression Scale to measure anxiety and depression; and the Pittsburgh Sleep Quality Index to measure sleep disturbances.

Breast Cancer Worry

Five studies reported significant increases in breast cancer worry after receiving BRCA test results. A good-quality prospective cohort study used a single question to measure worry on a four-item Likert scale: “During the last 2 weeks, how often did you worry about
developing breast cancer?" Women who were mutation carriers had a significant increase in worry compared with women with true negative or uninformative results 1 and 7 months after disclosure of genetic testing results (p<0.05). A fair-quality case-control study found no differences in worry between women who were carriers and women who were noncarriers with high-risk family history, as reported by the Cancer-Related Worry scale. However, when results were combined for both groups, their levels of worry were significantly higher than that of low-risk women who were not tested (p=0.022).

A decrease in breast cancer worry for both women who were carriers and women who were noncarriers from baseline to 3 years after disclosure of genetic test results was reported in one study (mean decrease of 1.3 and 2.2, respectively), as measured by the CWS-R. This decrease was significant for women who were mutation carriers (p=0.03) and did not differ between groups. A study of 17 women who were mutation carriers reported an increase in breast cancer worry from baseline to 1 year after disclosure of genetic test results and a decrease at 2 years, though scores remained in the mild distress range, as measured by the IES (5.2 vs. 23.8 vs. 17.2; p=0.05). In a good-quality cohort study, women who were carriers had higher breast cancer worry, as measured by the IES, compared with women who did not get tested (mean, 16.1 vs. 12.3, respectively; p=0.045). One cohort study included a logistic regression bivariate analysis of responses of women undergoing genetic testing. In women without cancer, a positive genetic test result was associated with distress (p=0.03), while a negative result was associated with pleasant experiences with the testing process (p=0.008).

### Anxiety

Two studies reported significant decreases in anxiety scores after women received genetic test results compared with pretest evaluations, based on HADS and IES scores. One study reported a significant decrease regardless of mutation status (mean, 5.6 pretest vs. 4.2 at 1 year posttest; p<0.001), while the other reported a significant decrease only in women who were noncarriers (p=0.001). A fair-quality prospective cohort study reported an increase in anxiety scores over time on the GHQ. In this study, 18 percent of women who were carriers and 17 percent of women who were noncarriers were identified as having anxiety, based on the GHQ 3 years after receiving genetic test results.

Two prospective cohort studies, one good-quality and one fair-quality, reported significantly higher anxiety scores (p<0.05 in both studies), as measured by the IES or IES-R, in women receiving a positive genetic test result compared with women receiving a true negative or uninformative test result. Only one of these studies reported results in the moderate distress range on the IES at baseline for all groups; women with a true negative or uninformative test result had scores decreasing to below case threshold by 7 months. One good-quality prospective cohort study reported higher anxiety scores, as measured by the HADS, in women who did not get genetic testing, but had a family history of breast cancer, compared with women who received a positive genetic test result (mean, 5.3 vs. 4.2, respectively; p<0.05). However, there were no differences between groups in the prevalence of HADS-defined anxiety (24% in both groups).

In a good-quality cohort study, women who were noncarriers had lower anxiety scores on the
STAI at 7 to 10 days followup (mean, 31.6 vs. 38.5 vs. 36.8, respectively; p=0.024) compared with women who were carriers and women who did not get tested, though all scores indicated high anxiety. Four studies reported no differences in anxiety either over time or between women who were carriers, noncarriers, and age-matched controls, with all below the case cutoff threshold.

Depression

Only one good-quality prospective cohort study reported higher depression scores, as measured by the HADS, in women who did not get genetic testing, but had a family history of breast cancer, compared with women receiving positive BRCA test results (mean, 2.9 vs. 1.7, respectively; p<0.05), though scores did not reach the threshold for clinical depression. Four studies reported no differences in depression either over time or between women who were carriers, noncarriers, and age-matched controls, with all scores below the case cutoff threshold. In a good-quality cohort study, women who were noncarriers had lower depression scores, as measured by the Beck Depression Inventory, at 4 months followup (mean, 3.6 vs. 6.2 vs. 6.4, respectively; p=0.024) compared with women who were carriers and women who did not get tested, though scores did not reach the threshold for clinical depression.

Sleep Disturbances

A fair-quality case-control study reported more subjective sleep problems, as measured by the Pittsburgh Sleep Quality Index, in women who were carriers compared with women who were noncarriers and age-matched controls (mean, 7.29 vs. 3.94 vs. 4.21, respectively; p=0.013). However, actual sleep duration, latency, and wakefulness, as measured by a wrist monitor, showed no differences between groups.

Other Outcomes

Two small (n=13 and n=7) descriptive case-series studies did not meet eligibility criteria, but provided outcomes relevant to harms to familial relationships.

A study of women with true negative test results reported that they were relieved to find out they were not carriers, and several women described feeling particularly reassured that their children would also not have the mutation. Most women (10/13 [67%]) believed their risk of developing breast or ovarian cancer continued to be slightly higher than that of the general population and therefore chose to undergo intensive screening. These women also decreased their communication about mutation status with other family members, especially those who were BRCA-positive.

A study of women with test results indicating the presence of BRCA mutations indicated that women were still grappling with how to live with their carrier status 3 years after disclosure of test results. Some women felt comforted by other mutation carriers in the family, but felt less comfortable by the noncarriers. Several women had undergone risk-reducing mastectomy, oophorectomy, or both, and although they felt assured knowing they had done everything they could to reduce their risks of developing cancer, they also felt a loss of their natural breasts and
ovarian hormones. This study also described that women struggled with what to tell their daughters, and how and when to tell them about their mutation status.

**Risk Perception**

A good-quality prospective cohort study reported an 18 percent increase in the number of women who perceived their risk of breast cancer to be high or very high 5 years after receiving a positive test result for a BRCA mutation versus before receiving results (p=0.016). Women who were noncarriers had a corresponding 47 percent decrease (p<0.001). Also, 20 percent more women who were mutation carriers perceived their risk of ovarian cancer to be high or very high (p=0.007), while 27 percent of women who were noncarriers perceived their risk to be low (p<0.001).

**Supplemental Information on the Impact of Genetic Testing on Family Members**

Testing for BRCA mutations and disclosure of mutation status can have an impact beyond the patient in the clinician’s office. While there are conflicting opinions and rulings on a clinician’s ethical and legal duty to warn a patient’s family about hereditary disease risk, patients may want to inform family members themselves. Studies indicate that most patients feel a responsibility to share their BRCA test results with family members in order to benefit them.

A descriptive study of 162 women who were tested for BRCA mutations and 444 relatives indicated that 69.4 percent of tested women shared their test results with at-risk relatives, but more often with female (sisters or daughters) rather than male relatives (brothers and sons) (79.9% vs. 60.4%; p<0.001). More women who tested positive for a BRCA mutation indicated that they had a difficult time explaining the results compared with those with true negative or indeterminate results (14.6% vs. 0% vs. 1.4%, respectively; p<0.001). In addition, women who tested positive were more likely to indicate that they and their relatives were upset when communicating the results compared with women who had true negative or indeterminate results (upset relatives, 52.4% vs. 10.0% vs. 7.4%, respectively; p<0.001; upset patient, 19.5% vs. 0% vs. 1.9%, respectively; p<0.001).

A descriptive study of 115 women who were BRCA mutation carriers reported that all participants disclosed test results to some at-risk relatives, and 88 percent disclosed to all at-risk relatives. However, only 56.8 percent of at-risk relatives subsequently underwent testing, although female relatives were more likely to have testing compared with male relatives (73% vs. 49%, respectively; p<0.01).

Four descriptive studies focused on disclosure of BRCA test results to children. Two small studies indicated that women who were mutation carriers who disclosed their positive test results to their children did so because of their concern about passing along the gene. In a study of 13 tested parents and 22 adult children, 77 percent of children felt the disclosure had no significant impact on their emotional health, while 18 percent reported a negative impact. Only 31.8 percent of children had undergone BRCA testing by the time of the survey, but 87
percent of those who had not undergone testing indicated intention to do so. A small study of children ages 11 to 17 years who had mothers with BRCA mutations reported normal scores on anxiety and depression measures (STAI) after hearing of their mother’s test results. However, 70 percent of children had mothers with breast cancer, and 57 percent of them had worrisome thoughts about their mother’s cancer that affected their feelings at least some of the time. Children who worried about their own cancer risk were more likely to be withdrawn (p=0.02) and have somatic problems (p=0.003), and children who worried about a family member’s cancer risk were more likely to have thought problems (p=0.02).

**Supplemental Information on the Effects of Direct-to-Consumer Marketing of BRCA Mutation Testing**

Until the U.S. Supreme Court decision against DNA patents in June 2013, Myriad Genetics held patents on the direct DNA sequencing of BRCA1 and BRCA2 mutations and was the exclusive provider of clinical testing in the United States. Myriad allowed other laboratories to conduct direct DNA sequencing for research purposes under strict constraints. Testing for specific known mutations, including previously identified familial types and Ashkenazi Jewish founder mutations, does not require full sequence testing and has been provided by other laboratories. Although other types of genetic tests were patented in the United States, they were nonexclusively licensed. For example, genetic testing for familial colorectal cancer has been available from multiple laboratories.

Myriad launched its initial direct-to-consumer advertising campaign in 2002, targeting potential patients in specific U.S. markets. Advertising included print and electronic media to raise awareness of breast cancer susceptibility genes and encourage women to speak to their physicians about testing. A study to determine the impact of the marketing campaign on patients and physicians was conducted by the Centers for Disease Control and Prevention. This study surveyed randomly selected women from the community as well as family physicians, internists, obstetrician/gynecologists, and oncologists in 2003, comparing two pilot cities with marketing campaigns (Atlanta and Denver) with two control cities that had no marketing (Seattle and Raleigh-Durham).

In pilot cities, women reported increased awareness of the BRCA test (p<0.05) and seeing an advertisement for the test (p<0.05). Cities did not differ by women’s interests in having the test, overall knowledge about genetic testing for breast and ovarian cancer, and if they had ever talked to health care providers or friends/family about the test. Physicians’ knowledge did not differ between sites. In pilot cities, there were increases in patients asking about testing (adjusted odds ratio [AOR], 2.1 [95% CI, 1.6 to 2.9]), asking for referrals (AOR, 1.6 [95% CI, 1.1 to 2.4]), and asking directly for testing (AOR, 2.1 [95% CI, 1.5 to 3.0]). In pilot cities, 14 percent of physicians reported an increase in the number of times they ordered BRCA testing in the previous 6 months compared with 7 percent of physicians in control cities (AOR, 1.9 [95% CI, 1.2 to 3.1]).

A telephone survey to assess the impact of direct-to-consumer marketing among women of varying genetic risk was conducted in 315 women enrolled in a registry of families with cancer in Denver, a Myriad marketing site. In this study, high-risk women were more knowledgeable
about the test and more likely to recall media advertisements than low-risk women (60% vs. 39%; \(p<0.01\)). Approximately 40 percent of women were interested in testing and 10 percent had increased worry about cancer after viewing the advertisements. However, women across all risk groups overstated the benefits of testing, and equal numbers of high- and low-risk women thought they would benefit from testing (51% vs. 60%).

Another study in Denver surveyed 750 low-risk women, 100 high-risk women, and 180 primary care providers in a managed care organization.\(^{271}\) Sixty-two percent of patient respondents described exposure to the Myriad advertisements, and 63 percent with exposure reported that the advertisements caused no anxiety. However, some women reported anxiety from the advertisements, including women with high levels of perceived breast cancer risk (AOR, 3.23 [95% CI, 1.35 to 7.73]) and Hispanic women (AOR, 4.19 [95% CI, 1.48 to 11.83]). Women who viewed the advertisements had greater knowledge about testing. Eighty-four percent of physicians reported that the advertisements caused no strain on the doctor-patient relationship, and 80 percent reported no effect on daily clinical practice.

A study of referrals to genetic counseling in the same managed care organization in Denver was compared with a similar organization in a nonmarketed city.\(^{272}\) Results indicated a 244 percent increase in referrals during the marketing campaign compared with the previous year (\(p<0.001\)), although the proportion of referrals of high-risk women declined from 69 percent to 48 percent (\(p<0.001\)) during the campaign. No changes in practice were detected in the nonmarketed organization.

Myriad has recently launched a new campaign directly targeting mammography imaging centers and primary care, obstetrician/gynecology, and surgery practices. This strategy involves risk stratification using a simple checklist administered by a physician or nonphysician (e.g., mammography technician), patient consent, and specimen collection with subsequent testing by Myriad. Results are then sent to the ordering physician who follows up as needed. The impact of this approach has not yet been evaluated.

**Key Question 4. Do Interventions Reduce the Incidence of BRCA-Related Cancer and Mortality in Women With Increased Risk?**

**Summary**

No trials of the effectiveness of intensive screening for breast or ovarian cancer in women who are BRCA mutation carriers with cancer or mortality outcomes have been published. Six observational studies that reported test characteristics of breast and ovarian cancer screening are described. Overall, the sensitivity of screening for breast cancer with MRI was higher than with mammography (71% vs. 41%), while specificity was comparable (90% vs. 95%). Sensitivity of screening for ovarian cancer was 43 percent for TVUS and 71 percent for serum CA-125 testing, and specificity was 99 percent.
There are no trials of risk-reducing medications specifically in women who are BRCA mutation carriers. A systematic review and meta-analysis of four tamoxifen and two raloxifene placebo-controlled RCTs and one head-to-head trial (Study of Tamoxifen and Raloxifene Trial [STAR]) provided efficacy outcomes for women who had various risk levels. Trials were limited by heterogeneity, and data on doses, duration, and timing of use were lacking. Tamoxifen and raloxifene reduced invasive breast cancer by 30 to 68 percent compared with placebo (7 to 9/1,000 women over 5 years); tamoxifen had a greater effect than raloxifene in the STAR trial (5/1,000 women over 5 years). Reduction was greater in women with family history of breast cancer, but CIs were overlapping. Reduction was significant for ER-positive but not ER-negative breast cancer. Noninvasive breast cancer and mortality were not significantly reduced and did not differ between medications.

Four studies reported descriptive outcomes of risk-reducing mastectomy, one study reported outcomes after salpingo-oophorectomy, and three studies reported outcomes after oophorectomy. Comparison groups varied between studies, although results were consistent. Risk-reducing bilateral mastectomy reduced breast cancer by 85 to 100 percent in high-risk women and women who were mutation carriers; oophorectomy or salpingo-oophorectomy reduced breast cancer 37 to 100 percent and ovarian cancer 69 to 100 percent in high-risk women and women who were mutation carriers. Breast cancer–specific mortality was reduced by 81 to 100 percent after risk-reducing mastectomy in one study and all-cause mortality was reduced by 55 to 100 percent after risk-reducing salpingo-oophorectomy in another study.

Evidence

Intensive Screening

Breast Cancer. No studies from the previous review met inclusion criteria for the updated review. No RCTs of the effectiveness of intensive screening to reduce breast cancer incidence or mortality in women who are at increased risk were identified by searches. Four observational studies, including three prospective studies273-275 and one retrospective analysis of a prospective study,276 provided descriptive information about test characteristics of screening modalities (Table 17, Appendix C10). In these studies, prevalent cases were defined as women with cancer detected on the first round of screening and incident cases were those detected on subsequent rounds.273,277,278

The Dutch MRI Screening Study (MRISC), a prospective study, evaluated performance characteristics of breast cancer screening in 2,157 women with 15 percent or higher cumulative lifetime risks of breast cancer, including 594 women who were BRCA mutation carriers.278 Screening included biannual clinical breast examinations and annual concurrent contrast enhanced MRI and mammography. Digital mammography replaced film during the study period. In this study, women were categorized by mutation status or as high- or moderate-risk based on their family histories and risk factors as applied to modified Claus tables. The average age of participants at study entry was 40 years, and they were followed for a mean of 4 years. There were 97 breast cancer cases (78 invasive, 19 ductal carcinoma in situ [DCIS]) detected in 94 women, including 78 screen-detected cancer cases (15 prevalent, 63 incident), six of which were
detected at risk-reducing mastectomy, and 13 interval cancer cases detected by the woman between screening rounds after initial negative results.

Analysis of results of 75 women with breast cancer indicated significantly higher sensitivity of MRI versus mammography (71% vs. 41%; p=0.0016). Both modalities had high specificity (MRI, 90%; mammography, 95%). Including only women with invasive cancer increased the sensitivity of MRI to 77 percent and decreased that of mammography to 36 percent (MRI vs. mammography, p=0.00005). In women who were BRCA1 carriers, the sensitivity of MRI was 67 percent versus 25 percent for mammography (p=0.0129), and for BRCA2, 69 percent versus 62 percent (p=1.0). Additional comparisons of the sensitivity of modalities between risk groups and by carrier status were not statistically significant. At diagnosis, 80 percent of invasive tumors were 2 cm or less in size, 39 percent were grade 3, and 31 percent were node positive. Women who were BRCA1 carriers were more likely to experience interval cancer, were younger at diagnosis, and had larger, higher grade tumors at diagnosis compared with other risk groups (p<0.05 for comparisons between all subgroups).

The Magnetic Resonance Imaging Breast Screening study was a prospective multicenter study conducted in the United Kingdom that evaluated screening of high-risk women using annual contrast enhanced MRI and mammography. The study enrolled 649 women, including 120 who were BRCA mutation carriers, with a median age at entry of 40 years. The duration of followup varied, but each woman completed at least two annual screenings. Thirty-five cancer cases (29 invasive, six DCIS) were detected, including two interval cancer cases.

The sensitivity of screening all women using mammography plus MRI (94%) was higher than that of using either method alone (MRI, 77%; mammography, 40%), though specificity was reduced when the methods were combined (77%) compared with either MRI alone (81%) or mammography (93%) alone. Including only invasive cancer cases increased MRI sensitivity to 86 percent, reduced mammography sensitivity to 31 percent, and increased the sensitivity of combined methods to 97 percent.

In women who were BRCA1 mutation carriers or were related to carriers, the sensitivity of screening with MRI alone (92%) or combined with mammography (92%) was higher than that of mammography alone (23%). However, the specificity of MRI alone (79%) or MRI plus mammography (74%) was less than that of mammography alone (92%). In women who were BRCA2 mutation carriers or were related to carriers, the sensitivity of screening with MRI plus mammography (92%) was higher than that of either method alone (MRI, 58%; mammography, 50%). The specificity of mammography alone (94%) was higher than that of MRI alone (82%) or MRI plus mammography (78%). At diagnosis, invasive cancer cases were an average 15 mm in size, 66 percent were grade 3, and 19 percent were node positive.

A prospective study of 1,325 high-risk Italian women, including 48 who were BRCA mutation carriers, evaluated a breast cancer screening program of mammography, ultrasound, and clinical breast examinations. MRI screening was introduced later in the study for women who were mutation carriers. Screening intervals varied by risk category, age, and modality and ranged between 6 months and 2 years. After a median followup of 55 months, 44 breast cancer cases (28 invasive, 16 DCIS) were detected, including 36 screen-detected cases and eight interval cases. In
four women who were mutation carriers with screen-detected breast cancer, the sensitivity of screening with mammography was 50 percent, ultrasound 75 percent, ultrasound plus mammography 75 percent, and MRI 100 percent. At diagnosis, 61 percent of invasive breast cancer cases were stage I, 64 percent were less than 15 mm in size, and 36 percent were node positive.

A retrospective chart review of a prospective study of 73 women at a single institution in the United States evaluated outcomes after screening using MRI alternating with mammography every 6 months in addition to six monthly clinical breast examinations. Participants were mutation carriers or first-degree relatives at a high-risk cancer clinic with a median age of 44 years who had two screening cycles and were followed for a median of 2 years. Thirteen breast cancer cases (10 invasive, three DCIS) were detected in 11 patients. The sensitivity and specificity of MRI was 92 and 87 percent respectively.

Ovarian Cancer. The previous review included a descriptive study of TVUS screening in 1,610 women with family histories of ovarian cancer and reported that only six of 61 women with abnormal scans had ovarian cancer. A recently published large U.S. screening RCT, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, reported no mortality benefit of screening average-risk women ages 55 to 74 years with TVUS and serum CA-125 testing compared with usual care after a median followup of 12.4 years. This trial did not report outcomes specifically for high-risk women, including those who were BRCA mutation carriers.

One new descriptive study identified in updated searches reported test characteristics of TVUS and serum CA-125 testing (Appendix C10). A European prospective descriptive study evaluated the use of annual CA-125 measurement and TVUS from ages 30 to 35 years in women who were at increased risk. In 459 women who were BRCA carriers with complete data amounting to 1,116 annual screening visits, the sensitivity of serum CA-125 testing alone was 71 percent, TVUS alone was 43 percent, and combined modalities was 71 percent. Corresponding specificities were 99 percent for each modality alone and combined. The positive predictive value was 33 percent for serum CA-125 testing alone, 20 percent for TVUS alone, and 23 percent for combined modalities. Three percent of women had abnormalities detected by one or both screening modalities, and seven ovarian cancer cases were diagnosed.

Risk-Reducing Medications

The previous review identified no trials that evaluated the use of risk-reducing medications specifically in women who are mutation carriers, although the National Surgical Adjuvant Breast and Bowel Project (NSABP P-1) trial of tamoxifen described results for 288 women who were mutation carriers and who developed breast cancer during the trial. Of the eight women with breast cancer who had BRCA1 mutations, five received tamoxifen and three received placebo (RR, 1.67 [95% CI, 0.32 to 10.70]). Of 11 women with breast cancer and BRCA2 mutations, three received tamoxifen and eight received placebo (RR, 0.38 [95% CI, 0.06 to 1.56]). Also, 86 percent (6/7) of women with BRCA1 mutations had ER-negative breast cancer, and 67 percent (6/9) with BRCA2 mutations had ER-positive breast cancer.

The updated review identified no RCTs that evaluated use of risk-reducing medications
specifically in women who are BRCA mutation carriers, although several RCTs of women who had various levels of risk have been published and summarized in meta-analyses.116,283 Four placebo-controlled trials of tamoxifen include the NSABP P-1 trial,284 Royal Marsden trial,285 Italian Randomized Tamoxifen Prevention Trial,286 and the International Breast Cancer Intervention Study (IBIS-I).287 Placebo-controlled trials of raloxifene include the Raloxifene Use for the Heart Trial (RUTH)73 and the Multiple Outcomes of Raloxifene Evaluation trial, with its followup study, Continuing Outcomes Relevant to Evista.288 The STAR289 trial was a head-to-head trial that compared raloxifene with tamoxifen. Inclusion criteria varied between trials, duration of active treatment ranged from 4 to 8 years, and followup ranged from 6 to 13 years. Additional details of the trials are provided in Appendix C11. Trials meeting fair-quality criteria were limited by incomplete reporting of followup,284,285,287 inadequate maintenance of comparable groups,284,285,287 high (>30%) crossover between groups,284 and low (<65%) numbers of participants completing all treatment years.285,286

Results of a published meta-analysis indicate that women randomized to either tamoxifen (RR, 0.70 [95% CI, 0.59 to 0.82]; 4 trials; 7 cases/1,000 women over 5 years) or raloxifene (RR, 0.44 [95% CI, 0.27 to 0.71]; 2 trials; 9/1,000 women) had reduced risks for invasive breast cancer compared with women randomized to placebo (Table 18).116,283 Updated results of the head-to-head trial indicated greater risk reduction with tamoxifen compared with raloxifene (RR for raloxifene, 1.24 [95% CI, 1.05 to 1.47]; 5/1,000 women).289 Tamoxifen and raloxifene reduced ER-positive but not ER-negative or noninvasive cancer in placebo-controlled trials, and had similar effects in the STAR trial. All-cause mortality was not reduced in placebo trials and was similar in the STAR trial.

Although no trials evaluated breast cancer incidence specifically in women who were BRCA mutation carriers, all trials evaluated breast cancer incidence by family history, except IBIS-I, in which 97 percent of participants reported some degree of family history.287 No trials evaluated breast cancer or all-cause mortality outcomes based on familial risk. Trials defined a positive family history as breast cancer in any first-degree relative, except the Royal Marsden trial, which also included second-degree relatives.285

In women randomized to tamoxifen, invasive breast cancer risk was further reduced for those with the highest numbers of affected relatives in the NSABP P-1 (RR for no relatives, 0.54 [95% CI, 0.34 to 0.83]; RR for ≥3 relatives, 0.49 [95% CI, 0.16 to 1.34]), although CIs were overlapping284 (Figure 5). The Royal Marsden trial reported similar findings (RR for 0–2 relatives, 0.51 [95% CI, 0.27 to 0.96]; RR for ≥3 relatives, 0.43 [95% CI, 0.19 to 0.95]).285 The Italian trial reported increased breast cancer risk in women with familial risk using tamoxifen, but the risk estimate was not statistically significant (RR, 1.43 [95% CI, 0.65 to 3.15]).286

In women randomized to raloxifene, the Multiple Outcomes of Raloxifene Evaluation and Continuing Outcomes Relevant to Evista trials indicated a greater reduction in breast cancer risk in women with at least one affected first-degree relative (adjusted hazard ratio [HR] for no relatives, 0.55 [95% CI, 0.36 to 0.84]; HR for ≥1 relative, 0.16 [95% CI, 0.06 to 0.42])288 (Figure 6). RUTH indicated no significant effect of family history.73 The raloxifene trials were primarily designed to determine its effect on osteoporosis and heart disease outcomes and only a minority of participants reported family histories of breast cancer. In the STAR trial comparing
tamoxifen and raloxifene, the effect of family history was not statistically significant.\textsuperscript{289}

**Risk-Reducing Surgery**

**Mastectomy.** Four studies met inclusion criteria; one from the previous review\textsuperscript{290,291} and three from updated searches.\textsuperscript{292-294} The prior evidence review included a retrospective descriptive study based on data from patients’ medical records.\textsuperscript{290,291} In women who underwent risk-reducing mastectomy, breast cancer was reduced by 92 percent in high-risk women compared with sister controls, and by 89.5 percent in moderate-risk women compared with Gail model-based expected incidence.\textsuperscript{291} Postmastectomy breast cancer–related deaths were reduced by 81 percent in high-risk women compared with sister controls, and by 100 percent in moderate-risk women compared with expected rates.\textsuperscript{290} When the high-risk group was evaluated for BRCA status, none of the 18 women who were mutation carriers developed postmastectomy breast cancer compared with the 4.5 (low-penetrance model) and 6.1 (high-penetrance model) cases that were expected.\textsuperscript{295}

Since the prior review, three new prospective studies reported breast cancer outcomes after risk-reducing bilateral mastectomy\textsuperscript{292-294} (Table 19, Appendix C12). Cohort studies met criteria for good-quality\textsuperscript{294} or fair-quality,\textsuperscript{292} and one descriptive study could not be rated for quality.\textsuperscript{293} The fair-quality study was limited by a lack of information about groups at baseline, attrition, and followup.\textsuperscript{292}

A study enrolling women from 22 North American and European centers evaluated outcomes for women with BRCA mutations.\textsuperscript{292} During 2.7 years of followup, no women who had risk-reducing mastectomies were diagnosed with breast cancer compared with 34 of 585 (5.8%) women who did not have mastectomies.

Another study compared observed with expected breast cancer cases in women with BRCA mutations or who were otherwise considered at high risk. Results indicated that none of 307 women who had bilateral mastectomies were diagnosed with breast cancer, while 21.3 cases were expected.\textsuperscript{293} In a study of women who were mutation carriers in Denmark, three of 96 (0.8% per person-year) women who underwent mastectomy were diagnosed with breast cancer versus 16 of 211 (1.7% per person-year) who did not (HR, 0.39 [95% CI, 0.12 to 1.36]), although the study was inadequately powered for this outcome.\textsuperscript{294}

**Salpingo-Oophorectomy or Oophorectomy.** Four studies met inclusion criteria; one from the previous review\textsuperscript{229} and three from updated searches.\textsuperscript{185,292,296} The previous evidence review included a prospective cohort study of women from families with high ovarian cancer risk who had risk-reducing oophorectomy compared with first-degree relatives who were at similar risk and did not have surgery.\textsuperscript{229} Eight ovarian cancer cases occurred in 346 relatives without surgery (2.3%) versus two cases of carcinomatosis in 44 women with surgery (4.5%). Also, 14 cases of breast cancer occurred in relatives without surgery (4.0%) versus three cases in women with surgery (6.8%). Mean followup time was not reported for this study, but person-years ranged from 460 to 1,665. This study met criteria for poor-quality and was limited by a lack of information about groups at baseline, methods for ascertaining exposures and outcomes, followup, and attrition.\textsuperscript{229}
One new study of risk-reducing salpingo-oophorectomy\textsuperscript{292} and two new studies of oophorectomy\textsuperscript{185,296} in high-risk women and women who were mutation carriers met inclusion criteria (Table 19, Appendix C12). Two studies\textsuperscript{185,292} met criteria for fair-quality and one was descriptive.\textsuperscript{296} The fair-quality studies were limited by a lack of information about groups at baseline, attrition, and followup.\textsuperscript{185,292}

In a prospective cohort study evaluating the outcomes of women who were BRCA mutation carriers at 22 North American and European centers, salpingo-oophorectomy was significantly associated with reduced incidence of ovarian or primary peritoneal cancer (1.3\% vs. 5.8\%; HR, 0.28 [95\% CI, 0.12 to 0.69]).\textsuperscript{292} In addition, salpingo-oophorectomy was associated with reduced breast cancer incidence (11.6\% vs. 21.6\%; HR, 0.54 [95\% CI, 0.37 to 0.79]) and all-cause mortality (1.8\% vs. 5.9\%; HR, 0.45 [95\% CI, 0.21 to 0.95]). Reductions in breast cancer–specific (0.5\% vs. 2.3\%; HR, 0.27 [95\% CI, 0.05 to 1.33]) and ovarian cancer–specific mortality (0.7\% vs. 2.5\%; HR, 0.39 [95\% CI, 0.12 to 1.29]) were not statistically significant.

In a prospective cohort study of women from families with known \textit{BRCA1} mutation carriers, oophorectomy was associated with reduced breast cancer incidence (18\% vs. 42\%; HR, 0.38 [95\% CI, 0.15 to 0.97]).\textsuperscript{185} Risk reduction was most pronounced in women who had the procedure at a younger age.

A retrospective study compared observed versus expected breast cancer incidence rates in women who underwent oophorectomy.\textsuperscript{296} In this study, oophorectomy was associated with reduced risks that were more pronounced in women who were younger than age 50 years and premenopausal at time of surgery (O/E = 1/3.9; RR, 0.26 [95\% CI, 0.001 to 0.99]) compared with older postmenopausal women (O/E = 3/5.4; RR, 0.56 [95\% CI, 0.11 to 1.33]).

**Key Question 5. What Are the Potential Adverse Effects of Interventions to Reduce Risk for BRCA-Related Cancer?**

**Summary**

For breast cancer screening, the adverse effects of intensive screening were described in three studies of physical harms and two studies of anxiety. Results indicated that false-positive rates, unnecessary imaging, and unneeded surgeries were higher in women undergoing intensive screening using MRI versus mammography. Most women experienced no anxiety after breast cancer screening with MRI, mammography, or clinical breast examination. Two studies described harms of ovarian cancer screening; one reported an unneeded diagnostic surgery rate of 55\% in women who were mutation carriers screened with TVUS and serum CA-125 testing.

There are no trials of risk-reducing medications specifically in women who are BRCA mutation carriers. A systematic review and meta-analysis of four tamoxifen and two raloxifene placebo-controlled RCTs and one head-to-head trial provided adverse event outcomes for women who had various levels of risk. Trials were limited by heterogeneity and data on long-term effects were incomplete. Tamoxifen and raloxifene increased thromboembolic events compared with
placebo (4 to 7/1,000 women over 5 years) and tamoxifen had a greater effect than raloxifene (4/1,000 women over 5 years). Tamoxifen increased endometrial cancer compared with placebo (4/1,000 women over 5 years) and raloxifene (5/1,000 women over 5 years), and increased cataracts compared with raloxifene (15/1,000 women over 5 years). Both caused undesirable side effects in some women, such as vasomotor symptoms.

Case-series and before-after studies described surgical complications, physical effects, and distress measures related to risk-reducing surgery. Studies lacked important outcomes, enrolled small numbers of participants, and had no comparison groups. Some women experienced physical complications of surgery, had postsurgical symptoms, or changes in body image, while some women had improved anxiety.

Evidence

Intensive Screening

Breast Cancer. The previous review identified no studies with information about the harms of intensive screening for breast cancer. The updated review includes three studies, in four publications, reporting false-positive or false-negative results, unneeded procedures, or recall rates (Table 20, Appendix C13),274,276,277,297 and two studies about discomfort, pain, or anxiety (Table 21, Appendix C14).275,298

In studies of false-positive or false-negative results, unneeded procedures, or recall rates, women with increased familial risk of breast cancer were recruited from the Netherlands, the United Kingdom, and the United States. Two studies used prospective designs,274,277,297 and one retrospectively analyzed data from a completed prospective study.276 Sample sizes ranged from 73 to 1,909, and 18 to 100 percent of participants were BRCA mutation carriers. Mean/median age at entry was 40 to 44 years, and mean/median followup was approximately 2 years or at least two annual scans by the time of analysis.277,297

Two studies reported false-positive rates of mammography compared with MRI.276,297 The Dutch MRISC reported results by screening round, and defined the false-positive rate as the number of positive test results in women who did not have cancer. The false-negative rate was defined as the number of negative test results in women who had cancer. This study reported significantly higher false-positive rates for MRI compared with mammography in the first and subsequent imaging rounds (first round with prior mammography, 14% vs. 5.5%; subsequent rounds, 8.2% vs. 4.6%; p<0.001 for both rounds).297 False-negative results for MRI were lower than for mammography, although numbers were small.

In a study of six monthly breast cancer screenings using MRI alternating with mammography, a result was considered a false-positive if initial findings on screening appeared suspicious, but followup clinical examination, imaging, or biopsy resulted in a final benign assessment. This study reported similar false-positive results for both modalities (MRI, 11%; mammography, 15%), and did not report false-negative findings.276

Two studies reported the number of unneeded additional imaging procedures or biopsies.276,277
These procedures were considered unneeded because final results were benign and women may never have undergone the procedures if the original screening test had not been performed. The Dutch MRISC determined the need for additional procedures using the Breast Imaging Reporting and Data System (BI-RADS) score from the screening examination. Women with BI-RADS scores of 3 (probably benign) or 0 (need additional imaging evaluation) underwent further evaluations using ultrasound with or without fine-needle aspiration or repeat mammography or MRI. Women with BI-RADS scores of 4 (suspicious abnormality) or 5 (highly suggestive of malignancy) underwent biopsy. Results indicated that 43 percent of women with unneeded biopsies had preceding screening MRI and 28 percent had mammography.277

A study that retrospectively analyzed data from a prospectively followed cohort of women who were BRCA mutation carriers or their first-degree relatives found that alternating MRI with mammography screening every 6 months yielded a greater proportion of unneeded imaging procedures (targeted ultrasound) in women screened with mammography (8/11) than with MRI (4/8).276 However, rates of unneeded biopsies were similar (3/11 for mammography and 2/8 for MRI).

Recall rates for annual MRI were higher than for annual mammography in a descriptive study conducted in the United Kingdom that included women who were mutation carriers (MRI, 11% per woman-year; mammography, 3.9% per woman-year; combined, 13% per woman-year).274 In this study, 245 of 279 recalls were for benign findings, amounting to 8.5 recalls per cancer detected.

A fair-quality prospective cohort study of women with a mean age of 40.9 years compared discomfort, pain, and anxiety of women undergoing intensive screening with annual mammography, MRI, and biannual clinical breast examinations with women only receiving biannual clinical breast examinations.275 These outcomes did not differ between groups, as measured by the Medical Outcomes Study 36-Item Short Form (Table 21, Appendix C14).275 Most women experienced no anxiety after each type of screening intervention (72% after mammography, 63% after MRI, 78% after clinical breast examination).

In a before-after study of MRI plus mammography, ultrasound, and clinical breast examination, women who were recalled reported higher anxiety scores compared with women who were not recalled at 4 to 6 weeks after screening (8.8 vs. 5.9, respectively; p=0.03).298 These represent midrange scores, as measured by the HADS. Between-group differences were not significant by 6 months (7.1 vs. 5.9, respectively).

Ovarian Cancer. Two studies met inclusion criteria, one from the previous review279 and one from updated searches.281 A prospective descriptive study included in the previous review estimated false-positive results for TVUS when used for screening for ovarian cancer in 1,601 self-referred asymptomatic women with at least one relative who was diagnosed with ovarian cancer.279 Forty-three percent of women were screened with only one ultrasound. In this study, 3.8 percent (61/1,601) of screened women had suspicious findings on TVUS and were referred to surgery. Cancer was detected in six of 61 referred cases, yielding a false-positive rate of 3.4 percent (95% CI, 2.6 to 4.5). Addition of color flow imaging to ultrasound reduced the number of false-positive cases from 55 to six.
The updated review identified a descriptive study conducted in the Netherlands that reported the number of unneeded diagnostic surgeries associated with ovarian cancer screening using annual serum CA-125 measurements and annual TVUS in 459 women who were BRCA mutation carriers (Appendix C13). Abnormalities were detected in 9 percent (40/459) of women with complete data, which included 3 percent (38/1,116) of screening visits, as well as visits for symptomatic complaints. Of 26 diagnostic procedures, cancer was not detected in 67 percent (4/6) following abnormal CA-125 measurement compared with 100 percent (9/9) following abnormal TVUS findings. Combined modalities resulted in an unneeded diagnostic surgery rate of 55 percent (6/11).

**Risk-Reducing Medications**

No studies evaluated the adverse effects of risk-reducing medications specifically in women who are BRCA mutation carriers, although adverse effects were reported in several RCTs of women who had various levels of risk and have been summarized in meta-analyses. Studies include four placebo-controlled trials of tamoxifen, two placebo-controlled trials of raloxifene, and a head-to-head RCT of tamoxifen versus raloxifene. No adverse effect outcomes were provided specifically by mutation status or family history risk in these trials. Details of the trials are provided in Appendix C11. Fair-quality trials were limited by incomplete reporting of followup, inadequate maintenance of comparable groups, high (>30%) crossover between groups, and low (<65%) numbers of participants completing all treatment years.

In these trials, thromboembolic events were increased for tamoxifen (RR, 1.93 [95% CI, 1.41 to 2.64]; 4 trials; 4 cases/1,000 women over 5 years) and raloxifene (RR, 1.60 [95% CI, 1.15 to 2.23]; 2 trials; 7/1,000 women over 5 years) compared with placebo (Table 22). Raloxifene caused fewer events than tamoxifen in STAR (RR, 0.77 [95% CI, 0.60 to 0.93]; 4/1,000 women over 5 years). Coronary heart disease events or stroke were not increased in placebo-controlled trials, and did not differ in STAR, although women randomized to raloxifene had higher stroke mortality than placebo in RUTH (RR, 1.49 [95% CI, 1.00 to 2.24]).

Tamoxifen caused more cases of endometrial cancer (RR, 2.13 [95% CI, 1.36 to 3.32]; 3 trials; 4/1,000 women over 5 years), and was related to more benign gynecologic conditions, surgical procedures (including hysterectomy), and uterine bleeding than placebo. Raloxifene did not increase risk for endometrial cancer or uterine bleeding. In the STAR trial, raloxifene caused fewer cases of endometrial cancer (RR, 0.55 [95% CI, 0.36 to 0.83]; 5/1,000 women over 5 years), hyperplasia, and procedures than tamoxifen. Women using tamoxifen had more cataract surgeries than placebo in the NSABP P-1 trial. Raloxifene did not increase risk for cataracts or cataract surgery compared with placebo, and caused fewer cataracts than tamoxifen in STAR (RR, 0.80 [95% CI, 0.72 to 0.95]; 15/1,000 women).

Most common side effects were vasomotor symptoms and vaginal discharge, itching, or dryness for tamoxifen and vasomotor symptoms and leg cramps for raloxifene. In STAR, raloxifene users reported more musculoskeletal problems, dyspareunia, and weight gain, while tamoxifen users had more gynecological problems, vasomotor symptoms, leg cramps, and bladder control symptoms.
Risk-Reducing Surgery

*Mastectomy.* The prior review found no studies that met inclusion criteria for the physical harms of mastectomy, though it described a series of 112 high-risk women, including 79 who were mutation carriers, undergoing risk-reducing mastectomy with immediate reconstruction. Twenty-one percent had physical complications, including hematomas, contracture, or implant rupture.300

Four descriptive studies about surgical complications, physical effects, or distress related to risk-reducing surgery met inclusion criteria for the updated review.301-305 Three studies reported information on physical harms of risk-reducing mastectomy.

In a case-series of 122 women who had undergone mastectomy, 64.4 percent reported postsurgical symptoms of numbness, pain, tingling, infection, swelling, breast hardness, bleeding, organizing hematoma, failed reconstruction, breathing problems, thrombosis, and pulmonary embolism.301 In a study of pain after surgery using the Health-Related Quality of Life tool, there were no significant differences between women’s scores obtained before mastectomy and either 6 months or 1 year postmastectomy.302

A case-series from the Karolinska University evaluated the physical effects of risk-reducing mastectomy and immediate breast reconstruction in 59 high-risk women.303 Questionnaires were sent to study subjects at least 2 years after the mastectomy and at least 1 year after any corrective procedures. Eleven patients had postoperative infections and three of them needed implant extraction, four reported hematomas, two needed revisions of flap necrosis, and 35 required corrective procedures. Of the 55 patients who completed the questionnaires, 48 reported postmastectomy pain and discomfort. Of these, five required occasional pain medication and 12 reported that pain affected their daily lives.

Four descriptive studies, in five publications, provided data about distress due to mastectomy to reduce risk for BRCA-related cancer in women who were at increased risk because of family history or BRCA mutation (*Table 23, Appendix C14*).301-305

A before-after study enrolled 90 high-risk women who had risk-reducing bilateral mastectomies, including 41 percent (37/90) *BRCA1* mutation carriers, 14 percent (13/90) *BRCA2* mutation carriers, 29 percent (26/90) with 50 percent lifetime risk, and 9 percent (9/90) with 25 percent lifetime risk. Results indicated significant decreases in anxiety scores, as measured by the HADS, 6 months and 1 year after surgery compared with before surgery (mean, 3.80 vs. 3.83 vs. 5.59, respectively; p=0.0004).302,304 The study also reported decreased pleasure in sexual activity, as measured by the pleasure subscale of the Sexual Activity Questionnaire (SAQ), 1 year after surgery compared with 6 months after surgery and before surgery (mean, 11.18 vs. 12.21 vs. 12.28, respectively; p=0.005). Depression scores, body image concerns, or any other portion of the SAQ were not significantly different.

A case-series study of 59 women undergoing risk-reducing mastectomy compared with a reference sample of 1,725 women from a previous study of women considering risk-reducing mastectomy reported no significant differences on any psychological or sexual activity measures.303 These measures also did not differ in a separate case-series of women undergoing
risk-reducing mastectomy that compared women younger versus older than age 50 years.301

A descriptive case-series study, utilizing semistructured interviews, described physical and psychological effects in 13 women 10 years after risk-reducing mastectomy. Most women reported that their family lives were unchanged (8/13 [62%]), although 39 percent (5/13) reported a negative effect on their relationship with their spouse, due to decreased sensation and changed body appearance.305 Most women considered the cosmetic results positive (10/13 [77%]) and most had discussed breast cancer risk with their daughters (10/11 [91%]).

Salpingo-Oophorectomy. The prior review found no studies that met inclusion criteria, though it included a descriptive study of risk-reducing salpingo-oophorectomy in women who were mutation carriers that included 70 percent of participants with personal histories of breast cancer. Four out of 80 women who underwent salpingo-oophorectomy without hysterectomy experienced complications of wound infection, bladder perforation, small bowel obstruction, and uterine perforation.79

Only one new study was identified for the updated review. A before-after study of women who were mutation carriers with a mean age of 47.5 years included 47 women with personal histories of breast cancer and 67 women without. Most women reported significant worsening of vasomotor symptoms (p<0.01), as measured by the Menopause-Specific Quality of Life-Intervention scale, and decreased sexual functioning (p<0.05), as measured by the SAQ, after risk-reducing salpingo-oophorectomy.306
CHAPTER 4. DISCUSSION

Summary of Review Findings

A summary of the findings of the systematic review and meta-analysis is provided in Table 24. No studies directly addressed the overarching question regarding the effectiveness of risk assessment, genetic counseling, and genetic testing in reducing cancer incidence and mortality (key question 1).

Several studies of the accuracy of methods to assess familial risk for BRCA-related cancer by nongenetics specialists met inclusion criteria for key question 2a, but no studies met criteria for key question 3a regarding potential adverse effects (Figure 7). Although various clinical criteria for referral to genetic counseling have been developed, their accuracy in predicting mutation or cancer risk has not been evaluated. A published systematic review of studies of 13 general breast cancer risk models, such as the Gail model, indicated that they are modest predictors of individual risk (c-statistic, 0.55 to 0.65). Ten studies evaluated the accuracy of five familial risk models that predict risk specifically for BRCA mutations and are intended to guide referrals to genetic counseling. These include the FHAT, Manchester Scoring System, RST, PAT, and FHSS-7. Results indicated high accuracy (c-statistic, >0.80), although some models have only been evaluated in single studies. Reference standards and study designs varied across studies, limiting comparisons between models. Risk was most often based on self-reported information; thus, the accuracy of risk models was limited by the accuracy of reported family history in each study.

A new systematic review and several new RCTs and cohort, case-control, and before-after studies of distress, accuracy of risk perception, and intention for genetic testing evaluated benefits and harms of genetic counseling (key questions 2b and 3b). No studies reported increased measures of breast cancer worry after women received genetic counseling; seven studies reported decreased worry, while one study reported no changes. Also, no studies reported significant increases in anxiety or depression after receiving genetic counseling, while three studies reported significant decreases and three reported no changes. In most studies, anxiety and depression scores were below clinical thresholds.

Eight new studies reported that the accuracy of a woman’s perception of her breast cancer risk improved after genetic counseling. Two new studies reported decreased intention to undergo genetic testing after genetic counseling. The new studies expand and support the results of 11 studies included in the previous evidence review (Figure 7). Studies were limited by differences in their designs and measures, use of dissimilar comparison groups, and enrollment of small numbers of women from specialty clinics.

Key question 2c concerns how consistently and accurately BRCA mutation status predicts risk for BRCA-related cancer (clinical validity). To address this question, 31 new cohort, cross-sectional, and descriptive studies were combined with 39 earlier studies for meta-analysis estimates of the prevalence and penetrance of BRCA mutations in various groups of women (Figure 8). Prevalence varied by population, including 0.2 to 0.3 percent in unselected women; 1.8 percent for BRCA1 and 1.3 percent for BRCA2 in women with breast cancer; 6 percent in
women with breast cancer onset at age 40 years or younger; 4.4 percent for *BRCA1* and 5.6 percent for *BRCA2* in women with ovarian cancer; and 13.6 percent for *BRCA1*, 7.9 percent for *BRCA2*, and 19.8 percent for combined *BRCA1* and *BRCA2* in women with high-risk families. In Ashkenazi Jewish women, prevalence was 2.1 percent in unselected populations and 10.2 percent in those with high-risk families.

In high-risk women with positive test results, risk for breast cancer to age 70 years included 46 to 70 percent for *BRCA1* and 50 to 71 percent for *BRCA2*; risk for ovarian cancer was 41 percent for *BRCA1* and 17 percent for *BRCA2* (*Figure 8*). In Ashkenazi Jewish women, risk to age 75 years was 34 percent for breast cancer and 21 percent for ovarian cancer. No estimates are available for women with variants of uncertain significance. In women with uninformative negative test results, the SIR for breast cancer was 3.81 (95% CI, 3.06 to 4.75). In women with true negative test results, the SIR for breast cancer was 1.13 (95% CI, 0.81 to 1.58). Estimates for ovarian cancer were highly heterogeneous. Limitations included differences between laboratory techniques for research and clinical care, lack of studies outside of high-risk populations, and bias in estimates from women or families with cancer.

Studies of potential adverse effects of genetic testing (key question 3c) reported that breast cancer worry and anxiety increased for women with positive results and decreased for others, although results differed (*Figure 8*). Risk perception improved after receiving test results. Studies were limited by high loss to followup and differences between comparison groups. Other relevant outcomes were not studied, including false-negative or false-positive results, genetic discrimination, and insurability.

Interventions to reduce the incidence of BRCA-related cancer and mortality in women with increased risk include intensive screening, risk-reducing medications, and risk-reducing surgery (key question 4). No trials evaluated the effectiveness of intensive screening. Although no trials of risk-reducing medications specifically in women who are BRCA mutation carriers were available, several RCTs that included women with various levels of risk are relevant. Tamoxifen and raloxifene reduced invasive breast cancer by 30 to 68 percent compared with placebo, and tamoxifen had a greater effect than raloxifene in a head-to-head trial (*Figure 9*). Results suggested that reduction was greater in women with more relatives with breast cancer, but CIs overlapped. Reduction was significant for ER-positive but not ER-negative breast cancer. Noninvasive breast cancer and mortality were not significantly reduced and did not differ between medications. Trials were limited by heterogeneity and data were lacking on doses, duration, and timing of use.

For high-risk women and women who are mutation carriers, observational studies indicated that risk-reducing bilateral mastectomy reduced breast cancer by 85 to 100 percent, and oophorectomy or salpingo-oophorectomy reduced breast cancer by 37 to 100 percent and ovarian cancer by 69 to 100 percent. Breast cancer–specific mortality was reduced by 81 to 100 percent after risk-reducing mastectomy in one study, and all-cause mortality was reduced by 55 to 100 percent after risk-reducing salpingo-oophorectomy in another. Comparison groups varied between studies, although results were consistent.

Studies of the potential adverse effects of intensive screening for breast cancer (key question 5)
indicated that false-positive rates, unnecessary imaging, and unneeded surgery were higher in women undergoing intensive screening using MRI compared with mammography (Figure 9). In one study, most women experienced no anxiety after breast cancer screening with MRI, mammography, or clinical breast examination. Studies of ovarian cancer screening reported high unneeded diagnostic surgery rates after screening with TVUS and serum CA-125 testing.

Trials of risk-reducing medications indicated that tamoxifen and raloxifene increased thromboembolic events compared with placebo and tamoxifen had a greater effect than raloxifene. Tamoxifen increased endometrial cancer and cataracts. Both caused undesirable side effects for some women, such as vasomotor symptoms.

Case-series and before-after studies described surgical complications, physical effects, and distress measures related to risk-reducing surgery. Some women experienced physical complications of surgery, postsurgical symptoms, or changes in body image, while some women had improved anxiety. Studies lacked important outcomes, and the few available studies had small numbers of participants and no comparison groups.

**Limitations**

Limitations of this review include using only English-language articles and studies applicable to the United States, although this focus improves its relevance to the USPSTF recommendation. Also, the number, quality, and applicability of studies evaluated in the evidence review varied widely. Limitations of studies specific to each key question are briefly described in Table 24.

Most studies in this review were conducted in highly-selected samples of women, many with preexisting breast or ovarian cancer, from high-risk groups, or from previously identified kindreds. How the results of studies based on these highly-selected women in research settings translate to a general screening population is unknown. In some cases, data to determine penetrance came exclusively from one study, and when multiple studies were available, they were heterogeneous. Estimates may therefore be unreliable. Most studies used research laboratory techniques to detect clinically significant mutations that differ from the DNA sequencing available clinically. The clinical significance of mutations was determined by each study, and was based on likely functional significance and/or previous evidence of increased cancer risk.

Data are not available to determine the optimal age at which to test and how age at testing influences benefits and harms. Whether testing for BRCA mutations reduces cause-specific or all-cause mortality and improves quality of life is unknown. The harms associated with receiving a false-negative test result or a result indicating mutations of unknown significance are not known.

The systematic review focused on five key questions that limited its scope. Several relevant issues were not addressed. These include the impact of modifier genes on estimates of penetrance and estimates for cancer susceptibility genes other than BRCA1 and BRCA2. The prevalence of BRCA1 and BRCA2 mutations outside of U.S. or European populations was
also not evaluated. Indications for testing in women who have previously been diagnosed with breast or ovarian cancer, or estimation of their risk of contralateral breast cancer, were not considered because the review focused on women without cancer. For example, women with triple-negative (i.e., HER2-negative, ER-negative, and PR-negative) breast cancer may be more likely to carry BRCA1 mutations. Also, the review did not consider indications for use of the BRCA Rearrangement Test as an adjunct to standard clinical testing, an emerging practice in the United States. The clinical utility of genetic testing is determined by outcomes following testing. Clinical utility was not explicitly included in the key questions, although the review considered use of risk-reducing interventions after genetic testing. Most studies relating to clinical utility are descriptive case-series and important outcomes are lacking. Finally, men were not included in the scope of this review except as family members of the women under evaluation.

Evidence of harms often relied on observational studies with designs that lacked quality rating criteria. Existing studies show that most women do not experience adverse effects from BRCA risk assessment, counseling, and testing. However, the long-term impact is unknown because most studies followed patients for less than 1 year. Studies used several types of measures and scales that limited comparisons between studies and prohibited meta-analysis. Measures of anxiety or depression often lacked clinical thresholds, and when available, few studies reported results based on the number of individuals who met them. No studies measured genetic discrimination as a harm of testing.

Treatment effects are influenced by several factors that were not evaluated in studies. The effectiveness of salpingo-oophorectomy in reducing risk for breast cancer depends on the age at which the procedure is performed, and it becomes less effective when performed after menopause. However, it is not clear how and when the benefit/harm ratio shifts for individuals facing this decision. Also, the type of risk-reducing intervention selected by women who are mutation carriers may depend on the specific mutation; for example, women with BRCA1 mutations have a higher risk of ovarian cancer than those with BRCA2 mutations. Medications are most effective in reducing risk for ER-positive breast tumors, although they have not been specifically evaluated in women with BRCA mutations. The proportion of ER-positive tumors varies from 28 percent in women with BRCA1 mutations to 63 percent in women with BRCA2 mutations. How these factors influence patient decisionmaking and eventual clinical outcomes is unknown.

Emerging and Future Research

In order to determine the appropriateness of risk assessment and testing for BRCA mutations in primary care, more information is needed about mutation prevalence and impact in the general population. Research has focused on highly-selected women in referral centers and generally reported short-term outcomes. Issues such as access to testing; effectiveness of screening approaches, including risk stratification; use of system supports; and patient acceptance and education require additional study. Who should perform risk assessment and genetic counseling services, how it should be done, and what skills are needed are unresolved questions. Trials comparing types of providers and protocols could address these issues. What happens after patients are identified as high-risk in clinical settings is also unknown. The consequences of
genetic testing for individuals and their relatives require more study. Well-designed investigations that use standardized measures and enroll subjects who reflect the general population, including minority women, are needed.

An expanded database or registry of patients who receive genetic counseling and testing for BRCA mutations would provide essential information about predictors of cancer, response to interventions, and other modifying factors. Traditionally, all clinical testing through direct DNA sequencing in the United States was done by a single private laboratory, and patient data were inaccessible. Developing a centralized accessible database with key variables to address these issues as testing practices change in the wake of the recent U.S. Supreme Court decision on DNA patents would be a major advance in this field. Additional data from women of varying socioeconomic, racial, and ethnic groups are needed. Currently available risk prediction tools and interventions may not apply to these populations.

Additional research on interventions is needed. Without effectiveness trials of intensive screening, practice standards have preceded supporting evidence. For example, while intensive screening with annual TVUS and serum CA-125 testing is recommended for high-risk women, there are no trials of screening effectiveness, and a descriptive study of 3,532 European women who were at increased risk of ovarian cancer, receiving TVUS and serum CA-125 testing, and followed for up to 16 years indicated no stage shifts in disease incidence. Trials of risk-reducing medications in women who are mutation carriers that include aromatase inhibitors, evaluation of the effect of age at intervention on outcomes, and measurement of long-term outcomes are also needed. Comparisons of salpingo-oophorectomy versus more limited surgery would inform current practice. Studies of factors related to acceptance of risk-reducing interventions based on genetic information would be useful, such as determining if cancer incidence in relatives is reduced because they adopt risk-reducing interventions. This information could improve patient decisionmaking and lead to better health outcomes.

Conclusions

Risk assessment by nongenetics specialists using familial risk models to determine individual risks for BRCA mutations can accurately guide referrals for genetic counseling. Comprehensive risk evaluations by genetic counselors provide estimates of individual risks for mutations and identify optimal candidates for genetic testing. Genetic counseling reduces distress, improves patients’ risk perception, and reduces their intentions for genetic testing. Results of genetic testing provide estimates of an individual’s chances of developing BRCA-related cancer depending on the specific test results. Women with positive test results have a 34 to 71 percent chance of developing breast cancer and 17 to 41 percent chance of developing ovarian cancer by age 70 years. Estimates for women with variants of uncertain significance are not available. Women with uninformative negative results have nearly a four-fold increase in risk for breast cancer; those with true negative results have no increased risk for breast cancer, while estimates for ovarian cancer are uncertain.

Although intensive screening for breast and ovarian cancer with MRI, TVUS, and serum CA-125 testing are recommended by experts for women who are mutation carriers, their effectiveness has
not been evaluated. Intensive breast cancer screening with MRI increases sensitivity, but also causes more false-positive results and procedures; screening for ovarian cancer is not accurate and leads to more procedures. Tamoxifen and raloxifene reduce risk for breast cancer in women with varying levels of risk, but increase risk for thromboembolic events. Tamoxifen also increases risk for endometrial cancer. Risk-reducing mastectomy and salpingo-oophorectomy are effective in reducing breast and ovarian cancer in women who are mutation carriers and high-risk women.

The process of familial risk assessment by nongenetics specialists, referral and evaluation by genetic counselors, genetic testing, and use of intensive screening and risk-reducing medications and surgeries is complex. Each step of the pathway requires careful interpretation of information, consideration of future risks, and shared decisionmaking before moving on to the next step. Services must be well integrated and highly individualized in order to optimize benefits and minimize harms for patients as well as their families. Additional studies are necessary to better inform practice.
REFERENCES


230. Sutcliffe S, Pharoah PD, Easton DF, et al. Ovarian and breast cancer risks to women in families with two or more cases of ovarian cancer. *Int J Cancer.* 2000;87:110-17. PMID: 10861460


264. ACLU and PUBPAT ask Supreme Court to rule that patents on breast cancer genes are invalid [press release]. New York: American Civil Liberties Union; September 25, 2012.


Figure 1. Analytic Framework and Key Questions

Key Questions
1. Does risk assessment, genetic counseling, and genetic testing lead to reduced incidence of BRCA-related cancer and reduced cause-specific and all-cause mortality?
2a. What is the accuracy of methods to assess familial cancer risk for BRCA-related cancer when performed by a nongenetics specialist in a clinical setting?
2b. What are the benefits of genetic counseling in determining eligibility for genetic testing for BRCA-related cancer?
2c. What is the clinical validity of genetic testing for deleterious mutations in women with increased risk for BRCA-related cancer?
3. What are the potential adverse effects of a) risk assessment, b) genetic counseling, and c) genetic testing?
4. Do interventions reduce the incidence of BRCA-related cancer and mortality in women with increased risk?
5. What are the potential adverse effects of interventions to reduce risk for BRCA-related cancer?

* Clinically significant mutations of BRCA1, BRCA2, or related syndromes.
† Testing may be done on the unaffected woman, her relative with cancer, or relative with highest risk, as appropriate.
‡ Interventions include increased early detection through intensive screening (earlier and more frequent mammography, breast magnetic resonance imaging), risk-reducing medications (tamoxifen, raloxifene), and risk-reducing surgery (mastectomy, salpingo-oophorectomy).

Uninformative negative test = no known mutation in relatives, none detected in patient; True negative test = known mutation in relatives but none detected in patient.
Figure 2. Included Studies of Prevalence and Penetrance

Prevalence

- Unselected populations: 4 studies
- High-risk populations
  - Early-onset cancer
  - Selected cohorts
  - High-risk families: 20 studies, Table 8
- Ashkenazi Jewish population: 9 studies, Table 10

Penetrance

- BRCA-positive: 30 studies and 3 meta-analyses, Tables 11-12
  - Detected deleterious BRCA1 or BRCA2 mutations
- Variant of uncertain significance: 0 studies
- Uninformative negative: 3 studies, Table 14, Figure 4
  - No known deleterious genetic mutations in relatives, none detected in the patient
- True negative: 10 studies, Table 15, Figure 5
  - Known confirmed deleterious genetic mutation in relatives, none detected in the patient
Figure 3. Meta-Analysis of Studies of Breast and Ovarian Cancer Incidence in Women With Uninformative Negative Results

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N</th>
<th>Observed Rate*</th>
<th>Expected Rate*</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sutcliffe, 2000</td>
<td>435</td>
<td>36.8</td>
<td>11.1</td>
<td>3.32 (1.52 to 6.31)</td>
</tr>
<tr>
<td>Kauff, 2005</td>
<td>321</td>
<td>73.6</td>
<td>22.6</td>
<td>3.25 (1.40 to 6.40)</td>
</tr>
<tr>
<td>Metcalfe, 2009</td>
<td>1492</td>
<td>71.4</td>
<td>18.1</td>
<td>3.94 (3.09 to 5.02)</td>
</tr>
<tr>
<td>Subtotal (I² = 0.0%, p = 0.825)</td>
<td></td>
<td></td>
<td></td>
<td>3.81 (3.06 to 4.75)</td>
</tr>
<tr>
<td><strong>Ovarian</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sutcliffe, 2000</td>
<td>382</td>
<td>18.8</td>
<td>1.6</td>
<td>11.60 (3.12 to 29.70)</td>
</tr>
<tr>
<td>Kauff, 2005</td>
<td>321</td>
<td>9.2</td>
<td>2.4</td>
<td>3.88 (0.05 to 21.60)</td>
</tr>
<tr>
<td>Metcalfe, 2009</td>
<td>1492</td>
<td>2.2</td>
<td>2.6</td>
<td>0.85 (0.23 to 3.12)</td>
</tr>
<tr>
<td>Subtotal (I² = 77.4%, p = 0.012)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Per 10,000 person-years.

**Abbreviations:** CI = confidence interval; SIR = standardized incidence ratio.
Figure 4. Meta-Analysis of Studies of Breast Cancer Incidence in Women With True Negative Results

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N</th>
<th>Observed Rate*</th>
<th>Expected Rate*</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kramer, 2005</td>
<td>353</td>
<td>8.1</td>
<td>12.4</td>
<td>0.65 (0.21 to 1.52)</td>
</tr>
<tr>
<td>Rowan, 2007</td>
<td>101</td>
<td>41.7</td>
<td>13.9</td>
<td>2.90 (1.00 to 8.60)</td>
</tr>
<tr>
<td>Smith, 2007</td>
<td>153</td>
<td>36.7</td>
<td>17.1</td>
<td>2.10 (0.40 to 6.20)</td>
</tr>
<tr>
<td>Gronwald, 2007</td>
<td>131</td>
<td>NA</td>
<td>NA</td>
<td>2.08 (0.05 to 11.61)</td>
</tr>
<tr>
<td>Domchek, 2010</td>
<td>378</td>
<td>20.4</td>
<td>24</td>
<td>0.85 (0.23 to 2.18)</td>
</tr>
<tr>
<td>van der Kolk, 2010</td>
<td>202</td>
<td>NA</td>
<td>NA</td>
<td>2.20 (1.00 to 4.17)</td>
</tr>
<tr>
<td>Harvey, 2011</td>
<td>722</td>
<td>19.5</td>
<td>17.1</td>
<td>1.14 (0.51 to 2.53)</td>
</tr>
<tr>
<td>Korde, 2011</td>
<td>395</td>
<td>14.3</td>
<td>17.2</td>
<td>0.82 (0.45 to 1.74)</td>
</tr>
<tr>
<td>Kurian, 2011</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.39 (0.04 to 3.81)</td>
</tr>
<tr>
<td>Bernholtz, 2012</td>
<td>307</td>
<td>15.8</td>
<td>18.8</td>
<td>0.84 (0.51 to 1.30)</td>
</tr>
<tr>
<td>Overall (I² = 24.3%, p = 0.219)</td>
<td></td>
<td></td>
<td></td>
<td>1.13 (0.81 to 1.58)</td>
</tr>
</tbody>
</table>

*Per 10,000 person-years.

**Abbreviations:** CI = confidence interval; NA = not applicable; SIR = standardized incidence ratio.
**Figure 5. Invasive Breast Cancer Risk Reduction With Tamoxifen Use, by Family History**

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. affected relatives</th>
<th>N tamoxifen</th>
<th>N placebo</th>
<th>Rate of breast cancer, <em>(a)</em> tamoxifen vs. placebo</th>
<th>Risk estimate for breast cancer (95% CI)</th>
<th>Favors tamoxifen</th>
<th>Favors placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP P-1‡</td>
<td>0</td>
<td>1548</td>
<td>1597</td>
<td>3.5 vs. 6.5</td>
<td>0.54 (0.34 to 0.83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3763</td>
<td>3738</td>
<td>3.2 vs. 5.5</td>
<td>0.57 (0.42 to 0.77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1072</td>
<td>1094</td>
<td>4.9 vs. 7.8</td>
<td>0.63 (0.39 to 0.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>214</td>
<td>181</td>
<td>5.5 vs. 11</td>
<td>0.49 (0.16 to 1.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Royal Marsden‡†</td>
<td>0-2</td>
<td>857</td>
<td>876</td>
<td>2.7 vs. 5.3</td>
<td>0.51 (0.27 to 0.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>381</td>
<td>355</td>
<td>3.9 vs. 9.1</td>
<td>0.43 (0.19 to 0.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italian‡‡</td>
<td>0</td>
<td>2359</td>
<td>2407</td>
<td>1.8 vs. 2.4</td>
<td>0.73 (0.50 to 1.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥1</td>
<td>341</td>
<td>301</td>
<td>4.3 vs. 3.0</td>
<td>1.43 (0.65 to 3.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBIS-I§§</td>
<td>NR</td>
<td>3579</td>
<td>3575</td>
<td>4.3 vs. 5.9</td>
<td>0.74 (0.58 to 0.94)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Per 1,000 women-years.
† Analysis restricted to ER-positive tumors.
‡ Type of breast cancer not reported.
§ Results not presented by family history (97% of participants had some family history).

**Abbreviations:** CI = confidence interval; IBIS-I = International Breast Cancer Intervention Study; Italian = Italian Randomized Tamoxifen Prevention Trial; NSABP P-1 = National Surgical Adjuvant Breast and Bowel Project P-1 Trial.
Figure 6. Invasive Breast Cancer Risk Reduction With Raloxifene Use, by Family History

### Compared With Placebo

<table>
<thead>
<tr>
<th>Trial</th>
<th>FH of breast cancer</th>
<th>N raloxifene</th>
<th>N placebo</th>
<th>Annual rate of breast cancer,* (%)</th>
<th>Risk estimate for breast cancer (95% CI)</th>
<th>Favors raloxifene</th>
<th>Favors placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUTH</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>0.13 vs. 0.25</td>
<td>0.63 (0.34-0.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>452</td>
<td>445</td>
<td>0.34 vs. 0.39</td>
<td>0.89 (0.34-2.31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MORE/CORE</td>
<td>No</td>
<td>4373</td>
<td>2196</td>
<td>0.80 vs. 1.9</td>
<td>0.55 (0.36-0.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>636</td>
<td>313</td>
<td>0.50 vs. 4.2</td>
<td>0.16 (0.06-0.42)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Compared With Tamoxifen

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of affected relatives</th>
<th>N raloxifene</th>
<th>N tamoxifen</th>
<th>Annual rate of breast cancer‡, raloxifene vs. tamoxifen</th>
<th>Risk estimate for breast cancer (95% CI)</th>
<th>Favors raloxifene</th>
<th>Favors tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAR</td>
<td>0</td>
<td>2791</td>
<td>2838</td>
<td>6.2 vs. 4.8</td>
<td>1.29 (0.96-1.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5135</td>
<td>5046</td>
<td>4.1 vs. 3.5</td>
<td>1.17 (0.90-1.51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>1828</td>
<td>1852</td>
<td>6.0 vs. 4.4</td>
<td>1.34 (0.93-1.96)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Per 10,000 women-years.
† Adjusted for age, estradiol level.
‡ Per 1,000 women-years.

**Abbreviations:** CI = confidence interval; CORE = Continuing Outcomes Relevant to Evista Trial; FH = family history; MORE = Multiple Outcomes for Raloxifene Evaluation Trial; NR = not reported; RUTH = Raloxifene Use for the Heart Trial; STAR = Study of Tamoxifen and Raloxifene Trial.
Figure 7. Summary of Key Questions 2a, 3a and 2b, 3b

**KQ 2a. Accuracy of Risk Assessment**

<table>
<thead>
<tr>
<th>Risk Models</th>
<th>Discriminatory Accuracy (c statistic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral criteria</td>
<td>No studies</td>
</tr>
<tr>
<td>General risk models</td>
<td>0.55–0.65 for breast cancer risk; models do predict mutation risk</td>
</tr>
<tr>
<td>Family history models</td>
<td>≧0.80 for mutation risk</td>
</tr>
</tbody>
</table>

**KQ 3a. Adverse Effects of Risk Assessment**

No studies

**KQs 2b, 3b. Benefits and Adverse Effects of Genetic Counseling**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Number of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increase</td>
</tr>
<tr>
<td>Breast cancer worry</td>
<td>0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>0</td>
</tr>
<tr>
<td>Risk accuracy</td>
<td>15</td>
</tr>
<tr>
<td>Intention to test</td>
<td>1</td>
</tr>
</tbody>
</table>

NS = differences between counseled/noncounseled groups or before/after counseling are not statistically significant.
Figure 8. Summary of Key Questions 2c and 3c

<table>
<thead>
<tr>
<th>KQ 2c. Clinical Validity of Genetic Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
</tr>
<tr>
<td>Unselected</td>
</tr>
<tr>
<td>High-risk</td>
</tr>
<tr>
<td>Breast or ovarian cancer onset ≤40 yrs</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Breast cancer cohort</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Ovarian cancer cohort</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Family history of breast or ovarian cancer</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Family history of breast or ovarian cancer</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Chance of Cancer (mutation penetrance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>% to age 70 or 75 yrs</td>
</tr>
<tr>
<td>1 person tested</td>
<td>BRCA1: 46% BC, 41% OC</td>
</tr>
<tr>
<td></td>
<td>BRCA2: 50% BC, 17% OC</td>
</tr>
<tr>
<td>&gt;1 person tested</td>
<td>BRCA1: 70% BC, 46% OC</td>
</tr>
<tr>
<td></td>
<td>BRCA2: 71% BC, 23% OC</td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>Combined: 34% BC, 21% OC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variant of Unknown Significance</th>
<th>No studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Standardized incidence rate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KQ 3c. Adverse Effects of Genetic Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Breast cancer worry</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Depression</td>
</tr>
</tbody>
</table>

NS = Differences between counseled/noncounseled groups or before/after counseling are not statistically significant.

Abbreviations: BC = breast cancer; OC = ovarian cancer.
Figure 9. Summary of Key Questions 4 and 5

<table>
<thead>
<tr>
<th>KQ 4. Benefits of Interventions</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td><strong>Risk Reduction</strong></td>
</tr>
<tr>
<td><strong>Intensive Screening</strong></td>
<td>No effectiveness studies</td>
</tr>
<tr>
<td><strong>Risk-Reducing Medications</strong></td>
<td></td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>30%–68%*</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>No significant reduction</td>
</tr>
<tr>
<td>Mortality</td>
<td>No significant reduction</td>
</tr>
<tr>
<td><strong>Risk-Reducing Surgery</strong></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>RRM: 85%–100%; RRSO: 37%–100%†</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>RRSO: 69%–100%</td>
</tr>
<tr>
<td>Mortality</td>
<td>RRM: 81%–100% breast cancer; RRSO: 55%–100% all-cause</td>
</tr>
</tbody>
</table>

* Risk reduction for all women; analysis by family history was similar.
† Includes studies of oophorectomy alone.
‡ Includes some women with symptoms.

