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

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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.

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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 review[1,2] 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 *BRCA1* or *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.[6,7] 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.[8-10] 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.[11,12] *BRCA1* mutations increase ovarian, fallopian tube, or peritoneal cancer risk to 39 percent, and *BRCA2* mutations to 10 to 17 percent.[11,12] These mutations are estimated to occur in 1 in 300 to 500 women in the general population,[13-16] and account for 5 to 10 percent of breast cancer overall.[13,17]

Specific BRCA mutations, known as founder mutations, are clustered among certain ethnic groups, including Ashkenazi Jews,[18-20] blacks,[21] and Hispanics,[22,23] and among families in the Netherlands,[24] Iceland,[25,26] and Sweden.[27] Several additional genes not included in this review are also associated with hereditary susceptibility to breast and ovarian cancer,[7,28,29] 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.[30-35] 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.[36] 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.[36] 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.[37,38] 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.[28] 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.[39] 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.[39]

Ovarian cancer is the fifth leading cause of cancer death in women in the United States,[38] accounting for an estimated 22,240 new cases and 14,030 deaths in 2013.[40] 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.[39] 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.[39] 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.[39]

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.[41-45] 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,[46-49] 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]

Genetic 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., Couch[46]), Bayesian analysis (e.g., BRCAPRO,[12,53] BOADICEA[54]), and patient data (Myriad prevalence tables[55]), 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 *BRCA1* or *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 *BRCA1* and *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.[65] Approximately 12 percent of high-risk families without a *BRCA1* or *BRCA2* coding-region mutation may have other clinically significant genomic rearrangements.[65,66] 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.[50] 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.[67] Placebo-controlled randomized, controlled trials (RCTs) of tamoxifen indicate reduced primary ER-positive breast cancer in women with family histories of breast cancer.[68-72] 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.[73,74] SERMs also have important adverse effects, including thromboembolism, endometrial cancer (tamoxifen), and vasomotor and other symptoms.[75,76] Exemestane, an aromatase inhibitor, also reduces risk for primary breast cancer in women with increased risk[77] 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.[78]

Risk-reducing mastectomy and salpingo-oophorectomy are also options for women who are BRCA mutation carriers.[79-82] Bilateral total simple mastectomy with or without reconstruction is

currently the most common approach.[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[85] and breast cancer can still occur postmastectomy.[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.[87,88] Despite this approach, the occurrence of peritoneal carcinomatosis remains a possibility.[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.[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.[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.[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.[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,[1,2] the USPSTF and Agency for Healthcare Research and Quality (AHRQ) determined the key questions for this update using the methods of the USPSTF.[100] 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 nongenetics 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,[100,101] 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.[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.[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 *BRCA1* or *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,[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.[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.[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.[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).

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 cancer[43] 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 investigators[114] 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**

A1).[50] 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[115,116] included 19 studies[117-137] 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,[128] and subsequently modified with Surveillance Epidemiology and End Results data.[126] 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.[128] 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).[119,121-124,126,127,129,135,136] 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,[117-124,126,127,129,131-135] 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**).[56,138-146] 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.[142] 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.[142] The sensitivity and specificity of the FHAT for a clinically significant *BRCA1* or *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 *BRCA1* or *BRCA2* mutation using BRCAPRO, and 74 and 54 percent using Claus methods. Additional validation studies of the FHAT have replicated its accuracy,[145] and its concordance statistics range from 0.68 to 0.83 across a wide variety of conditions.[144,146]

Manchester Scoring System. The Manchester Scoring System was developed in the United Kingdom to predict *BRCA1* or *BRCA2* mutations at the 10 percent likelihood level.[141] 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 *BRCA1* and *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 *BRCA1* and *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.[56,139,141,144,145]

RST. The RST was developed to help primary care clinicians make appropriate referrals for genetic counseling in response to the USPSTF 2005 recommendation.[140] 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.[140] 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.[147]

PAT. The PAT was also designed to identify women at increased risk for BRCA-related cancer in U.S. primary care settings.[143] 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.[143] 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

reporting of randomization technique,[151,152,154,157,160,164] noncomparable groups at baseline,[151,161,162] and no specified eligibility criteria.[151]

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[152,154,155,157,164] and genetic counseling versus no counseling,[148,151,160-162] while others compared outcomes before and after genetic counseling.[149,150,153,156,158,159,163] The types of genetic counseling services provided are summarized in **Table 6**.

Studies used the Cancer Worry Scale (CWS) and the State-Trait Anxiety Inventory (STAI) to measure breast cancer worry; the Hospital Anxiety and Depression Scale (HADS), Impact of Events Scale (IES), General Health Questionnaire (GHQ), and Visual Analogue Scale to measure anxiety and depression; and general Likert scales to measure intention to undergo genetic testing and risk perception. These are described in **Table 7**.

Breast Cancer Worry

No studies reported increases in measures of breast cancer worry after women received genetic counseling; eight studies reported decreases,[150,152-155,157,158,162] while one study reported no changes.[151]

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; $p=0.002$).[157] 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; $p<0.001$).[152] 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.[154] 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.[151]

A fair-quality prospective cohort study reported that more women receiving counseling experienced decreases in cancer-specific distress, as measured by the IES.[162] 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.[162] 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.[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).[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).[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.[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.[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,[154,163,164] while three studies reported no changes.[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.[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).[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.[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.[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.[158] 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.[150] In this study, only baseline scores indicated mild anxiety, and followup scores were below the clinical threshold for anxiety, as measured by the HADS.[150]

Risk Perception

A fair-quality systematic review of 19 studies published before February 2007 reported results of studies of risk perception after genetic counseling.[165] 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,[152,156-158,160,161,163,169] including four cited in the 2007 published systematic review,[152,156,158,169] were consistent in reporting improved accuracy of breast cancer risk perception after genetic counseling. One study reported less accuracy.[153] These findings differ from the prior USPSTF review, in which results were inconclusive.[57-59,166-171] 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.[151] 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.[157] 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.[153]

Only one before-after study assessed the accuracy of risk perception for developing ovarian cancer.[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.[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.[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.[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 review[13,15,16,19,20,46,47,122,188,203-231] (**Appendixes 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

overestimate prevalence in unselected or general populations.[15] 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.[13,16,174,195,199,204,207,208,218,220,223]

For *BRCA1*, the meta-analysis indicated a prevalence of 4.26 percent (95% CI, 2.61 to 6.87; 10 studies)[13,16,174,195,204,207,208,218,220,223] 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)[13,195] 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)[13,16,174,195,220] 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.[195] For *BRCA1* or *BRCA2*, the combined prevalence estimate was 5.98 percent (95% CI, 1.87 to 17.47)[16,208,220] 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).[13,194,204,223] The prevalence of *BRCA2* was 1.31 percent (95% CI, 0.67 to 1.95), based on one study.[13]

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),[195,204,216, 228] 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.[195]

Prevalence was also reported for racial and ethnic minorities in three studies;[195,204,223] 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[174] to 30.8 percent[193] for *BRCA1* and from 6.1 percent[174] to 15.4 percent[193] 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),[174,183,188,193,194,199,200,202,207,211,232] with significant heterogeneity among studies (I^2=86%; p<0.001). Heterogeneity remained high in a sensitivity analysis that excluded an outlier[193] (I^2=89%; p<0.001). Estimates were similar in sensitivity analyses that excluded two studies with mixed populations of race/ethnicity.[46,194] 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.[212]

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).[174,183,188,193,194,199,202,211] 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.[212]