Abbreviations: CA-125 = cancer antigen-125; MRI = magnetic resonance imaging; RRM = risk-reducing mastectomy; RRSO = risk-reducing salpingo-oophorectomy; TVUS = transvaginal ultrasound.
<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Approximate cost (U.S. $)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comprehensive testing</td>
<td>Gene sequencing of the entire length of both BRCA1 and BRCA2 and a five-site rearrangement panel of specific large-scale rearrangements.</td>
<td>&gt;$3000</td>
</tr>
<tr>
<td>Single site testing</td>
<td>One specific gene mutation when the mutation in the family has already been identified.</td>
<td>$475</td>
</tr>
<tr>
<td>Multisite panel</td>
<td>Three specific gene changes common among Ashkenazi Jewish ancestry.</td>
<td>$575</td>
</tr>
<tr>
<td>BRCA Rearrangement Test</td>
<td>Large-scale rearrangements within the BRCA genes that would not have been detected through comprehensive testing.</td>
<td>$700</td>
</tr>
</tbody>
</table>

*Reflects costs prior to the recent U.S. Supreme Court decision against DNA patents.
Table 2. Recommendations of Other Groups

<table>
<thead>
<tr>
<th>Organization, year</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Society of Clinical Oncology, 2010&lt;sup&gt;327&lt;/sup&gt;</td>
<td>ASCO recommends genetic testing when: 1) there is personal or family history suggestive of genetic cancer susceptibility, 2) the test can be adequately interpreted, and 3) the results will aid in diagnosis or medical management of the patient or family members at hereditary risk of cancer. ASCO recommends genetic testing only when pre- and post-test counseling is included.</td>
</tr>
<tr>
<td>American Congress of Obstetricians and Gynecologists, 2009&lt;sup&gt;323&lt;/sup&gt;</td>
<td>For patients who are likely to have hereditary breast and ovarian cancer syndrome, ACOG recommends further genetic risk assessment for women who have more than a 20%–25% chance of having an inherited predisposition to breast or ovarian cancer. ACOG also suggests genetic risk assessment may also be appropriate for patients with a 5%–10% chance of having hereditary risk. Recommended screening and prevention plans are based on individual risk factors and family history.</td>
</tr>
<tr>
<td>American Society of Human Genetics, 1994&lt;sup&gt;322&lt;/sup&gt;</td>
<td>Testing should initially be offered and performed on an investigational basis by appropriately trained health care professionals who have a therapeutic relationship with the patient and are fully aware of the genetic, clinical, and psychological implications of testing, as well as of the limitations of existing test procedures. Linkage analysis is recommended for select high-risk families, if it will provide for more refined counseling than is currently available from family history alone. It is premature to offer population screening, until the risks associated with specific BRCA1 mutations are determined.</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network, 2012&lt;sup&gt;50&lt;/sup&gt;</td>
<td>NCCN recommends risk assessment and counseling if the hereditary breast and/or ovarian cancer syndrome testing criteria are met. Genetic testing is recommended if criteria are met (see Appendix A1).</td>
</tr>
<tr>
<td>European Society for Medical Oncology, 2011&lt;sup&gt;324&lt;/sup&gt;</td>
<td>In all cases in which a patient may be referred for BRCA testing, the ESMO Guidelines Working Group recommends informed consent and genetic counseling be completed first. Carriers should be encouraged to advise close family members to obtain genetic counseling.</td>
</tr>
<tr>
<td>National Society of Genetic Counselors, 2012&lt;sup&gt;326&lt;/sup&gt;</td>
<td>Genetic testing should be offered to individuals with a personal or family history suggestive of an inherited cancer syndrome; when the test can be adequately interpreted; if testing will influence medical management of the patient or relatives; when potential benefits outweigh potential risks; if testing is voluntary; and when the individual seeking testing or their legal proxy can provide informed consent.</td>
</tr>
<tr>
<td>Society of Gynecologic Oncologists Education Committee, 2007&lt;sup&gt;329&lt;/sup&gt;</td>
<td>The SGO Education Resource Panel for Hereditary Cancers believes that individuals with a personal risk of having an inherited predisposition to cancer of greater than approximately 20%–25% should undergo genetic risk assessment. It also believes that it is reasonable to offer genetic risk assessment to any individual with greater than approximately 5%–10% chance of having an inherited predisposition to cancer. Genetic testing for cancer predisposition requires informed consent that should include pretest education and counseling concerning the risks, benefits, and limitations of testing, including the implications of both positive and negative genetic test results.</td>
</tr>
</tbody>
</table>
Table 3. Risk Stratification Models

<table>
<thead>
<tr>
<th>Model</th>
<th>Included variables</th>
<th>Calibration expected/observed cases (95% CI)*</th>
<th>Discriminatory accuracy c-statistic (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gail Model Variations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gail-2 5-year risk</td>
<td>Age; y, ≥14; 12–13; ≤12; ≥20; 20–24; 25–29 or none; ≥30; 0; 1; ≥2 AH: 0; ≥1</td>
<td>1.03 (0.88 to 1.21); 0.94 (0.89 to 0.99); 0.96 (0.84 to 1.17); 0.79; 1.12; 1.03</td>
<td>0.55 (0.51 to 0.60); 0.60; 0.60; 0.59 (0.54 to 0.63); 0.60; 0.61 (0.60 to 0.62)</td>
</tr>
<tr>
<td>Gail-2 10-year risk</td>
<td>Age; y, ≥14; 12–13; ≤12; ≥20; 20–24; 25–29 or none; ≥30; 0; 1; ≥2 AH: 0; ≥1</td>
<td>0.69 (0.54 to 0.90); 0.74 (0.67 to 0.80)</td>
<td></td>
</tr>
<tr>
<td>African American Gail 5-year risk</td>
<td>Age; y, ≤13; &gt;13; 0; 1; ≥2 AH: 0; ≥1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Models with Breast Density</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen 5-year risk</td>
<td>Age; y, ≥14; 12–13; ≤12; ≥20; 20–24; 25–29 or none; ≥30; 0; 1; ≥2 Bx: 0; 1; ≥2</td>
<td>Breast density (%), BMI Not reported</td>
<td>0.64; 0.64; 0.64; 0.64; 0.64; 0.64; 0.64; 0.64</td>
</tr>
<tr>
<td>BCSC† (pre-menopausal) 1-year risk</td>
<td>Age; y, ≥14; 12–13; ≤12; ≥20; 20–24; 25–29 or none; ≥30; 0; 1; ≥2 Bx: yes; no; unknown Breast density (BIRADS)‡</td>
<td>1.00; 1.00; 1.00; 1.00; 1.00; 1.00; 1.00; 1.00</td>
<td>0.63 (0.60 to 0.66); 0.63 (0.60 to 0.66); 0.63 (0.60 to 0.66); 0.63 (0.60 to 0.66); 0.63 (0.60 to 0.66); 0.63 (0.60 to 0.66); 0.63 (0.60 to 0.66); 0.63 (0.60 to 0.66)</td>
</tr>
<tr>
<td>BCSC† (post-menopausal) 1-year risk</td>
<td>Age; y, ≥14; 12–13; ≤12; ≥20; 20–24; 25–29 or none; ≥30; 0; 1; ≥2 Bx: yes; no; unknown Breast density (BIRADS); prior false-positive mammogram, BMI, menopause type, HT, race/ethnicity</td>
<td>1.01; 1.01; 1.01; 1.01; 1.01; 1.01; 1.01; 1.01</td>
<td>0.62 (0.62 to 0.63); 0.62 (0.62 to 0.63); 0.62 (0.62 to 0.63); 0.62 (0.62 to 0.63); 0.62 (0.62 to 0.63); 0.62 (0.62 to 0.63); 0.62 (0.62 to 0.63); 0.62 (0.62 to 0.63)</td>
</tr>
<tr>
<td>BCSC 5-year risk</td>
<td>Age; y, ≥14; 12–13; ≤12; ≥20; 20–24; 25–29 or none; ≥30; 0; 1; ≥2 Bx: yes; no Breast density (BIRADS), race/ethnicity</td>
<td>1.01; 1.01; 1.01; 1.01; 1.01; 1.01; 1.01; 1.01</td>
<td>0.66 (0.65 to 0.66); 0.66 (0.65 to 0.66); 0.66 (0.65 to 0.66); 0.66 (0.65 to 0.66); 0.66 (0.65 to 0.66); 0.66 (0.65 to 0.66); 0.66 (0.65 to 0.66); 0.66 (0.65 to 0.66)</td>
</tr>
<tr>
<td><strong>Other Models</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosner-Colditz†</td>
<td>Age; y, ≥14; 12–13; ≤12; ≥20; 20–24; 25–29 or none; ≥30; 0; 1; ≥2 AH: 0; ≥1 Benign breast disease presence or type</td>
<td>1.00 (0.93 to 1.07); 1.00 (0.93 to 1.07); 1.00 (0.93 to 1.07); 1.00 (0.93 to 1.07); 1.00 (0.93 to 1.07); 1.00 (0.93 to 1.07); 1.00 (0.93 to 1.07); 1.00 (0.93 to 1.07)</td>
<td>0.57 (0.55 to 0.59); 0.57 (0.55 to 0.59); 0.64 (0.63 to 0.66); 0.64 (0.63 to 0.66); 0.64 (0.63 to 0.66); 0.64 (0.63 to 0.66); 0.64 (0.63 to 0.66); 0.64 (0.63 to 0.66)</td>
</tr>
<tr>
<td>Rosner-Colditz-2†</td>
<td>Age; y, ≥14; 12–13; ≤12; ≥20; 20–24; 25–29 or none; ≥30; 0; 1; ≥2 AH: 0; ≥1 Benign breast disease presence or type</td>
<td>1.01 (0.94 to 1.09); 1.01 (0.94 to 1.09); 1.01 (0.94 to 1.09); 1.01 (0.94 to 1.09); 1.01 (0.94 to 1.09); 1.01 (0.94 to 1.09); 1.01 (0.94 to 1.09); 1.01 (0.94 to 1.09)</td>
<td>0.63 (0.61 to 0.65); 0.63 (0.61 to 0.65); 0.63 (0.61 to 0.65); 0.63 (0.61 to 0.65); 0.63 (0.61 to 0.65); 0.63 (0.61 to 0.65); 0.63 (0.61 to 0.65); 0.63 (0.61 to 0.65)</td>
</tr>
</tbody>
</table>

BRCA-Related Cancer  85  Pacific Northwest EPC
Table 3. Risk Stratification Models

<table>
<thead>
<tr>
<th>Model</th>
<th>Included variables</th>
<th>Other factors</th>
<th>Calibration expected/observed cases (95% CI)*</th>
<th>Discriminatory accuracy c-statistic (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyer-Cuzick 10-year risk</td>
<td>Age, y; Menarche age, y; Age at birth of first child, y; First-degree relatives with breast cancer, n</td>
<td>BMI, height, menopause age, family history of ovarian/other cancer, age of cancer onset, bilateral or male breast cancer</td>
<td>1.09 (0.85 to 1.41)</td>
<td>0.76 (0.70 to 0.82); 0.54 (0.42 to 0.65)</td>
</tr>
<tr>
<td>Italian-1§ 5-year risk</td>
<td>Age, y; Menarche age, y; Age at birth of first child, y; First-degree relatives with breast cancer, n</td>
<td>Age of relative at diagnosis, diet score, alcohol use, BMI, HT, physical activity</td>
<td>1.04</td>
<td>0.59 (vitamin);ments (diet)</td>
</tr>
<tr>
<td>Italian-2† 20-year risk</td>
<td>Age, y; Menarche age, y; Age at birth of first child, y; First-degree relatives with breast cancer, n</td>
<td>Occupational and leisure physical activity, education, alcohol use, BMI</td>
<td>Not reported</td>
<td>0.62 (0.56 to 0.69) (age &lt;50 years); 0.57 (0.52 to 0.61) (age ≥50 y)</td>
</tr>
<tr>
<td>Chlebowski 5-year risk</td>
<td>Age, y; Menarche age, y; Age at birth of first child, y; First-degree relatives with breast cancer, n</td>
<td>BMI, menopause age, HT use and duration, race, alcohol use, parity, breastfeeding, smoking status, physical activity</td>
<td>Not reported</td>
<td>0.61 (0.59 to 0.63); 0.62 (0.60 to 0.64) (ER+); 0.53 (0.47 to 0.58) (ER-)</td>
</tr>
<tr>
<td>Chlebowski-simplified 5-year risk</td>
<td>Age, y; Menarche age, y; Age at birth of first child, y; First-degree relatives with breast cancer, n</td>
<td>BMI, menopause age, HT use and duration, race, alcohol use, parity, breastfeeding, smoking status, physical activity</td>
<td>Not reported</td>
<td>0.58 (0.56 to 0.60) (ER+)</td>
</tr>
</tbody>
</table>

* For invasive breast cancer, other outcomes are specifically indicated.
† Invasive and noninvasive breast cancer.
‡ BI-RADS categories include: 0 = unknown; 1 = entirely fat; 2 = scattered fibroglandular densities; 3 = heterogeneously dense; 4 = extremely dense.
§ Includes an Italian population and used incidence rates from the Italian Multicenter case-control study of Diet and Breast Cancer and from Italian cancer registries.

Abbreviations: AH = atypical hyperplasia; BCSC = Breast Cancer Surveillance Consortium; BI-RADS = Breast Imaging Reporting and Data System; BMI = body mass index; Bx = biopsy; CI = confidence interval; DCIS = ductal carcinoma in situ; ER- = estrogen receptor negative; ER+ = estrogen receptor positive; HT = hormone therapy; LCIS= lobular carcinoma in situ; PR- = progesterone receptor negative; PR+ = progesterone receptor positive.
Table 4. Familial Risk Stratification Models to Predict Individual Risk for Deleterious BRCA Mutations in Primary Care Settings

<table>
<thead>
<tr>
<th>Model</th>
<th>Data collection and calculation</th>
<th>Relatives with breast and ovarian cancer</th>
<th>Other factors</th>
<th>Reference standard</th>
<th>Performance characteristics for predicting risk for BRCA mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ontario Family History Assessment Tool (FHAT)</td>
<td>Clinical scoring tool; referral threshold of 10 is equivalent to a 2-fold relative risk for breast or ovarian cancer</td>
<td>1st-, 2nd-, 3rd-degree</td>
<td>Age at diagnosis; bilateral breast cancer; breast and ovarian cancer in same person; male breast cancer; colon and prostate cancer</td>
<td>BRCA; Claus</td>
<td>Sensitivity 91%–94%; specificity 15%–51%; PPV 31%; c statistic 0.68–0.83</td>
</tr>
<tr>
<td>Manchester Scoring System</td>
<td>Clinical scoring tool; referral if ≥2 positive responses</td>
<td>1st-, 2nd-, 3rd-degree</td>
<td>Type of cancer (breast, ovarian, pancreatic, or prostate), affected family members, and age at diagnosis</td>
<td>BRCA; Myriad II; BOADICEA; FHAT</td>
<td>Sensitivity 58%–93%; specificity 33%–71%; c statistic 0.75–0.80</td>
</tr>
<tr>
<td>Referral Screening Tool (RST)</td>
<td>Clinical scoring tool; referral if ≥2 positive responses</td>
<td>1st-, 2nd-degree</td>
<td>Breast cancer at age ≤50 (self or relatives); ovarian cancer at any age (self or relatives); ≥2 breast cancer cases at age &gt;50 on same side of family; male breast cancer; Jewish ancestry</td>
<td>BRCA; Myriad II; BOADICEA; FHAT</td>
<td>Sensitivity 81%; specificity 92%; PPV 0.80; NPV 0.92; c statistic 0.87</td>
</tr>
<tr>
<td>Pedigree Assessment Tool (PAT)</td>
<td>Clinical scoring tool; score ≥8 was optimal threshold</td>
<td>1st-, 2nd-, 3rd-degree</td>
<td>Breast cancer at age ≤50 or &gt;50; ovarian cancer at any age; male breast cancer; Ashkenazi Jewish ancestry</td>
<td>Myriad II</td>
<td>Sensitivity 100%; specificity 93%; PPV 0.63; NPV 1.00; c statistic 0.96 (compared with Gail 5-year 0.39; Gail lifetime 0.59)</td>
</tr>
<tr>
<td>FHS-7</td>
<td>Clinical scoring tool; one positive response was threshold</td>
<td>1st-degree with breast or ovarian cancer</td>
<td>Any relatives with breast cancer at age ≤50; bilateral breast cancer; breast and ovarian cancer in same person; male breast cancer; ≥2 relatives with breast and/or ovarian cancer; ≥2 relatives with breast and/or colon cancer</td>
<td>Claus; Gail; Tyrer-Cuzick; Penn II</td>
<td>Sensitivity 88%; specificity 56%; PPV 0.63; NPV 1.00; c statistic 0.96</td>
</tr>
</tbody>
</table>

Abbreviations: BOADICEA = Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; NPV = negative predictive value; PPV = positive predictive value.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>N</th>
<th>Provider of genetic counseling</th>
<th>Setting</th>
<th>Measures</th>
<th>Quality rating</th>
<th>Breast cancer worry</th>
<th>Anxiety</th>
<th>Depression</th>
<th>Risk perception</th>
<th>Intent to participate in testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current report</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increase</td>
<td>Decrease</td>
<td>Increase</td>
<td>Decrease</td>
<td>More Accurate</td>
</tr>
<tr>
<td>Bennett et al., 2008&lt;sup&gt;153&lt;/sup&gt;</td>
<td>128</td>
<td>Genetic counselor</td>
<td>Cancer Genetics Service Center</td>
<td>DUKE-SSQ, HADS, IES, MCMQ, NSI</td>
<td>NA</td>
<td>0</td>
<td>X</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bennett et al., 2009&lt;sup&gt;149&lt;/sup&gt;</td>
<td>128</td>
<td>Genetic counselor</td>
<td>Cancer Genetics Service Center</td>
<td>DUKE-SSQ, IES, MCMQ</td>
<td>NA</td>
<td>0</td>
<td>X</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bloom, 2006&lt;sup&gt;151&lt;/sup&gt;</td>
<td>163</td>
<td>Master's level counselor</td>
<td>Telephone counseling</td>
<td>NSI</td>
<td>Poor</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bowen et al., 2006&lt;sup&gt;152&lt;/sup&gt;</td>
<td>221</td>
<td>Psychologist, genetic counselor</td>
<td>University</td>
<td>NSI, BSI</td>
<td>Fair</td>
<td>0</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Brain et al., 2011&lt;sup&gt;155&lt;/sup&gt;</td>
<td>263</td>
<td>Clinician</td>
<td>NR</td>
<td>CWS-R</td>
<td>NA</td>
<td>0</td>
<td>X</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Braithwaite et al, 2005&lt;sup&gt;154&lt;/sup&gt;</td>
<td>72</td>
<td>Clinical nurse specialist</td>
<td>NR</td>
<td>NSI, STAI, HADS</td>
<td>Fair</td>
<td>0</td>
<td>X</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Fry et al., 2003&lt;sup&gt;155&lt;/sup&gt;</td>
<td>263</td>
<td>Genetics consultant &amp; specialist breast surgeon vs. geneticist &amp; genetics nurse specialist</td>
<td>Familial Breast Cancer Clinic</td>
<td>CWS</td>
<td>Fair</td>
<td>0</td>
<td>X</td>
<td>0</td>
<td>X§</td>
<td>NR</td>
</tr>
<tr>
<td>Gurmankin et al, 2005&lt;sup&gt;156&lt;/sup&gt;</td>
<td>125</td>
<td>Health care provider</td>
<td>University breast and ovarian cancer risk evaluation program</td>
<td>STAI, NSI</td>
<td>NA</td>
<td>0</td>
<td>X</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Helmes et al, 2006&lt;sup&gt;157&lt;/sup&gt;</td>
<td>340†</td>
<td>Board certified genetic counselor</td>
<td>NR</td>
<td>NSI</td>
<td>Fair</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Table 5. Studies of Genetic Counseling
<table>
<thead>
<tr>
<th>Author, year</th>
<th>N</th>
<th>Provider of genetic counseling</th>
<th>Setting</th>
<th>Measures</th>
<th>Quality rating</th>
<th>Breast cancer worry</th>
<th>Anxiety</th>
<th>Depression</th>
<th>Risk perception</th>
<th>Intent to participate in testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hopwood et al, 2004&lt;sup&gt;158&lt;/sup&gt;</td>
<td>256</td>
<td>Genetic counselor</td>
<td>Cancer genetic service centers</td>
<td>NSI, GHQ, CWS</td>
<td>NA</td>
<td>0</td>
<td>X**</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kelly et al, 2008&lt;sup&gt;159&lt;/sup&gt;</td>
<td>78</td>
<td>Genetic counselor</td>
<td></td>
<td>NSI</td>
<td>NA</td>
<td>0</td>
<td>X</td>
<td>0</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Matloff et al, 2006&lt;sup&gt;160&lt;/sup&gt;</td>
<td>64&lt;sup&gt;¶&lt;/sup&gt;</td>
<td>Certified genetic counselor</td>
<td></td>
<td>NSI</td>
<td>Fair</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mikkelsen et al, 2007&lt;sup&gt;161&lt;/sup&gt;</td>
<td>1971</td>
<td>Physicians</td>
<td>Clinical department</td>
<td>IES</td>
<td>Fair</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mikkelsen et al, 2009&lt;sup&gt;162&lt;/sup&gt;</td>
<td>1971</td>
<td>Physicians</td>
<td>Clinical department</td>
<td>HADS</td>
<td>Fair</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pieterse et al, 2011&lt;sup&gt;163&lt;/sup&gt;</td>
<td>77&lt;sup&gt;¶&lt;/sup&gt;</td>
<td>Clinical geneticists, residents in clinical genetics, genetic counselors</td>
<td>Department of medical genetics</td>
<td>VAS, NSI, PPC, STAI, IES</td>
<td>NA</td>
<td>0</td>
<td>X</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Roshanai et al, 2009&lt;sup&gt;164&lt;/sup&gt;</td>
<td>163</td>
<td>Specialist nurse</td>
<td>Cancer genetics clinic</td>
<td>SPIKES, HADS</td>
<td>Fair</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
<td>X</td>
<td>NR</td>
</tr>
<tr>
<td>Prior Report</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowen et al, 2002&lt;sup&gt;165&lt;/sup&gt;</td>
<td>354</td>
<td>Genetic counselor or trained health counselor</td>
<td></td>
<td>NSI</td>
<td>Fair</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bowen et al, 2004&lt;sup&gt;166&lt;/sup&gt;</td>
<td>354</td>
<td>Genetic counselor or trained health counselor</td>
<td></td>
<td>NSI</td>
<td>Fair</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Brain et al, 2002&lt;sup&gt;167&lt;/sup&gt;</td>
<td>740&lt;sup&gt;¶&lt;/sup&gt;</td>
<td>Clinical geneticist and genetic nurse specialist</td>
<td></td>
<td>STAI, NSI</td>
<td>Good</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>X</td>
<td>0</td>
</tr>
<tr>
<td>Author, year</td>
<td>N</td>
<td>Provider of genetic counseling</td>
<td>Setting</td>
<td>Measures</td>
<td>Quality rating</td>
<td>Breast cancer worry</td>
<td>Anxiety</td>
<td>Depression</td>
<td>Risk perception</td>
<td>Intent to participate in testing</td>
</tr>
<tr>
<td>-------------</td>
<td>-----</td>
<td>--------------------------------</td>
<td>--------------------------------</td>
<td>-------------------------------</td>
<td>----------------</td>
<td>---------------------</td>
<td>---------</td>
<td>------------</td>
<td>-----------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Burke et al, 2000</td>
<td>356</td>
<td>Genetic counselor</td>
<td>Medical office</td>
<td>NSI</td>
<td>Fair</td>
<td>X</td>
<td>X</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cull et al, 1998</td>
<td>144</td>
<td>Geneticist and breast surgeon</td>
<td>Breast cancer family clinic</td>
<td>NSI, STAI, GHQ</td>
<td>Good</td>
<td>0</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>X</td>
</tr>
<tr>
<td>Hopwood et al, 1998</td>
<td>174</td>
<td>Family history clinics</td>
<td>Family history clinics</td>
<td>NSI, GHQ, PAS</td>
<td>Fair</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lerman et al, 1996</td>
<td>227</td>
<td>Genetic counselor</td>
<td>Cancer centers</td>
<td>IES</td>
<td>Fair</td>
<td>0</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>X</td>
</tr>
<tr>
<td>Lerman et al, 1999</td>
<td>364</td>
<td>Oncology nurses or genetic counselor</td>
<td>Hospital cancer center</td>
<td>IES</td>
<td>Fair</td>
<td>0</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>X</td>
</tr>
<tr>
<td>Lobb et al, 2004</td>
<td>193</td>
<td>Clinical geneticists, oncologist, genetic counselors</td>
<td>NR</td>
<td>NSI, IES, HADS</td>
<td>Good</td>
<td>0</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Watson et al, 1998</td>
<td>115</td>
<td>Clinical geneticist</td>
<td>Hospitals</td>
<td>GHQ-12, CWS, VAS</td>
<td>Good</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Watson et al, 1999</td>
<td>283</td>
<td>Clinical geneticists</td>
<td>Genetic counseling centers</td>
<td>NSI, GHQ, IES, STAI</td>
<td>Good</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>X</td>
</tr>
</tbody>
</table>

X=significant relationship; 0=studied, but not significant; NA=rating criteria not available; NR=not reported.

*Both interventions vs. control.
†Both treatment groups vs. control.
‡Pre vs. post.
§Pre vs. post and A vs. B.
∥Counseling vs. GRACE.
¶Randomized.
**Both intervention groups.
††Time effect-change from pre to post.
†††Interventions vs. control.
§§At 2-week followup; NS by 8 months.
‖‖Study done in a country other than the United States (e.g. Scotland, Australia, or England).
¶¶Both treatment groups at treatment end.
****Video after counseling subjects at 1-month followup.
†††African American subjects only.
††††Risk provided as odds ratio.
**Table 5. Studies of Genetic Counseling**

**Abbreviations:** BSI = Brief Symptom Inventory; CWS = Cancer Worry Scale; GHQ = General Health Questionnaire; HADS = Hospital Anxiety and Depression Scale; IES = Impact of Event Scale; NR = not reported; NSI = nonstandard instrument; PAS = Psychiatric Assessment Schedule; PPC = Perceived Personal Control; SPIKES = Setting, Patient’s perception, Invitation, Knowledge, Exploring/Empathy, Strategy/Summary; STAI = State-Trait Anxiety Inventory; VAS = Visual Analog Scale.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Setting</th>
<th>Provider of genetic counseling</th>
<th>Components of genetic counseling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong et al, 2005</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Genetic counseling not specified.</td>
</tr>
<tr>
<td>Bennett et al, 2008</td>
<td>Cancer Genetics Service Center</td>
<td>Genetic counselor</td>
<td>Women with family history of breast/ovarian cancer referred by general practitioner or other medical specialists into the service. After assessment of information in family health questionnaire by genetic specialists, individual genetic risk of developing familial breast and ovarian cancer was calculated as a percentage of lifetime risk and stratified into high, moderate, and population risk levels. Women considered high risk for breast/ovarian cancer were offered counseling, genetic testing, and annual mammography; woman at moderate risk were offered annual mammography.</td>
</tr>
<tr>
<td>Bennett et al, 2009</td>
<td>Cancer Genetics Service Center</td>
<td>Genetic counselor</td>
<td>See Bennett 2008.</td>
</tr>
<tr>
<td>Bloom et al, 2006</td>
<td>Telephone counseling</td>
<td>Master's level counselor</td>
<td>Telephone counseling session included: establishment of rapport and determination of special concerns, emotional readiness, risk notification by providing modified Gail model lifetime risk estimate and discussing in terms of pretest self-assessment of risk, deescalation of tension regarding breast cancer checkup, evaluation of coping skills, reinforcement of problem solving and coping skills, information on health protective behaviors, early detection through American Cancer Society screening, and information on genetic testing when requested.</td>
</tr>
<tr>
<td>Bowen et al, 2006</td>
<td>University</td>
<td>Psychologist, genetic counselor</td>
<td>Group psychological counseling: Psychologist led four 2-hour, weekly sessions of 5 to 6 women per group, with each session including a 20-min group cohesion activity followed by 1 of 4 major intervention components: risk assessment and perception, education, stress management, and problem solving and social support. Individual genetic counseling: Genetic counselor provided 1-hour counseling sessions and sessions covered several topics, including participant's family background, breast cancer risk assessment, BRCA1 and BRCA2 mutations in the Ashkenazi Jewish population, nongenetic risk factors for breast cancer, and breast screening.</td>
</tr>
<tr>
<td>Brain et al, 2011</td>
<td>Not reported</td>
<td>Clinician</td>
<td>Women with a family history of breast cancer receive a specialist genetic assessment service. Control group received general risk level (low/population, moderate, or high) based on age, reproductive history, and minimal family history; intervention group received a specific percentage based on Claus model based on detailed family pedigree; genetic testing was available to women in intervention group at high risk (≥25% risk).</td>
</tr>
<tr>
<td>Braithwaite et al, 2005</td>
<td>Not reported</td>
<td>Clinical nurse specialist</td>
<td>Risk counseling: Received pedigree with information from family history and assessed risk as low, moderate, or high based on GRACE guidelines; participants were mailed letters summarizing content afterward. GRACE: Completed pedigrees in GRACE and assessed their risk, learning their risk assessment and how to manage their risk; received a numerical estimate of lifetime risk, a visual display of cumulative risk with general population as comparator, and a qualitative description; clinical nurse specialists then offered to book mammography and arrange meetings with geneticists, where appropriate.</td>
</tr>
<tr>
<td>Author, year</td>
<td>Setting</td>
<td>Provider of genetic counseling</td>
<td>Components of genetic counseling</td>
</tr>
<tr>
<td>-------------</td>
<td>---------</td>
<td>-------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Fry et al, 2003&lt;sup&gt;155&lt;/sup&gt;</td>
<td>Familial Breast Cancer Clinic</td>
<td>Genetics consultant and specialist breast surgeon; geneticist and genetics nurse specialist</td>
<td><strong>Standard (regional) service:</strong> Self-report family history and baseline questionnaire completed by all women; genetics consultant and genetics nurse specialist assigned categorical risk via Cancer Research Campaign. Women at low risk received a letter; women at moderate or high risk were offered an appointment at familiar breast cancer clinic where a genetics consultant discussed risk status and breast surgeon discussed risk management. Where appropriate, clinical exams and mammography were included in the appointment. Patients’ general practitioners received summary data, and patients received followup questionnaires 4 weeks and 6 months later. <strong>Novel (community-based) service:</strong> All women sent an appointment for a community-based clinic near their residence. Meetings run by genetics nurse specialist where family history collected and compared to published criteria (Cancer Research Campaign) to determine risk. Women at low risk offered information, reassurance, and discharged. Women at increased risk (moderate or high) were offered an appointment at a regional center with a geneticist and genetics nurse specialist, and asked to complete followup questionnaires at 4 weeks and 6 months.</td>
</tr>
<tr>
<td>Gurmankin et al, 2005&lt;sup&gt;156&lt;/sup&gt;</td>
<td>University breast and ovarian cancer risk evaluation program</td>
<td>Health care provider</td>
<td><strong>Precounseling interview:</strong> Assessed patient's breast cancer risk perception, BRCA mutation risk perception, worry about breast cancer, family history of cancer, breast cancer risk reduction behaviors, and demographic information. <strong>Postcounseling interview:</strong> Assessed patient's breast cancer risk, BRCA mutation risk, recall of actual risk information, and worry about breast cancer.</td>
</tr>
<tr>
<td>Helmes et al, 2006&lt;sup&gt;157&lt;/sup&gt;</td>
<td>Not reported</td>
<td>Board certified genetic counselor</td>
<td><strong>In-person counseling:</strong> Review of family history, discussion of breast cancer risk, and education about breast cancer genes; discussed genetic testing considerations, including implications of results, testing strategies, potential risks and benefits of test, costs and psychological effects of test; gave information packet with personal risk information comparing woman's risk with average woman's risk, personal computer-drawn 3-generation pedigree, brochures on self-breast exams, Pap test, and mammography; genetics visual aids, and list of community resources. <strong>Telephone counseling:</strong> Information packet was sent in the mail with instructions to open at the beginning of the telephone counseling, which was identical in content and structure to in-person counseling.</td>
</tr>
<tr>
<td>Hopwood et al, 2004&lt;sup&gt;158&lt;/sup&gt;</td>
<td>Cancer genetic service centers</td>
<td>Genetic counselor</td>
<td>Genetic counseling prior to testing varied by participating center, but offered or recommended some of the following: risk estimation (based on molecular genetic analysis or more often on family history), genetic risk counseling, clinical exam, screening/surveillance for early tumor detection (mammography, endoscopy), information on preventive strategies (surgery, diet), family planning advice, and referral for psychological assessment/support.</td>
</tr>
<tr>
<td>Kelly et al, 2008&lt;sup&gt;159&lt;/sup&gt;</td>
<td>Not reported</td>
<td>Genetic counselor</td>
<td>Review of family cancer history, personal risk factors for breast and ovarian cancer, mechanisms of cancer inheritance, meaning of a positive and negative test result, and risks and benefits associated with testing.</td>
</tr>
<tr>
<td>Matloff et al, 2006&lt;sup&gt;160&lt;/sup&gt;</td>
<td>Not reported</td>
<td>Certified genetic counselor</td>
<td>Personalized letter summarizing patient data.</td>
</tr>
<tr>
<td>Mikkelsen et al, 2007&lt;sup&gt;161&lt;/sup&gt;</td>
<td>University clinical departments</td>
<td>Physicians</td>
<td>Information on incidence of sporadic breast cancer, genetics, inheritance patterns, and estimated personal lifetime risk of inherited cancer.</td>
</tr>
<tr>
<td>Mikkelsen et al, 2009&lt;sup&gt;162&lt;/sup&gt;</td>
<td>University clinical departments</td>
<td>Physicians</td>
<td>Information on incidence of sporadic breast cancer, genetics, inheritance patterns, and estimated personal lifetime risk of inherited cancer.</td>
</tr>
<tr>
<td>Author, year</td>
<td>Setting</td>
<td>Provider of genetic counseling</td>
<td>Components of genetic counseling</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>--------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Pieterse et al., 2011&lt;sup&gt;163&lt;/sup&gt;</td>
<td>Department of medical genetics</td>
<td>Clinical geneticists, residents in clinical genetics, genetic counselors</td>
<td>Session topics included family's occurrence of breast and other cancers, inheritance, and criteria on probability of inherited breast cancer, and the likelihood of hereditary breast cancer running in the family was estimated.</td>
</tr>
<tr>
<td>Roshanai et al, 2009&lt;sup&gt;164&lt;/sup&gt;</td>
<td>University cancer genetic clinic</td>
<td>Specialist nurse</td>
<td>Included pedigree explanation, Buckman's Breaking Bad News model to inform at-risk relatives, pamphlet, videotape, copies of pedigree, and medical records.</td>
</tr>
<tr>
<td>Prior report</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowen et al, 2002&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Not reported</td>
<td>Genetic counselor or trained health counselor</td>
<td><strong>Individual genetic counseling:</strong> Telephone contact with genetic counselor to review pedigree information and one 2-hour session following protocol based on standard genetic practice, with a letter sent to participant within 2 weeks summarizing the session. <strong>Group psychosocial counseling:</strong> Group of 4–6 participants met for four 2-hour sessions with trained health counselor, participants received risk assessment sheet, personalizing the group discussion to her own risk status, main topics: risk assessment, perception, screening, stress management and problem solving, social support.</td>
</tr>
<tr>
<td>Bowen et al, 2004&lt;sup&gt;62&lt;/sup&gt;</td>
<td>Not reported</td>
<td>Genetic counselor or trained health counselor</td>
<td><strong>Individual genetic counseling:</strong> Telephone contact with genetic counselor to review pedigree information and one 2-hour session following protocol based on standard genetic practice, with a letter sent to participant within 2 weeks summarizing the session. <strong>Group psychosocial counseling:</strong> Group of 4–6 participants met for four 2-hour sessions with trained health counselor, participants received risk assessment sheet, personalizing the group discussion to her own risk status, main topics: risk assessment, perception, screening, stress management and problem solving, social support.</td>
</tr>
<tr>
<td>Brain et al, 2002&lt;sup&gt;166&lt;/sup&gt;</td>
<td>Not reported</td>
<td>Clinical geneticist and genetic nurse specialist</td>
<td>Breast cancer surveillance, option to enter UK Tamoxifen Prevention Trial, annual surgical followup with surveillance and advice, genetic risk assessment and counseling.</td>
</tr>
<tr>
<td>Burke et al, 2000&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Unclear</td>
<td>Genetic counselor</td>
<td>Adapted genetic counseling protocol for women with intermediate risk included precounseling telephone call gathering a complete family history, in-person genetic counseling session discussing breast cancer risk factors, focusing on issues relevant to the participant, reviewed pedigree information, communicated likelihood of mutation in participant's family, risk estimate sheet given to participant based on the Gail and Claus models and National Cancer Institute statistics for average risk, information about genetic testing, recommendations for breast cancer screening, and a followup letter summarizing the genetic counseling session.</td>
</tr>
<tr>
<td>Cull et al, 1998&lt;sup&gt;59&lt;/sup&gt;</td>
<td>Breast cancer family clinic</td>
<td>Geneticist and breast surgeon</td>
<td>Individual meeting with geneticist to discuss individual risk and with breast surgeon to discuss risk management, participants either received a copy of the educational video about 10 days before the clinic consultation or took the video home after the postclinic assessment.</td>
</tr>
<tr>
<td>Hopwood et al, 1998&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Family history clinics</td>
<td>Unclear</td>
<td>Family history consultation, not otherwise described.</td>
</tr>
<tr>
<td>Lerman et al, 1996&lt;sup&gt;168&lt;/sup&gt;</td>
<td>Comprehensive cancer centers</td>
<td>Genetic counselor</td>
<td>Discussion of individual factors contributing to elevated risk, presentation of individualized risk data, recommendations for annual mammography and clinical breast exams, and instruction in breast self-exam.</td>
</tr>
<tr>
<td>Author, year</td>
<td>Setting</td>
<td>Provider of genetic counseling</td>
<td>Components of genetic counseling</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>--------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Lerman et al, 1999&lt;sup&gt;60&lt;/sup&gt;</td>
<td>Hospital and cancer center</td>
<td>Oncology nurses or genetic counselor</td>
<td><strong>Education only</strong>: Topics discussed included individual risk factors for breast and ovarian cancer and patterns of inheritance for breast and ovarian cancer susceptibility, subjects given qualitative estimates of risk of developing breast and ovarian cancer, and pedigrees reviewed, potential benefits, limitations, and risks of genetic testing for inherited breast and ovarian cancer susceptibility reviewed. <strong>Education plus counseling</strong>: Provided the same education and materials described above and subjects were guided through questions exploring personal issues related to cancer and genetic testing, discussed the emotional impact of having a family history of cancer, psychosocial implications of genetic testing for inherited breast and ovarian cancer susceptibility, anticipated reactions to positive and negative test result, and intentions to communicate test results to family members and friends.</td>
</tr>
<tr>
<td>Lobb et al, 2004&lt;sup&gt;169&lt;/sup&gt;</td>
<td>Not reported</td>
<td>Clinical geneticists, oncologist, genetic counselors</td>
<td>Counselors provided counseling at their discretion and study was to assess the different aspects of counseling, which included information giving concerning: breast cancer genetics, genetic testing, family history and risk, prophylactic surgery, breast cancer prevention, screening and management; communication style including: facilitating patient involvement, facilitating understanding, patient centeredness and partnership building, and supportive and counseling communications.</td>
</tr>
<tr>
<td>Watson et al, 1998&lt;sup&gt;171&lt;/sup&gt;</td>
<td>Hospitals</td>
<td>Clinical geneticist</td>
<td>Consultation provided information on pedigree based on risk calculation and information regarding management options based on risk level, with instructions offered on self-exam and clinical exam, with the intervention group also receiving an audiotape of the consultation to take home.</td>
</tr>
<tr>
<td>Watson et al, 1999&lt;sup&gt;172&lt;/sup&gt;</td>
<td>Genetic counseling centers</td>
<td>Clinical geneticists</td>
<td>Not described.</td>
</tr>
</tbody>
</table>
Table 7. Standardized Measures Used to Assess Distress

<table>
<thead>
<tr>
<th>Measure</th>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck Depression Inventory&lt;sup&gt;334&lt;/sup&gt;</td>
<td>BDI</td>
<td>A 21-question, multiple choice, self-report inventory for measuring the severity of depression. Scores of 0 to 9 indicate minimal depression, 10 to 18 mild depression, 19 to 29 moderate depression, and 30 to 63 severe depression.</td>
</tr>
<tr>
<td>Beck Hopelessness Scale&lt;sup&gt;307&lt;/sup&gt;</td>
<td>BHS</td>
<td>A 20-item scale to quantify hopelessness, with scores ranging from 0 to 20 and a score above 9 indicating suicidal ideations.</td>
</tr>
<tr>
<td>Body Image after Breast Cancer&lt;sup&gt;333&lt;/sup&gt;</td>
<td>BIBC</td>
<td>A 53-item questionnaire to assess the long-term impact of breast cancer on body image in 6 key areas: vulnerability, body stigma, limitations, body concerns, transparency, arm concerns.</td>
</tr>
<tr>
<td>Body Image Scale&lt;sup&gt;441&lt;/sup&gt;</td>
<td>BIS</td>
<td>A 10-item questionnaire for assessing body image changes in patients with cancer.</td>
</tr>
<tr>
<td>Brief Symptom Inventory&lt;sup&gt;328&lt;/sup&gt;</td>
<td>BSI</td>
<td>A 53-item self-reported psychological symptom scale.</td>
</tr>
<tr>
<td>Center for Epidemiologic Studies-Depression&lt;sup&gt;449&lt;/sup&gt;</td>
<td>CES-D</td>
<td>Measures symptoms of depression on a 20-item scale with scores ranging from 0 to 60; scores above 15 indicating high levels of depressive symptoms.</td>
</tr>
<tr>
<td>Coping Orientation to Problems Experienced Scale&lt;sup&gt;38&lt;/sup&gt;</td>
<td>COPE</td>
<td>Covers 14 coping strategies as potential responses to stressors.</td>
</tr>
<tr>
<td>Decision Regret Scale&lt;sup&gt;337&lt;/sup&gt;</td>
<td>DRS</td>
<td>A 5-item questionnaire to measure dissatisfaction or misgiving after making a medical decision.</td>
</tr>
<tr>
<td>DUKE Social Support Questionnaire&lt;sup&gt;445&lt;/sup&gt;</td>
<td>DUKE-SSQ</td>
<td>Used to measure access to and satisfaction with social support on 8 items with scores ranging from 1 to 5. Affective subscale (DUKE-SSQ-A) includes items 1, 2, and 8; confident subscale (DUKE-SSQ-C) includes items 3-7.</td>
</tr>
<tr>
<td>Emotional Approach Coping Scale&lt;sup&gt;350&lt;/sup&gt;</td>
<td>None</td>
<td>A 52-item questionnaire to measure both problem solving (items 1-20) and emotion-based (items 21-32) coping strategies. An additional 4 questions pertain to alcohol and drug use.</td>
</tr>
<tr>
<td>EuroQol-5 Dimensions&lt;sup&gt;383&lt;/sup&gt;</td>
<td>EQ-5D</td>
<td>A short, self-reported questionnaire designed to evaluate an individual’s state of overall health in 5 areas: mobility, self-care, usual activities, pain/discomfort, anxiety/depression.</td>
</tr>
<tr>
<td>General Health Questionnaire&lt;sup&gt;442&lt;/sup&gt;</td>
<td>GHQ</td>
<td>A 60-item questionnaire to screen individuals for psychiatric disorders, scores are given as means and scores above 3 indicate disorders; a 30-item version of the same questionnaire uses a threshold of 6 to indicate general psychological distress.</td>
</tr>
<tr>
<td>Health-Related Quality of Life&lt;sup&gt;330&lt;/sup&gt;</td>
<td>HR-QOL</td>
<td>A 14-item self-report questionnaire to assess an individual’s quality of life based on healthy days (items 1-4), activity limitations (items 5-9), and symptoms (items 10-14).</td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale&lt;sup&gt;335&lt;/sup&gt;</td>
<td>HADS</td>
<td>A 14-item self-report scale for the detection of depression and anxiety in hospitalized patients. Scores range from 1 to 21, interpreted as normal (0 to 7), mild (8 to 10), moderate (11 to 14), and severe (15 to 21). Subscales for anxiety (HADS-A) and depression (HADS-D).</td>
</tr>
<tr>
<td>Impact of Events Scale&lt;sup&gt;359&lt;/sup&gt;</td>
<td>IES</td>
<td>A 17-item questionnaire to measure an individual’s level of distress in relation to a specific event or condition. Scores range from 0 to 75; scores 9 to 25 indicate moderate difficulties and above 26 indicate clinical adaptation difficulties. Several variations are also used: Impact of Events Scale-Revised (IES-R) 22-items (items A-V); Impact of Events Subscale-Intrusive Events (IES-I) (items A, B, C, F, I, N, P, T); Impact of Events Subscale-Avoidance (IES-A) (items E, G, H, K, L, M, Q, V); Impact of Events Subscale-Hyperarousal (IES-H) (items D, J, O, R, S, U).</td>
</tr>
<tr>
<td>Lerman Breast Cancer Worry Scale&lt;sup&gt;336&lt;/sup&gt;</td>
<td>CWS or LCWS</td>
<td>A 3-item questionnaire to measure how frequently an individual worries about getting breast cancer and the impact of worrying on mood and performance of daily activities. A 6-item version of the same questionnaire has scores ranging from 6 to 24; higher scores mean greater levels of worry.</td>
</tr>
<tr>
<td>Medical Coping Modes Questionnaire&lt;sup&gt;340&lt;/sup&gt;</td>
<td>MCMQ</td>
<td>A 19-item self-report questionnaire to quantify coping styles into 1 of 4 categories: confrontive, avoidant, resigned, nondominant.</td>
</tr>
</tbody>
</table>
Table 7. Standardized Measures Used to Assess Distress

<table>
<thead>
<tr>
<th>Measure</th>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Outcomes Study 36-Item Short Form(^{344}) Swedish Short Term-36 Health Survey(^{353})</td>
<td>SF-36 or MOS SF-36</td>
<td>A 36-question health questionnaire for measuring health and well-being in 8 core areas: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, mental health. The Swedish Short Term-36 Health Survey is one of many variations.</td>
</tr>
<tr>
<td>Menopause-Specific Quality of Life Questionnaire(^{346})</td>
<td>MENQOL</td>
<td>A 29-item self-administered questionnaire to assess health-related quality of life postmenopause.</td>
</tr>
<tr>
<td>Multidimensional Fatigue Symptom Inventory-Short Form(^{352})</td>
<td>MFSI-SF</td>
<td>A 30-item questionnaire to measures perceived sleep disturbance.</td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index(^{347})</td>
<td>PSQI</td>
<td>A measure of subjective sleep disturbance in clinical populations.</td>
</tr>
<tr>
<td>Post-Traumatic Growth Inventory(^{332})</td>
<td>PTGI</td>
<td>An instrument for assessing positive outcomes reported by persons who have experienced traumatic events.</td>
</tr>
<tr>
<td>Sexual Activity Questionnaire(^{354})</td>
<td>SAQ</td>
<td>A 3-section self-reported questionnaire to assess sexual functioning, including hormonal status, reasons for sexual inactivity, sexual functioning.</td>
</tr>
<tr>
<td>State-Trait Anxiety Inventory(^{331})</td>
<td>STAI</td>
<td>Measures an individual's current anxiety feelings. Scores range from 10 to 40. Scores above 22 indicate high anxiety.</td>
</tr>
<tr>
<td>Symptom Checklist-90(^{347})</td>
<td>SCL-90</td>
<td>A 90-question self-reported questionnaire to assess psychological status in the following categories somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism.</td>
</tr>
<tr>
<td>Visual Analogue Scale(^{355})</td>
<td>VAS</td>
<td>Any of a number of pain self-assessment tools where subjects indicate their level of pain in response to a continuous visual scale (no pain to worst pain ever experienced).</td>
</tr>
</tbody>
</table>
**Table 8. Prevalence of BRCA1 and BRCA2 Mutations in High-Risk Populations**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Population</th>
<th>Gene</th>
<th>Inclusion criteria</th>
<th>Early-onset</th>
<th>Population-based</th>
<th>High-risk</th>
<th>Ashkenazi Jewish</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newman et al, 1998</td>
<td>Caucasian North Carolina</td>
<td>BRCA1</td>
<td>Women diagnosed as having first invasive breast cancer between 20 and 74 years</td>
<td>X</td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Newman et al, 1998</td>
<td>African American North Carolina</td>
<td>BRCA1</td>
<td>Women diagnosed as having first invasive breast cancer between 20 and 74 years</td>
<td>X</td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Anton-Culver et al, 2000</td>
<td>Caucasian Orange County, CA</td>
<td>BRCA1</td>
<td>Population-based sample of breast cancer cases</td>
<td>X</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anton-Culver et al, 2000</td>
<td>Hispanic Orange County, CA</td>
<td>BRCA1</td>
<td>Population-based sample of breast cancer cases</td>
<td>X</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newman et al, 1998</td>
<td>African American and Caucasian North Carolina</td>
<td>BRCA1</td>
<td>Women diagnosed as having first invasive breast cancer between 20 and 74 years; age 20-39 years</td>
<td>X</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anton-Culver et al, 2000</td>
<td>Total Orange County, CA</td>
<td>BRCA1</td>
<td>Population-based series of breast cancer cases; age &lt;40 years</td>
<td>X</td>
<td>Yes/no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anton-Culver et al, 2000</td>
<td>Total Orange County, CA</td>
<td>BRCA1</td>
<td>Population-based series of breast cancer cases; age &lt;40 years</td>
<td>X</td>
<td>Yes/no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anglian BCSG, 2000</td>
<td>U.K.</td>
<td>BRCA1/2</td>
<td>Population-based series of breast cancer from registry; age 35-44 years</td>
<td>X</td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Anglian BCSG, 2000</td>
<td>U.K.</td>
<td>BRCA1/2</td>
<td>Population-based series of breast cancer from registry; age &lt;35 years</td>
<td>X</td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>FitzGerald et al, 1996</td>
<td>Boston, MA</td>
<td>BRCA1</td>
<td>Breast cancer diagnosed &lt;30 years</td>
<td>X</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peto et al, 1999</td>
<td>U.K.</td>
<td>BRCA1/2</td>
<td>1) Women diagnosed with breast cancer &lt;36 years 2) Women diagnosed with breast cancer 36-45 years</td>
<td>X</td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Couch et al, 1997</td>
<td>U.S.</td>
<td>BRCA1</td>
<td>1) Women with breast cancer who had a “familial risk factor” for breast cancer</td>
<td>X</td>
<td></td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
Table 8. Prevalence of BRCA1 and BRCA2 Mutations in High-Risk Populations

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Population</th>
<th>Gene</th>
<th>Inclusion criteria</th>
<th>Early-onset</th>
<th>Population-based</th>
<th>High-risk</th>
<th>Ashkenazi Jewish</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tommasi et al, 2005</td>
<td>Italy</td>
<td>BRCA1</td>
<td>Consecutive series of breast cancer patients plus a positive family history</td>
<td>X</td>
<td>NR</td>
<td>X</td>
<td>No</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Janezic et al, 1999</td>
<td>Orange County, CA</td>
<td>BRCA1</td>
<td>Population-based series of consecutive ovarian cancer cases</td>
<td>X</td>
<td>No</td>
<td>X</td>
<td>No</td>
</tr>
<tr>
<td>Stratton et al, 1997</td>
<td>U.K.</td>
<td>BRCA1</td>
<td>Women diagnosed with ovarian cancer before age 70 years</td>
<td>X</td>
<td>NR</td>
<td>X</td>
<td>No</td>
</tr>
<tr>
<td>Anton-Culver et al, 2000</td>
<td>Caucasian</td>
<td>BRCA1</td>
<td>Population-based sample of ovarian cancer cases</td>
<td>X</td>
<td>No</td>
<td>X</td>
<td>No</td>
</tr>
<tr>
<td>Anton-Culver et al, 2000</td>
<td>Orange County, CA</td>
<td>BRCA1</td>
<td>Population-based sample of ovarian cancer cases</td>
<td>X</td>
<td>No</td>
<td>X</td>
<td>No</td>
</tr>
<tr>
<td>Risch et al, 2006</td>
<td>Canada Hispanic</td>
<td>BRCA1/2</td>
<td>Population-based series of consecutive ovarian cancer</td>
<td>X</td>
<td>No</td>
<td>X</td>
<td>No</td>
</tr>
<tr>
<td>Risch et al, 2006</td>
<td>Canada Hispanic</td>
<td>BRCA1/2</td>
<td>Population-based series of consecutive ovarian cancer</td>
<td>X</td>
<td>No</td>
<td>X</td>
<td>No</td>
</tr>
<tr>
<td>Risch et al, 2006</td>
<td>Total Canada</td>
<td>BRCA1/2</td>
<td>Population-based series of consecutive ovarian cancer, age &lt;41 years</td>
<td>X</td>
<td>Yes/no</td>
<td>X</td>
<td>No</td>
</tr>
<tr>
<td>Gayther et al, 1999</td>
<td>U.K. Familial Ovarian Cancer Registry</td>
<td>BRCA1/2</td>
<td>Families with ≥2 cases of ovarian cancer</td>
<td>X</td>
<td>No</td>
<td>X</td>
<td>No</td>
</tr>
<tr>
<td>Breast and ovarian cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beristain et al, 2007</td>
<td>Spain</td>
<td>BRCA1/2</td>
<td>1) Early-onset breast cancer &lt;40 years</td>
<td>X</td>
<td>NR</td>
<td>X</td>
<td>NR</td>
</tr>
<tr>
<td>Gayther et al, 1997</td>
<td>UK</td>
<td>BRCA2</td>
<td>1) Families with multiple cases of breast cancer</td>
<td>X</td>
<td>NR</td>
<td>X</td>
<td>No</td>
</tr>
<tr>
<td>Frank et al, 2002</td>
<td>Myriad</td>
<td>BRCA1/2</td>
<td>Tested by Myriad for full gene</td>
<td>X</td>
<td>No</td>
<td>X</td>
<td>No</td>
</tr>
<tr>
<td>Weitzel et al, 2005</td>
<td>Hispanic</td>
<td>BRCA1/2</td>
<td>Families presenting to the high-risk clinic for testing who were part of the Hereditary Cancer Registry. Had a calculated BRCA mutation probability &gt;5% by any method.</td>
<td>X</td>
<td>No</td>
<td>X</td>
<td>No</td>
</tr>
<tr>
<td>Konecny et al, 2011</td>
<td>Slovakia</td>
<td>BRCA1/2</td>
<td>Families presenting to high-risk clinic based on family history of breast and/or ovarian cancer</td>
<td>X</td>
<td>NR</td>
<td>X</td>
<td>NR</td>
</tr>
<tr>
<td>Seymour et al, 2008</td>
<td>Italy</td>
<td>BRCA1/2</td>
<td>Families presenting to high-risk clinic based on family history of breast and/or ovarian cancer</td>
<td>X</td>
<td>NR</td>
<td>X</td>
<td>NR</td>
</tr>
<tr>
<td>Marroni et al, 2004</td>
<td>Italy</td>
<td>BRCA1/2</td>
<td>High-risk families presenting for BRCA testing</td>
<td>X</td>
<td>NR</td>
<td>X</td>
<td>NR</td>
</tr>
<tr>
<td>Nanda et al, 2005</td>
<td>Asian</td>
<td>BRCA1/2</td>
<td>Families who presented for BRCA testing in high-risk clinics who had ≥2 cases of breast or ovarian</td>
<td>X</td>
<td>No</td>
<td>X</td>
<td>No</td>
</tr>
</tbody>
</table>

BRCA-Related Cancer
Table 8. Prevalence of BRCA1 and BRCA2 Mutations in High-Risk Populations

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Population</th>
<th>Gene</th>
<th>Inclusion criteria</th>
<th>Early-onset</th>
<th>Population-based</th>
<th>High-risk</th>
<th>Ashkenazi Jewish</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanda et al, 2005[193]</td>
<td>Total NonAshkenazi Jewish</td>
<td>BRCA1/2</td>
<td>Families who presented for BRCA testing in high-risk clinics who had ≥2 cases of breast or ovarian cancer among FDRs or SDRs</td>
<td>X</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nanda et al, 2005[193]</td>
<td>Caucasian</td>
<td>BRCA1/2</td>
<td>Families who presented for BRCA testing in high-risk clinics who had ≥2 cases of breast or ovarian cancer among FDRs or SDRs</td>
<td>X</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nanda et al, 2005[193]</td>
<td>African American</td>
<td>BRCA1/2</td>
<td>Families who presented for BRCA testing in high-risk clinics who had ≥2 cases of breast or ovarian cancer among FDRs or SDRs</td>
<td>X</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nanda et al, 2005[193]</td>
<td>Hispanic</td>
<td>BRCA1/2</td>
<td>Families who presented for BRCA testing in high-risk clinics who had ≥2 cases of breast or ovarian cancer among FDRs or SDRs</td>
<td>X</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaziri et al, 2001[24]</td>
<td>U.S.</td>
<td>BRCA1/2</td>
<td>Families in the Familial Cancer Registry who had ≥2 cases of breast or ovarian cancer among FDRs</td>
<td>X</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuhausen et al, 2009[194]</td>
<td>California, Ontario, Australia</td>
<td>BRCA1/2</td>
<td>Population-based case probands from cancer registries</td>
<td>X</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuhausen et al, 2009[194]</td>
<td>Philadelphia, New York, Utah</td>
<td>BRCA1/2</td>
<td>Families who presented for BRCA testing in high-risk clinics with a family history of breast and/or ovarian cancer</td>
<td>X</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamboom et al, 2010[195]</td>
<td>Estonia</td>
<td>BRCA1/2</td>
<td>Women diagnosed with breast cancer prior to age 45 years</td>
<td>X</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamboom et al, 2010[195]</td>
<td>Estonia</td>
<td>BRCA1/2</td>
<td>Families where the proband was diagnosed with breast or ovarian cancer and at least one relative was diagnosed with these cancers.</td>
<td>X</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Women tested, N</th>
<th>BRCA1 positive, n</th>
<th>BRCA2 positive, n</th>
<th>BRCA1 or BRCA2 positive, n</th>
<th>BRCA1 mutation frequency</th>
<th>BRCA2 mutation frequency</th>
<th>BRCA1 or BRCA2 mutation frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anglian BCSG, 2000[19]</td>
<td>1220</td>
<td>8</td>
<td>16</td>
<td>24</td>
<td>0.6%</td>
<td>1.3%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Anton-Culver et al, 2000[19]</td>
<td>42</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 8. Prevalence of BRCA1 and BRCA2 Mutations in High-Risk Populations

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Women tested, N</th>
<th>BRCA1 positive, n</th>
<th>BRCA2 positive, n</th>
<th>BRCA1 or BRCA2 positive, n</th>
<th>BRCA1 mutation frequency</th>
<th>BRCA2 mutation frequency</th>
<th>BRCA1 or BRCA2 mutation frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anton-Culver et al, 2000&lt;sup&gt;13&lt;/sup&gt;</td>
<td>41</td>
<td>2</td>
<td></td>
<td></td>
<td>4.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anton-Culver et al, 2000&lt;sup&gt;14&lt;/sup&gt;</td>
<td>17</td>
<td>0</td>
<td></td>
<td></td>
<td>0.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anglian BCSG, 2000&lt;sup&gt;13&lt;/sup&gt;</td>
<td>341</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td>0.8%</td>
<td>1.2%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Anglian BCSG, 2000&lt;sup&gt;13&lt;/sup&gt;</td>
<td>57</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>3.5%</td>
<td>7.0%</td>
<td>11%</td>
</tr>
<tr>
<td>FitzGerald et al, 1996&lt;sup&gt;25&lt;/sup&gt;</td>
<td>26</td>
<td>2</td>
<td></td>
<td></td>
<td>7.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peto et al, 1999&lt;sup&gt;16&lt;/sup&gt;</td>
<td>204</td>
<td>9</td>
<td>6</td>
<td>15</td>
<td>3.5%</td>
<td>2.4%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Peto et al, 1999&lt;sup&gt;16&lt;/sup&gt;</td>
<td>363</td>
<td>7</td>
<td>8</td>
<td>15</td>
<td>1.9%</td>
<td>2.2%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Malone et al, 2000&lt;sup&gt;26&lt;/sup&gt;</td>
<td>203</td>
<td>12</td>
<td>7</td>
<td>19</td>
<td>5.9%</td>
<td>3.4%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Same population as Langston et al, 1996&lt;sup&gt;17&lt;/sup&gt;</td>
<td>235</td>
<td>16</td>
<td>11</td>
<td>27</td>
<td>7.1%</td>
<td>4.9%</td>
<td>12%</td>
</tr>
<tr>
<td>Anglian BCSG, 2000&lt;sup&gt;13&lt;/sup&gt;</td>
<td>155</td>
<td>10</td>
<td></td>
<td></td>
<td>6.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eccles et al, 1998&lt;sup&gt;17&lt;/sup&gt;</td>
<td>45</td>
<td>0</td>
<td></td>
<td></td>
<td>0.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eccles et al, 1998&lt;sup&gt;17&lt;/sup&gt;</td>
<td>30</td>
<td>8</td>
<td></td>
<td></td>
<td>27%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Couch et al, 1997&lt;sup&gt;16&lt;/sup&gt;</td>
<td>146</td>
<td>21</td>
<td></td>
<td></td>
<td>14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tommassi et al, 2005&lt;sup&gt;25&lt;/sup&gt;</td>
<td>100</td>
<td>7</td>
<td></td>
<td></td>
<td>7.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Ovarian cancer**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Women tested, N</th>
<th>BRCA1 positive, n</th>
<th>BRCA2 positive, n</th>
<th>BRCA1 or BRCA2 positive, n</th>
<th>BRCA1 mutation frequency</th>
<th>BRCA2 mutation frequency</th>
<th>BRCA1 or BRCA2 mutation frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janezic et al, 1999&lt;sup&gt;16&lt;/sup&gt;</td>
<td>104</td>
<td>2</td>
<td></td>
<td></td>
<td>1.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stratton et al, 1997&lt;sup&gt;25&lt;/sup&gt;</td>
<td>374</td>
<td>13</td>
<td></td>
<td></td>
<td>3.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anton-Culver et al, 2000&lt;sup&gt;25&lt;/sup&gt;</td>
<td>99</td>
<td>4</td>
<td></td>
<td></td>
<td>4.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anton-Culver et al, 2000&lt;sup&gt;25&lt;/sup&gt;</td>
<td>12</td>
<td>0</td>
<td></td>
<td></td>
<td>0.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risch et al, 2006&lt;sup&gt;16&lt;/sup&gt;</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Same population as Risch, 2001&lt;sup&gt;25&lt;/sup&gt;</td>
<td>927</td>
<td>67</td>
<td>52</td>
<td>119</td>
<td>7.2%</td>
<td>5.6%</td>
<td>13%</td>
</tr>
<tr>
<td>Gayther et al, 1999&lt;sup&gt;17&lt;/sup&gt;</td>
<td>112</td>
<td>40</td>
<td>8</td>
<td>48</td>
<td>36%</td>
<td>7.0%</td>
<td>43%</td>
</tr>
</tbody>
</table>

**Breast and ovarian cancer**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Women tested, N</th>
<th>BRCA1 positive, n</th>
<th>BRCA2 positive, n</th>
<th>BRCA1 or BRCA2 positive, n</th>
<th>BRCA1 mutation frequency</th>
<th>BRCA2 mutation frequency</th>
<th>BRCA1 or BRCA2 mutation frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beristain et al, 2007&lt;sup&gt;17&lt;/sup&gt;</td>
<td>72</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Beristain et al, 2007&lt;sup&gt;17&lt;/sup&gt;</td>
<td>164</td>
<td>6</td>
<td>10</td>
<td>16</td>
<td>3.6%</td>
<td>6.1%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Gayther et al, 1997&lt;sup&gt;21&lt;/sup&gt;</td>
<td>290</td>
<td>64</td>
<td>25</td>
<td>89</td>
<td>22%</td>
<td>8.6%</td>
<td>31%</td>
</tr>
<tr>
<td>Frank et al, 2002&lt;sup&gt;17&lt;/sup&gt;</td>
<td>6724</td>
<td>1055</td>
<td></td>
<td></td>
<td>16%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weitzel et al, 2005&lt;sup&gt;17&lt;/sup&gt;</td>
<td>110</td>
<td>25</td>
<td>9</td>
<td>34</td>
<td>23%</td>
<td>8.1%</td>
<td>31%</td>
</tr>
<tr>
<td>Konecny et al, 2011&lt;sup&gt;18&lt;/sup&gt;</td>
<td>104</td>
<td>12</td>
<td></td>
<td></td>
<td>12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Konecny et al, 2011&lt;sup&gt;18&lt;/sup&gt;</td>
<td>585</td>
<td>85</td>
<td></td>
<td></td>
<td>15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seymour et al, 2008&lt;sup&gt;18&lt;/sup&gt;</td>
<td>247</td>
<td>21</td>
<td></td>
<td></td>
<td>8.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marroni et al, 2004&lt;sup&gt;18&lt;/sup&gt;</td>
<td>560</td>
<td>80</td>
<td></td>
<td></td>
<td>14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marroni et al, 2004&lt;sup&gt;18&lt;/sup&gt;</td>
<td>464</td>
<td>53</td>
<td></td>
<td></td>
<td>11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nanda et al, 2005&lt;sup&gt;18&lt;/sup&gt;</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Nanda et al, 2005&lt;sup&gt;18&lt;/sup&gt;</td>
<td>126</td>
<td>31</td>
<td>17</td>
<td>48</td>
<td>25%</td>
<td>13%</td>
<td>38%</td>
</tr>
<tr>
<td>Nanda et al, 2005&lt;sup&gt;18&lt;/sup&gt;</td>
<td>78</td>
<td>24</td>
<td>12</td>
<td>36</td>
<td>31%</td>
<td>15%</td>
<td>46%</td>
</tr>
<tr>
<td>Nanda et al, 2005&lt;sup&gt;18&lt;/sup&gt;</td>
<td>43</td>
<td>7</td>
<td>5</td>
<td>12</td>
<td>16%</td>
<td>12%</td>
<td>28%</td>
</tr>
<tr>
<td>Nanda et al, 2005&lt;sup&gt;18&lt;/sup&gt;</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Vaziri et al, 2004&lt;sup&gt;17&lt;/sup&gt;</td>
<td>104</td>
<td>18</td>
<td>2</td>
<td>20</td>
<td>17.30%</td>
<td>1.9%</td>
<td>19.2%</td>
</tr>
<tr>
<td>Neuhausen et al, 2009&lt;sup&gt;18&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>4.0%</td>
<td>3.7%</td>
<td>NR</td>
</tr>
</tbody>
</table>
Table 8. Prevalence of BRCA1 and BRCA2 Mutations in High-Risk Populations

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Women tested, N</th>
<th>BRCA1 positive, n</th>
<th>BRCA2 positive, n</th>
<th>BRCA1 or BRCA2 positive, n</th>
<th>BRCA1 mutation frequency</th>
<th>BRCA2 mutation frequency</th>
<th>BRCA1 or BRCA2 mutation frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuhausen et al, 2009</td>
<td>4084</td>
<td>NR</td>
<td>193</td>
<td>NR</td>
<td>4.7%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Neuhausen et al, 2009</td>
<td>4531</td>
<td>233</td>
<td>NR</td>
<td>NR</td>
<td>5.2%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Neuhausen et al, 2009</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>9.9%</td>
<td>8.6%</td>
<td>NR</td>
</tr>
<tr>
<td>Tamboom et al, 2010</td>
<td>64</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>6.3%</td>
<td>0.0%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Tamboom et al, 2010</td>
<td>47</td>
<td>6</td>
<td>1</td>
<td>7</td>
<td>12.8%</td>
<td>2.1%</td>
<td>14.9%</td>
</tr>
</tbody>
</table>

Abbreviations: FDR = first-degree relative; NR = not reported; SDR = second-degree relative.
Table 9. Summary of Meta-Analysis of Studies of Prevalence of BRCA1 and BRCA2 Mutations in High-Risk Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Gene</th>
<th>Cancer type</th>
<th>Prevalence, % (95% CI)</th>
<th>$I^2$ (p-value)</th>
<th>Studies, n (ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-onset breast or ovarian cancer</td>
<td><strong>BRCA1</strong></td>
<td>B</td>
<td>4.63 (2.47 to 8.52)</td>
<td>NA</td>
<td>5, 13, 16, 203, 216, 220</td>
</tr>
<tr>
<td>≤35 years</td>
<td><strong>BRCA1</strong></td>
<td>B</td>
<td>4.26 (2.61 to 6.87)</td>
<td>NA</td>
<td>10, 16, 114, 193, 204, 207, 209, 216, 218, 220, 223</td>
</tr>
<tr>
<td>≤40 years</td>
<td><strong>BRCA1</strong></td>
<td>O</td>
<td>5.17 (2.39 to 9.59)</td>
<td>NA</td>
<td>2, 13, 193</td>
</tr>
<tr>
<td>≤45 years</td>
<td><strong>BRCA1</strong></td>
<td>B</td>
<td>3.25 (1.72 to 6.06)</td>
<td>NA</td>
<td>11, 13, 114, 193, 195, 204, 207, 209, 216, 218, 220, 223</td>
</tr>
<tr>
<td>≤35 years</td>
<td><strong>BRCA2</strong></td>
<td>B</td>
<td>3.31 (1.17 to 9.00)</td>
<td>NA</td>
<td>3, 13, 16, 220</td>
</tr>
<tr>
<td>≤40 years</td>
<td><strong>BRCA2</strong></td>
<td>B</td>
<td>2.90 (1.35 to 6.14)</td>
<td>NA</td>
<td>5, 13, 16, 114, 193, 204, 207, 209, 220</td>
</tr>
<tr>
<td>≤40 years</td>
<td><strong>BRCA2</strong></td>
<td>O</td>
<td>0.64 (0.02 to 3.50)</td>
<td>NR</td>
<td>193</td>
</tr>
<tr>
<td>≤45 years</td>
<td><strong>BRCA2</strong></td>
<td>B</td>
<td>2.31 (1.11 to 4.77)</td>
<td>NA</td>
<td>6, 13, 114, 193, 220</td>
</tr>
<tr>
<td>≤35 years</td>
<td><strong>BRCA1 &amp; BRCA2</strong></td>
<td>B</td>
<td>7.78 (3.99 to 14.63)</td>
<td>NA</td>
<td>5, 13, 16, 114, 193, 220</td>
</tr>
<tr>
<td>≤40 years</td>
<td><strong>BRCA1 &amp; BRCA2</strong></td>
<td>B</td>
<td>5.98 (1.87 to 17.47)</td>
<td>NA</td>
<td>3, 13, 16, 220</td>
</tr>
<tr>
<td>≤40 years</td>
<td><strong>BRCA1 &amp; BRCA2</strong></td>
<td>O</td>
<td>6.37 (3.10 to 11.40)</td>
<td>NR</td>
<td>193</td>
</tr>
<tr>
<td>≤45 years</td>
<td><strong>BRCA1 &amp; BRCA2</strong></td>
<td>B</td>
<td>4.63 (1.91 to 10.80)</td>
<td>NA</td>
<td>5, 13, 16, 114, 193, 220</td>
</tr>
</tbody>
</table>

Selected high-risk cohorts

<table>
<thead>
<tr>
<th>Gene</th>
<th>Cancer type</th>
<th>Prevalence, % (95% CI)</th>
<th>$I^2$ (p-value)</th>
<th>Studies, n (ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1</strong></td>
<td>B</td>
<td>1.84 (0.72 to 4.63)</td>
<td>91% (0.190)</td>
<td>4, 13, 194, 204, 223</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td>B</td>
<td>1.31 (0.67 to 1.95)</td>
<td>NA</td>
<td>193</td>
</tr>
<tr>
<td><strong>BRCA1</strong></td>
<td>O</td>
<td>4.41 (2.47 to 7.74)</td>
<td>70% (0.006)</td>
<td>4, 194, 204, 216, 223</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td>O</td>
<td>5.61 (4.13 to 7.09)</td>
<td>NA</td>
<td>193</td>
</tr>
</tbody>
</table>

High-risk families

<table>
<thead>
<tr>
<th>Gene</th>
<th>Cancer type</th>
<th>Prevalence, % (95% CI)</th>
<th>$I^2$ (p-value)</th>
<th>Studies, n (ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1</strong></td>
<td>B</td>
<td>13.58 (10.09 to 17.07)</td>
<td>86% (&lt;0.001)</td>
<td>11, 13, 16, 114, 183, 188, 193, 194, 199, 200, 202, 207, 211</td>
</tr>
<tr>
<td><strong>BRCA1</strong></td>
<td>O</td>
<td>35.71 (26.92 to 44.51)</td>
<td>NA</td>
<td>193</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td>B</td>
<td>7.90 (5.30 to 10.50)</td>
<td>73% (0.117)</td>
<td>8, 114, 163, 168, 190, 193, 194, 199, 202, 211</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td>O</td>
<td>7.14 (2.13 to 12.15)</td>
<td>NA</td>
<td>193</td>
</tr>
<tr>
<td><strong>BRCA1 &amp; BRCA2</strong></td>
<td>B</td>
<td>19.78 (12.98 to 26.57)</td>
<td>94% (&lt;0.001)</td>
<td>6, 114, 163, 183, 191, 197, 211</td>
</tr>
<tr>
<td><strong>BRCA1 &amp; BRCA2</strong></td>
<td>O</td>
<td>42.86 (33.79 to 51.92)</td>
<td>NA</td>
<td>193</td>
</tr>
</tbody>
</table>

Ashkenazi Jewish

<table>
<thead>
<tr>
<th>Gene</th>
<th>Cancer type</th>
<th>Prevalence, % (95% CI)</th>
<th>$I^2$ (p-value)</th>
<th>Studies, n (ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1 &amp; BRCA2</strong></td>
<td>NA</td>
<td>2.08 (1.28 to 2.88)</td>
<td>89% (&lt;0.001)</td>
<td>4, 191, 214, 209</td>
</tr>
<tr>
<td><strong>BRCA1</strong></td>
<td>NA</td>
<td>1.01 (0.64 to 1.37)</td>
<td>74% (0.004)</td>
<td>5, 191, 209, 214, 229</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td>NA</td>
<td>1.02 (0.72 to 1.33)</td>
<td>60% (0.028)</td>
<td>5, 191, 216, 214, 229</td>
</tr>
</tbody>
</table>

Abbreviations: B = breast; CI = confidence interval; NA = not applicable; NR = not reported; O = ovarian.
Table 10. Prevalence of BRCA1 and BRCA2 Mutations in Ashkenazi Jewish Populations

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Population</th>
<th>Women tested, N</th>
<th>BRCA1 positive, n</th>
<th>BRCA2 positive, n</th>
<th>BRCA1 or BRCA2 positive, n</th>
<th>BRCA1 mutation frequency</th>
<th>BRCA2 mutation frequency</th>
<th>BRCA1 or BRCA2 mutation frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fodor et al, 1998&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Population based (U.S.)</td>
<td>1715</td>
<td>20</td>
<td>18</td>
<td>38</td>
<td>1.2%</td>
<td>1.0%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Hartge et al, 1999&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Population based (U.S.)</td>
<td>3742</td>
<td>48</td>
<td>41</td>
<td>89</td>
<td>1.3%</td>
<td>1.1%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Struwing et al, 1997&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Population based (U.S.)</td>
<td>2080</td>
<td>10</td>
<td>12</td>
<td>22</td>
<td>0.5%</td>
<td>0.6%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Metcalfe et al, 2010&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Population based (Canada)</td>
<td>1255</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oddoux et al, 1996&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Population based (U.S.)</td>
<td>2717</td>
<td>35</td>
<td></td>
<td></td>
<td>1.3%</td>
<td></td>
<td>1.4%</td>
</tr>
<tr>
<td>Roa et al, 1996&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Population based (U.S.)</td>
<td>2687</td>
<td>37</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roa et al, 1996&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Population based (Israel)</td>
<td>403</td>
<td>3</td>
<td></td>
<td></td>
<td>0.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roa et al, 1996&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Population based (Israel)</td>
<td>398</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.5%</td>
</tr>
<tr>
<td>Struwing et al, 1995&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Population based (U.S.)</td>
<td>327</td>
<td>3</td>
<td></td>
<td></td>
<td>0.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Struwing et al, 1995&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Population based (Israel)</td>
<td>369</td>
<td>3</td>
<td></td>
<td></td>
<td>0.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author, year</td>
<td>Population or risk group</td>
<td>N</td>
<td>Breast cancer risk</td>
<td>Ovarian cancer risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------</td>
<td>---</td>
<td>-------------------</td>
<td>--------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRCA1 % (95% CI)</td>
<td>BRCA2 % (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRCA1 and BRCA2 % (95% CI)</td>
<td>BRCA1 % (95% CI)</td>
<td>BRCA2 % (95% CI)</td>
<td>BRCA1 and BRCA2 % (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk to age 50 years</td>
<td>Cancer registry (U.K.)</td>
<td>8</td>
<td>32 (2 to 62)</td>
<td>11 (1 to 74)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anglian Breast Cancer Study Group, 2000</td>
<td>Cancer registry (U.K.)</td>
<td>16</td>
<td>18 (2 to 32)</td>
<td>3 (0 to 19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen et al., 2006</td>
<td>High-risk (U.S.)</td>
<td>283</td>
<td>28 (24 to 34)</td>
<td>13 (9.7 to 17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen et al., 2006</td>
<td>High-risk (U.S.)</td>
<td>143</td>
<td>23 (19 to 29)</td>
<td>4 (2.2 to 6.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hopper et al., 1999</td>
<td>Cancer registry &lt;40 years (Australia)</td>
<td>18</td>
<td></td>
<td>10 (0 to 24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marroni et al., 2004</td>
<td>High-risk (Italy)</td>
<td>80</td>
<td>27 (20 to 34)</td>
<td>14 (7 to 22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marroni et al., 2004</td>
<td>High-risk (Italy)</td>
<td>53</td>
<td>26 (18 to 34)</td>
<td>3 (0 to 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk to age 70 years</td>
<td>Cancer registry (U.K.)</td>
<td>8</td>
<td>47 (7 to 82)</td>
<td>36 (4 to 99)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anglian Breast Cancer Study Group, 2000</td>
<td>Cancer registry (U.K.)</td>
<td>16</td>
<td>56 (5 to 80)</td>
<td>10 (1 to 55)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antoniou et al., 2002</td>
<td>Cancer registry (U.K.)</td>
<td>Unclear</td>
<td>35.3</td>
<td>50.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen et al., 2006</td>
<td>High-risk (U.S.)</td>
<td>283</td>
<td>46 (39 to 54)</td>
<td>39 (30 to 50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen et al., 2006</td>
<td>High-risk (U.S.)</td>
<td>143</td>
<td>45 (36 to 51)</td>
<td>22 (14 to 32)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hopper et al., 1999</td>
<td>Cancer registry &lt;40 years (Australia)</td>
<td>18</td>
<td></td>
<td>36 (15 to 65)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lubinski et al., 2012</td>
<td>Known mutation carriers (26 centers in Canada, U.S., and Poland)—U.S. Results</td>
<td>614</td>
<td>76 (NR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lubinski et al., 2012</td>
<td>Known mutation carriers (26 centers in Canada, U.S., and Poland)—Polish Results</td>
<td>863</td>
<td>57 (NR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marroni et al., 2004</td>
<td>High-risk (Italy)</td>
<td>80</td>
<td>39 (27 to 52)</td>
<td>43 (21 to 66)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marroni et al., 2004</td>
<td>High-risk (Italy)</td>
<td>53</td>
<td>44 (29 to 58)</td>
<td>15 (4 to 26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metcalfe et al., 2010</td>
<td>Known mutation carriers (6 countries) 0 FDRs</td>
<td>3011</td>
<td>56</td>
<td>38</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metcalfe et al., 2010</td>
<td>Known mutation carriers (6 countries) 1 FDR</td>
<td>3011</td>
<td>57</td>
<td>46</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metcalfe et al., 2010</td>
<td>Known mutation carriers (6 countries) ≥2 FDRs</td>
<td>3011</td>
<td>72</td>
<td>85</td>
<td>68</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 11. Penetrance of BRCA-Related Cancer in BRCA-Positive Women: Single Individual Tested

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Population or risk group</th>
<th>N</th>
<th>Breast cancer risk</th>
<th>Ovarian cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRCA1 % (95% CI)</td>
<td>BRCA2 % (95% CI)</td>
</tr>
<tr>
<td>Risk to age 80 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Canada)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risch et al, 2001 [22]</td>
<td>Ovarian cancer registry</td>
<td>21</td>
<td>11.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Canada)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risch et al, 2006 [23]</td>
<td>Ovarian cancer registry</td>
<td>75</td>
<td>90 (77 to 97)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Canada)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risch et al, 2006 [23]</td>
<td>Ovarian cancer registry</td>
<td>54</td>
<td>41 (26 to 60)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Canada)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** BCLC = Breast Cancer Linkage Consortium; CI = confidence interval; FDR = first-degree relative; LoD = logarithm (base 10) of odds; NR = not reported.
### Table 12. Penetrance of BRCA-Related Cancer in BRCA-Positive Women: Multiple Individuals Tested

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Population or risk group</th>
<th>N</th>
<th>Breast cancer risk</th>
<th>Ovarian cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRCA1 % (95% CI)</td>
<td>BRCA2 % (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRCA1 and BRCA2 % (95% CI)</td>
<td>BRCA1 % (95% CI)</td>
</tr>
<tr>
<td><strong>Risk to age 50 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al-Mulla et al, 2009&lt;sup&gt;172&lt;/sup&gt;</td>
<td>U.K. Exon 2</td>
<td>30</td>
<td>30% (95% CI)</td>
<td>30% (95% CI)</td>
</tr>
<tr>
<td>Al-Mulla et al, 2009&lt;sup&gt;172&lt;/sup&gt;</td>
<td>U.K. Exon 11</td>
<td>58</td>
<td>80% (95% CI)</td>
<td>80% (95% CI)</td>
</tr>
<tr>
<td>Al-Mulla et al, 2009&lt;sup&gt;172&lt;/sup&gt;</td>
<td>U.K. Other exons</td>
<td>28</td>
<td>85% (95% CI)</td>
<td>85% (95% CI)</td>
</tr>
<tr>
<td>Al-Mulla et al, 2009&lt;sup&gt;172&lt;/sup&gt;</td>
<td>U.K. Exon 13</td>
<td>20</td>
<td>92% (95% CI)</td>
<td>92% (95% CI)</td>
</tr>
<tr>
<td>Antoniou et al, 2006&lt;sup&gt;173&lt;/sup&gt;</td>
<td>French Canadian</td>
<td>25</td>
<td>20 (0 to 45)</td>
<td>1 (0 to 10)</td>
</tr>
<tr>
<td>Antoniou et al, 2006&lt;sup&gt;173&lt;/sup&gt;</td>
<td>French Canadian</td>
<td>27</td>
<td>21 (0 to 55)</td>
<td>0.4 (0 to 2)</td>
</tr>
<tr>
<td>Evans et al, 2008&lt;sup&gt;176&lt;/sup&gt;</td>
<td>U.K.</td>
<td>223</td>
<td>48 (SE, 0.023)</td>
<td>21 (SE, 0.02)</td>
</tr>
<tr>
<td>Evans et al, 2008&lt;sup&gt;176&lt;/sup&gt;</td>
<td>U.K.</td>
<td>162</td>
<td>42 (SE, 0.027)</td>
<td>4 (SE, 0.012)</td>
</tr>
<tr>
<td>Ford et al, 1998&lt;sup&gt;180&lt;/sup&gt;</td>
<td>High-risk (BCLC)</td>
<td>32</td>
<td>28 (9 to 44)</td>
<td>0.4 (0 to 1.1)</td>
</tr>
<tr>
<td>Kramer et al, 2005&lt;sup&gt;185&lt;/sup&gt;</td>
<td>U.S. Overall</td>
<td>23</td>
<td>0.44 (SE, 0.07)</td>
<td></td>
</tr>
<tr>
<td>Kramer et al, 2005&lt;sup&gt;185&lt;/sup&gt;</td>
<td>U.S. With ovaries</td>
<td>23</td>
<td>0.49 (SE, 0.09)</td>
<td></td>
</tr>
<tr>
<td>Milne et al, 2008&lt;sup&gt;192&lt;/sup&gt;</td>
<td>Spain</td>
<td>155</td>
<td>35 (15 to 47)</td>
<td>10 (0 to 25)</td>
</tr>
<tr>
<td>Milne et al, 2008&lt;sup&gt;192&lt;/sup&gt;</td>
<td>Spain</td>
<td>164</td>
<td>32 (17 to 44)</td>
<td>2 (0 to 9)</td>
</tr>
<tr>
<td>Sutcliffe et al, 2000&lt;sup&gt;230&lt;/sup&gt;</td>
<td>Ovarian cancer registry (U.K.) BRCA 1/2 combined</td>
<td>319</td>
<td>700%</td>
<td>400%</td>
</tr>
<tr>
<td>van der Kolk et al, 2010&lt;sup&gt;201&lt;/sup&gt;</td>
<td>Netherlands Positive index</td>
<td>111</td>
<td>51 (47 to 54)</td>
<td>21 (18 to 24)</td>
</tr>
<tr>
<td>van der Kolk et al, 2010&lt;sup&gt;201&lt;/sup&gt;</td>
<td>Netherlands Positive index</td>
<td>74</td>
<td>46 (41 to 51)</td>
<td>7 (4 to 9)</td>
</tr>
<tr>
<td><strong>Risk to age 70 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antoniou et al, 2006&lt;sup&gt;173&lt;/sup&gt;</td>
<td>French Canadian</td>
<td>25</td>
<td>72 (0 to 93)</td>
<td>38 (0 to 78)</td>
</tr>
<tr>
<td>Antoniou et al, 2006&lt;sup&gt;173&lt;/sup&gt;</td>
<td>French Canadian</td>
<td>27</td>
<td>75 (0 to 97)</td>
<td>49 (0 to 81)</td>
</tr>
<tr>
<td>Brose et al, 2002&lt;sup&gt;176&lt;/sup&gt;</td>
<td>U.S. Age-adjusted risk</td>
<td>147</td>
<td>73 (68 to 78)</td>
<td>41 (36 to 46)</td>
</tr>
<tr>
<td>Evans et al, 2008&lt;sup&gt;176&lt;/sup&gt;</td>
<td>U.K.</td>
<td>223</td>
<td>68 (SE, 0.033)</td>
<td>60 (SE, 0.037)</td>
</tr>
<tr>
<td>Evans et al, 2008&lt;sup&gt;176&lt;/sup&gt;</td>
<td>U.K.</td>
<td>162</td>
<td>75 (SE, 0.033)</td>
<td>30 (SE, 0.046)</td>
</tr>
<tr>
<td>Ford et al, 1998&lt;sup&gt;180&lt;/sup&gt;</td>
<td>High-risk (BCLC)</td>
<td>32</td>
<td>84 (43 to 95)</td>
<td>27 (0 to 47)</td>
</tr>
<tr>
<td>Kramer et al, 2005&lt;sup&gt;185&lt;/sup&gt;</td>
<td>U.S. Overall</td>
<td>23</td>
<td>0.76 (SE, 0.08)</td>
<td></td>
</tr>
<tr>
<td>Kramer et al, 2005&lt;sup&gt;185&lt;/sup&gt;</td>
<td>U.S. With ovaries</td>
<td>23</td>
<td>0.92 (SE, 0.08)</td>
<td></td>
</tr>
</tbody>
</table>
Table 12. Penetrance of BRCA-Related Cancer in BRCA-Positive Women: Multiple Individuals Tested

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Population or risk group</th>
<th>N</th>
<th>Breast cancer risk</th>
<th>Ovarian cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRCA1 % (95% CI)</td>
<td>BRCA2 % (95% CI)</td>
</tr>
<tr>
<td>Milne et al., 2008</td>
<td>Spain</td>
<td>155</td>
<td>52 (26 to 69)</td>
<td>22 (0 to 40)</td>
</tr>
<tr>
<td>Milne et al., 2008</td>
<td>Spain</td>
<td>164</td>
<td>47 (29 to 60)</td>
<td></td>
</tr>
<tr>
<td>Sutcliffe et al., 2006</td>
<td>Ovarian cancer registry (U.K.) BRCA 1/2 combined</td>
<td>319</td>
<td></td>
<td>11%</td>
</tr>
<tr>
<td>van der Kolk et al., 2010</td>
<td>Netherlands Negative index</td>
<td>111</td>
<td>60 (54 to 65)</td>
<td>52 (45 to 58)</td>
</tr>
<tr>
<td>van der Kolk et al., 2010</td>
<td>Netherlands Positive index</td>
<td>111</td>
<td>71 (67 to 76)</td>
<td>59 (53 to 64)</td>
</tr>
<tr>
<td>van der Kolk et al., 2010</td>
<td>Netherlands Negative index</td>
<td>74</td>
<td>78 (69 to 88)</td>
<td>13 (7 to 19)</td>
</tr>
<tr>
<td>van der Kolk et al., 2010</td>
<td>Netherlands Positive index</td>
<td>74</td>
<td>87 (82 to 93)</td>
<td>34 (25 to 44)</td>
</tr>
</tbody>
</table>

Abbreviations: BCLC = Breast Cancer Linkage Consortium; CI = confidence interval; SE = standard error.
Table 13. Summary of Meta-Analysis of Studies of Breast and Ovarian Cancer Penetration in BRCA-Positive Women in High-Risk Populations

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk age, y</th>
<th>Penetration, % (95% CI)</th>
<th>Single individual tested</th>
<th>All studies combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Multiple individuals tested</td>
<td>Studies, n (ref)</td>
<td>Penetration, % (95% CI)</td>
</tr>
<tr>
<td><strong>BRCA1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>50</td>
<td>47 (40 to 53)</td>
<td>60% (0.032)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>70 (61 to 79)</td>
<td>83% (&lt;0.001)</td>
<td>6</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>50</td>
<td>14 (3.8 to 23)</td>
<td>94% (&lt;0.001)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>46 (35 to 57)</td>
<td>85% (&lt;0.001)</td>
<td>5</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>50</td>
<td>40 (33 to 46)</td>
<td>57% (0.056)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>71 (59 to 83)</td>
<td>69% (0.012)</td>
<td>5</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>50</td>
<td>3 (1 to 4)</td>
<td>88% (&lt;0.001)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>23 (12 to 34)</td>
<td>67% (0.016)</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; NA = not applicable.
Table 14. Penetrance of BRCA-Related Cancer in Women With Uninformative Negative Results

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Population or risk group</th>
<th>Ascertainment</th>
<th>N</th>
<th>Risk to age, y</th>
<th>Cases observed, n</th>
<th>Cases expected, n</th>
<th>Relative risk (95% CI)</th>
<th>Cases observed, n</th>
<th>Cases expected, n</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kauff et al, 2005</td>
<td>FDRs in high-risk families who test negative for BRCA</td>
<td>Families with breast cancer but no ovarian cancer</td>
<td>165 families 321 FDRs</td>
<td>85</td>
<td>8</td>
<td>2.46</td>
<td>3.25 (1.4 to 6.4)</td>
<td>1</td>
<td>0.26</td>
<td>3.88 (0.05 to 21.6)</td>
</tr>
<tr>
<td>Kauff et al, 2005</td>
<td>SDRs in high-risk families who test negative for BRCA</td>
<td>Families with breast cancer but no ovarian cancer</td>
<td>165 families 262 SDRs</td>
<td>85</td>
<td>4</td>
<td>2.18</td>
<td>1.83 (0.49 to 4.69)</td>
<td>0</td>
<td>0.26</td>
<td>0 (NA to 14.3)</td>
</tr>
<tr>
<td>Kauff et al, 2005</td>
<td>Probandsin high-risk families who test negative for BRCA</td>
<td>Families with breast cancer but no ovarian cancer</td>
<td>165 families 165 probands</td>
<td>85</td>
<td>7</td>
<td>1.43</td>
<td>4.9 (1.96 to 10.11)</td>
<td>0</td>
<td>0.14</td>
<td>0 (NA to 25.6)</td>
</tr>
<tr>
<td>Metcalfe et al, 2009</td>
<td>FDRs in high-risk families who test negative for BRCA</td>
<td>FDRs of breast cancer cases</td>
<td>365 families 1492 women</td>
<td>75</td>
<td>65</td>
<td>16.49</td>
<td>3.94 (3.09 to 5.02)</td>
<td>2</td>
<td>2.34</td>
<td>0.85 (0.23 to 3.12)</td>
</tr>
<tr>
<td>Sutcliffe et al, 2000</td>
<td>FDRs and SDRs in high-risk families who test negative for BRCA</td>
<td>Families with ≥2 FDRs with ovarian cancer</td>
<td>56 families 382 relatives</td>
<td>85</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>0.35</td>
<td>11.6 (3.12 to 29.7)</td>
</tr>
<tr>
<td>Sutcliffe et al, 2000</td>
<td>FDRs and SDRs in high-risk families who test negative for BRCA</td>
<td>Families with ≥2 FDRs with ovarian cancer</td>
<td>57 families 435 relatives</td>
<td>85</td>
<td>9</td>
<td>2.71</td>
<td>3.32 (1.52 to 6.31)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; FDR = first-degree relative; NA = not applicable; SDR = second-degree relative.
Table 15. Penetrance of BRCA-Related Cancer in Women With True Negative Results

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Population or risk group</th>
<th>N</th>
<th>Cases observed, n</th>
<th>Cases expected, n</th>
<th>Relative risk (95% CI)</th>
<th>Cases observed, n</th>
<th>Cases expected, n</th>
<th>Relative risk (95% CI)</th>
<th>Genotype</th>
<th>Prospective</th>
<th>Oophorectomy adjustment</th>
<th>Invasive only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernholtz, 2012</td>
<td>True negatives Total</td>
<td>307</td>
<td>20</td>
<td>23.8</td>
<td>0.84 (0.51 to 1.30)</td>
<td></td>
<td></td>
<td></td>
<td>Known</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Domchek, 2010</td>
<td>True negatives FDRs or SDRs</td>
<td>378</td>
<td>2</td>
<td>3.8</td>
<td>0.52 (0.13 to 2.09)</td>
<td>0</td>
<td>0.4</td>
<td>NR</td>
<td>Known</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Domchek, 2010</td>
<td>True negatives FDRs or SDRs</td>
<td>378</td>
<td>2</td>
<td>0.9</td>
<td>2.3 (0.57 to 9.19)</td>
<td></td>
<td></td>
<td></td>
<td>Known</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Gronwald, 2007</td>
<td>True negatives FDRs</td>
<td>131</td>
<td>2.5</td>
<td>1.2</td>
<td>2 (not given)</td>
<td></td>
<td></td>
<td></td>
<td>Known</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>Harvey, 2011</td>
<td>True negatives Total</td>
<td>722</td>
<td>6</td>
<td>1.14 (0.51 to 2.53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Known</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Harvey, 2011</td>
<td>True negatives FDRs and SDRs</td>
<td>442</td>
<td></td>
<td></td>
<td>1.29 (0.58 to 2.88)</td>
<td></td>
<td></td>
<td></td>
<td>Known</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Harvey, 2011</td>
<td>True negatives*</td>
<td>424</td>
<td></td>
<td></td>
<td>0.48 (0.12 to 1.93)</td>
<td></td>
<td></td>
<td></td>
<td>Known</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Korde, 2011</td>
<td>True negatives FDRs</td>
<td>102</td>
<td></td>
<td></td>
<td>0.66 (0.13 to 1.94)</td>
<td></td>
<td></td>
<td></td>
<td>Known or inferred</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Korde, 2011</td>
<td>True negatives FDRs</td>
<td>102</td>
<td></td>
<td></td>
<td>1.33 (0.49 to 2.91)</td>
<td></td>
<td></td>
<td></td>
<td>Known or inferred</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Korde, 2011</td>
<td>True negatives SDRs</td>
<td>182</td>
<td></td>
<td></td>
<td>0.97 (0.35 to 2.11)</td>
<td></td>
<td></td>
<td></td>
<td>Known or inferred</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Korde, 2011</td>
<td>True negatives TDRs</td>
<td>111</td>
<td></td>
<td></td>
<td>0.69 (0.01 to 3.83)</td>
<td></td>
<td></td>
<td></td>
<td>Known or inferred</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Korde, 2011</td>
<td>True negatives Total</td>
<td>395</td>
<td>10</td>
<td>12</td>
<td>0.75 (0.34 to 1.41)</td>
<td></td>
<td></td>
<td></td>
<td>Known or inferred</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Korde, 2011</td>
<td>True negatives Total</td>
<td>395</td>
<td>10</td>
<td>12</td>
<td>0.82 (0.39 to 1.51)</td>
<td></td>
<td></td>
<td></td>
<td>Known or inferred</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Korde, 2011</td>
<td>True negatives Total</td>
<td>395</td>
<td>10</td>
<td></td>
<td>0.95 (0.45 to 1.74)</td>
<td></td>
<td></td>
<td></td>
<td>Known or inferred</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Kramer, 2005</td>
<td>True negatives Total</td>
<td>353</td>
<td>5</td>
<td></td>
<td>0.85 (0.21 to 1.52)</td>
<td></td>
<td></td>
<td></td>
<td>Known or inferred</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>Kurian, 2011</td>
<td>True negatives FDRs</td>
<td>NR</td>
<td></td>
<td></td>
<td>0.39 (0.04 to 3.81)</td>
<td></td>
<td></td>
<td></td>
<td>Untested were probabilistically assigned</td>
<td>Unknown</td>
<td>Unknown</td>
<td>No</td>
</tr>
<tr>
<td>Rowan, 2007</td>
<td>True negatives FDRs or SDRs</td>
<td>101</td>
<td>3</td>
<td>1</td>
<td>2.9 (1.0 to 8.6)</td>
<td>0</td>
<td>1.7</td>
<td>NR</td>
<td>Known</td>
<td>Yes</td>
<td>Unknown</td>
<td>Yes</td>
</tr>
<tr>
<td>Smith, 2007</td>
<td>True negatives Total</td>
<td>258</td>
<td>28</td>
<td>5.3</td>
<td>5.3 (3.5 to 7.7)</td>
<td>4</td>
<td>0.9</td>
<td>4.6 (1.2 to 11.7)</td>
<td>Known</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Smith, 2007</td>
<td>True negatives FDRs</td>
<td>184</td>
<td>18</td>
<td>3.6</td>
<td>5 (2.9 to 7.8)</td>
<td></td>
<td></td>
<td></td>
<td>Known</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 15. Penetration of BRCA-Related Cancer in Women With True Negative Results

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Population or risk group</th>
<th>N</th>
<th>Breast cancer</th>
<th>Ovarian cancer</th>
<th>Genotype</th>
<th>Prospective</th>
<th>Oophorectomy adjustment</th>
<th>Invasive only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith, 2007</td>
<td>True negatives FDRs</td>
<td>166</td>
<td>13</td>
<td>3.2</td>
<td>4 (2.1 to 6.9)</td>
<td>Known</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Smith, 2007</td>
<td>True negatives FDRs</td>
<td>153</td>
<td>3</td>
<td>1.4</td>
<td>2.1 (0.4 to 6.2)</td>
<td>Known</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>van der Kolk, 2010</td>
<td>True negatives FDRs</td>
<td>128</td>
<td>5</td>
<td>2.5</td>
<td>2 (0.7 to 4.7)</td>
<td>Known</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>van der Kolk, 2010</td>
<td>True negatives FDRs</td>
<td>74</td>
<td>4</td>
<td>1.6</td>
<td>2.5 (0.7 to 6.3)</td>
<td>Known</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*No family history in the nonmutation carrying parental line.

**Abbreviations:** FDR = first-degree relative; NR = not reported; SDR = second-degree relative; TDR = third-degree relative.
<table>
<thead>
<tr>
<th>Author, year, quality rating</th>
<th>N, study design</th>
<th>Mutation status</th>
<th>Genetic counseling</th>
<th>Comparison</th>
<th>Measure of distress</th>
<th>Breast cancer worry</th>
<th>Anxiety</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current report</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arver et al, 2004&lt;sup&gt;235&lt;/sup&gt; NA</td>
<td>63; pre-post</td>
<td>Positive or negative</td>
<td>Genetically trained oncologist and oncology nurse</td>
<td>A) Pretest B) 2 months post results C) 1 year post results</td>
<td>HADS, SF-36</td>
<td>NR</td>
<td>X decrease C &amp; B vs. A</td>
<td>0</td>
</tr>
<tr>
<td>Dagan and Shochat, 2009&lt;sup&gt;236&lt;/sup&gt; Fair</td>
<td>73; case-control</td>
<td>Positive or negative</td>
<td>Unknown</td>
<td>A) Carriers (n=17) B) Noncarriers (n=20) C) Age-matched controls (n=36)</td>
<td>HR-QOL, CRW, BSI</td>
<td>X higher A &amp; B vs. C</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ertmanski et al, 2009&lt;sup&gt;237&lt;/sup&gt; NA</td>
<td>56; pre-post</td>
<td>Positive</td>
<td>Unknown</td>
<td>A) Pretest B) 1 month post results C) 1 year post results</td>
<td>STAI, IES</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Foster et al, 2007&lt;sup&gt;238&lt;/sup&gt; Fair</td>
<td>154; prospective cohort</td>
<td>Positive or negative</td>
<td>Unknown</td>
<td>A) Carriers (n=53) B) Noncarriers (n=101)</td>
<td>GHQ, CWS-R</td>
<td>X decrease over time for A &amp; B</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Geirdal et al, 2005&lt;sup&gt;240&lt;/sup&gt; Good</td>
<td>10,244; prospective cohort</td>
<td>Positive or unknown</td>
<td>Unknown</td>
<td>A) Positive (n=68) B) Not tested but FBOC (n=176) C) Not tested, age-matched controls (n=10,000)</td>
<td>HADS, GHQ, BHS, IES</td>
<td>NR</td>
<td>X higher B vs. A</td>
<td>X higher B vs. A</td>
</tr>
<tr>
<td>Geirdal and Dahl, 2008&lt;sup&gt;239&lt;/sup&gt; Good</td>
<td>242; prospective cohort</td>
<td>Positive or unknown</td>
<td>Unknown</td>
<td>A) Positive (n=68) B) Not tested, but FBOC (n=174)</td>
<td>HADS, COPE</td>
<td>NR</td>
<td>X higher B vs. A</td>
<td>NR</td>
</tr>
<tr>
<td>Kinney et al, 2005&lt;sup&gt;243&lt;/sup&gt; Poor</td>
<td>52; prospective cohort</td>
<td>Positive or negative</td>
<td>Certified genetic professional</td>
<td>A) Carriers (n=NR) B) Noncarriers (n=NR)</td>
<td>STAI, IES, CES-D</td>
<td>NR</td>
<td>X decrease B only over time</td>
<td>NR</td>
</tr>
<tr>
<td>Low et al, 2008&lt;sup&gt;244&lt;/sup&gt; Fair</td>
<td>47; prospective cohort</td>
<td>Positive, true negative, or uncertain (grouped with true negative)</td>
<td>Genetic counselor</td>
<td>A) Positive (n=7) B) True negative + uncertain (n=40)</td>
<td>IES-R, COPE, PTGI</td>
<td>NR</td>
<td>X higher A vs. B</td>
<td>NR</td>
</tr>
<tr>
<td>Metcalfe et al, 2012&lt;sup&gt;249&lt;/sup&gt; NA</td>
<td>17; pre-post</td>
<td>Positive</td>
<td>Unknown</td>
<td>A) Pretest B) 1 year post results C) 2 years post results</td>
<td>IES</td>
<td>X increase B vs. A &amp; C</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Reichelt et al, 2004&lt;sup&gt;245&lt;/sup&gt; Good</td>
<td>209; prospective cohort</td>
<td>Positive, negative, or unknown</td>
<td>Medical geneticist or experienced genetic counselor</td>
<td>A) Carriers (n=141) B) Noncarriers (68)</td>
<td>HADS, GHQ, BHS, IES</td>
<td>NR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reichelt et al, 2008&lt;sup&gt;246&lt;/sup&gt; NA</td>
<td>181; pre-post</td>
<td>Positive or true negative</td>
<td>Genetic counselor</td>
<td>A) Pretest B) 6 weeks post results C) 18 months post results</td>
<td>HADS, IES</td>
<td>NR</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
### Table 16. Studies of Distress After Genetic Testing

<table>
<thead>
<tr>
<th>Author, year, quality rating</th>
<th>N, study design</th>
<th>Mutation status</th>
<th>Genetic counseling</th>
<th>Comparison</th>
<th>Measure of distress</th>
<th>Breast cancer worry</th>
<th>Anxiety</th>
<th>Depression</th>
</tr>
</thead>
</table>
| van Dijk et al, 2006<sup>246</sup> Good | 132; prospective cohort | Positive, true negative, or uninformative | Unknown | A) Positive (n=22)  
B) True negative (n=41)  
C) Uninformative (n=69) | IES, NSI | X higher A vs. B & C | X higher A vs. B & C | NR |
| Prior report | | | | | | | | |
| Meiser et al, 2002<sup>250</sup> Good | 143; prospective cohort | Positive or negative | Unknown | A) Carriers (n=30)  
B) Noncarriers (n=59)  
C) Not tested (n=51) | BDI, IES, MBSS, STAI, NSI | X higher A vs. C | X lower B vs. A & C | X lower B vs. A & C |

X = statistically significant; 0 = studied but not significant.

**Abbreviations:** BDI = Beck Depression Inventory; BHS = Beck Hopelessness Scale; BSI = Brief Symptom Inventory; CES-D = Center for Epidemiologic Studies-Depression Scale; COPE = Emotional Approach Coping Scale; CRW = Cancer-Related Worry Scale; CWS-R = Cancer Worry Scale-Revised; FBOC = familial breast and/or ovarian cancer; GHQ = General Health Questionnaire; HADS = Hospital Anxiety and Depression Scale; HR-QOL = Health Related-Quality of Life; IES = Impact of Events Scale; IES-R = Impact of Events Scale-Revised; MBSS = Miller Behavioral Style Scale; NA = not applicable; NR = not reported; NSI = not standardized instrument; PTGI = Post-Traumatic Growth Inventory; SF-36 = Swedish SF-36 Health Survey; STAI = State-Trait Anxiety Inventory.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Risk categories, n</th>
<th>Inclusion criteria</th>
<th>Mean age at entry, y (range)</th>
<th>Screening interval</th>
<th>Followup, mo</th>
<th>Mammography vs. MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortesi et al, 2006&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Mutation carrier: 48 High: 674 Intermediate: 257 Slight increase: 346</td>
<td>BRCA carrier Positive FH Male breast cancer Suspected positive FH</td>
<td>42 (20-75) 42 (15-75) 43 (19-67) 40 (18-75)</td>
<td>Varied by risk category and age</td>
<td>Median, 55</td>
<td>Mutation carrier† 50 vs. 100 NR</td>
</tr>
<tr>
<td>Leach et al, 2005&lt;sup&gt;24&lt;/sup&gt; MARIBS study</td>
<td>BRCA1: 39 BRCA2: 86 High: 424</td>
<td>BRCA1 carrier/relative BRCA2 carrier/relative FH positive/other mutation/syndrome</td>
<td>Median, 40 (31-55)</td>
<td>Annual</td>
<td>Variable, ≥2 scans per woman</td>
<td>BRCA1 BRCA2 All women 23 vs. 92; C=92 50 vs. 58; C=92 40 vs. 77; C=94 92 vs. 79; C=74 94 vs. 82; C=78 93 vs. 81; C=77</td>
</tr>
<tr>
<td>Le-Petross et al, 2011&lt;sup&gt;27&lt;/sup&gt;</td>
<td>BRCA1: 37 BRCA2: 36</td>
<td>BRCA1 carrier/relative BRCA2 carrier/relative</td>
<td>Median 44 (23-75)</td>
<td>Bi-annual, alternating</td>
<td>Median, 24</td>
<td>BRCA1/2 Unable to report§ vs. 92 82 vs. 87</td>
</tr>
<tr>
<td>Rijnsburger et al, 2010&lt;sup&gt;28&lt;/sup&gt; Dutch MRISC study</td>
<td>BRCA1: 422 BRCA2: 172 High: 1069 Moderate: 489 Other: 5</td>
<td>BRCA1 carrier BRCA2 carrier 30%-50% lifetime risk for BC∥ (high-risk) 15%-30% lifetime risk for BC∥ (moderate-risk) Other mutation carrier</td>
<td>BRCA1: 39 BRCA2: 40 High risk: 41 Moderate risk: 40</td>
<td>Annual</td>
<td>48</td>
<td>BRCA1 BRCA2 High Moderate 25 vs. 67‡ 62 vs. 69 46 vs. 77 47 vs. 67 95 vs. 91 94 vs. 92 95 vs. 89 95 vs. 90</td>
</tr>
</tbody>
</table>

*Includes women from families with known mutations or breast cancer. †MRI was not used to screen other risk categories. ‡p<0.05. §All screen-detected cancers were detected by MRI only; mammography was not performed after detection with MRI to calculate sensitivity. ∥Based on modified Claus tables.

**Abbreviations:** BC = breast cancer; C = mammography plus MRI; FH = family history; MARIBS = Magnetic Resonance Imaging Breast Screening; MRI = magnetic resonance imaging; MRISC = Magnetic Resonance Imaging Screening Study; NA = not applicable; NR = not reported.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Raloxifene vs. tamoxifen</th>
<th>Tamoxifen vs. placebo</th>
<th>Raloxifene vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk ratio (95% CI)</td>
<td>Events reduced/increased, n (95% CI)*</td>
<td>Risk ratio (95% CI) (Trials, n)†</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>1.24 (1.05 to 1.47)§</td>
<td>5 (1 to 9) fewer tamoxifen</td>
<td>0.70 (0.59 to 0.82) (4)</td>
</tr>
<tr>
<td>ER+ invasive breast cancer</td>
<td>0.93 (0.72 to 1.24)‖</td>
<td>0.58 (0.42 to 0.79) (4)</td>
<td>3.67 (0.78)</td>
</tr>
<tr>
<td>ER- invasive breast cancer</td>
<td>1.15 (0.75 to 1.77)‖</td>
<td>1.19 (0.92 to 1.55) (4)</td>
<td>1.25 (0.67 to 2.31) (2)</td>
</tr>
<tr>
<td>Noninvasive breast cancer</td>
<td>1.22 (0.95 to 1.59)§</td>
<td>0.85 (0.54 to 1.35)¶</td>
<td>1.47 (0.75 to 2.91) (2)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.84 (0.70 to 1.02)§</td>
<td>1.07 (0.90 to 1.27) (4)</td>
<td>0.84 (0.64 to 1.10)** (2)</td>
</tr>
</tbody>
</table>

*Numbers of events reduced for benefits or increased for harms compared with placebo or other comparator per 1,000 women, assuming 5 years of use.
†If meta-analysis.
‡Per 1,000 women. Estimated from a meta-analysis of rates from the placebo groups from the same trials included in the risk ratios.
§Updated results from the Study of Tamoxifen and Raloxifene (STAR), 2010.
‖Initial results from STAR, 2006.
¶Risk ratio for noninvasive breast cancer was significantly reduced in the 2005 National Surgical Adjuvant Breast and Bowel Project P-1 (60 vs. 93 events; RR, 0.63 [95% CI, 0.45-0.89]).
**Updated meta-analysis.

**Abbreviations:** CI = confidence interval; ER- = estrogen receptor negative; ER+ = estrogen receptor positive; SE = standard error.
Table 19. Studies of Risk-Reducing Surgery

<table>
<thead>
<tr>
<th>Author, year, quality rating</th>
<th>Inclusion criteria</th>
<th>Risk factors Enrolled, n</th>
<th>Mean age at surgery, y</th>
<th>Breast cancer incidence Risk estimate (95% CI)</th>
<th>Ovarian cancer incidence Risk estimate (95% CI)</th>
<th>Mortality Risk estimate (95% CI)</th>
<th>Mean followup,* y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mastectomy</strong></td>
<td>Surgery vs. no surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domchek et al, 2010 Fair</td>
<td>BRCA 1/2 carrier No history of salpingo-oophorectomy</td>
<td>BRCA1 positive n=415†</td>
<td>37</td>
<td>0/43 vs. 19/372 HR NA</td>
<td>NR</td>
<td>NR</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA2 positive n=245‡</td>
<td>39</td>
<td>0/32 vs. 15/213 HR NA</td>
<td>NR</td>
<td>NR</td>
<td>2.5</td>
</tr>
<tr>
<td>Skytte et al, 2011 Good</td>
<td>BRCA1/2 carrier No history of mastectomy or salpingo-oophorectomy</td>
<td>BRCA1 positive n=201</td>
<td>NR</td>
<td>3/96 vs. 16/211 HR 0.39 (0.12 to 1.36)</td>
<td>NR</td>
<td>NR</td>
<td>NR³</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA2 positive n=10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Salpingo-oophorectomy or oophorectomy</strong></td>
<td>Surgery vs. no surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domchek et al, 2010 Fair</td>
<td>BRCA1/2 carrier No history of salpingo-oophorectomy</td>
<td>BRCA1 positive n=1003†</td>
<td>42</td>
<td>14% (32/236) vs. 20% (129/633) HR 0.63 (0.41 to 0.96)</td>
<td>2% (6/342) vs. 7% (49/661) HR 0.31 (0.12 to 0.82)</td>
<td>All cause: 2% (8/327) vs. 7% (43/608) HR 0.52 (0.24 to 1.14)</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA2 positive n=554‡</td>
<td>46</td>
<td>7% (7/100) vs. 23% (94/401) HR 0.36 (0.16 to 0.82)</td>
<td>0/123 vs. 14/431 HR NA</td>
<td>All cause: 0/120 vs. 17/403 HR NA</td>
<td>5.8</td>
</tr>
<tr>
<td>Kramer et al, 2005 Fair</td>
<td>BRCA1-positive family‡‡; no history of bilateral mastectomy</td>
<td>BRCA1 positive n=98</td>
<td>NR</td>
<td>18% (6/33) vs. 42% (27/65) HR 0.38 (0.15 to 0.97)</td>
<td>NR</td>
<td>NR</td>
<td>16.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA1 negative n=353</td>
<td>NR</td>
<td>3% (1/34) vs. 1% (4/319) HR NR</td>
<td>NR</td>
<td>NR</td>
<td>16.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Undetermined mutation status n=222</td>
<td>NR</td>
<td>0% (0/18) vs. 2.5% (5/204) HR NA</td>
<td>NR</td>
<td>NR</td>
<td>16.5</td>
</tr>
<tr>
<td><strong>Surgery group (observed vs. expected)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olson et al, 2004 Fair</td>
<td>Women with bilateral oophorectomy</td>
<td>High-risk Surgery &lt;60 years n=55</td>
<td>&lt;60</td>
<td>3/55 vs. 5.4 RR 0.56 (0.11 to 1.33)</td>
<td>NR</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgery &lt;50 years n=41</td>
<td>&lt;50</td>
<td>1/41 vs. 3.9 RR 0.26 (0.001 to 0.99)</td>
<td>NR</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate risk Surgery &lt;60 years n=193</td>
<td>&lt;60</td>
<td>9/193 vs. 10.9 RR 0.83 (0.38 to 1.44)</td>
<td>NR</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgery &lt;50 years n=130</td>
<td>&lt;50</td>
<td>5/130 vs. 7.7 RR 0.65 (0.21 to 1.32)</td>
<td>NR</td>
<td>NR</td>
<td>NA</td>
</tr>
</tbody>
</table>
### Table 19. Studies of Risk-Reducing Surgery

<table>
<thead>
<tr>
<th>Author, year, quality rating</th>
<th>Inclusion criteria</th>
<th>Risk factors Enrolled, n</th>
<th>Mean age at surgery, y</th>
<th>Breast cancer incidence Risk estimate (95% CI)</th>
<th>Ovarian cancer incidence Risk estimate (95% CI)</th>
<th>Mortality Risk estimate (95% CI)</th>
<th>Mean followup,* y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mastectomy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartmann et al, 1999&lt;sup&gt;99&lt;/sup&gt;</td>
<td>Family history of breast cancer</td>
<td>High risk n=214</td>
<td>42</td>
<td>3/214 vs. 37 expected***; risk reduction, 92% (77% to 98%)</td>
<td>n=2</td>
<td>Breast cancer: 2/214 vs.10 expected***; risk reduction, 81% (31% to 98%)</td>
<td>14 (median)</td>
</tr>
<tr>
<td>Hartmann et al, 2001&lt;sup&gt;101&lt;/sup&gt;</td>
<td></td>
<td>Moderate risk n=425</td>
<td></td>
<td>4/425 vs. 37 expected‡‡; risk reduction, 89.5% (p&lt;0.001)</td>
<td>n=0</td>
<td>Breast cancer: 0/425 vs. 10 expected‡‡; risk reduction, 100% (70% to 100%)</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td></td>
<td>BRCA1 or BRCA2 positive††† n=18</td>
<td>41</td>
<td>0/18 vs. 6.1/18 expected‡‡‡; risk reduction, 100% (51% to 100%)</td>
<td>NR</td>
<td>NR</td>
<td>13.4 (median)</td>
</tr>
</tbody>
</table>

| **Oophorectomy (surgery vs. no surgery)** | | | | | | | |
| Struwing et al, 1995<sup>229</sup> | Families with ≥3 cases of ovarian cancer or ≥2 cases of ovarian cancer and ≥1 cases of breast cancer <age 50 | First-degree relatives of breast or ovarian cancer cases n=390 N =12 families | NR | 3/44 vs. 14/346 Risk estimate: NR | 2/44 vs. 8/346 Risk estimate: NR | NR | NR |

*Based on followup to censoring date.
†BRCA1 carriers evaluated in group including those with and without surgery.
‡BRCA2 carriers evaluated in group including those with and without surgery.
§Total at-risk time in surgery group was 378.7 years vs. 934.6 years in the no surgery group.
||Expected incidence based on life tables.
‖Study included women with prior breast cancer; only data on women with no prior breast cancer included in evidence review.
**Total number of women with BRCA1/2 mutation, regardless of breast cancer history; study did not provide the number of women with a mutation and no prior history of breast cancer.
††Oophorectomy performed.
‡‡Families testing positive for BRCA1 mutation; families had multiple breast and ovarian cancer cases prior to testing.
‡‡‡Expected incidence based on Gail model.
║One first-degree relative with breast cancer before age 50 years or one first-degree relative with ovarian cancer at any age and at least one other first- or second-degree relative with either diagnosis at any age.
‖‖One first-degree relative with breast cancer at any age.
**Based on control group of sisters.
†††Subgroup of high-risk group.
‡‡‡Based on high-penetrance model.
§§§Based on low-penetrance model.
‖‖‖Incidence includes post-oophorectomy ovarian carcinomatosis.
¶¶¶Followup for ovarian cancer incidence was 1665 person-years for no surgery group, 460 person-years for surgery group; followup for breast cancer incidence was 1587 person-years for no surgery group, 484 person-years for surgery group.

**Abbreviations:** CI = confidence interval; HR = hazard ratio; NA = not applicable; NR = not reported; RR = relative risk.
### Table 20. Harms of Intensive Screening for Breast Cancer Using Mammography vs. MRI in High-Risk Women

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N (BRCA1/2) # of cancer cases</th>
<th>Age at entry, y</th>
<th>Screening interval Followup, y</th>
<th>False-positive rate</th>
<th>False-negative, n</th>
<th>Recall rates</th>
<th>Unneeded* additional exams or imaging Unneeded* biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kriege et al, 2004&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1909 (14/4) 39 BRCA1 45 BRCA2</td>
<td>Mean, 40</td>
<td>Annual, same-day Mean, 2.7</td>
<td>n=39 cancers First imaging round (prior mammography): 5.5% vs. 14%; p&lt;0.001 Subsequent imaging rounds: 4.6% vs. 8.2%; p&lt;0.001</td>
<td>n=39 cancers First imaging round (prior mammography): 12 vs. 1 Subsequent imaging rounds: 12 vs. 4</td>
<td>NR</td>
<td>n=45 cancers Exams†: 207 vs. 420 Biopsy: 28% (7/25‡) vs. 43% (24/56‡)</td>
</tr>
<tr>
<td>Dutch MRISC study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leach et al, 2005&lt;sup&gt;2&lt;/sup&gt;</td>
<td>649 (13/6) 33</td>
<td>Median, 40</td>
<td>Annual, same-day Variable followup, ≥2 scans</td>
<td>NR</td>
<td>NR</td>
<td>279 recalls overall 3.9% vs. 11% per woman-year Combined tests: 13% per woman-year 245/279 recalls for benign findings 8.5 recalls per cancer detected</td>
<td>All study arms§ Ultrasound: 38% (93/245) Core biopsy: 13% (32/245) FNA: 19% (47/245) Surgery: 3% (7/245) 0.21 benign biopsies per cancer detected</td>
</tr>
<tr>
<td>MARIBS study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Le-Petross et al, 2011&lt;sup&gt;3&lt;/sup&gt;</td>
<td>73 (51/49) 13</td>
<td>Median, 44</td>
<td>Biannual, alternating mammography with MRI Median, 2</td>
<td>15% (11/73) vs. 11% (8/73)</td>
<td>NR</td>
<td>NR</td>
<td>Imaging: 73% (8/11) vs. 50% (4/8) Biopsy: 27% (3/11) vs. 25% (2/8) Imaging plus biopsy: 0% vs. 25% (2/8)</td>
</tr>
</tbody>
</table>

*Women who were diagnosed as cancer free.
†Additional investigation included ultrasound ± fine needle biopsy or repeat mammography or repeat MRI.
‡Women with BIRADS ≥3 on mammography or MRI.
§Results not reported by imaging arm.

**Abbreviations:** BIRADS = Breast Imaging Reporting and Data System; FNA = fine needle aspiration; MARIBS = Magnetic Resonance Imaging Breast Screening; MRI = magnetic resonance imaging; MRISC = Magnetic Resonance Imaging Screening Study; NA = not applicable; NR = not reported.
Table 21. Distress Due to Intensive Screening for Breast Cancer in Women Who Are Mutation Carriers

<table>
<thead>
<tr>
<th>Author, year, quality rating</th>
<th>N, study design</th>
<th>Mutation status</th>
<th>Comparison</th>
<th>Measures of distress</th>
<th>Anxiety</th>
<th>Depression</th>
<th>Sexual activity</th>
<th>Body image</th>
<th>General QOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rijnsburger et al, 2004, Fair</td>
<td>288; prospective cohort and pre-post</td>
<td>35 BRCA1/2 mutation positive</td>
<td>A) CBE (n=287) B) CBE + mammography (n=134) C) CBE + MRI (n=109)</td>
<td>SF-36, EQ-5D, VAS, SCL-90</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Spiegel et al, 2011, NA</td>
<td>55; pre-post</td>
<td>BRCA1: 30/55 (54.5%) BRCA2: 25/55 (45.5%)</td>
<td>A) Recall examinations (n=18) B) No recall examinations (n=37)</td>
<td>HADS, WIS</td>
<td>X increase A vs. B*</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
</tbody>
</table>

X = statistically significant difference; 0 = studied but not significant.
*At 4 to 6 weeks after screening only, returned to baseline levels by 6 months.

**Abbreviations:** CBE = clinical breast examination; EQ-5D = EuroQoL-5 Dimensions; HADS = Hospital Anxiety and Depression Scale; MRI = magnetic resonance imaging; NA = not applicable; NR = not reported; QOL = quality of life; SCL-90 = Symptom Checklist-90; SF-36 = Short-Form 36-Item Health Survey; VAS = Visual Analogue Scale; WIS = Breast Cancer Worry Interference Scale.
Table 22. Results of Trials of Risk-Reducing Medications: Adverse Effects

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Raloxifene vs. tamoxifen</th>
<th>Tamoxifen vs. placebo</th>
<th>Raloxifene vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk ratio (95% CI)</td>
<td>Events reduced/increased, n (95% CI)*</td>
<td>Risk ratio (95% CI) (Trials, n)†</td>
</tr>
<tr>
<td>Thromboembolic events§</td>
<td>0.75 (0.60 to 0.93)</td>
<td>4 (1 to 7) more tamoxifen</td>
<td>1.93 (1.41 to 2.64) (4)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0.72 (0.54 to 0.95)</td>
<td>3 (1 to 5) more tamoxifen</td>
<td>1.45 (0.89 to 2.37) (2)</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>0.80 (0.57 to 1.11)</td>
<td>2.69 (1.12 to 6.47) (2)</td>
<td>0.19 (0.07)</td>
</tr>
<tr>
<td>Coronary heart disease events</td>
<td>1.10 (0.85 to 1.43)††</td>
<td>1.00 (0.79 to 1.27) (4)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0.96 (0.64 to 1.43)††</td>
<td></td>
<td>1.36 (0.89 to 2.08) (4)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>0.55 (0.36 to 0.83)</td>
<td>5 (2 to 9) more tamoxifen</td>
<td>2.13 (1.36 to 3.32) (3)</td>
</tr>
<tr>
<td>Cataracts</td>
<td>0.80 (0.72 to 0.95)</td>
<td>15 (8 to 22) more tamoxifen</td>
<td>1.25 (0.93 to 1.67)†† (3)</td>
</tr>
</tbody>
</table>

*Numbers of events increased for harms compared with placebo or other comparator per 1000 women, assuming 5 years of use.
†If meta-analysis.
‡Per 1000 women. Estimated from a meta-analysis of rates from the placebo groups from the same trials included in the risk ratios.
§Includes deep vein thrombosis and pulmonary embolus.
¶Updated results from the Study of Tamoxifen and Raloxifene (STAR), 2010.
¶¶Initial results from STAR, 2006.
**Updated meta-analysis.
††The risk ratio for cataracts was significantly increased in the NSABP P-1, 1998 (574 vs. 507 events; RR, 1.14 [95% CI, 1.01 to 1.29]).

**Abbreviations**: CI = confidence interval; NR = not reported; SE = standard error.
Table 23. Distress Due to Risk-Reducing Surgery

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N, study design</th>
<th>Mutation status</th>
<th>Comparison</th>
<th>Measures of distress</th>
<th>Anxiety</th>
<th>Depression</th>
<th>Sexual activity</th>
<th>Body image</th>
<th>General QOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brandberg et al, 2008&lt;sup&gt;302&lt;/sup&gt;</td>
<td>90; pre-post</td>
<td>37/90 (41.1%) BRCA1 13/90 (14.4%) BRCA2 2/90 (2.2%) unknown mutation</td>
<td>A) Before surgery (n=81) B) 6 months after (n=71) C) 1 year after (n=65)</td>
<td>NSI, SAQ, BIS, HADS, SF-36</td>
<td>X decrease B &amp; C vs. A</td>
<td>0</td>
<td>X* decrease C vs. A &amp; B</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Brandberg et al, 2012&lt;sup&gt;304&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gahm et al, 2010&lt;sup&gt;303&lt;/sup&gt;</td>
<td>1784; case-series</td>
<td>NR</td>
<td>A) Surgery (n=59) B) Control (n=1725)</td>
<td>NSI, SF-36, DRS</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Metcalfe et al, 2004&lt;sup&gt;301&lt;/sup&gt;</td>
<td>60; case-series</td>
<td>21.7% BRCA1/2</td>
<td>A) Age &lt;50 years (n=46) B) Age ≥50 years (n=14)</td>
<td>BSI, BIBC, IES, SAQ</td>
<td>0</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Salpingo-oophorectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finch et al, 2011&lt;sup&gt;306&lt;/sup&gt;</td>
<td>67; pre-post</td>
<td>BRCA1 or BRCA2</td>
<td></td>
<td>MENQOL, SAQ</td>
<td>NR</td>
<td>NR</td>
<td>X decrease B vs. A</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

X = statistically significant difference; 0 = studied but not significant. 
*For pleasure subscale of SAQ only.

**Abbreviations:** BIBC=Body Image after Breast Cancer; BIS = Body Image Scale; BSI=Brief Symptom Inventory; DRS=Decision Regret Scale; HADS=Hospital Anxiety and Depression Scale; IES=Impact of Events Scale; MENQOL=Menopause-Specific Quality of Life-Intervention; NSI=not standard instrument; NR = not reported; QOL=quality of life; SAQ=Sexual Activity Questionnaire; SF-36 = Short-Form 36-Item Health Survey.
Table 24. Summary of Evidence

| Key Question 1. Does risk assessment, genetic counseling, and genetic testing lead to reduced incidence of BRCA-related cancer and reduced cause-specific and all cause mortality? |
|---|---|---|---|---|---|---|
| No studies | NA | NA | NA | NA | NA | NA |

| Key Question 2a. What is the accuracy of methods to assess familial cancer risk for BRCA-related cancer when performed by a nongenetics specialist in a clinical setting? |
|---|---|---|---|
| Systematic review of 13 general risk models; 10 studies of 5 familial risk models; no studies of the accuracy of referral criteria or adverse effects of risk assessment. | Diagnostic accuracy; cohort; case-control | Reference standards and study designs varied across studies; risk was based on self-reported information. | Consistent | High | Good |

| Key Question 2b, 3b. What are the benefits and potential adverse effects of genetic counseling for determining eligibility for genetic testing for BRCA-related cancer? |
|---|---|---|---|---|
| 16 studies of distress, accuracy of risk perception, and intention for genetic testing. | RCT, cohort, case-control, before-after | Noncomparable comparison groups; small studies; outcome measures varied. | Consistent | High | Fair |

| Key Question 2c. What is the clinical validity of genetic testing for deleterious mutations in women with increased risk for BRCA-related cancer? |
|---|---|---|
| 32 new and 38 earlier studies provided data for meta-analysis estimates to determine the likelihood of BRCA mutations in women in specific risk populations (prevalence) and their chances of developing breast or ovarian cancer based on results of genetic testing (penetrance). | Cohort, cross-sectional, descriptive studies | Studies are heterogeneous; laboratory techniques differed; no studies outside high-risk populations; bias in estimates; no studies in women with variants of uncertain significance. | Consistent | Moderate | Fair |

| Key Question 3c. What are the potential adverse effects of genetic testing? |
|---|---|---|---|---|
| 13 studies of distress measures and risk perception | Cohort; case-control; before-after | No studies of other outcomes; high loss to followup; comparison groups and measures varied. | Mixed | High | Fair |

BRCA-Related Cancer 123
Pacific Northwest EPC
Table 24. Summary of Evidence

<table>
<thead>
<tr>
<th>Studies, n</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Overall quality</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive screening: no effectiveness studies</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Risk-reducing medications: systematic review; 6 placebo-controlled trials (4 tamoxifen, 2 raloxifene) and 1 head-to-head trial (STAR)</td>
<td>RCT</td>
<td>No results for BRCA mutation carriers; trials are heterogeneous and data are lacking on doses, duration, and timing of use.</td>
<td>Consistent</td>
<td></td>
<td>Good</td>
<td>Tamoxifen and raloxifene reduced invasive breast cancer by 30%-68% compared with placebo; reduction was greater for women with family history of breast cancer, but confidence intervals were overlapping. Reduction was significant for ER+ but not ER- cancer. Noninvasive breast cancer and mortality were not significantly reduced.</td>
</tr>
<tr>
<td>Risk-reducing surgery: 4 studies of mastectomy and 3 of oophorectomy or salpingo-oophorectomy</td>
<td>Cohort</td>
<td>Comparison groups varied.</td>
<td>Consistent</td>
<td>High</td>
<td>Fair</td>
<td>For high-risk women and mutation carriers, mastectomy reduced breast cancer 85%-100% and breast cancer mortality 81%-100%; salpingo-oophorectomy reduced breast cancer 37%-100%, ovarian cancer 69%-100%, and all-cause mortality 55%-100%.</td>
</tr>
</tbody>
</table>

Key Question 5. What are the potential adverse effects of interventions to reduce risk for BRCA-related cancer?

<table>
<thead>
<tr>
<th>Studies, n</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Overall quality</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive screening: 3 studies of physical harms of breast cancer screening and 2 studies of anxiety; 1 study of physical harms of ovarian cancer screening</td>
<td>Cohort</td>
<td>No RCTs; screening intervals and false-positive calculations varied between studies; some studies lacked within-cohort comparison groups.</td>
<td>Consistent</td>
<td>High</td>
<td>Poor</td>
<td>False-positive rates, unnecessary imaging, and unneeded surgeries were higher for women undergoing intensive screening for breast and ovarian cancer. Most women experienced no anxiety after screening with MRI, mammography, or clinical breast examination, although women recalled had transient anxiety.</td>
</tr>
<tr>
<td>Risk-reducing medications: no studies provided results by mutation status; 1 systematic review; 6 placebo-controlled trials (4 tamoxifen, 2 raloxifene) and 1 head-to-head trial</td>
<td>RCT</td>
<td>No results for BRCA mutation carriers; trials are heterogeneous and data on long-term effects are incomplete.</td>
<td>Consistent</td>
<td>High</td>
<td>Good</td>
<td>Tamoxifen and raloxifene increased thromboembolic events compared with placebo. Tamoxifen increased endometrial cancer and cataracts compared with raloxifene. Both caused undesirable side effects for some women.</td>
</tr>
<tr>
<td>Risk-reducing surgery: 5 studies of complications, physical effects, or distress</td>
<td>Case-series; before-after studies</td>
<td>Lack of studies; small numbers of participants; no comparison groups.</td>
<td>NA</td>
<td>Low</td>
<td>Poor</td>
<td>Some women experienced physical complications of surgery, had postsurgical symptoms, or changes in body image. Some women had improved anxiety.</td>
</tr>
</tbody>
</table>

**Abbreviations:** BC = breast cancer; FHAT = Family History Assessment Tool; MRI = magnetic resonance imaging; NA = not applicable; OC = ovarian cancer; PAT = Pedigree Assessment Tool; RCT = randomized, controlled trial; RST = Referral Screening Tool; SIR = standardized incidence rate; STAR = Study of Tamoxifen and Raloxifene.
Appendix A1. Referral Criteria, Adapted From National Comprehensive Cancer Network Guidelines

Table 1. Criteria for Further Genetic Risk Evaluation

| a) Unaffected individual and a family history of ≥1 of these: | ≥2 breast primaries, either in 1 individual or 2 different individuals from the same side of family (maternal or paternal) |
| | ≥1 ovarian cancer primary from the same side of the family (maternal or paternal) |
| | First- or second-degree relative with breast cancer age ≤45 years |
| | A combination of breast cancer with ≥1 of the following: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumor, diffuse gastric cancer, dermatologic manifestations and/or marocephaly, or leukemia/lymphoma on the same side of the family (especially if early-onset) |
| | A known mutation in a breast cancer susceptibility gene within the family |
| | Male breast cancer |

| b) Individuals at increased risk, may have modified inclusion (e.g., Ashkenazi Jewish with above at any age) |

- One or more of these criteria is suggestive of hereditary breast/ovarian cancer (HBOC) syndrome that warrants further personalized risk assessment, genetic counseling, and management. The maternal and paternal sides should be considered independently. Other malignancies reported in some HBOC families include prostate and melanoma.
- Individuals with limited family history, such as less than 2 first- or second-degree female relatives or female relatives surviving beyond age 45 years in either lineage, may have an underestimated probability of familial mutation.
- For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancer should be included.
- Close blood relatives include first-, second-, and third-degree relatives.
- For the purposes of these guidelines, fallopian tube and primary peritoneal cancer are included. Ovarian/fallopian tube/primary peritoneal cancer are component tumors of hereditary nonpolyposis colorectal cancer/Lynch syndrome; be attentive for clinical evidence of this syndrome.
- Two breast primaries include bilateral (contralateral) disease or 2 or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.

Table 2. Criteria for Genetic Testing for HBOC Syndrome

| a) Individual from a family with a known deleterious BRCA1 or BRCA2 mutation |
| b) Personal history of breast cancer and ≥1 of these: |
| Diagnosed at age ≤54 years |
| Diagnosed at age ≥50 years with ≥1 close blood relatives with breast cancer at age 50 years and/or ≥1 close blood relatives with epithelial ovarian cancer at any age |
| 2 breast primaries when first breast cancer diagnosis occurred at age ≤50 years |
| Diagnosed at age ≤60 years with a triple negative breast cancer |
| Diagnosed at age ≤50 years with a limited family history |
| Diagnosed at any age, with ≥2 close blood relatives with breast and/or epithelial ovarian cancer at any age |
| Diagnosed at any age with ≥2 close blood relatives with pancreatic cancer at any age |
| Close male blood relative with breast cancer |
| Individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish) |
| Personal history of epithelial ovarian cancer |
| Personal history of male breast cancer |
| Personal history of pancreatic cancer at any age with ≥2 close blood relatives with breast and/or ovarian cancer and/or pancreatic cancer at any age |

| c) No personal history of breast cancer, but ≥1 of these: |
| First- or second-degree blood relative meeting any of the above criteria |
| Third-degree blood relative with breast cancer and/or ovarian cancer with ≥2 close blood relatives with breast cancer (≥1 with breast cancer at age ≤50 years) and/or ovarian cancer |

- Testing of unaffected family members should only be considered when no affected family member is available, and then the unaffected family member with the highest probability of mutation should be tested. Significant limitations of interpreting test results should be discussed.
- Testing for Ashkenazi Jewish founder-specific mutation(s) should be performed first. Full sequencing may be considered if ancestry also includes nonAshkenazi Jewish relatives or other HBOC criteria are met. Founder mutations exist in other populations.
Appendix A1. Referral Criteria, Adapted From National Comprehensive Cancer Network Guidelines

- Individuals with limited family history, such as less than 2 first- or second-degree female relatives or female relatives surviving beyond age 45 years in either lineage, may have an underestimated probability of familial mutation.
- For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancer should be included.
- Close blood relatives include first-, second-, and third-degree relatives.
- For the purposes of these guidelines, fallopian tube and primary peritoneal cancer are included. Ovarian/fallopian tube/primary peritoneal cancer are component tumors of hereditary nonpolyposis colorectal cancer/Lynch syndrome; be attentive for clinical evidence of this syndrome.
- Two breast primaries include bilateral (contralateral) disease or 2 or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.
Appendix A2. Definitions of Terms Used in Systematic Review

<table>
<thead>
<tr>
<th>Term or Phrase</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA-related cancer</td>
<td>Predominantly breast, ovarian, fallopian tube, and peritoneal</td>
</tr>
<tr>
<td>Genetic counseling</td>
<td>A service delivered by a qualified health professional that provides a comprehensive evaluation of familial risk for inherited disorders using kindred analysis and other methods, patient education, discussion of the benefits and harms of genetic testing, interpretation of results after testing, and discussion of management options</td>
</tr>
<tr>
<td>True negative test</td>
<td>Known confirmed deleterious genetic mutation in relatives, and none detected in the patient</td>
</tr>
<tr>
<td>Uninformative negative test</td>
<td>No known deleterious genetic mutations in relatives, and none detected in the patient</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>An abnormality of the BRCA1 or BRCA2 gene, but it is not known whether it is associated with an increased risk for cancer</td>
</tr>
<tr>
<td>Analytic validity*</td>
<td>Technical test performance measured by analytic sensitivity and specificity, reliability, and assay robustness</td>
</tr>
<tr>
<td>Clinical validity*</td>
<td>The test's ability to accurately and reliably predict the future disorder measured by clinical sensitivity and specificity, and predictive values of positive and negative tests that take into account the disorder prevalence</td>
</tr>
<tr>
<td>Clinical utility*</td>
<td>Balance of benefits and harms when the test is used to influence patient management. For risk assessment, clinical utility is determined by improved health outcomes based on prevention or early detection strategies</td>
</tr>
</tbody>
</table>

Appendix B1. Search Strategies

Ethical, legal, and social implications of genetic testing

Database: Ovid MEDLINE(R) without Revisions <2004to 2012>
Search Strategy:
--------------------------------------------------------------------------------
1     exp Breast Neoplasms/ or exp ovarian neoplasms/ (140349)
2     exp Mass Screening/ or gene.mp. or genes.mp. or genetic$.mp. or brca$.mp. (1445145)
3     exp LEGISLATION/ (75)
4     exp JURISPRUDENCE/ (74415)
5     lj.fs. (120944)
6     3 or 4 or 5 (161388)
7     exp bioethical issues/ or exp bioethics/ or ethic$.mp. or bioethic$.mp. (67517)
8     exp human rights/ (62937)
9     6 or 7 or 8 (229177)
10    1 and 2 and 9 (529)
11    limit 10 to (human and english language) (471)
--------------------------------------------------------------------------------

Genetic testing

Database: Ovid MEDLINE(R) without Revisions <2004 to 2012>
Search Strategy:
--------------------------------------------------------------------------------
1     exp Preventive Medicine/ (5575)
2     exp Family Practice/ (30023)
3     exp Primary Health Care/ (46956)
4     exp Physicians, Family/ (8506)
5     1 or 2 or 3 or 4 (83722)
6     exp Breast Neoplasms/ or exp ovarian cancer/ (140349)
7     exp Genetic Predisposition to Disease/ (64428)
8     exp Genetic Screening/ (18587)
9     6 and (7 or 8) (5051)
10    exp Breast Neoplasms/ge or exp ovarian cancer/ge (26159)
11    9 or 10 (26498)
12    5 and 11 (107)
--------------------------------------------------------------------------------

Genetic counseling

Database: Ovid MEDLINE(R) without Revisions <2004 to 2012>
Search Strategy:
--------------------------------------------------------------------------------
Appendix B1. Search Strategies

Prediction of disease occurrence

Database: Ovid MEDLINE(R) without Revisions <2004 to 2012>
Search Strategy:

1 exp Breast Neoplasms/mo, pc, ep, eh or exp ovarian neoplasms/mo, pc, ep, eh (26852)
2 exp GENES, BRCA1/ or exp BRCA1 PROTEIN/ or brca1.mp. (7633)
3 exp GENES, BRCA2/ or exp BRCA2 PROTEIN/ or brca2.mp. (4955)
4 2 or 3 (8589)
5 exp Breast Neoplasms/ge or exp ovarian neoplasms/ge (26159)
6 (sensitivity and specificity).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (248591)
7 exp "Sensitivity and Specificity"/ (297204)
8 risk$.mp. or exp RISK/ (972965)
9 5 and (6 or 7 or 8) (8244)
10 1 and 4 and 9 (1154)

Harms of risk assessment and testing

Database: Ovid MEDLINE(R) without Revisions <2004 to 2012>
Search Strategy:

1 exp Breast Neoplasms/ or exp ovarian neoplasms/ (140349)
2 exp genetic screening/ae or exp genetic services/ae or exp genetic counseling/ae or exp genetic screening/px or exp genetic services/px or genetic counseling/px (1216)
3 exp Breast Neoplasms/ge or exp ovarian neoplasms/ge (26159)
4 exp stress, psychological/ (45845)
5 ((psycholog$ or emotion$ or mental$) adj3 (stress$ or strain$ or burden$ or toll$)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (46774)
**Appendix B1. Search Strategies**

6 exp anxiety/ or anxious$.mp. or anxiet$.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (74486)
7 4 or 5 or 6 (117272)
8 (1 and 2) or (3 and 7) (519)

**General interventions**

Database: Ovid MEDLINE(R) without Revisions <2004 to 2012>
Search Strategy:

1 exp Breast Neoplasms/nu, pc, dh, rt, dt, rh, su, th, tr or exp ovarian Neoplasms/nu, pc, dh, rt, dt, rh, su, th, tr (64932)
2 exp Treatment Outcome/ or treatment outcome$.mp. (481071)
3 exp "Outcome Assessment (Health Care)="/ or outcome assessment$.mp. (506781)
4 1 or 2 or 3 (568295)
5 exp Breast Neoplasms/mo, ep, eh or exp ovarian Neoplasms/mo, ep, eh (21305)
6 exp Breast Neoplasms/ or exp ovarian neoplasms/ (140349)
7 exp MORTALITY/ or mortal$.mp. or mortality.fs. (447369)
8 exp INCIDENCE/ or incidence$.mp. or epidemiology.fs. or ethnology.fs. (866897)
9 7 or 8 (1173771)
10 6 and 9 (32386)
11 5 or 10 (32386)
12 exp RISK/ (521470)
13 risk$.mp. (946578)
14 exp Genetic Predisposition to Disease/ or genetic predisposition to disease$.mp. (64440)
15 pedigree.mp. or exp PEDIGREE/ (35569)
16 12 or 13 or 14 or 15 (1034441)
17 exp Breast Neoplasms/ge or exp ovarian neoplasms/ge (26159)
18 exp GENES, BRCA1/ or exp BRCA1 PROTEIN/ or brca1.mp. (7633)
19 exp GENES, BRCA2/ or exp BRCA2 PROTEIN/ or brca2.mp. (4955)
20 17 or 18 or 19 (29475)
21 4 and 11 and 16 and 20 (769)

**Harms of interventions**

Database: Ovid MEDLINE(R) without Revisions <2004 to 2012>
Search Strategy:

1 exp Breast Neoplasms/dt, su or exp ovarian neoplasms/dt, su (44424)
Appendix B1. Search Strategies

2  exp Breast Neoplasms/pc or exp ovarian neoplasms/pc (7801)
3  chemoprevention.mp. or exp CHEMOPREVENTION/ (14341)
4  primary prevention.mp. or exp Primary Prevention/ (52812)
5  2 or 3 or 4 (73750)
6  postoperative complications.mp. or exp Postoperative Complications/ (194521)
7  intraoperative complications.mp. or exp Intraoperative Complications/ (23574)
8  ae.xs. or ct.fs. (11782)
9  exp stress, psychological/ (45845)
10  ((psycholog$ or emotion$ or mental$) adj3 (stress$ or strain$ or burden$ or toll)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (46774)
11  ((psycholog$ or emotion$ or mental$) adj3 (stress$ or strain$ or burden$ or fear$ or toll)).mp. (47508)
12  exp anxiety/ or anxiet$.mp. or anxious$.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (74486)
13  9 or 10 or 11 or 12 (117833)
14  6 or 7 or 8 or 13 (337084)
15  1 and 5 and 14 (49)

BRCA studies

Database: Ovid MEDLINE(R) without Revisions <2004 to 2012>
Search Strategy:
--------------------------------------------------------------------------------
1  exp case control studies/ (417789)
2  brca$.mp. (8951)
3  1 and 2 (663)
4  exp breast neoplasms/ (113859)
5  exp ovarian neoplasms/ (30269)
6  4 or 5 (140349)
7  3 and 6 (578)

Prediction models

Database: Ovid MEDLINE(R) without Revisions <2004 to 2012>
Search Strategy:
--------------------------------------------------------------------------------
Appendix B1. Search Strategies

1 (gail adj model$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (120)
2 (claus adj model$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (23)
3 1 or 2 (135)
4 exp Models, Statistical/ (183287)
5 exp risk/ (521470)
6 exp Breast Neoplasms/ge [Genetics] (21383)
7 4 and 5 and 6 (487)
8 3 or 7 (613)
9 limit 8 to humans (613)
10 limit 9 to abstracts (584)
11 limit 9 to english (601)
12 10 or 11 (613)

Prophylactic surgery interventions

Database: Ovid MEDLINE(R) without Revisions <2004 to 2012>
Search Strategy:

--------------------------------------------------------------------------------
1 exp Breast Neoplasms/pc [Prevention & Control] (7136)
2 exp Ovarian Neoplasms/pc [Prevention & Control] (1016)
3 (mastectom$ or oophoectom$ or ovariectom$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (27586)
4 1 or 2 (7801)
5 3 and 4 (872)
6 (family adj5 histor$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (26320)
7 exp Genetic Predisposition to Disease/ (64428)
8 brca.mp. (1378)
9 (brca1 or brca2).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (8589)
10 6 or 7 or 8 or 9 (93492)
11 5 and 10 (488)
12 limit 11 to human (488)
Appendix B1. Search Strategies

13     limit 12 to english language (446)
14     limit 12 to abstracts (380)
15     13 or 14 (479)

Tamoxifen and raloxifene

Database: Ovid MEDLINE(R) without Revisions <2004 to 2012>
Search Strategy:

--------------------------------------------------------------------------------
1     exp Breast Neoplasms/pc [Prevention & Control] (7136)
2     exp Ovarian Neoplasms/pc [Prevention & Control] (1016)
3     1 or 2 (7801)
4     (family adj5 histor$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (26320)
5     exp Genetic Predisposition to Disease/ (64428)
6     brca.mp. (1378)
7     (brca1 or brca2).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (8589)
8     4 or 5 or 6 or 7 (93492)
9     exp Selective Estrogen Receptor Modulators/ (12837)
10     (serm or serms or tamoxifen or raloxifene).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (14849)
11     9 or 10 (16490)
12     3 and 8 and 11 (153)
13     exp Contraceptives, Oral/ (13048)
14     3 and 8 and 13 (54)
15     12 or 14 (195)
16     limit 15 to humans (195)
17     limit 16 to abstracts (166)
18     limit 16 to english (176)
19     17 or 18 (191)
### Appendix B2. Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic adult (age 18 years or older) women with a family history of breast and/or ovarian cancer</td>
<td>Men, children, women with prior history of breast and/or ovarian cancer, no family history of breast and/or ovarian cancer</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td></td>
</tr>
<tr>
<td>Risk assessment, genetic counseling, and genetic testing for deleterious BRCA1 or BRCA2 mutations, interventions primarily aimed at reducing the risk of BRCA-related cancer in women with deleterious mutations: intensive screening (e.g., earlier and more frequent mammography, breast magnetic resonance imaging), use of medications (e.g., tamoxifen, raloxifene), and risk-reducing surgery (e.g., mastectomy, oophorectomy)</td>
<td>Surveillance, referral practices, testing for polymorphisms</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>Invasive breast cancer, invasive ovarian cancer, other BRCA-related cancer (fallopian tube, peritoneal), mortality (all cause, cancer-specific). Harms include inaccurate risk assessment; inappropriate testing; false-positive and false-negative results; adverse impact on the patient’s relationships with family; false reassurance; incomplete testing; misinterpretation of the test result; anxiety; cancer worry; immediate and long-term harms associated with breast imaging, risk-reducing medications, and risk-reducing surgery; and ethical, legal, and social implications</td>
<td>Increased detection, predictors of adherence, uptake of screening or risk-reducing interventions</td>
</tr>
<tr>
<td><strong>Study types and designs</strong></td>
<td></td>
</tr>
<tr>
<td>Randomized, controlled trials; prospective and retrospective cohort studies; case-control studies; cross-sectional studies (for harms); systematic reviews; and meta-analyses</td>
<td>Case reports</td>
</tr>
</tbody>
</table>
Appendix B3. U.S. Preventive Services Task Force Quality Rating Criteria

Randomized, Controlled Trials (RCTs) and Cohort Studies

Criteria:

- Initial assembly of comparable groups: RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Studies will be graded “fair” if any or all of the following problems occur, without the important limitations noted in the “poor” category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Studies will be graded “poor” if any of the following major limitations exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Case Control Studies

Criteria:

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variable

Definition of ratings based on criteria above:

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than
Appendix B3. U.S. Preventive Services Task Force Quality Rating Criteria

80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.

**Fair:** Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate less than 80 percent or attention to some but not all important confounding variables.

**Poor:** Major selection or diagnostic work-up biases, response rates less than 50 percent, or inattention to confounding variables.

**Systematic Reviews**

**Criteria:**
- Search dates reported?
- Search methods reported?
- Comprehensive search?
- Inclusion criteria reported?
- Selection bias avoided?
- Validity criteria reported?
- Validity assessed appropriately?
- Methods used to combine studies reported?
- Findings combined appropriately?
- Conclusions supported by data?

**Definitions of ratings based on above criteria:**

**Good:** Meets all criteria: reports comprehensive and reproducible search methods and results; reports pre-defined criteria to select studies and reports reasons for excluding potentially relevant studies; adequately evaluates quality of included studies and incorporates assessments of quality when synthesizing data; reports methods for synthesizing data and uses appropriate methods to combine data qualitatively or quantitatively; conclusions supported by the evidence reviewed.

**Fair:** Studies will be graded fair if they fail to meet one or more of the above criteria, but the limitations are not judged as being major.

**Poor:** Studies will be graded poor if they have a major limitation in one or more of the above criteria.

**Source:** Harris et al, 2001^{100}
Appendix B4. List of Reviewers

**Expert reviewers**

**Bruce Nedrow Calogne, M.D., M.P.H.**, President and CEO, Colorado Trust; Chair, Centers for Disease Control and Prevention Evaluating Genomic Applications for Practice and Prevention (EGAPP) Workgroup; Associate Professor of Family Medicine, Department of Family Medicine, University of Colorado Denver School of Medicine (UCD) and Associate Professor of Preventive Medicine and Biometrics, UCD Colorado School of Public Health

**Kelly Metcalfe, R.N., Ph.D.**, Associate Professor, Lawrence S. Bloomberg Faculty of Nursing, University of Toronto

**Steven Narod, M.D.**, Senior Scientist, Women’s College Research Institute; Director, Familial Breast Cancer Research Unit, Women’s College Research Institute; Professor, Dalla Lana School of Public Health, University of Toronto; Professor, Department of Medicine, University of Toronto; Tier 1 Canada Research Chair in Breast Cancer

**Mark Robson, M.D.**, Clinical Director, Clinical Genetics Service, Memorial Sloan Kettering Cancer Center

**Federal reviewers**

**Joseph Chin, M.D.**, Office of Clinical Standards and Quality, Centers for Medicare and Medicaid Services

**Mark H. Greene, M.D.**, Chief, Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health

**Katherine Kolor, Ph.D.**, Office of Public Health Genomics, Centers for Disease Control and Prevention

**Jacqueline Miller, M.D.**, Office of Public Health Genomics, Centers for Disease Control and Prevention
Appendix B5. Literature Flow Diagram

Abstracts of potentially relevant articles identified through MEDLINE, Cochrane*, and other sources† (n = 5268)

Excluded abstracts (n = 3668)

Full-text articles reviewed for relevance to key questions (n = 1600)

Excluded full-text articles (n = 1460)

Final included articles‡§: 140

KQ 1a 0
KQ 2a 10
KQ 2c 70
KQ 3c 14
KQ 4 7
KQ 5 13

KQs 2b & 3b 27
KQ 3a 0
KQ 3b 27
KQ 4 7
KQ 5 13

*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
†Identified from reference lists, hand searching, and suggestions by experts.
‡Studies that provided data and contributed to the body of evidence were considered “included.”
§Studies may contribute data to more than one key question.

Abbreviation: KQ = key question.
Appendix B6. Excluded Studies List

Key to exclusion codes

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Background</td>
</tr>
<tr>
<td>3</td>
<td>Wrong population</td>
</tr>
<tr>
<td>4</td>
<td>Wrong intervention</td>
</tr>
<tr>
<td>5</td>
<td>Wrong publication type</td>
</tr>
<tr>
<td>6</td>
<td>Conducted prior to 2004</td>
</tr>
<tr>
<td>7</td>
<td>Foreign language study, otherwise included</td>
</tr>
<tr>
<td>8</td>
<td>Wrong outcome</td>
</tr>
</tbody>
</table>

Myriad Genetic Laboratories, Inc.
Exclusion code: 2

Exclusion code: 2

*Tarasoff v. Regents of the University of California* 551 P.2d 334, Supreme Court of California 1976
Exclusion code: 5

Exclusion code: 2

FL recognizes duty to warn patient of transmissibility of genetic disease to child - *Pate v. Threlkel*, 661 So.2d 278 (Fla. 1995), rehearing denied (Oct 10, 1995), Supreme Court of Florida 1995
Exclusion code: 5

Exclusion code: 2

Exclusion code: 5

Exclusion code: 5

*Molloy v. Meier*, C9 02 1821 C2 02 1837 C9 02 1821 C2 02 1837 C2 02 1837, Court Appeals of Minnesota 2003
Exclusion code: 5

*Genetic susceptibility to breast and ovarian cancer: Assessment, counseling and testing guidelines*: New York State Department of Health; 2004
Exclusion code: 2

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Appendix B6. Excluded Studies List

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 2

Exclusion code: 5

Exclusion code: 3

Exclusion code: 3

Exclusion code: 5

Exclusion code: 5

Exclusion code: 8

Exclusion code: 8

Exclusion code: 5

Exclusion code: 8

Exclusion code: 8

Exclusion code: 5

Appendix B6. Excluded Studies List

Exclusion code: 5

Exclusion code: 2

Exclusion code: 5

Exclusion code: 4

Exclusion code: 3

Exclusion code: 3

Exclusion code: 8

Exclusion code: 5

Exclusion code: 5

Altschuler A, Somkin CP. Women's decision making about whether or not to use breast cancer chemoprevention. _Women Health._ 2005;41(2):81-95, [PMID: 16219589]  
Exclusion code: 8

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

American Congress of Obstetricians and Gynecologists, ACOG Committee on Practice Bulletins--Gynecology. ACOG Committee on Genetics, Society of Gynecologic Oncologists. ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. _Obstet._
Appendix B6. Excluded Studies List

Exclusion code: 5
Exclusion code: 2
Exclusion code: 5
Exclusion code: 2
Exclusion code: 3
Exclusion code: 3
Exclusion code: 5
Exclusion code: 3
Exclusion code: 4
Exclusion code: 8
Exclusion code: 2
Exclusion code: 3
Exclusion code: 8
Andrykowski MA, Boerner LM, Salsman JM, Pavlik E. Psychological Response to Test Results in an Ovarian Cancer Screening Program: A Prospective, Longitudinal Study. Health Psychol. 2004;23(6):622-630, [PMID: 15546230]
Exclusion code: 3
Exclusion code: 3
Appendix B6. Excluded Studies List

Exclusion code: 3

Exclusion code: 5

Exclusion code: 4

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 8

Exclusion code: 6

Exclusion code: 5

Arason A, Jonasdottir A, Barkardottir RB, et al. A population study of mutations and LOH at breast cancer gene loci in tumours from sister pairs: two recurrent mutations seem to account
Appendix B6. Excluded Studies List

Exclusion code: 2

Exclusion code: 3

Exclusion code: 3

Exclusion code: 8

Exclusion code: 3

Exclusion code: 6

Exclusion code: 8

Exclusion code: 5

Exclusion code: 3

Exclusion code: 6

Exclusion code: 3

Exclusion code: 5

Exclusion code: 4

Exclusion code: 5

Exclusion code: 3
Appendix B6. Excluded Studies List


Appendix B6. Excluded Studies List

Exclusion code: 4
Exclusion code: 8
Exclusion code: 3
Exclusion code: 5
Exclusion code: 8
Exclusion code: 2
Exclusion code: 2
Exclusion code: 2
Exclusion code: 3
Exclusion code: 2
Exclusion code: 3
Exclusion code: 2
Exclusion code: 3
Exclusion code: 5
Exclusion code: 8
Baxter NN, Goodwin PJ, McLeod RS, Dion R, Devins G, Bombardier C. Reliability and
Exclusion code: 2

Exclusion code: 5

Exclusion code: 2

Exclusion code: 8

Exclusion code: 5

Exclusion code: 2

Exclusion code: 3

Exclusion code: 8

Exclusion code: 5

Screening for ovarian cancer: a systematic review (Structured abstract). 2012.
Exclusion code: 5

Exclusion code: 2

Exclusion code: 2

Exclusion code: 5

Exclusion code: 4

Exclusion code: 3

Bennett P, Phelps C, Brain K, Hood K, Gray J. A randomized controlled trial of a brief self-help coping intervention designed to reduce distress when awaiting genetic risk information. *J.*
Appendix B6. Excluded Studies List

Psychosom. Res. 2007;63(1):59-64, [PMID: 17586338]
Exclusion code: 3

Exclusion code: 8

Exclusion code: 8

Exclusion code: 3

Exclusion code: 5

Exclusion code: 8

Exclusion code: 5

Exclusion code: 2

Exclusion code: 5

Exclusion code: 6

Exclusion code: 6

Exclusion code: 8

Exclusion code: 8

Exclusion code: 2
Appendix B6. Excluded Studies List


Bober SL, Hoke LA, Duda RB, Regan MM, Tung NM. Decision-making about tamoxifen in women at high risk for breast cancer: clinical
Appendix B6. Excluded Studies List

Exclusion code: 8

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 8

Exclusion code: 2

Exclusion code: 3

Cancer Inst.* 2006;98(17):1172-1173, [PMID: 16954464]
Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 2
Appendix B6. Excluded Studies List


Brandt A, Lorenzo Bermejo J, Sundquist J, Hemminki K. Breast cancer risk in women who
Appendix B6. Excluded Studies List


Appendix B6. Excluded Studies List


Burke W, Daly M, Garber JE, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2, Cancer
Appendix B6. Excluded Studies List

Exclusion code: 2

Exclusion code: 5

Exclusion code: 7

Exclusion code: 5

Exclusion code: 3

Exclusion code: 3

Exclusion code: 4

Exclusion code: 6

Exclusion code: 3

Exclusion code: 2

Exclusion code: 3

Exclusion code: 3

Exclusion code: 2

Exclusion code: 5

Exclusion code: 3

Cameron LD, Reeve J. Risk perceptions, worry, and attitudes about genetic testing for breast cancer, Lung, Colorectal and Ovarian (PLCO) cancer screening randomized controlled trial. *Pacific Northwest EPC*
Appendix B6. Excluded Studies List


Casey WJ, 3rd, Rebecca AM, Andres LA, et al. Safety and efficacy of perforator flap breast...
Exclusion code: 3

Exclusion code: 5

Exclusion code: 3

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

What is the impact of genetic counselling in women at increased risk of developing hereditary breast cancer: a meta-analytic review (Provisional abstract). 2012.