For *BRCA1* and *BRCA2* combined, the prevalence was 19.78 percent (95% CI, 12.98 to 26.57).[46, 174,183,188,193,199,200,207,211] In a study in which subjects were ascertained based on family histories of two or more cases of ovarian cancer, the estimate was 42.86 percent (95% CI, 33.79 to 51.92).[212] In a sensitivity analysis excluding an outlier,[193] prevalence decreased to 15.93 percent (95% CI, 9.21 to 22.66), although there was significant heterogeneity (I^2=94%; p<0.001). Estimates were similar in sensitivity analyses that excluded one study with mixed populations of race/ethnicity.[47]

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.[21] No *BRCA1* or *BRCA2* mutations were detected in three Hispanic individuals tested in another study.[193] 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*.[193]

Ashkenazi Jewish. Five studies provided estimates of *BRCA1* prevalence in Ashkenazi Jewish populations unselected by personal or family history of breast cancer,[19,20,191,209,214] and six studies provided estimates for *BRCA2* prevalence[19,20,191,209,214,224] (**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)[20,209, 214] and for *BRCA2* was 1.17 percent (95% CI, 0.95 to 1.38)[20,209,214,224] (**Table 11**). For *BRCA1* and *BRCA2* combined, prevalence was 2.08 percent (95% CI, 1.28 to 2.88).[20,191,209, 214] There was significant heterogeneity among studies (I^2=89%; p<0.001), with the most recent publication[191] 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%).[214] 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),[20,209,214] 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,[1,2] 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.[19,47,219]

Penetrance

Penetrance is the probability of developing BRCA-related cancer in women who have a given *BRCA1* or *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.

BRCA-Positive Results in High-Risk Populations. There were significant methodological differences across studies that reported penetrance in women who were *BRCA1*or *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.[13,15,176,187,188,190,195,225] For *BRCA1* mutations, breast cancer penetrance was 46 percent (95% CI, 40 to 51) to age 70 years[13,15,176,188,190] (**Table 13**); for *BRCA2*, penetrance was 50 percent (95% CI, 40 to 60) to age 70 years.[13,15,176,188,190]

Eight studies reported estimates based on testing multiple individuals per family.[172,173,178,185,192,201,206,210] For *BRCA1* mutations, breast cancer penetrance was 70 percent (95% CI, 61 to 79) to age 70 years;[173,178,185,192,201,206] for *BRCA2*, penetrance was 71 percent (95% CI, 59 to 83) to age 70 years.[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 *BRCA1* and 49 percent (95% CI, 40 to 57) for *BRCA2*.[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 *BRCA1* and 45 percent (95% CI, 31 to 56) for *BRCA2*.[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.[13,15,176,188,190,195,225] For *BRCA1* mutations, ovarian cancer penetrance was 41 percent (95% CI, 32 to 49) to age 70 years;[13,15,176,188,190] for *BRCA2*, penetrance was 17 percent (95% CI, 11 to 24) to age 70 years.[13,15,176,188] There was no significant heterogeneity between studies.

Six studies reported estimates based on testing multiple individuals per family.[173,178,192,201,206,210] For *BRCA1* mutations, ovarian cancer penetrance was 46 percent (95% CI, 35 to 57) to age 70 years;[173,178,192,201,206] for *BRCA2*, penetrance was 23 percent (95% CI, 12 to 34) to age 70 years.[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 nonAshkenazi 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 review[1,2] 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**).[182,189,230] 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.[189] The other studies included families with breast cancer (SIR, 3.88 [95% CI, 0.05 to 21.6])[182] and families with at least two first-degree relatives with ovarian cancer (SIR, 11.6 [95% CI, 3.12 to 29.7]).[230]

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**).[175,177,180,181,184-186,196,198,201] 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.[180,186] 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[180] 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.[175,177,180,198]

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**).[198,201] One study reported an SIR of 0 (95% CI, 0 to 12) for *BRCA1* and 0 (95% CI, 0 to 24) for *BRCA2*.[201] A second study reported an increased risk of ovarian cancer with a SIR of 4.6 (95% CI, 1.2 to 11.7).[198] 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,[235-249] as well as one included previously.[250] 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,[239,240,242,245,248,250] two for fair-quality,[238,244] and one for poor-quality.[243] The remaining studies included a fair-quality case-control study[236,247] and five studies with before-after designs for which quality rating criteria were not available.[235,237,241,246,249] Limitations of studies included unclear enrollment of the cohort,[238,243,244] high loss to followup,[244] and significant differences between groups at baseline or lack of reporting of baseline participant characteristics.[238,243,244]

The studies varied in size from 17 to 10,244 women; however, the largest study was dominated by the control group (n=10,000).[240] 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,[236,238-240,242-245,247,248,250] while others compared outcomes before and after genetic testing.[235,237,241,246,249]

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.[236,241,248-250] 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?"[248] 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.[236] 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.[238] 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; $p=0.05$).[249] 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; $p=0.045$).[250] 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 ($p=0.008$).[241]

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.[235,243] One study reported a significant decrease regardless of mutation status (mean, 5.6 pretest vs. 4.2 at 1 year posttest; $p<0.001$),[235] while the other reported a significant decrease only in women who were noncarriers ($p=0.001$).[243] A fair-quality prospective cohort study reported an increase in anxiety scores over time on the GHQ.[238] 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[248] and one fair-quality,[244] 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.[248] 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; $p<0.05$).[239,240] 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.[250] Four studies reported no differences in anxiety either over time[237,246] or between women who were carriers, noncarriers, and age-matched controls,[236,245] 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.[240] Four studies reported no differences in depression either over time[235,246] or between women who were carriers, noncarriers, and age-matched controls,[236,245] 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.[250]

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).[247] 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.[251,252]

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.[251] 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.[252] Some women felt comforted by other mutation carriers in the family, but felt less comforted 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).[242] 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,[253] patients may want to inform family members themselves.[254,255] Studies indicate that most patients feel a responsibility to share their BRCA test results with family members in order to benefit them.[256,257]

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).[258] 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.[259] 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.[260,261] 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.[262] 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.[263] 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,[264,265] 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.[266] 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.[267]

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.[268] 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 ($p<0.05$).[268] 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.[268] Physicians' knowledge did not differ between sites.[269] 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]).[269] 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]).[269]

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.[270] 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 Raloxifen 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 studies[273-275] 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.[274] 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.[273] 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.[276] 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.[279] 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.[280] 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**).[281] 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.[281] 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.[282] 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 STAR[289] 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 overlapping[284] (**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.[289]

Risk-Reducing Surgery

Mastectomy. Four studies met inclusion criteria; one from the previous review[290,291] and three from updated searches.[292-294] The prior evidence review included a retrospective descriptive study based on data from patients' medical records.[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.[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.[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.[295]

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

A study enrolling women from 22 North American and European centers evaluated outcomes for women with BRCA mutations.[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.[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.[294]

Salpingo-Oophorectomy or Oophorectomy. Four studies met inclusion criteria; one from the previous review[229] and three from updated searches.[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.[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.[229]

One new study of risk-reducing salpingo-oophorectomy[292] and two new studies of oophorectomy[185,296] in high-risk women and women who were mutation carriers met inclusion criteria (**Table 19**, **Appendix C12**). Two studies[185,292] met criteria for fair-quality and one was descriptive.[296] The fair-quality studies were limited by a lack of information about groups at baseline, attrition, and followup.[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]).[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 *BRCA1* mutation carriers, oophorectomy was associated with reduced breast cancer incidence (18% vs. 42%; HR, 0.38 [95% CI, 0.15 to 0.97]).[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.[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 percent 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 review[279] 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[281] (**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.[116,283] Studies include four placebo-controlled trials of tamoxifen,[284-287] two placebo-controlled trials of raloxifene,[73,288] and a head-to-head RCT of tamoxifen versus raloxifene.[289] 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,[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]

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**).[116,283] 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).[289] 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]).[299]

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.[116,283] Raloxifene did not increase risk for endometrial cancer or uterine bleeding.[116,283] 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.[289] Women using tamoxifen had more cataract surgeries than placebo in the NSABP P-1 trial.[284] 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).[289]

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.[289]

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 (26/30) with 50 percent lifetime risk, and 9 percent (98/90) 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 FHS-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[307-311] and estimates for cancer susceptibility genes other than *BRCA1* and *BRCA2*.[312-315] 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,[201,316-319] 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.[320] 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[265] 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.[321] 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.