Exclusion code: 5

Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer (Structured abstract). 2012.
Exclusion code: 5

A systematic review of the effectiveness of magnetic resonance imaging (MRI) as an addition to mammography and ultrasound in screening young women at high risk of breast cancer (Structured abstract). 2012.
Exclusion code: 5

Exclusion code: 5

Exclusion code: 6

Exclusion code: 6

Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis (Provisional abstract). 2012.
Appendix B6. Excluded Studies List

Exclusion code: 2

Exclusion code: 3

Magnetic resonance imaging of the breast in screening women considered to be at high genetic risk of breast cancer (Provisional abstract). 2012.
Exclusion code: 2

Interventions to improve risk communication in clinical genetics: systematic review (Structured abstract). 2012.
Exclusion code: 8

Impact of gene expression profiling tests on breast cancer outcomes (Provisional abstract). 2012.
Exclusion code: 5

Diagnostic accuracy of methods for the detection of BRCA1 and BRCA2 mutations: a systematic review (Structured abstract). 2012.
Exclusion code: 8

Cancer surveillance based on imaging techniques in carriers of BRCA1/2 gene mutations: a systematic review (Structured abstract). 2012.
Exclusion code: 5

Body image after bilateral prophylactic mastectomy: an integrative literature review (Structured abstract). 2012.
Exclusion code: 5

Comparative effectiveness of screening and prevention strategies among BRCA1/2-affected mutation carriers (Structured abstract). 2012.
Exclusion code: 5

Exclusion code: 5

Genetic nurse counsellors can be an acceptable and cost-effective alternative to clinical geneticists for breast cancer risk genetic counselling: evidence from two parallel randomised controlled equivalence trials (Structured abstract). 2012.
Exclusion code: 5

Exclusion code: 5

Prevention with tamoxifen or other hormones versus prophylactic surgery in BRCA1/2-positive women: a decision analysis (Structured...
Appendix B6. Excluded Studies List

Exclusion code: 5

Exclusion code: 5

Exclusion code: 3

Exclusion code: 5

Exclusion code: 5

Exclusion code: 3

Exclusion code: 3

Exclusion code: 2

Exclusion code: 5

Exclusion code: 8

Chappuis PO. [Breast cancer screening different from that used for the general population: who is concerned and with which approach?]. Rev Med Suisse. 2006;2(66):1296-1298, 1301-1292, 1304-1295, [PMID: 16775990]
Exclusion code: 7

Exclusion code: 8

Exclusion code: 3

Exclusion code: 8

Chen L, Hsu L, Malone K. A frailty-model-based approach to estimating the age-dependent penetrance function of candidate genes using population-based case-control study designs: an application to data on the BRCA1 gene.
Appendix B6. Excluded Studies List

**Biometrics.** 2009;65(4):1105-1114, [PMID: 19210733]
Exclusion code: 5

Exclusion code: 5

Exclusion code: 4

Exclusion code: 8

Exclusion code: 8

Exclusion code: 2

Exclusion code: 8

Exclusion code: 3

Exclusion code: 2

Exclusion code: 8

Exclusion code: 3

Exclusion code: 8

Exclusion code: 8

Exclusion code: 5

Appendix B6. Excluded Studies List

Exclusion code: 2


Exclusion code: 2


Exclusion code: 3


Exclusion code: 7


Exclusion code: 8


Exclusion code: 4


Exclusion code: 5


Exclusion code: 2


Exclusion code: 2


Exclusion code: 6


Exclusion code: 5


Exclusion code: 6

Collier R. Young women with breast cancer genes face tough choices. CMAJ. 2012;184(8):E401-402, [PMID: 22508975]

Exclusion code: 5


Exclusion code: 4

Appendix B6. Excluded Studies List

Exclusion code: 2

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 5

Exclusion code: 2

Exclusion code: 2

Exclusion code: 5

Exclusion code: 2

Exclusion code: 7

Exclusion code: 8

Exclusion code: 2

Exclusion code: 5

Exclusion code: 3

Exclusion code: 5
Appendix B6. Excluded Studies List

Exclusion code: 3

Exclusion code: 2

Exclusion code: 5

Exclusion code: 8

Exclusion code: 8

Exclusion code: 8

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 8

Exclusion code: 2

Exclusion code: 7

Exclusion code: 7

Exclusion code: 2

Exclusion code: 2

Cypowyj C, Eisinger F, Huwart L, Sobol H, Morin M, Julian-Reynier C. Subjective interpretation of inconclusive BRCA1/2 cancer genetic test results and transmission of
Appendix B6: Excluded Studies List

Exclusion code: 3

Exclusion code: 8

Exclusion code: 8

Exclusion code: 8

Exclusion code: 5

Exclusion code: 5

Exclusion code: 3

Exclusion code: 7

Exclusion code: 7

Exclusion code: 2

Exclusion code: 5

Exclusion code: 2

Exclusion code: 2

Exclusion code: 5

Exclusion code: 5

Exclusion code: 7
Appendix B6. Excluded Studies List

Exclusion code: 5

Exclusion code: 4

Exclusion code: 5

Exclusion code: 5

Exclusion code: 2

Exclusion code: 2

Exclusion code: 8

Exclusion code: 2

Exclusion code: 3

Exclusion code: 3

Exclusion code: 6

Exclusion code: 7

Exclusion code: 5

Exclusion code: 8

Appendix B6. Excluded Studies List

Exclusion code: 3

Exclusion code: 8

Exclusion code: 5

Exclusion code: 2

Exclusion code: 2

Exclusion code: 5

Exclusion code: 2

Exclusion code: 5

Exclusion code: 3

Exclusion code: 8

Exclusion code: 5

Exclusion code: 3

Exclusion code: 5

Exclusion code: 5

Appendix B6. Excluded Studies List

Exclusion code: 5

Exclusion code: 5

Exclusion code: 2

Exclusion code: 5

Domchek SM, Rebbeck TR. Preventive surgery is associated with reduced cancer risk and mortality in women with BRCA1 and BRCA2 mutations. *LDI Issue Brief.* 2010;16(2):1-4, [PMID: 21545057]
Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 6

Exclusion code: 8

Exclusion code: 3

Exclusion code: 3

Exclusion code: 8

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3
Appendix B6. Excluded Studies List


Dyer C. US Supreme Court is asked to rule on validity of patents on BRCA1 and BRCA2 genes. *BMJ.* 2012;345:e6624, [PMID: 23033368] Exclusion code: 2


Appendix B6. Excluded Studies List

Exclusion code: 5

Exclusion code: 8

Personalised risk communication for informed decision making about taking screening tests. 2011.
Exclusion code: 5

Exclusion code: 8

Exclusion code: 5

Exclusion code: 3

Exclusion code: 6

Exclusion code: 2

Exclusion code: 3

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 3

Exclusion code: 3
Appendix B6. Excluded Studies List

Exclusion code: 2

Exclusion code: 8

Exclusion code: 2

Exclusion code: 5

Exclusion code: 2

Exclusion code: 2

Exclusion code: 8

Exclusion code: 5

Exclusion code: 8

Exclusion code: 3

Exclusion code: 8

Esserman L, Kaklamani V. Lessons learned from genetic testing. *JAMA.* 2010;304(9):1011-1012, [PMID: 20810382]
Exclusion code: 5

Exclusion code: 5

Exclusion code: 8

Esteban Cardenosa E, Bolufer Gilabert P, de Juan Jimenez I, et al. Relationship of BRCA1...
Appendix B6. Excluded Studies List


Fackenthal JD, Zhang J, Zhang B, et al. High prevalence of BRCA1 and BRCA2 mutations in

BRCA-Related Cancer 170 Pacific Northwest EPC
Exclusion code: 3

Exclusion code: 3

Exclusion code: 8

Exclusion code: 2

Exclusion code: 3

Exclusion code: 3

Exclusion code: 8

Exclusion code: 6

Exclusion code: 5

Exclusion code: 3

Exclusion code: 3

Exclusion code: 2

Exclusion code: 8

Exclusion code: 2
Appendix B6. Excluded Studies List

Exclusion code: 3

The clinical effectiveness and cost-effectiveness of genotyping for CYP2D6 for the management of women with breast cancer treated with tamoxifen: a systematic review (Structured abstract). 2012.
Exclusion code: 3

Exclusion code: 4

Exclusion code: 2

Exclusion code: 2

Exclusion code: 8

Exclusion code: 8

Exclusion code: 8

Exclusion code: 6

Exclusion code: 6

Exclusion code: 2

Exclusion code: 3

Friebel TM, Domchek SM, Neuhausen SL, et al. Bilateral prophylactic oophorectomy and bilateral prophylactic mastectomy in a prospective cohort of unaffected BRCA1 and
Appendix B6. Excluded Studies List

Exclusion code: 8

Exclusion code: 5

Exclusion code: 3

Exclusion code: 5

Exclusion code: 2

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 8

Exclusion code: 3

Exclusion code: 5

Exclusion code: 2

Exclusion code: 8

Exclusion code: 2

Appendix B6. Excluded Studies List

*Cancer Inst.* 2007;99(23):1782-1792, [PMID: 18042936]
Exclusion code: 3

Exclusion code: 2

Exclusion code: 8

Exclusion code: 3

Exclusion code: 3

Exclusion code: 5

Exclusion code: 3

Geirsdal AO, Dahl AA. The relationship between psychological distress and personality in women from families with familial breast/ovarian or hereditary non-polyposis colorectal cancer in the absence of demonstrated mutations. *J Genet Couns.* 2008;17(4):384-393, [PMID: 18607701]
Exclusion code: 8

Exclusion code: 7

Exclusion code: 2

Exclusion code: 7

Exclusion code: 5

Exclusion code: 8

Exclusion code: 5

Exclusion code: 2

Appendix B6. Excluded Studies List


Appendix B6. Excluded Studies List

Exclusion code: 3
Exclusion code: 2

Exclusion code: 4

Exclusion code: 5

Exclusion code: 2

Exclusion code: 5

Exclusion code: 8

Exclusion code: 5

Exclusion code: 2

Exclusion code: 8

Exclusion code: 2

Exclusion code: 2

Exclusion code: 3

Exclusion code: 3

Exclusion code: 2
Appendix B6. Excluded Studies List


Halapy E, Chiarelli AM, Klar N, Knight JA. Accuracy of breast screening among women...
Appendix B6. Excluded Studies List

Exclusion code: 3

Exclusion code: 3

Exclusion code: 8

Exclusion code: 5

Exclusion code: 8

Exclusion code: 3

Exclusion code: 8

Exclusion code: 6

Exclusion code: 3

Exclusion code: 3

Exclusion code: 8

Exclusion code: 5

Exclusion code: 5

Exclusion code: 8

Exclusion code: 2

Exclusion code: 8
Appendix B6. Excluded Studies List

Exclusion code: 3

Exclusion code: 6

Exclusion code: 3

Exclusion code: 3

Exclusion code: 2

Exclusion code: 8

Exclusion code: 2

Exclusion code: 6

Exclusion code: 8

Exclusion code: 4

Exclusion code: 5

Exclusion code: 2

Exclusion code: 4

Exclusion code: 5

Hashemian AH, Hajizadeh E, Kazemnejad A, Atri M, Mehdipour P. Penetration of
Appendix B6. Excluded Studies List

Exclusion code: 3

Exclusion code: 5

Exclusion code: 8

Genetic testing for susceptibility to ovarian cancer (Structured abstract). 2012.
Exclusion code: 5

Breast cancer susceptibility 1 and 2 (BRCA1/2) sequence variant testing for susceptibility to hereditary breast cancer (Structured abstract). 2012.
Exclusion code: 5

Comprehensive screening for large rearrangements in BRCA1/2 for assessment of breast cancer risk (Structured abstract). 2012.
Exclusion code: 5

Exclusion code: 5

BRCA1 and BRCA2 sequence variant analysis for susceptibility to hereditary ovarian cancer (Structured abstract). 2012.
Exclusion code: 5

MammaPrint for prognosis of breast cancer recurrence (Structured abstract). 2012.
Exclusion code: 5

Impact of intensive screening in women with an increased risk of breast cancer because of a familiar predisposition - primary research (Brief record). 2012.
Exclusion code: 5

Mammography in women under 50 by GP in families with hereditary breast cancer - primary research (Brief record). 2012.
Exclusion code: 5

Evaluation of mammographic surveillance services in women under 50 with a family history of breast cancer (Project record). 2012.
Exclusion code: 5

Exclusion code: 3

Heijnsdijk EAM, Warner E, Gilbert FJ, et al. Differences in natural history between breast
Appendix B6. Excluded Studies List


Hopwood P, Howell A, Laloo F, Evans G. Do women understand the odds? Risk perceptions
Appendix B6. Excluded Studies List


Appendix B6. Excluded Studies List

Exclusion code: 3

Exclusion code: 3

Exclusion code: 8

Exclusion code: 8

Exclusion code: 5

Exclusion code: 3

Exclusion code: 2

Exclusion code: 3

Exclusion code: 8

Exclusion code: 4

Exclusion code: 7

Exclusion code: 8

Exclusion code: 2

Exclusion code: 6

Appendix B6. Excluded Studies List

Exclusion code: 5


Appendix B6. Excluded Studies List

Exclusion code: 8

Exclusion code: 7

Exclusion code: 8

Exclusion code: 3

Exclusion code: 8

Exclusion code: 5

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 8

Exclusion code: 3

Exclusion code: 5

Exclusion code: 8

Exclusion code: 5

Exclusion code: 8
Appendix B6. Excluded Studies List


Keogh LA, Hopper JL, Rosenthal D, Phillips K. Australian clinicians and chemoprevention for
Appendix B6. Excluded Studies List

Exclusion code: 3

Exclusion code: 8

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 3

Exclusion code: 3

Exclusion code: 7

Exclusion code: 5

Exclusion code: 7

Exclusion code: 3

King HM. Risk reduction decision making in women with BRCA1/2 gene mutations, King, Heidi M : U South Florida, US; 2009
Exclusion code: 4

Exclusion code: 2

Exclusion code: 5
Appendix B6. Excluded Studies List

Exclusion code: 3

Exclusion code: 8

Exclusion code: 8

Exclusion code: 2

Exclusion code: 8

Exclusion code: 5

Exclusion code: 5

Exclusion code: 8

Exclusion code: 2

Exclusion code: 8

Exclusion code: 5

Exclusion code: 3

Kopans DB. The U.S. Preventive Services Task Force guidelines are not supported by the scientific evidence. *Radiology.* 2010;257(1):294-295; author reply 295, [PMID: 20851947]
Exclusion code: 5

Exclusion code: 5
Appendix B6. Excluded Studies List

Exclusion code: 8

Exclusion code: 2

Exclusion code: 8

Exclusion code: 8

Exclusion code: 8

Kram V, Peretz T, Sagi M. Acceptance of preventive surgeries by Israeli women who had undergone BRCA testing. *Fam Cancer.* 2006;5(4):327-335, [PMID: 16724248]
Exclusion code: 8

Exclusion code: 8

Exclusion code: 2

Exclusion code: 5

Exclusion code: 3

Exclusion code: 8

Exclusion code: 4

Exclusion code: 6

Exclusion code: 7

Appendix B6. Excluded Studies List

Exclusion code: 5


Exclusion code: 2


Exclusion code: 3


Exclusion code: 3


Exclusion code: 3


Exclusion code: 3


Exclusion code: 8


Exclusion code: 5


Exclusion code: 5

Kuusisto KM, Bebel A, Vihtinen M, Schleutker J, Sallinen S. Screening for BRCA1, BRCA2, CHEK2, PALB2, BRIP1, RAD50, and CDH1 mutations in high-risk Finnish BRCA1/2-founder mutation-negative breast and/or ovarian cancer individuals. *Breast Cancer Res.* 2011;13(1), [PMID: 21356067]

Exclusion code: 3


Exclusion code: 3


Exclusion code: 3


Exclusion code: 3


Exclusion code: 3

Kwong A, Ng EKO, Law FBF, et al. High-resolution melting analysis for rapid screening of BRCA2 founder mutations in Southern...
Appendix B6. Excluded Studies List

Exclusion code: 5

Exclusion code: 8

Exclusion code: 8

Exclusion code: 8

Exclusion code: 3

Exclusion code: 5

Exclusion code: 3

Exclusion code: 8

Exclusion code: 3

Exclusion code: 2

Exclusion code: 3

Exclusion code: 8

Exclusion code: 8

Exclusion code: 2

Exclusion code: 8

Appendix B6. Excluded Studies List

Exclusion code: 3

Exclusion code: 8

Exclusion code: 8

Landsbergen KM, Prins JB, Kamm YJL, Brunner HG, Hoogerbrugge N. Female BRCA mutation carriers with a preference for prophylactic mastectomy are more likely to participate an educational-support group and to proceed with the preferred intervention within 2 years. *Fam Cancer*. 2010;9(2):213-220, [PMID: 19967456]
Exclusion code: 8

Exclusion code: 3

Exclusion code: 3

Exclusion code: 8

Exclusion code: 6

Exclusion code: 7

Exclusion code: 5

Exclusion code: 3

Lee E-H, Park SK, Park B, et al. Effect of BRCA1/2 mutation on short-term and long-term...
Appendix B6. Excluded Studies List


Appendix B6. Excluded Studies List


Appendix B6. Excluded Studies List

Exclusion code: 8

Exclusion code: 5

Exclusion code: 8

Exclusion code: 3

Exclusion code: 4

Exclusion code: 5

Exclusion code: 3

Exclusion code: 3

Exclusion code: 5

Exclusion code: 5

Exclusion code: 2

Exclusion code: 5

Exclusion code: 5

Exclusion code: 2

Exclusion code: 8
Exclusion code: 3

Exclusion code: 7

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 3

Exclusion code: 8

Exclusion code: 8

Exclusion code: 3

Exclusion code: 5

Exclusion code: 5

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Appendix B6. Excluded Studies List

Exclusion code: 8

Exclusion code: 3

Exclusion code: 5

Exclusion code: 5

Exclusion code: 3

Exclusion code: 2

Exclusion code: 3

Exclusion code: 8

Exclusion code: 3

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 3

Exclusion code: 2

Exclusion code: 3

Malpas P. The right to remain in ignorance about genetic information--can such a right be
Appendix B6. Excluded Studies List

Exclusion code: 5

Exclusion code: 8

Exclusion code: 8

Exclusion code: 8

Exclusion code: 5

Exclusion code: 3

Exclusion code: 3

Manne S, Audrain J, Schwartz M, Main D, Finch C, Lerman C. Associations between relationship support and psychological reactions of participants and partners to BRCA1 and

Exclusion code: 8

Exclusion code: 2

Exclusion code: 3

Exclusion code: 5

Exclusion code: 3

Impact of gene expression profiling tests on breast cancer outcomes (Structured abstract). 2012.
Exclusion code: 5

Exclusion code: 5

Appendix B6. Excluded Studies List

Exclusion code: 3

Exclusion code: 3

Exclusion code: 7

Exclusion code: 5

Exclusion code: 5

Exclusion code: 2

Exclusion code: 5

Exclusion code: 5

Exclusion code: 8

Exclusion code: 7

Exclusion code: 5

Exclusion code: 2

Exclusion code: 5

Exclusion code: 5

Matthijs G. The European opposition against the BRCA gene patents. Fam Cancer. 2006;5(1):95-102, [PMID: 16528613]
Exclusion code: 5

Exclusion code: 3

Mavaddat N, Barrowdale D, Andrulis I. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). Cancer
Appendix B6. Excluded Studies List

Exclusion code: 2

Exclusion code: 5

Exclusion code: 8

Exclusion code: 5

Exclusion code: 5

A clinical systematic review of BRCA1 and BRCA2 genetic testing for breast and ovarian cancers (Structured abstract). 2012.
Exclusion code: 5

Exclusion code: 5

Exclusion code: 6

Exclusion code: 2

Exclusion code: 3

Exclusion code: 8

Exclusion code: 8

Exclusion code: 8

Exclusion code: 8
Appendix B6. Excluded Studies List


Appendix B6. Excluded Studies List


Miramar MD, Calvo MT, Rodriguez A, et al. Genetic analysis of BRCA1 and BRCA2 in breast/ovarian cancer families from Aragon (Spain): two novel truncating mutations and a large genomic deletion in BRCA1. *Breast
Appendix B6. Excluded Studies List

Exclusion code: 4

Exclusion code: 5

Exclusion code: 8

Exclusion code: 6

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 2

Exclusion code: 2

Exclusion code: 5

Exclusion code: 5


Exclusion code: 5


Exclusion code: 5


Exclusion code: 8


Exclusion code: 3


Exclusion code: 8


Exclusion code: 2


Exclusion code: 8


Exclusion code: 2


Exclusion code: 2


Exclusion code: 2


Exclusion code: 2


Exclusion code: 2


Exclusion code: 5

MRI screening for breast cancer: screening for breast cancer with MRI in genetically high-risk women. Horizon Scanning Prioritising Summary
Appendix B6. Excluded Studies List

Exclusion code: 5

Murday V, Pears R, Ball J, Eeles R, Hodgson S. An audit of screening for familial breast cancer before 50 years in the South Thames Region - Have we got it right? Fam Cancer. 2004;3(1):29-34, [PMID: 15131403]
Exclusion code: 8

Exclusion code: 2

Exclusion code: 3

Exclusion code: 5

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 7

Exclusion code: 5

Exclusion code: 3

Exclusion code: 5

Exclusion code: 3

Exclusion code: 5

Exclusion code: 5

Appendix B6. Excluded Studies List

Exclusion code: 3

Exclusion code: 8

Exclusion code: 4

Exclusion code: 5

Exclusion code: 6


Exclusion code: 2

Exclusion code: 5

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 5
National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast
Appendix B6. Excluded Studies List

Exclusion code: 2

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 3

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 5

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Appendix B6. Excluded Studies List

*Cancer Inst.* 2011;103(9):710-711, [PMID: 21515834]
Exclusion code: 5

Exclusion code: 2

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 2

Exclusion code: 5

Predictive genetic testing for breast and prostate cancer (Structured abstract). 2012.
Exclusion code: 5

Exclusion code: 3

Exclusion code: 4

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 8

O'Doherty K, Suthers GK. Risky communication: pitfalls in counseling about risk, and how to avoid them. *J Genet Couns.* 2007;16(4):409-417, [PMID: 17473963]
Appendix B6. Excluded Studies List

Exclusion code: 5


Exclusion code: 3


Exclusion code: 5


Exclusion code: 5


Exclusion code: 2


Exclusion code: 8


Exclusion code: 8


Exclusion code: 3


Exclusion code: 5


Exclusion code: 5


Exclusion code: 3


Exclusion code: 3


Exclusion code: 3


Exclusion code: 8


Exclusion code: 8

Appendix B6. Excluded Studies List

Exclusion code: 5
Exclusion code: 8
Exclusion code: 5
Exclusion code: 3
Exclusion code: 2
Ozakinci G. Psychological and behavioral outcomes of genetic testing for BRCA1/2 mutations among Ashkenazi Jewish women. New Brunswick, NJ, Rutgers, The State University of New Jersey; 2004
Exclusion code: 8
Exclusion code: 3
Exclusion code: 3
Exclusion code: 3
Exclusion code: 3
Exclusion code: 2
Exclusion code: 3
Exclusion code: 3
Exclusion code: 3
Exclusion code: 4
Exclusion code: 8

Exclusion code: 3

Exclusion code: 5

Exclusion code: 8

Exclusion code: 4

Exclusion code: 8

Patenaude AF. Helping your patients to deal with a predisposition to genetic disease. *JAAPA.* 2009;22(11):68-69, [PMID: 1999182]
Exclusion code: 5

Exclusion code: 5

Exclusion code: 8

Exclusion code: 5

Patenaude AF, Orozco S, Li X, et al. Support needs and acceptability of psychological and peer consultation: attitudes of 108 women who had undergone or were considering prophylactic
Appendix B6. Excluded Studies List

Exclusion code: 4

Exclusion code: 8

Exclusion code: 8

Exclusion code: 2

Exclusion code: 3

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 3

Perry CE. *Managing susceptibility to hereditary breast and ovarian cancer,* Perry, Cynthia E : U San Diego, US; 2006
Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 3
Appendix B6. Excluded Studies List


Pijpe A, Andreiu N, Easton DF, et al. Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations:
Appendix B6. Excluded Studies List

Exclusion code: 3

Exclusion code: 2

Exclusion code: 5

Exclusion code: 8

Exclusion code: 6

Exclusion code: 2

Power TE. *The decision to undergo genetic testing for BRCA1/2 in a community sample of Ashkenazi Jewish women: Coping with the risk of cancer or coping with anticipated emotion?*, Power, Tara E : U Western Ontario, Canada; 2006
Exclusion code: 8

Exclusion code: 2

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 8

Exclusion code: 5

Appendix B6. Excluded Studies List

Exclusion code: 5
Exclusion code: 8
Exclusion code: 4
Exclusion code: 5
Exclusion code: 4
Exclusion code: 5
Exclusion code: 8
Radner LL. *Cancer-free women living with the breast cancer gene mutation: A narrative investigation*, Radner, Lori L : Michigan School of Professional Psychology, US; 2012
Exclusion code: 4
Exclusion code: 2
Exclusion code: 3
Rahm AK. *Direct-to-consumer genetics: Media messages and public perceptions*. Denver: Health and Behavioral Science, University of Colorado Denver; 2010
Exclusion code: 2
Exclusion code: 8
Exclusion code: 2
Exclusion code: 8
Exclusion code: 3
Exclusion code: 4
Rebbeck TR. Prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers. *Eur. J.*
Appendix B6. Excluded Studies List

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 5

Exclusion code: 4

Exclusion code: 8

Exclusion code: 4

Exclusion code: 5

Exclusion code: 3

Exclusion code: 3

Exclusion code: 8

Exclusion code: 3
Appendix B6. Excluded Studies List


Robson M, Offit K. Clinical practice. Management of an inherited predisposition to
Appendix B6. Excluded Studies List

Exclusion code: 5

Exclusion code: 8

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 5

Exclusion code: 8

Exclusion code: 8

Exclusion code: 6

Exclusion code: 3

Exclusion code: 6

Exclusion code: 3

Exclusion code: 8

Exclusion code: 5

Exclusion code: 3

Roussi P, Sherman KA, Miller SM, et al. Identification of cognitive profiles among women considering BRCA1/2 testing through the utilisation of cluster analytic techniques.
Appendix B6. Excluded Studies List


Appendix B6. Excluded Studies List

Exclusion code: 5

Exclusion code: 3

Exclusion code: 5

Exclusion code: 2

Exclusion code: 6

Exclusion code: 5

Exclusion code: 3

Exclusion code: 8

Exclusion code: 3

Exclusion code: 8

Exclusion code: 3

Exclusion code: 2

Exclusion code: 3

Exclusion code: 8


Sheehan J, Sherman KA, Lam T, Boyages J. Regret associated with the decision for breast reconstruction: The association of negative body
Exclusion code: 3

Exclusion code: 5

Exclusion code: 3

Exclusion code: 2

Exclusion code: 3

Exclusion code: 8

Exclusion code: 3

Exclusion code: 8

Exclusion code: 5

Exclusion code: 8

Exclusion code: 7

Exclusion code: 6

Exclusion code: 5

Exclusion code: 4

Slattery ML, Baumgartner KB, Giuliano AR, Byers T, Herrick JS, Wolff RK. Replication of five GWAS-identified loci and breast cancer risk among Hispanic and non-Hispanic white women
Appendix B6. Excluded Studies List


- Spector DJ. *Breast cancer risk, risk perception and lifestyle behaviors among women with a family history of the disease: A mixed-method study*, Pacific Northwest EPC
Appendix B6. Excluded Studies List

Exclusion code: 8

Exclusion code: 8

Exclusion code: 8

Exclusion code: 8

Exclusion code: 7

Exclusion code: 3

Exclusion code: 2

Exclusion code: 8

**Steed L. Further validity and reliability evidence for Beck Hopelessness Scale scores in a nonclinical sample. Educational and Psychological Measurement. 2001;61(2):303-316.**
Exclusion code: 2

**Steele SL. Psychological distress, executive cognitive function and mammography utilization among a high-risk African-American sample, Steele, Sharon Lee: Howard U , US; 2007**
Exclusion code: 4

Exclusion code: 5

Exclusion code: 2

Exclusion code: 3

Exclusion code: 3
Appendix B6. Excluded Studies List


Exclusion code: 5


http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC
Appendix B6. Excluded Studies List

Exclusion code: 3

Exclusion code: 6

Exclusion code: 2

Exclusion code: 5

Exclusion code: 7

Exclusion code: 5

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 6

Exclusion code: 8

Exclusion code: 8

Exclusion code: 2

Appendix B6. Excluded Studies List

Exclusion code: 3


Exclusion code: 2


Exclusion code: 5


Exclusion code: 2


Exclusion code: 8


Exclusion code: 4


Exclusion code: 2


Exclusion code: 2 (included later)


Exclusion code: 2


Exclusion code: 4


Exclusion code: 8


Exclusion code: 8


Exclusion code: 3

Tilburt JC, James KM, Sinicrope PS, et al. Factors influencing cancer risk perception in...
Appendix B6. Excluded Studies List

Exclusion code: 3

Exclusion code: 5

Exclusion code: 8

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 3

Exclusion code: 3

Exclusion code: 8

Exclusion code: 5

Exclusion code: 3

Exclusion code: 5

Exclusion code: 2

Exclusion code: 6
Appendix B6. Excluded Studies List


Vadaparampil ST, Ropka M, Stefanek ME. Measurement of psychological factors associated with genetic testing for hereditary breast...
Exclusion code: 6

Exclusion code: 5

Exclusion code: 8

Exclusion code: 2

Exclusion code: 8

Exclusion code: 8

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 6

Exclusion code: 8

Exclusion code: 6

Exclusion code: 6

Exclusion code: 3

Appendix B6. Excluded Studies List

Exclusion code: 8

Exclusion code: 3

Exclusion code: 5

Exclusion code: 6

Exclusion code: 5

Exclusion code: 5

Exclusion code: 3

Exclusion code: 3

Exclusion code: 5

Exclusion code: 2

Exclusion code: 5

Exclusion code: 8

Exclusion code: 5

Exclusion code: 2

Exclusion code: 2
Appendix B6. Excluded Studies List

Exclusion code: 8

Exclusion code: 4

Vos J, Gomez-Garcia E, Oosterwijk JC, et al. Opening the psychological black box in genetic counseling. The psychological impact of DNA testing is predicted by the counselees' perception, the medical impact by the pathogenic or uninformative BRCA 1/2-result. *Psychooncology*. 2012;21(1):29-42, [PMID: 21072753]
Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 3

Exclusion code: 2

Exclusion code: 2

Exclusion code: 8

Exclusion code: 8

Exclusion code: 8

Exclusion code: 3

Exclusion code: 3
Appendix B6. Excluded Studies List


Appendix B6. Excluded Studies List

Exclusion code: 2

Exclusion code: 3

Exclusion code: 3

Exclusion code: 5

Exclusion code: 8

Exclusion code: 2

Exclusion code: 8

Exclusion code: 8

Exclusion code: 8

Exclusion code: 5

Exclusion code: 3

Exclusion code: 2

Exclusion code: 8

Exclusion code: 3

Exclusion code: 3

Exclusion code: 2
Appendix B6. Excluded Studies List

Exclusion code: 5

Exclusion code: 5

Exclusion code: 8

Exclusion code: 5

Exclusion code: 3

Exclusion code: 8

Exclusion code: 4

Exclusion code: 3

Exclusion code: 2

Exclusion code: 2

Exclusion code: 2

Exclusion code: 3

Exclusion code: 8

Exclusion code: 8
Appendix B6. Excluded Studies List

Exclusion code: 8

Exclusion code: 5

Exclusion code: 4

Exclusion code: 6

Exclusion code: 5

Exclusion code: 6

Exclusion code: 2

Exclusion code: 3

Exclusion code: 5

Exclusion code: 5

Exclusion code: 2
## Appendix C1. Quality Ratings for Randomized, Controlled Trials

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloom et al, 2006 151</td>
<td>Unclear</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bowen et al, 2002 37</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bowen et al, 2004 42</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bowen et al, 2006 152</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Brain et al, 2002 156</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Braithwaite et al, 2005 154</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Burke et al, 2000 58</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cull et al, 1998 39</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cuzick et al, 2002 IBIS-I Trial</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fisher et al, 2005 NSABP P-1 Trial</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes: intervention</td>
<td>Yes: intervention</td>
<td>Yes: after unblinding, 32% crossover from placebo to medication</td>
</tr>
<tr>
<td>Fry et al, 2003 150</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Grady et al, 2008 RUTH Trial</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Helmes et al, 2006 157</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lerman et al, 1996 162</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lerman et al, 1999 66</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lippman et al, 2006 MORE/CORE Trials</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Matloff et al, 2006 160</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Powles et al, 2007 Royal Marsden Trial</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes; after median of 70 months, 58% still on treatment</td>
</tr>
<tr>
<td>Roshanai et al, 2009 164</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## Appendix C1. Quality Ratings for Randomized, Controlled Trials

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Veronesi et al, 2007</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes; 61% completed treatment period</td>
</tr>
<tr>
<td>Vogel et al, 2010</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes: intervention No: followup</td>
<td>Yes: intervention No: followup</td>
<td>Yes</td>
</tr>
<tr>
<td>Watson et al, 1998</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Loss to followup differential/high</th>
<th>Intention-to-treat analysis</th>
<th>Post-randomization exclusions</th>
<th>Outcomes Prespecified</th>
<th>Funding source</th>
<th>External validity</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloom et al, 2006</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Grant 4EB-5800, California Breast Cancer Research Program</td>
<td>Population-based from San Francisco area</td>
<td>Poor</td>
</tr>
<tr>
<td>Bowen et al, 2002</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>National Cancer Institute and National Human Genome Institute (HG01190)</td>
<td>Women in general public with breast cancer</td>
<td>Fair</td>
</tr>
<tr>
<td>Bowen et al, 2004</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>National Human Genome Institute, National Cancer Institute, and National Office for Research on Women’s Health (HG/CA01190)</td>
<td>Women in Seattle area with lower risk of breast cancer</td>
<td>Fair</td>
</tr>
<tr>
<td>Bowen et al, 2006</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>National Human Genome Research Institute (HG01190)</td>
<td>Ashkenazi Jewish women from large metropolitan area</td>
<td>Fair</td>
</tr>
<tr>
<td>Brain et al, 2002</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Medical Research Council, National Assembly for Wales, NHS R&amp;D (Wales), and Imperial Cancer Research Fund (Dr. Gray is supported by Tenovus, a cancer charity)</td>
<td>Cancer clinics, Wales</td>
<td>Good</td>
</tr>
<tr>
<td>Braithwaite et al, 2005</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>CUK (Cancer Research U.K.) (CI345/A169)</td>
<td>Greater London area</td>
<td>Fair</td>
</tr>
</tbody>
</table>
## Appendix C1. Quality Ratings for Randomized, Controlled Trials

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Loss to followup differential/high</th>
<th>Intention-to-treat analysis</th>
<th>Post-randomization exclusions</th>
<th>Outcomes Prespecified</th>
<th>Funding source</th>
<th>External validity</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burke et al, 2000&lt;sup&gt;15&lt;/sup&gt;</td>
<td>No</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>The National Institutes of Health (HGO1190)</td>
<td>Women in Seattle area with intermediate family history of breast cancer</td>
<td>Fair</td>
</tr>
<tr>
<td>Cull et al, 1998&lt;sup&gt;19&lt;/sup&gt;</td>
<td>No/Yes</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>NHS R&amp;D (Cancer) Programme and Imperial Cancer Research Fund</td>
<td>Women from 4 Scottish cancer family clinics</td>
<td>Good</td>
</tr>
<tr>
<td>Cuzick et al, 2007&lt;sup&gt;28&lt;/sup&gt; IBIS-I Trial See also Cuzick, 2002&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>CUK; National Health and Medical Research Council Australia</td>
<td>Women at increased risk for breast cancer; general population and clinic recruitment; United Kingdom, Europe, Australia, New Zealand</td>
<td>Fair</td>
</tr>
<tr>
<td>Fisher et al, 2005&lt;sup&gt;54&lt;/sup&gt; NSABP P-1 Trial See also Fisher et al, 1998&lt;sup&gt;71&lt;/sup&gt;</td>
<td>No/Unclear</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>National Cancer Institute; U.S. Department of Health and Human Services</td>
<td>Women at increased risk for breast cancer; clinical centers; United States and Canada</td>
<td>Fair</td>
</tr>
<tr>
<td>Fry et al, 2003&lt;sup&gt;195&lt;/sup&gt;</td>
<td>No/Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Chief Scientists's Office and Cancer Research U.K.</td>
<td>General population recruitment</td>
<td>Fair</td>
</tr>
<tr>
<td>Grady et al, 2008&lt;sup&gt;13&lt;/sup&gt; RUTH Trial See also Barrett-Connor et al, 2006&lt;sup&gt;299&lt;/sup&gt;</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Eli Lily and Company</td>
<td>Postmenopausal women with history of heart disease or at increased risk of coronary events; multinational sites, including United States</td>
<td>Good</td>
</tr>
<tr>
<td>Helmes et al, 2006&lt;sup&gt;197&lt;/sup&gt;</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>National Human Genome Research Institute</td>
<td>Large network of PCPs</td>
<td>Fair</td>
</tr>
<tr>
<td>Lerman et al, 1996&lt;sup&gt;199&lt;/sup&gt;</td>
<td>No</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>Public Health Service grants ROICA57767 and K07CA01604 from the National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services</td>
<td>Georgetown University Medical Center and Washington Hospital Center</td>
<td>Fair</td>
</tr>
<tr>
<td>Lerman et al, 1999&lt;sup&gt;207&lt;/sup&gt;</td>
<td>No/Yes</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>National Institutes of Mental Health and National Human Genome Research Institute (MH/HG54435)</td>
<td>Cancer treatment centers</td>
<td>Fair</td>
</tr>
<tr>
<td>Lippman et al, 2006&lt;sup&gt;208&lt;/sup&gt; MORE/CORE Trials See also Cummings et al, 1999&lt;sup&gt;74&lt;/sup&gt;</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Costs of publication of this article defrayed in part by payment of page charges; funding source NR</td>
<td>Postmenopausal women with osteoporosis; clinical centers; multinational, including United States</td>
<td>Good</td>
</tr>
</tbody>
</table>
### Appendix C1. Quality Ratings for Randomized, Controlled Trials

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Loss to followup differential/high</th>
<th>Intention-to-treat analysis</th>
<th>Post-randomization exclusions</th>
<th>Outcomes Prespecified</th>
<th>Funding source</th>
<th>External validity</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matloff et al, 2006</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Susan G. Komen Foundation</td>
<td>General population recruitment</td>
<td>Fair</td>
</tr>
<tr>
<td>Powles et al, 2007</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>National Health Service; CUK</td>
<td>Breast cancer clinics in United Kingdom</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td>Royal Marsden Trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>See also Powles et al, 1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roshanai et al, 2009</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Swedish Cancer Society</td>
<td>Cancer genetic clinics</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td>Roshanai et al, 2009</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veronesi et al, 2007</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Italian National Research Council; Italian Foundation for Cancer Research; American-Italian Cancer Foundation; Italian League Against Cancer</td>
<td>Postmenopausal women; general population and clinic recruitment; Italy</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td>Italian Randomized Tamoxifen Prevention Trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>See also Veronesi et al, 1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vogel et al, 2010</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>National Cancer Institute; U.S. Department of Health and Human Services</td>
<td>Postmenopausal women with increased risk of breast cancer; multiple clinical centers; United States and Canada</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td>See also Vogel et al, 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watson et al, 1998</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Cancer Research Campaign (Project CP1026)</td>
<td>Women with a family history of breast cancer attending two London genetic clinics</td>
<td>Good</td>
</tr>
</tbody>
</table>

**Abbreviations:** CORE = Continuing Outcomes Relevant to Evista; CRC = Cancer Research Campaign; CUK = Cancer Research United Kingdom; IBIS-I = International Breast Cancer Intervention Study; MORE = Multiple Outcomes of Raloxifene Evaluation; NHS = National Health Service; NR = not reported; NSABP = National Surgical Adjuvant Breast and Bowel Project P-1; PCPs = primary care physicians; R&D = research and design; RUTH = Raloxifene Use for the Heart; STAR = Study of Tamoxifen and Raloxifene.
### Appendix C2. Quality Ratings for Cohort Studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Attempt to enroll a random sample or consecutive patients meeting inclusion criteria</th>
<th>Groups comparable at baseline</th>
<th>Used accurate methods for ascertaining exposures, potential confounders, and outcomes</th>
<th>Outcome assessors and/or data analysts blinded to treatment</th>
<th>Report attrition</th>
<th>Appropriate statistical analyses on potential confounders</th>
<th>Important differential or overall high loss to followup</th>
<th>Outcomes prespecified, defined, and ascertained using accurate methods</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domchek et al, 2010</td>
<td>Yes</td>
<td>Not reported</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Not reported</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Foster et al, 2007</td>
<td>Unclear</td>
<td>Not reported</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Geirdal et al, 2005</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>Geirdal and Dahl, 2008</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>Hopwood et al, 1998</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Julian-Reynier et al, 2011</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>Kinney et al, 2005</td>
<td>No</td>
<td>Not reported</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Not reported</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Kramer et al, 2005</td>
<td>Yes</td>
<td>Not reported</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Not reported</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Lobb et al, 2004</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>Low et al, 2008</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Meiser et al, 2002</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>Mikkelsen et al, 2007</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Mikkelsen et al, 2009</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Reichelt et al, 2004</td>
<td>Yes</td>
<td>Not reported</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>Rijnsburger et al, 2004</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Unclear: not reported</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Skytte et al, 2011</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>Struwing et al, 1995</td>
<td>Yes</td>
<td>Not reported</td>
<td>Not reported</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Not reported</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>van Dijk et al, 2006</td>
<td>Yes</td>
<td>Not reported</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>Watson et al, 1999</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Good</td>
</tr>
</tbody>
</table>
## Appendix C3. Quality Ratings for Case-Control Studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Did study attempt to enroll all or random sample of cases using predefined criteria?</th>
<th>Were controls derived from the same population as the cases?</th>
<th>Were groups comparable at baseline on key prognostic factors?</th>
<th>Were enrollment rates similar in cases and controls invited to participate?</th>
<th>Did study use accurate methods for identifying outcomes?</th>
<th>Did study use accurate methods for ascertaining exposures and potential confounders?</th>
<th>Did study perform appropriate statistical analyses on potential confounders?</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong et al, 2005&lt;sup&gt;148&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Dagan and Shochat, 2009&lt;sup&gt;237&lt;/sup&gt;, Shochat and Dagan, 2010&lt;sup&gt;248&lt;/sup&gt;</td>
<td>Yes</td>
<td>Unclear</td>
<td>Matched</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
</tr>
</tbody>
</table>
## Appendix C4. Quality Rating for Systematic Review

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Search dates</th>
<th>Search methods reported</th>
<th>Comprehensive search</th>
<th>Inclusion criteria reported</th>
<th>Selection bias avoided</th>
<th>Validity criteria reported</th>
<th>Validity assessed appropriately</th>
<th>Methods used to combine studies reported</th>
<th>Findings combined appropriately</th>
<th>Conclusions supported by data</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smerecnik et al, 2009&lt;sup&gt;165&lt;/sup&gt;</td>
<td>2000 to 2007</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Not reported</td>
<td>No</td>
<td>Not reported</td>
<td>Yes</td>
<td>Fair</td>
</tr>
</tbody>
</table>
## Appendix C5. Familial Risk Assessment Models

### Ontario Family History Assessment Tool (FHAT)\(^{142}\)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast and ovarian cancer</td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>10</td>
</tr>
<tr>
<td>Sibling</td>
<td>7</td>
</tr>
<tr>
<td>2nd/3rd degree relative</td>
<td>5</td>
</tr>
<tr>
<td>Breast cancer relatives</td>
<td></td>
</tr>
<tr>
<td>Parent</td>
<td>4</td>
</tr>
<tr>
<td>Sibling</td>
<td>3</td>
</tr>
<tr>
<td>2nd/3rd degree relative</td>
<td>2</td>
</tr>
<tr>
<td>Male relative (add to above)</td>
<td>2</td>
</tr>
<tr>
<td>Breast cancer characteristics</td>
<td></td>
</tr>
<tr>
<td>Onset age 20-29</td>
<td>6</td>
</tr>
<tr>
<td>Onset age 30-39</td>
<td>4</td>
</tr>
<tr>
<td>Onset age 40-49</td>
<td>2</td>
</tr>
<tr>
<td>Pre (peri) menopausal</td>
<td>2</td>
</tr>
<tr>
<td>Bilateral/multifocal</td>
<td>3</td>
</tr>
<tr>
<td>Ovarian cancer relatives</td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>7</td>
</tr>
<tr>
<td>Sibling</td>
<td>4</td>
</tr>
<tr>
<td>2nd/3rd degree relative</td>
<td>3</td>
</tr>
<tr>
<td>Ovarian cancer onset age</td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>6</td>
</tr>
<tr>
<td>40-60</td>
<td>4</td>
</tr>
<tr>
<td>&gt;60</td>
<td>2</td>
</tr>
<tr>
<td>Prostate cancer onset</td>
<td></td>
</tr>
<tr>
<td>Age &lt;50</td>
<td>1</td>
</tr>
<tr>
<td>Colon cancer onset</td>
<td></td>
</tr>
<tr>
<td>Age &lt;50</td>
<td>1</td>
</tr>
<tr>
<td><strong>Family Total</strong></td>
<td><strong>Referral</strong></td>
</tr>
<tr>
<td></td>
<td>≥10</td>
</tr>
</tbody>
</table>

Referral with score ≥10 corresponds to doubling of lifetime risk for breast cancer (22%).

### Manchester Scoring System\(^{141}\)

<table>
<thead>
<tr>
<th>Risk Factor (age of onset for relative in direct lineage)</th>
<th>BRCA1 Score</th>
<th>BRCA2 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female breast cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>30-39</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>40-49</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>50-59</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>≥60</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Male breast cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>5(^*)</td>
<td>8(^†)</td>
</tr>
<tr>
<td>≥60</td>
<td>5(^*)</td>
<td>5(^†)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>≥60</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>≥60</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total individual genes</strong></td>
<td><strong>10</strong></td>
<td><strong>10</strong></td>
</tr>
<tr>
<td><strong>Total for combined=15</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Probability of ≥10% chance of BRCA1 or BRCA2 mutation individually or combined.

* If BRCA2 tested.

† If BRCA1 tested.
Appendix C5. Familial Risk Assessment Models

**Referral Screening Tool (RST)\textsuperscript{143}**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Breast cancer (\text{age} \leq 50)</th>
<th>Ovarian cancer at any age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yourself</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sister</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daughter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grandmother</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aunt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father’s side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grandmother</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aunt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 cases of breast cancer after age 50 on the same side of the family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male breast cancer at any age in any relative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jewish ancestry</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Referral if ≥2 checks in table.

**Pedigree Assessment Tool (PAT)\textsuperscript{144}**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score for every family member with breast or ovarian cancer diagnosis, including 2nd/3rd degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer at age ≥50</td>
<td>3</td>
</tr>
<tr>
<td>Breast cancer at age &lt;50</td>
<td>4</td>
</tr>
<tr>
<td>Ovarian cancer at any age</td>
<td>5</td>
</tr>
<tr>
<td>Male breast cancer at any age</td>
<td>8</td>
</tr>
<tr>
<td>Ashkenazi Jewish heritage</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

Score ≥8 is the optimal referral threshold.

**FHS-7\textsuperscript{145}**

1. Did any of your 1st degree relatives have breast or ovarian cancer?
2. Did any of your relatives have bilateral breast cancer?
3. Did any man in your family have breast cancer?
4. Did any woman in your family have breast and ovarian cancer?
5. Did any woman in your family have breast cancer before the age of 50 years?
6. Do you have 2 or more relatives with breast and/or ovarian cancer?
7. Do you have 2 or more relatives with breast and/or bowel cancer?

One positive response initiates referral.
<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Subcategory</th>
<th>Purpose</th>
<th>Study type</th>
<th>N</th>
<th>Country</th>
<th>Population/setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong et al, 2005 Good</td>
<td>Cancer worry Attitudes</td>
<td>To assess the association between race and use of genetic counseling for BRCA1/2 testing in women at risk of carrying a BRCA1/2 mutation and to evaluate the potential contributions of socioeconomic characteristics about genetic testing, and interactions with primary care physicians to this association</td>
<td>Case-control</td>
<td>Eligible: NR Enrolled: NR Randomized: NR Analyzed: 408 (217 cases, 191 controls)</td>
<td>U.S.</td>
<td>Visit to University of Pennsylvania Health System Cases: women from reference population who presented for genetic counseling, mean age 42.5 years, 29% Jewish Controls: random sample of women from reference population, mean age 53.1 years, 11% Jewish</td>
</tr>
<tr>
<td>Bennett et al, 2008</td>
<td>Psychological</td>
<td>To examine the relationship between measures of anxiety and depression and a number of variables identified to be associated with distress</td>
<td>Before and after</td>
<td>Eligible: 367 Enrolled: 319 Analyzed: 128</td>
<td>U.K.</td>
<td>Women referred for genetic risk assessment to a large Cancer Genetics Service for Wales (CGSW) center</td>
</tr>
<tr>
<td>Bennett et al, 2009</td>
<td>Cancer worry Psychological</td>
<td>To explore the relationship between a number of factors hypothesized to be associated with the frequency of intrusive worries close to the time women were informed of their genetic risk for developing breast and/or ovarian cancer</td>
<td>Before and after</td>
<td>Eligible: 221 Enrolled: 221 Analyzed: 128</td>
<td>U.K.</td>
<td>Women referred for genetic risk assessment to a large Cancer Genetics Service for Wales (CGSW) center</td>
</tr>
<tr>
<td>Bloom et al, 2006</td>
<td>Risk perception Cancer worry Health behaviors</td>
<td>To compare women in a telephone counseling intervention to controls and determine whether perceived risk would be more consistent with objective risk and whether there would be reduction in breast cancer worries, improvement in health protective behaviors, and an increase in breast cancer screening</td>
<td>RCT</td>
<td>Eligible: NR Enrolled: 163 Randomized: 163 (80 in intervention, 83 in control) Analyzed: 149 (71 in intervention, 78 in control)</td>
<td>U.S.</td>
<td>Sisters of women diagnosed with breast cancer at age ≤50; predominantly Euro-American and well educated; substantial majority receive regular breast cancer screening</td>
</tr>
<tr>
<td>Bowen et al, 2006</td>
<td>Risk perception Cancer worry Interest in genetic testing</td>
<td>To test the efficacy of 2 counseling methods in Ashkenazi Jewish women with average or moderately increased risk of breast cancer</td>
<td>RCT</td>
<td>Eligible: 347 Enrolled: 221 Randomized: 221 (68 to psychosocial counseling, 77 to genetic counseling, 75 to control) Analyzed: 96% followup rate</td>
<td>U.S.</td>
<td>Ashkenazi Jewish women from the greater Seattle area; mean age of 47 years; 100% Ashkenazi Jewish</td>
</tr>
</tbody>
</table>
### Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Subcategory</th>
<th>Purpose</th>
<th>Study type</th>
<th>N</th>
<th>Country</th>
<th>Population/setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain et al, 2011 NA</td>
<td>Cancer worry</td>
<td>To provide 6-year followup on women in TRACE study and the predictors of long-term cancer worry, perceived risk, and health behaviors</td>
<td>Before and after</td>
<td>Eligible: 545 Enrolled: 384 Analyzed: 263</td>
<td>U.K.</td>
<td>Women who took part in the TRACE study</td>
</tr>
<tr>
<td>Braithwaite et al, 2005 Fair</td>
<td>Risk perception</td>
<td>To examine the acceptability of the GRACE prototype to women with a family history of breast cancer and test the hypothesis that GRACE would perform as well as the nurse counselor at improving women’s risk perceptions without causing adverse emotional reactions</td>
<td>RCT</td>
<td>Eligible: 89 Enrolled: 72 Randomized: 72 (38 to GRACE, 34 to clinical nurse specialist) Analyzed: 58</td>
<td>U.K.</td>
<td>Women with a family history of breast cancer recruited through newspaper ads and posters</td>
</tr>
<tr>
<td>Fry et al, 2003 Fair</td>
<td>Perceived risk Cancer worry</td>
<td>To compare the psychological outcomes of 2 models of breast cancer genetics services</td>
<td>RCT</td>
<td>Eligible: 574 Enrolled: 373 Analyzed: 244</td>
<td>Scotland</td>
<td>Women referred by GP for breast cancer genetic risk counseling</td>
</tr>
<tr>
<td>Gurmankin et al, 2005 NA</td>
<td>Risk perception</td>
<td>To examine the risk perception derived from a risk communication with a health care provider during genetic counseling for breast cancer and BRCA1/2 mutation risks</td>
<td>Before and after</td>
<td>Eligible: NR Enrolled: 58 Analyzed: NR</td>
<td>U.S.</td>
<td>New patients at university cancer evaluation program; mean age of 46 years; most were white and had some college education or more</td>
</tr>
<tr>
<td>Helmes et al, 2006 Fair</td>
<td>Cancer worry Risk perception</td>
<td>To assess whether women participating in either in-person or telephone counseling sessions would have a more accurate perception of their personal breast cancer risk, increase their intentions for breast screening, have reduced levels of cancer worry, and have less interest in genetic testing</td>
<td>RCT</td>
<td>Eligible: 898 Enrolled: 340 Randomized: 340 (104 to the in-person arm, 121 to the telephone arm, 115 to control) Analyzed: 335 (102 in the in-person arm, 119 in the telephone arm, 114 control arm)</td>
<td>U.S.</td>
<td>Physicians network in Washington Mean age, 40.7 years</td>
</tr>
<tr>
<td>Hopwood et al, 2004 NA</td>
<td>Cancer worry Psychological factors</td>
<td>To assess changes in risk perception, psychological distress, health care behaviors, and use of health care resources; to assess satisfaction with services, to describe regional variations in outcomes</td>
<td>Before and after</td>
<td>Eligible: 271 Enrolled: 256 Analyzed: 234 (1 month), 202 (12 month), 192 (precounsel, 1 and 12 months)</td>
<td>U.K.</td>
<td>Cancer genetic services centers Age range, 49-52 years</td>
</tr>
<tr>
<td>Author, year Quality</td>
<td>Subcategory</td>
<td>Purpose</td>
<td>Study type</td>
<td>N</td>
<td>Country</td>
<td>Population/setting</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>---------</td>
<td>------------</td>
<td>---</td>
<td>---------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Kelly et al, 2008159\ NA</td>
<td>Risk perception</td>
<td>To examine change in subjective risk of ovarian cancer over time in response to genetic counseling and testing in the short- and long-term; discrepancy between subjective and objective estimates of ovarian cancer risk; and new methods for conceptualizing subjective risk derived from the Common Sense Model</td>
<td>Before and after</td>
<td>Eligible: 78 Enrolled: 78 (40 to no personal history of breast cancer, 38 to personal history) Analyzed: NR</td>
<td>U.S.</td>
<td>Women were recruited from the community Mean age, 48.64 years</td>
</tr>
<tr>
<td>Matloff et al, 2006160 Fair</td>
<td>Risk perception</td>
<td>To examine if a personalized risk assessment and genetic counseling intervention would affect knowledge, risk perception, and decisionmaking in a group of women who had 1 FDR with breast cancer compared with a control group</td>
<td>RCT</td>
<td>Eligible: NR Enrolled: NR Randomized: 64 (32 in each group) Analyzed: 54 completed 1 month followup (28 control and 26 intervention), 48 completed 6 month followup (25 control and 23 intervention)</td>
<td>U.S.</td>
<td>Women recruited through advertisements in New Haven, CT</td>
</tr>
<tr>
<td>Mikkelsen et al, 2007161 Fair</td>
<td>Risk perception</td>
<td>To explore the impact of genetic counseling on perceived personal lifetime risk of breast cancer, the accuracy of risk perception, and possible predictors of inaccurate risk perception 1 year following counseling</td>
<td>Prospective cohort</td>
<td>Eligible: 3257 (568 in counseling group, 689 in reference group 1, 2000 in reference group 2) Enrolled: 1971 (319 in counseling group, 381 in comparison group 1, and 1271 in group 2) Analyzed: 1602 (213 in counseling group, 319 in comparison group 1, and 1070 in group 2)</td>
<td>Denmark</td>
<td>Danish women at risk of hereditary breast and ovarian cancer</td>
</tr>
<tr>
<td>Mikkelsen et al, 2009162 Fair</td>
<td>Psychological factors Cancer worry Quality of life changes</td>
<td>To clarify the psychosocial impact of genetic counseling for hereditary breast and ovarian cancer</td>
<td>Prospective cohort</td>
<td>Eligible: 3257 (568 in counseling group, 689 in reference group 1, 2000 in reference group 2) Enrolled: 1971 (319 in counseling group, 381 in comparison group 1, and 1271 in group 2) Analyzed: 1602 (213 in counseling group, 319 in comparison group 1, and 1070 in group 2)</td>
<td>Denmark 2007</td>
<td>Danish women at risk of hereditary breast and ovarian cancer</td>
</tr>
</tbody>
</table>
## Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Subcategory</th>
<th>Purpose</th>
<th>Study type</th>
<th>N</th>
<th>Country</th>
<th>Population/setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pieterse et al, 2011</td>
<td>Risk perception accuracy, correct knowledge, perceived personal control, generalized state anxiety, and cancer-related distress</td>
<td>To assess changes in cognitions (accurate risk perception, correct knowledge, perceived personal control) and distress (state anxiety, cancer-related stress reactions) from before to immediately and 6 months after concluding breast cancer genetic counseling in female counselees, and whether changes in cognitions and distress were similar in affected versus unaffected women</td>
<td>Before and after</td>
<td>Eligible: 204 Enrolled: 77 Randomized: N/A Analyzed: 77</td>
<td>The Netherlands</td>
<td>Women seeking counseling for hereditary cancer at University Medical Center in the Netherlands, surveys exchanged through the mail</td>
</tr>
<tr>
<td>Roshanai et al, 2009</td>
<td>Risk perception Psychological factors</td>
<td>To investigate the effect of an informational intervention on counselees’ knowledge, risk perception, communication of information to at-risk relatives and satisfaction with the service</td>
<td>RCT</td>
<td>Eligible: 210 Randomized: 163 (85 in intervention, 78 in control group) Analyzed: 147 at precounseling (73 in intervention, 74 in control); 144 for risk perception (71 in intervention, 73 in control); 147 2 weeks postcounseling (73 in intervention, 74 in control); 139 at 8 months postcounseling (68 in intervention, 71 in control)</td>
<td>Sweden</td>
<td>Swedish women visiting a university cancer genetic clinic, mainly referred due to breast cancer or family history of breast, ovarian or colorectal cancer (groups separated for analysis)</td>
</tr>
<tr>
<td>Author, year</td>
<td>Quality</td>
<td>Subcategory</td>
<td>Purpose</td>
<td>Study type</td>
<td>N</td>
<td>Country</td>
</tr>
<tr>
<td>-------------</td>
<td>---------</td>
<td>-------------</td>
<td>---------</td>
<td>------------</td>
<td>---</td>
<td>---------</td>
</tr>
<tr>
<td>Bowen et al, 2002</td>
<td>Fair</td>
<td>Interest in genetic testing</td>
<td>To test the effects of breast cancer risk on interest in genetic testing in women who have a family history of breast cancer</td>
<td>RCT</td>
<td>Eligible: 561</td>
<td>U.S.</td>
</tr>
<tr>
<td>Bowen et al, 2004</td>
<td>Fair</td>
<td>Cancer worry Psychological factors Risk perception</td>
<td>To test the effects of 2 types of breast cancer risk counseling (group psychosocial or individual genetic) on perceived risk, negative affect, and worry about breast cancer</td>
<td>RCT</td>
<td>Eligible: 561</td>
<td>U.S.</td>
</tr>
<tr>
<td>Brain et al, 2002</td>
<td>Good</td>
<td>Psychological factors</td>
<td>To compare the psychological impact of a multidisciplinary specialist genetics service with surgical provision in women at high risk and lower risk of familial breast cancer</td>
<td>RCT</td>
<td>Eligible: 1,000</td>
<td>Wales</td>
</tr>
<tr>
<td>Burke et al, 2000</td>
<td>Fair</td>
<td>Cancer worry Risk perception</td>
<td>To assess whether modified traditional genetic counseling causes women with an intermediate risk of breast cancer to have a more realistic view of their risk, of genetic testing, and to decrease breast cancer worry</td>
<td>RCT</td>
<td>Eligible: 793</td>
<td>U.S.</td>
</tr>
</tbody>
</table>
### Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Subcategory</th>
<th>Purpose</th>
<th>Study type</th>
<th>N</th>
<th>Country</th>
<th>Population/setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cull et al, 1998</td>
<td>Good</td>
<td>Psychological factors</td>
<td>To evaluate use of video for education on the genetic basis of breast cancer and on strategies for breast cancer risk management in a breast cancer family clinic</td>
<td>RCT</td>
<td>Eligible: 159</td>
<td>U.K.</td>
<td>A consecutive series of women newly referred to the breast cancer family clinic were invited by mail to participate; 24% of the video before and 30% of the video after group were referred by another hospital clinic; 1 subject in each group had been referred from another genetic clinic. The remaining were referred by GPs</td>
</tr>
<tr>
<td>Hopwood et al, 1998</td>
<td>Fair</td>
<td>Psychological factors</td>
<td>To understand psychological support needs for women at high genetic risk for breast cancer</td>
<td>Cohort</td>
<td>Eligible: 176</td>
<td>England</td>
<td>All were consecutive first-time attendees at the Family History Clinics (Manchester, U.K.)</td>
</tr>
<tr>
<td>Lerman et al, 1996</td>
<td>Fair</td>
<td>Cancer worry</td>
<td>To study effect of individualized breast cancer risk counseling</td>
<td>RCT</td>
<td>Eligible: 438</td>
<td>U.S.</td>
<td>Subjects identified by relatives under treatment for breast cancer at either Fox Chase Cancer Center or Duke Comprehensive Cancer Center</td>
</tr>
<tr>
<td>Lerman et al, 1999</td>
<td>Fair</td>
<td>Cancer worry</td>
<td>To investigate racial differences in response to 2 alternate pretest education strategies for BRCA1 genetic testing: a standard education model and an education plus counseling model</td>
<td>RCT</td>
<td>Eligible: 581</td>
<td>U.S.</td>
<td>Subjects were recruited from 2 cancer centers (Georgetown University Medical Center or Washington Hospital Center)</td>
</tr>
<tr>
<td>Lobb et al, 2004</td>
<td>Good</td>
<td>Psychological factors</td>
<td>To examine the effect of different consultant communication styles on a variety of outcomes</td>
<td>Longitudinal</td>
<td>Eligible: NR for unaffected group</td>
<td>Australia</td>
<td>Women from high-risk breast cancer families attending their first consultation before genetic testing</td>
</tr>
</tbody>
</table>
## Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Subcategory</th>
<th>Purpose</th>
<th>Study type</th>
<th>N</th>
<th>Country</th>
<th>Population/setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson et al, 1999 Good</td>
<td>Psychological factors</td>
<td>To investigate perception of genetic risk and the psychological effects of genetic counseling in women with a family history of breast cancer</td>
<td>Prospective cohort</td>
<td>Eligible: 303</td>
<td>England</td>
<td>First-time genetic clinic attendees recruited from 4 South London genetic counseling centers (Royal Marsden NHS Trust Hospital [2 separate clinics], Mayday University Hospital, and St. Georges’ Hospital)</td>
</tr>
<tr>
<td>Armstrong et al, 2005 Good</td>
<td>Cases vs. controls</td>
<td>Mean age (years): 42.5 (range, 19-66) vs. 53.1 (range, 20-89) Race/ethnicity: African American: 7.4% vs. 29% Asian American: 3.3% vs. 3.2% White: 85% vs. 66% Hispanic: 0% vs. 2.1% Other: 4.6% vs. 0% Religious heritage: Jewish: 29% vs. 11% Christian: 52% vs. 60% Other: 13% vs. 13% NR: 5.9% vs. 16%</td>
<td>Inclusion: Women ages 18-80 years seeing a primary care physician within the University of Pennsylvania Health System in the 3 years prior to the start of the study, with FDR or SDR with a breast or ovarian cancer diagnosis Exclusion: Personal diagnosis of breast or ovarian cancer, identified as being unable to participate because of illness or mental incapacity by their primary care physician Controls: Previously participated in BRCA1/2 genetic counseling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bennett et al, 2008 NA</td>
<td>Mean age, 43.3 years</td>
<td>Inclusion: Women undergoing assessment for risk of breast/ovarian cancer at the CGSW and who completed followup questionnaires Exclusion: Did not complete risk assessment process before the end of the study</td>
<td></td>
<td>23% low risk</td>
<td>45% moderate risk</td>
<td>31% high risk</td>
</tr>
<tr>
<td>Bennett et al, 2009 NA</td>
<td>Mean age, 44.3 years (SD, 10.81; range, 18-76)</td>
<td>Inclusion: Women undergoing assessment for risk of breast/ovarian cancer at the CGSW and who completed followup questionnaires Exclusion: Did not complete risk assessment process before the end of the study</td>
<td></td>
<td>30/128 (23.4%) at population risk 61/128 (47.7%) at moderate risk 37/128 (28.9%) at high risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloom et al, 2006 Poor</td>
<td>Mean age, 47.4 years (SD, 7.2) 77% Euro-American 6.1% African American 9.2% Latina 8.0% Asian/Other</td>
<td>Inclusion: Not reported Exclusion: Prior breast cancer</td>
<td></td>
<td>All had ≥1 FDR (sister) with breast cancer diagnosis at age ≤50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Demographics</th>
<th>Inclusion/exclusion criteria</th>
<th>Risk level definition</th>
</tr>
</thead>
</table>
| Bowen et al, 2006<sup>152</sup>    | Fair    | Mean age, 47 years | Inclusion: Women ages 18-74 years with ≥1 Ashkenazi Jewish ancestor who lived within 60 miles of Seattle  
Exclusion: Personal history of breast or ovarian cancer, family history consistent with an autosomal dominant inheritance of breast cancer predisposition | ≥1 Ashkenazi Jewish ancestor                                                           |
| Brain et al, 2011<sup>153</sup>    | NA      | Mean age, 42.3 years (SD, 8.22) | Inclusion: Women who took part in TRACE study and were approved by physician to be contacted  
Exclusion: NR | Moderate risk not otherwise described                                                   |
| Braithwaite et al, 2005<sup>154</sup> | Fair    | GRACE (n=37) vs. counseling (n=34)  
Age (years): 18-34: 62.2% vs. 67.6%  
35-49: 27% vs. 20.6%  
≥50: 10.8% vs. 11.8%  
Ethnicity: White: 91.9% vs. 94.1%  
Other: 8.1% vs. 5.8% | Inclusion: Having ≥1 FDR or SDR with breast cancer  
Exclusion: Personal history of breast cancer | All had ≥1 FDR or SDR with breast cancer                                                   |
| Fry et al, 2003<sup>155</sup>      | Fair    | Mean age (SD)  
Standard service: 37.3 (9.4)  
Novel service: 39.1 (9.6) | Inclusion: Women who lived in the region and were able to give informed consent and complete a baseline questionnaire  
Exclusion: Women who were symptomatic or diagnosed with breast and/or ovarian cancer, or women who had previously consulted with another clinic about their family history of cancer | Criteria for significantly increased risk: Having a FDR with breast cancer diagnosis before age 40; having 2 FDRs or SDRs on the same side of the family with breast cancer diagnosis before age 60 or with ovarian cancer; having 3 FDRs or SDRs on the same side of the family with breast or ovarian cancer; having a FDR with breast cancer in both breasts; and having a male relative with breast cancer |
| Gurmankin et al, 2005<sup>156</sup> | NA      | Mean age of 45.9 years (SD, 10.5)  
88% White  
10% Black  
2% Other  
42% Ashkenazi Jewish | Inclusion: Females only  
Exclusion: Health care provider indicated they were too ill to participate | NR                                                                                      |
<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Demographics</th>
<th>Inclusion/exclusion criteria</th>
<th>Risk level definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helmes et al, 2006 Fair</td>
<td>Mean age (years):  In-person counseling: 39.9 (SD, 9.2) Telephone counseling: 40.4 (SD, 9.7) Delayed counseling: 41.8 (SD, 10.1)</td>
<td>Inclusion: Women ages 18-64 years within 60 miles of research institute, planning to live in area for 1 year, spoke English, telephone in home, covered by commercial health insurance plan Exclusion: Women with personal history of breast/ovarian cancer, personal history of genetic counseling or testing for cancer risk</td>
<td>14.7% had family history of breast cancer</td>
</tr>
<tr>
<td>Hopwood et al, 2004 NA</td>
<td>Average across all 5 cancer genetics services: Mean age, 41 years (range, 22-72) 94% Female 2% Ethnic minority</td>
<td>Inclusion: Women seen at a cancer genetics services center Exclusion: Women who had been diagnosed with cancer, age &lt;18 years</td>
<td>NR</td>
</tr>
<tr>
<td>Kelly et al, 2008 NA</td>
<td>Mean age, 48.64 years (SD, 12.69) 100% Ashkenazi Jewish women</td>
<td>Inclusion: Ashkenazi Jewish women with personal or family histories suggestive of an inherited predisposition to breast and/or ovarian cancer Exclusion: Prior history of ovarian cancer, men, women having prophylactic oophorectomies</td>
<td>≥1 Ashkenazi Jewish grandparent</td>
</tr>
<tr>
<td>Matloff et al, 2006 Fair</td>
<td>Mean age, 49 years (range, 41-55) 21% Ashkenazi Jewish</td>
<td>Inclusion: Women age ≥40 years with ≥1 FDR with breast cancer, had gone through natural menopause Exclusion: Taking menopausal therapy, having had cancer, atypical hyperplasia, or LCIS, being a known carrier of a BRCA1/2 mutation, having heart disease, women with family history that placed them at &gt;10% risk of carrying a mutation</td>
<td>≥1 FDR with breast cancer</td>
</tr>
<tr>
<td>Mikkelsen et al, 2007 Fair</td>
<td>Median age (years): Counseling: 39 (range, 18-72) Group 1: 56 (range, 28-76) Group 2: 45 (range, 18-75)</td>
<td>Inclusion: Women age ≥18 years who attended an initial genetic counseling session for breast or ovarian cancer Exclusion: Women affected with breast or ovarian cancer at baseline or who developed cancer during the followup period</td>
<td>NR</td>
</tr>
<tr>
<td>Mikkelsen et al, 2009 Fair</td>
<td>Median age (years): Counseling: 39 (range, 18-72) Group 1: 56 (range, 28-76) Group 2: 45 (range, 18-75)</td>
<td>Inclusion: Women age &gt;18 years who attended an initial genetic counseling session for breast or ovarian cancer Exclusion: Women affected with breast or ovarian cancer at baseline or who developed cancer during the followup period</td>
<td>NR</td>
</tr>
</tbody>
</table>
## Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Demographics</th>
<th>Inclusion/exclusion criteria</th>
<th>Risk level definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pieterse et al, 2011 NA</td>
<td>Age ≥18 years</td>
<td><strong>Inclusion:</strong> Patients sought counseling for hereditary cancer; were first among their 1st- and 2nd-degree relatives to request counseling; were first-time attendees; and age &gt;18 years</td>
<td>Seeking counseling for hereditary cancer</td>
</tr>
</tbody>
</table>
| Roshanai et al, 2009 Fair | Female: 90.5% (n=133) Male: 9.5% (n=14) Median age, females (years): 56 (range, 23-84) | **Inclusion:** Women age ≥18 years; able to read, write, and speak Swedish | Risk estimated by geneticist: Intervention n (%) vs. control n (%)
≤20%: 5 (15) vs. 3 (23)
21%-40%: 29 (72.5) vs. 37 (77)
>40%: 3 (9) vs. 1 (4) |
| Prior report | Psychological counseling arm: Mean age, 41.9 years (SD, 11.3) 90% White, nonHispanic 3.5 % White, Hispanic 0.9% African American 2.6% Asian or Pacific Islander 1.8% Native American 0.9% Multiracial Genetic counseling arm: Mean age, 42.8 years (SD, 11.8) 94% White, nonHispanic 0.0% White, Hispanic 0.8% African American 1.7% Asian or Pacific Islander 1.7% Native American 1.7% Multiracial Control arm: Mean age, 42.4 years (SD, 11.5) 93% White, nonHispanic 0.0% White, Hispanic 2.5% African American 3.3% Asian or Pacific Islander 0.0% Native American 0.8% Multiracial | **Inclusion:** Women ages 18-74, lived within 60 miles of research center, agreed to participate in counseling and complete questionnaires, and had ≥1 relative affected by breast cancer **Exclusion:** Lack of family history of breast cancer, age outside the 18-74 range, >1 close relative affected by breast cancer, living outside the catchment area and lack of interest in completing the study | Family history: Close relatives affected by breast cancer included grandmothers, mothers, sisters, and aunts Risk level: Gail and Claus scores, along with population data |
| Bowen et al, 2004 Fair | Mean age, years (SD) Genetic counseling: 42.6 (11.8) Psychosocial counseling: 42.1 (11.4) Delayed intervention: 42.5 (11.5) | **Inclusion:** Women ages 18-74 with ≥1 relative with breast cancer, no personal history of breast or ovarian cancer, no family history consistent with a BRCA mutation for breast cancer risk, living within 60 mile radius of research center, willingness to complete research activities and completed and returned baseline questionnaire **Exclusion:** NR | Family history: Self-report of any family history of breast cancer Risk level: Calculated by use of Gail and Claus models, along with population data |
### Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Demographics</th>
<th>Inclusion/exclusion criteria</th>
<th>Risk level definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain et al., 2002</td>
<td>Good</td>
<td>Mean age, years (SD) Low vs. moderate vs. high risk Control group: 48.6 (10.25) vs. 40.5 (9.13) vs. 39.2 (7.33) Trial group: 52.9 (7.75) vs. 41.6 (8.52) vs. 33.7 (8.19)</td>
<td>Inclusion: Women with a 1st-degree female relative diagnosed with breast cancer before age 50 years or with bilateral breast cancer diagnosed at any age, ≥2 FDRs with breast cancer, or a FDR and SDR with breast cancer Exclusion: Personal history of breast cancer, previously received genetic counseling, or was not a resident of Wales</td>
<td>Family history risk definition: 1st-degree female relative diagnosed with breast cancer before age 50; 1st-degree female relative with bilateral breast cancer at any age; ≥2 FDRs with breast cancer; or a FDR and SDR with breast cancer. Risk definition: In trial group, risk was assessed on detailed pedigree data collected and analyzed by geneticist using Claus model. In control group, surgical assessment of risk was based on info collected on age, reproductive history, and minimal family history</td>
</tr>
<tr>
<td>Burke et al, 2000</td>
<td>Fair</td>
<td>Genetic counseling arm: Average age, 43 years (SD, 12) 94% White Control group arm: Average age, 42 years (SD, 12) 93% White</td>
<td>Inclusion: Women ages 18-74, lived within 60 miles of Seattle, and had ≥1 biological relative who has been diagnosed with breast cancer Exclusion: A personal history of breast or ovarian cancer and a family history indicative of autosomal dominant inheritance of breast cancer</td>
<td>Intermediate family history of breast cancer: ≥1 biological relative with breast cancer but whose pedigree suggests a low likelihood of autosomal dominant transmission. Family history indicative of autosomal dominant inheritance of breast cancer: ≥2 1st-degree or 1 1st- and 1 2nd-degree relative with either breast cancer before age 50 or ovarian cancer at any age, or ≥2 paternal 2nd-degree relatives with either breast cancer before age 50 or ovarian cancer at any age. The Claus model showed that these women would have ≥20% breast cancer risk by age 79</td>
</tr>
<tr>
<td>Cull et al, 1998</td>
<td>Good</td>
<td>Mean age, 39 years (SD, 8)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hopwood et al, 1998</td>
<td>Fair</td>
<td>Mean age, 36.19 years (range, 22.63-46.35)</td>
<td>Inclusion: Women ages 18-45 living within a 25 mile radius of the FHC with risk ≥2-fold greater than the population for breast cancer Exclusion: NR</td>
<td>Risk was ≥2-fold greater than the population for breast cancer (i.e., 1:6 lifetime risk or greater as assessed using the Claus model)</td>
</tr>
</tbody>
</table>
## Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Demographics</th>
<th>Inclusion/exclusion criteria</th>
<th>Risk level definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lerman et al, 1996 Fair</td>
<td>18% ages 35-40 years 41% ages 41-49 years 42% age ≥50 years 90% White 10% Black</td>
<td><strong>Inclusion:</strong> Women age ≥35 years and a family history of breast cancer  <strong>Exclusion:</strong> A personal history of cancer and younger than age 35 years</td>
<td>≥1 FDR with breast cancer; breast cancer risk estimates for individual women were calculated using subject's Gail model variables and estimated the lifetime probability of developing breast cancer, 95% CIs, and the estimated lifetime risk for a woman of the same age with the lowest risk of disease</td>
</tr>
<tr>
<td>Lerman et al, 1999 Fair</td>
<td>24% Black 34% age &lt;40 years 66% age ≥40 years 76% White 41% age &lt;40 years 59% age ≥40 years</td>
<td><strong>Inclusion:</strong> Caucasian and African American women with a family history of breast cancer or ovarian cancer  <strong>Exclusion:</strong> Personal history of cancer (except basal cell or squamous cell skin cancer)</td>
<td>≥1 FDR affected with breast cancer and/or ovarian cancer</td>
</tr>
<tr>
<td>Lobb et al, 2004 Good</td>
<td>Mean age, 38.7 years (range, 19-60)</td>
<td><strong>Inclusion:</strong> Women attending their first consultation before genetic testing with no prior testing for or carrier of BRCA1 or BRCA2  <strong>Exclusion:</strong> Unable to give informed consent, age &lt;18 years, showed evidence of severe mental illness, and nonfluent in English</td>
<td>NR</td>
</tr>
<tr>
<td>Watson et al, 1998 Good</td>
<td>Median age, 37 years (range, 28-56) for participants from the Royal Marsden Hospital Median age, 41 years (range, 23-71) for participants from St. George's Hospital</td>
<td><strong>Inclusion:</strong> Women with a family history of breast cancer, first visit to genetic clinic, never having been clinically affected with cancer, no known mental illness, and age ≥18 years  <strong>Exclusion:</strong> NR</td>
<td>NR</td>
</tr>
<tr>
<td>Watson et al, 1999 Good</td>
<td>Median age, 37 years (range, 19-76)</td>
<td><strong>Inclusion:</strong> Women with a family history of breast cancer, never clinically affected by cancer, no known serious mental illness, age ≥18 years, and able to complete a questionnaire  <strong>Exclusion:</strong> NR</td>
<td>Breast cancer risk calculated using CASH model based on the number of breast cancer cases in 1st- and 2nd-degree relatives, age of family members at disease onset, and age of woman presenting for genetic counseling</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Interventions</th>
<th>Measures</th>
<th>Duration of followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current report</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Armstrong et al, 2005 Good</td>
<td>A) Genetic counseling prior to testing, otherwise not described  B) Controls</td>
<td></td>
<td>1999-2003  Not applicable</td>
</tr>
</tbody>
</table>
### Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Interventions</th>
<th>Measures</th>
<th>Duration of followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennett et al, 2008&lt;sup&gt;150&lt;/sup&gt; NA</td>
<td>CGSW referral guidelines and BRCAPRO risk calculation model</td>
<td>Medical Coping Modes Questionnaire (MCMQ, scale NR) Impact of Events Scale (IES, subscales 0 to 28) DUKE Social Support Questionnaire (DUKE-SSQ, scale 1 to 5) Hospital Anxiety and Depression Scale (HADS, subscales 0 to 21) Perceived health Quality of Life</td>
<td>Year NR 1 week following risk notification</td>
</tr>
<tr>
<td>Bennett et al, 2009&lt;sup&gt;149&lt;/sup&gt; NA</td>
<td>CGSW referral guidelines and BRCAPRO risk calculation model</td>
<td>Impact of Events Scale (IES, subscales 0 to 28) Medical Coping Modes Questionnaire (MCMQ, scale NR) DUKE Social Support Questionnaire (DUKE-SSQ, scale 1 to 5)</td>
<td>Year NR Approximately 5 to 7 weeks</td>
</tr>
<tr>
<td>Bloom et al, 2006&lt;sup&gt;151&lt;/sup&gt; Poor</td>
<td>A) Telephone counseling from a master's level counselor within 2 weeks; breast cancer worries measured by 4-point Likert scale; perceived risk measured on 5-point scale; rating chances of diagnosis (0%-100%). Telephone counseling session included establishment of rapport and determination of special concerns, emotional readiness; risk notification by providing modified Gail model lifetime risk estimate and discussing in terms of her pretest self-assessment of risk; deescalation of tension regarding breast cancer checkup; evaluation of coping skills, reinforcement of problem solving and coping skills; information on health protective behaviors; early detection through American Cancer Society screening; and information on genetic testing when requested. B) Delayed telephone counseling following the posttest NSI: 3-item measure of breast cancer worry: perceived risk of breast cancer, health behaviors, and breast cancer screening</td>
<td>1999-2002 6 months</td>
<td></td>
</tr>
<tr>
<td>Bowen et al, 2006&lt;sup&gt;152&lt;/sup&gt; Fair</td>
<td>A) Group psychosocial counseling: psychologist led four 2-hour, weekly sessions of 5 to 6 women per group. Each session included 20-minute group cohesion activities followed by 1 of 4 major intervention components: risk assessment and perception, education, stress management, and problem solving and social support. B) Individual genetic counseling: genetic counselor provided 1-hour counseling sessions, individually. Sessions covered several topics, including participant's family background, breast cancer risk assessment, <em>BRCA1/2</em> mutations in the Ashkenazi Jewish population, nongenetic risk factors for breast cancer, and breast screening. C) Delayed counseling: no counseling, served as control NSI: Continuous scale of 0-100 to assess risk perception BSI: 53-item self-reported psychological symptom scale</td>
<td>Year NR 6 months</td>
<td></td>
</tr>
<tr>
<td>Brain et al, 2011&lt;sup&gt;153&lt;/sup&gt; NA</td>
<td>A) Claus model B) Generalized risk level based on age, reproductive history, and minimal family history</td>
<td>Cancer Worry Scale-Revised (CWS-R, scale 6 to 24) Perceived risk (single item scale, 1 to 5)</td>
<td>Year NR 6 years</td>
</tr>
</tbody>
</table>
## Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Interventions</th>
<th>Measures</th>
<th>Duration of followup</th>
</tr>
</thead>
</table>
| Braithwaite et al, 2005 | Both interventions were 1 session; cognitive outcomes assessed at baseline, postclinic, and at 3 months  
A) Risk counseling arm: Clinical nurse specialist undertook counseling sessions and drew pedigree with information from family history and assessed risk as low, moderate, or high based on GRACE guidelines. Participants were mailed letters summarizing content afterward  
B) GRACE: Participants completed their pedigrees in GRACE and assessed their risk, learning their risk assessment and how to manage their risk. They received a numerical estimate of lifetime risk; a visual display of cumulative risk with general population as comparator; and a qualitative description. Clinical nurse specialists then offered to book mammography and arrange meetings with geneticists, where appropriate | NSI: Measured attitude, perceived benefit, risk perception, and satisfaction and risk communication on a likert scale  
STAI: Measures an individual’s current anxiety feelings  
HADS: 14-item self-report scale for the detection of depression and anxiety in hospitalized patients | Year NR  
3 months |
| Fry et al, 2003 | Standard (regional) service: Self-report family history and baseline questionnaire; genetics consultant and genetics nurse specialist assigned categorical risk via Cancer Research Campaign. Women at low risk receive informative letter; women at moderate/high risk offered appointment at familial breast cancer clinic where a genetics consultant discusses risk status and breast surgeon discusses risk management. Where appropriate, clinical exams and mammography included. Patients’ GPs receive summary data, and patients receive followup questionnaires 4 weeks and 6 months later  
Novel (community-based) service: Women sent an appointment for a community-based clinic near their residence. Meetings run by genetics nurse specialist where family history collected and compared to published criteria (Cancer Research Campaign) to determine risk. Women at low risk offered information, reassurance, and discharged. Women at moderate/high risk offered appointment at a regional center with a geneticist and genetics nurse specialist, and asked to complete followup questionnaires at 4 weeks and 6 months | Cancer Worry Scale (scale 5 to 24)  
GHQ-30 | 6 months |
| Gurmankin et al, 2005 | A) Precounseling interview assessed patient's breast cancer risk perception, BRCA1/2 mutation risk perception, worry about breast cancer, family history of cancer, breast cancer risk reduction behaviors, and demographic information  
B) Postcounseling interview assessed patient's breast cancer risk, BRCA1/2 mutation risk, recall of actual risk information, worry about breast cancer, completion of the Spielberger Trait Anxiety Inventory (20-80 score range) and | STAI: Measures an individual’s current anxiety feelings  
NSI: Scale of 0 to 100 to assess risk perception  
Scale of 1 to 7 to assess cancer worry | October 2002 to February 2004  
1 week |
## Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Interventions</th>
<th>Measures</th>
<th>Duration of followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helmes et al, 2006&lt;sup&gt;157&lt;/sup&gt; Fair</td>
<td>A) In-person counseling: board-certified genetic counselor conducted counseling consisting of a review of family history, discussion of breast cancer risk, and education about breast cancer genes. Also discussed genetic testing considerations, including implications of results, testing strategies, potential risks and benefits of test, cost of test, and psychological effects of test. Information packet was provided that contained personal risk information comparing the woman's risk with average woman's risk; personal computer-drawn 3-generation pedigree; brochures on self-breast exams, Pap smear, and mammography; genetics visual aids; list of community resources; and cover letter B) Telephone counseling: information packet was sent in the mail with instructions to open at the beginning of the telephone counseling, which was identical in content and structure to in-person counseling. C) Control group did not receive counseling</td>
<td>NSI: Scale of 0 to 100 to assess risk perception Scale of 1-4 to measure intention to obtain breast cancer screening 4-item questionnaire to assess interest in genetic testing</td>
<td>Year NR 3 months</td>
</tr>
<tr>
<td>Hopwood et al, 2004&lt;sup&gt;158&lt;/sup&gt; NA</td>
<td>A) Genetic counseling, otherwise not described</td>
<td>NSI: 5-response category assessment of perceived cancer risk GHQ: 60-item questionnaire to screen individuals for psychiatric disorders</td>
<td>Year NR At 1 month and 1 year following precounseling</td>
</tr>
<tr>
<td>Kelly et al, 2008&lt;sup&gt;159&lt;/sup&gt; NA</td>
<td>A) Genetic counseling included review of family cancer history, personal risk factors for breast and ovarian cancer, mechanisms of cancer inheritance, meaning of a positive and negative test result, and risks and benefits associated with testing</td>
<td>CWS: 3-item questionnaire to measure how frequently an individual worries about getting breast cancer</td>
<td>Year NR 6 months</td>
</tr>
<tr>
<td>Matloff et al, 2006&lt;sup&gt;160&lt;/sup&gt; Fair</td>
<td>A) Counseling session with personalized letter summarizing patient data B) Controls who received no counseling</td>
<td>NSI: Reviewed detailed information about menopause, the risks and benefits of each menopause therapy option, and a disease risk factor assessment</td>
<td>August 2002 to January 2004 6 months</td>
</tr>
<tr>
<td>Mikkelsen et al, 2007&lt;sup&gt;161&lt;/sup&gt; Fair</td>
<td>A) Genetic counseling: information on incidence of sporadic breast cancer, genetics, inheritance patterns, and estimated personal lifetime risk of inherited cancer B) Comparison group 1: women referred for mammography C) Comparison group 2: random sample of women</td>
<td>IES: 17-item questionnaire to measure an individual's level of distress in relation to a specific event or condition</td>
<td>2003-2004 1 year</td>
</tr>
<tr>
<td>Mikkelsen et al, 2009&lt;sup&gt;162&lt;/sup&gt; Fair</td>
<td>A) Genetic counseling: information on incidence of sporadic breast cancer, genetics, inheritance patterns, and estimated personal lifetime risk of inherited cancer B) Comparison group 1: women referred for mammography C) Comparison group 2: random sample of women</td>
<td>HADS: 14-item self-report scale for the detection of depression and anxiety in hospitalized patients</td>
<td>2003-2004 1 year</td>
</tr>
</tbody>
</table>
Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Interventions</th>
<th>Measures</th>
<th>Duration of followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pieterse et al, 2011 NA</td>
<td>163</td>
<td>A) First session topics included family's occurrence of breast and other cancers, inheritance, and criteria on probability of inherited breast cancer. Likelihood of hereditary breast cancer running in family was estimated. Genetic testing was offered to counselees or affected relatives when they had an a priori chance (≥10%) of carrying BRCA gene. Counselees eligible for testing informed of medical consequences and options. Periodic surveillance recommended to all counselees at increased risk (&gt;20%). Counselees and referring physician receive summary letter about genetic and risk information. Counselors distributed postcounseling questionnaire after last session and asked participants to complete it within a day. 6 months later, counselees were sent a followup questionnaire. All 3 of these questionnaires assessed cognitions and distress. Counselors completed a questionnaire after counselee's last visit. Counseling spanned 1 to 4 visits over 6 to 24 months; STAI, IES, and VAS were used to measure anxiety levels</td>
<td>VAS: Any of a number of pain self-assessment tools where subjects indicate their level of pain in response to a continuous visual scale NSI: Scale of 0 to 100 to assess risk perception Scale of 0 to 7 to assess hereditary breast cancer knowledge PPC: Construct reflecting the degree to which a person believes that a situation is under their control STAI: Measures an individual’s current anxiety feelings IES: 17-item questionnaire to measure an individual’s level of distress in relation to a specific event or condition</td>
<td>24 months (6 months after last counseling session)</td>
</tr>
<tr>
<td>Roshanai et al, 2009 Fair</td>
<td>164</td>
<td>A) Genetic counseling from specialist nurse: pedigree explanation; Buckman's Breaking Bad News model to inform at-risk relatives; pamphlet, videotape, copies of pedigree and medical records B) Control group received standard care given at the clinic: genetic counseling from a specialist nurse, no additional information, and no help in identifying at-risk relatives</td>
<td>SPIKES: A 6-step protocol for delivering bad news HADS: 14-item self-report scale for the detection of depression and anxiety in hospitalized patients</td>
<td>2003-2005 At 2 weeks and at 8 months postcounseling</td>
</tr>
<tr>
<td>Prior report</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowen et al, 2002 Fair</td>
<td>57</td>
<td>A) IGC: Phone call to review pedigree information followed by a single 2-hour counseling session. Subject given information on her own risk for breast cancer using Gail and Claus scores along with population data. Information given on genetic testing, current knowledge about nonhereditary risk factors, and current screening techniques. Summary letter provided B) PGC: Four 2-hour group meetings with 4 to 6 women led by a health counselor. Included: risk assessment and perception, education, stress management, problem solving and social support. Personal risk for breast cancer, interpretation, and appropriate screening provided privately to subjects. C) CG: Offered choice of counseling modality after the final followup</td>
<td>NSI: 3-item questionnaire to assess awareness, candidacy, and interest in genetic testing Tolerance for ambiguity assessed using a questionnaire derived from previous research 5-point response scale to beliefs about genetic testing</td>
<td>Years: 6 months</td>
</tr>
</tbody>
</table>
### Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Interventions</th>
<th>Measures</th>
<th>Duration of followup</th>
</tr>
</thead>
</table>
| Bowen et al, 2004 <sup>62</sup> Fair | Telephone screening survey to determine eligibility followed by mailed baseline survey. Those who returned completed surveys were randomized to individual genetic counseling (IGC), group psychosocial counseling (PC), or a delayed intervention control group (CG)  
A) IGC: Telephone contact with genetic counselor to review pedigree information. One 2-hour session following protocol based on standard genetic practice. Letter sent to participant within 2 weeks summarizing the session  
B) PC: Group of 4 to 6 participants met for four 2-hour sessions with trained health counselor. Each participant received her own risk assessment sheet, personalizing the group discussion to her own risk status. Main topics: risk assessment and perception, screening, stress management and problem solving, and social support  
C) CG: Offered counseling following study completion. For ICG and PC, brief survey on reactions to counseling within 4 weeks of last counseling contact. Mailed second assessment 6 months after randomization, with a reminder call and offer of phone completion to those who did not return survey after 2 weeks | NSI: 4-item questionnaire to assess risk perception  
Survey to assess reactions to counseling | Years: 6 months |
| Brain et al, 2002 <sup>166</sup> Good | A) Control group: 1) breast cancer surveillance; 2) surgical assessment of individual breast cancer risk; 3) option to enter U.K. Tamoxifen Prevention Trial; and 40 annual surgical followup with surveillance and advice  
B) Trial group: components 1, 3, and 4 of control group with genetic risk assessment and counseling | STAI: Measures an individual’s current anxiety feelings  
NSI: 3-item scale to assess interest in genetic testing | Years: Immediately |
| Burke et al, 2000 <sup>58</sup> Fair | Random assignment to 3 groups: individual genetic counseling (120 women), psychosocial group counseling (113 women, reported elsewhere [Bowen 1999]), control (123 women)  
A) Adapted genetic counseling protocol for women with intermediate risk included precounseling telephone call, baseline questionnaire, individual genetic counseling session, immediate followup questionnaire, 6 month followup questionnaire, mailed summary letter  
B) Control group was offered group counseling following completion of the study | NSI: Questionnaire to assess breast cancer worry, opinions on genetic testing, and risk perception | Year NR 6 months |
### Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Interventions</th>
<th>Measures</th>
<th>Duration of followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cull et al, 1998&lt;sup&gt;167&lt;/sup&gt; Good</td>
<td></td>
<td>A) Subjects sent information about study with initial clinic appointment 4 weeks before the appointment. They were asked to return baseline questionnaires and forms within 2 weeks if wanting to participate. Those who did so were randomized either to the Video Before group, and were sent a copy of the educational video about 10 days before the clinic consultation, or to the Video After group, taking the video home after the postclinic assessment. B) Clinic consultation: individual meeting with geneticist to discuss individual risk and with breast surgeon to discuss risk management. Clinicians noted session length and rated assessment of it. Postclinic assessment included completion of instruments. Followup assessment by mail 4 weeks later</td>
<td>NSI: 12-response category assessment of risk perception 4-point scale to assess genetic risk Multiple choice questionnaire to assess objective risk STAI: Measures an individual’s current anxiety feelings GHQ: 30-item questionnaire to screen individuals for psychiatric disorders</td>
<td>Year NR 1 month following clinic consultation</td>
</tr>
<tr>
<td>Hopwood et al, 1998&lt;sup&gt;167&lt;/sup&gt; Fair</td>
<td></td>
<td>A) Postal questionnaire prior to counseling B) At attendance for risk counseling, women were asked to complete GHQ together with several other self-report measures C) Questionnaires completed again at 3, 6, 9, and 12 months later D) Three months after Family History Consultation, home visit conducted with research interviews, including administration of the Psychiatric Assessment Schedule. Additional structured questions assessed attitude to risk information, reaction, and concerns about cancer</td>
<td>NSI: 5-item questionnaire to assess risk perception GHQ: 60-item questionnaire to screen individuals for psychiatric disorders PAS: Semistructured clinical interview designed for use with respondents who have learning disability</td>
<td>3, 6, 9, and 12 months following genetic counseling</td>
</tr>
<tr>
<td>Lerman et al, 1996&lt;sup&gt;168&lt;/sup&gt; Fair</td>
<td></td>
<td>A) Study group: 1) discussion of individual factors contributing to elevated risk, 2) presentation of individualized risk data, 3) recommendations for annual mammography and clinical breast exams, 4) instruction in breast self-exam B) Control group: 1) interview assessment of current health practices, 2) age-specific recommendations for variety of cancer screening tests, 3) encouragement to quit smoking, 4) suggestions for reducing dietary fat to ≤30%, 5) recommendations for regular aerobic exercise</td>
<td>IES: 17-item questionnaire to measure an individual’s level of distress in relation to a specific event or condition</td>
<td>Year NR 3 months</td>
</tr>
</tbody>
</table>
## Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Interventions</th>
<th>Measures</th>
<th>Duration of followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lerman et al, 1999</td>
<td>Fair</td>
<td>A) Education only: topics discussed included individual risk factors for breast and ovarian cancer and patterns of inheritance for breast and ovarian cancer susceptibility. Subjects given qualitative estimates of their risk of developing breast and ovarian cancer. Pedigrees were reviewed. Potential benefits, limitations, and risks of genetic testing for inherited breast and ovarian cancer susceptibility also reviewed. B) Education plus counseling: provided the same education and materials described above. Subjects guided through a set of questions that explored personal issues related to cancer and genetic testing. Subjects discussed the emotional impact of having a family history of cancer, psychosocial implications of genetic testing for inherited breast and ovarian cancer susceptibility, anticipated reactions to a positive and negative test result, and intentions to communicate test results to family members and friends.</td>
<td>IES: 17-item questionnaire to measure an individual’s level of distress in relation to a specific event or condition</td>
<td>Year NR 1 month</td>
</tr>
<tr>
<td>Lobb et al, 2004</td>
<td>Good</td>
<td>A) Self-administered questionnaires were mailed 2 weeks before and 4 weeks after their genetic consultation. Consultations were taped and retained for analysis. Questionnaires included Breast Cancer Genetics Knowledge, Expectations, Perceived Risk, IES, HADS, and Satisfaction with Genetic Counseling Scale. B) Women came to the center for their genetic consultation. The consultation was recorded, analyzed, and coded to capture 10 aspects of genetic counseling. Not all counselors incorporated all aspects, and this was the basis for the study.</td>
<td>NSI: Scale of 0 to 7 to assess genetic clinic expectations Scale of 0 to 9 to assess information sought Scale of 0 to 100 to assess risk perception IES: 15-item scale measuring intrusion and avoidance responses in relation to a specific stressor HADS: 14-item self-report scale for the detection of depression and anxiety in hospitalized patients</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Watson et al, 1998</td>
<td>Good</td>
<td>All subjects were referred for genetic counseling with a clinical geneticist who provided a consultation (randomized at clinic immediately after consultation to minimize bias), including pedigree based on risk calculation and information regarding management options based on risk level. All were part of consultation A) Consultation plus audiotape group offered instructions on self-exam and clinical exam and received an audiotape of the consultation B) Consultation-only group offered instructions on self-exam and clinical exam</td>
<td>GHQ-12: 12-item questionnaire to screen individuals for psychiatric disorders CWS: 3-item questionnaire to measure how frequently an individual worries about getting breast cancer VAS: Any of a number of pain self-assessment tools where subjects indicate their level of pain in response to a continuous visual scale</td>
<td>Year NR 6 months</td>
</tr>
</tbody>
</table>
## Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Interventions</th>
<th>Measures</th>
<th>Duration of followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson et al, 1999</td>
<td>Good</td>
<td>A) Self-administered questionnaires given at genetic clinic immediately, pre-, and post-genetic consultation, and by postal survey at 1-, 6-, and 12-month followup</td>
<td>NSI: Lifetime risk perception assessed as a 1 in x odds ratio Relative risk assessed on a 5-point scale Breast cancer incidence assessed as 1 in x GHQ: 12-item questionnaire to screen individuals for psychiatric disorders IES: 17-item questionnaire to measure an individual’s level of distress in relation to a specific event or condition STAI: Measures an individual’s current anxiety feelings</td>
<td>Years: 12 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong et al, 2005</td>
<td>Good</td>
<td>Logistic regression model of association between race and use of genetic counseling: OR (95% CI) African American (vs. white): 0.28 (0.09 to 0.89) Increased age: 0.97 (0.93 to 0.99) Increased probability of BRCA mutation: 1.25 (1.10 to 1.42) Increased risk perception for breast cancer: 2.88 (1.98 to 4.21) Increased risk perception for ovarian cancer: 1.56 (1.02 to 2.38) Increased ovarian cancer worry: 1.56 (1.02 to 2.38) Belief that testing leads to discrimination: 0.74 (0.57 to 0.96) Increased belief that testing provides reassurance: 1.60 (1.15 to 2.23) Gynecologist discussed BRCA testing: 1.79 (1.02 to 3.13) PCP discussed BRCA testing: 1.93 (1.00 to 3.74) NS associations: marital status, education, income, health insurance, increased breast cancer worry, belief that testing provides information, belief that testing creates anxiety, and number of visits to gynecologist or PCP</td>
<td>African Americans are less likely to undergo genetic counseling than whites. Women who believe testing is likely to lead to discrimination were not likely to undergo genetic counseling. Older women were less likely to undergo genetic counseling than younger women. Women with an increased risk perception for either breast or ovarian cancer were likely to undergo genetic counseling.</td>
<td>The American Cancer Clinical Research Training Grant and the Robert Wood Johnson Generalist Physician Faculty Scholar Award</td>
</tr>
<tr>
<td>Author, year Quality</td>
<td>Results</td>
<td>Conclusions</td>
<td>Funding source</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>---------</td>
<td>-------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>Bennett et al, 2008 [150] NA</td>
<td><strong>Baseline vs. followup after risk assessment</strong>&lt;br&gt;Mean scores (SE)&lt;br&gt;HADS-D: 4.44 (3.77) vs. 4.05 (3.85); NS&lt;br&gt;HADS-A: 8.02 (4.56) vs. 7.03 (4.41); NS&lt;br&gt;IES-I: 13.17 (10.57) vs. 7.76 (8.95); p&lt;0.001&lt;br&gt;IES-A: 12.19 (10.78) vs. 8.45 (9.61); p&lt;0.01&lt;br&gt;Perceived health, quality of life (scale, 0 to 100): 76.74 (20.10) vs. 77.96 (17.68); p&lt;0.05&lt;br&gt;DUKE-SSQ (scale not described): 27.15 (11.93) vs. 24.97 (11.02); p&lt;0.01</td>
<td>Following risk status disclosure, women did not have changes in their level of anxiety or depression, as measured by the HADS; their intrusive thoughts and avoidance of intrusive thoughts declined after notification, while their perceived quality life of health and satisfaction increased. This indicates the level or risk disclosed does not negatively impact women’s psychological well-being.</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Bennett et al, 2009 [149] NA</td>
<td><strong>Baseline vs. followup after risk assessment</strong>&lt;br&gt;IES-I (estimated from graph)&lt;br&gt;High risk: 12.5 vs. 7.8 (p&lt;0.001)&lt;br&gt;Moderate risk: 12.5 vs. 7.9 (p&lt;0.001)&lt;br&gt;Low risk: 11.8 vs. 8.2 (p&lt;0.001)&lt;br&gt;Between-group differences were NS (p=0.694)&lt;br&gt;IES-A (estimated from graph)&lt;br&gt;High risk: 13.1 vs. 8.3 (p&lt;0.05)&lt;br&gt;Moderate risk: 10.6 vs. 8.9 (p&lt;0.05)&lt;br&gt;Low risk: 10 vs. 11.3 (p&lt;0.05)&lt;br&gt;Between-group differences for low vs. moderate and high risk was significant (p&lt;0.05)</td>
<td>Levels of worry fell among all women following risk assessment, regardless of risk status assignment. Only women with low (population) risk had high frequencies of avoidance after risk assessment. Intrusive worries were associated with a lack of confidant support and a confrontive coping response.</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>
## Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anxious</strong></td>
</tr>
<tr>
<td>Quality</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
### Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain et al, 2011</td>
<td>NA</td>
<td>A vs. B</td>
<td>Mean perceived risk after risk assessment: 3.83 (SD, 0.51) vs. 3.97 (SD, 0.38); p=0.01 All other outcomes were NS between groups</td>
<td>Women's cancer worry decreased over time regardless of intervention group, though there was a significant effect immediately after risk assessment, this effect was gone by 9 months followup.</td>
</tr>
<tr>
<td>Braithwaite et al, 2005</td>
<td>Fair</td>
<td>A vs. B</td>
<td>Mean baseline cancer worry (scale, 1 to 4): 1.92 vs. 1.81 Mean baseline STAI-state anxiety (scale, 20 to 80): 35.73 vs. 40.00 (p&lt;0.01) Perceptions of risk information Participants were positive about risk information from both interventions on credibility, trustworthiness, accuracy, clarity, and helpfulness. Nurse counseling scored significantly higher than GRACE for all; significant differences in participants' satisfaction with risk information. Clinical nurse specialist arm was &quot;very satisfied&quot; with risk information (p&lt;0.01)</td>
<td>No significant differences between GRACE and nurse counseling in risk perception or cancer worry. Nurse counseling was superior to GRACE on patient attitudes and satisfaction indicators.</td>
</tr>
<tr>
<td>Fry et al, 2003</td>
<td>Fair</td>
<td>A (standard) vs. B (novel)</td>
<td>Cancer worry Baseline: 11.5 (3.2) vs. 11.3 (3.0) 4 weeks: 10.3 (2.4) vs. 10.2 (2.7) 6 months: 9.9 (2.5) vs. 9.7 (2.7) GHQ-30 total score: median (IQR) Baseline: 2 (9) vs. 2 (7.3) 4 weeks: 1 (8) vs. 2 (8.5) 6 months: 0 (4) vs. 0 (5) GHQ-30 case-level distress: n (%) Baseline: 66 (36) vs. 58 (31) 4 weeks: 32 (21) vs. 27 (22) 6 months: 29 (21) vs. 28 (23)</td>
<td>All women experienced a significant reduction in CWS scores, with greatest reductions from baseline to 4 weeks (p&lt;0.000) and a smaller, but still significant, reduction from 4 weeks to 6 months (p=0.003). Women experienced a significant drop in case-level distress from baseline to 4 weeks (p=0.004), but there were no other significant differences in numbers of women with case-level distress between trial arms or time points.</td>
</tr>
<tr>
<td>Gurmankin et al, 2005</td>
<td>NA</td>
<td>Mean breast cancer risk perception: 44% Risk perception change from baseline: +17% (p&lt;0.001) Accuracy of recall Risk information patients recalled was higher than risk communicated to them (+6% p=0.02 vs. 8% p=0.001) Patients' belief in recall was positive for breast cancer, showing postcounseling risk perceptions higher than risk information they recalled being told (+9% p=0.001)</td>
<td>Patients' breast cancer risk perceptions following risk communication were higher than corresponding actual risk communicated to them (+19% p&lt;0.001). Inaccurate risk perception (high or low) can lead patients to make different medical decisions than they would with accurate risk perception. They could engage in interventions or experience unnecessary stress if perceived risks are inaccurately high.</td>
<td>The American Cancer Society and a Robert Wood Johnson Faculty Scholar Award</td>
</tr>
</tbody>
</table>
## Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helmes et al, 2006¹⁵⁷</td>
<td><strong>A vs. B vs. C (change from baseline to followup)</strong></td>
<td>Mean risk perception (scale, 0 to 100): -10.29 vs. -8.65 vs. +1.14 (p&lt;0.001) Mean cancer worry (scale, 4 to 16): -0.9 vs. -0.82 vs. -0.38 (p=0.002) Breast health intentions (score, 1 to 4): 0 vs. +0.01 vs. +0.02 (NS) Interest in genetic testing (score, 1 to 4): -0.61 vs. -0.52 vs. +0.51 (p&lt;0.001)</td>
<td>There were no differences between in-person and telephone counseling; however, both intervention groups decreased risk perception, cancer worry, and interest in genetic testing compared to the group that did not receive counseling. Counseling and no counseling had no affect on breast health intentions. National Human Genome Research Institute grant HG01190</td>
</tr>
<tr>
<td>Hopwood et al, 2004¹⁵⁸</td>
<td><strong>Precounseling vs. 1-month followup vs. 12-months followup</strong></td>
<td>Underestimated risk: 49/162 (30%) vs. 37/162 (23%) vs. 36/162 (22%) Mean GHQ (scale, 0 to 28): 3.4 vs. 3.0 vs. 3.4 (NS) Mean CWS (scale, 1 to 16): 11.6 vs. 10.9 vs. 10.8 (p&lt;0.001)</td>
<td>Cancer distress decreased after counseling and continued to be low 1 year later. NHS Research and Development Directorate, Programme for Cancer; Project NCP/B42</td>
</tr>
<tr>
<td>Kelly et al, 2008¹⁵⁹</td>
<td><strong>Precounseling vs. postcounseling (ovarian cancer)</strong></td>
<td>Accuracy of risk perception (estimated from graph): 1 vs. -5 Mean risk assessment (0% to 100%): 30.81 (SD, 3.84) vs. 25.45 (SD, 3.45) Postcounseling vs. postresult vs. 6-month followup Mean risk assessment (0% to 100%) Those with positive result (n=7): 27.86 (SD, 8.01) vs. 31.43 (SD, 7.46) vs. 22.14 (SD, 7.23) Those with informative negative result (n=5): 27.00 (SD, 6.63) vs. 11.00 (SD, 2.45) vs. 15.00 (SD, 5.00) Those with uninformative negative result (n=28): 24.50 (SD, 4.48) vs. 19.76 (SD, 4.29) vs. 17.82 (SD, 3.20)</td>
<td>All women underestimated their risk of developing ovarian cancer. The New Jersey Commission on Cancer Research and the Mid-Atlantic Region Human Genetics Network</td>
</tr>
<tr>
<td>Matloff et al, 2006¹⁶⁰</td>
<td><strong>A vs. B</strong> Mean discrepancy between perceived risk for self and average woman Baseline: 16.3 (SD, 17.9) vs. 22.3 (SD, 24.3) 1 month: 0.8 (SD, 22.3) vs. 21.1 (SD, 25.4) 6 months: 3.6 (SD, 20.1) vs. 18.3 (SD, 23.0) <strong>A only</strong> Mean discrepancy between perceived risk for self and actual risk Baseline: 36.9 (SD, 20.4) 1 month: 18.9 (SD, 28.6) 6 months: 17.1 (SD, 25.9)</td>
<td>After counseling, accuracy of perceived risk of breast cancer increased.</td>
<td>Susan G. Komen Foundation</td>
</tr>
<tr>
<td>Mikkelsen et al, 2007¹⁶¹</td>
<td><strong>A vs. B vs. C</strong> Perceived absolute lifetime risk of breast cancer (%) Mean within-group changes from baseline to 1-year followup: -6.6 (95% CI, -3.0 to -10.2) vs. 1.6 (95% CI, 3.6 to -0.5) vs. 1.1 (95% CI, 2.2 to 0.0) Mean between-group changes: -8.2 (95% CI, -12.2 to -4.1) counseling vs. group 1; -7.7 (95% CI, -11.4 to -4.0) counseling vs. group 2 Change in risk accuracy of perceived lifetime risk of breast cancer (%) Overestimate: -12 vs. 5 vs. 2 Accurate at 1-year followup: 16 vs. -5 vs. -2 (p=0.03 for A vs. B and</td>
<td>Genetic counseling helped to increase risk accuracy even 1 year after counseling. Danish Cancer Society, Grant Number PP 02 010, the Center of Innovation and Development in Nursing Education in the County of Aarhus and Aarhus University Research Foundation</td>
<td></td>
</tr>
</tbody>
</table>
## Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roshanai et al, 2009(^{164})</td>
<td>Fair</td>
<td>The only significant difference between intervention and control was immediately after counseling and at 2 weeks, when controls showed more accurate estimation of risk; groups showed the same results at 8-months followup. No significant difference for anxiety or depression between control and intervention at any time point; both groups significantly decreased over time (p&lt;0.01).</td>
<td>At 8-months followup, 74% of counselees in control and intervention groups had informed relatives; 96% of relatives of intervention counselees and 89% of relatives of controls reported being informed. The majority (75% of intervention relatives and 67% of controls) reported receiving sufficient information.</td>
<td>The Swedish Cancer Society</td>
</tr>
</tbody>
</table>
| Pieterse et al, 2011\(^{163}\) | NA | Risk perception accuracy: N (%)
Pre-counseling vs. immediately postcounseling vs. 6-months postcounseling
Underestimation: 1 (3) vs. 5 (16) vs. 8 (24)
Correct estimation: 0 (-) v. 10 (32) vs. 6 (18)
Overestimation: 29 (97) vs. 16 (52) vs. 19 (57)
Total number of counselees: 3 (unaffected group) | Counseling educates women on lifetime breast cancer risk; correct knowledge on breast cancer genetics decreased over time. Benefits gained immediately after counseling seem to remain over time. | Dutch Cancer Society supported original study (Grant number NIVEL 1999-2090); author supported by a post-doctoral fellowship from the Dutch Cancer Society. |
| Mikkelsen et al, 2009\(^{162}\) | Fair | A vs. B vs. C
HADS-A score decreased from baseline to 1 year: 4.7% (95% CI, -3.5 to 12.8) vs. 2.5% (95% CI, -4.5 to 9.5) vs. 1.1% (95% CI, -2.3 to 4.7); decrease in anxiety in group 1 was in women in nonsystematic screening (7.0% [95% CI, -4.1 to 18.1]), with a slight increase in women in systematic screening (1.1% [95% CI, -7.5 to 9.8])
Baseline vs. 2-weeks followup vs. 6-months followup vs. 12-months followup
Cancer-specific distress: 52% vs. 50% vs. 41% vs. 41%
Comparing women referred for mammography vs. no genetic counseling (41% to 35%) or to a random sample from the general population (from 32% to 30%) with no counseling. More women with genetic counseling experienced decrease in cancer-specific distress; difference statistically significant when compared to general population (p=0.006) and subgroup of women with mammography screening (p=0.05). | An 11% (95% CI, 1.4 to 20.8) decrease in cancer-specific distress in genetic counseling group from baseline to 1-year followup exceeded decrease in groups 1 and 2, with significance in group 2 (p=0.006) and subgroup of group 1 in systematic screening (p=0.05). | Danish Cancer Society, Grant Number PP 02 010, the Center of Innovation and Development in Nursing Education in the County of Aarhus and Aarhus University Research Foundation, and the Danish Nurses’ Organization |
| Bowen et al, 2002\(^{57}\) | Fair | Counseling on risk slightly changed levels of interest in genetic testing in women with a family history. Those who participated in counseling were less interested in genetic testing and less likely to view themselves as good candidates. Stigma and access beliefs about genetic testing were related to the effect of counseling on whether women thought they should participate in testing. As women gained more information, they were slightly less likely to want to participate in testing. | Individual counseling was more predictive of women's increased awareness than psychosocial group counseling. | The National Cancer Institute and the National Human Genome Institute (HG01190) |

Note: p=0.07 for A vs. C.)
### Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowen et al, 2004</td>
<td>Fair</td>
<td>Women’s perceived risk for breast cancer decreased by 50% for the 2 counseling groups relative to control (p&lt;0.01). Cancer worry decreased in both counseling groups by 1 scale point (p&lt;0.05). There were no differential effects of counseling type on perceived risk or cancer worry. Women in psychosocial counseling experienced more anxiety change than those in the other groups. Depression was not impacted by study group.</td>
<td>Some women reported high levels of attendance and satisfaction with counselors and counseling; women in the genetic counseling arm reported more frequently talking about concerns than did women in psychosocial groups. Perceived risk and worry can be reduced with both types of short-term interventions.</td>
<td>The National Human Genome Institute, the National Cancer Institute, and the National Office for Research on Women’s Health (HG/CA01190)</td>
</tr>
<tr>
<td>Brain et al, 2002</td>
<td>Good</td>
<td>State anxiety: Significant main effect of time, with decreased anxiety from baseline to followup (p=0.03). Breast cancer worry: Significant overall reduction from baseline to followup. Significant interaction between risk information and time. Decline in women at low risk (t(106), 5.92; p&lt;0.001) and moderate risk (t(443), 12.13; p&lt;0.001), but not at high risk. Satisfaction: Significantly lower in high-risk group (p&lt;0.001). Perception of risk: Marginally significant trend to increased perceived risk in high-risk women in the trial group. Interest in genetic testing: Effect of risk information not significant.</td>
<td>Specialists other than geneticists might provide assessment of breast cancer risk, reassuring those at reduced risk and targeting high-risk women for specialist genetic counseling and testing services. Low-risk women: Anxiety and cancer concerns were reduced with personal risk information. High levels of satisfaction, whether or not information based on detailed genetic analysis. High-risk women: Risk information, even unfavorable, does not appear to create significant anxiety. Concerns about breast cancer risk remained and they were less satisfied with consultation in either group. Implication: Breast cancer worry may impact quality of life for women who recognize they are at high risk.</td>
<td>The Medical Research Council, National Assembly for Wales, NHS R&amp;D (Wales), and Imperial Cancer Research Fund. Dr. Gray is supported by Tenovus, a cancer charity</td>
</tr>
<tr>
<td>Burke et al, 2000</td>
<td>Fair</td>
<td>Significant differences between counseling and control groups in mean perceived risk of breast cancer (F=27.9; p&lt;0.009). Significant differences over time in perceived risk for the counseling group (F=65.9; p&lt;0.001). Interaction between group and time for perceived risk was significant (F=50.6; p&lt;0.001). Low overestimators of breast cancer risk reduced risk estimates by an average of 19 percentage points after counseling, compared with high overestimators who reduced risk estimates by an average of 36 percentage points (F=13.41; p&lt;0.00001). After counseling, those who perceived themselves as candidates for testing decreased from 82% to 60%; interest in testing was reduced from 91% to 60%. 82 (70%) liked the counseling very much. 65 (56%) found the counseling very useful and 26 (22%) found it moderately useful. After receiving risk estimates, 39 (33%) were a lot less worried and 37 (32%) were a little less worried.</td>
<td>Most participants saw a benefit to counseling and afterward had a more accurate understanding of their risk. Counseling reduced interested in genetic testing.</td>
<td>The National Institutes of Health (HGO1190)</td>
</tr>
</tbody>
</table>
### Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
</table>
| Cull et al, 1998 | Good | **Duration of Consultation:** VB group spent less time with surgeon (mean, 11.8 min vs. 14.6; p< 0.05), but their time with geneticist was not significantly shorter.  
**Risk Assessment:** No significant difference between VB or VA in accuracy of estimate at baseline. VB retained accuracy from clinic to followup. VA were more likely to underestimate at followup (p<0.05).  
**Understanding of Risk Information:** Subjective: at baseline and at followup, no significant difference. Objective: VB had higher scores (p<0.01) and a higher proportion of correct responses to more items. Followup: no significant differences after adjusting for education level (t=0.34).  
**Emotional Distress:** No significant difference in groups in anxiety or distress levels.  
**Use of Video and Family Discussion:** VB: 94% watched video at least 1 time from start to finish. 76% reported it offered new information. VA: 41/42 who gave followup data watched the video at least once and 41% of them said it gave new information. In both VA and VB, most (66% and 65%, respectively) watched it alone and most discussed it with a partner. | Women who saw the video before their clinic visit were not deterred from attending. Compliance with the study and satisfaction with the clinic visit were higher among those who viewed the video beforehand. | The NHS R&D (Cancer) Programme and the Imperial Cancer Research Fund |
| Hopwood et al, 1998 | Fair | GHQ scores: Compliance at baseline was 85% (n=34) and 94% at 3 months (n=148). Prevalence of psychological distress, with a cutoff score of >5, was 31% at baseline and 26% at 3 months. An examination of the 4 subscales of GHQ showed that 9.7% scored a ≥5 on the somatic scale, 14% on the anxiety subscale, and 3% each on the depression and suicidal ideation subscales at baseline. At 3 months, proportions were 12%, 15%, 6.8%, and 3.4%, respectively. When analysis was restricted to 105 women with evaluable assessments on all occasions, prevalence was 31% and 25%, respectively. Baseline scores compared with precounseling risk estimates showed no significant difference (p=0.087). Significant differences between psychological distress and perceived risk postcounseling (p=0.0053). Women with accurate risk knowledge postcounseling had significantly lower scores than those who underestimated (p=0.0034) or who overestimated (p=0.0447).  
**Psychiatric Assessment Schedule:** Psychiatric disorder was confirmed in 21 (13.3%) of the study participants at 3 months. Most women had multiple concerns, but none reported risk counseling as a precipitant for their distress.  
**Estimation of risk:** Prior to risk counseling, 10% accurately estimated risk of breast cancer, while 50% accurately estimated after (p=0.0000). More women continued to overestimate (17%) than underestimate (11%). In general, giving women an accurate estimate of their probability of breast cancer when they perceived it to be much lower did not appear to trigger | Prevalence rate for psychological distress when measured by a self-report questionnaire was double that ascertained by psychiatric interview, which is regarded as the gold standard. Interview data suggests that psychiatric morbidity was not apparently caused by the genetic counseling. This suggests that routine genetic risk consultations do not facilitate disclosure of distress or unresolved grief, and the use of a screening instrument together with a second-stage assessment interview should be explored further. | The Cancer Research Campaign |
### Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lerman et al, 1996</strong>&lt;sup&gt;168&lt;/sup&gt; <strong>Fair</strong></td>
<td>Breast cancer preoccupation: IES average score on measure of breast cancer preoccupation was 6.9 ± 0.71 (mean ± SE). No significant baseline difference in risk comprehension between groups; however, significant change in risk comprehension at 3-months followup due to movement in risk counseling group from overestimation to accurate or underestimation. IES scores: All groups evidenced a reduction in distress from baseline to 1 month. However, this decrease, although not a significant difference, was smallest among African American women who received education plus counseling.</td>
<td>Among women with less formal education, counseling led to significant reductions in distress by the 3-months followup, suggesting a possible increased adherence to mammography.</td>
<td>Public Health Service grants ROICA57767 and K07CA01604 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services</td>
</tr>
<tr>
<td><strong>Lerman et al, 1999</strong>&lt;sup&gt;60&lt;/sup&gt; <strong>Fair</strong></td>
<td>Genetic testing intention: Family history and baseline genetic testing intentions both made significant independent contributions to 1-month genetic testing intentions. Women with stronger family history of cancer had greater increases in intentions. Only in African Americans, education plus counseling led to greater increases in intentions than education only (p=0.003). IES scores: All groups evidenced a reduction in distress from baseline to 1 month. However, this decrease, although not a significant difference, was smallest among African American women who received education plus counseling.</td>
<td>Overall: African American women were found to differ significantly from Caucasian women in the effects of the interventions on testing intentions and provision of a blood sample. Effects were independent of socioeconomic status and referral mechanism.</td>
<td>The National Institutes of Mental Health and National Human Genome Research Institute grant MH/HG54435</td>
</tr>
<tr>
<td><strong>Lobb et al, 2004</strong>&lt;sup&gt;169&lt;/sup&gt; <strong>Good</strong></td>
<td>Anxiety: Women who had more aspects of genetic testing discussed had a decrease in anxiety after 4 weeks (p=0.03). Women receiving a letter summarizing their consultation had lower anxiety (p=0.012) and a trend toward less anxiety about breast cancer (p=0.089). Women who received ≥4 supportive communications were more anxious about breast cancer (p=0.000). Depression: Women whose consultants facilitated understanding more had a decrease in depression (p=0.052). Risk Accuracy: Women receiving a letter summarizing their consultation had increased risk accuracy (p=0.023).</td>
<td>Women who understood what was being presented to them had decreased depression. This can imply that women may feel overwhelmed with the amount of information they receive and may feel worse if they are not helped to understand it. Providing a written summary of the consultation helped with accurate risk perception.</td>
<td>The University of Sydney Cancer Research Fund</td>
</tr>
<tr>
<td><strong>Watson et al, 1998</strong>&lt;sup&gt;171&lt;/sup&gt; <strong>Good</strong></td>
<td>CWS scores: For both groups, median score was 11 (range, 6-22) (95% CI, 10-12 for cases and 95% CI, 10-11 for controls); mean, 11.14 (SD, 3.23) for cases and mean, 11.39 (SD, 3.37) for controls. Scores fell in subjects given a tape of consultation from a median of 11 at baseline to 10 at 1 month, then 9 at 6 months. Relative risk scores: At 1-month followup, 41% accurately recalled their risk of developing cancer, 25% overestimated, 11% underestimated, 23% didn’t know/didn’t remember. Results suggest that risk figure, regardless of accuracy, doesn’t reflect more general view about risk compared with average women. When rRisk figure was given as odds ratio compared with other formats (percentage or descriptive terms), 71% were accurate in recall compared with 25% when given in other formats. Risk questionnaire scores: Usefulness of information rated on a visual analog scale. Average ratings were high, ranging from 8.5 (population</td>
<td>Overall: GHQ-12 scores: For combined groups, median score was 1 (range, 0-11). 36 subjects had a score indicative of psychological morbidity (&gt;3) at baseline and 31 at 1-month and 6-month followup.</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Appendix C6. Evidence Table of Genetic Counseling

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson et al, 1999 Good</td>
<td>GHQ: One third had notable levels of distress. There was no statistically significant change in general mental health at each followup compared with precounseling level. Cancer Anxiety and Helplessness/IES: No statistically significant changes in levels of cancer-specific distress. Followup assessment revealed that 13% (35/268) had received some psychological intervention during the 12 months since attending the clinic. Of these, 7% (n=19) had received psychotropic medication, 4% (n=10) had engaged in psychological counseling, and 2% (n=6) had received both forms of intervention. Levels of state anxiety: Anxiety levels at precounseling were at similar levels to those reported in healthy women attending for breast cancer screening (mean, 38.7), with a significant downward shift immediately postcounseling (mean, 35.2; p&lt;0.001). Perceived risk: Specific figures about risk, provided within genetic counseling, tend not to be remembered. Continual overestimators may be worrying unnecessarily and excessively about breast cancer risk and underestimators appear undisturbed by the information that their risk is greater than they thought. Underestimators were not significantly different from the rest of the sample in terms of their scores for intrusive and avoidant thoughts about breast cancer risk when assessed precounseling. However, at 12 months, their scores were significantly lower than the rest on each of the scales (avoidance, p=0.02; intrusion, p=0.006), indicating that in the long term they are less likely to report having intrusive thoughts about breast cancer risk. High levels of cancer-specific distress were found in pregenetic counseling, with 28% reporting that they worried about breast cancer &quot;frequently or constantly&quot; and 18% worry about breast cancer as a &quot;severe or definite&quot; problem. Following genetic counseling, levels of cancer-specific distress were unchanged. General mental health remained unchanged over time (33% psychiatric cases were detected pregenetic counseling, and 27% 12 months after genetic counseling).</td>
<td>High levels of cancer-related worry compare unfavorably to previously gathered data on general population risk samples. Genetic counseling does not alleviate cancer-specific distress in a substantial minority of women; this contradicts previous U.S. findings. A single counseling session may not shift worries in some women. General levels of psychological morbidity unaffected by genetic counseling. Substantial minority of women who do not benefit from counseling and continue to overestimate risk, and worry was unrelied. Study highlights problems with genetic counseling (e.g., some women continue to overestimate risk despite being told otherwise). Anxiety is not alleviated by genetic counseling, and women who continue to overestimate their risk and worry about breast cancer are likely to go on seeking unnecessary screening.</td>
<td>The Cancer Research Campaign (CRC project CP1026)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CASH = Cancer and Steroid Hormone Study; CI = confidence interval; CG = control group; FDR = first-degree relative; GHQ = General Health Questionnaire; FHC = family history clinic; GRACE = Genetic Risk Assessment in the Clinical Environment; HADS = Hospital Anxiety and Depression Scale; ICG = individual genetic counseling; IES = Impact of Event Scale; LCIS = lobular carcinoma in situ; NHS = National Health Service; NR = not reported; OR = odds ratio; PC = psychosocial counseling; PCP = primary care
## Appendix C7. Evidence Table of Prevalence of BRCA1 and BRCA2 Mutations

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Data source/parent study</th>
<th>Setting</th>
<th>Population</th>
<th>Inclusion/exclusion criteria</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beristain et al, 2007</td>
<td>NA</td>
<td>NR</td>
<td>Individuals with suspicious personal or family history.</td>
<td>Cases met 1 of the following criteria: 1) patients without family history of breast and/or ovarian cancer, but showing early onset breast cancer (age &lt;40); 2) patients from families with 2 cases of female breast cancer, 1 diagnosed at age &lt;50; 3) patients of families with ≥3 cases of female breast cancer; 4) patients from families with ≥1 case of breast cancer or ovarian cancer in association with ≥1 case of male breast cancer; 5) patients from families with ≥1 cases of ovarian cancer or breast and ovarian cancer in the same individual; 6) patients from families with ≥2 cases of ovarian cancer. Each index case was the youngest individual affected with breast and/or ovarian cancer alive in each family.</td>
<td>Basque Country, Spain</td>
</tr>
<tr>
<td>Konecny et al, 2011</td>
<td>NA</td>
<td>High-risk clinics</td>
<td>Individuals referred for genetic analysis on the basis of family history.</td>
<td>Families were included if they met any of the following criteria: 1) the presence of ≥2 patients with diagnosed breast or ovarian cancer among the direct relatives and ≥1 case diagnosed at age &lt;45; 2) the presence of bilateral breast or ovarian cancer among the direct relatives diagnosed at any age; 3) occurrence of duplex breast and ovarian cancer in ≥1 patient diagnosed at any age; 4) the presence of sporadic breast or ovarian cancer diagnosed at age &lt;35 years; 5) the presence of ≥1 case of male breast cancer diagnosed at any age.</td>
<td>Slovakia</td>
</tr>
<tr>
<td>Nanda et al, 2005</td>
<td>NA</td>
<td>Genetics clinic</td>
<td>Families presenting to high-risk clinic.</td>
<td>Families with ≥2 cases of breast cancer, ovarian cancer, or both among FDRs and SDRs. Families were excluded if any individual had previously been tested for a BRCA1 or BRCA2 mutation.</td>
<td>U.S.: University of Chicago, Mayo Clinic, Rush University, UCSF</td>
</tr>
<tr>
<td>Neuhausen et al, 2009</td>
<td>Breast Cancer Family Registry</td>
<td>Population and clinic-based family registries</td>
<td>Probands and their families recruited through population and clinic-based registries.</td>
<td>Population-based families from the California Breast CFR recruited case probands &lt;65 years at diagnosis; &lt;70 years at diagnosis from the Ontario Breast CFR; and case probands stratified by age from the Australian Breast CFR. Clinic-based families from the Philadelphia and New York Breast CFRs recruited affected and unaffected probands with a family history of breast and/or ovarian cancer; families with ≥3 cases of breast or ovarian cancer, especially if ≥1 occurred before age 45, were recruited to the Utah Breast CFR; and affected and unaffected probands with ≥2 affected relatives were recruited to the Australian Breast CFR. Ashkenazi Jewish women with a personal or family history of breast cancer were recruited through the New York, Philadelphia, Ontario and Australian Breast CFRs.</td>
<td>U.S., Canada, Australia</td>
</tr>
</tbody>
</table>
### Appendix C7. Evidence Table of Prevalence of BRCA1 and BRCA2 Mutations

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Data source/parent study</th>
<th>Setting</th>
<th>Population</th>
<th>Inclusion/exclusion criteria</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seymour et al, 2008</td>
<td>Cancer Prevention Units in the Forli-Cesena and Ravenna provinces of north-central Italy</td>
<td>Genetics clinic</td>
<td>Women undergoing breast checkups who completed a questionnaire on family history.</td>
<td>Healthy or affected individuals from families meeting 1 of the following criteria: 1) ≥1 relative diagnosed with a) BC at age &lt;36 years, b) BC and OC in the same patient at any age, c) bilateral BC at age &lt;51 years, d) male BC at any age, e) OC of fallopian tube cancer at age &lt;46 years; or 2) a) 2 relatives diagnosed with BC at age &lt;51 years, b) 1 relative with BC at age &lt;51 years and 1 relative with bilateral BC at any age, c) 1 relative with BC at age &lt;51 years and 1 relative with OC or fallopian tube cancer at any age, d) 2 relatives diagnosed with OC of fallopian tube cancer at any age; or 3) ≥3 relatives diagnosed with BC at any age.</td>
<td>Italy</td>
</tr>
<tr>
<td>Tamboom et al, 2010</td>
<td>Estonian Cancer Registry</td>
<td>North Estonia Medical Centre's Centre of Oncology and the Hematology and Oncology Clinic of Tartu University Hospital</td>
<td>Early onset, familial, and predictive cases.</td>
<td>Early onset cases were identified if diagnosed with breast cancer &lt;45 years. Early onset cases with a familial history of breast or ovarian cancer were classified as familial cases. Familial cases were identified as individuals with breast or ovarian cancer, including early onset, with ≥1 relative with these cancers. Predictive testing cases included individuals with high-risk families (≥2 relatives diagnosed with breast or ovarian cancer) who did not have breast or ovarian cancer themselves.</td>
<td>Estonia</td>
</tr>
<tr>
<td>Tommasi et al, 2005</td>
<td>Dipartimento Donna of the National Cancer Institute of Bari, Italy</td>
<td>Surgical department</td>
<td>Women with a first diagnosis of breast cancer undergoing surgery.</td>
<td>A preliminary investigation of cancer syndromes was performed by a surgeon and the patients eligible for genetic counseling were referred.</td>
<td>Italy</td>
</tr>
<tr>
<td>Vaziri et al, 2001</td>
<td>Familial Cancer Registry of the Cleveland Clinic Foundation</td>
<td>Clinic</td>
<td>Breast and breast-ovarian cancer families recruited through the registry.</td>
<td>An affected proband with ≥2 family members with cancer; 2 of whom must have either breast cancer (&lt;50 years) or ovarian cancer; and ≥1 with breast, ovarian, colon, prostate or pancreatic cancer. Cases must be present in ≥2 generations.</td>
<td>U.S.</td>
</tr>
<tr>
<td>Weitzel et al, 2005</td>
<td>City of Hope's Cancer Screening &amp; Prevention Program Network</td>
<td>High-risk clinics; Hereditary Cancer Registry</td>
<td>All patients presenting for genetic cancer risk assessment.</td>
<td>Probands of Hispanic origin who enrolled in the registry between October 1998 and October 2004 and underwent testing. Participants with Hispanic origin only on 1 parental side were eligible if that side was significant for a history of breast cancer.</td>
<td>Hispanic; U.S.</td>
</tr>
<tr>
<td>Unselected populations (Ashkenazi Jewish)</td>
<td>Article published in a national newspaper in May 2008</td>
<td>Ashkenazi or Sephardic Jews.</td>
<td>Women who self identified as (Ashkenazi or Sephardic) Jewish, who were between the ages of 25 and 80 years, and who resided in Ontario. Not selected on the basis of family or personal history of cancer.</td>
<td>Ontario, Canada</td>
<td></td>
</tr>
</tbody>
</table>

*BRCA-Related Cancer* 278  Pacific Northwest EPC
## Appendix C7. Evidence Table of Prevalence of BRCA1 and BRCA2 Mutations

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Primary risk measure</th>
<th>Comparison group</th>
<th>Family history/risk level definition</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence high-risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beristain et al, 2007</td>
<td>Post intervention series</td>
<td>Prevalence</td>
<td>NA</td>
<td>See inclusion/exclusion criteria</td>
<td>236 index cases</td>
</tr>
<tr>
<td>Konecny et al, 2011</td>
<td>Post intervention series</td>
<td>Prevalence</td>
<td>NA</td>
<td>See inclusion/exclusion criteria</td>
<td>585 families</td>
</tr>
<tr>
<td>Nanda et al, 2005</td>
<td>Post intervention series</td>
<td>Prevalence</td>
<td>NA</td>
<td>NR</td>
<td>155 families</td>
</tr>
<tr>
<td>Neuhausen et al, 2009</td>
<td>Post intervention series</td>
<td>Prevalence</td>
<td>NA</td>
<td>See inclusion/exclusion criteria</td>
<td>BRCA1: 4531 probands BRCA2: 4084 probands 1385 Ashkenazi Jewish probands 1360 individuals</td>
</tr>
<tr>
<td>Seymour et al, 2008</td>
<td>Post intervention series</td>
<td>Prevalence</td>
<td>NA</td>
<td>See inclusion/exclusion criteria</td>
<td>363 families 707 individuals</td>
</tr>
<tr>
<td>Tamboom et al, 2010</td>
<td>Post intervention series</td>
<td>Prevalence</td>
<td>NA</td>
<td>See inclusion/exclusion criteria</td>
<td>64 early onset 47 familial 33 predictive</td>
</tr>
<tr>
<td>Tommasi et al, 2005</td>
<td>Case series</td>
<td>Prevalence</td>
<td>NA</td>
<td>Patients were classified as having a family history of breast cancer if 1 of the following conditions was met: 1) ≥3 relatives (1st or 2nd degree) had breast or ovarian cancer; 2) 2 relatives &lt;50 years had breast cancer; 3) 1 relative &lt;36 years had breast cancer; 4) the patient had bilateral cancer and ≥1 relative with breast cancer (or a relative with bilateral cancer); 5) male breast cancer. The Myriad II program was used to compute the probability of finding a BRCA1 mutation. Individuals were classified as having an increased risk if this probability was ≥10%, and a low risk when the probability was &lt;10%.</td>
<td>100 patients</td>
</tr>
<tr>
<td>Vaziri et al, 2001</td>
<td>Post intervention series</td>
<td>Prevalence</td>
<td>NA</td>
<td>See inclusion/exclusion criteria</td>
<td>104 families</td>
</tr>
<tr>
<td>Weitzel et al, 2005</td>
<td>Post intervention series</td>
<td>Prevalence</td>
<td>NA</td>
<td>A calculated BRCA mutation probability of ≥5% by any model.</td>
<td>110 probands</td>
</tr>
<tr>
<td><strong>Unselected populations (Ashkenazi Jewish)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metcalfe et al, 2010</td>
<td>Post intervention series</td>
<td>NA</td>
<td>NA</td>
<td>NR</td>
<td>2080 women</td>
</tr>
</tbody>
</table>

### Demographics

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Demographics</th>
<th>Participation rate</th>
<th>Genes included</th>
<th>Laboratory methods</th>
<th>Tissue source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence high-risk</strong></td>
<td></td>
<td></td>
<td>BRCA1 &amp; BRCA2</td>
<td>The full coding sequences and intronic boundaries were amplified using PCR. CSGE method was used to screen. Genomic fragments with altered mobility patterns were sequenced.</td>
<td>Blood</td>
</tr>
<tr>
<td>Beristain et al, 2007</td>
<td>NR</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>The full coding sequences and intronic boundaries were amplified using PCR. CSGE method was used to screen. Genomic fragments with altered mobility patterns were sequenced.</td>
<td>Blood</td>
</tr>
</tbody>
</table>

BRCA-Related Cancer
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Demographics</th>
<th>Participation rate</th>
<th>Genes included</th>
<th>Laboratory methods</th>
<th>Tissue source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Konecny et al, 2011183</td>
<td>Gender: NR Mean age at diagnosis (BRCA1 vs. BRCA2): 42.7 years (range: 22 to 75) vs. 46 years (range: 33 to 59) Race/ethnicity: Slovak</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>A combination of PCR amplification, SSCP analysis, and direct sequencing was used. Allelic discrimination analysis was used to detect mutation p.Cys61Gly. The MLPA analysis was used.</td>
<td>Blood</td>
</tr>
<tr>
<td>Nanda et al, 2005192</td>
<td>Race/ethnicity: 50% Caucasian (nonHispanic, nonJewish) 28% African American 19% Ashkenazi Jewish 2% Hispanic 1% Asian</td>
<td>117/160 (73%)</td>
<td>BRCA1 &amp; BRCA2</td>
<td>80% were analyzed by Myriad using direct DNA sequencing; 20% were screened by SSCP or dHPLC, followed by sequencing of those with variant results. Individuals who self identified as Ashkenazi Jewish were initially screened for the 3 common founder mutations. Complete sequencing was performed only if the initial screening did not detect 1 of these founder mutations.</td>
<td>NR</td>
</tr>
<tr>
<td>Neuhausen et al, 2009193</td>
<td>Gender: 100% female Age (years) of mutation carriers at diagnosis BRCA1 vs. BRCA2 affected: &lt;30: 43 vs. 21 30-39: 193 vs.107 40-49: 168 vs.100 50-59: 51 vs. 65 &gt;60: 19 vs. 28 Unknown: 1 vs. 0 BRCA2 affected: &lt;30: 21 30-39: 107 40-49: 110 50-59: 65 &gt;60: 28 Unknown: 0 Race/ethnicity 1385 Ashkenazi Jewish BRCA1 vs. BRCA2 probands excluding Ashkenazi Jewish: 63% vs. 61% nonHispanic white 12% vs. 13% Hispanic 9% vs. 10% African American 12% vs. 12% Asian/Pacific Islander 3% vs. 3% other/multiple race 1% vs. 1% unknown</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>Initially, 2-D gel scanning, DHPLC, EMD and PTT. EGAN and CSGE have also been used in the California samples. More recently, majority of testing is performed by Myriad Genetic Laboratories using BRC-Analysis.</td>
<td>Blood and/or buccal samples and tumor tissue</td>
</tr>
<tr>
<td>Seymour et al, 2008196</td>
<td>100% female Median age at diagnosis: 46.6 years (range: 20 to 80) Race/ethnicity: Italian</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>PCR amplification and direct sequencing. Variants were confirmed by resequencing the reverse DNA strand.</td>
<td>Blood</td>
</tr>
</tbody>
</table>
## Appendix C7. Evidence Table of Prevalence of BRCA1 and BRCA2 Mutations

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Demographics</th>
<th>Participation rate</th>
<th>Genes included</th>
<th>Laboratory methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamboom et al., 2010&lt;sup&gt;198&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>SSCP-HA followed by direct DNA sequencing and MDE. All mutations were confirmed using PCR.</td>
</tr>
<tr>
<td>Tommasi et al., 2005&lt;sup&gt;199&lt;/sup&gt;</td>
<td>100% female</td>
<td>NR</td>
<td>BRCA1</td>
<td>PCR amplification and pre-screening using dHPLC analysis, followed by DNA sequencing. If a mutation was identified, it was confirmed using a second sample from the patient.</td>
</tr>
<tr>
<td>Vaziri et al., 2001&lt;sup&gt;201&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>PCR amplification, CSGE, and PTT. Family-specific mutations were amplified and directly sequenced using tissue-derived genomic DNA.</td>
</tr>
<tr>
<td>Weitzel et al., 2005&lt;sup&gt;202&lt;/sup&gt;</td>
<td>99% female</td>
<td>98%</td>
<td>BRCA1</td>
<td>Full sequencing of exons and flanking intronic sequences by Myriad Genetic Laboratories. 5 specific BRCA1 rearrangements for assays done after 2001.</td>
</tr>
<tr>
<td>Metcalfe et al., 2010&lt;sup&gt;190&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>Tested for the 3 Jewish founder BRCA1 (185delAG and 5382insC) and BRCA2 (6174delT) mutations. All mutations were confirmed by direct sequencing.</td>
</tr>
</tbody>
</table>

### Unselected populations (Ashkenazi Jewish)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Parts of genes studied</th>
<th>Who was tested</th>
<th>Results/conclusions</th>
<th>Quality considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beristain et al., 2007&lt;sup&gt;174&lt;/sup&gt;</td>
<td>Exons and intronic boundaries</td>
<td>Proband</td>
<td>16/236 (6.8% of index cases) had mutations</td>
<td>NR</td>
</tr>
<tr>
<td>Konecny et al., 2011&lt;sup&gt;183&lt;/sup&gt;</td>
<td>Whole coding region</td>
<td>NR</td>
<td>BRCA1: 85/585 (15%) families BRCA2: 12/104 (12%) families</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Appendix C7. Evidence Table of Prevalence of *BRCA1* and *BRCA2* Mutations

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Parts of genes studied</th>
<th>Who was tested?</th>
<th>Results/conclusions</th>
<th>Definition of clinically significant</th>
<th>How was cancer status ascertained?</th>
<th>Confounders</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanda et al, 2005&lt;sup&gt;192&lt;/sup&gt;</td>
<td>Full sequence</td>
<td>In each family, the individual with the highest probability of being a mutation carrier was tested.</td>
<td><em>BRCA1</em>: 28% -Hispanic: 0% -Asian: 0% -African American: 16% -Caucasian: 31% -Ashkenazi Jewish: 41% <em>BRCA2</em>: 16% -Hispanic: 0% -Asian: 0% -African American: 12% -Caucasian: 15% -Ashkenazi Jewish: 28%</td>
<td>As previously described in Frank et al, 1998.</td>
<td>NR</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td>Neuhausen et al, 2009&lt;sup&gt;193&lt;/sup&gt;</td>
<td>Full sequence</td>
<td>Proband and affected family members; Ashkenazi Jewish women for the 3 founder mutations</td>
<td><em>BRCA1</em> vs. <em>BRCA2</em> probands Excluding Ashkenazi Jewish: 233/4531 (5.1%) vs. 193/4084 (4.7%)</td>
<td>As defined by the BIC and Myriad Genetic Laboratories.</td>
<td>NR</td>
<td>Age and cancer status were reported.</td>
<td>NA</td>
</tr>
<tr>
<td>Seymour et al, 2008&lt;sup&gt;196&lt;/sup&gt;</td>
<td>Coding regions and flanking introns</td>
<td>Proband and some relatives</td>
<td><em>BRCA1</em> or <em>BRCA2</em>: 21/247 (8.5%) families</td>
<td>NR, although a distinction is made between deleterious and nondeleterious mutations.</td>
<td>Personal and family cancer status was reported by the proband and verified during genetic counseling sessions.</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td>Tamboom et al, 2010&lt;sup&gt;198&lt;/sup&gt;</td>
<td>Full sequence</td>
<td>Probands, families, and predictive cases</td>
<td>Early onset vs. familial vs. predictive <em>BRCA1</em> 4/64 (6%) vs. 6/47 (13%) vs. 1/33 (3%) <em>BRCA2</em> (16 familial cases only) Total: 2/16 (12.5%)</td>
<td>As defined by the BIC database or those which result in a stop codon.</td>
<td>Cancer status was reported by the proband and confirmed in the Estonian Cancer Registry.</td>
<td>Age and cancer status were reported.</td>
<td>NA</td>
</tr>
<tr>
<td>Tommasi et al, 2005&lt;sup&gt;199&lt;/sup&gt;</td>
<td>Coding region</td>
<td>Proband</td>
<td><em>BRCA1</em>: 7/100 (7%) patients</td>
<td>NR, although a distinction is made between deleterious and nondeleterious mutations.</td>
<td>Cancer status was reported by the proband and updated in genetic counseling.</td>
<td>NR</td>
<td>NA</td>
</tr>
</tbody>
</table>
### Appendix C7. Evidence Table of Prevalence of BRCA1 and BRCA2 Mutations

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Parts of genes studied</th>
<th>Who was tested?</th>
<th>Results/conclusions</th>
<th>Definition of clinically significant</th>
<th>How was cancer status ascertained?</th>
<th>Confounders</th>
<th>Method</th>
</tr>
</thead>
</table>
| Vaziri et al, 2001 | Coding region          | Proband and affected family members | Patients vs. affected family members                       | BRCA1: 18/104 (17.3%) vs. 18/25 (72%)  
BRCA2: 2/104 (1.9%) vs. 4/4 (100%) | NR                                 | NR          | NR     | NA     |
| Weitzel et al, 2005 | Exons and flanking intronic sequence | Proband                           | 34 (31%) had deleterious mutations (25 in BRCA1, 9 in BRCA2) | NR                                 | Cancer status was reported by the proband. | NR          | NA     |
| Metcalfe et al, 2010 | Founder mutations       | Individual                         | Prevalence of mutation: 22/2080 (1.1%) found to have 1 of 3 founder mutations 
BRCA1: 2/0.05%  
BRCA2: 2/0.06% | 1 of 3 founder mutations | Cancer status for the family was reported by the proband through questionnaire. | Age, cancer status, vital status, and prophylactic surgery were reported. | NA     |