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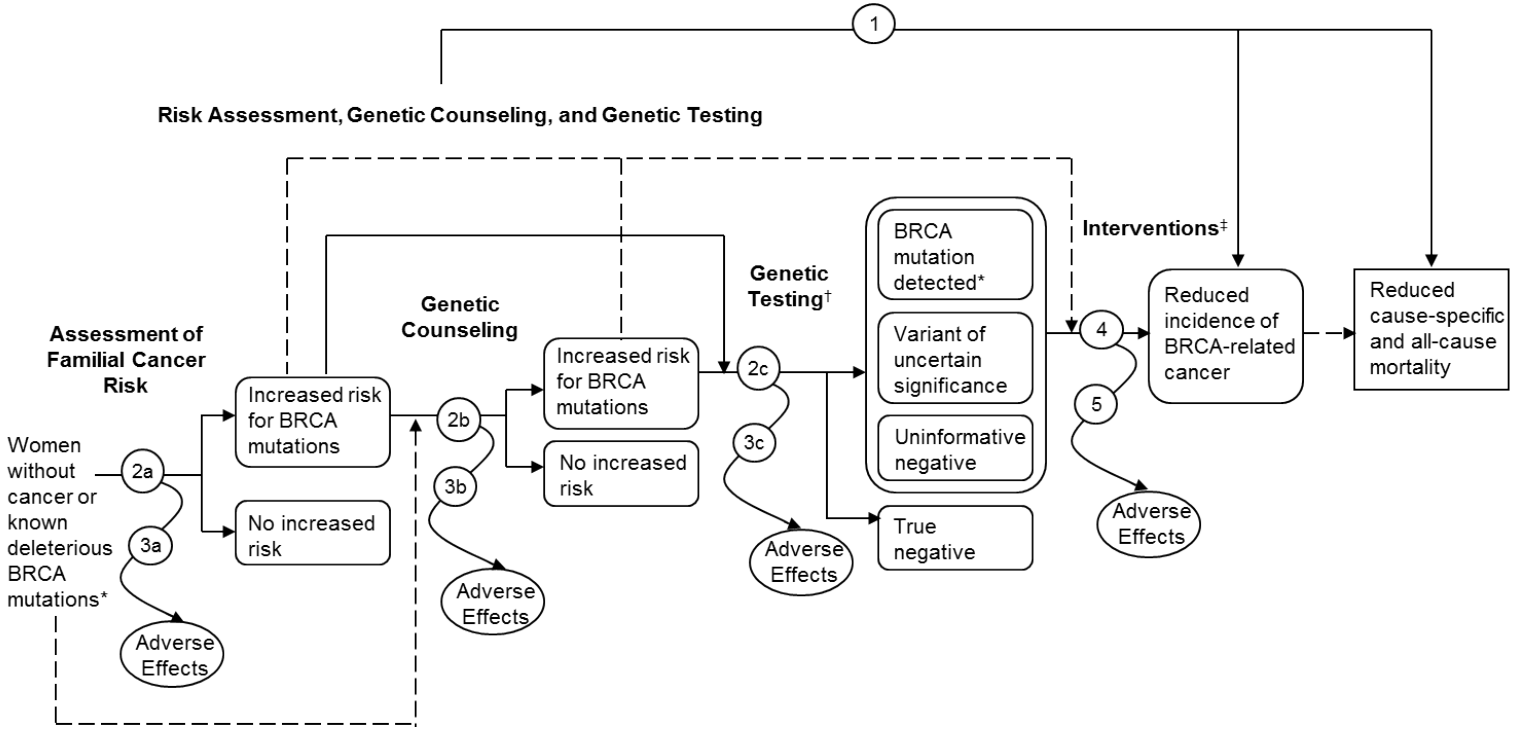
Figure 1. Analytic Framework and Key Questions



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

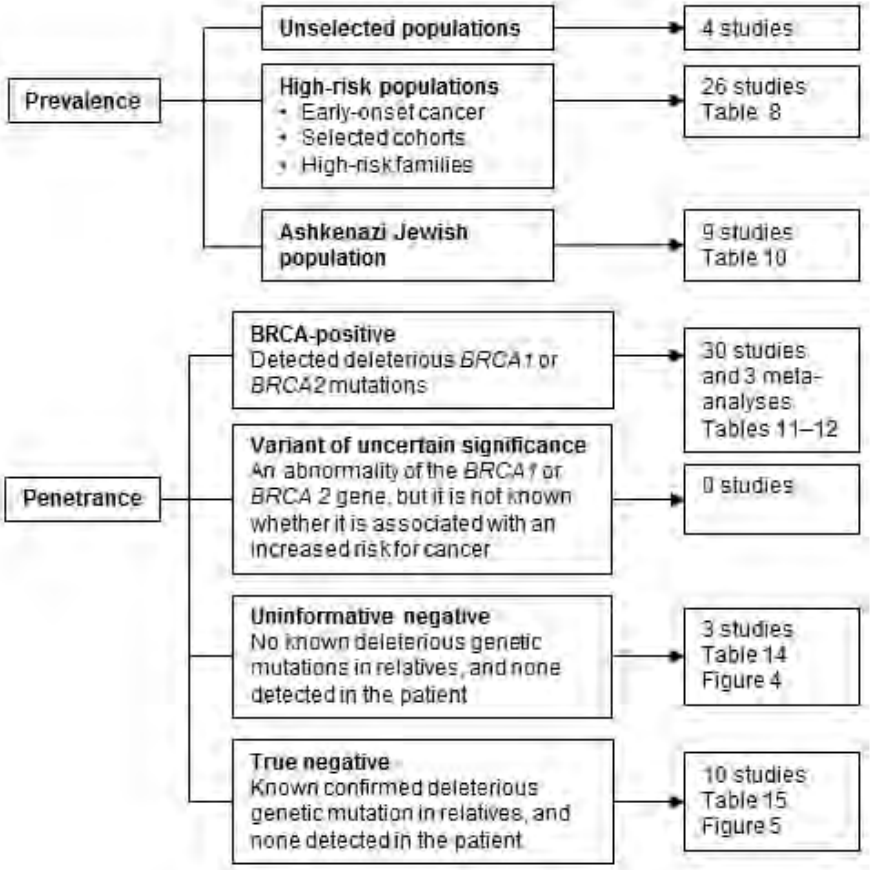
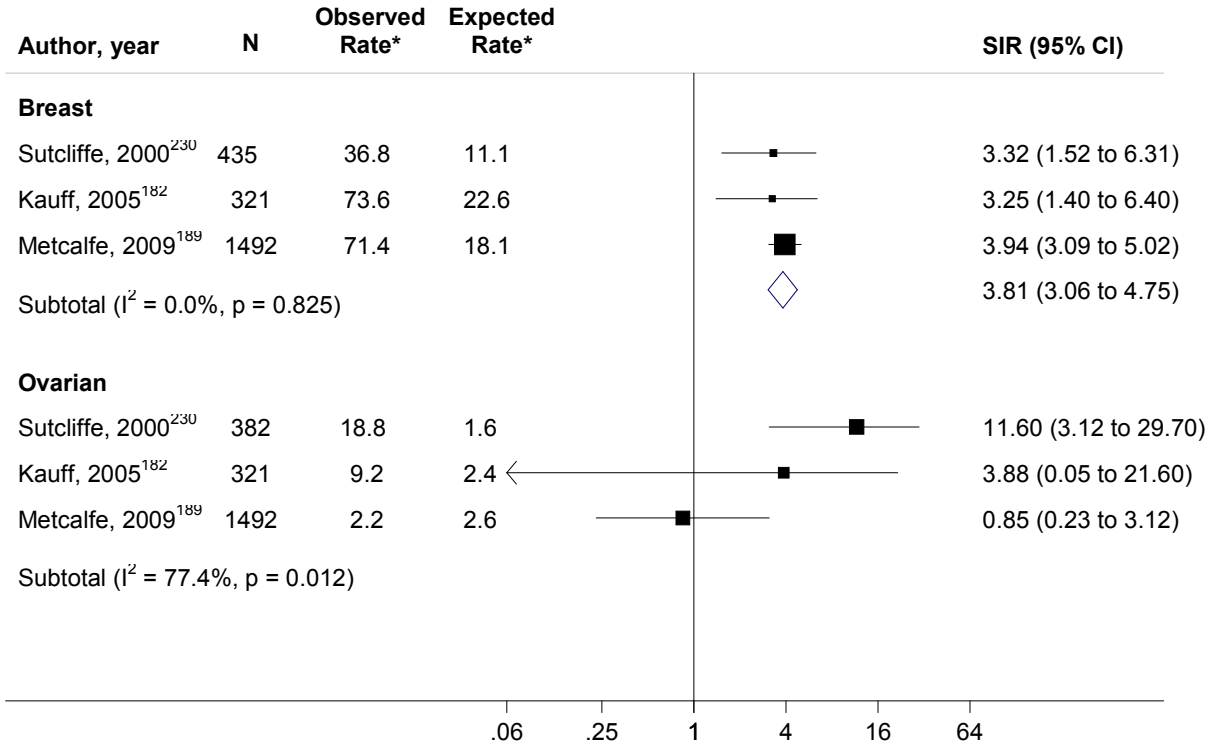


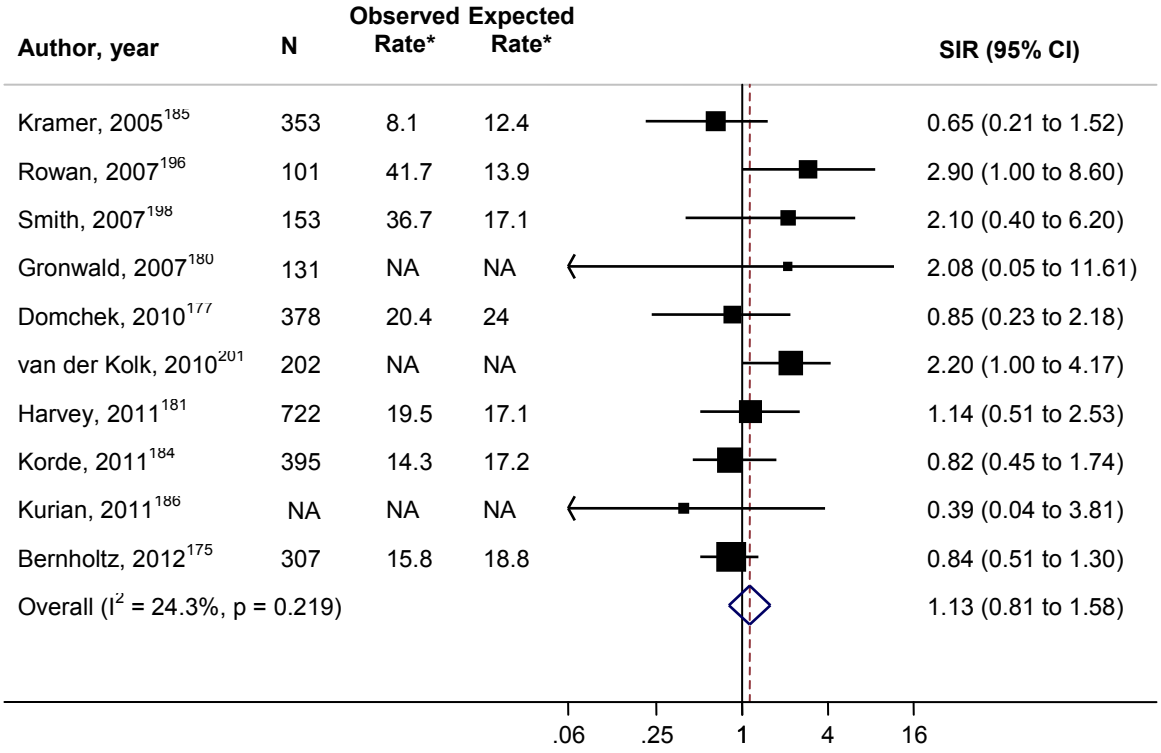
Figure 3. Meta-Analysis of Studies of Breast and Ovarian Cancer Incidence in Women With Uninformative Negative Results



*Per 10,000 person-years.

Abbreviations: CI = confidence interval; SIR = standardized incidence ratio.

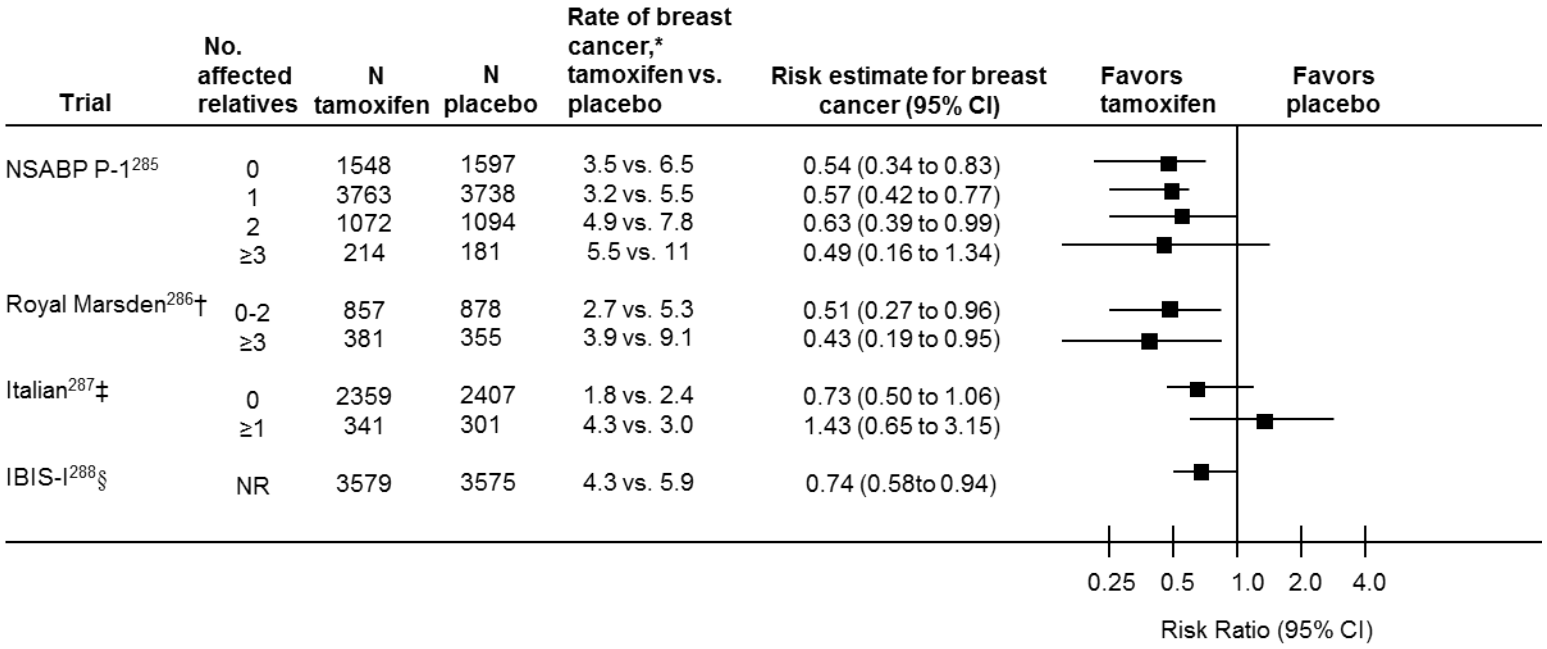
Figure 4. Meta-Analysis of Studies of Breast Cancer Incidence in Women With True Negative Results