**Unselected populations (Ashkenazi Jewish)**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Parts of genes studied</th>
<th>Who was tested?</th>
<th>Results/conclusions</th>
<th>Definition of clinically significant</th>
<th>How was cancer status ascertained?</th>
<th>Confounders</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** BC = breast cancer; BIC = Breast Cancer Information Core; CFR = Cancer Family Registry; CSGE = conformation sensitive gel electrophoresis; dHPLC = denaturing high performance liquid chromatography; EGAN = Exploratory Gene Association Networks; EMD = enzymatic mutation testing; FDR = first degree relative; IVS = intervening sequence; MDE = mutation detection enhancement; MLPA = multiplex ligation dependent probe amplification; NA = not applicable; NR = not reported; OC = ovarian cancer; PCR = polymerase chain reaction; PTT = protein truncation test; SDR = second degree relative; SSCP-HA = single strand conformation polymorphism - hederoduplex analysis; UCSF = University of California, San Francisco.
### Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Data source/parent study</th>
<th>Setting</th>
<th>Population</th>
<th>Inclusion/exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA uncertain or uninformative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kauff et al, 2005&lt;sup&gt;182&lt;/sup&gt;</td>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>Genetics clinic</td>
<td>BRCA mutation negative site-specific breast cancer kindreds with a living female proband. All probands, 1st-, and 2nd-degree relatives age &gt;18 years at the time that BRCA test results were transmitted to the proband.</td>
<td>Proband's were included if the kindred had ≥3 cases of breast cancer in the same lineage, 1 of the breast cancers in a kindred was diagnosed when the patient was age &lt;50 years, no ovarian cancer was present anywhere in the lineage, and BRCA mutation screening did not detect a deleterious or unclassified missense mutation in the proband's BRCA1 or BRCA2 gene. If the proband reported her heritage to be exclusively Ashkenazi, testing negative for the 3 Ashkenazi founder mutations was sufficient for inclusion. The proband was defined as the youngest living individual with breast cancer in the kindred who had personally undergone BRCA mutation testing. If the family had no member who had both been diagnosed with breast cancer and had undergone genetic testing, the proband was defined as the first unaffected individual in the kindred who underwent testing.</td>
</tr>
<tr>
<td>Metcalfe et al, 2009&lt;sup&gt;189&lt;/sup&gt;</td>
<td>NA</td>
<td>Genetics clinic</td>
<td>All female FDRs of the breast cancer cases age &gt;18 years at the time the pedigree was drawn.</td>
<td>Inclusion: In database of families who have received testing for BRCA1/2 at 1 of 2 Canadian centers between 1993 and 2003, ≥1 woman affected with breast cancer had been tested and was found not to carry a BRCA1 or BRCA2 mutation.</td>
</tr>
<tr>
<td><strong>BRCA true negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bernholz et al, 2012&lt;sup&gt;175&lt;/sup&gt; [True negative group only]</td>
<td>Israeli Cancer Registry</td>
<td>Oncogenetics unit, Sheba medical center</td>
<td>Jewish, female mutation carriers and their family members referred for oncogenetic counseling.</td>
<td>High-risk status was assigned based on: 1) FDR with breast and ovarian cancer, 2) FDR with bilateral breast cancer and ≥1 breast cancer diagnosed at age &lt;50 years, 3) 1st- or 2nd-degree male relative who developed breast cancer, 4) FDRs or SDRs with ovarian cancer, 5) 3 FDRs or SDRs diagnosed with breast cancer at any age, or 6) 1 FDR and 1 SDR with breast cancer diagnosed at age &lt;50 years. Excluded if non-Jewish origin and/or unwillingness to participate.</td>
</tr>
<tr>
<td>Domchek et al, 2010&lt;sup&gt;177&lt;/sup&gt;</td>
<td>Memorial Sloan Kettering Cancer Center and University of Pennsylvania</td>
<td>Genetics clinic</td>
<td>Women who do not carry a known family mutation in BRCA1 or BRCA2.</td>
<td>Women who had genetic testing at the University of Pennsylvania or Memorial Sloan Kettering Cancer Center who agreed to participate in research were considered for inclusion. Women were eligible if they were a close relative of an individual with a known deleterious BRCA1 or BRCA2 mutation, had undergone genetic testing for the known family mutation in BRCA1 or BRCA2, had ≥1 followup since having genetic testing, had no prior cancer diagnosis at the time of their genetic testing (apart from in situ cervical cancer or nonmelanoma skin cancer), and had not undergone bilateral mastectomy prior to genetic testing or subsequent to genetic testing.</td>
</tr>
<tr>
<td>Gronwald et al, 2007&lt;sup&gt;180&lt;/sup&gt;</td>
<td>NA</td>
<td>18 hospitals in Poland</td>
<td>Women who do not carry a known family mutation in BRCA1 or BRCA2.</td>
<td>The probands were unselected breast cancer patients diagnosed before age 50 years who were found to carry a BRCA1 or BRCA2 mutation. Living sisters of probands were included in this study if they received genetic testing for the family mutation.</td>
</tr>
<tr>
<td>Author, year</td>
<td>Data source/parent study</td>
<td>Setting</td>
<td>Population</td>
<td>Inclusion/exclusion criteria</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Harvey et al, 2011</td>
<td>Australian Cancer Incidence and Mortality data</td>
<td>1 of 16 family cancer clinics in Australia and New Zealand; Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab)</td>
<td>Women who were blood relatives of mutation carriers who tested negative for the known mutation in their family.</td>
<td>Women were eligible if they were 1) blood relatives (not married to) of mutation carriers with a known pathogenic, large deletion, or splice site mutation in BRCA1 or BRCA2; 2) had tested negative for the known mutation in their family; 3) had no personal history of cancer at enrollment (other than in situ cervical carcinoma or nonmelanoma skin cancer); and 4) had not had risk-reducing surgery before enrollment in kConFab.</td>
</tr>
<tr>
<td>Korde et al, 2011</td>
<td>NCI cohort</td>
<td>NR</td>
<td>Mutation negative women in families with known deleterious BRCA1/2 mutations.</td>
<td>All bloodline individuals within 3 degrees of relatedness to a known mutation carrier. Excluded because of missing date of birth or because researchers had not had contact with the individual or a family member within ≥3 degrees of relatedness.</td>
</tr>
<tr>
<td>Kramer et al, 2005</td>
<td>NCI</td>
<td>Families participating in research studies</td>
<td>Self or physician-referred families.</td>
<td>Analysis was restricted to 23 families with a known BRCA1 mutation out of a larger cohort of 60 HBOC families.</td>
</tr>
<tr>
<td>Kurian et al, 2011</td>
<td>BCFR</td>
<td>Population-based cancer registries</td>
<td>Women with incident breast cancer and their female 1st-degree family members, including mothers and full sisters.</td>
<td>Inclusion: Northern California site: Diagnosed with breast cancer at age &lt;65 years through the Greater Bay Area Cancer Registry. Ontario site: Diagnosed at age &lt;70 years through the Ontario Cancer Registry. These 2 sites recruited all patients diagnosed between ages 18 and 34 years or having a family history of cancer suggestive of increased genetic susceptibility, and a random sample of patients without these features. Australian site: All women diagnosed from age 18 to 39 years and random samples of women diagnosed from age 40 to 59 years through the Victorian and New South Wales Cancer Registries. Most probands were enrolled between 1996 and 2000; from 2001 and 2009, contributing sites recruited families with specific criteria of interest, including oversampling of racial and ethnic minorities.</td>
</tr>
<tr>
<td>Rowan et al, 2007</td>
<td>NA</td>
<td>Familial breast cancer center</td>
<td>Women who do not carry a known family mutation in BRCA1 or BRCA2.</td>
<td>Inclusion: Resident in Ontario, Canada ages 30 to 70 years. A FDR or SDR with a documented BRCA1 or BRCA2 mutation, the participant being negative for this mutation, and no history of breast, ovarian, or other cancer at the date of disclosure of the participant's genetic test result.</td>
</tr>
</tbody>
</table>
# Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Data source/ parent study</th>
<th>Setting</th>
<th>Population</th>
<th>Inclusion/exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al, 2007</td>
<td>M6-ICE Study</td>
<td>Genetics clinic</td>
<td>Women who do not carry a known family mutation in BRCA1 or BRCA2</td>
<td>Families were identified from those being tested for BRCA1/2 mutations in specialist genetic clinics, and detailed 3-generation family history was elicited. Families were only included if a BRCA1/2 mutation was identified. Patients were only included if they have breast or ovarian cancer and tested negative for the family mutation.</td>
</tr>
<tr>
<td>van der Kolk et al, 2010* [Testing Negative Group Only]</td>
<td>University Medical Center Groningen</td>
<td>Genetics clinic</td>
<td>Women who do not carry a known family mutation in BRCA1 or BRCA2</td>
<td>Screening is carried out if the family history meets 1 of the following: 1) 1 breast cancer case at age &lt;35 years, 2) 2 breast cancer cases in 1st-degree relatives with 1 case at age &lt;50 years, 3) ≥3 FDRs with breast cancer in 2 successive generations, 4) the occurrence of breast and ovarian cancer in FDRs, and 5) the occurrence of male breast cancer.</td>
</tr>
<tr>
<td>Chen et al, 2006</td>
<td>Cancer Genetics Network</td>
<td>282 Ashkenazi Jewish families were population-based, the remainder were from genetics clinics</td>
<td>Families presenting to high-risk clinic.</td>
<td>Families were recruited from 8 centers including: Georgetown University, University of Pennsylvania, Duke University, Johns Hopkins University, Baylor College of Medicine, MD Anderson Cancer Center, University of Texas Southwestern Medical School, and Huntsman Cancer Institute. Criteria for inclusion varied across centers, but most families had a positive family history of breast or ovarian cancer. On average, there were &gt;3 diagnoses of breast or ovarian cancer per family. There were 282 Ashkenazi Jewish families recruited at Baylor that were population-based.</td>
</tr>
<tr>
<td>Finkelman et al, 2012 [Prospective participants only]</td>
<td>Prevention and Observation of Surgical End Points (PROSE) Consortium</td>
<td>22 international centers in the PROSE consortium</td>
<td>Jewish and non-Jewish women with a confirmed disease-associated BRCA1/2 mutation.</td>
<td>Participants were excluded if they did not have a confirmed disease-associated BRCA1/2 mutation or if they had a mutation in both BRCA1 and BRCA2. For BC analysis, participants were excluded if they had BC or were censored before ascertainment, or if they were missing necessary data to determine followup. For OC analyses, participants were excluded if they had OC or were censored before ascertainment, or if they were missing necessary data to determine followup.</td>
</tr>
<tr>
<td>Lubinski et al, 2012</td>
<td>26 centers in Canada, United States, and Poland</td>
<td>Clinical centers</td>
<td>Unaffected women with a BRCA1 mutation.</td>
<td>A woman was eligible if she was a carrier of a deleterious mutation in BRCA1, was between age 25 and 65 years at baseline, and if she did not have a prior mastectomy or known diagnosis of breast or ovarian cancer.</td>
</tr>
<tr>
<td>Marroni et al, 2004</td>
<td>NA</td>
<td>Clinical centers</td>
<td>Families receiving BRCA testing.</td>
<td>Eligibility criteria for genetic testing varied across centers and within centers over time; families with multiple cases of breast or ovarian cancer or early-onset cancer cases were preferentially selected.</td>
</tr>
</tbody>
</table>
## Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Data source/ parent study</th>
<th>Setting</th>
<th>Population</th>
<th>Inclusion/exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metcalfe et al, 2010 190</td>
<td>Hereditary Breast Cancer Clinical Study Group</td>
<td>33 centers in 6 countries</td>
<td>Women who were known to be carriers of a deleterious mutation in BRCA1 or BRCA2.</td>
<td>A woman was eligible if molecular analysis established that she was a carrier of a deleterious mutation in BRCA1 or BRCA2. For estimation of breast cancer risk: Ages 25 to 65 years at the time of completion of the baseline questionnaire, did not have breast cancer or a prophylactic mastectomy at or before baseline, and had been followed for ≥2 years after baseline. Followed until development of breast cancer, prophylactic mastectomy, or death, whichever occurred first. For ovarian cancer risk estimation: Ages 25 to 65 years at baseline, no ovarian cancer diagnosis or prophylactic oophorectomy at baseline, ≥2 years of followup. Followed until the development of ovarian or fallopian tube cancer, prophylactic oophorectomy, death, or date of last followup, whichever occurred first.</td>
</tr>
<tr>
<td>Risch et al, 2006 1895</td>
<td>Ontario Cancer Registry Registry for ovarian cancer</td>
<td>All patients diagnosed with invasive and borderline ovarian cancer.</td>
<td>All patients diagnosed from January 1, 1995 to December 31, 1999 with invasive ovarian cancer and from January 1, 1995 to December 31, 1997 with borderline ovarian tumors. Ages 20 to 79 years and resident in Ontario at the time of diagnosis of a new primary tumor.</td>
<td></td>
</tr>
</tbody>
</table>

### BRCA positive-multi

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Data source/ parent study</th>
<th>Setting</th>
<th>Population</th>
<th>Inclusion/exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mulla et al, 2009 172</td>
<td>NA</td>
<td>NR</td>
<td>Patients and their family members in moderate- or high-risk families.</td>
<td>Moderaete- or high-risk families.</td>
</tr>
<tr>
<td>Antoniou et al, 2006 173</td>
<td>INHERIT BRCA Network of referring physicians</td>
<td>Families with family history suggestive of a genetic component.</td>
<td>Family meets ≥1 of the following criteria: 1) ≥4 individuals with breast and/or ovarian cancer diagnosed at any age in FDRs or SDRs, 2) 3 FDRs affected with breast and/or ovarian cancer at any age, or 3) deleterious mutation already identified in the BRCA1/2 genes. 8 additional families that did not meet those criteria were recruited when the analysis of pedigrees was suggestive of a genetic component (e.g., monozygotic twins affected with breast cancer at an early age; 4 related individuals with early-onset breast cancer; 1 case of male breast cancer plus a women affected with early breast cancer). Age &gt;18 years and mentally competent.</td>
<td></td>
</tr>
<tr>
<td>Evans et al, 2008 178</td>
<td>NA</td>
<td>Genetics clinic</td>
<td>Families presenting to high-risk clinic.</td>
<td>Families were identified from those being tested for BRCA1/2 mutations in specialist genetic clinics, and detailed 3-generation family history was elicited. Families were only included if a BRCA1 or BRCA2 mutation was identified.</td>
</tr>
<tr>
<td>Kramer et al, 2005 185 [Mutation Carrier Group Only]</td>
<td>NCI</td>
<td>Families participating in research studies</td>
<td>Self- or physician-referred families.</td>
<td>Analysis was restricted to 23 families with a known BRCA1 mutation out of a larger cohort of 60 HBOC families.</td>
</tr>
</tbody>
</table>
### Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Data source/parent study</th>
<th>Setting</th>
<th>Population</th>
<th>Inclusion/exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milne et al, 2008</td>
<td>NA</td>
<td>Genetics clinic</td>
<td>Families testing positive for deleterious mutations in BRCA1 or BRCA2.</td>
<td>Families were selected for mutation testing if they contained ≥3 cases of breast or ovarian cancer in the same family line, ≥2 FDRs diagnosed with breast cancer before age 50 years, ≥1 case of breast cancer and 1 case of ovarian or bilateral breast cancer in the same family line, ≥1 woman with both breast and ovarian cancer, and/or ≥1 case of male breast cancer. Once a mutation was identified in the family, the family was eligible only if ≥1 other member was tested for the family mutation.</td>
</tr>
<tr>
<td>van der Kolk et al, 2010 [Mutation Carriers Group Only]</td>
<td>University Medical Center Groningen</td>
<td>Genetics clinic</td>
<td>Families presenting to high-risk clinic.</td>
<td>Screening is carried out if the family history meets 1 of the following inclusion criteria: 1) 1 breast cancer case at age &lt;35 years, 2) 2 breast cancer cases in FDRs with 1 case at age &lt;50 years, 3) ≥3 FDRs with breast cancer in 2 successive generations, 4) the occurrence of breast and ovarian cancer in FDRs, and 5) the occurrence of male breast cancer.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Primary risk measure</th>
<th>Comparison group</th>
<th>Family history/risk level definition</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kauff et al, 2005</td>
<td>U.S.</td>
<td>Retrospective cohort study</td>
<td>SIR</td>
<td>Age-specific cancer incidence rates from the SEER program.</td>
<td>See inclusion/exclusion criteria. Family history was collected via questionnaire sent to the proband.</td>
<td>165 probands 583 FDRs or SDR</td>
</tr>
<tr>
<td>Metcalfe et al, 2009</td>
<td>Ontario, British Columbia</td>
<td>Retrospective cohort study</td>
<td>Cumulative incidence SIR</td>
<td>Expected rates for Ontario and British Columbia were obtained from the registry data recorded in “Cancer Incidence in Five Continents (Volume VII).”</td>
<td>Each family contained breast cancer diagnosed before age 50 years, or 3 cases of breast cancer diagnosed at any age. Family history of cancer diagnosis was based on report from the proband or another family member.</td>
<td>365 families 874 breast cancers at baseline 1492 FDRs who did not have breast cancer at baseline</td>
</tr>
</tbody>
</table>

<p>| Bernholtz et al, 2012 [True negative group only] | Israel | Post intervention series | SIR | Israeli Cancer Registry | See inclusion/exclusion criteria. | 884 families 1318 female individuals 307 were noncarriers true negatives |
| Domchek et al, 2010 | U.S. | Cohort Families: penetrance | SIR | Expected number of cases were based on SEER 2013 incidence rates for invasive breast and ovarian cancer and for in situ breast cancer from 1992 to 2005 in women age ≥18 years (all races). | See inclusion/exclusion criteria. | 249 families 405 true negatives were identified 378 had followup information |</p>
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Primary risk measure</th>
<th>Comparison group</th>
<th>Family history/ risk level definition</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gronwald et al, 2007&lt;sup&gt;180&lt;/sup&gt;</td>
<td>Poland</td>
<td>Cohort Families: penetrance</td>
<td>OR</td>
<td>Expected number of breast cancer cases was determined for Poland from the &quot;Cancer Incidence in Five Continents (Volume VIII).&quot; using age-specific estimates.</td>
<td>NR</td>
<td>188 families 261 sisters (140 received genetic testing)</td>
</tr>
<tr>
<td>Harvey et al, 2011&lt;sup&gt;181&lt;/sup&gt;</td>
<td>Australia</td>
<td>Prospective</td>
<td>SIR</td>
<td>Australian Cancer Incidence and Mortality data</td>
<td>See inclusion/exclusion criteria. Women were considered at risk from enrollment until 1 of the following events: bilateral mastectomy, bilateral oophorectomy, invasive cancer diagnosis (other than nonmelanoma skin cancer), death, or last followup.</td>
<td>722 mutation-negative women</td>
</tr>
<tr>
<td>Korde et al, 2011&lt;sup&gt;184&lt;/sup&gt;</td>
<td>U.S.</td>
<td>Cohort Families: penetrance</td>
<td>Observed to expected risk ratio</td>
<td>Age-, race-, and calendar time-specific expected number of breast cancer cases were derived from the SEER 2009 Cancer Registry.</td>
<td>Degree of relatedness to closest relative with known BRCA mutation (1st, 2nd, or 3rd-degree). Adjustment for intact ovaries vs. oophorectomy age category.</td>
<td>395 women 28 families</td>
</tr>
<tr>
<td>Kramer et al, 2005&lt;sup&gt;185&lt;/sup&gt; [Mutation Negative Group Only]</td>
<td>U.S.</td>
<td>Post intervention series</td>
<td>Cumulative risk</td>
<td>NA</td>
<td></td>
<td>23 families 673 females total 353 were BRCA1 mutation negative for the known family mutation</td>
</tr>
<tr>
<td>Kurian et al, 2011&lt;sup&gt;186&lt;/sup&gt;</td>
<td>Melbourne and Sydney, Australia, Ontario, Canada, and Northern California, U.S.</td>
<td>Cohort Families: penetrance</td>
<td>Risk ratio, HR</td>
<td>Baseline incidence rates were estimated by combining carrier prevalence estimates with population-based breast cancer incidence rates, specific for each proband's country of residence, and for probands from the Northern California BCFR (which oversampled racial and ethnic minorities) for race/ethnicity, by using categories of African American, Asian American, Hispanic, and nonHispanic white.</td>
<td></td>
<td>Probands: Australia (n=799) Canada (n=1034) U.S. (n=1214) FDRs: approximately 9,000</td>
</tr>
</tbody>
</table>
### Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Primary risk measure</th>
<th>Comparison group</th>
<th>Family history/ risk level definition</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rowan et al, 2007&lt;sup&gt;195&lt;/sup&gt;</td>
<td>Ontario, Canada</td>
<td>Cohort</td>
<td>SIR</td>
<td></td>
<td>NR</td>
<td>104 subjects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Families:</td>
<td></td>
<td></td>
<td></td>
<td>64 families</td>
</tr>
<tr>
<td></td>
<td></td>
<td>penetrance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith et al, 2007&lt;sup&gt;197&lt;/sup&gt;</td>
<td>Manchester and Birmingham, England</td>
<td>Cohort</td>
<td>SIR</td>
<td></td>
<td>NR</td>
<td>277 families</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Families:</td>
<td></td>
<td></td>
<td></td>
<td>258 individuals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>penetrance</td>
<td></td>
<td></td>
<td></td>
<td>tested negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>for the family</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mutation (28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>with breast</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cancer, 4 with</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ovarian cancer)</td>
</tr>
<tr>
<td>van der Kolk et al, 2010&lt;sup&gt;201&lt;/sup&gt;</td>
<td>Netherlands</td>
<td>Cohort</td>
<td>SIR</td>
<td></td>
<td>NR</td>
<td>185 families</td>
</tr>
<tr>
<td>[Testing Negative Group Only]</td>
<td></td>
<td>Families:</td>
<td></td>
<td></td>
<td></td>
<td>111 segregating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>penetrance</td>
<td></td>
<td></td>
<td></td>
<td>BRCA1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>74 segregating</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BRCA2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1188 women total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>128 noncarriers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>for BRCA1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>74 noncarriers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>for BRCA2</td>
</tr>
</tbody>
</table>

#### BRCA positive-single

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Primary risk measure</th>
<th>Comparison group</th>
<th>Family history/ risk level definition</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al, 2006&lt;sup&gt;122&lt;/sup&gt;</td>
<td>U.S.</td>
<td>Post</td>
<td>Age-specific</td>
<td></td>
<td>NR</td>
<td>676 Ashkenazi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>intervention</td>
<td>cumulative risk; RR</td>
<td></td>
<td></td>
<td>Jewish families</td>
</tr>
<tr>
<td></td>
<td></td>
<td>series</td>
<td></td>
<td></td>
<td></td>
<td>1272 families</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>of other</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ethnicities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1948 counselees</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>had genetic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>testing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>performed (1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>from each</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pedigree)</td>
</tr>
<tr>
<td>Finkelman et al, 2012&lt;sup&gt;179&lt;/sup&gt;</td>
<td>U.S.</td>
<td>Prospective</td>
<td>HR</td>
<td>NA</td>
<td>N/A</td>
<td>2362 BC analyses</td>
</tr>
<tr>
<td>[Prospective participants only]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1874 nonJewish vs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>488 Jewish)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3787 OC analyses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(3034 nonJewish vs. 753 Jewish)</td>
</tr>
</tbody>
</table>
## Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Primary risk measure</th>
<th>Comparison group</th>
<th>Family history/ risk level definition</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marroni et al, 2004</td>
<td>Italy</td>
<td>Post intervention series</td>
<td>Cumulative incidence</td>
<td>Cancer registry data</td>
<td>NR</td>
<td>568 families 80 segregating BRCA1 52 segregating BRCA2 435 not segregating a BRCA mutation</td>
</tr>
<tr>
<td>Metcalfe et al, 2010</td>
<td>Canada, U.S., Poland, Austria, Italy, France</td>
<td>Post intervention series</td>
<td>Penetrance</td>
<td>NA</td>
<td>A) ≥1 FDR or SDR with breast or ovarian cancer, b) no FDR or SDR with these cancers.</td>
<td>3011 women</td>
</tr>
<tr>
<td>Risch et al, 2006</td>
<td>Ontario, Canada</td>
<td>Case series</td>
<td>Cumulative incidence</td>
<td>NA</td>
<td>NR</td>
<td>1171 women 977 with invasive ovarian cancer (75 were BRCA1 mutation carriers and 54 were BRCA2 mutation carriers) 194 with borderline tumors None of the patients with borderline tumors were BRCA mutation carriers</td>
</tr>
</tbody>
</table>

### BRCA positive-multi

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Primary risk measure</th>
<th>Comparison group</th>
<th>Family history/ risk level definition</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Mulla et al, 2009</td>
<td>Yorkshire and Humberside, U.K.</td>
<td>Post intervention series</td>
<td>Cumulative incidence, HR</td>
<td>NA</td>
<td>High-risk: Members of families with 4 confirmed cases of breast and/or ovarian cancer, with breast cancer occurring before age 60 years or ovarian cancer at any age. Moderate risk: Families with 3 cases of cancer.</td>
<td>241 patients and their family members 131 families 219 subjects with available clinical and mutation data</td>
</tr>
<tr>
<td>Antoniou et al, 2006</td>
<td>French Canadian</td>
<td>Post intervention series</td>
<td>Cumulative risk</td>
<td>NA</td>
<td>NR</td>
<td>191 families 25 families segregating BRCA1 27 families segregating BRCA2</td>
</tr>
</tbody>
</table>
## Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Primary risk measure</th>
<th>Comparison group</th>
<th>Family history/ risk level definition</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans et al, 2008&lt;sup&gt;178&lt;/sup&gt;</td>
<td>Manchester and Birmingham, England</td>
<td>Post intervention series</td>
<td>Age-specific cumulative risk</td>
<td>NA</td>
<td>NR</td>
<td>385 families 2466 individuals 223 families segregating BRCA1 162 families segregating BRCA2</td>
</tr>
<tr>
<td>Kramer et al, 2005&lt;sup&gt;185&lt;/sup&gt; [Mutation Carrier Group Only]</td>
<td>U.S.</td>
<td>Post intervention series</td>
<td>Cumulative risk</td>
<td>NA</td>
<td>NR</td>
<td>23 families 673 females</td>
</tr>
<tr>
<td>Milne et al, 2008&lt;sup&gt;191&lt;/sup&gt;</td>
<td>Spain</td>
<td>Post intervention series</td>
<td>Age-specific cumulative risk</td>
<td>NA</td>
<td>NR</td>
<td>319 families 155 families segregating BRCA1 164 families segregating BRCA2</td>
</tr>
<tr>
<td>van der Kolk et al, 2010&lt;sup&gt;201&lt;/sup&gt; [Mutation Carriers Group Only]</td>
<td>Netherlands</td>
<td>Post intervention series</td>
<td>Cumulative incidence</td>
<td>NA</td>
<td>NR</td>
<td>185 families 1188 women total 111 segregating BRCA1 74 segregating BRCA2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Demographics</th>
<th>Participation rate</th>
<th>Genes included</th>
<th>Laboratory methods</th>
<th>Tissue source</th>
<th>Parts of genes studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kauff et al, 2005&lt;sup&gt;192&lt;/sup&gt;</td>
<td>Mean age: 51.6 years 100% female 67% Ashkenazi Jewish ancestry Followup: Mean, 40.6 months (range, 15.3 to 82.4 months)</td>
<td>165/207 (80%)</td>
<td>BRCA1 &amp; BRCA2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Metcalfe et al, 2009&lt;sup&gt;189&lt;/sup&gt;</td>
<td>Baseline: Mean age: 48.2 years (range, 17 to 99) 100% women Race/ethnicity: NR Followup: Mean age: 54.3 years (range, 24 to 101) Mean followup period: 6.1 years (range, 1 to 10 years)</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>Methods changed over time and between centers but used a combination of PTT, DGGE, dHPLC, and direct sequencing</td>
<td>NR</td>
<td>All coding regions</td>
</tr>
</tbody>
</table>
## Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Demographics</th>
<th>Participation rate</th>
<th>Genes included</th>
<th>Laboratory methods</th>
<th>Tissue source</th>
<th>Parts of genes studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernholtz et al, 2012&lt;sup&gt;235&lt;/sup&gt; [True negative group only]</td>
<td>100% female</td>
<td>Mean age at testing: 43.0 years (SD, 13.0; range, 19.7 to 92.8)</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>PCR and restriction enzyme digests. An assay as previously described in Shiri et al, 2000. Full sequence analysis performed by Myriad Genetics and other private labs.</td>
<td>NR</td>
</tr>
<tr>
<td>Domchek et al, 2010&lt;sup&gt;177&lt;/sup&gt;</td>
<td>100% female</td>
<td>Median age at genetic testing: 44 years (range, 18 to 91) Race/ethnicity: 91% Caucasian 5.1% African American 0.8% Hispanic/Latino 3.2% unknown</td>
<td>378/405 (93%)</td>
<td>BRCA1 &amp; BRCA2</td>
<td>Direct sequencing. Individuals of Ashkenazi Jewish descent were also tested for the 3 founder mutations in BRCA1 (185delAG, 5382insC) and BRCA2 (6174delT).</td>
<td>NR</td>
</tr>
<tr>
<td>Gronwald et al, 2007&lt;sup&gt;180&lt;/sup&gt;</td>
<td>100% female</td>
<td>Mean age: NR Race/ethnicity: Polish</td>
<td>188/198 (95%) families</td>
<td>BRCA1</td>
<td>See Lubinski et al 2006 reference.</td>
<td>NR</td>
</tr>
<tr>
<td>Harvey et al, 2011&lt;sup&gt;181&lt;/sup&gt;</td>
<td>100% female</td>
<td>Median age at enrollment: 43.0 years (range, 18 to 88) Race/ethnicity: NR Median followup time: 6.1 years (range, 0.1 to 12.4)</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>NR</td>
<td>Blood</td>
</tr>
<tr>
<td>Korde et al, 2011&lt;sup&gt;184&lt;/sup&gt;</td>
<td>100% female</td>
<td>Mean age at cohort entry: 31.3 years Race/ethnicity: NR</td>
<td>395/415 (95%)</td>
<td>BRCA1 &amp; BRCA2</td>
<td>Mutation status was based on either direct testing for the family mutation or direct inference (participants were inferred to be mutation-negative if they were descendants of an individual who tested negative).</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Demographics</th>
<th>Participation rate</th>
<th>Genes included</th>
<th>Laboratory methods</th>
<th>Tissue source</th>
<th>Parts of genes studied</th>
</tr>
</thead>
</table>
| Kramer et al, 2005 [Mutant Negative Group Only] | 100% female  
Age: NR  
Race/ethnicity: NR | NR | BRCA1 | Various methods were used to screen for mutations in the families, with results confirmed by direct sequencing. Ultimately, affected individuals from all families negative by screening methods were fully sequenced by Myriad Genetics. In addition, all families with no mutation detected by sequencing were studied (by Myriad) for the presence of large germline deletions in BRCA1. After a mutation was found in a family, other members were offered clinical mutation testing for the known mutation. | NR | Full sequence |
| Kurian et al, 2011 | 100% female  
Race/ethnicity:  
61% Caucasian  
11% African American  
11% Hispanic  
14% Asian  
2% other  
Average age at diagnosis (breast vs. ovarian) (years):  
BRCA1 families: 42 vs. 54  
BRCA2 families: 44 vs. 51  
Neither: 51 vs. 50 | NR | BRCA1 & BRCA2 | U.S.: Exon grouping analysis (EGAN) or capillary exon grouping analysis (cEGAN).  
Ontario and USA: RNA/DNA-based protein truncation test with complementary 5' sequencing or complete gene sequencing by Myriad.  
Australia: Exon and flanking intron sequencing, protein truncation, 2-dimensional gel scanning, site-specific testing for founder mutations, multiplex ligand dependent probe amplification, and BRACAnalysis by Myriad (full sequencing of BRCA1 and BRCA2 with testing for 5 large rearrangements in BRCA1).  
For all sites, all mutations were confirmed by sequencing. | NR | U.S.: Coding regions and splice sites.  
Australia: Exon and flanking introns, or founder mutations, or full gene. |
| Rowan et al, 2007 | 100% female  
Age: 30 to 70 years  
Race/ethnicity: NR  
Median followup time: 8 years (range, 1 to 10 years) | NR | BRCA1 & BRCA2 | Mutation status was based on direct testing. | NR | NR |
## Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Demographics</th>
<th>Participation rate</th>
<th>Genes included</th>
<th>Laboratory methods</th>
<th>Tissue source</th>
<th>Parts of genes studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al, 2007&lt;sup&gt;37&lt;/sup&gt;</td>
<td>100% female&lt;br&gt;Median age: 50 years (range, 23 to 87)&lt;br&gt;Race/ethnicity: NR</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>Patients with breast or ovarian cancer who tested negative for the family mutations had a 2nd blood sample taken, and ≥2 techniques (sequencing, single-strand conformational polymorphism, protein truncation test) were used to establish the negative status. In addition, the mutation was confirmed by testing ≥2 samples from the index case or from another family member. Confirmation of mutation status for women who tested negative for the family mutation but who did not have breast or ovarian cancer was not reported.</td>
<td>Blood</td>
<td>Family mutation</td>
</tr>
<tr>
<td>van der Kolk et al, 2010&lt;sup&gt;201&lt;/sup&gt; [Testing Negative Group Only]</td>
<td>NR</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>Denaturing gradient gel electrophoresis, the protein truncation test, direct sequencing, and multiplex ligation-dependent probe amplification.</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Chen et al, 2006&lt;sup&gt;122&lt;/sup&gt;</td>
<td>2.7% male&lt;br&gt;Mean age: 52.8 years&lt;br&gt;Race/ethnicity: 35% Ashkenazi Jewish</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>An array of techniques were used for BRCA1, including SSCP (n=209), sequencing (n=499), targeted mutation screening (n=8), sequencing for mutations 185delAG and 5382insC (n=10), CSGE (n=378), SSCP plus ASO (n=18), targeted mutation screening plus sequencing (n=60), targeted mutation screening plus CSGE (n=21), or other (n=28). For BRCA2, the techniques were SSCP (n=178), sequencing (n=509), CSGE (n=260), ASO (n=9), ASO plus CSGE (n=18), ASO plus sequencing (n=60), or other (n=63).</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Finkelman et al, 2012&lt;sup&gt;179&lt;/sup&gt; [Prospective participants only]</td>
<td>Non-Jewish vs. Jewish&lt;br&gt;100% female&lt;br&gt;Mean age at ascertainment, BC: 39.1 (range, 2.0 to 89.3) vs. 42.7 (range, 10.2 to 90.4)&lt;br&gt;Mean age at ascertainment, OC: 41.5 (range, 2.0 to 89.3) vs. 45.1 (range, 10.2 to 90.4)&lt;br&gt;Race/ethnicity: NR&lt;br&gt;Mean followup time, BC: 5.2 (range, 0.0 to 33.3) vs. 4.7 (range, 0.0 to 33.1)&lt;br&gt;Mean followup time, OC: 5.6 (range, 0.0 to 33.3) vs. 5.0 (range, 0.0 vs. 33.1)</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Author, year</td>
<td>Demographics</td>
<td>Participation rate</td>
<td>Genes included</td>
<td>Laboratory methods</td>
<td>Tissue source</td>
<td>Parts of genes studied</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------------------------------------</td>
<td>--------------------</td>
<td>----------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>---------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Lubinski et al, 2012</td>
<td>North America vs. Poland 100% female Mean age: 43.6 years (range, 25 to 74) vs. 40.1 years (range, 25 to 74) Race/ethnicity: NR Mean follow-up time: 4.8 (range, 0 to 14.9) vs. 4.0 (range, 0 to 10)</td>
<td>NR</td>
<td>BRCA1</td>
<td></td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Marroni et al, 2004</td>
<td>100% female Age: NR Race/ethnicity: NA (Italian)</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>3 centers used both direct automatic sequencing and PTT-SSCP, 1 center used both PTT-SSCP and FAMA, and the last center used PTT-SSCP only.</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Metcalfe et al, 2010</td>
<td>NR</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td></td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Risch et al, 2006</td>
<td>100% female Mean age: NR Race/ethnicity: 44% British Isles 28% Mixed European 11% French Canadian 17% Other</td>
<td>1171/2338 (50%) eligible subjects</td>
<td>BRCA1 &amp; BRCA2</td>
<td>All samples were screened for 11 common mutations (3 in Ashkenazi Jewish and 6 in French Canadian). If no mutations were found, exon 11 of BRCA1 and exons 10 and 11 of BRCA2 were then screened with the protein truncation test. If no mutations were found, remaining coding exons and exon-intron boundaries were screened using fluorescent multiplex DGGE for BRCA1 and dHPLC for BRCA2. All variants were confirmed by direct DNA sequencing.</td>
<td>Blood</td>
<td>Coding exons and exon-intron boundaries.</td>
</tr>
</tbody>
</table>

**BRCA positive-multi**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Demographics</th>
<th>Participation rate</th>
<th>Genes included</th>
<th>Laboratory methods</th>
<th>Tissue source</th>
<th>Parts of genes studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Mulla et al, 2009</td>
<td>40 (18%) males 179 (82%) females Mean age: 47.7 years Race/ethnicity: NR</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>Level 1: Amplification refractory mutation system PCR for BRCA1 exons 2 and 20 and BRCA2 exon 11, multiplex ligation-dependent probe amplification of exon 13 Level 2: Direct sequencing of exon 11 Level 3: SSCP analysis and sequencing of all BRCA1 coding exons</td>
<td>Blood</td>
<td>Mutations at exon 2 (185delAG) and exon 20 (5382insC) of BRCA1, exon 11 (6147delT) of BRCA2; duplication of exon 13 (Exon13dup6kb) and exon 11; all BRCA1 coding exons.</td>
</tr>
<tr>
<td>Antoniou et al, 2006</td>
<td>NR</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>Level 1: Panel of 18 truncating mutations Level 2: Full length BRCA1/2 sequencing by Myriad using comprehensive BRCAnalysis Level 3: Multiplex ligation probe amplification to detect deleterious rearrangements</td>
<td>Blood</td>
<td>Full sequence</td>
</tr>
</tbody>
</table>
Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Demographics</th>
<th>Participation rate</th>
<th>Genes included</th>
<th>Laboratory methods</th>
<th>Tissue source</th>
<th>Parts of genes studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans et al, 2008</td>
<td>100% female</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>A whole gene test, including a test for large deletions.</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kramer et al, 2005</td>
<td>100% female</td>
<td>NR</td>
<td>BRCA1</td>
<td>Various methods were used to screen for mutations in the families, with results</td>
<td>NR</td>
<td>Full sequence</td>
</tr>
<tr>
<td></td>
<td>Age: NR</td>
<td></td>
<td></td>
<td>confirmed by direct sequencing. Ultimately, affected individuals from all families</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Race/ethnicity: NR</td>
<td></td>
<td></td>
<td>negative by screening methods were fully sequenced by Myriad Genetics. In addition,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>all families with no mutation detected by sequencing were studied (by Myriad) for</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>the presence of large germline deletions in BRCA1. After a mutation was found in</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>a family, other members were offered clinical mutation testing for the known mutation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milne et al, 2008</td>
<td>NR</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>A range of methods.</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>van der Kolk et al,</td>
<td>NR</td>
<td>NR</td>
<td>BRCA1 &amp; BRCA2</td>
<td>Denaturing gradient gel electrophoresis, the protein truncation test, direct</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td></td>
<td>sequencing, and multiplex ligation-dependent probe amplification.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Who was tested?</th>
<th>Results/conclusions</th>
<th>Definition of clinically significant</th>
<th>How was cancer status ascertained?</th>
<th>Confounders</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA uncertain or uninformative</td>
<td>Proband</td>
<td>Observed vs. expected BC: 19 vs. 6.07; SIR, 3.13 (95% CI, 1.88 to 4.89); p&lt;0.001</td>
<td>Cancer status was reported by the proband by questionnaire.</td>
<td>Collected data included age and cancer status. Not reported whether prophylactic surgery or vital status were collected.</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Metcalfe et al, 2009</td>
<td>≥1 woman affected with breast cancer was tested in each family</td>
<td>BC: SIR, 3.9 (95% CI, 3.1 to 5.0); p&lt;0.0001 OC: SIR, 0.85 (95% CI, 0.23 to 3.12); p=0.82</td>
<td>Cancer status was reported by the proband and other family members by telephone interview.</td>
<td>Collected data included age, cancer status, prophylactic surgery, and vital status.</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>
## Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Who was tested?</th>
<th>Results/conclusions</th>
<th>Quality considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA true negative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bernholtz et al., 2012&lt;sup&gt;235&lt;/sup&gt;</td>
<td>All mutation carrying families and 1318 female individuals genotyped for mutation carriers from within the 884 families.</td>
<td>Observed in study vs. expected in Israeli population BC: 20 vs. 23.8; SIR, 0.84 (95% CI, 0.51 to 1.30) BC &lt;50 years: 9 vs. 6.4; SIR, 1.41 (95% CI, 0.64 to 2.67) BC &gt;50 years: 11 vs. 17.42; SIR, 0.63 (95% CI, 0.31 to 1.13) No significant difference in age at diagnosis in true negatives between BRCA1 and BRCA2 (p=0.347). Mean age of diagnosis in BRCA1 carriers was significantly younger than diagnosis among true negatives within BRCA1 families (p=0.001) but not among families with a BRCA2 mutation (p=0.061).</td>
<td>NR</td>
</tr>
<tr>
<td>Domchek et al., 2010&lt;sup&gt;177&lt;/sup&gt;</td>
<td>All subjects were tested for the known mutation in the family.</td>
<td>Observed vs. expected Invasive BC: 2 vs. 3.8; age-adjusted SIR, 0.52 (95% CI, 0.13 to 2.09) In situ BC: 2 vs. 0.9; age-adjusted SIR, 2.3 (95% CI, 0.57 to 9.19) OC: 0 vs. 0.4</td>
<td>NR</td>
</tr>
<tr>
<td>Gronwald et al., 2007&lt;sup&gt;180&lt;/sup&gt;</td>
<td>140/261 (54%) of sisters received direct testing. Genotypes are assigned probabilistically for untested women, adjusted for cancer status and vital status.</td>
<td>Observed vs. expected in study vs. expected in Polish population BC: 1/72 (1.4%) vs. 2.5 vs. 1.2; OR, 21/17 (5.8%) affected sisters was a phenocopy</td>
<td>NR</td>
</tr>
</tbody>
</table>
# Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Who was tested?</th>
<th>Results/conclusions</th>
<th>Definition of clinically significant</th>
<th>How was cancer status ascertained?</th>
<th>Confounders</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvey et al, 2011&lt;sup&gt;181&lt;/sup&gt;</td>
<td>Unaffected mutation negative women coming from families with known mutations.</td>
<td>SIR of BC in the observed cohort compared with the most recent BC incidence rates from the Australian Cancer Incidence and Mortality data 1st-, 2nd- or 3rd-degree relatives: 1.14 (95% CI, 0.51 to 2.53) 1st- or 2nd-degree relatives: 1.29 (95% CI, 0.58 to 2.88) No family history: 0.48 (95% CI, 0.12 to 1.93)</td>
<td>NR</td>
<td>Cancer status was verified by pathology reports.</td>
<td>Information was collected on age, cancer status, prophylactic surgery, and vital status.</td>
<td>NA</td>
</tr>
<tr>
<td>Korde et al, 2011&lt;sup&gt;184&lt;/sup&gt;</td>
<td>All subjects tested, or genotype was available by direct inference.</td>
<td>Observed vs. expected BC: 10 vs. 12; O/E, 0.82 (95% CI, 0.39 to 1.51); O/E of invasive disease only, 0.95 (95% CI, 0.45 to 1.74)</td>
<td>NR</td>
<td>Cancer status was obtained from the subject or a family member by questionnaire. All cancer diagnoses were confirmed by review of the pathology reports.</td>
<td>Information was collected on age, cancer status, vital status, and prophylactic surgery. Did not distinguish between DCIS and invasive breast cancer.</td>
<td>NA</td>
</tr>
<tr>
<td>Kramer et al, 2005&lt;sup&gt;185&lt;/sup&gt; [Mutation Negative Group Only]</td>
<td>All women in the family who agree to testing. Women were inferred positive based on having a child who was found to carry the mutation. Women were inferred negative based on having a parent that tested negative for the family mutation. A total of 451/673 (67%) had a known or inferred genotype.</td>
<td>Observed BC: 5/353 mutation-negative women Cumulative risk of BC at age 50 years: 0.017 (SE, 0.012) Cumulative risk of BC at age 70 years: 0.068 (SE, 0.033)</td>
<td>NR</td>
<td>Cancer status was initially reported by family members by questionnaire. Reported cancers were confirmed through death certificates, medical records, pathology reports, and central review of pathology slides.</td>
<td>Information was collected on prophylactic surgery, age, cancer status, and vital status.</td>
<td>NA</td>
</tr>
</tbody>
</table>
### Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Who was tested?</th>
<th>Results/conclusions</th>
<th>Definition of clinically significant</th>
<th>How was cancer status ascertained?</th>
<th>Confounders</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurian et al, 2011&lt;sup&gt;186&lt;/sup&gt;</td>
<td>All probands tested. If a proband tested positive for a mutation, her FDRs who had provided DNA samples were tested for the same mutation. Untested FDRs were assigned probabilities of mutation carriage conditional on the known genotypes in the family.</td>
<td>BC risk True negative vs. FDRs from families without BRCA1/2 mutations: RR, 0.39 (95% CI, 0.04 to 3.81) Carriers vs. noncarriers of the risk allele for an unobserved gene that represents all unobserved genetic and nongenetic factors: HR, 13.4 (95% CI, 8.7 to 22.5)</td>
<td>Mutations were classified as deleterious if they were protein-truncating, missense, or splice-site mutations as defined by the Breast Cancer Information Core.</td>
<td>It is not clear how family cancer status information was collected or verified.</td>
<td>It is not clear whether information was collected on prophylactic surgery or vital status. Did not distinguish between DCIS and invasive breast cancer.</td>
<td>NA</td>
</tr>
<tr>
<td>Rowan et al, 2007&lt;sup&gt;195&lt;/sup&gt;</td>
<td>All subjects tested.</td>
<td>Observed vs. expected BC: 3 vs. 1.0; SIR, 2.9 (95% CI, 1.0 to 8.6) OC: 0 vs. NR</td>
<td>NR</td>
<td>Personal cancer history was collected by survey.</td>
<td>It is not clear whether information was collected on prophylactic surgery. Did not distinguish between DCIS and invasive breast cancer.</td>
<td>NA</td>
</tr>
<tr>
<td>Smith et al, 2007&lt;sup&gt;197&lt;/sup&gt;</td>
<td>Multiple members of each family were tested. Untested individuals had genotypes assigned probabilistically based on age and cancer status.</td>
<td>SIR of BC All relatives: 5.3 (95% CI, 3.5 to 7.7) All FDRs: 5.0 (95% CI, 2.9 to 7.8) FDRs whose cases of BC and OC are explained by the identified mutation: 3.2 (95% CI, 2.0 to 4.9) FDRs testing negative for the family mutations who were unaffected at the time of testing: 2.1 (95% CI, 0.4 to 6.2) SIR of OC: 4.6 (95% CI, 1.2 to 11.7) Phenocopies (i.e., women who test negative for the family BRCA1/2 mutation but who develop breast or ovarian cancer) constitute up to 24% of tested women with breast cancer after the identification of the mutation in the proband.</td>
<td>NR</td>
<td>Cancer status was reported by a family member and confirmed by means of hospital or pathology records, regional cancer registries, or death certification.</td>
<td>Information was collected on age, cancer status, vital status, and prophylactic surgery. Did not distinguish between DCIS and invasive breast cancer.</td>
<td>NA</td>
</tr>
</tbody>
</table>
## Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Who was tested?</th>
<th>Results/conclusions</th>
<th>Definition of clinically significant</th>
<th>How was cancer status ascertained?</th>
<th>Confounders</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Kolk et al, 2010&lt;sup&gt;201&lt;/sup&gt; [Testing Negative Group Only]</td>
<td>Proband and some family members. Noncarriers were defined as women who tested negative for a known familial mutation in either <em>BRCA1</em> or <em>BRCA2</em>.</td>
<td>Observed vs. expected BC in <em>BRCA1</em> group: 5 vs. 2.5; age-and period-adjusted SIR, 2.0 (95% CI, 0.7 to 4.7) OC in <em>BRCA1</em> group: 0 vs. 0.3; age-and period-adjusted SIR, 0 (95% CI, 0 to 12) BC in <em>BRCA2</em> group: 4 vs. 1.6; age-and period-adjusted SIR, 2.5 (95% CI, 0.7 to 6.3) OC in <em>BRCA2</em> group: 0 vs. 0.2; age-and period-adjusted SIR, 0 (95% CI, 0 to 20.4)</td>
<td>NR</td>
<td>Cancer status was reported by the family. Cancer cases were confirmed by hospital or pathology records or else through a first degree family member.</td>
<td>DCIS was included as breast cancer. Information was collected on age, cancer status, vital status, and prophylactic surgery.</td>
<td>NA</td>
</tr>
</tbody>
</table>

### BRCA positive-single

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Who was tested?</th>
<th>Results/conclusions</th>
<th>Definition of clinically significant</th>
<th>How was cancer status ascertained?</th>
<th>Confounders</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al, 2006&lt;sup&gt;122&lt;/sup&gt;</td>
<td>Proband</td>
<td><em>BRCA1</em> carriers vs. <em>BRCA2</em> carriers Cumulative BC risk at age 70: 0.46 (95% CI, 0.39 to 0.54) vs. 0.43 (95% CI, 0.36 to 0.51) Cumulative OC risk at age 70: 0.39 (95% CI, 0.30 to 0.50) vs. 0.22 (95% CI, 0.14 to 0.32)</td>
<td>NR</td>
<td>NR</td>
<td>It is not clear if information was collected on prophylactic surgery or vital status.</td>
<td>The retrospective likelihood approach was used.</td>
</tr>
<tr>
<td>Finkelmann et al, 2012&lt;sup&gt;179&lt;/sup&gt; [Prospective participants only]</td>
<td>Proband</td>
<td>BC vs. OC <em>BRCA1</em>, 185delAG (ref nonCJM): HR, 1.23 (95% CI, 0.87 to 1.73) vs. 0.97 (95% CI, 0.58 to 1.63) <em>BRCA1</em>, 5382insC (ref nonCJM): HR, 1.53 (95% CI, 0.96 to 2.45) vs. 0.61 (95% CI, 0.27 vs. 1.38) <em>BRCA2</em>, 6174delT (ref nonCJM): HR, 0.35 (95% CI, 0.18 to 0.69) vs. 1.34 (95% CI, 0.48 to 3.73) Jewish (ref nonJewish): HR, 0.76 (95% CI, 0.56 to 1.01) vs. 0.93 (95% CI, 0.59 to 1.46) RRSO (ref no): HR, 0.62 (95% CI, 0.47 to 0.83) vs. 0.08 (95% CI, 0.04 to 0.16) No significant difference in BC hazard reduction from RRSO was observed in specific CJM carriers (joint Wald test; p=0.61)</td>
<td>NR</td>
<td>NR</td>
<td>Information was collected on prophylactic surgery, age, cancer status, and vital status.</td>
<td>Cumulative incidence of cancer based on method adapted from Antoniou et al, 2003.</td>
</tr>
<tr>
<td>Author, year</td>
<td>Who was tested?</td>
<td>Results/conclusions</td>
<td>Definition of clinically significant</td>
<td>How was cancer status ascertained?</td>
<td>Confounders</td>
<td>Method</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------</td>
<td>-----------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lubinski et al, 2012</td>
<td>Proband</td>
<td>North America vs. Poland Cumulative incidence: 15.9% (95% CI, 12.0 to 19.8) vs. 12.1% (95% CI, 8.0 to 16.2) Average annual risk of BC: 2.4% (95% CI, 1.8 to 2.9) vs. 1.7% (95% CI, 1.2 to 2.1) Penetrance to age 70: 71.7% vs. 48.6% Penetrance to age 70 after adjusting for oophorectomy: 76.3% vs. 57.5% Residence in Poland vs. North America: adjusted HR, 0.54 (95% CI, 0.34 to 0.86); p=0.01 Adjusted for oophorectomy, age at study entry, age of menarche, parity (0, 1, 2, 3, 4+), oral contraceptive use (ever/never), tamoxifen use (ever/never), hormone replacement therapy (ever/never), smoking (ever/never), regular alcohol use (ever/never), and family history (number of FDRs and SDRs with BC).</td>
<td>NR</td>
<td>Cancer status was reported by the proband and 70% were confirmed with pathology reports.</td>
<td>Information was collected on prophylactic surgery, age, cancer status, and vital status.</td>
<td>Theoretical penetrance curves up to age 70, for age-specific cancer rates calculated based on 5-year intervals.</td>
</tr>
<tr>
<td>Marroni et al, 2004</td>
<td>Probands. Not reported if other family members tested.</td>
<td>Penetrance (BRCA1 vs. BRCA2) BC by age 50: 27% (95% CI, 20 to 34) vs. 26% (95% CI, 18 to 34) BC by age 70: 39% (95% CI, 27 to 52) vs. 44% (95% CI, 29 to 58) OC by age 50: 14% (95% CI, 7 to 22) vs. 3% (95% CI, 0 to 7) OC by age 70: 43% (95% CI, 21 to 66) vs. 15% (95% CI, 4 to 26)</td>
<td>NR</td>
<td>Cancer status was reported by family members for FDRs and SDRs of the proband.</td>
<td>It is not clear if information was collected on prophylactic surgery</td>
<td>Parameter estimates are based on the retrospective likelihood, the likelihood of the genetic data (the observed test results) conditional on the phenotype. Obtained penetrance estimates via a Metropolis-Hastings Markov Chain Monte Carlo</td>
</tr>
</tbody>
</table>
### Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Who was tested?</th>
<th>Results/conclusions</th>
<th>Definition of clinically significant</th>
<th>How was cancer status ascertained?</th>
<th>Confounders</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metcalfe et al, 2010</td>
<td>Proband</td>
<td>0 FDRs vs. 1 FDR vs. ≥2 FDRs diagnosed with BC at age ≤50 years</td>
<td>BRCA1 penetrance for BC by age 70: 56% vs. 57% vs. 72% BRCA2 penetrance for BC by age 70: 38% vs. 46% vs. 85% 0 FDRs vs. 1 FDR vs. ≥2 FDRs diagnosed with OC BRCA1 penetrance for OC by age 70: 39% vs. 55% vs. 68%</td>
<td>NR</td>
<td>Cancer status was reported by the proband.</td>
<td>(MCMC) method implemented in BRCAPRO.</td>
</tr>
</tbody>
</table>

Information was collected on age, cancer status, prophylactic surgery, and vital status.

Age and mutation specific cancer rates were calculated for the 2 sites of cancer for 5-year intervals. Based on these rates, penetrance curves were constructed by applying the observed cancer rates annually to a theoretical cohort of healthy women from age 25 to 70 years.
### Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Who was tested?</th>
<th>Results/conclusions</th>
<th>Definition of clinically significant</th>
<th>How was cancer status ascertained?</th>
<th>Confounders</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risch et al, 2006&lt;sup&gt;189&lt;/sup&gt;</td>
<td>Proband</td>
<td>BRCA1 vs. BRCA2 Cumulative incidence for BC by age 80: 90% (95% CI, 77 to 97) vs. 41% (95% CI, 26 to 60) Cumulative incidence for OC by age 80: 24% (95% CI, 15 to 38) vs. 8.4% (95% CI, 3.9 to 17)</td>
<td>Founder mutations; shortened, non-functional proteins; substitutions producing premature termination codons; mutations reported previously as documented in the BIC database or elsewhere.</td>
<td>Investigators reviewed pathology reports to determine eligibility for the proband. Family history information was reported by the proband through telephone interview.</td>
<td>It is not clear if information was collected on prophylactic surgery</td>
<td>Cumulative incidence of cancer to age 80 years for all cancer sites was based on Ontario general population age-specific incidence and mortality data. The DevCan computer program was used to calculate cancer site specific incidence according to mutation status. The sum of the incidence to age 80 years for the 3 groups (non-carriers, BRCA1 carriers, and BRCA2 carriers) totaled the population incidence.</td>
</tr>
<tr>
<td>Al-Mulla et al, 2009&lt;sup&gt;172&lt;/sup&gt;</td>
<td>Probands and their family members</td>
<td>Median age at onset for BC (years) 185delAG mutation in exon 2: 55 4184delTCAA mutation in exon 11: 47 Exon 13 duplication: 41</td>
<td>NR</td>
<td>Not clear.</td>
<td>Information was collected on age, cancer status, and vital status.</td>
<td>Cox proportional hazards regression adjusting for clustering within families using robust standard errors by the method of Lin and Wei.</td>
</tr>
</tbody>
</table>

**Definition of clinically significant**
- Founder mutations
- Shortened, non-functional proteins
- Substitutions producing premature termination codons
- Mutations reported previously as documented in the BIC database or elsewhere.
# Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Who was tested?</th>
<th>Results/conclusions</th>
<th>Definition of clinically significant</th>
<th>How was cancer status ascertained?</th>
<th>Confounders</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antoniou et al, 2006&lt;sup&gt;172&lt;/sup&gt;</td>
<td>Families were included that had ≥1 mutation carrier identified and ≥1 further family member had DNA testing after the mutation carrier was identified.</td>
<td>Cumulative risk (BRCA1 vs. BRCA2) BC by age 50: 20% (95% CI, 0 to 45) vs. 21% (95% CI, 0 to 55) BC by age 70: 72% (95% CI, 0 to 93) vs. 75% (95% CI, 0 to 97) OC by age 50: 1% (95% CI, 0 to 10) vs. 0.4% (95% CI, 0 to 2) OC by age 70: 38% (95% CI, 0 to 78) vs. 49% (95% CI, 0 to 81)</td>
<td></td>
<td>Cancer status of family members was reported by the proband. In most instances, the diagnoses of breast and/or ovarian cancer were confirmed by examining a pathology report.</td>
<td>It was not reported whether prophylactic surgery was collected.</td>
<td>Penetrance parameters were estimated by maximum likelihood using a modified segregation analysis implemented in MENDEL.</td>
</tr>
<tr>
<td>Evans et al, 2008&lt;sup&gt;178&lt;/sup&gt;</td>
<td>Index case and some family members. Testing is offered to all blood relatives. Where possible, all affected women with breast/ovarian cancer are tested.</td>
<td>BRCA1 vs. BRCA2 Penetrance of BC to age 70: 68% (95% CI, 65 to 71) vs. 75% (95% CI, 72 to 78) Risk of OC to age 70: 60% (95% CI, 65 to 71) vs. 30% (95% CI, 26 to 35) There was evidence of a strong cohort effect with women born after 1940 having a cumulative risk of 22% for breast cancer by age 40 years compared to 8% in women born before 1930 (p=0.0005).</td>
<td></td>
<td>Cancer status of family members was reported by the proband for 1st, 2nd, and 3rd degree relatives. All cases of breast or abdominal cancers are confirmed by means of hospital/pathology records, cancer registries, or death certification.</td>
<td>Information was collected on age, cancer status, prophylactic surgery, and vital status. DCIS was included as breast cancer.</td>
<td>Penetrance analysis was performed by including all mutation positive individuals and appropriate numbers of untested FDRs on a proportional basis.</td>
</tr>
<tr>
<td>Kramer et al, 2005&lt;sup&gt;185&lt;/sup&gt; [Mutation Carrier Group Only]</td>
<td>All women in the family who agree to testing. Women were inferred positive based on having a child who was found to carry the mutation. Women were inferred negative based on having a parent that tested negative for the family mutation. A total of 451/673 (67%) had a known or inferred genotype.</td>
<td>Risk of BC (SE) BRCA1 carriers at age 50: 0.44 (0.07) BRCA1 carriers at age 70: 0.76 (0.08) 10-year BC risk (SE) in mutation carriers BC free with intact ovaries vs. same who have undergone oophorectomy At age 40 years: 0.32 (0.13) vs. 0.11 (0.10) At age 50 years: 0.28 (0.14) vs. 0.19 (0.12) At age 60 years: 0.25 (0.18) vs. 0.14 (0.13)</td>
<td></td>
<td>Cancer status was initially reported by family members by questionnaire. Reported cancers were confirmed through death certificates, medical records, pathology reports, and central review of pathology slides.</td>
<td>Information was collected on prophylactic surgery, age, cancer status, and vital status.</td>
<td>Cumulative, age specific probabilities of developing breast cancer were estimated using the Kaplan-Meier product-limit method, with age as the time variable, modified to account for late entry. Analysis was repeated with oophorectomy as a censoring.</td>
</tr>
</tbody>
</table>
### Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Who was tested?</th>
<th>Results/conclusions</th>
<th>Definition of clinically significant</th>
<th>How was cancer status ascertained?</th>
<th>Confounders</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milne et al.</td>
<td>Probands and ≥1</td>
<td><em>BRCA1</em></td>
<td>Deleterious if <em>BRCA1</em> deleterious</td>
<td>Cancer status was ascertained</td>
<td>Information was not provided</td>
<td>Penetration study using Cox proportional hazards model. Oophorectomy was treated as a time-dependent covariate. Follow-up time was divided into 10-year intervals. A competing risks model was then used to estimate the 10-year cumulative incidence.</td>
</tr>
</tbody>
</table>
### Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Who was tested?</th>
<th>Results/conclusions</th>
<th>Definition of clinically significant</th>
<th>How was cancer status ascertained?</th>
<th>Confounders</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>family member were tested.</td>
<td>Penetration to age 70: 52% (95% CI, 26 to 69) for BC and 22% (95% CI, 0 to 40) for OC. Cumulative risk to age 70: 47% (95% CI, 29 to 60) for BC and 18% (95% CI, 0 to 35) for OC.</td>
<td>they a) were classified as &quot;clinically important&quot; by the BCIC; b) produced a premature stop codon at or before codon 1853 in BRCA; c) were protein truncating mutations occurring before exon 27 in BRCA2; d) were single base changes occurring at highly conserved bases of the splice donor of acceptor site and predicted to adversely affect splicing or shown to have other functional consequences; and/or e) produced an amino acid change with strong evidence of reported by the proband, and confirmed by other family members, when possible. Attempts were made to confirm the details of all reported cancers, including requesting pathology reports where possible.</td>
<td>collected on age, cancer status, prophylactic surgery, and vital status.</td>
<td>parameters were estimated by maximum likelihood using a modified segregation analysis implemented in MENDEL.</td>
<td></td>
</tr>
</tbody>
</table>
**Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Who was tested?</th>
<th>Results/conclusions</th>
<th>Definition of clinically significant pathogenicity</th>
<th>How was cancer status ascertained?</th>
<th>Confounders</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Kolk et al, 2010 ([Mutation Carriers Group Only])</td>
<td>Probands and some family members. Obligate carriers were defined if a child as well as a parent or sibling carried a BRCA mutation.</td>
<td>Cumulative incidence (BRCA1 vs. BRCA2) BC by age 70 excluding index cases: 60% (95% CI, 55 to 66) vs. 78% (95% CI, 69 to 88) OC by age 70 excluding index cases: 52% (95% CI, 45 to 59) vs. 13% (95% CI, 7.4 to 19)</td>
<td>NR</td>
<td>Cancer status was reported by the family. Cancer cases were confirmed by hospital or pathology records or else through a first degree family member.</td>
<td>DCIS was included as breast cancer. Information was collected on age, cancer status, vital status, and prophylactic surgery.</td>
<td>Cumulative incidence was estimated using Kaplan-Meier survival analysis.</td>
</tr>
</tbody>
</table>

**Abbreviations:** ASO = allele specific oligohybridization; BC = breast cancer; BCFR = Breast Cancer Family Registry; BCIC = Breast Cancer Information Core; CI = confidence interval; CJM = common Jewish mutations; CSGE = conformation sensitive gel electrophoresis; DCIS = ductal carcinoma in situ; DGGE = denaturing gradient gel electrophoresis; dHPLC = denaturing high performance liquid chromatography; DNA = deoxyribonucleic acid; FAMA = fluorescence assisted mutation analysis; FDR = first-degree relative; HBOC = hereditary breast and ovarian cancer; HR = hazard ratio; INHERIT = INterdisciplinary HEalth Research International Team on BReast CAncer Susceptibility; MCMC = Metropolis-Hastings Markov Chain Monte Carlo; NA = not applicable; NCI = National Cancer Institute; NR = not reported; O/E = observed to expected ratio; OC = ovarian cancer; OR = odds ratio; PCR = polymerase chain reaction; PROSE = Prevention and Observation of Surgical End Points Consortium; PTT = protein truncation test; RNA = ribonucleic acid; RR = relative risk; SDR = second-degree relative; SE = standard error; SEER = Surveillance, Epidemiology, and End Results; SIR = standardized incidence ratio; SSCP = single strand conformation polymorphism.
### Appendix C9. Evidence Table of Distress After Genetic Testing

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Subcategory</th>
<th>Purpose</th>
<th>Study type</th>
<th>N</th>
<th>Country</th>
<th>Population/Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arver et al, 2004 NA</td>
<td>Psychological</td>
<td>To prospectively evaluate the psychological consequences during the 1st year following pre-symptomatic testing with respect to anxiety, depression, and QOL in self-referred individuals tested for breast/ovarian or colon cancer genes known in their families.</td>
<td>Before and after</td>
<td>Eligible: NR</td>
<td>Enrolled: 66</td>
<td>Analyzed: 63 at week 1 and 2 months, 61 at 6 months, 59 at 12 months</td>
</tr>
<tr>
<td>Dagan and Shochat, 2009 Fair Same population as Shochat and Dagan, 2010</td>
<td>Psychological Cancer worry</td>
<td>To investigate the association between BRCA1/2 status and HR-QOL in Ashkenazi asymptomatic women.</td>
<td>Case-control</td>
<td>Eligible: 152 (39 carriers, 77 noncarriers, 36 controls)</td>
<td>Enrolled: 73 (17 carriers, 20 noncarriers, 36 controls)</td>
<td>Analyzed: 73 (17 carriers, 20 noncarriers, 36 controls)</td>
</tr>
<tr>
<td>Ertmanski et al, 2009 NA</td>
<td>Psychological</td>
<td>To predict which women might suffer from abnormally high levels of anxiety and depression after receiving a positive genetic test result.</td>
<td>Before and after</td>
<td>Eligible: NR</td>
<td>Analyzed: 56</td>
<td></td>
</tr>
<tr>
<td>Geirdal et al, 2005 Good Same population as Geirdal and Dahl, 2008</td>
<td>Psychological</td>
<td>To explore psychological distress in women at risk of FBOC and HNPC cancer and without access to genetic testing, and to compare them with mutation carriers and with healthy women from the general population.</td>
<td>Prospective cohort</td>
<td>Eligible: 10,321 (253 FBOC, 10,000 normal controls, 68 BRCA1 mutation carriers)</td>
<td>Enrolled: 10,244 (176 FBOC, 10,000 normal controls, 68 BRCA1 mutation carriers)</td>
<td>Analyzed: 10,244 (176 FBOC, 10,000 normal controls, 68 BRCA1 mutation carriers)</td>
</tr>
<tr>
<td>Geirdal and Dahl, 2008 Good Same population as Geirdal et al, 2005</td>
<td>Psychological</td>
<td>To examine how coping strategies used by women with FBOC were associated with caseness of anxiety disorder and to explore if a similar pattern of associations were observed in the carrier group.</td>
<td>Prospective cohort</td>
<td>Eligible: 333 (253 FBOC, 80 BRCA1 mutation carriers)</td>
<td>Enrolled: 242 (174 FBOC, 68 BRCA1 mutation carriers)</td>
<td>Analyzed: 242 (174 FBOC, 68 BRCA1 mutation carriers)</td>
</tr>
<tr>
<td>Author, year Quality</td>
<td>Subcategory</td>
<td>Purpose</td>
<td>Study type</td>
<td>N</td>
<td>Country</td>
<td>Population/Setting</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>---------</td>
<td>------------</td>
<td>---</td>
<td>---------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Graves et al, 2012 NA</td>
<td>Psychological</td>
<td>To examine long-term psychosocial outcomes in a large U.S. sample.</td>
<td>Case-series</td>
<td>241</td>
<td>U.S.</td>
<td>Women at the Lombardi Comprehensive Cancer Center Familial Cancer Registry</td>
</tr>
<tr>
<td>Julian-Reynier et al, 2011 Good</td>
<td>Risk perception</td>
<td>To describe the sequences of preventive decisions made by women up to 5 years after disclosure of their test results and the surveillance/surgical options chosen by various age groups.</td>
<td>Prospective cohort</td>
<td>331</td>
<td>France</td>
<td>French Cancer Genetic Network</td>
</tr>
<tr>
<td>Kinney et al, 2005 Poor</td>
<td>Psychological</td>
<td>To evaluate the effect of receiving genetic test results on general and cancer-specific psychological distress in African Americans at high risk for carrying a deleterious BRCA1 mutation.</td>
<td>Prospective cohort</td>
<td>NR</td>
<td>U.S.</td>
<td>Members of a high-risk African American kindred that was identified previously with the BRCA1 mutation</td>
</tr>
<tr>
<td>Low et al, 2008 Fair</td>
<td>Psychological</td>
<td>To examine the relationship between mutation carrier status, personal cancer history, and the potential positive impact of genetic testing.</td>
<td>Prospective cohort</td>
<td>NR</td>
<td>U.S.</td>
<td>UCLA Familial Cancer Registry and Genetic Evaluation Program</td>
</tr>
<tr>
<td>Metcalfe et al, 2012 NA</td>
<td>Psychological</td>
<td>To report on cancer-related distress levels, uptake of cancer risk reduction options, and the resulting breast and ovarian cancer risk in Jewish women 2 years after receiving a positive BRCA mutation result.</td>
<td>Before and after</td>
<td>22</td>
<td>Canada</td>
<td>Jewish women responding to a newspaper ad</td>
</tr>
<tr>
<td>Reichelt et al, 2004 Good</td>
<td>Psychological</td>
<td>To examine the short-term psychological impact of receiving definite results concerning BRCA1 mutation status in a clinical setting.</td>
<td>Prospective cohort</td>
<td>301</td>
<td>Norway</td>
<td>Unit of Medical Genetics, The Norwegian Radium Hospital</td>
</tr>
<tr>
<td>Reichelt et al, 2008 NA</td>
<td>Psychological</td>
<td>To examine the levels of psychological and cancer-specific distress at 18 months after getting genetic test results in women with demonstrated BRCA1 mutations and to explore associations with baseline characteristics.</td>
<td>Before and after</td>
<td>NR</td>
<td>Norway</td>
<td>Section for Hereditary Cancer, Department of Medical Genetics, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway</td>
</tr>
</tbody>
</table>
# Appendix C9. Evidence Table of Distress After Genetic Testing

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Subcategory</th>
<th>Purpose</th>
<th>Study type</th>
<th>N</th>
<th>Country</th>
<th>Population/Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Dijk et al, 2006</td>
<td>Good</td>
<td>Cancer worry</td>
<td>To assess whether the pedigree-based familial risk estimation and the personal cancer history can explain cancer worry and distress among women who receive an uninformative DNA test result.</td>
<td>Prospective cohort</td>
<td>Eligible: NR Enrolled: 133 Analyzed: 132</td>
<td>The Netherlands</td>
<td>Department of Clinical Genetics in Leiden or Rotterdam between 1995 and 2002, in families where a BRCA mutation was already detected</td>
</tr>
<tr>
<td>Meiser et al, 2002</td>
<td>Good</td>
<td>Psychological</td>
<td>To study the psychological adjustment of women who have undergone testing for BRCA1/2 breast and ovarian cancer susceptibility.</td>
<td>Prospective cohort</td>
<td>Eligible: NR Enrolled: 143 (30 carriers, 60 noncarriers, and 53 controls) Analyzed: 140 (30 carriers, 59 noncarriers, and 51 controls)</td>
<td>Australia</td>
<td>Women in outreach clinics who had BRCA1/2 testing, were healthy with a family history of breast or ovarian cancer, and approached 1 of 14 familial cancer clinics (FCC) and 6 associated clinics</td>
</tr>
</tbody>
</table>

## Current report

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Demographics</th>
<th>Inclusion/Exclusion criteria</th>
<th>Risk level definition</th>
<th>Mutation status</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arver et al, 2004</td>
<td>NA</td>
<td>Mean age of 40.5 years (SD 11.1)</td>
<td>Inclusion: Healthy females belonging to a family with a known mutation in 1 of the genes (BRCA1, BRCA2, MLH1, MSH2), wishing for genetic testing, age ≥18 years, Swedish speaking</td>
<td>Women with a 50% or 25% risk of being gene carriers</td>
<td>BRCA carriers and noncarriers</td>
<td>Hospital Anxiety and Depression Scale (HADS, each subscale 0 to 21) Swedish SF-36 Health Survey (SF-36, scale NR)</td>
</tr>
<tr>
<td>Dagan and Shochat, 2009</td>
<td>Fair</td>
<td>Mean age of 51.5 years (SD 8.9) Carriers: 51.4 years (SD 9.1) Non-carriers: 54.5 years (SD 9.4) Controls: 50.0 years (SD 8.3)</td>
<td>Inclusion: Asymptomatic BRCA1/2 carriers and noncarriers who had genetic testing at Rambam Health Care Campus Control: Age-matched low-risk community control, with no family history of breast/ovarian cancer and not tested for BRCA1/2 mutations Exclusion: Major chronic illnesses, pregnancy, age ≤1 year</td>
<td>FDR and/or SDR with breast or ovarian cancer and/or relative with other cancer</td>
<td>BRCA carriers and noncarriers</td>
<td>Health-Related Quality of Life (HR-QOL, scale NR) Cancer Related Worry (CRW, scale NR) The Brief Symptom Inventory (BSI, scale NR)</td>
</tr>
</tbody>
</table>
Appendix C9. Evidence Table of Distress After Genetic Testing

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Demographics</th>
<th>Inclusion/Exclusion criteria</th>
<th>Risk level definition</th>
<th>Mutation status</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ertmanski et al, 2009</td>
<td>NR for women without breast cancer</td>
<td>Inclusion: Women who tested positive for BRCA mutation and completed both baseline and followup measures Exclusion: NR</td>
<td>Positive family history of early onset breast or ovarian cancer</td>
<td>BRCA positive</td>
<td>State-Trait Anxiety Inventory (STAI, scale 1 to 10) Impact of Events Scale (IES, scale 0 to 75)</td>
</tr>
<tr>
<td>Foster et al, 2007</td>
<td>Median age 42 years (range: 23-72)</td>
<td>Inclusion: Unaffected by cancer and from families with a BRCA1/2 mutation identified in an affected blood relative Exclusion: NR</td>
<td>50% risk of inheriting a BRCA1/2 mutation, this was lower if intervening relative had died</td>
<td>BRCA carriers and noncarriers</td>
<td>General Health Questionnaire (GHQ-28, scale 0 to 28) Cancer worry scale-revised (CWS-R, scale 6 to 24)</td>
</tr>
<tr>
<td>Geirdal et al, 2005</td>
<td>Mean age (years): FBOC: 40.5 (SD 9.7) BRCA1 carriers: 42.0 (SD 10.6) Controls: 42.5 (SD 10.9)</td>
<td>Inclusion: Self-referred or referred from doctors to Section for Genetic Counseling, at risk for FBOC or BRCA positive Controls: random sample of age-matched women completing same questionnaires Exclusion: NR</td>
<td>Family history of ≥2 FDRs (or SDR though males) with early onset (&lt;50 years) breast cancer and/or multiple cases of breast cancers in the same lineage compatible with dominant inheritance in the family and/or a combination of early onset breast cancer and ovarian cancer in the family</td>
<td>BRCA positive FBOC, mutation status unknown</td>
<td>Hospital Anxiety and Depression Scale (HADS, each subscale 0 to 21) General Health Questionnaire (GHQ-28, scale 0 to 84) Beck Hopelessness Scale (BHS, scale 0 to 20) Impact of Event Scale (IES, IES-I subscale 0 to 35 and IES-A subscale 0 to 40)</td>
</tr>
<tr>
<td>Geirdal and Dahl, 2008</td>
<td>Mean age (years): FBOC: 40.5 (SD 9.7) BRCA1 carriers: 42.0 (SD 10.6)</td>
<td>Inclusion: FBOC: Women age ≥18 years, had been to genetic counseling at Section for Genetic Counseling, carried a demonstrable mutation Exclusion: FBOC: Any identifiable mutation in family, diagnosed with breast or ovarian cancer BRCA1 positive: Diagnosed with breast or ovarian cancer</td>
<td>Family history of ≥2 FDRs (or SDRs though males) with early onset (&lt;50 years) breast cancer and/or multiple cases of breast cancers in the same lineage compatible with dominant inheritance in the family and/or a combination of early onset breast cancer and ovarian cancer in the family</td>
<td>BRCA positive FBOC, mutation status unknown</td>
<td>Hospital Anxiety and Depression Scale (HADS, anxiety subscale 0 to 21) Coping Orientation to Problems Experienced Scale (COPE, scale varied for each coping strategy)</td>
</tr>
<tr>
<td>Julian-Reynier et al, 2011</td>
<td>Mean age (years) Carriers: 37.2 Noncarriers: 41.7</td>
<td>Inclusion: BRCA1/2 mutation carriers and noncarriers in the same families Exclusion: NR</td>
<td>BRCA1/2 mutation carriers or members of families where a mutation was identified</td>
<td>BRCA1/2</td>
<td>Perception of personal risk of cancer (6-point Likert scale) Preventive health behaviors</td>
</tr>
</tbody>
</table>
## Appendix C9. Evidence Table of Distress After Genetic Testing

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Demographics</th>
<th>Inclusion/Exclusion criteria</th>
<th>Risk level definition</th>
<th>Mutation status</th>
<th>Measures</th>
</tr>
</thead>
</table>
| Kinney et al, 2005243 Poor | NR for women without breast cancer | **Inclusion:** Women age ≥18 years and members of the family identified in the genetic linkage study as having *BRCA1* mutation  
**Exclusion:** NR | All women from *BRCA1* mutation positive family | *BRCA1* carriers and noncarriers | State-Trait Anxiety Inventory (STAI, scale 1 to 10)  
Impact of Events Scale (IES, scale 0 to 75)  
Center for Epidemiologic Studies-Depression (CES-D, scale NR) |
| Low et al, 2008244 Fair | NR for women without breast cancer | **Inclusion:** Age ≥18 years with family history of breast, ovarian, or other cancer consistent with *BRCA1/2* heredity and/or 10% prior probability of carrying a *BRCA1/2* mutation based on published risk assessment data  
**Exclusion:** Did not complete followup data | Personal and/or family history consistent with *BRCA1/2* heredity and/or 10% prior probability of carrying a *BRCA1/2* mutation | *BRCA* positive and negative Variant of uncertain significance was grouped with negative results | Impact of Events Scale-Revised (IES-R, scale NR)  
Brief COPE (scale NR)  
Emotional Approach Coping Scale (scale NR)  
Post-Traumatic Growth Inventory (PTGI, scale 0 to 105) |
| Metcalfe et al, 2012249 NA | Mean age of 46 years (range: 28-67) | **Inclusion:** Women self-identified as Jewish, ages 25 to 70 years, residing in Ontario, and positive for a *BRCA* mutation  
**Exclusion:** Not reported | All were positive for *BRCA* mutation | 8/19 (42%)  
*BRCA1*  
11/19 (58%)  
*BRCA2* | Impact of Events Scale (IES, scale 0 to 75, IES-I subscale 0 to 35, IES-A subscale 0 to 40) |
| Reichelt et al, 2004245 Good | Mean age (years): Tested: 43.9 (SD 11.7)  
Not tested: 33.0 (SD 11.7) | **Inclusion:** Age ≥18 years and risk based on clinical criteria  
**Exclusion:** None | 50% risk for FDRs to carriers  
25% risk for SDRs through males to carriers | *BRCA* carriers and noncarriers Unknown status, for those who refused testing | Hospital Anxiety and Depression Scale (HADS, each subscale 0 to 21)  
General Health Questionnaire (GHQ-28, scale 0 to 84)  
Beck Hopelessness Scale (BHS, scale 0 to 20)  
Impact of Event Scale (IES, IES-I subscale 0 to 35 and IES-A subscale 0 to 40) |
| Reichelt et al, 2008246 NA | NR for women without breast cancer | **Inclusion:** Women age >18 years, with a known *BRCA1* mutation in a close relative  
**Exclusion:** None | Known *BRCA1* mutation in close relative | *BRCA* positive and negative | Hospital Anxiety and Depression Scale (HADS, scale 0 to 42)  
Impact of Events Scale-Intrusive subscale (IES-I, scale 0 to 35) |
## Appendix C9. Evidence Table of Distress After Genetic Testing