*Per 10,000 person-years.

Abbreviations: CI = confidence interval; NA = not applicable; SIR = standardized incidence ratio.

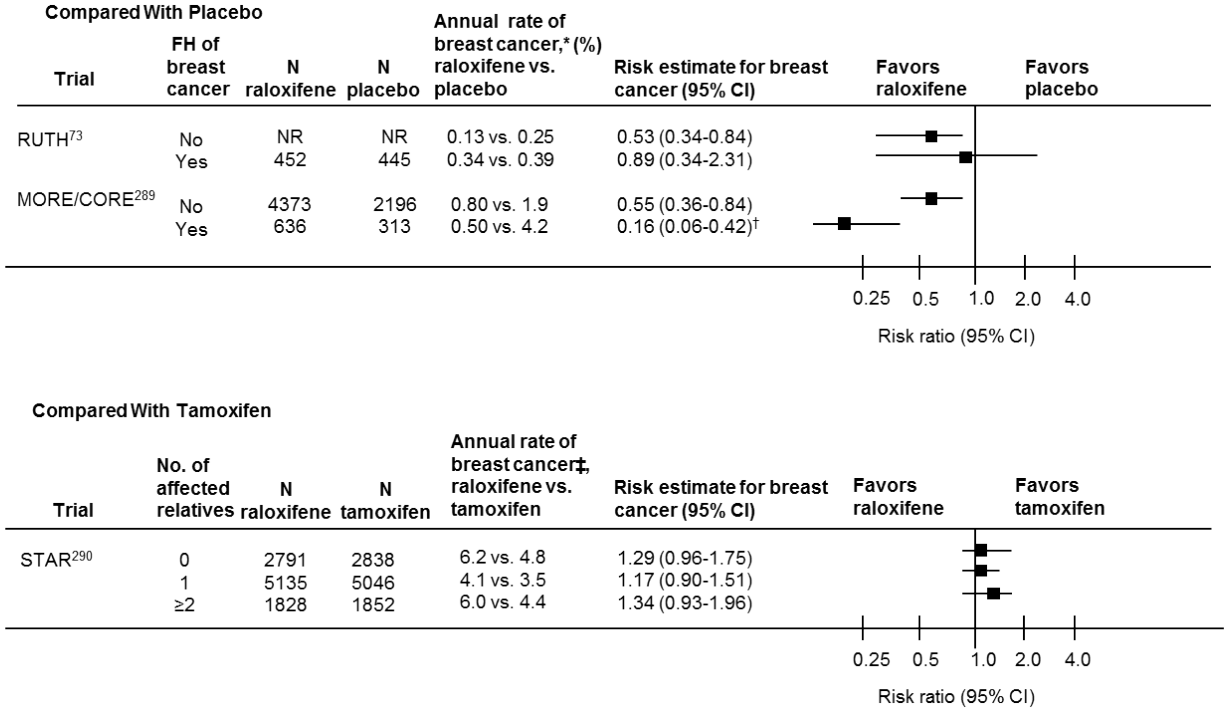
Figure 5. Invasive Breast Cancer Risk Reduction With Tamoxifen Use, by Family History



* 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.

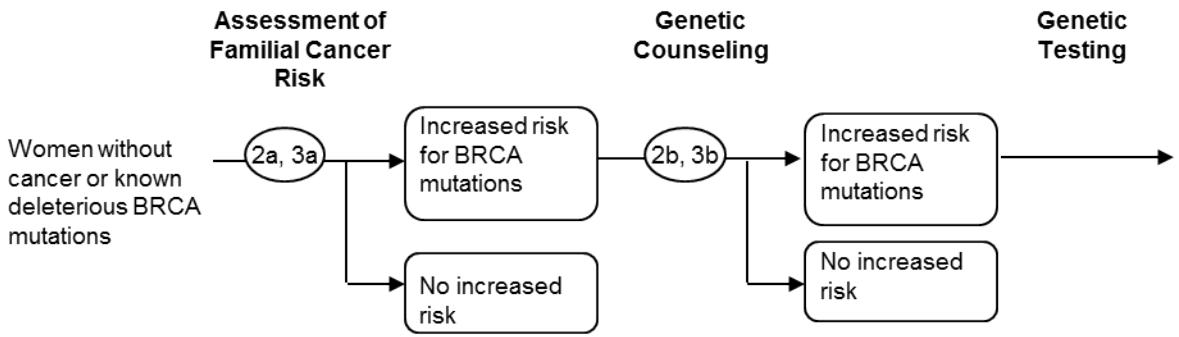
Figure 6. Invasive Breast Cancer Risk Reduction With Raloxifene Use, by Family History



* 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

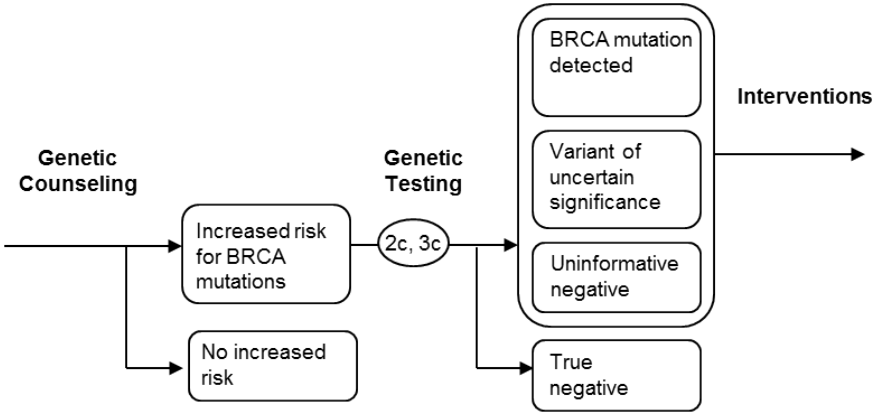


KQ 2a. Accuracy of Risk Assessment	
Risk Models	**Discriminatory Accuracy (c statistic)**
Referral criteria	No studies
General risk models	0.55–0.65 for breast cancer risk; models do predict mutation risk
Family history models	>0.80 for mutation risk
KQ 3a. Adverse Effects of Risk Assessment	
No studies	