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Demographics</th>
<th>Inclusion/Exclusion criteria</th>
<th>Risk level definition</th>
<th>Mutation status</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shochat and Dagan, 2010&lt;sup&gt;247&lt;/sup&gt;</td>
<td>Mean age of 51.5 years (SD 8.9) Carriers: 51.4 years (SD 9.1) Noncarriers: 54.5 years (SD 9.4) Controls: 50.0 years (SD 8.3)</td>
<td>Inclusion: Asymptomatic BRCA1/2 carriers and noncarriers who had undergone genetic testing at Rambam Health Care Campus Control: Age-matched low-risk community control, with no family history of breast/ovarian cancer and not tested for BRCA1/2 mutations Exclusion: Major chronic illnesses, pregnancy, age ≤1 year</td>
<td>FDR and/or SDR with breast or ovarian cancer and/or relative with other cancer</td>
<td>BRCA carriers and noncarriers</td>
<td>Wrist activity monitors Daily sleep log Pittsburgh Sleep Quality Index (PSQI, each subscale 4-point Likert) Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF, scale 0 to 120) The Brief Symptom Inventory (BSI, scale NR) Cancer Related Worry (CRW, scale NR)</td>
</tr>
<tr>
<td>van Dijk et al, 2006&lt;sup&gt;248&lt;/sup&gt; Good</td>
<td>NR for women without breast cancer</td>
<td>Inclusion: Women from a family with a previously detected BRCA mutation, age ≥18 years, and had not previously received genetic counseling elsewhere Exclusion: NR</td>
<td>BRCA mutation previously detected in family and individuals with a probability of mutation detection of ≥10%; women with an uninformative result were separated into 2 risk groups, 1) &lt;30% personal risk estimate for low risk and 2) ≥30% personal risk estimate for high-risk</td>
<td>BRCA positive, true negative, and uninformative results</td>
<td>Impact of Events Scale (IES, scale 0 to 75) Breast cancer worry question of &quot;During the last 2 weeks, how often did you worry about developing breast cancer?&quot; (Likert scale ranging from 1=almost never to 4=almost all the time)</td>
</tr>
<tr>
<td>Prior report</td>
<td>Mean age of 40 years (SD 11.1)</td>
<td>Inclusion: Eligible for genetic testing and at risk for developing hereditary breast cancer with an affected living relative to provide blood sample Exclusion: History of breast or ovarian cancer, limited English literacy, and being tested for founder mutations only</td>
<td>25% mutation (BRCA1/2) carrier risk: Subjects from high-risk family with closest affected relative or relative with a BRCA mutation is 2nd degree 50% risk: Subjects from high-risk family who has either a 1st degree affected relative or unaffected relative with a known pathogenic BRCA1/2 mutation</td>
<td>BRCA carriers and noncarriers</td>
<td>Miller Behavioural Style Scale (scale NR) Impact of Events Scale (IES, scale 0 to 75) State-Trait Anxiety Inventory (STAI, scale 20 to 80) Beck Depression Inventory (BDI, scale 0 to 63)</td>
</tr>
</tbody>
</table>
Appendix C9. Evidence Table of Distress After Genetic Testing

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Current report</th>
<th>Duration of followup</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current report</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arver et al, 2004&lt;sup&gt;235&lt;/sup&gt; NA</td>
<td>1995-1999 At 1 week, 2, 6, and 12 months</td>
<td><strong>Pretest vs. 1 week posttest vs. 2 months posttest vs. 6 months posttest vs. 1 year posttest</strong> Mean on psychological scale: HADS-A (estimated from graph): 5.6 vs. 4.6 vs. 4.0 vs. 4.0 vs. 4.2; p&lt;0.001 over time, only pretest is above normal value HAD-D (estimated from graph): 2.4 vs. 2.4 vs. 2.4 vs. 2.4 vs. 2.6; p=NS SF-36 general health (SD): 78.7 (19.2) vs. 78.8 (18.1) vs. 79.6 (20.2) vs. 81.0 (20.1) vs. 81.0 (20.3); p=NS SF-36 vitality: 67.0 (21.9) vs. 66.4 (19.8) vs. 71.9 (21.8) vs. 68.2 (25.4) vs. 69.3 (23.4); p=NS SF-36 social function: 87.3 (15.6) vs. 86.5 (20.0) vs. 91.1 (17.5) vs. 89.1 (19.4) vs. 89.0 (18.2); p=NS SF-36 role emotional: 83.8 (30.5) vs. 82.5 (34.8) vs. 79.2 (38.6) vs. 88.0 (29.2) vs. 86.2 (33.1) SF-36 mental health: 77.4 (18.7) vs. 74.9 (20.0) vs. 80.1 (19.5) vs. 78.6 (17.9) vs. 78.3 (19.6); p=NS</td>
<td>Anxiety went down over time, however depression and QOL were not affected. The results were not separated out by carriers and noncarriers though.</td>
<td>King Gustav V's Jubilee Fund and the Swedish Cancer Society</td>
<td></td>
</tr>
<tr>
<td>Dagan and Shochat, 2009&lt;sup&gt;236&lt;/sup&gt; Fair NA</td>
<td>January 2006-November 2007 Mean followup of 8.0 years (SD 1.9)</td>
<td><strong>Carriers (n=17) vs. noncarriers (n=20) vs. controls (n=36)</strong> Mean on psychological scale (SD): CRW: 0.75 (0.5) vs. 0.67 (0.5) vs. 0.45 (0.4); p=NS BSI total: 0.66 (0.7) vs. 0.35 (0.4) vs. 0.50 (0.4); p=NS HR-QOL total: 74.4 (19.2) vs. 80.3 (13.7) vs. 83.0 (10.2); p=NS HR-QOL role limitation due to emotional problems subscale: 74.5 (36.4) vs. 91.7 (21.3) vs. 97.2 (9.3); p=0.01 HR-QOL role limitation due to physical problems subscale: 79.4 (30.9) vs. 85.0 (28.6) vs. 95.1 (13.1); p=0.05</td>
<td>Carriers had higher QOL distress regarding role limitation due to emotional problems and physical problems compared to noncarriers and controls.</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Ertmanski et al, 2009&lt;sup&gt;237&lt;/sup&gt; NA</td>
<td>January 2005-December 2007 At 1 month and 1 year</td>
<td><strong>Pretest vs. 1 month posttest vs. 1 year posttest</strong> Mean STAI-Anxiety: 6.6 vs. 6.5 vs. 6.5 At 1 month posttest, IES mean score was 23.8, which is considered a low level of negative psychological reaction</td>
<td>For women not affected by breast cancer themselves, testing positive for the BRCA mutation did not increase anxiety and did not have a negative psychological impact.</td>
<td>Polish Ministry of Science and Higher Education grant number 2 PO5 D 129 29</td>
<td></td>
</tr>
<tr>
<td>Foster et al, 2007&lt;sup&gt;238&lt;/sup&gt; Fair</td>
<td>1997-2000 3 years</td>
<td><strong>Carriers (n=53) vs. noncarriers (n=101)</strong> Mean on psychological scales (SD): GHQ at baseline: 2.7 (4.6) vs. 2.6 (3.8); p=NS GHQ at 3 year posttest: 4.5 (6.3) vs. 3.7 (5.3); p=0.03 for carriers baseline vs. posttest; p=NS for between-groups differences CWS-R at baseline: 11.7 (3.1) vs. 11.5 (3.4); p=NS CWS-R at 3 year posttest: 10.4 (3.6) vs. 9.3 (2.1); p=0.03 for carriers baseline vs. posttest; p=NS for between-groups differences</td>
<td>Overtime cancer worry decreased for both carriers and noncarriers, while general distress increased for both groups, with 18% of carriers and 17% of noncarriers identified as cases using the GHQ-28 at 3 year followup.</td>
<td>Award C1226/A137 from Cancer Research U.K.</td>
<td></td>
</tr>
</tbody>
</table>
## Appendix C9. Evidence Table of Distress After Genetic Testing

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Duration of followup</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Geirdal et al., 2005</strong>&lt;sup&gt;240&lt;/sup&gt;</td>
<td>January 2000-December 2001</td>
<td>FBOC (n=176) vs. carriers (n=68) vs. controls (n=10,000)</td>
<td>Women in FBOC group, but who had not undergone genetic testing were more anxious, more depressed, and higher general distress than women who were known to be BRCA mutation carriers.</td>
<td>Norwegian Foundation for Health and Rehabilitation, National Council for Mental Health, Norway, and a donation from Edith Kongshe, Oslo</td>
</tr>
<tr>
<td>Quality: Good</td>
<td></td>
<td>Mean differences on psychological scales (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HADS-D: 2.4 (2.9) vs. 1.7 (2.4) vs. 3.2 (2.9); p&lt;0.05 FBOC vs. carriers</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HADS-A: 5.2 (3.8) vs. 4.2 (3.6) vs. 4.5 (3.5); p&lt;0.05 FBOC vs. carriers</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GHQ-28: 3.3 (5.4) vs. 2.3 (4.0) vs. NR; p&lt;0.05 FBOC vs. carriers</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IES-I: 10.2 (8.7) vs. 9.8 (7.6) vs. NR; p=NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IES-A: 8.3 (7.9) vs. 8.4 (7.6) vs. NR; p=NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BHS: 3.7 (2.5) vs. 3.8 (2.6) vs. NR; p=NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Geirdal and Dahl, 2008</strong>&lt;sup&gt;239&lt;/sup&gt;</td>
<td>January 2000-December 2001</td>
<td>FBOC (n=174) vs. carriers (n=68)</td>
<td>Women in FBOC group, but who had not undergone genetic testing were more anxious than BRCA1 mutation carriers. FBOC groups used many more coping strategies compared with BRCA1 mutation carriers, however mutation carriers were more accepting of their breast cancer risk than those in the FBOC group and therefore may not have used other coping strategies.</td>
<td>Norwegian Foundation for Health and Rehabilitation, National Council for Mental Health, Norway, and a donation from Edith Kongshe, Oslo</td>
</tr>
<tr>
<td>Quality: Good</td>
<td></td>
<td>Mean (SD) on subscales of COPE with significant differences, higher scores=strategy used more often</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active coping: 10.2 (3.2) vs. 8.7 (3.2); p=0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Planning: 9.1 (3.5) vs. 7.9 (3.7); p=0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suppression of competing activities: 6.7 (2.7) vs. 5.2 (2.3); p&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Focus on and venting of emotions: 8.1 (3.6) vs. 6.2 (2.7); p&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seeking instrumental support: 10.2 (3.6) vs. 7.4 (3.1); p&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seeking emotional support: 9.4 (3.3) vs. 7.9 (2.7); p=0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acceptance: 12.4 (3.1) vs. 13.3 (2.9); p=0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mental disengagement: 6.7 (2.8) vs. 6.0 (2.2); p=0.03 NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>COPE subscales: positive reinterpretation and growth, restraint coping, denial, behavioral disengagement, turning to religion, and use of humor</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Graves et al, 2012</strong>&lt;sup&gt;241&lt;/sup&gt;</td>
<td>Years NR</td>
<td>Logistic regression bivariate analysis (statistically significant associations)</td>
<td>Among unaffected women, BRCA1/2 carriers reported higher genetic testing distress and lower positive experiences compared with BRCA1/2 true negatives.</td>
<td>Department of Defense grant DAMD BC021733, Jess and Mildred Fisher Center for Familial Cancer Research, and Lombardi Comprehensive Cancer Center’s Familial Cancer Registry and Clinical and Molecular Epidemiology Shared Resources</td>
</tr>
<tr>
<td>Quality: NA</td>
<td>Median of 5 years posttest</td>
<td>Positive genetic test with genetic testing distress: p=0.03 Negative genetic test with positive experiences: p=0.008 Multiple regression analysis (statistically significant associations)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Genetic testing distress</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model 1 adjusting for marital status, pretest cancer distress, and receipt of RRM accounted for 13% of variance in genetic testing distress; p=0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model 2 adjusting for model 1 and genetic test result (positive or true negative) accounted for an additional 12% of variance in genetic testing distress; p=0.00001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive experiences</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| | | Model 1 adjusting for income and pretest cancer distress accounted for 8% of variance in positive; p=0.04 Model 2 adjusting for model 1 and genetic test result (positive or
## Appendix C9. Evidence Table of Distress After Genetic Testing

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Duration of followup</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Julian-Reynier et al, 2011&lt;sup&gt;242&lt;/sup&gt;</td>
<td>Good</td>
<td>2000-2006 5 years</td>
<td><strong>Carriers (n=101) vs. noncarriers (n=145)</strong> &lt;br&gt;Change from before test result to after test result of those who perceived personal risk as high &lt;br&gt;Breast cancer risk: +18% vs. -47%; p=0.016 for carriers change and p&lt;0.001 for noncarriers change &lt;br&gt;Ovarian cancer risk: +20% vs. -27%; p=0.007 for carriers change and p&lt;0.001 for noncarriers change</td>
<td>Carriers perception of risk increased after receiving genetic test results, while noncarriers perception of risk decreased.</td>
<td>Institute National du Cancer</td>
</tr>
<tr>
<td>Kinney et al, 2005&lt;sup&gt;243&lt;/sup&gt;</td>
<td>Poor</td>
<td>Year NR 4 month</td>
<td>Noncarriers unaffected with breast cancer decreased anxiety from baseline to 1 month followup; p=0.001, data not shown</td>
<td>Noncarriers anxiety went down after receiving genetic test results.</td>
<td>National Human Genome Research Institute, National Institute of Nursing Research and the National Cancer Institute</td>
</tr>
<tr>
<td>Low et al, 2008&lt;sup&gt;244&lt;/sup&gt;</td>
<td>Fair</td>
<td>September 1998-Fall 2003 Average of 20.9 months</td>
<td><strong>Carriers (n=7) vs. noncarriers (n=40)</strong> &lt;br&gt;Mean on psychological scale (SE) &lt;br&gt;PTGI total score (estimated from graph): 14 vs. 22; p=NR &lt;br&gt;IES-R at 1-month posttest: 5.83 (2.47) vs. 1.37 (0.10); p&lt;0.05 &lt;br&gt;Approach coping score: 2.32 (0.18) vs. 2.37 (0.14); p=NS</td>
<td>Women with BRCA positive mutations reported greater distress after testing than noncarriers, but did not report differences in positive life changes.</td>
<td>STOP CANCER Research Career Development Award</td>
</tr>
<tr>
<td>Metcalfe et al, 2012&lt;sup&gt;245&lt;/sup&gt;</td>
<td>NA</td>
<td>Years NR 2 years</td>
<td><strong>Pretest vs. 1 year posttest vs. 2 years posttest</strong> &lt;br&gt;Mean IES-I (SD): 1.1 (1.9) vs. 10.9 (8.6) vs. 6.9 (6.2); p=0.02 &lt;br&gt;Mean IES-A (SD): 4.1 (8.7) vs. 12.9 (8.2) vs. 10.4 (9.4); NS &lt;br&gt;Mean IES-total (SD): 5.2 (10.5) vs. 23.8 (14.5) vs. 17.2 (14.5); p=0.05 &lt;br&gt;<strong>2 years posttest clinical distress levels</strong> &lt;br&gt;2/19 (11%) severe distress (score ≥44) &lt;br&gt;4/19 (21%) moderate distress (score 26-43) &lt;br&gt;7/19 (37%) mild distress (score 9-25) &lt;br&gt;6/19 (32%) subclinical distress (score &lt;9)</td>
<td>Intrusive behaviors increased 1 year posttest but decreased by 2 years, with most women (69%) scoring in the mild or subclinical distress level at 2 years</td>
<td>NR</td>
</tr>
<tr>
<td>Reichelt et al, 2004&lt;sup&gt;246&lt;/sup&gt;</td>
<td>Good</td>
<td>September 1997-October 1999 6 weeks</td>
<td><strong>Carriers (n=141) vs. noncarriers (n=68)</strong> &lt;br&gt;Mean on psychological scales (SD) at followup: all p=NS &lt;br&gt;IES-I: 9.8 (7.6) vs. 9.3 (8.0) &lt;br&gt;IES-A: 8.4 (7.6) vs. 7.6 (7.4) &lt;br&gt;HADS-A: 4.2 (3.6) vs. 4.1 (3.9) &lt;br&gt;HADS-D: 1.7 (2.4) vs. 2.3 (2.7) &lt;br&gt;GHQ-28: 2.3 (4.0) vs. 2.4 (4.5) &lt;br&gt;BHS: 3.8 (2.6) vs. 4.0 (2.8)</td>
<td>Women who chose to get tested had higher baseline depression than those who decided not to get tested. There were no differences at followup between women who were tested and found to be mutation carriers and those who were not mutation carriers.</td>
<td>A grant from the Norwegian Research Council</td>
</tr>
</tbody>
</table>
## Appendix C9. Evidence Table of Distress After Genetic Testing

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Duration of followup</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reichelt et al, 2008&lt;sup&gt;246&lt;/sup&gt;</td>
<td>September 1997-October 1999 At 6 weeks and 8 months</td>
<td><strong>Pretest vs. 6 weeks posttest vs. 18 months posttest</strong> Mean psychological scales (SD) HADS: 6.6 (6.1) vs. 5.6 (5.1) vs. 6.9 (6.9); p=NS IES-I: 9.0 (7.8) vs. 9.0 (7.8) vs. 8.7 (7.9); p=NS</td>
<td>This study did not separate out women without cancer by carrier status. Results show no differences in distress before testing or up to 18 months after testing.</td>
<td>Norwegian Research Council grant number 115586/320</td>
</tr>
<tr>
<td>Shochat and Dagan, 2010&lt;sup&gt;247&lt;/sup&gt;</td>
<td>January 2006-November 2007 Mean followup of 8.0 years (SD 1.9)</td>
<td><strong>Carriers (n=17) vs. noncarriers (n=20) vs. controls (n=36)</strong> Reported sleep problems (PSQI &gt;5): 53% vs. 20% vs. 28%; p=0.03 for carriers vs. other groups Mean on sleep measures (SD) PSQI total: 7.29 (4.34) vs. 3.94 (2.49) vs. 4.21 (2.80); p=0.013 for carriers vs. noncarriers Sleep latency (minutes, recorded by wrist monitor): 12.23 (14.36) vs. 5.41 (5.93) vs. 9.44 (8.05); p=NS Sleep duration (minutes, recorded by wrist monitor): 435.96 (47.68) vs. 407.46 (55.56) vs. 434.40 (52.19); p=NS Sleep efficiency (% recorded by wrist monitor): 94.46 (10.65) vs. 96.80 (2.43) vs. 97.26 (2.85); p=NS Wake after sleep onset (minutes, recorded by wrist monitor): 18.08 (23.90) vs. 12.82 (10.64) vs. 11.51 (10.03); p=NS Correlations between PSQI total score and other measures CRW: 0.417 vs. 0.125 vs. 0.029; p=NS BSI: 0.437 vs. 0.546 vs. 0.057; p=0.013 for noncarriers MFSI-SF: 0.418 vs. 0.315 vs. 0.430; p=0.009 for controls Linear regression model predictors of PSQI total score (poor sleep quality) Menopausal symptoms and lower level of education combined accounted for 12.6% of the variance; p=0.019 Menopausal symptoms, lower level of education, and fatigue combined accounted for 23.0% of the variance; p=0.001 Menopausal symptoms, lower level of education, fatigue, and carrier status combined accounted for 28% of the variance; p&lt;0.001</td>
<td>Carriers reported more sleep problems compared to noncarriers and healthy controls. However, actual sleep duration, latency and wakefulness after sleep onset were not significantly different between groups.</td>
<td>NR</td>
</tr>
</tbody>
</table>
Appendix C9. Evidence Table of Distress After Genetic Testing

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Duration of followup</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Dijk et al, 2006 Good</td>
<td>1998-2002 At 1 and 7 months</td>
<td>Positive (n=22) vs. true negative (n=41) vs. uninformative low risk (n=35) vs. uninformative high risk (n=34) Mean on psychological scales (SD) IES at pretest: 21.55 (14.70) vs. 14.85 (11.99) vs. 13.54 (11.97) vs. 22.53 (14.22); p&lt;0.05 for uninformative low risk group vs. positive and true negative groups IES at 1 month following test result: 24.14 (13.21) vs. 10.85 (13.62) vs. 7.40 (8.57) vs. 14.38 (12.41); p&lt;0.05 for positive group vs. other groups IES at 7 months following test result: 24.09 (15.57) vs. 8.32 (13.30) vs. 6.31 (8.44) vs. 14.00 (14.51); p&lt;0.05 for positive group vs. other groups and p&lt;0.05 for uninformative high risk group vs. uninformative low risk group Breast cancer worry at pretest: 2.41 (0.73) vs. 1.88 (0.87) vs. 1.94 (0.73) vs. 2.21 (0.81); p&lt;0.05 positive group vs. true negative and uninformative low risk groups Breast cancer worry at 1 month following test result: 2.64 (1.00) vs. 1.29 (0.75) vs. 1.51 (0.66) vs. 1.68 (0.81); p&lt;0.05 for positive group vs. other groups Breast cancer worry at 7 months following test result: 2.18 (0.96) vs. 1.24 (0.70) vs. 1.37 (0.55) vs. 1.59 (0.66); p&lt;0.05 for positive group vs. other groups</td>
<td>Women unaffected with breast cancer but with a positive mutation had higher levels of distress and cancer worry. However, at times they were similar in their level of distress and cancer worry as those who received an uninformative test result but were at high risk.</td>
<td>The Dutch Cancer Society Grant number UL 98-1740</td>
</tr>
</tbody>
</table>
### Appendix C9. Evidence Table of Distress After Genetic Testing

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Duration of followup</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
</table>
| Meiser et al, 2002 | Good | November 1996-October 2000 12 months | Carriers (n=30) vs. noncarriers (n=59) vs. controls (n=51)  
Baseline mean scores (SD): p=NS for all  
Breast cancer worry: 13.1 (13.1) vs. 13.4 (14.6) vs. 16.0 (14.8)  
STAI: 36.1 (11.2) vs. 33.6 (12.1) vs. 33.6 (10.7)  
BDI: 5.5 (5.7) vs. 6.3 (6.7) vs. 5.9 (5.6)  
7-10 day followup mean scores (SD)  
Breast cancer worry: 21.2 (14.4) vs. 13.9 (16.1) vs. 14.9 (12.3); p=0.005 carriers vs. controls; p=NR carriers vs. noncarriers  
STAI: 38.5 (13.8) vs. 31.6 (11.1) vs. 36.8 (12.1); p=0.024 noncarriers vs. others  
BDI: 5.3 (6.2) vs. 5.7 (7.0) vs. 7.2 (6.8); p=NS  
4 month followup mean scores (SD)  
Breast cancer worry: 17.7 (18.6) vs. 8.1 (13.5) vs. 13.1 (13.5); p=NS carriers vs. controls; p=NR carriers vs. noncarriers  
STAI: 36.8 (15.3) vs. 32.2 (10.8) vs. 36.3 (14.2); p=NS  
BDI: 6.2 (8.7) vs. 3.6 (5.4) vs. 6.4 (6.3); p=0.024 noncarriers vs. others  
12 month followup mean scores (SD)  
Breast cancer worry: 16.1 (14.9) vs. 8.2 (14.2) vs. 12.3 (14.8); p=0.045 carriers vs. controls, p=NR carriers vs. noncarriers  
STAI: 31.7 (10.5) vs. 36.2 (12.9) vs. 39.0 (12.2); p=0.007 noncarriers vs. control  
BDI: 4.0 (5.1) vs. 5.4 (6.4) vs. 6.9 (7.00); p=NS | Those without deleterious BRCA mutations derive psychological benefits from genetic testing. Those who test positive for deleterious BRCA mutations may anticipate a sustained increase in breast cancer distress following disclosure, although no other adverse effects were found in this group | Project Grants Nos. 970929 and 113877 from National Health and Medical Research Council of Australia |

**Abbreviations:** BDI = Beck Depression Inventory; BHS = Beck Hopelessness Scale; BSI = Brief Symptom Inventory; CES-D = Center for Epidemiologic Studies-Depression Scale; COPE = Emotional Approach Coping Scale; CRW = Cancer-Related Worry; CWS-R = Cancer Worry Scale-Revised; FBOC = familial breast ovarian cancer; FCC = family cancer clinic; FDR = first-degree relative; GHQ = General Health Questionnaire; HADS = Hospital Anxiety and Depression Scale; HNPCC = hereditary nonpolyposis colorectal cancer; HR-QOL = Health Related-Quality of Life; IES = Impact of Events Scale; MSFI-SF = Multidimensional Fatigue Symptom Inventory-Short Form; NR = not reported; NS = not significant; PSQI = Pittsburgh Sleep Quality Index; PTGI = Post-Traumatic Growth Inventory; SD = standard deviation; SDR = second-degree relative; SE = standard error; SF-36 = Swedish SF-36 Health Survey; STAI = State-Trait Anxiety Inventory; UCLA = University of California, Los Angeles.
<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Design</th>
<th>Purpose</th>
<th>Population/setting</th>
<th>Inclusion/exclusion criteria</th>
<th>Risk level definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortesi et al, 2006</td>
<td>Prospective cohort (Expected incidence ratio derived from registry data)</td>
<td>To describe the results of an intensive surveillance program and document effectiveness of the program in selecting individuals at risk of breast cancer</td>
<td>Italy</td>
<td>Women with increased risk of breast cancer</td>
<td>Risk level was defined by Gail model, Claus tables, modified BCAPRO model, and study defined criteria (see Inclusion). Carrier (Gail model lifetime risk of 50%-85%): presence of mutant BRCA genes. High-risk (Gail model lifetime risk of 30%-50%): ≥3 relatives with breast cancer (or ovarian cancer) in 2 different generations; 1 breast/ovarian cancer case is a FDR of the other 2; ≥1 case has been diagnosed at age &lt;40 years or with bilateral breast cancer; breast cancer diagnosed at age &lt;35 years, regardless of family history; breast and ovarian cancer in same woman, regardless of family history. Intermediate risk (Gail model lifetime risk of 18%-29%): male breast cancer, regardless of family history. Slightly increased risk (Gail model lifetime risk of 6%-18%): breast/ovarian cancer without any of the described criteria.</td>
</tr>
<tr>
<td>Modena Study Group for Familial Breast and Ovarian Cancer participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leach, 2005 NAMARIBS study</td>
<td>Prospective cohort, one-arm</td>
<td>To compare contrast enhanced MRI with mammography for breast cancer screening in women genetically predisposed to breast cancer</td>
<td>U.K.</td>
<td>Women attending 1 of 22 participating centers in the U.K. with increased breast cancer risk</td>
<td>Known carrier of a deleterious BRCA1/2 or TP53 mutation: FDR of someone with 1 of these deleterious mutations; strong family history of breast or ovarian cancer or both; or family history consistent with classic Li-Fraumeni syndrome.</td>
</tr>
</tbody>
</table>
### Appendix C10. Evidence Table of Intensive Screening Interventions

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Design</th>
<th>Purpose</th>
<th>Population/setting</th>
<th>Inclusion/exclusion criteria</th>
<th>Risk level definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le-Petross et al, 2011</td>
<td>Retrospective analysis of prospective cohort, one-arm</td>
<td>To investigate the efficacy of alternating screening mammography and breast MRI every 6 months in women with a genetically high risk of developing breast cancer for breast cancer detection</td>
<td>United States</td>
<td>Women age ≥18 years, having undergone alternating screening mammography and breast MRI every 6 months at study institution, either confirmed BRCA1/2 carriers or FDR of confirmed BRCA1/2 carrier.</td>
<td>Based on BRCA status.</td>
</tr>
<tr>
<td>Rijnsburger et al, 2010</td>
<td>Prospective cohort (Registry data/data from another prospective study used for cancer characteristics comparison)</td>
<td>To evaluate the long-term results of the Dutch MRI Screening (MRISC) study, including separate analyses of BRCA1/2 mutation carriers and survival results</td>
<td>The Netherlands</td>
<td>Women ages 25 to 75 years with cumulative lifetime risk of breast cancer ≥15% due to genetic or familial predisposition (women could be tested before age 25 years if family member diagnosed before age 30).</td>
<td>Based on cumulative lifetime risk determined using modified Claus tables: BRCA1/2 carriers, or other mutations: 50%-85% risk. High-risk: 30%-50% risk. Moderate risk (no documented gene mutation): 15%-30% risk.</td>
</tr>
<tr>
<td>Hermsen et al, 2007</td>
<td>Prospective cohort, one-arm (staging compared to 2 external comparison groups; unscreened family members with cancer, combined data from multiple studies)</td>
<td>To assess efficacy of annual gynecological screening, accounting for compliance to protocol</td>
<td>The Netherlands</td>
<td>Women with BRCA1/2 mutation screened at 1 of participating centers.</td>
<td>Based on BRCA status.</td>
</tr>
</tbody>
</table>

### Ovarian Cancer

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Design</th>
<th>Purpose</th>
<th>Population/setting</th>
<th>Inclusion/exclusion criteria</th>
<th>Risk level definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacific Northwest EPC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author, year Quality</td>
<td>N</td>
<td>Baseline Demographics</td>
<td>Screening method and interval</td>
<td>Scoring criteria</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>---</td>
<td>----------------------</td>
<td>----------------------------</td>
<td>-----------------</td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortesi et al, 2006</td>
<td>273</td>
<td>Mean age at</td>
<td>From 1994 to September 2000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modena Study Group</td>
<td></td>
<td>surveillance</td>
<td>all women underwent:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>for Familial Breast</td>
<td></td>
<td>(range), years</td>
<td>A) Mammography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and Ovarian Cancer</td>
<td></td>
<td>Carrier: 42 (20-75)</td>
<td>B) Ultrasonography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>participants</td>
<td></td>
<td>High-risk: 42 (15-75)</td>
<td>C) CBE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intermediate risk:</td>
<td>D) Transvaginal ultrasound</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>43 (19-67)</td>
<td>and serum CA 125 levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slightly increased</td>
<td>Testing interval varied by</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>risk: 40 (18-75)</td>
<td>assessed risk (see below).</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>From October 2000 mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>carrier surveillance</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>modified to include:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>E) CE MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRCA risk: Started at age 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>with annual mammography</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and MRI, biannual CBE and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ultrasound plus transvaginal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ultrasound and serum CA 125</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>levels.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High risk: Started at age 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>with mammography every 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>years until age 36 and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>annually, biannual CBE and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ultrasound plus annual</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>transvaginal ultrasound and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>serum CA 125 levels.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermediate risk: Started</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>at age 30 with mammography</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>every 2 years until age 40</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and then annually,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>biannual CBE and ultrasound</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>plus annual transvaginal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ultrasound and serum CA 125</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>levels. Slightly increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>risk: Started at age 30 with</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 mammogram &lt; 40 years,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>then every 18 to 24 months,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and annual CBE and ultrasound.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Note: if possible, all exams performed on the same day during the 2nd week of the menstrual cycle in premenopausal women; additional investigation using fine needle aspiration or core biopsy performed as required.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leach, 2005 NAMARIBS study</td>
<td>649 analyzed 82 (13%) with known BRCA1 mutation 38 (6%) with known BRCA2 mutation</td>
<td>Median age at entry, years: 40 (range, 31-55; only 1 woman age &gt;50 years)</td>
<td>All women underwent:</td>
<td>Scoring system based on morphological and dynamic contrast uptake characteristics validated against histology (area under receiver operator curve=0.88 [95% CI, 0.83-0.94]) and diagnostic accuracy tested using subset of present study and 100 symptomatic cases (sensitivity, 91% [95% CI, 83-96]; specificity, 81% [95% CI, 79-83]). Note: All scoring was double reported; in statistical analysis, scoring system was paired to BIRADS as follows: for MRI; score of B, suspicious = BIRADS 0, 3, or 4 and score of A, malignant = BIRADS 5; for mammography; score M3, indeterminate = BIRADS 0-3, M4, suspicious = BIRADS 4, and M5, malignant = 5.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A) Annual mammography from age 35 years (or younger if FDR developed cancer at age &lt;35 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B) Annual CE MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Note: if possible, exams done on same day, between days 6 and 16 of menstrual cycle. Note: In women with equivocal results, high specificity MRI exam or repeat screening MRI done 2 to 6 weeks later, followed by ultrasound, fine needle aspiration, localization, and tissue sampling by conventional methods as appropriate. Note: 93% of mammographic examinations were 2-view, 7% 1-view.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix C10. Evidence Table of Intensive Screening Interventions

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>N</th>
<th>Baseline Demographics</th>
<th>Screening method and interval</th>
<th>Scoring criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Le-Petross et al, 2011</strong>&lt;sup&gt;278&lt;/sup&gt; NA</td>
<td>321 screened &lt;br&gt;73 analyzed &lt;br&gt;(37 [51%] BRCA1, 36 [49%] BRCA2)</td>
<td>Median age at entry, years: 44 &lt;br&gt;(range, 23-75) &lt;br&gt;Mean age at diagnosis, years: 51 &lt;br&gt;(range, 43-64)</td>
<td>All women underwent CBE every 6 months plus: &lt;br&gt;A) Mammography every 6 months alternating with &lt;br&gt;B) MRI every 6 months</td>
<td>BIRADS</td>
</tr>
<tr>
<td><strong>Rijnsburger et al, 2010</strong>&lt;sup&gt;276&lt;/sup&gt; See also Kriege et al, 2004&lt;sup&gt;277&lt;/sup&gt; NA</td>
<td>Dutch MRISC study &lt;br&gt;2275 enrolled &lt;br&gt;2157 analyzed &lt;br&gt;(422 BRCA1, 172 BRCA2, 5 other mutation, 1069 high risk, 489 moderate risk)</td>
<td>Mean age at entry, years: &lt;br&gt;Cohort: 40.1 &lt;br&gt;(range, 19-75) &lt;br&gt;BRCA1: 38.7 &lt;br&gt;BRCA2: 40.0 &lt;br&gt;High risk: 40.8 &lt;br&gt;Moderate risk: 40.0</td>
<td>All women underwent: &lt;br&gt;A) Biannual CBE &lt;br&gt;B) Annual mammography &lt;br&gt;C) Annual contrast enhanced MRI</td>
<td>BIRADS</td>
</tr>
<tr>
<td><strong>Hermsen et al, 2007</strong>&lt;sup&gt;281&lt;/sup&gt; NA</td>
<td>883 (683 BRCA1, 200 BRCA2) &lt;br&gt;459 for analysis of screening/compliance (data available for all screen visits)</td>
<td>Median age, years: &lt;br&gt;BRCA1: 40 (range, 21-76) &lt;br&gt;BRCA2: 44 (range, 25-77)</td>
<td>All women underwent: &lt;br&gt;A) Annual serum CA-125 measurement &lt;br&gt;B) Annual TVUS &lt;br&gt;Starting at age 35 years or 5 years earlier than youngest diagnosed ovarian cancer in the family</td>
<td>CA-125: &gt;35kU1-1 abnormal if resulted in extra screen visit or diagnostic operation. TVUS: Abnormal or normal.</td>
</tr>
</tbody>
</table>

### Ovarian Cancer

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Duration/ Followup</th>
<th>Outcome: Test characteristics</th>
<th>Cancer incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cortesi et al, 2006</strong>&lt;sup&gt;273&lt;/sup&gt; NA Modena Study Group for Familial Breast and Ovarian Cancer participants</td>
<td>1992-2005Median, 55 months (range, 1-151 months)</td>
<td>44 breast cancers detected; 64% (n=28) invasive, 36% (n=16) DCIS &lt;br&gt;36 screen-detected &lt;br&gt;Carriers: n=5 cancers (4 invasive, 1 DCIS) &lt;br&gt;High risk: n=23 (14 invasive, 9 DCIS) &lt;br&gt;Intermediate risk: n=11 (8 invasive, 3 DCIS) &lt;br&gt;Slightly increased risk: n=5 (2 invasive, 3 DCIS) &lt;br&gt;Sensitivity, A vs. B vs. A+B vs. E &lt;br&gt;All: 78% (28/36) vs. 50% (18/36) vs. 97% (35/36) vs. 100% (4/4) &lt;br&gt;Carriers: 50% (2/4) vs. 75% (3/4) vs. 75% (3/4) vs. 100% (4/4) &lt;br&gt;High risk: 90% (19/21) vs. 52% (11/21) vs. 100% (21/21) &lt;br&gt;Intermediate risk: 50% (4/8) vs. 450% (4/8) vs. 100% (8/8) &lt;br&gt;Slightly increased risk: 100% (3/3) vs. 0% (0/3) vs. 100% (3/3)</td>
<td>Breast cancer incidence in study population vs. expected incidence &lt;br&gt;All: SIR, 4.9 (95% CI, 1.6-7.6), p&lt;0.001 &lt;br&gt;Carriers: SIR, 20.3 (95% CI, 3.1-83.9), p&lt;0.001 &lt;br&gt;High-risk: SIR, 4.5 (95% CI, 1.5-8.3), p&lt;0.001 &lt;br&gt;Intermediate risk: SIR, 7.0 (95% CI, 2.0-17.1), p=0.0018 &lt;br&gt;Slightly increased risk: SIR not significantly increased &lt;br&gt;Note: SIR=ratio of observed to expected number of cancers; expected number of cancers based on Modena Cancer Registry rates from 1998 to 2002 in 5-year age groups from 25 to &gt;85 years; observed women-years at risk were multiplied by expected cancer incidence to estimate total number of cancers expected.</td>
</tr>
</tbody>
</table>
### Appendix C10. Evidence Table of Intensive Screening Interventions

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Duration/ Followup</th>
<th>Outcome: Test characteristics</th>
<th>Cancer incidence</th>
</tr>
</thead>
</table>
| Leach, 2005"*  
NAMARIBS study | Study recruitment 1997-2003 Variable screening episodes per individual but screening continued until each women had at least 2 annual scans (in 2004) | **All cancers (n=35)**  
Sensitivity (95% CI), A vs. B  
46% (24-58) vs. 77% (60-90), p=0.01  
A plus B: 94% (81-99)  
Specificity (95% CI), A vs. B  
93% (92-95) vs. 81% (80-83), p<0.001  
A plus B: 77% (75-79)  
PPV (95% CI), A vs. B  
10% (5.8-17) vs. 7.3% (4.9-10)  
NPV (95% CI), A vs. B  
99% (98-99) vs. 99% (99-100)  
Area under receiver operator curve, A vs. B  
0.70 (0.68-0.72) vs. 0.85 (0.84-0.87), p=0.035  
**Excluding DCIS (n=6)**  
Sensitivity (95% CI), A vs. B  
31% (15-51) vs. 86% (68-96), p=0.0009  
A plus B: 97% (82-100)  
**BRCA1 carriers or relative with BRCA1 mutation (n=139)**  
Sensitivity (95% CI), A vs. B  
23% (5-54) vs. 92% (64-100), p=0.004  
A plus B: 92% (64-100)  
Excluding 1 DCIS case: 25% (5.5-57) vs. 100% (74-100)  
Specificity (95% CI), A vs. B  
92% (88-94) vs. 79% (75-83), p<0.0001  
A plus B: 74% (69-78)  
PPV (95% CI), A vs. B  
9.1% (1.9-24) vs. 14% (7.2-23)  
**BRCA2 carriers or relative with BRCA2 mutation (n=86)**  
Sensitivity (95% CI), A vs. B  
50% (21-79) vs. 58% (28-84), p=1.0  
A plus B: 92% (62-100)  
Excluding 3 DCIS cases: 33% (7.5-70) vs. 67% (30-93), p=0.45  
Specificity (95% CI), A vs. B  
94% (91-97) vs. 82% (77-87), p=0.0001  
A plus B: 78% (72-83)  
PPV (95% CI), A vs. B  
9.1% (1.9-24) vs. 14% (7.2-23)  
Note: Anonymous testing was restricted to women with breast cancer so that women with BRCA-positive relatives but no breast cancer themselves were not tested; sensitivities refer only to tested mutation carriers, specificities are only preliminary estimates.  
**Incident screens (n=15 cancers, n=1217 noncancers); observed incidence rate was 1.9% per year**  
Sensitivity (95% CI), A vs. B  
Any cancer: 40% (16-68) vs. 80% (52-96), p=0.11  
15 incident cancers, observed incidence rate was 1.9% per year
### Appendix C10. Evidence Table of Intensive Screening Interventions

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Duration/ Followup</th>
<th>Outcome: Test characteristics</th>
<th>Cancer incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le-Petross et al, 2011&lt;sup&gt;276&lt;/sup&gt;</td>
<td>NA</td>
<td>Records from 1997-2009; Median followup, 2 years (range, 1-6 years); Median number of screening cycles, 2 (range, 1-6 cycles); 29% completed 1 cycle, 31% completed 2 cycles, 25% completed 3 cycles, 15% completed 4, 5, or 6 cycles</td>
<td>Sensitivity (95% CI), A vs. B: Not able to report vs. 92% (0.76-1.00) Specificity (95% CI), A vs. B: 82% (0.72-0.92) vs. 87% (0.79-0.95)</td>
<td>13 cancers detected (10 invasive, 3 DCIS) in 11 patients 5/13 cancers detected on first screening cycle (likely prevalent), 8/13 incident cancers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Number of cancers detected by cycle in 11 patients: Post cycle 1: 5 cancers Post cycle 2: 2 cancers Post cycle 3: 3 cancers Post cycle 4: 1 cancer</td>
<td></td>
</tr>
</tbody>
</table>
| | | | Number of screen-detected breast cancers; total, invasive, DCIS: 
- **BRCA1**: 21/35, 19/31, 2/4 
- **BRCA2**: 15/18, 12/13, 3/5 
- Other mutation: 1/5, 0/0, 1/1 
- High risk: 26/27, 22/23, 4/4 
- Moderate risk: 15/16, 11/11, 4/5 
- Total: 78/97, 64/78, 14/19 | Incidence of cancer per population group; total, invasive, DCIS: 
- **BRCA1**: 35, 31, 4 
- **BRCA2**: 18, 13, 5 
- Other mutation: 5, 0, 1 
- High risk: 27, 23, 4 
- Moderate risk: 16, 11, 5 
- Total: 97, 78, 19 |

Notes:
- Sensitivity (95% CI), A vs. B
- Specificity (95% CI), A vs. B
- 12/13 cancers identified on MRI (1/13 on prophylactic mastectomy), but not mammography 6 months prior; no cancer detected by mammography alone; no cancer palpable by CBE
- 5/13 cancers detected on targeted ultrasound post MRI detection
- Screening method comparisons based on 75 breast cancers with data that included results for both imaging methods
- Sensitivity (95% CI), A vs. B vs. C
- Any breast cancer: 21% (12-32) vs. 41% (30-53) vs. 71% (59-81), p=0.0016 for B vs. C Invasive: 22% (11.8-32) vs. 36% (24-49) vs. 77% (65-87), p<0.00005 for B vs. C DCIS: 15% (1.9-45) vs. 69% (39-91) vs. 39% (14-68), p=0.388 for B vs. C
## Appendix C10. Evidence Table of Intensive Screening Interventions

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Duration/ Followup</th>
<th>Outcome: Test characteristics</th>
<th>Cancer incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mutation (any breast cancer)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA1: 13% (2.8-34) vs. 25% (9.8-47) vs. 67% (45-84), p=0.0129 for B vs. C</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA2: 7.7% (0.2-36) vs. 62% (33-86) vs. 69% (39-91), p=1.0 for B vs. C</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk group (any breast cancer)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High: 32% (13-56) vs. 46% (24-68) vs. 77% (55-92)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate: 33% (9.9-65) vs. 47% (21-73) vs. 67% (38-88)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA1 vs. BRCA2 sensitivity of methods compared: Mammography, p =0.04; all other comparisons between groups and screening methods were nonsignificant. Specificity of methods did not differ between groups.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Specificity (95% CI), A vs. B vs. C</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any breast cancer: 98% (97.5-98.2) vs. 95 (94.0-95.1) vs. 90 (88.9-90.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mutation (any breast cancer)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA1: 97% (95.7-97.9) vs. 95% (93.0-95.9) vs. 91% (89.1-92.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA2: 98% (96.4-99.4) vs. 94% (90.9-96.0) vs. 92% (88.7-94.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk group (any breast cancer)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High: 98% (97.7-98.7) vs. 95% (93.8-95.3) vs. 89% (87.9-90.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate: 98% (96.9-98.6) vs. 95% (93.5-95.9) vs. 93% (90.9-91.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPV (95% CI), A vs. B vs. C</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any breast cancer: 10% (5.7-17) vs. 8.5% (5.8-12) vs. 7.7% (5.8-9.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mutation (any breast cancer)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA1: 8.8% (1.8-24) vs. 9.5% (3.6-20) vs. 14% (8.5-22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA2: 14% (0.4-58) vs. 26% (12-45) vs. 23% (11-39)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk group (any breast cancer)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High: 9.8% (3.7-20) vs. 5.3% (2.6-9.5) vs. 4.5% (2.6-7.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate: 12% (3.4-28) vs. 8.5% (3.5-17) vs. 6.2% (3.0-11)</td>
<td></td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td></td>
<td>15 cancers diagnosed in cohort</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1993-2005 1473 person-years</td>
<td>Based on 459 women with data on each visit: 7 cancers diagnosed (2 prevalent, 2 interval, 3 incident)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sensitivity (95% CI), A vs. B vs. A+B</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>All cancers: 42% (14-70) vs. 25% (1-50) vs. 42% (14-70)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excluding occult cancers: 71% (38-100) vs. 43% (6-80) vs. 71% (38-100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Specificity (95% CI), A vs. B vs. A+B</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>All cancers: 99% for all (CI range, 98-100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excluding occult cancers: 99% for all (CI range, 98-100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPV (95% CI), A vs. B vs. A+B</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>All cancers: 33% (9-57) vs. 20% (0-40) vs. 23% (5-40)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excluding occult cancers: 33% (9-57) vs. 20% (0-40) vs. 23% (5-40)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NPV (95% CI), A vs. B vs. A+B</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>All cancers: 99% (99-100) for all</td>
<td></td>
</tr>
</tbody>
</table>

### BRCA-Related Cancer

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Duration/ Followup</th>
<th>Outcome: Test characteristics</th>
<th>Cancer incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ovarian Cancer</td>
<td></td>
</tr>
<tr>
<td>Hermsen et al, 2007</td>
<td>1993-2005 1473 person-years</td>
<td>15 cancers diagnosed in cohort</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Based on 459 women with data on each visit: 7 cancers diagnosed (2 prevalent, 2 interval, 3 incident)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sensitivity (95% CI), A vs. B vs. A+B</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>All cancers: 42% (14-70) vs. 25% (1-50) vs. 42% (14-70)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excluding occult cancers: 71% (38-100) vs. 43% (6-80) vs. 71% (38-100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Specificity (95% CI), A vs. B vs. A+B</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>All cancers: 99% for all (CI range, 98-100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excluding occult cancers: 99% for all (CI range, 98-100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPV (95% CI), A vs. B vs. A+B</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>All cancers: 33% (9-57) vs. 20% (0-40) vs. 23% (5-40)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excluding occult cancers: 33% (9-57) vs. 20% (0-40) vs. 23% (5-40)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NPV (95% CI), A vs. B vs. A+B</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>All cancers: 99% (99-100) for all</td>
<td></td>
</tr>
</tbody>
</table>

### Note:
- Expected number of cases based on data from population-based studies of breast cancer cases, families of BRCA1/2 carriers; SIR=expected/observed cases based on reference curves derived from refitting BOADICEA.
- Expected number of cases based on data from population-based studies of breast cancer cases, families of BRCA1/2 carriers; SIR=expected/observed cases based on reference curves derived from refitting BOADICEA.
### Appendix C10. Evidence Table of Intensive Screening Interventions

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Duration/ Followup</th>
<th>Outcome: Test characteristics</th>
<th>Cancer incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Excluding occult cancers: 100% for all (CI range, 99-100)</td>
<td>model of genetic susceptibility to breast cancer and including data from population-based studies of breast cancer families and cases.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Duration/ Followup</th>
<th>Outcome: Cancer characteristics</th>
<th>Outcome: Disease-free survival Mortality</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortesi et al, 2006&lt;sup&gt;273&lt;/sup&gt;</td>
<td>273</td>
<td>NA</td>
<td>Staging: 61% (n=17) stage I; 25% (n=7) stage II; 7% (n=2) stage III; 7% (n=2) stage IV</td>
<td>Post treatment, 4 recurrences and 3 deaths (2 for disease progression, 1 from heart failure). Actuarial 5 year survival rate was 93%.</td>
<td>Rate of cancer detected in women at high risk for breast cancer was significantly higher than expected in an age-matched general population. Results support increased screening surveillance program to identify and monitor high-risk individuals.</td>
<td>Italian consortium for Hereditary Breast and Ovarian Cancer; COFIN-MURST 2003-2005; Fondazione Cassa di Risparmio di Modena; Associazione Angela Serra per la ricerca sul Cancro</td>
</tr>
<tr>
<td>Modena Study Group for Familial Breast and Ovarian Cancer participants</td>
<td></td>
<td></td>
<td>Size: 29% (n=8) &lt;10 mm in diameter; 36% (n=10) were 10-15 mm in diameter; 32% (n=9) &gt;15 mm in diameter; 1 was inflammatory breast cancer</td>
<td>Interval cancers: n=8, all identified with CBE; interval cancer rate, 1.3 per 1000; diagnosed with CBE only (n=4); CBE plus ultrasound (n=3); CBE plus ultrasound plus mammography (n=1); time interval from last negative screen to diagnosis ranged from 1 to 14 months</td>
<td>NR</td>
<td>Grant from U.K. Medical Research Council; MRI cost paid from subvention funding for research from U.K. National Health Service</td>
</tr>
<tr>
<td>Leach, 2005&lt;sup&gt;74&lt;/sup&gt; NAMARIBS study</td>
<td>276</td>
<td>NA</td>
<td>Grade: 10% (3/29) grade 1; 24% (7/29) grade 2; (66%) 19/29 grade 3</td>
<td>NR</td>
<td>Contrast-enhanced MRI is more sensitive than mammography for breast cancer detection in women with familial risk for breast cancer. Specificity was acceptable for both. Detected tumors were small and mostly node negative, suggesting that annual screening with mammography and contrast-enhanced MRI would detect most tumors in this risk group.</td>
<td></td>
</tr>
<tr>
<td>Le-Petross et al, 2011&lt;sup&gt;276&lt;/sup&gt;</td>
<td>276</td>
<td>NA</td>
<td>Size on MRI: Mean, 14 mm (range, 1-30 mm) Nodal status: 9% (1/11) women node-positive</td>
<td>NR</td>
<td>Screening women at increased genetic risk of breast cancer by alternating mammography with MRI every 6 months has a higher cancer yield than</td>
<td></td>
</tr>
</tbody>
</table>

**BRCA-Related Cancer**
### Appendix C10. Evidence Table of Intensive Screening Interventions

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Outcome: Cancer characteristics</th>
<th>Outcome: Disease-free survival Mortality</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Characteristics of detected breast cancer <em>(includes 78 screen-detected cancers and 11 interval cancers)</em></td>
<td>Disease-free and overall survival in 89 patients  11/93 patients with breast cancer had relapse, 7/11 were mutation carriers  5 patients had distant metastasis, all were mutation carriers  4 patients died, 3/31 (9.7%) <em>BRCA1</em> and 1/16 (6.3%) <em>BRCA2</em>  Cumulative metastasis-free and overall survival at 6 years in 43 mutation carriers with invasive cancer were 84% and 93%; other groups had 100% cumulative survival</td>
<td>studies that screened using both modalities at the same time point.</td>
<td>Dutch government; Cancer Genomics Center</td>
</tr>
</tbody>
</table>
| Rijnsburger et al, 2010
d See also Kriege et al, 2004
d NA | Tumor size: 40% (30/76) < 1 cm, 39% (29/76) 1-2 cm, 20% (15/76) > 2 cm; p1=0.003, p2=0.0045  Nodal status negative: 69% (50/72); p1=0.42, p2=1 | Sensitivity of MRI superior to mammography for detection of breast cancer in women at increased risk. *BRCA1*-associated cancers have younger age at diagnosis, lower mammographic sensitivity, high number of interval cancers, low number of DCIS, and unfavorable tumor size at diagnosis. | Dutch government; Cancer Genomics Center |
| Dutch MRISC study | Histology: 29% (21/72) grade 1, 32% (23/72) grade 2, 39% (28/72) grade 3; p1<0.001, p2=0.15 | BRCA1: 10/35, 10/31, 0/4  BRCA2: 1/18, 1/18, 0/5  Other mutation: 0/0, 0/0, 0/0  High risk: 1/27, 1/23, 0/4  Moderate risk: 1/16, 0/11, 1/5  Total: 13/97, 12/78, 1/19 | Studies that screened using both modalities at the same time point. | Dutch government; Cancer Genomics Center |
|                     | Note: Age at diagnosis, number of interval cancers, and estrogen and progesterone receptor status significantly different between subgroups  Number of interval cancers (total, invasive, DCIS)  *BRCA1*: 10/35, 10/31, 0/4  *BRCA2*: 1/18, 1/18, 0/5  Other mutation: 0/0, 0/0, 0/0  High risk: 1/27, 1/23, 0/4  Moderate risk: 1/16, 0/11, 1/5  Total: 13/97, 12/78, 1/19  Note: denominator includes 6 breast cancers detected at prophylactic mastectomy  Kriege 2004 breast cancer characteristics, study group vs. control 1 vs. control 2 (based on 50 screen-detected cancers in study group, 1500 in control group 1, and 45 in control group 2) | Note: denominator includes 6 breast cancers detected at prophylactic mastectomy  Kriege 2004 breast cancer characteristics, study group vs. control 1 vs. control 2 (based on 50 screen-detected cancers in study group, 1500 in control group 1, and 45 in control group 2) | Dutch government; Cancer Genomics Center |
|                     | Note: Age at diagnosis, number of interval cancers, and estrogen and progesterone receptor status significantly different between subgroups  Number of interval cancers (total, invasive, DCIS)  *BRCA1*: 10/35, 10/31, 0/4  *BRCA2*: 1/18, 1/18, 0/5  Other mutation: 0/0, 0/0, 0/0  High risk: 1/27, 1/23, 0/4  Moderate risk: 1/16, 0/11, 1/5  Total: 13/97, 12/78, 1/19  Note: denominator includes 6 breast cancers detected at prophylactic mastectomy  Kriege 2004 breast cancer characteristics, study group vs. control 1 vs. control 2 (based on 50 screen-detected cancers in study group, 1500 in control group 1, and 45 in control group 2) | Note: denominator includes 6 breast cancers detected at prophylactic mastectomy  Kriege 2004 breast cancer characteristics, study group vs. control 1 vs. control 2 (based on 50 screen-detected cancers in study group, 1500 in control group 1, and 45 in control group 2) | Dutch government; Cancer Genomics Center |
|                     | Note: Age at diagnosis, number of interval cancers, and estrogen and progesterone receptor status significantly different between subgroups  Number of interval cancers (total, invasive, DCIS)  *BRCA1*: 10/35, 10/31, 0/4  *BRCA2*: 1/18, 1/18, 0/5  Other mutation: 0/0, 0/0, 0/0  High risk: 1/27, 1/23, 0/4  Moderate risk: 1/16, 0/11, 1/5  Total: 13/97, 12/78, 1/19  Note: denominator includes 6 breast cancers detected at prophylactic mastectomy  Kriege 2004 breast cancer characteristics, study group vs. control 1 vs. control 2 (based on 50 screen-detected cancers in study group, 1500 in control group 1, and 45 in control group 2) | Note: denominator includes 6 breast cancers detected at prophylactic mastectomy  Kriege 2004 breast cancer characteristics, study group vs. control 1 vs. control 2 (based on 50 screen-detected cancers in study group, 1500 in control group 1, and 45 in control group 2) | Dutch government; Cancer Genomics Center |
|                     | Note: Age at diagnosis, number of interval cancers, and estrogen and progesterone receptor status significantly different between subgroups  Number of interval cancers (total, invasive, DCIS)  *BRCA1*: 10/35, 10/31, 0/4  *BRCA2*: 1/18, 1/18, 0/5  Other mutation: 0/0, 0/0, 0/0  High risk: 1/27, 1/23, 0/4  Moderate risk: 1/16, 0/11, 1/5  Total: 13/97, 12/78, 1/19  Note: denominator includes 6 breast cancers detected at prophylactic mastectomy  Kriege 2004 breast cancer characteristics, study group vs. control 1 vs. control 2 (based on 50 screen-detected cancers in study group, 1500 in control group 1, and 45 in control group 2) | Note: denominator includes 6 breast cancers detected at prophylactic mastectomy  Kriege 2004 breast cancer characteristics, study group vs. control 1 vs. control 2 (based on 50 screen-detected cancers in study group, 1500 in control group 1, and 45 in control group 2) | Dutch government; Cancer Genomics Center |
|                     | Note: Age at diagnosis, number of interval cancers, and estrogen and progesterone receptor status significantly different between subgroups  Number of interval cancers (total, invasive, DCIS)  *BRCA1*: 10/35, 10/31, 0/4  *BRCA2*: 1/18, 1/18, 0/5  Other mutation: 0/0, 0/0, 0/0  High risk: 1/27, 1/23, 0/4  Moderate risk: 1/16, 0/11, 1/5  Total: 13/97, 12/78, 1/19  Note: denominator includes 6 breast cancers detected at prophylactic mastectomy  Kriege 2004 breast cancer characteristics, study group vs. control 1 vs. control 2 (based on 50 screen-detected cancers in study group, 1500 in control group 1, and 45 in control group 2) | Note: denominator includes 6 breast cancers detected at prophylactic mastectomy  Kriege 2004 breast cancer characteristics, study group vs. control 1 vs. control 2 (based on 50 screen-detected cancers in study group, 1500 in control group 1, and 45 in control group 2) | Dutch government; Cancer Genomics Center |
|                     | Note: Age at diagnosis, number of interval cancers, and estrogen and progesterone receptor status significantly different between subgroups  Number of interval cancers (total, invasive, DCIS)  *BRCA1*: 10/35, 10/31, 0/4  *BRCA2*: 1/18, 1/18, 0/5  Other mutation: 0/0, 0/0, 0/0  High risk: 1/27, 1/23, 0/4  Moderate risk: 1/16, 0/11, 1/5  Total: 13/97, 12/78, 1/19  Note: denominator includes 6 breast cancers detected at prophylactic mastectomy  Kriege 2004 breast cancer characteristics, study group vs. control 1 vs. control 2 (based on 50 screen-detected cancers in study group, 1500 in control group 1, and 45 in control group 2) | Note: denominator includes 6 breast cancers detected at prophylactic mastectomy  Kriege 2004 breast cancer characteristics, study group vs. control 1 vs. control 2 (based on 50 screen-detected cancers in study group, 1500 in control group 1, and 45 in control group 2) | Dutch government; Cancer Genomics Center |
|                     | Note: Age at diagnosis, number of interval cancers, and estrogen and progesterone receptor status significantly different between subgroups  Number of interval cancers (total, invasive, DCIS)  *BRCA1*: 10/35, 10/31, 0/4  *BRCA2*: 1/18, 1/18, 0/5  Other mutation: 0/0, 0/0, 0/0  High risk: 1/27, 1/23, 0/4  Moderate risk: 1/16, 0/11, 1/5  Total: 13/97, 12/78, 1/19  Note: denominator includes 6 breast cancers detected at prophylactic mastectomy  Kriege 2004 breast cancer characteristics, study group vs. control 1 vs. control 2 (based on 50 screen-detected cancers in study group, 1500 in control group 1, and 45 in control group 2) | Note: denominator includes 6 breast cancers detected at prophylactic mastectomy  Kriege 2004 breast cancer characteristics, study group vs. control 1 vs. control 2 (based on 50 screen-detected cancers in study group, 1500 in control group 1, and 45 in control group 2) | Dutch government; Cancer Genomics Center |
## Appendix C10. Evidence Table of Intensive Screening Interventions

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Outcome: Cancer characteristics</th>
<th>Outcome: Disease-free survival</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ovarian Cancer</strong></td>
<td>Stage: 80% (8/10) stage III/IV (4/5 incident, 4/5 interval cancers) vs. 77% (20/26) in unscreened family members with cancer</td>
<td>After mean followup of 28 months from diagnosis: 3/15 cases died of ovarian cancer</td>
<td>Annual screening with TVUS and serum CA-125 is an ineffective method for detecting ovarian cancer in women at increased risk due to family history.</td>
<td>Biocare Foundation</td>
</tr>
<tr>
<td>Hermsen et al, 2007</td>
<td>Interval cancers: n=5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Incident plus interval cancer.

**Abbreviations:** BIRADS = Breast Imaging- Reporting and Data System; BMI = body mass index; CA-125 = cancer antigen-125; CBE = clinical breast examination; CE = contrast enhanced; CI = confidence interval; DCIS = ductal carcinoma in situ; FDR = first-degree relative; MRI = magnetic resonance imaging; MRISC = Magnetic Resonance Imaging Screening Study; NA = not applicable; NPV = negative predictive value; NR = not reported; PPV = positive predictive value; SIR = standardized incidence ratio; TP53 = tumor protein 53; TVUS = transvaginal ultrasound; US = ultrasound.
Appendix C11. Evidence Table of Risk-Reducing Medications

<table>
<thead>
<tr>
<th>Trial Quality</th>
<th>Design</th>
<th>Purpose</th>
<th>Intervention</th>
<th>Country/population/setting</th>
<th>Inclusion/exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen vs. placebo</td>
<td>RCT</td>
<td>To report the updated analysis of IBIS-I, focusing on the period after active treatment was completed</td>
<td>Oral tamoxifen 20 mg/day or placebo</td>
<td>United Kingdom (60% of participants), Europe, Australia, and New Zealand (37% of participants)</td>
<td>Women had to have risk factors for breast cancer indicating 2-fold RR if they were ages 45 to 70 years, 4-fold RR if ages 40 to 44 years, or 10-fold RR if ages 35 to 39 years. Specifically, women were eligible from age 45 years if they had 1) mother or sister diagnosed with breast cancer before age 50 years, 2) 2 FDRs or SDRs with breast cancer at any age, or 3) FDR with breast cancer at any age, and were nulliparous or had previous hyperplastic benign lesion. Women were eligible from age 40 years if they had 1) atypical ductal or lobular hyperplasia, 2) FDR with bilateral breast cancer at any age, 3) 2 FDRs or SDRs with breast cancer, 1 of whom was diagnosed before age 50 years. Women were eligible from age 35 years if they had either 1) lobular carcinoma in situ or 2) 2 FDRs with breast cancer, both diagnosed before the age of 50 years. Any woman with estimated 10-year risk of ≥5% based on complex model was eligible after approval by study chairman.</td>
</tr>
<tr>
<td>IBIS-I</td>
<td>Fair</td>
<td>See also Cuzick 2002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSABP P-1</td>
<td>RCT</td>
<td>To update the findings from the NSABP P-1 Trial after 7 years of followup</td>
<td>Oral tamoxifen 20 mg/day vs. placebo</td>
<td>United States and Canada</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>See also Fisher et al, 1998</td>
<td></td>
<td>Note: 2 groups compared directly, no expected incidence rates</td>
<td>Women at increased risk for breast cancer</td>
<td>Women at increased risk for breast cancer due to 1) age ≥60 years, 2) ages 35 to 59 years with 5-year predicted risk of ≥1.66% by Gail model, 3) history of lobular carcinoma in situ, as well as 10 years of life expectancy, no clinical or mammographic evidence of breast cancer, not pregnant and not planning on becoming pregnant during study, normal white blood cell and platelet counts, normal hepatic and renal function, available for followup, have undergone endometrial sampling.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Included in the trial were women who had undergone hormone replacement therapy, oral contraception, or androgens within 3 months of randomization; history of DVT or pulmonary embolism.</td>
</tr>
</tbody>
</table>
## Appendix C11. Evidence Table of Risk-Reducing Medications

<table>
<thead>
<tr>
<th>Trial Quality</th>
<th>Design</th>
<th>Purpose</th>
<th>Intervention</th>
<th>Country/population/setting</th>
<th>Inclusion/exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal Marsden</td>
<td>RCT</td>
<td>To identify any long-term prevention of breast cancer associated with tamoxifen treatment after 20 years of followup of the Royal Marsden trial</td>
<td>Oral tamoxifen 20 mg/day or placebo</td>
<td>United Kingdom</td>
<td>Healthy women ages 30 to 70 years, with no clinical or screening evidence of breast cancer; at increased risk of breast cancer because of family history; with 1) ≥1 FDR age &lt;50 years at breast cancer diagnosis, 2) 1 FDR with bilateral breast cancer, or 3) 1 FDR with breast cancer diagnosed at any age plus ≥1 other affected FDR or SDR with breast cancer; personal history of benign breast biopsy and FDR with breast cancer and those using hormone replacement therapy also eligible. Exclusion: Women with history of any cancer, DVT, or pulmonary embolism; risk of pregnancy; or using oral contraceptives.</td>
</tr>
<tr>
<td>Italian Randomized Tamoxifen Prevention</td>
<td>RCT</td>
<td>To update the results of the Italian Randomized Tamoxifen Prevention Trial after 11 years of followup, focusing on the occurrence of breast cancer</td>
<td>Oral tamoxifen 20 mg/day vs. placebo</td>
<td>Italy (97% of patients), South America, Greece</td>
<td>Healthy women at average risk for breast cancer. Exclusion: Women with severe concurrent illness or history of cardiac disease, endometriosis, and suspected or certain previous DVT.</td>
</tr>
<tr>
<td>RUTH</td>
<td>RCT</td>
<td>To provide further details about breast cancer incidence by tumor characteristics, duration of treatment, and subgroup in the RUTH trial</td>
<td>Oral raloxifene 60 mg/day vs. placebo</td>
<td>Multinational</td>
<td>Women age ≥55 years; ≥1 year from final menstrual period; with documented coronary heart disease or increased risk for coronary heart disease based on risk factors (older age, diabetes, hypertension, smoking, hyperlipidemia). Exclusion: Women suspected of having breast cancer or those with a history of breast cancer; recent myocardial infarction, coronary artery bypass grafting or percutaneous coronary angioplasty, or severe heart failure; history of venous thromboembolism; recent unexplained uterine bleeding; life expectancy &lt;5 years; chronic liver or renal disease; recent use of oral or transdermal estrogens or current use of sex hormones or SERMs.</td>
</tr>
</tbody>
</table>
# Appendix C11. Evidence Table of Risk-Reducing Medications

<table>
<thead>
<tr>
<th>Trial Quality</th>
<th>Design</th>
<th>Purpose</th>
<th>Intervention</th>
<th>Country/population/setting</th>
<th>Inclusion/exclusion criteria</th>
</tr>
</thead>
</table>
| **MORE and CORE**<sup>288</sup> Good | RCT    | To assess the effect of raloxifene, indicated for osteoporosis treatment and prevention, on invasive breast cancer in subgroups of postmenopausal women by defined risk factors for breast cancer | **MORE**: Oral raloxifene 60 or 120 mg/day vs. placebo  
**CORE**: Oral raloxifene 60mg/day vs. placebo  
Note: 5-year predicted risk based on the modified Gail model score at baseline of CORE trial per each woman's risk factors | Multinational  
Postmenopausal women with osteoporosis  
Recruited from 180 clinical centers in 25 countries, including the U.S. | Inclusion  
Women age ≤80 years; ≥2 years postmenopausal; with documented osteoporosis.  
Exclusion  
Women with a history of breast cancer, invasive endometrial cancer, stroke, or venous thromboembolism in the preceding 10 years.  
Note: only eligibility requirement for CORE was to have been enrolled in MORE trial. |
| **Tamoxifen vs. raloxifene** | RCT    | To update the findings from the STAR trial | Oral tamoxifen 20 mg/day vs. oral raloxifene 60 mg/day  
Note: expected breast cancer incidence rates based on Gail model of risk per woman's risk factors | United States and Canada  
Women with increased risk for breast cancer  
Recruited from nearly 200 clinical centers | Inclusion  
Women age ≥35 years; postmenopausal; 5-year predicted breast cancer risk ≥1.7% (per Gail model); not taking tamoxifen, raloxifene, hormone therapy, oral contraceptives, or androgens for ≥3 months before randomization; not currently on warfarin or cholestyramine; no history of stroke, transient ischemic attack, pulmonary embolism, or DVT; no atrial fibrillation; no uncontrolled diabetes or uncontrolled hypertension; no psychiatric condition that would interfere with adherence; performance status that would not restrict normal activity; no history of previous malignancy except basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, or LCIS of the breast. |
## Appendix C11. Evidence Table of Risk-Reducing Medications

<table>
<thead>
<tr>
<th>Trial</th>
<th>Quality</th>
<th>Assignment/attrition</th>
<th>Demographics</th>
<th>Surveillance</th>
<th>Duration/follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen vs. placebo</td>
<td>IBIS I&lt;sup&gt;287&lt;/sup&gt;</td>
<td><strong>IBIS</strong>&lt;sup&gt;328&lt;/sup&gt;</td>
<td>7154 randomized: 3579 vs. 3575 4861 (68%) completed 5 years of treatment: 2287 (64%) vs. 2574 (72%) Approximately 85% of women returned ≥1 questionnaire during posttreatment followup</td>
<td>Tamoxifen vs. placebo Mean (SD) age, years: 50.7 (7.0) vs. 50.8 (6.7) 3913 (55%) ages 45 to 54 years Family history: 6939 (97%) of women reported some family history of breast cancer Cuzick 2002 FDR with breast cancer at age ≤50 years: 1689/3573 (47%) vs. 1744/3566 (49%) FDR with bilateral breast cancer: 579/3573 (16%) vs. 601/3566 (17%) ≥2 FDRs or SDRs with breast cancer: 2204/3573 (62%) vs. 2206/3566 (62%) During treatment, women followed every 6 months by clinic visit or phone call. Compliance measured by pill counts at each 6 month visit. Posttreatment, followed by annual mailed questionnaire for women in U.K. and Europe or annual clinic visits for women in Australia and New Zealand.</td>
<td>5 years of treatment Median followup was 95.6 months</td>
</tr>
<tr>
<td></td>
<td>Fair</td>
<td>See also Cuzick 2002&lt;sup&gt;288&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen vs. placebo</td>
<td>NSABP P-1&lt;sup&gt;71&lt;/sup&gt;</td>
<td><strong>NSABP P-1</strong>&lt;sup&gt;1294&lt;/sup&gt;</td>
<td>57,641 approached 14,453 agreed to be medically evaluated for eligibility 13,954 met eligibility requirements 13,388 randomized; 6681 vs. 6707 13,207 had followup and were included in analysis; 6597 vs. 6610</td>
<td>Age distribution at randomization: 39% ages 35-49 years 31% ages 50-59 years 30% age ≥60 years FDRs with breast cancer, n (tamoxifen vs. placebo): None: 1548 (26%) vs. 1597 (24%) 1: 3763 (57%) vs. 3738 (57%) 2: 1072 (16%) vs. 1094 (17%) ≥3: 214 (3.2%) vs. 181 (2.7%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Fair</td>
<td>See also Fisher et al, 1998&lt;sup&gt;71&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen vs. placebo</td>
<td>Royal Marsden&lt;sup&gt;285&lt;/sup&gt;</td>
<td><strong>Royal Marsden</strong>&lt;sup&gt;285&lt;/sup&gt;</td>
<td>2508 consented 14 withdrew consent prior to randomization 1250 randomized to tamoxifen, 12 excluded from analysis (all previous DCIS) 1238 analyzed 1244 randomized to placebo, 11 excluded from analysis (10 previous DCIS, 1 invasive cancer) 1233 analyzed</td>
<td>Tamoxifen vs. placebo Median age, years (range): 47 (31-70) vs. 47 (30-70) Age &lt;50 years: n=774 vs. 749 FDRs or SDRs with breast cancer, n: 0/not known: 8 vs. 10 1: 373 vs. 372 2: 476 vs. 496 3: 257 vs. 228 4: 81 vs. 82 ≥5: 43 vs. 45 Note: no significant differences between groups</td>
<td>Followup visits every 6 months with clinical breast exam and assessment for acute toxicity. Data forms completed at each visit. Medical problems and changes to family history were recorded at each visit. Mammography done annually.</td>
</tr>
<tr>
<td></td>
<td>Fair</td>
<td>See also Powles et al, 1998&lt;sup&gt;70&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix C11. Evidence Table of Risk-Reducing Medications

<table>
<thead>
<tr>
<th>Trial</th>
<th>Quality</th>
<th>Assignment/attrition</th>
<th>Demographics</th>
<th>Surveillance</th>
<th>Duration/follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Italian Randomized Tamoxifen Prevention</strong>&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Fair</td>
<td>Tamoxifen vs. placebo 13,419 recruited 4,898 refused 1499 ineligible 527 not contactable 996 missing 5408 randomized; 2700 vs. 2708 2119 withdrew: 1085 vs. 1034 (56 for ineligibility, 99 due to major changes in protocol, 394 for major adverse events, 1407 voluntarily, 154 lost to followup, 9 deaths) 3289 completed 5 years of treatment: 1615 vs. 1674</td>
<td>Median age at entry: 51 years FDRs with breast cancer, n: None: 2359 (87%) vs. 2407 (89%) ≥1: 341 (13%) vs. 301 (11%)</td>
<td>During treatment, women had a physical and blood tests every 6 months and mammography annually. After trial completion, or in case of dropout, women were followed annually. Information about major endpoints (death, adverse events, cancer diagnosis) continuously collected.</td>
<td>Mean duration of treatment, 4.2 years Mean followup, 9.1 years (cancers other than breast endpoint) 11.2 years (breast cancer endpoint)</td>
</tr>
<tr>
<td><strong>Raloxifene vs. placebo</strong></td>
<td>Good</td>
<td>Raloxifene vs. placebo 10,101 enrolled and randomized: 5044 vs. 5057 Completed 5 years of followup: 4060 (80%) vs. 3979 (79%)</td>
<td>Raloxifene vs. placebo Mean age at baseline, years (SD): 67.5 (6.6) vs. 67.5 (6.7) Family history of breast cancer, n: 452 (9.8%) vs. 445 (9.7%)</td>
<td>Breast cancer risk assessment at baseline. Clinical breast exam at baseline and every 2 years after. Mammogram within 1 year of randomization and every 2 years after. Participants attended study visits or contacted by telephone semiannually to assess adherence, adverse events, and outcomes of interest.</td>
<td>Median exposure to drug was 5.05 years Median followup, 5.6 years (analysis of data collected before February 2006)</td>
</tr>
<tr>
<td><strong>MORE and CORE</strong>&lt;sup&gt;268&lt;/sup&gt;</td>
<td>Good</td>
<td>7705 randomized in MORE: 2557 to raloxifene 60 mg/day, 2572 to raloxifene 120 mg/day, 2567 to placebo 4011 enrolled in CORE: 2725 to raloxifene 60 mg/day, 1286 to placebo</td>
<td>Characteristics at beginning of MORE Age ≥65 years, n (%): 4621/7705; 2563 (60%) of combined raloxifene groups; 1550 (60%) of placebo group Age &lt;65 years, n (%): 3084 total; 2058 (40%) of combined raloxifene groups; 1026 (40%) of placebo group Family history of breast cancer, n (%): 949/7705; 636 (13%) of combined raloxifene groups; 313 (12%) of placebo group</td>
<td>MORE: Mammograms at baseline, 2, 3, 4 years and optional at year 1. Biannual study visits for clinical breast exam and questions about breast cancer diagnosis, biopsy, surgery since last visit. CORE: Mammograms within 1 year of study entry and at 2 and 4 years. Annual study visits for clinical breast exam and questions about breast cancer diagnosis, biopsy, surgery since last visit.</td>
<td>4 years of treatment in MORE, 4 years in CORE (median time from end of MORE to enrollment in CORE, 10.6 months (range, 2.6-62 months); mean time from randomization in MORE to end of CORE, 7.8 years (includes period between trials)</td>
</tr>
</tbody>
</table>
### Appendix C11. Evidence Table of Risk-Reducing Medications

<table>
<thead>
<tr>
<th>Trial Quality</th>
<th>Assignment/attrition</th>
<th>Demographics</th>
<th>Surveillance</th>
<th>Duration/follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen vs. raloxifene</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAR</td>
<td>Good</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>See also Vogel et al, 2006</td>
<td></td>
<td>Characteristics at entry of women included in the STAR update analysis</td>
<td>Followup occurred at 6 months after treatment initiation and every 6 months thereafter for 5 years. After 5 years, followup occurred annually. Biannual clinical breast exam and annual mammography. Annual gynecological examinations, complete blood count, routine serum chemistry tests. Outcomes assessed at each visit and verified with medical reports when applicable.</td>
<td>Mean duration of treatment was 43.5 months (SD, 20.7) for tamoxifen group and 46.8 months (SD, 20.0) for raloxifene group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age, years: 58.5 (SD 7.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age distribution: 9% &lt;50 years; 50% ages 50-59 years; 32% ages 60-69 years; 8.8% age ≥70 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FDRs with breast cancer, n (%); tamoxifen vs. raloxifene: None: 2838 (29) vs. 2791 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1: 5046 (52) vs. 5135 (53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2: 1532 (16) vs. 1561 (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥3: 320 (3.3) vs. 267 (2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Note: adherence to 5 years of therapy was within study limits; since unblinding (April 2006), women who had not completed 5-year course of tamoxifen were offered option to switch to raloxifene for remaining portion of treatment course, which 879 women did</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Characteristics at entry of women included in the STAR update analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age, years: 58.5 (SD 7.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age distribution: 9% &lt;50 years; 50% ages 50-59 years; 32% ages 60-69 years; 8.8% age ≥70 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FDRs with breast cancer, n (%); tamoxifen vs. raloxifene: None: 2838 (29) vs. 2791 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1: 5046 (52) vs. 5135 (53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2: 1532 (16) vs. 1561 (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥3: 320 (3.3) vs. 267 (2.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial Quality</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen vs. placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBIS-1</td>
<td>Number of events and rate of breast cancers; tamoxifen vs. placebo: Total breast cancers: 142 vs. 195; rate,* 4.97 vs. 6.82; RR, 0.73 (95% CI, 0.58-0.91) Invasive breast cancers: 124 vs. 168; rate,* 4.34 vs. 5.88; RR, 0.74 (95% CI, 0.58-0.94) DCIS: 17 vs. 27; rate,* 0.60 vs. 0.94; RR, 0.63 (95% CI, 0.32-1.20)</td>
<td>Risk reducing effect of tamoxifen persists after ≥10 years of followup in a cohort of women, in which 97% reported some family history of breast cancer.</td>
<td>Cancer Research United Kingdom; National Health and Medical Research Council Australia</td>
</tr>
<tr>
<td>See also Cuzick 2002</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**BRCA-Related Cancer**

337

Pacific Northwest EPC
<table>
<thead>
<tr>
<th>Trial Quality</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSABP P-1</strong>&lt;sup&gt;74&lt;/sup&gt;</td>
<td><strong>Tamoxifen vs. placebo</strong></td>
<td><strong>In women with FDRs with breast cancer, tamoxifen reduced the incidence of invasive breast cancer versus placebo; statistically significant reduction of risk for those with 1 or 2 FDRs with breast cancer, nonsignificant with ≥3 relatives</strong></td>
<td><strong>National Cancer Institute; U.S. Department of Health and Human Services</strong></td>
</tr>
<tr>
<td>Fair</td>
<td>Number and rates* of invasive breast cancer by number of FDRs with breast cancer: None: 33 vs. 62; rate,* 3.48 vs. 6.47; difference, 2.99; RR, 0.54 (95% CI, 0.34-0.83) 1: 73 vs. 124; rate,* 3.16 vs. 5.52; difference, 2.36; RR, 0.57 (95% CI, 0.42-0.77) 2: 32 vs. 52; rate,* 4.91 vs. 7.84; difference, 2.93; RR, 0.63 (95% CI, 0.39-0.99) ≥3: 7 vs. 12; rate,* 5.48 vs. 11.24; difference, 5.76; RR, 0.49 (95% CI, 0.16-1.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>See also Fisher et al, 1998&lt;sup&gt;71&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Royal Marsden</strong>&lt;sup&gt;265&lt;/sup&gt;</td>
<td><strong>Tamoxifen vs. placebo</strong></td>
<td><strong>In women with a family history of breast cancer (FDRs or SDRs with breast cancer), less invasive ER-positive breast cancer observed in tamoxifen arm than in placebo arm; statistically significant</strong></td>
<td><strong>National Health Service; Cancer Research U.K.</strong></td>
</tr>
<tr>
<td>Fair</td>
<td>Invasive ER-positive breast cancer events and rate* by family history, number of relatives: 0-2: 14 vs. 28; rate, 2.7 vs. 5.3; HR, 0.51 (95% CI, 0.27-0.96); p=0.04 ≥3: 9 vs. 19; rate, 3.9 vs. 9.1; HR, 0.43 (95% CI, 0.19-0.95); p=0.04 P for interaction (between tamoxifen and placebo, after adjusting for menopausal status at randomization, HT use during treatment) = 0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>See also Powles et al, 1998&lt;sup&gt;70&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Italian Randomized Tamoxifen Prevention</strong>&lt;sup&gt;296&lt;/sup&gt;</td>
<td><strong>Tamoxifen vs. placebo</strong></td>
<td><strong>In women with ≥1 FDR with breast cancer, more breast cancer observed in tamoxifen arm than in placebo arm; not statistically significant difference</strong></td>
<td><strong>Italian National Research Council; Italian Foundation for Cancer Research; American-Italian Cancer Foundation; Italian League Against Cancer</strong></td>
</tr>
<tr>
<td>Fair</td>
<td>Number and rates of breast cancer by number of FDRs with breast cancer: None: 46 vs. 64; rate,* 1.75 vs. 2.41; difference, 0.66; RR, 0.73 (95% CI, 0.50-1.06) ≥1: 16 vs. 10; rate,* 4.29 vs. 3.00; difference, -1.29; RR, 1.43 (95% CI, 0.65-3.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>See also Veronesi et al, 1998&lt;sup&gt;72&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Raloxifene vs. placebo</strong></td>
<td><strong>In women with a family history of breast cancer (FDR with breast cancer), raloxifene reduced the incidence of invasive breast cancer versus placebo; nonsignificant reduction</strong></td>
<td><strong>Eli Lilly and Company</strong></td>
<td></td>
</tr>
<tr>
<td><strong>RUTH</strong>&lt;sup&gt;19&lt;/sup&gt;</td>
<td><strong>Raloxifene vs. placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>Number of cases (annualized rate†, %) of invasive breast cancer by family history: No: 29 (0.13) vs. 53 (0.25); HR, 0.53 (95% CI, 0.34-0.84) Yes: 8 (0.34) vs. 9 (0.39); HR, 0.89 (95% CI, 0.34-2.31) P for interaction=0.34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Appendix C11. Evidence Table of Risk-Reducing Medications

<table>
<thead>
<tr>
<th>Trial Quality</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
</table>
| **MORE and CORE**<sup>288</sup> | Raloxifene vs. placebo  
Number of cases, incidence rates, and risk reduction of invasive breast cancer by family history:  
No: 36 (0.8%) vs. 42 (1.9%); rate†, 15 vs. 35; absolute risk reduction, 20  
Yes: 3 (0.5%) vs. 13 (4.2%); rate†, 9 vs. 81; absolute risk reduction, 72  
Risk for invasive breast cancer in women receiving raloxifene vs. placebo by family history:  
No: HR, 0.42 (95% CI, 0.27-0.66)  
Yes: HR, 0.11 (95% CI, 0.03-0.38)  
*p=0.04 for interaction between family history of breast cancer and treatment  
Adjusted risk for invasive breast cancer in women receiving raloxifene by family history:  
No: HR, 0.55 (95% CI, 0.36-0.84); *p=0.005  
Yes: HR, 0.16 (95% CI, 0.06-0.42); *p<0.001 | Raloxifene was associated with significantly lower incidence of invasive breast cancer over 8 years of followup in women at higher risk of breast cancer  
Statistically significant interaction between treatment and risk reduction by family history status in women with family history of breast cancer (FDR with breast cancer); raloxifene associated with 89% reduction in risk of invasive breast cancer vs. placebo; risk reduction present after adjustment  
Family history of breast cancer was a risk factor for breast cancer in the placebo group, but not the raloxifene group | Costs of publication of this article defrayed in part by payment of page charges; funding source NR |
| **Tamoxifen vs. raloxifene** | Number of events and annual rates of invasive breast cancer by number of FDRs with breast cancer; tamoxifen vs. raloxifene;  
None: 82 vs. 105; rate,* 4.77 vs. 6.17; difference, -1.40; RR, 1.29 (95% CI, 0.96-1.75)  
1: 112 vs. 135; rate,* 3.51 vs. 4.10; difference, -0.59; RR, 1.17 (95% CI, 0.90-1.51)  
≥2: 53 vs. 70; rate,* 4.44 vs. 5.96; difference, -1.52; RR, 1.34 (95% CI, 0.93-1.96) | In women with a FDR with breast cancer, tamoxifen reduced the incidence of invasive breast cancer more than raloxifene, though difference not statistically significant | National Cancer Institute; U.S. Department of Health and Human Services |

* Per 1000 women-years.  
† Per 10,000 women-years.  