KQs 2b, 3b. Benefits and Adverse Effects of Genetic Counseling			
	Number of Studies		
Measure	**Increase**	**Decrease**	**NS**
Breast cancer worry	0	8	9
Anxiety	0	5	8
Depression	0	1	6
Risk accuracy	15	2	5
Intention to test	1	4	0

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

Figure 8. Summary of Key Questions 2c and 3c



KQ 2c. Clinical Validity of Genetic Testing

Population	Mutation Prevalence
Unselected	0.2%–0.3%
High-risk	
Breast or ovarian cancer onset ≤40 yrs	*BRCA1*: 4.3% *BRCA2*: 2.9% Combined: 6.0%
Breast cancer cohort	*BRCA1*: 1.8% *BRCA2*: 1.3%
Ovarian cancer cohort	*BRCA1*: 4.4% *BRCA2*: 5.6%
Family history of breast or ovarian cancer	*BRCA1*: 13.6% *BRCA2*: 7.9% Combined: 19.8%
Ashkenazi Jewish	
Unselected	*BRCA1*: 1% *BRCA2*: 1% Combined: 2.1%
Family history of breast or ovarian cancer	*BRCA1*: 6.4% *BRCA2*: 1.1% Combined: 10.2%

Test Result	Chance of Cancer (mutation penetrance)
Positive	% to age 70 or 75 yrs
1 person tested	*BRCA1*: 46% BC; 41% OC *BRCA2*: 50% BC; 17% OC
>1 person tested	*BRCA1*: 70% BC; 46% OC *BRCA2*: 71% BC; 23% OC
Ashkenazi Jewish	Combined: 34% BC; 21% OC
Variant of Unknown Significance	No studies
Negative	Standardized incidence rate
Uninformative	Breast: 3.81 (3.06–3.32) Ovarian: 0.85–11.6
True	Breast: 1.26 (0.79–2.01) Ovarian: 0–4.6

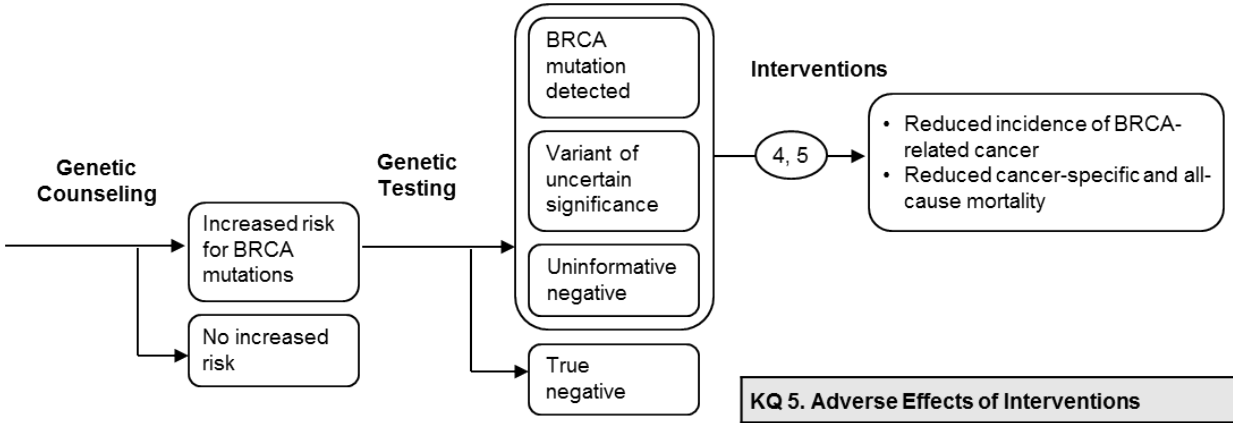
KQ 3c. Adverse Effects of Genetic Testing

Measure	Number of Studies		
	Increase	Decrease	NS
Breast cancer worry	4	1	0
Anxiety	5	3	4
Depression	1	1	4

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



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

KQ 5. Adverse Effects of Interventions	
Intervention	**Rates**
Intensive Screening (per episode or year)	
False-positive	4.6%–15% mammogram; 8.2%–14% MRI; 3.4% TVUS
Recall	3.9% mammogram; 11% MRI
Unneeded biopsy	27%–28% mammogram; 25%–43% MRI; 100% TVUS‡; 67% CA-125‡
Risk-Reducing Medication (over 5 years)	
Venous thrombosis	0.4%–0.7%
Endometrial cancer	Tamoxifen: 0.4%
Risk-Reducing Surgery	
Complications	RRM: 3%–59%; RRSO: no studies
Symptoms	RRM: 64%–87%; RRSO: no studies
Quality of life	RM: decrease anxiety; sexual RRSO: decrease sexual

* 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 1. Types of Clinical Testing for BRCA Mutations in the United States[96]

Test	Description	Approximate cost (U.S. $)*
Comprehensive testing	Gene sequencing of the entire length of both *BRCA1* and *BRCA2* and a five-site rearrangement panel of specific large-scale rearrangements.	>$3000
Single site testing	One specific gene mutation when the mutation in the family has already been identified.	$475
Multisite panel	Three specific gene changes common among Ashkenazi Jewish ancestry.	$575
BRCA Rearrangement Test	Large-scale rearrangements within the BRCA genes that would not have been detected through comprehensive testing.	$700

*Reflects costs prior to the recent U.S. Supreme Court decision against DNA patents.

Table 2. Recommendations of Other Groups

Organization, year	Recommendations
American Society of Clinical Oncology, 2010[327]	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.
American Congress of Obstetricians and Gynecologists, 2009[323]	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.
American Society of Human Genetics, 1994[322]	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.
National Comprehensive Cancer Network, 2012[50]	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**).
European Society for Medical Oncology, 2011[324]	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.
National Society of Genetic Counselors, 2012[326]	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.
Society of Gynecologic Oncologists Education Committee, 2007[325]	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.