**Abbreviations:** CI = confidence interval; DCIS = ductal carcinoma in situ; DVT = deep vein thrombosis; ER = estrogen receptor; FDR = first-degree relative; HR = hazard ratio; HT = hormone therapy; IBIS-I = International Breast Cancer Intervention Study; LCIS = lobular carcinoma in situ; MORE = Multiple Outcomes of Raloxifene Evaluation Trial; NR = not reported; CORE = Continuing Outcomes Relevant to Evista Trial; NSABP = National Surgical Adjuvant Breast and Bowel Project; RCT = randomized, controlled trial; RR = relative risk; RUTH = Raloxifene Use for the Heart Trial; SD = standard deviation; SDR = second-degree relative; SERM = selective estrogen receptor modulator; STAR = Study of Tamoxifen and Raloxifene Trial.
## Appendix C12. Evidence Table of Risk-Reducing Surgery

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Design</th>
<th>Purpose</th>
<th>Sample size</th>
<th>Population/setting</th>
<th>Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salpingo-oophorectomy or oophorectomy vs. no oophorectomy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domchek et al, 2010</td>
<td>Fair</td>
<td>Prospective cohort</td>
<td>To assess the relationship of RRM or RRSO with cancer outcomes.</td>
<td>Eligible: 2482 Analyzed: 1458 with no prior breast cancer (935 BRCA1, 523 BRCA2)</td>
<td>1974-2008 U.K., Europe, and North America Women from 22 centers in the PROSE consortium</td>
<td>NR</td>
</tr>
<tr>
<td>Kramer et al, 2005</td>
<td>Fair</td>
<td>Prospective cohort</td>
<td>To assess whether population differences in oophorectomy prevalence might significantly influence breast cancer penetrance estimates in BRCA1 mutation families.</td>
<td>Eligible: 673 (98 BRCA1 positive, 23 from BRCA1 families)</td>
<td>Year: NR U.S. Women from self-referred and physician-referred families affected by hereditary breast/ovarian cancer with a BRCA1 mutation and participating in ongoing studies at the National Cancer Institute</td>
<td>NR</td>
</tr>
<tr>
<td>Olson et al, 2004</td>
<td>NA</td>
<td>Retrospective cohort</td>
<td>To estimate the potential risk reduction of breast cancer for women who underwent oophorectomy and had a family history of breast cancer but unknown BRCA status.</td>
<td>Eligible: 851 Analyzed: 634</td>
<td>1970-1994 U.S./review of Mayo Clinic Surgical Index Followup survey completed by patient or surrogates (if patient deceased)</td>
<td>Surrogate respondent vs. self-respondent Age at surgery, years (n): 21-30: 1 (4%) vs. 16 (3%) 31-40: 1(4%) vs. 88 (14%) 41-50: 11 (41%) vs. 319 (53%) 51-60: 14 (52%) vs. 184 (30%) Age at questionnaire response (followup) of self-respondents, years (n): 31-40: 9 (1%) 41-50: 48 (8%) 51-60: 172 (28%) 61-70: 231 (38%) 71-80: 124 (20%) 81-90: 20 (3%) Deceased: n=30</td>
</tr>
<tr>
<td><strong>Mastectomy vs. no mastectomy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domchek et al, 2010</td>
<td>Fair</td>
<td>Prospective cohort</td>
<td>To assess the relationship of RRM or RRSO with cancer outcomes.</td>
<td>Eligible: 2482 Analyzed: 1458 with no prior breast cancer (935 BRCA1, 523 BRCA2)</td>
<td>1974-2008 U.K., Europe, and North America Women from 22 centers in the PROSE consortium</td>
<td>NR</td>
</tr>
<tr>
<td>Evans et al, 2009</td>
<td>NA</td>
<td>Prospective cohort</td>
<td>To assess effectiveness of risk-reducing surgery in women at high risk of breast cancer, including carriers and noncarriers of BRCA1/2 mutation.</td>
<td>Eligible: 550 Enrolled: 314 women with no prior breast cancer</td>
<td>1987-1992 Europe Multidisciplinary family history clinics established at 10 centers</td>
<td>Mean age of women undergoing mastectomy at Manchester site, years: 41 (range, 21-60) Age range at all sites, years: 21-72</td>
</tr>
</tbody>
</table>

**BRCA-Related Cancer** 340 Pacific Northwest EPC
## Appendix C12. Evidence Table of Risk-Reducing Surgery

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
<th>Purpose</th>
<th>Sample size</th>
<th>Population/setting</th>
<th>Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skytte et al, 2011</td>
<td>Prospective cohort</td>
<td>To compare incidence of breast cancer after RRM in healthy BRCA mutation carriers versus nonoperated mutation carriers and background population.</td>
<td>Eligible: 307 with mutation (201 BRCA1, 106 BRCA2)</td>
<td>January 1996-February 2008 Denmark Women from clinical genetics departments at multiple sites with mutation status diagnosed</td>
<td>Median age at entry into study, years: 36.2 (range, 17.9-86.3) Mean age at group entry, years (mastectomy vs. no mastectomy): 37.1 vs. 37.7 &lt;40 years: 64/96 (67%) vs. 127/211 (60%) Note: age at group entry = age at mastectomy for mastectomy group and age at BRCA diagnosis for no mastectomy group</td>
</tr>
<tr>
<td>Hartmann et al, 1999</td>
<td>Retrospective cohort</td>
<td>To define the effect of RRM on incidence of breast cancer and risk of death from breast cancer</td>
<td>Eligible: 639 Analyzed: 639</td>
<td>1960-1993 U.S.; Mayo Clinic medical records of women who underwent RRM</td>
<td>Mean age at surgery, 42 (range, 18-79)</td>
</tr>
<tr>
<td>Hartmann et al, 2001</td>
<td>Retrospective cohort</td>
<td>To report the effect of RRM on breast cancer risk in BRCA1/2 carriers identified from a high-risk cohort</td>
<td>18 BRCA1/2</td>
<td>BRCA1/2 mutation carriers undergoing RRM and enrolled as high-risk participants in prior study (Hartmann 1999)</td>
<td>Mean age at surgery, 41 (range, 20-75)</td>
</tr>
<tr>
<td>Struewing et al, 1995</td>
<td>Prospective cohort</td>
<td>To determine the incidence of post-oophorectomy carcinomatosis and quantify the effectiveness of risk-reducing surgery</td>
<td>Eligible: 16 families Analyzed: 12 families (390 1st-degree relatives of breast or ovarian cancer cases)</td>
<td>Women with high genetic risk of ovarian cancer and oophorectomy matched to high-risk women who did not undergo surgery from National Cancer Institute, Creighton University, and U.K.</td>
<td>NR</td>
</tr>
</tbody>
</table>

### Prior Report

#### Mastectomy

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
<th>Purpose</th>
<th>Sample size</th>
<th>Population/setting</th>
<th>Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hartmann et al, 1999</td>
<td>Retrospective cohort</td>
<td>To define the effect of RRM on incidence of breast cancer and risk of death from breast cancer</td>
<td>Eligible: 639 Analyzed: 639</td>
<td>1960-1993 U.S.; Mayo Clinic medical records of women who underwent RRM</td>
<td>Mean age at surgery, 42 (range, 18-79)</td>
</tr>
<tr>
<td>Hartmann et al, 2001</td>
<td>Retrospective cohort</td>
<td>To report the effect of RRM on breast cancer risk in BRCA1/2 carriers identified from a high-risk cohort</td>
<td>18 BRCA1/2</td>
<td>BRCA1/2 mutation carriers undergoing RRM and enrolled as high-risk participants in prior study (Hartmann 1999)</td>
<td>Mean age at surgery, 41 (range, 20-75)</td>
</tr>
</tbody>
</table>

#### Oophorectomy

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
<th>Purpose</th>
<th>Sample size</th>
<th>Population/setting</th>
<th>Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Struewing et al, 1995</td>
<td>Prospective cohort</td>
<td>To determine the incidence of post-oophorectomy carcinomatosis and quantify the effectiveness of risk-reducing surgery</td>
<td>Eligible: 16 families Analyzed: 12 families (390 1st-degree relatives of breast or ovarian cancer cases)</td>
<td>Women with high genetic risk of ovarian cancer and oophorectomy matched to high-risk women who did not undergo surgery from National Cancer Institute, Creighton University, and U.K.</td>
<td>NR</td>
</tr>
</tbody>
</table>
## Appendix C12. Evidence Table of Risk-Reducing Surgery

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Inclusion/exclusion criteria</th>
<th>Risk definition</th>
<th>Followup</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salpingo-oophorectomy or oophorectomy vs. no oophorectomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domchek et al, 2010[^292] Fair</td>
<td><strong>Inclusion</strong> Women with BRCA1/2 mutations, no prior ovarian cancer, no salpingo-oophorectomy at time of ascertainment, and minimum 6 months followup. <strong>Exclusion</strong> Women with cancer diagnosis within first 6 months of followup, women who had RRM prior to ascertainment excluded from all breast cancer end points, and women with occult ovarian cancer during RRSO excluded from ovarian cancer end points.</td>
<td>BRCA status</td>
<td>Patients followed until end of 2009. Median followup was 3.65 years for those who had surgery and 4.29 years for those who did not. <strong>Oophorectomy &amp; breast cancer outcomes:</strong> BRCA1 followed mean 4.7 years to censoring BRCA2 followed mean 4.7 years to censoring <strong>Oophorectomy &amp; ovarian cancer outcomes:</strong> BRCA1 followed mean 5.6 years to censoring BRCA2 followed mean 5.8 years to censoring</td>
</tr>
<tr>
<td>Kramer et al, 2005[^185] Fair</td>
<td><strong>Inclusion</strong> Female, bloodline family member from BRCA1-positive family, no history of breast cancer before ascertainment, no history of bilateral mastectomy, age ≥20 years by study closing date. <strong>Exclusion</strong> Breast cancer diagnosed before family ascertainment and families with variants of uncertain significance.</td>
<td>BRCA status</td>
<td>Mean followup: 16.5 years; 11,105 person-years of observation Mean followup per patient (years) BRCA1 positive: 14.1 BRCA1 negative: 17.6 BRCA1 unknown: 15.8</td>
</tr>
<tr>
<td>Olson et al, 2004[^296] NA</td>
<td><strong>Inclusion</strong> Women age &lt;60 years with bilateral oophorectomy during study dates. <strong>Exclusion</strong> Women who had hysterectomy alone or only had 1 ovary removed, had prophylactic mastectomy at any time, or had any history of cancer prior to surgery, aside from nonmelanoma skin cancer.</td>
<td>High risk ≥1 1st-degree relative with breast cancer at age &lt;50 or 1 1st-degree relative with ovarian cancer at any age and ≥1 other 1st- or 2nd-degree relative with either diagnosis at any age. Moderate risk Only 1 1st-degree relative with breast cancer at any age. Low risk No breast or ovarian cancer family history</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Mastectomy vs. no mastectomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domchek et al, 2010[^292] Fair</td>
<td><strong>Inclusion</strong> Women with BRCA1/2 mutations, no prior ovarian cancer, no salpingo-oophorectomy at time of ascertainment, and minimum 6 months followup. <strong>Exclusion</strong> Women with cancer diagnosis within first 6 months of followup, women who had RRM prior to ascertainment excluded from all breast cancer end points, and women with occult ovarian cancer during RRSO excluded from ovarian cancer end points.</td>
<td>BRCA status</td>
<td>Patients followed until end of 2009. Median followup was 3.65 years for those who had surgery and 4.29 years for those who did not. <strong>Mastectomy &amp; breast cancer outcomes:</strong> BRCA1 followed mean 2.7 years to censoring BRCA2 followed mean 2.5 years to censoring</td>
</tr>
</tbody>
</table>
## Appendix C12. Evidence Table of Risk-Reducing Surgery

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Inclusion/exclusion criteria</th>
<th>Risk definition</th>
<th>Followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans et al, 2009</td>
<td>293</td>
<td><strong>Inclusion</strong> Eligible for bilateral RRM if lifetime breast cancer risk in excess of 25% or eligible for unilateral RRM if already had a diagnosis of in situ or invasive breast cancer in the contralateral breast. Paris center offered surgery to <em>BRCA1/2</em> carriers only. <strong>Exclusion</strong> NR</td>
<td>Lifetime risk of breast cancer &gt;25% based on family history with or without mutation status or diagnosis of breast cancer in contralateral breast</td>
<td>Followup in all women with RRM, years: Median, 7.5; Mean, 6.1; 3,334 women-years Followup in women undergoing bilateral RRM: 2,155 women-years (Manchester site, 1,274 women-years) Followup in control women: 2,438 women-years</td>
</tr>
<tr>
<td>Skytte et al, 2011</td>
<td>Good</td>
<td><strong>Inclusion</strong> <em>BRCA1/2</em> mutation positive and women who did not have mastectomy or salpingo-oophorectomy prior to study. <strong>Exclusion</strong> Diagnosis of breast or ovarian cancer before BRCA testing and women who opted for risk-reducing surgery before receiving test result.</td>
<td>BRCA status</td>
<td>Median time from study entry to mastectomy: 7.7 years Total at-risk time in mastectomy group: 378.7 years Total at-risk time in no mastectomy group: 934.6 years</td>
</tr>
</tbody>
</table>

### Prior Report

#### Mastectomy

<table>
<thead>
<tr>
<th>Hartmann et al, 1999</th>
<th>290</th>
<th><strong>Inclusion</strong> Women with a family history of breast cancer who had bilateral RRM <strong>Exclusion</strong> Breast cancer detected in surgically treated breast; surgery for augmentation of reduction <strong>High-risk comparison group inclusion</strong> Sisters of high-risk subjects were recruited to the study</th>
<th><strong>High risk</strong> ≥2 1st-degree relatives with breast cancer; 1 1st-degree relative and ≥2 2nd- or 3rd-degree relatives with breast cancer; 1 1st-degree relative with breast cancer before age 45 years and 1 other relative with breast cancer; 1 1st-degree relative with breast cancer and ≥1 relatives with ovarian cancer; 2 2nd- or 3rd-degree relatives with breast cancer and ≥1 with ovarian cancer; 1 2nd- or 3rd-degree relative with breast cancer and ≥1 relatives with ovarian cancer; 2 2nd- or 3rd-degree relatives with breast cancer</th>
<th>Median, 14 years; with a minimum of 2 years for 99% of the subjects.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hartmann et al, 2001</td>
<td>291</td>
<td><strong>Inclusion</strong> Women with <em>BRCA1/2</em> mutations who had bilateral RRM mastectomy</td>
<td>BRCA status</td>
<td>13.1 years</td>
</tr>
</tbody>
</table>
## Appendix C12. Evidence Table of Risk-Reducing Surgery

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Inclusion/exclusion criteria</th>
<th>Risk definition</th>
<th>Followup</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oophorectomy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Struewing et al, 1995 | 229     | **Inclusion:** Families with ≥3 cases of ovarian cancer or ≥2 cases of ovarian cancer and ≥1 case of breast cancer before age 50. **Exclusion:** Families fitting criteria for Lynch Syndrome II. | Results presented by those with an affected 1st-degree relative and those with an affected 2nd-degree relative | Surgery vs. no surgery  
Ovarian cancer incidence  
1st-degree relative: 460 vs. 1665 person-years  
2nd-degree relative: 106 vs. 2123 person-years  
Breast cancer incidence  
1st-degree relative: 484 vs. 1587 person-years  
2nd-degree relative: 106 vs. 2131 person-years |

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salpingo-oophorectomy or oophorectomy vs. no oophorectomy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Domchek et al, 2010 | 292     | Number of cancer cases in women with no history of breast cancer; surgery vs. no surgery  
Risk-reducing salpingo-oophorectomy and ovarian or primary peritoneal cancer risk  
Total: 6/465 (1.3%) vs. 63/1092 (5.8%); HR, 0.28 (95% CI, 0.12-0.69)  
BRCA1: 6/342 (1.8%) vs. 49/661 (7.4%); HR, 0.31 (95% CI, 0.12-0.82)  
BRCA2: 0/123 vs. 14/431 (3.2%); HR N/A  
Note: HR adjusted for year of birth, oral contraceptive use, and stratified by center  
Risk-reducing salpingo-oophorectomy and breast cancer risk  
Total: 39/336 (12%) vs. 129/633 (20%); HR, 0.63 (95% CI, 0.41-0.96)  
BRCA1: 32/236 (14%) vs. 129/633 (20%); HR, 0.63 (95% CI, 0.41-0.96)  
BRCA2: 7/100 (7%) vs. 94/401 (23%); HR, 0.36 (95% CI, 18.1-82.7)  
Note: HR adjusted for year of birth and stratified by center  
Risk-reducing salpingo-oophorectomy and all-cause mortality  
Total: 8/447 (1.8%) vs. 60/151 (5.9%); HR, 0.45 (95% CI, 0.21-0.95)  
BRCA1: 8/327 (14%) vs. 43/608 (7.1%); HR, 0.52 (95% CI, 0.24-1.14)  
BRCA2: 0/120 vs. 17/403 (4.2%); HR N/A  
Note: HR adjusted for year of birth and stratified by center  
Risk-reducing salpingo-oophorectomy and breast cancer–specific mortality  
Total: 2/441 (0.5%) vs. 22/873 (2.3%); HR, 0.27 (95% CI, 0.05-1.33)  
BRCA1: 2/321 (1.0%) vs. 16/581 (2.8%); HR, 0.30 (95% CI, 0.06-1.53)  
BRCA2: 0/120 vs. 6/392 (1.5%); HR N/A  
Note: HR adjusted for year of birth and stratified by center  
Risk-reducing salpingo-oophorectomy and ovarian cancer–specific mortality  
Total: 3/442 (0.7%) vs. 24/875 (2.5%); HR, 0.39 (95% CI, 0.12-1.29)  
BRCA1: 3/322 (0.9%) vs. 20/585 (3.4%); HR, 0.46 (95% CI, 0.08-2.72)  
BRCA2: 0/120 vs. 4/390 (1.0%); HR N/A  
Note: HR adjusted for year of birth, oral contraceptive use, and stratified by center | Among a cohort of women with BRCA mutations, RRSO was associated with a lower risk of ovarian cancer, first diagnosis of breast cancer, all-cause mortality, breast cancer–specific mortality, and ovarian cancer–specific mortality. | Public Health Service; University of Pennsylvania Cancer Center; Cancer Genetics Network; Marjorie Cohen Research Fund; SPORE grant from the Dana-Farber/Harvard Cancer Center; U.S. Department of Defense; Utah Cancer Registry; Utah State Department; Nebraska State Cancer and Smoking-Related Diseases Research Program grants; Cancer Research U.K. Grant; National Cancer Institute; Dr. Olopade received funding as the Doris Duke Distinguished Clinical Scientist; Dr. Eeles received funding from the National Institute for Health Research |
# Appendix C12. Evidence Table of Risk-Reducing Surgery

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Quality Rating</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
</table>
| Kramer et al., 2005 | Fair    | 185            | Number of breast cancer cases; oophorectomy vs. no oophorectomy  

**BRCA1** positive (n=98): 6/33 (18%) vs. 27/65 (42%); HR, 0.38 (95% CI, 0.15 to 0.97); p=0.043  

**BRCA1** negative (n=353): 1/34 (2.9%) vs. 4/319 (1.3%); HR NR  

**BRCA1** status unknown (n=222): 0/18 vs. 5/204 (2.5%); HR NR  

Absolute risk reduction in women who had oophorectomy was most prominent when surgery was done at a younger age (<40 years), figure representation | In a cohort of **BRCA1** mutation carriers from multiple-case families, oophorectomy was associated with decreased risk of breast cancer; affect was strongest in younger women; oophorectomy status affects breast cancer penetrance | Intramural Research Program of National Cancer Institute; funding source not specifically reported |
| Olson et al, 2004  | NA      | 296            | Expected vs. observed number of cancer cases  

**Age of surgery <60 years**  
High risk (n=55): 5.4 vs. 3; RR, 0.56 (95% CI, 0.11-1.33)  
Moderate risk (n=193): 10.9 vs. 9; RR, 0.83 (95% CI, 0.38-1.44)  
**Age of surgery <50 years**  
High risk (n=41): 3.9 vs. 1; RR, 0.26 (95% CI, 0.001-0.99)  
Moderate risk (n=130): 7.7 vs. 5; RR, 0.65 (95% CI, 0.21-1.32)  
**Age of surgery <60 years and premenopausal before surgery**  
High risk (n=52): 5.1 vs. 3; RR, 0.59 (95% CI, 0.12-1.41)  
Moderate risk (n=186): 10.4 vs. 7; RR, 0.67 (95% CI, 0.27-1.24)  
**Age of surgery <50 years and premenopausal before surgery**  
High risk (n=40): 3.8 vs. 1; RR, 0.26 (95% CI, 0.00-1.00)  
Moderate risk (n=126): 7.4 vs. 3; RR, 0.41 (95% CI, 0.08-0.98) | The number of observed breast cancers in women in the cohort was lower than expected for nearly all levels of risk, and especially for those age <50 years and premenopausal prior to surgery | Fraternal Order of the Eagles and the National Cancer Institute |
| Domichek et al, 2010 | Fair    | 292            | Number of cancer cases in women with no history of breast cancer; surgery vs. no surgery  

Risk-reducing mastectomy and risk of first occurrence of breast cancer  
**Total:** 0/75 vs. 34/585 (5.8%)  
**BRCA1:** 0/43 vs. 19/372 (5.1%)  
**BRCA2:** 0/32 vs. 15/213 (7.0%) | In a cohort of women with **BRCA** mutations, RRM was associated with a lower risk of breast cancer | Public Health Service; University of Pennsylvania Cancer Center; Cancer Genetics Network; Marjorie Cohen Research Fund; SPORE grant from Dana-Farber/Harvard Cancer Center; U.S. Department of Defense; Utah Cancer Registry; Utah State Department; Nebraska State Cancer and Smoking-Related Diseases Research Program grants; Cancer Research U.K. Grant; National Cancer Institute; Dr. Olopade funded as the Doris Duke Distinguished Clinical Scientist; Dr. Eeles received funding from the National Institute for Health Research |
## Appendix C12. Evidence Table of Risk-Reducing Surgery

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skytte et al, 2011</td>
<td>Good</td>
<td>Number of breast cancer cases (incidence per person-year); mastectomy vs. no mastectomy: 3/96 (0.8%) vs. 16/211 (1.7%); HR, 0.394 (95%CI, 0.115-1.355); p=0.14. Note: 3/3 women with breast cancer in the mastectomy group and 12/16 women in no mastectomy group were BRCA1-positive. Note: All women diagnosed with cancer in mastectomy group had also had bilateral salpingo-oophorectomy; 1 woman diagnosed with breast cancer on date of mastectomy, contributed to the &quot;no mastectomy&quot; group at risk time and cancer incidence. Adjusting for age did not change significance (HR, 0.455; p=0.224). Effect of age was significant (p=0.008); in both groups, 1-year age difference associated with 4.2% increase in breast cancer risk. Annual incidence of breast cancer after mastectomy by carrier status: 1.1% for BRCA1 (n=67); 0 for BRCA2 (n=29).</td>
<td>Study of 307 healthy BRCA1/2 carriers suggests bilateral RRM reduces risk of breast cancer but does not completely eliminate it. Study size too small to show a significant difference</td>
<td>NR</td>
</tr>
<tr>
<td>Prior Report</td>
<td>Mastectomy</td>
<td>Overall: 425 subjects were classified moderate risk, 214 subjects high risk. 95% were alive at the time of the study. 7 were diagnosed with breast cancer (4 moderate risk, 3 high risk); all cases occurred after subcutaneous mastectomy. Cancer Diagnosis: 37 in the moderate-risk group (based on Gail model estimates) and 53 in the high-risk group (based on the high-risk comparison group) were expected to develop breast cancer had they not had mastectomy. RRM reduced risk in the moderate-risk group by 89.5% (p&lt;0.001) and in the high-risk group by 90%-94% (depending on adjusted analysis). 2 women in the high-risk group were diagnosed with ovarian cancer. Death Reduction: 10 in the moderate-risk group (based on Gail model estimates) and 31 in the high-risk group (based on the high-risk comparison group) were expected to die from breast cancer had they not had mastectomy. Death was reduced in the moderate-risk group by 100% (no deaths) (95% CI, 70-100) and in the high-risk group by 81%-94% (depending on adjusted analysis) (2 deaths).</td>
<td>In women with high risk of breast cancer on the basis of family history, RRM can significantly reduce the incidence of breast cancer</td>
<td>U.S. Department of Defense; National Cancer Institute; Donaldson Charitable Trust</td>
</tr>
<tr>
<td>Hartmann et al, 1999</td>
<td></td>
<td>Risk Reduction: Easton model (a high-penetrance model), 6.1 cases were expected; Struwing model (a low-penetrance model), 4.5 cases. Mastectomy resulted in risk reduction of 89.5% or 100% for the Easton model (95% CI, 41.4-99.7 and CI, 68-100) and 85% or 100% for the Struwing model (95% CI, 15.6-99.6 and CI, 54.1-100).</td>
<td>Risk-reducing mastectomy is associated with a substantial reduction in the incidence of breast cancer in known BRCA1/2 mutation</td>
<td>NR</td>
</tr>
</tbody>
</table>
## Appendix C12. Evidence Table of Risk-Reducing Surgery

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Struwing et al, 1995&lt;sup&gt;228&lt;/sup&gt;</td>
<td>Oophorectomy</td>
<td>Surgery vs. no surgery&lt;br&gt; <em>Preliminary Analysis from National Cancer Institute only</em>&lt;br&gt; Ovarian cancer incidence&lt;br&gt; 1st-degree relative: 2/44 vs. 8/346&lt;br&gt; 2nd-degree relative: 0 vs. 1&lt;br&gt; Note: Incidence includes post-oophorectomy ovarian carcinomatosis&lt;br&gt; Breast cancer incidence&lt;br&gt; 1st-degree relative: 3/44 vs. 14/346&lt;br&gt; 2nd-degree relative: 0 vs. 3</td>
<td>Findings suggest that there is a finite risk of post-oophorectomy carcinomatosis. Preliminary analysis suggests a statistically nonsignificant protective effect of surgery for ovarian cancer</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI = confidence interval; HR = hazard ratio; MRI = magnetic resonance imaging; NA = not applicable; NR = not reported; RR = relative risk; RRM = risk-reducing mastectomy; RRSO = risk-reducing salpingo-oophorectomy; PROSE = Prevention and Observation of Surgical Endpoints.
## Appendix C13. Evidence Table of Harms of Intensive Screening

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Subcategory</th>
<th>Study design</th>
<th>Country/population/setting</th>
<th>Inclusion/exclusion criteria</th>
<th>Risk level definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast cancer screening</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kriege et al, 2004</td>
<td>Physical harms of increased screening</td>
<td>Prospective cohort (breast cancer characteristics compared to registry data and women with breast cancer from another prospective cohort study)</td>
<td>The Netherlands</td>
<td>Inclusion Cumulative lifetime risk of breast cancer &gt;15% due to genetic or familial predisposition according to modified Claus tables; age at entry between 25 and 70 years (could be tested at before age 25 if family member diagnosed before age 30 years) Exclusion Women with symptoms suggestive of breast cancer or personal history of breast cancer; women proven not to have a mutation in a family with a proven mutation</td>
<td>Cumulative lifetime risk of breast cancer &gt;15% due to genetic or familial predisposition according to modified Claus tables</td>
</tr>
<tr>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kriege et al, 2006</td>
<td>Physical harms of increased screening</td>
<td>Prospective cohort (breast cancer characteristics compared to registry data and women with breast cancer from another prospective cohort study)</td>
<td>The Netherlands</td>
<td>Inclusion Cumulative lifetime risk of breast cancer &gt;15% due to genetic or familial predisposition according to modified Claus tables, age at entry between 25 and 70 years (could be tested at before age 25 if family member diagnosed before age 30 years), no previous breast cancer or symptoms suspicious for breast cancer Exclusion Women with symptoms suggestive of breast cancer or personal history of breast cancer; women proven not to have a mutation in a family with a proven mutation</td>
<td>Cumulative lifetime risk of breast cancer &gt;15% due to genetic or familial predisposition according to modified Claus tables</td>
</tr>
<tr>
<td>Leach et al, 2005</td>
<td>Physical harms of increased screening</td>
<td>Prospective cohort, one-arm</td>
<td>U.K.</td>
<td>Inclusion Asymptomatic women aged 35-49 years fulfilling 1 of the following: known carrier of a deleterious BRCA1, BRCA2, or TP53 mutation; FDR of someone with 1 of these deleterious mutations; strong family history of breast or ovarian cancer or both; or family history consistent with classic Li-Fraumeni syndrome. Aim was to include women whose affected FDRs had ≥60% chance of being a BRCA1 or BRCA2 mutation carrier or women with an annual risk of ≥0.9% Exclusion Women with previous breast cancer, those with any cancer such that prognosis was &lt;5 years, participants who had predictive genetic testing during study and whose results were negative, women who developed cancer during study period</td>
<td>Known carrier of a deleterious BRCA1, BRCA2, or TP53 mutation; FDR of someone with 1 of these deleterious mutations; strong family history of breast or ovarian cancer or both; or family history consistent with classic Li-Fraumeni syndrome</td>
</tr>
</tbody>
</table>
## Appendix C13. Evidence Table of Harms of Intensive Screening

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Subcategory</th>
<th>Study design</th>
<th>Country/population/setting</th>
<th>Inclusion/exclusion criteria</th>
<th>Risk level definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le-Petross et al, 2011&lt;sup&gt;278&lt;/sup&gt; NA</td>
<td>Physical harms of increased screening</td>
<td>Retrospective analysis of prospective cohort study, one-arm</td>
<td>U.S. Women at increased genetic risk of breast cancer at single institution</td>
<td>Inclusion &lt;br&gt; Women age ≥18 years, having undergone alternating screening mammography and breast MRI every 6 months at study institution, either confirmed BRCA1/2 carriers or FDR of confirmed BRCA1/2 carrier</td>
<td>Based on BRCA status or FDR of BRCA mutation carrier</td>
</tr>
</tbody>
</table>

**Ovarian cancer screening**

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Subcategory</th>
<th>Study design</th>
<th>Country/population/setting</th>
<th>Inclusion/exclusion criteria</th>
<th>Risk level definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hermsen et al, 2007&lt;sup&gt;281&lt;/sup&gt; NA</td>
<td>Physical harms of increased screening</td>
<td>Prospective cohort, one-arm (Staging compared to 2 external comparison groups; unscreened family members with cancer, combined data from multiple studies)</td>
<td>The Netherlands Women with BRCA mutation screened at 6 University Family Cancer Clinics</td>
<td>Inclusion &lt;br&gt; Women with BRCA1/2 mutation screened at 6 participating centers</td>
<td>Based on BRCA status</td>
</tr>
</tbody>
</table>

**Prior report**

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Subcategory</th>
<th>Study design</th>
<th>Country/population/setting</th>
<th>Inclusion/exclusion criteria</th>
<th>Risk level definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bourne et al, 1993&lt;sup&gt;279&lt;/sup&gt; NA</td>
<td>Physical harms of increased screening</td>
<td>Prospective cohort, one-arm</td>
<td>U.K. Self-referred asymptomatic women with a close relative diagnosed with ovarian cancer</td>
<td>Inclusion &lt;br&gt; Women age ≥25 years with ≥1 close relatives who had developed ovarian cancer; symptomless</td>
<td>Based on pedigree/pattern of inheritance</td>
</tr>
</tbody>
</table>
## Appendix C13. Evidence Table of Harms of Intensive Screening

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N</th>
<th>Demographics</th>
<th>Duration/followup</th>
<th>Screening method and interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast cancer screening</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kriege et al, 2004&lt;sup&gt;277&lt;/sup&gt;</td>
<td>277</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch MRISC study</td>
<td>Enrolled: 1952 Analyzed: 1909 n=358 mutation carriers (276 BRCA1, 77 BRCA2, 1 both BRCA1/2, 2 PTEN, and 2 TP53), n=1052 high risk, n=499 moderate risk</td>
<td>Mean age at entry, years: 40 (range, 19-72)</td>
<td>1999-2003 Median, 2.9 years (mean, 2.7; range, 0.1-3.9 years)</td>
<td>A) Biannual CBE B) Annual mammography C) Annual contrast enhanced MRI Note: When 1 of the examinations reported as &quot;probably benign finding&quot; or &quot;need additional imaging evaluation&quot; (BI-RADS 3 or 0), further investigation undertaken by ultrasonography ± fine needle aspiration, or mammography or repeated MRI; when 1 of the examinations reported as &quot;suspicious abnormality&quot; or &quot;highly suggestive of malignancy&quot; (BI-RADS 4 or 5), cytologic or histologic evaluation of biopsy specimen performed; when results of imaging were negative but clinical breast exam was uncertain or suspicious, additional investigations performed</td>
</tr>
<tr>
<td>Kriege et al, 2006&lt;sup&gt;297&lt;/sup&gt;</td>
<td>297</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch MRISC study</td>
<td>Analyzed: 1909 n=358 mutation carriers (276 BRCA1, 77 BRCA2, 1 both BRCA1 and BRCA2, 2 PTEN, and 2 TP53), n=1052 high-risk, n=499 moderate risk</td>
<td>Mean age at entry, years: 40 (range, 19-72)</td>
<td>1999-2003 Median, 2.9 years (mean, 2.7; range, 0.1-3.9 years)</td>
<td>A) Biannual CBE B) Annual mammography C) Annual contrast enhanced MRI Note: When 1 of the examinations reported as &quot;probably benign finding&quot; or &quot;need additional imaging evaluation&quot; (BI-RADS 3 or 0), further investigation undertaken by ultrasonography ± fine needle aspiration, or mammography or repeated MRI; when 1 of the examinations reported as &quot;suspicious abnormality&quot; or &quot;highly suggestive of malignancy&quot; (BI-RADS 4 or 5), cytologic or histologic evaluation of biopsy specimen performed; when results of imaging were negative but clinical breast exam was uncertain or suspicious, additional investigations performed</td>
</tr>
<tr>
<td>Leach et al, 2005&lt;sup&gt;274&lt;/sup&gt;</td>
<td>274</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAMARIBS study</td>
<td>649 n=82 (13%) with known BRCA1 mutation n=38 (6%) with known BRCA2 mutation</td>
<td>Median age at entry, years: 40 (range, 31-55; only 1 woman age &gt;50 years)</td>
<td>Study recruitment 1997-2003 Variable screening episodes per individual but screening continued until each women had ≥2 annual scans (in 2004)</td>
<td>A) Annual mammography from age 35 years (or younger if FDR developed cancer at age &lt;35 years) B) Annual CE MRI Note: In women with equivocal results, high specificity MRI exam done 2-6 weeks later (followed by ultrasound, fine needle aspiration, localization, and tissue sampling by conventional methods, as appropriate)</td>
</tr>
<tr>
<td>Le-Petross et al, 2011&lt;sup&gt;216&lt;/sup&gt;</td>
<td>216</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>Screened: 321 Analyzed: 73 (37 [51%] BRCA1, 36 [49%] BRCA2)</td>
<td>Median age at entry, years: 44 (range, 23-75)</td>
<td>Records from 1997-2009 Median followup, 2 years (range, 1-6 years) Mean followup from suspicious finding to diagnosis, 1.7 years (range, 1-3 years)</td>
<td>All women underwent: A) Mammography every 6 months B) MRI every 6 months Note: imaging was performed on an alternating basis, women had clinical breast exam every 6 months, ultrasound used to evaluate abnormal mammographic or MRI findings, biopsy as required</td>
</tr>
</tbody>
</table>
### Appendix C13. Evidence Table of Harms of Intensive Screening

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>N</th>
<th>Demographics</th>
<th>Duration/followup</th>
<th>Screening method and interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ovarian cancer screening</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hermens et al, 2007261</td>
<td>883 n=683 BRCA1, 200 BRCA2</td>
<td></td>
<td>1993-2005 1473 person-years</td>
<td>A) Annual serum CA-125 measurement</td>
</tr>
<tr>
<td></td>
<td>459 for analysis of screening/compliance (data available for all screening visits)</td>
<td></td>
<td></td>
<td>B) Annual TVUS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median age, years:</td>
<td>Starting at age 35 years or 5 years earlier than youngest diagnosed ovarian cancer in the family</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA1: 40 (range, 21-76)</td>
<td>Note: Biannual screens were done in some centers during the study period, but this was not systematically adopted</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA2: 44 (range, 25-77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prior report</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bourne et al, 1993279</td>
<td>1601</td>
<td></td>
<td></td>
<td>TVUS ± color flow imaging§ (screening interval NR)</td>
</tr>
<tr>
<td>NA</td>
<td></td>
<td>Mean age, years: 47 (range, 17-79)</td>
<td>Unclear duration 4 years</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Results</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast cancer screening</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kriege et al, 2004277</td>
<td>Based on 45 cancers, B vs. C: Additional investigations: Ultrasound, 889 times/627 women Fine needle aspiration, 312 times (267 times plus ultrasound, 45 times plus palpation) Biopsy, used 85 times/82 women (malignancy in 50 cases, lobular carcinoma in situ in 1 case; rate of positive histologic findings 60.0%) Unneeded additional exams*: 207 vs. 420 Unneeded biopsies: 28% (7/25*) vs. 43% (24/56†)</td>
<td>Grant from Dutch Health Insurance Council</td>
</tr>
<tr>
<td>NA</td>
<td>Imaging rounds of 39 evaluable invasive breast cancers, B vs. C: First imaging round, with prior mammography False positive rate (%): 5.5 vs. 14.0; P&lt;0.001 False negatives (n): 12 vs. 1 Subsequent imaging rounds False positive rate (%): 4.6 vs. 8.2; p&lt;0.001 False negatives (n): 12 vs. 4</td>
<td>Grant from Dutch Health Insurance Council</td>
</tr>
<tr>
<td>Dutch MRISC study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kriege et al, 2006279</td>
<td>Imaging rounds of 39 evaluable invasive breast cancers, B vs. C: First imaging round, with prior mammography False positive rate (%): 5.5 vs. 14.0; P&lt;0.001 False negatives (n): 12 vs. 1 Subsequent imaging rounds False positive rate (%): 4.6 vs. 8.2; p&lt;0.001 False negatives (n): 12 vs. 4</td>
<td>Grant from Dutch Health Insurance Council</td>
</tr>
<tr>
<td>NA</td>
<td>Imaging rounds of 39 evaluable invasive breast cancers, B vs. C: First imaging round, with prior mammography False positive rate (%): 5.5 vs. 14.0; P&lt;0.001 False negatives (n): 12 vs. 1 Subsequent imaging rounds False positive rate (%): 4.6 vs. 8.2; p&lt;0.001 False negatives (n): 12 vs. 4</td>
<td>Grant from Dutch Health Insurance Council</td>
</tr>
<tr>
<td>Dutch MRISC study</td>
<td>Based on 33 screen-detected cancers: Recall rates, A vs. B 279 exams led to recall (40 based purely on reader's judgment, not score) 3.9% vs. 11% per woman year A plus B: 13% per woman year 245 recalls for benign findings 73% diagnosed cancer-free using noninvasive tests Additional diagnostic procedures in 245 women without cancer: Ultrasound, n=93 Core biopsy, n=32 Fine needle aspiration, n=47 Surgery, n=7 (3% of recalled women without cancer, 27% of recalled women with cancer) 8.5 recalls per cancer detected 0.21 benign surgical biopsies per cancer detected</td>
<td>Grant from U.K. Medical Research Council; MRI cost paid from subvention funding for research from U.K. National Health Service</td>
</tr>
<tr>
<td>Leach et al, 2005274</td>
<td>Based on 33 screen-detected cancers: Recall rates, A vs. B 279 exams led to recall (40 based purely on reader's judgment, not score) 3.9% vs. 11% per woman year A plus B: 13% per woman year 245 recalls for benign findings 73% diagnosed cancer-free using noninvasive tests Additional diagnostic procedures in 245 women without cancer: Ultrasound, n=93 Core biopsy, n=32 Fine needle aspiration, n=47 Surgery, n=7 (3% of recalled women without cancer, 27% of recalled women with cancer) 8.5 recalls per cancer detected 0.21 benign surgical biopsies per cancer detected</td>
<td>Grant from U.K. Medical Research Council; MRI cost paid from subvention funding for research from U.K. National Health Service</td>
</tr>
<tr>
<td>NAMARIBS study</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BRCA-Related Cancer 351 Pacific Northwest EPC
### Appendix C13. Evidence Table of Harms of Intensive Screening

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Results</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of women per 1000 screening episodes needing diagnostic surgical biopsy was 0.4% (7/1881) for benign lesions, 0.5% (9/1881) for malignant lesions</strong>&lt;br&gt;PPV of diagnostic surgical biopsy=56%&lt;br&gt;62% (172/279) of suspicious findings on MRI resolved without invasive procedure, n=16 women had diagnostic surgery to complete diagnosis, n=91 had some form of percutaneous biopsy procedure&lt;br&gt;Preoperative diagnosis of cancer made in 24/33 (73%) of screen-detected cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Le-Petross et al, 2011&lt;sup&gt;276&lt;/sup&gt;</td>
<td>NA</td>
<td>13 cancers in 11 women (12 on screen, 1 on prophylatic mastectomy)&lt;br&gt;20/73 women underwent biopsy, 11 cancers diagnosed by biopsy in 10 women&lt;br&gt;Overall biopsy yield for MRI was 50% (10/20)&lt;br&gt;False positive, A vs. B&lt;br&gt;11/73 (15%) vs. 8/73 (11%)&lt;br&gt;Required further imaging: 8 vs. 4&lt;br&gt;Required biopsy: 3 vs. 2&lt;br&gt;Required imaging plus biopsy: 0 vs. 2</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Number of women per 1000 screening episodes needing diagnostic surgical biopsy was 0.4% (7/1881) for benign lesions, 0.5% (9/1881) for malignant lesions</strong>&lt;br&gt;PPV of diagnostic surgical biopsy=56%&lt;br&gt;62% (172/279) of suspicious findings on MRI resolved without invasive procedure, n=16 women had diagnostic surgery to complete diagnosis, n=91 had some form of percutaneous biopsy procedure&lt;br&gt;Preoperative diagnosis of cancer made in 24/33 (73%) of screen-detected cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian cancer screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hermsen et al, 2007&lt;sup&gt;281&lt;/sup&gt;</td>
<td>NA</td>
<td>15 cancers diagnosed in cohort&lt;br&gt;10 cancers diagnosed during followup&lt;br&gt;5 screen-detected&lt;br&gt;Based on 459 women with data on each visit:&lt;br&gt;7 cancers diagnosed (2 prevalent, 2 interval, 3 incident)&lt;br&gt;Abnormalities were found by 1 or both screening modalities in 3% (38/1116) of screening visits. Overall, abnormalities were found in 9% (40/459) of women (some due to physical complaints), resulting in 26 diagnostic operations&lt;br&gt;Benign‡ diagnostic surgery, A vs. B&lt;br&gt;67% (4/6) vs. 100% (9/9)&lt;br&gt;A+B: 55% (6/11)&lt;br&gt;Note: Not all benign diagnostic surgeries were done due to abnormal screen findings; some surgeries were undertaken to follow up on abnormal findings from CA-125 measurement ± TVUS done to assess symptomatic complaints</td>
<td>NIHR Biomedical Research Centre at Central Manchester Foundation Trust</td>
</tr>
<tr>
<td>Prior report</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bourne et al, 1993&lt;sup&gt;279&lt;/sup&gt;</td>
<td>NA</td>
<td>11 cancers diagnosed (6 screen-detected, 5 interval)&lt;br&gt;3.8% (61/1601) with positive screening result, referral to surgery&lt;br&gt;False-positive cases: 55/61 referred cases (cancer detected in 6/61 referred cases)&lt;br&gt;False-positive rate: 3.4% (95% CI, 2.6-4.5 [55/1595])&lt;br&gt;Addition of color flow imaging and criterion of morphological score ≥5 or pulsatility index &lt;1:&lt;br&gt;Retrospective addition (applied to positive ultrasound results) = 15 false-positive cases&lt;br&gt;Prospective addition (applied at the time of ultrasound exam) = 6 false-positive cases&lt;br&gt;Note: 43% of women had only 1 TVUS (prevalent screen)</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Additional investigation included ultrasound ± fine needle biopsy, or repeat mammography, or repeat MRI.<br>†Women with BI-RADS score ≥3 on mammography or MRI.<br>‡Surgery for final benign diagnosis.<br>§Color flow imaging applied prospectively to 600 ultrasound exams; retrospectively after a positive ultrasound result to the remainder.

**Abbreviations:** BI-RADS = Breast Imaging-Reporting and Data System; BMI = body mass index; CA-125 = cancer antigen-125; CBE = clinical breast examination; CE = contrast enhanced; FDR = first-degree relative; MARIBS = Magnetic Resonance Imaging Breast Screening; MRI = magnetic resonance imaging; MRISC = Magnetic Resonance Imaging Screening Study; NA = not applicable; NIHR = National Institute for Health Research; NR = not reported; PPV = positive predictive value; PTEN = phosphatase and tensin homolog; TP53 = tumor protein 53; TVUS = transvaginal ultrasound.
## Appendix C14. Evidence Table of Psychological and Sexual Functioning Harms of Interventions

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Subcategory</th>
<th>Purpose</th>
<th>Study type</th>
<th>N</th>
<th>Country</th>
<th>Population/ Setting</th>
<th>Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brandberg et al, 2008</td>
<td>Sexual functioning</td>
<td>Psychological</td>
<td>To prospectively evaluate body image, sexuality, emotional reactions, and quality of life in a sample of women having increased risk for breast cancer before RRM, and 6 months and 1 year after.</td>
<td>Eligible: NR Enrolled: 90 Analyzed: 65</td>
<td>Sweden</td>
<td>Karolinska University Hospital</td>
<td>Age (years): 20-29: 7/90 (8%) 30-39: 33/90 (37%) 40-49: 35/90 (39%) 50-59: 13/90 (14%) 60-69: 2/90 (2%)</td>
</tr>
<tr>
<td>Brandberg et al, 2012</td>
<td>Sexual functioning</td>
<td>Psychological</td>
<td>To examine the impact of RRSO on menopausal symptoms and sexual functioning in women who carry a BRCA1/2 mutation.</td>
<td>Eligible: NR Enrolled: 67</td>
<td>Canada</td>
<td>University Health Network</td>
<td>Not reported separately for women without breast cancer</td>
</tr>
<tr>
<td>Gahm et al, 2010</td>
<td>Sexual functioning</td>
<td>QOL Pain</td>
<td>To analyze the physical effects and to report effects on sexual functioning and health-related quality of life at least 2 years after RRM.</td>
<td>Case-series</td>
<td>Sweden</td>
<td>Karolinska University Hospital</td>
<td>Mean age of 40 years (range, 25-65)</td>
</tr>
<tr>
<td>Metcalfe et al, 2004</td>
<td>Sexual functioning</td>
<td>Psychological</td>
<td>To assess psychosocial functioning in a population-based series of women who have previously undergone RRM in a specified time period.</td>
<td>Case-series</td>
<td>Canada</td>
<td>Ontario hospitals in the Central East Health Information Partnership</td>
<td>Mean age of 43.5 years (SD, 7.8) at time of surgery and 47.8 years (SD, 8.6) at time of questionnaire</td>
</tr>
<tr>
<td>Rijnsburger et al, 2004</td>
<td>QOL</td>
<td></td>
<td>To describe the short-term effects of screening for breast cancer in high-risk women on health-related quality of life.</td>
<td>Prospective cohort</td>
<td>The Netherlands</td>
<td>MRI Screening Study conducted at 6 family cancer centers</td>
<td>Mean age of 40.9 years (SD, 8.9)</td>
</tr>
<tr>
<td>Spiegel et al, 2011</td>
<td>Psychological</td>
<td></td>
<td>To compare women with recall examinations following MRI to those without recall examinations on breast cancer worry and anxiety.</td>
<td>Before and after</td>
<td>Canada</td>
<td>Women participating in an MRI screening trial</td>
<td>Mean age of 45 years (range, 25-60)</td>
</tr>
<tr>
<td>Wasteson et al, 2011</td>
<td>Risk perception</td>
<td>Psychological</td>
<td>To evaluate the long-term physical and psychological consequences of RRM in after 10 years.</td>
<td>Case-series</td>
<td>Sweden</td>
<td>Women at Karolinska University Hospital enrolled in retrospective study</td>
<td>Mean age of 45 years (range: 40-57)</td>
</tr>
</tbody>
</table>
### Appendix C14. Evidence Table of Psychological and Sexual Functioning Harms of Interventions

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Inclusion/Exclusion criteria</th>
<th>Risk level definition</th>
<th>Mutation status</th>
<th>Measures</th>
<th>Interventions</th>
</tr>
</thead>
</table>
| Brandberg et al, 2008 [302] Brandberg et al, 2012 [304] NA | **Inclusion:** Women who had RRM, including reconstruction  
**Exclusion:** Women with a breast cancer diagnosis | Lifetime risk definition not described  
50% lifetime risk: 26/90 (28.9%)  
25% lifetime risk: 8/90 (8.9%) | 37/90 (41.1%) **BRCA1**  
13/90 (14.4%) **BRCA2**  
2/90 (2.2%) unknown mutation | Impact on areas of life measures  
**Sexuality Activity Questionnaire** (SAQ, pleasure subscale 0 to 18, discomfort subscale 0 to 6, and habit subscale 0 to 3)  
**Body Image Scale (BIS)** (scale 0 to 30)  
**Hospital Anxiety and Depression Scale (HADS)** (subscales 0 to 21)  
**Swedish Short Term-36 Health Survey (SF-36)** (subscales 0 to 100) | A) RRM with reconstruction |
| Finch et al, 2011 [306] NA | **Inclusion:** Women age 30-70 years at time of surgery who had RRSO  
**Exclusion:** Diagnosed with occult cancer at surgery or with breast cancer during the 1 year followup period | High risk due to positive genetic mutation | **BRCA1 or BRCA2 positive** | **Menopause-Specific Quality of Life-Intervention (MENQOL, scale NR)**  
**Sexual Activity Questionnaire** | RRSO |
| Gahm et al, 2010 [303] NA | **Inclusion:** Women with increased risk for breast cancer who had RRM and immediate breast reconstruction  
**Exclusion:** Personal history of breast cancer | NR | NR | Pain and discomfort questionnaire (subscales 1 to 7)  
**Sexuality questionnaire**  
**Swedish Short Term-36 Health Survey (SF-36, subscales 0 to 100)**  
**Decision Regret Scale (DRS, scale NR)** | A) RRM with reconstruction  
B) Reference comparison group who did not have RRM |
| Metcalfe et al, 2004 [301] NA | **Inclusion:** Women who had RRM at an Ontario hospital and returned the questionnaire  
**Exclusion:** Prior or current diagnosis of invasive or in situ breast cancer | Strong family history: had either 1 1st-degree or 2 2nd-degree relatives with any of the following: 1) breast cancer diagnosed <50 years; 2) ovarian cancer; or 3) male breast cancer (55.0% of population, also did not have genetic testing done)  
Limited family history: none of the above (23.3% of population, did not have genetic testing done) | 21.7% had **BRCA1/2 mutation** | **Brief Symptom Inventory (BSI, scale 0 to 100)**  
**Body Image after Breast Cancer (BIBC, each subscale 1 to 5)**  
**Impact of Events Scale (IES, IES-I subscale 0 to 35 and IES-A subscale 0 to 40)**  
**Sexual activity questionnaire** (pleasure subscale 0 to 18, discomfort subscale 0 to 6, habit subscale 0 to 3) | A) RRM  
53/60 (88.3%) total  
7/60 (11.7%) subcutaneous |
## Appendix C14. Evidence Table of Psychological and Sexual Functioning Harms of Interventions

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Inclusion/Exclusion criteria</th>
<th>Risk level definition</th>
<th>Mutation status</th>
<th>Measures</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rijnsburger et al, 2004</td>
<td><strong>Inclusion:</strong> Women already under intensive surveillance and women who came for the first time to the clinic&lt;br&gt;<strong>Exclusion:</strong> Women with evident symptoms suspicious for breast cancer or previous breast cancer</td>
<td>Risk category 1: BRCA1/2 mutation carriers (50%-85% cumulative lifetime risk)&lt;br&gt;Risk category 2: 30%-50% cumulative lifetime risk&lt;br&gt;Risk category 3: 15%-30% cumulative lifetime risk</td>
<td>35 were BRCA1/2 mutation positive</td>
<td>Medical Outcomes Study 36-Item Short Form (SF-36, subscales 0 to 100)&lt;br&gt;EuroQoL-5 Dimensions (EQ-5D, scale 0-1)&lt;br&gt;Visual Analogue Scale (VAS, scale 0 to 100)&lt;br&gt;Symptom Checklist-90 (SCL-90, scale 12-60)</td>
<td>A) CBE (n=287)&lt;br&gt;B) CBE + mammography (n=134)&lt;br&gt;C) CBE + MRI (n=109)</td>
</tr>
<tr>
<td>Spiegel et al, 2011</td>
<td><strong>Inclusion:</strong> Women participating in MRI screening trial who agreed to participate&lt;br&gt;<strong>Exclusion:</strong> NR</td>
<td>All were mutation carriers</td>
<td>30/55 (54.5%) BRCA1&lt;br&gt;25/55 (45.5%) BRCA2</td>
<td>Hospital Anxiety and Depression Scale (HADS, subscales 0 to 21)&lt;br&gt;Breast Cancer Worry Interference Scale (WIS, scores 7 to 35)</td>
<td>All received annual mammography, MRI, and ultrasound and semiannual CBE&lt;br&gt;A) Women with recall exams (n=18)&lt;br&gt;B) Women without recall exams (n=37)</td>
</tr>
<tr>
<td>Wasteson et al, 2011</td>
<td><strong>Inclusion:</strong> Women enrolled in previous retrospective study of RRM with reconstruction, agreed to participate 10 years later&lt;br&gt;<strong>Exclusion:</strong> NR</td>
<td>Either BRCA positive or 25%-40% lifetime risk of breast cancer according to Mendelian laws and the estimated penetrance of the BRCA1/2 mutations, or to Claus tables</td>
<td>3/13 (23.1%) BRCA positive by 10 year followup</td>
<td>Semistructured interviews focused on experiences related to RRM with reconstruction</td>
<td>RRM with reconstruction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Duration of followup</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brandberg et al, 2008</td>
<td>October 1997 to December 2005&lt;br&gt;1 year</td>
<td><strong>Before RRM vs. 6 months after RRM vs. 1 year after RRM</strong>&lt;br&gt;Mean scales (SE)&lt;br&gt;HADS-A: 5.59 (0.55) vs. 3.80 (0.55) vs. 3.83 (0.52); p=0.0004&lt;br&gt;HADS-D: 2.53 (0.39) vs. 1.93 (0.31) vs. 1.98 (0.36); p=NS&lt;br&gt;SAQ, pleasure subscale: 12.82 (0.62) vs. 12.21 (0.66) vs. 11.18 (0.56); p=0.005&lt;br&gt;SAQ, discomfort subscale: 0.56 (0.15) vs. 0.53 (0.20) vs. 0.81 (0.19); p=NS&lt;br&gt;SAQ, habit subscale: 0.94 (0.06) vs. 0.82 (0.08) vs. 0.82 (0.08); p=NS&lt;br&gt;Bodily pain as reported by SF-36: 81.0 (2.98) vs. 80.7 (2.84) vs. 82.6 (3.29); p=NS</td>
<td>Anxiety decreased after surgery, while sexual pleasure increased. All other measures did not change over time.</td>
<td>Swedish Cancer Society, Swedish Association for Cancer and Traffic Victims, and Stockholm County Council</td>
</tr>
<tr>
<td>Brandberg et al, 2012</td>
<td>October 1997 to December 2005&lt;br&gt;1 year</td>
<td>Before RRM vs. 6 months after RRM vs. 1 year after RRM Mean scales (SE)&lt;br&gt;HADS-A: 5.59 (0.55) vs. 3.80 (0.55) vs. 3.83 (0.52); p=0.0004&lt;br&gt;HADS-D: 2.53 (0.39) vs. 1.93 (0.31) vs. 1.98 (0.36); p=NS&lt;br&gt;SAQ, pleasure subscale: 12.82 (0.62) vs. 12.21 (0.66) vs. 11.18 (0.56); p=0.005&lt;br&gt;SAQ, discomfort subscale: 0.56 (0.15) vs. 0.53 (0.20) vs. 0.81 (0.19); p=NS&lt;br&gt;SAQ, habit subscale: 0.94 (0.06) vs. 0.82 (0.08) vs. 0.82 (0.08); p=NS&lt;br&gt;Bodily pain as reported by SF-36: 81.0 (2.98) vs. 80.7 (2.84) vs. 82.6 (3.29); p=NS</td>
<td>Anxiety decreased after surgery, while sexual pleasure increased. All other measures did not change over time.</td>
<td>Swedish Cancer Society, Swedish Association for Cancer and Traffic Victims, and Stockholm County Council</td>
</tr>
</tbody>
</table>
### Appendix C14. Evidence Table of Psychological and Sexual Functioning Harms of Interventions

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Duration of followup</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finch et al, 2011306</td>
<td>October 2002 to June 2008 1 year</td>
<td>NS difference over time on any portion of impact on areas of life measures, any portion of BIS, and any subscales of SF-36.</td>
<td>Women had worse vasomotor symptoms and decrease in sexual functioning.</td>
<td>Toronto Fashion Show, Kristi Piia Callum Memorial Fellowship in Ovarian Cancer Research, and University of Toronto Open Fellowship</td>
</tr>
<tr>
<td>Gahm et al, 2010303</td>
<td>2004-2006 Mean followup of 29 months (range, 24-49)</td>
<td><strong>Mean SF-36 subscales (estimated from graph)</strong>&lt;br&gt;Physical functioning: 94 vs. 89; p=NS&lt;br&gt;Role functioning: 86 vs. 85; p=NS&lt;br&gt;Bodily pain: 87 vs. 72; p=0.002&lt;br&gt;General health: 79 vs. 77; p=NS&lt;br&gt;Vitality: 68 vs. 68; p=NS&lt;br&gt;Social functioning: 90 vs. 89; p=NS&lt;br&gt;Role emotional: 80 vs. 85; p=NS&lt;br&gt;Mental health: 80 vs. 80; p=NS&lt;br&gt;Pain and discomfort questionnaire responses after RRM&lt;br&gt;38/55 (69%) pain in breasts&lt;br&gt;20/55 (36%) pain affected sleep&lt;br&gt;12/55 (22%) pain affected daily activities&lt;br&gt;39/55 (71%) discomfort in breasts&lt;br&gt;48/55 (87%) pain or discomfort in breasts&lt;br&gt;No association between pain and age (OR, 0.99; p=0.771); pain and complication (OR, 0.60; p=0.538); or pain and reoperation (OR, 3.72; p=0.110)&lt;br&gt;Pain or discomfort not related with negative effects in sexual outcomes (p&gt;0.05 for both)&lt;br&gt;<strong>Postoperative complications</strong>&lt;br&gt;11/59 (18.6%) had infections&lt;br&gt;3/59 (5.1%) required implant extraction&lt;br&gt;4/59 (6.8%) had hematoma&lt;br&gt;2/55 (3.4%) required acute operative evacuation&lt;br&gt;2/55 (3.4%) had revision of flap necrosis&lt;br&gt;35/59 (59%) had corrective surgical procedures&lt;br&gt;24/59 (41%) had procedure involving implant pockets&lt;br&gt;<strong>Sexuality questionnaire responses after RRM</strong>&lt;br&gt;25/55 (45%) totally lost sexual sensations&lt;br&gt;22/55 (40%) substantially impaired sexual sensations&lt;br&gt;38/55 (68%) negative change in sexual importance of breasts&lt;br&gt;41/55 (75%) negative change in sexual enjoyment of breasts&lt;br&gt;32/55 (58.2%) no change in sexual intercourse&lt;br&gt;Sexual attractiveness changes varied substantially</td>
<td>Women who had RRM had less bodily pain than the reference group, but no other differences on the SF-36. Most women who had RRM experienced pain, discomfort, and decrease in sexual enjoyment, attractiveness, and enjoyment. However, almost all women felt the choice was a good one and would make the same decision.</td>
<td>None</td>
</tr>
</tbody>
</table>
### Appendix C14. Evidence Table of Psychological and Sexual Functioning Harms of Interventions

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Duration of followup</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metcalfe et al, 2004&lt;sup&gt;301&lt;/sup&gt;</td>
<td>January 1991 to June 2000</td>
<td>Regret scale responses after RRM&lt;br&gt;52/55 (94.5%) agreed the decision was right&lt;br&gt;51/55 (92.7%) would make the same decision again&lt;br&gt;48/55 (87.3%) said it was a wise decision</td>
<td>Most women were happy with their decision to have RRM. For most women, the surgery did not cause high levels of distress and there was no correlation with age.</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean scales (SD) for whole group after RRM&lt;br&gt;IES-I: 8.44 (8.11); 4/57 (7.0%) scored above clinical cut-off, of these all (100%) had a strong family history of breast cancer and 3/4 (75%) had a mother who died from breast cancer&lt;br&gt;IES-A: 8.79 (8.53); 5/57 (8.8%) scored above clinical cut-off, 3/5 (60%) had a strong family history of breast cancer, 1/5 (20%) had a BRCA mutation, and 1/5 (20%) had a mother who died of breast cancer&lt;br&gt;Sexual activity, pleasure: 12.25 (4.72)&lt;br&gt;Sexual activity, discomfort: 1.97 (2.13)&lt;br&gt;BIBC, vulnerability: 2.43 (0.81)&lt;br&gt;BIBC, body concerns: 3.09 (0.99)&lt;br&gt;BIBC, body stigma: 2.33 (0.89)&lt;br&gt;BIBC, transparency: 2.19 (0.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean scales (SD)&lt;br&gt;IES-I: 9.07 (8.57) vs. 6.31 (6.10); p=NS&lt;br&gt;IES-A: 8.61 (9.03) vs. 9.38 (6.85); p=NS&lt;br&gt;Sexual activity, pleasure: 12.75 (4.70) vs. 10.25 (4.56); p=NS&lt;br&gt;Sexual activity, discomfort: 1.78 (2.12) vs. 2.88 (2.03); p=NS&lt;br&gt;Sexual activity, habit: 1.18 (0.64) vs. 1.42 (0.79); p=NS&lt;br&gt;BIBC, vulnerability: 2.38 (0.80) vs. 2.60 (0.87); p=NS&lt;br&gt;BIBC, body concerns: 3.12 (1.03) vs. 2.99 (0.86); p=NS&lt;br&gt;BIBC, body stigma: 2.27 (0.91) vs. 2.52 (0.81); p=NS&lt;br&gt;BIBC, transparency: 2.26 (0.86) vs. 1.97 (0.46); p=NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postsurgical symptoms&lt;br&gt;38 (64.4%) of women reported postsurgical symptoms: numbness (27), pain (7), tingling (7), infection (7), swelling (2), breast hardness (2), bleeding (1), organizing hematoma (1), failed reconstruction (1), breathing complications (1), thrombosis (1), pulmonary embolism (1)&lt;br&gt;18 women reported only 1 symptom, 15 women reported 2 symptoms, and 5 women reported 3 symptoms as a result of surgery. No difference in reporting of postsurgical symptoms based on time elapsed since mastectomy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mean scales (SD)**

- IES-I: 8.44 (8.11)
- IES-A: 8.79 (8.53)
- Sexual activity, pleasure: 12.25 (4.72)
- Sexual activity, discomfort: 1.97 (2.13)
- BIBC, vulnerability: 2.43 (0.81)
- BIBC, body concerns: 3.09 (0.99)
- BIBC, body stigma: 2.33 (0.89)
- BIBC, transparency: 2.19 (0.79)

**Postsurgical symptoms**

- Numbness: 27
- Pain: 7
- Tingling: 7
- Infection: 7
- Swelling: 2
- Breast hardness: 2
- Bleeding: 1
- Organizing hematoma: 1
- Failed reconstruction: 1
- Breathing complications: 1
- Thrombosis: 1
- Pulmonary embolism: 1

---

Regret scale responses after RRM<br>52/55 (94.5%) agreed the decision was right<br>51/55 (92.7%) would make the same decision again<br>48/55 (87.3%) said it was a wise decision.
## Appendix C14. Evidence Table of Psychological and Sexual Functioning Harms of Interventions

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Duration of followup</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rijnsburger et al., 2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>2000-2002 1-4 weeks after screening</td>
<td>A vs. B vs. C Experienced no pain after screening: 92.6% vs. 14.3% vs. 88.0%; p=NR Experienced no discomfort after screening: 91.5% vs. 30.8% vs. 54.6%; p=NR Experienced no anxiety after screening: 77.9% vs. 72.4% vs. 63.0%; p=NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Before screening (T0) vs. day of screening (T1) vs. after screening (T2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean VAS: 81.9 vs. 79.0 vs. 80.7; p&lt;0.01 T0 vs. T1 and p&lt;0.05 T1 vs. T2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Before screening vs. after screening (A, B, and C groups combined) vs. reference group (Dutch general population)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean on SF-36 subscales; p=NS for before and after screening Physical functioning: 89.9 vs. 89.4 vs. 86.3; p&lt;0.01 for reference group vs. before screening Role-physical: 85.7 vs. 84.1 vs. 77.6; p&lt;0.01 for reference group vs. before screening Bodily pain: 82.4 vs. 83.0 vs. 72.8; p&lt;0.01 for reference group vs. before screening General health perceptions: 76.4 vs. 77.3 vs. 72.2; p&lt;0.01 for reference group vs. before screening Vitality: 67.1 vs. 68.9 vs. 64.8; p=NS Social functioning: 87.7 vs. 87.3 vs. 83.5; p&lt;0.01 for reference group vs. before screening Role-emotional: 85.2 vs. 88.1 vs. 80.1; p&lt;0.05 for reference group vs. before screening Mental health: 76.8 vs. 77.7 vs. 74.4; p&lt;0.05 for reference group vs. before screening Mean SCL-90: 17.5 vs. 17.1 vs. 18.7; p&lt;0.05 for reference group vs. before screening Mean ED-5D utility score (compared to Swedish reference group): 0.88 vs. 0.88 vs. 0.85; p&lt;0.01 for reference group vs. before screening</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women who received MRI experienced less pain and discomfort than those who received mammography. Women in screening showed better health-related quality of life per the SF-36 than the reference group.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Care Insurance Board, the Netherlands</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Spiegel et al, 2011 |
| 258 Years NR 6 months | **Before screening vs. 4-6 weeks after screening vs. 6 months after screening** |
| Mean HADS-A (SD): 7.15 (4.2) vs. 6.85 (4.5) vs. 6.31 (3.9); NS |
| Mean HADS-D (SD): 2.65 (3.6) vs. 2.60 (3.5) vs. 2.60 (3.5); NS |
| Mean WIS (SD): 10.27 (4.2) vs. 11.07 (4.9) vs. 10.44 (4.7); NS |
| **A vs. B 4-6 weeks after screening** |
| Mean HADS-A (SD): 8.8 (5.2) vs. 5.9 (3.9); p=0.03 |
| Mean HADS-D (SD): 3.3 (4.3) vs. 2.2 (3.1); NS |
| Mean WIS (SD): 13.6 (6.4) vs. 9.8 (3.5); NS |
| **A vs. B 6 months after screening** |
| Mean HADS-A (SD): 7.1 (3.8) vs. 5.9 (4.0); NS |
| Mean HADS-D (SD): 3.1 (4.3) vs. 2.3 (3.1); NS |
| Mean WIS (SD): 12.4 (6.3) vs. 9.4 (3.2); NS |
| Women who were recalled for examinations after screening had increased anxiety 4-6 weeks after screening, but by 6 months all scores returned to baseline levels. |
| Canadian Breast Cancer Research Alliance grant #012345 and private donation from Florence and Maury Rosenblatt |
### Appendix C14. Evidence Table of Psychological and Sexual Functioning Harms of Interventions

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quality</th>
<th>Duration of followup</th>
<th>Results</th>
<th>Conclusions</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wasteson et al, 2011</td>
<td>305</td>
<td>Median, 10 years (range, 9-12)</td>
<td>Affects 10 years after RRM with reconstruction 8/13 (61.5%) stated family life unchanged 4/13 (30.8%) stated positive affect on family life 5/13 (38.5%) stated negative affect on relationship with spouse (due to decreased sensation and changed body appearance) 10/13 (76.9%) considered cosmetic results positive 10/11 (90.9%) had discussed breast cancer risk with daughters</td>
<td>Most women stated positive affects 10 years after RRM with reconstruction.</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Abbreviations:** BRCA = Body Image after Breast Cancer; BIS = Body Image Scale; RRM = risk-reducing mastectomy; BSI = Brief Symptom Inventory; CBE = clinical breast exam; DRS = Decision Regret Scale; EQ-5D = EuroQoL-5 Dimensions; HADS = Hospital Anxiety and Depression Scale; IES = Impact of Events Scale; MENQOL = Menopause-Specific Quality of Life-Intervention; MRI = magnetic resonance imaging; NA = not applicable; NR = not reported; NS = not significant; OR = odds ratio; RRSO = risk-reducing salpingo-oophorectomy; QOL = quality of life; SAQ = Sexual Activity Questionnaire; SCL-90 = Symptom Checklist-90; SD = standard deviation; SE = standard error; SF-36 = Short-Form 36-Item Health Survey; VAS = Visual Analogue Scale.