Table 3. Risk Stratification Models

Model	Included variables						Calibration expected/observed cases (95% CI)*	Discriminatory accuracy c-statistic (95% CI)*
	Age, *y*	Menarche age, *y*	Age at birth of first child, *y*	First-degree relatives with breast cancer, *n*	Previous breast biopsy, *n*	Other factors		
Gail Model Variations								
Gail-2 5-year risk	<50; ≥50	≥14; 12–13; ≤12	<20; 20–24; 25–29 or none; ≥30	0; 1; ≥2	Bx: 0; 1; ≥2 AH: 0; ≥1	Not included	1.03 (0.88 to 1.21);[126] 0.94 (0.89 to 0.99);[132] 0.96 (0.84 to 1.17);[127] 0.79;[123] 1.12[121]	0.55 (0.51 to 0.60);[117] 0.60;[126] 0.58 (0.56 to 0.60);[119] 0.58;[132] 0.59 (0.54 to 0.63);[127] 0.60;[122] 0.61 (0.60 to 0.62)[135]
Gail-2 10-year risk	<50; ≥50	≥14; 12–13; ≤12	<20; 20–24; 25–29 or none; ≥30	0; 1; ≥2	Bx: 0; 1; ≥2 AH: 0; ≥1	Not included	0.69 (0.54 to 0.90)[133]	0.74 (0.67 to 0.80)[118]
African American Gail 5-year risk	<50; ≥50	≤13; >13	Not included	0; 1; ≥2	Bx: 0; 1; ≥2	African American race	1.08 (0.97 to 1.20)[129]	0.56 (0.54 to 0.58);[129] 0.56 (0.51 to 0.60)[117]
Models with Breast Density								
Chen 5-year risk	<50; ≥50	≥14; 12–13; ≤12	<20; 20–24; 25–29 or none; ≥30	0; 1; ≥2	Bx: 0; 1; ≥2	Breast density (%), BMI	Not reported	0.64[122]
BCSC† (pre-menopausal) 1-year risk	45–84 by 5-year groups	Not included	Not included	0; 1; ≥2; unknown	Bx: yes; no; unknown	Breast density (BIRADS)‡	1.00[119]	0.63 (0.60 to 0.66)[119]
BCSC† (post-menopausal) 1-year risk	45–84 by 5-year groups	Not included	<30; ≥30; none; unknown	0; 1; ≥2; unknown	Bx: 0; ≥1; unknown	Breast density (BIRADS), prior false-positive mammogram, BMI, menopause type, HT, race/ethnicity	1.01[119]	0.62 (0.62 to 0.63)[119]
BCSC 5-year risk	45–84 by 5-year groups	Not included	Not included	Yes; no	Bx: yes; no	Breast density (BIRADS), race/ethnicity	1.01 (0.99 to 1.03)[135]	0.66 (0.65 to 0.66)[135]
Other Models								
Rosner-Colditz†	<50; ≥50	14; 12–13; ≤12	<20; 20–24; 25–29 or none; ≥30	Yes; no	Not included	BMI, benign breast disease, menopause type, menopause age, HT use and duration, height, alcohol use, parity	1.00 (0.93 to 1.07)[133]	0.57 (0.55 to 0.59);[133] 0.64 (0.63 to 0.66) (ER+/PR+);[125] 0.61 (0.58 to 0.64) (ER-/PR-)[125]
Rosner-Colditz-2†	<50; ≥50	14; 12–13; ≤12	<20; 20–24; 25–29 or none; ≥30	Yes; no	AH: 0; ≥1	Benign breast disease presence or type	1.01 (0.94 to 1.09)[133]	0.63 (0.61 to 0.65);[133] 0.64 (type)[133]

Table 3. Risk Stratification Models

Model	Included variables						Calibration expected/observed cases (95% CI)*	Discriminatory accuracy c-statistic (95% CI)*
	Age, *y*	Menarche age, *y*	Age at birth of first child, *y*	First-degree relatives with breast cancer, *n*	Previous breast biopsy, *n*	Other factors		
Tyrer-Cuzick 10-year risk	<50; ≥50	≤12; >12	≤30; >30; none	1; 2; ≥2	Bx: 0; 1; ≥2 LCIS: 0; ≥1	BMI, height, menopause age, family history of ovarian/other cancer, age of cancer onset, bilateral or male breast cancer	1.09 (0.85 to 1.41)[118]	0.76 (0.70 to 0.82);[118] 0.54 (0.42 to 0.65)[120]
Italian-1§ 5-year risk	<50; ≥50	≥14; 12–13; ≤12	<20; 20–24; 25–29 or none; ≥30	0; 1; ≥2	Not included	Age of relative at diagnosis, diet score, alcohol use, BMI, HT, physical activity	1.04[121]	0.59 (vitamin);[121] 0.60 (diet)[121]
Italian-2† 20-year risk	<50; ≥50	14; 12–13; ≤12	<20; 20–24; 25–29 or none; ≥30	0; 1; ≥2	Bx: 0; 1; ≥2	Occupational and leisure physical activity, education, alcohol use, BMI	Not reported	0.62 (0.56 to 0.69) (age <50 years);[131] 0.57 (0.52 to 0.61) (age ≥50 y)[131]
Chlebowski 5-year risk	50–59; 60–69; 70–79	≥14; 12–13; ≤12	<20; 20–24; 25–29 or none; ≥30	0; ≥1	Bx: 0; 1; ≥2	BMI, menopause age, HT use and duration, race, alcohol use, parity, breastfeeding, smoking status, physical activity	Not reported	0.61 (0.59 to 0.63);[123] 0.62 (0.60 to 0.64) (ER+);[123] 0.53 (0.47 to 0.58) (ER-)[123]
Chlebowski-simplified 5-year risk	<50; ≥50	Not included	Not included	0; ≥1	Bx: 0; 1; ≥2	Not included	Not reported	0.58 (0.56 to 0.60) (ER+)[123]

* 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

Model	Data collection and calculation	Relatives with breast and ovarian cancer	Other factors	Reference standard	Performance characteristics for predicting risk for BRCA mutations
Ontario Family History Assessment Tool (FHAT)[142,144-146]	Clinical scoring tool; referral threshold of 10 is equivalent to a 2-fold relative risk for breast or ovarian cancer	1st-, 2nd-, 3rd-degree	Age at diagnosis; bilateral breast cancer; breast and ovarian cancer in same person; male breast cancer; colon and prostate cancer	BRCAPRO; Claus	Sensitivity 91%–94%; specificity 15%–51%; PPV 31%; c statistic 0.68–0.83
Manchester Scoring System[56,139,141,144-146]	Clinical scoring tool; referral if ≥2 positive responses	1st-, 2nd-, 3rd-degree	Type of cancer (breast, ovarian, pancreatic, or prostate), affected family members, and age at diagnosis	BRCAPRO; Myriad II; BOADICEA; FHAT	Sensitivity 58%–93%; specificity 33%–71%; c statistic 0.75–0.80
Referral Screening Tool (RST)[140]	Clinical scoring tool; referral if ≥2 positive responses	1st-, 2nd-degree	Breast cancer at age ≤50 (self or relatives); ovarian cancer at any age (self or relatives); ≥2 breast cancer cases at age >50 on same side of family; male breast cancer; Jewish ancestry	BRCAPRO; Myriad II; BOADICEA; FHAT	Sensitivity 81%; specificity 92%; PPV 0.80; NPV 0.92; c statistic 0.87
Pedigree Assessment Tool (PAT)[143]	Clinical scoring tool; score ≥8 was optimal threshold	1st-, 2nd-, 3rd-degree	Breast cancer at age ≤50 or >50; ovarian cancer at any age; male breast cancer; Ashkenazi Jewish ancestry	Myriad II	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)
FHS-7[138]	Clinical scoring tool; one positive response was threshold	1st-degree with breast or ovarian cancer	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	Claus; Gail; Tyrer-Cuzick; Penn II	Sensitivity 88%; specificity 56%; PPV 0.63; NPV 1.00; c statistic 0.96

Abbreviations: BOADICEA = Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; NPV = negative predictive value; PPV = positive predictive value.

Table 5. Studies of Genetic Counseling

Author, year	N	Provider of genetic counseling	Setting	Measures	Quality rating	Breast cancer worry		Anxiety		Depression		Risk perception		Intent to participate in testing	
						Increase	Decrease	Increase	Decrease	Increase	Decrease	More Accurate	Less Accurate	Increase	Decrease
Current report															
Bennett et al, 2008[150]	128	Genetic counselor	Cancer Genetics Service Center	DUKE-SSQ, HADS, IES, MCMQ,NSI	NA	0	X	0	0	0	0	NR	NR	NR	NR
Bennett et al, 2009[149]	128	Genetic counselor	Cancer Genetics Service Center	DUKE-SSQ, IES, MCMQ	NA	0	X	0	0	0	0	NR	NR	NR	NR
Bloom, 2006[151]	163	Master's level counselor	Telephone counseling	NSI	Poor	0	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bowen et al, 2006[152]	221	Psychologist, genetic counselor	University	NSI, BSI	Fair	0	0	NR	NR	NR	NR	0	0	NR	NR
Brain et al, 2011[153]	263	Clinician	NR	CWS-R	NA	0	X*	NR	NR	NR	NR	X†	0	0	X†
Braithwaite et al, 2005[154]	72	Clinical nurse specialist	NR	NSI, STAI, HADS	Fair	0	X	NR	NR	NR	NR	NR	NR	NR	NR
Fry et al, 2003[155]	263	Genetics consultant & specialist breast surgeon vs. geneticist & genetics nurse specialist	Familial Breast Cancer Clinic	CWS	Fair	0	X‡	0	X§	NR	NR	X‖	0	NR	NR
Gurmankin et al, 2005[156]	125	Health care provider	University breast and ovarian cancer risk evaluation program	STAI, NSI	NA	0	X	NR	NR	NR	NR	X	0	NR	NR
Helmes et al, 2006[157]	340¶	Board certified genetic counselor	NR	NSI	Fair	NR	NR	NR	NR	NR	NR	X‡	0	NR	NR

Table 5. Studies of Genetic Counseling

Author, year	N	Provider of genetic counseling	Setting	Measures	Quality rating	Breast cancer worry		Anxiety		Depression		Risk perception		Intent to participate in testing	
						Increase	Decrease	Increase	Decrease	Increase	Decrease	More Accurate	Less Accurate	Increase	Decrease
Hopwood et al, 2004[158]	256	Genetic counselor	Cancer genetic service centers	NSI, GHQ, CWS	NA	0	X**	NR	NR	NR	NR	X**	0	0	X**
Kelly et al, 2008[159]	78	Genetic counselor	NR	NSI	NA	0	X	0	0	NR	NR	0	0	NR	NR
Matloff et al, 2006[160]	64¶	Certified genetic counselor	NR	NSI	Fair	NR	NR	NR	NR	NR	NR	0	X‡	NR	NR
Mikkelsen et al, 2007[161]	1971	Physicians	Clinical department	IES	Fair	NR	NR	NR	NR	NR	NR	X††	0	NR	NR
Mikkelsen et al, 2009[162]	1971	Physicians	Clinical department	HADS	Fair	NR	NR	NR	NR	NR	NR	0‡‡	0	NR	NR
Pieterse et al, 2011[163]	77¶	Clinical geneticists, residents in clinical genetics, genetic counselors	Department of medical genetics	VAS, NSI, PPC, STAI, IES	NA	0	X	0	0	0	0	NR	NR	NR	NR
Roshanai et al, 2009[164]	163	Specialist nurse	Cancer genetics clinic	SPIKES, HADS	Fair	NR	NR	0	X	NR	NR	X	0	NR	NR
Prior Report															
Bowen et al, 2002[57]	354	Genetic counselor or trained health counselor	NR	NSI	Fair	NR	NR	NR	NR	NR	NR	NR	NR	0	X
Bowen et al, 2004[62]	354	Genetic counselor or trained health counselor	NR	NSI	Fair	NR	NR	NR	NR	NR	NR	NR	NR	0	X
Brain et al, 2002[166]	740¶	Clinical geneticist and genetic nurse specialist	NR	STAI, NSI	Good	0	0	0	X	0	0	X	0	NR	NR

Table 5. Studies of Genetic Counseling

Author, year	N	Provider of genetic counseling	Setting	Measures	Quality rating	Breast cancer worry		Anxiety		Depression		Risk perception		Intent to participate in testing	
						Increase	Decrease	Increase	Decrease	Increase	Decrease	More Accurate	Less Accurate	Increase	Decrease
Burke et al, 2000[58]	356	Genetic counselor	Medical office	NSI	Fair	X	X	0	X	NR	NR	X	0	NR	NR
Cull et al, 1998[59,‖‖]	144[¶]	Geneticist and breast surgeon	Breast cancer family clinic	NSI, STAI, GHQ	Good	0	0	NR	NR	NR	NR	X	0	NR	X
Hopwood et al, 1998[167]	174	Family history clinics	Family history clinics	NSI, GHQ, PAS	Fair	NR	NR	0	0	0	0	X¶¶	X***	NR	NR
Lerman et al, 1996[168]	227	Genetic counselor	Cancer centers	IES	Fair	0	0	0	0	NR	NR	X	0	NR	NR
Lerman et al, 1999[60]	364	Oncology nurses or genetic counselor	Hospital cancer center	IES	Fair	0	0	NR	NR	NR	NR	X	0	NR	NR
Lobb et al, 2004[169]	193	Clinical geneticists, oncologist, genetic counselors	NR	NSI, IES, HADS	Good	0	0	NR	NR	NR	NR	NR	NR	X†††	0
Watson et al, 1998[171]	115	Clinical geneticist	Hospitals	GHQ-12, CWS, VAS	Good	NR	NR	0	0	0	0	0	0	NR	NR
Watson et al, 1999[170]	283	Clinical geneticists	Genetic counseling centers	NSI, GHQ, IES, STAI	Good	0	0	0	0	0	0	X‡‡‡	0	NR	NR

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 6. Types of Genetic Counseling Provided in Included Studies

Author, year	Setting	Provider of genetic counseling	Components of genetic counseling
Current report			
Armstrong et al, 2005[148]	Not reported	Not reported	Genetic counseling not specified.
Bennett et al, 2008[150]	Cancer Genetics Service Center	Genetic counselor	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.
Bennett et al, 2009[149]	Cancer Genetics Service Center	Genetic counselor	See Bennett 2008.
Bloom et al, 2006[151]	Telephone counseling	Master's level counselor	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.
Bowen et al, 2006[152]	University	Psychologist, genetic counselor	**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.
Brain et al, 2011[153]	Not reported	Clinician	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).
Braithwaite et al, 2005[154]	Not reported	Clinical nurse specialist	**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.

Table 6. Types of Genetic Counseling Provided in Included Studies

Author, year	Setting	Provider of genetic counseling	Components of genetic counseling
Fry et al, 2003[155]	Familial Breast Cancer Clinic	Genetics consultant and specialist breast surgeon; geneticist and genetics nurse specialist	**Standard (regional) service:** 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. **Novel (community-based) service:** 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.
Gurmankin et al, 2005[156]	University breast and ovarian cancer risk evaluation program	Health care provider	**Precounseling interview:** 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. **Postcounseling interview:** Assessed patient's breast cancer risk, BRCA mutation risk, recall of actual risk information, and worry about breast cancer.
Helmes et al, 2006[157]	Not reported	Board certified genetic counselor	**In-person counseling:** 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. **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.
Hopwood et al, 2004[158]	Cancer genetic service centers	Genetic counselor	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.
Kelly et al, 2008[159]	Not reported	Genetic counselor	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.
Matloff et al, 2006[160]	Not reported	Certified genetic counselor	Personalized letter summarizing patient data.
Mikkelsen et al, 2007[161]	University clinical departments	Physicians	Information on incidence of sporadic breast cancer, genetics, inheritance patterns, and estimated personal lifetime risk of inherited cancer.
Mikkelsen et al, 2009[162]	University clinical departments	Physicians	Information on incidence of sporadic breast cancer, genetics, inheritance patterns, and estimated personal lifetime risk of inherited cancer.

Table 6. Types of Genetic Counseling Provided in Included Studies

Author, year	Setting	Provider of genetic counseling	Components of genetic counseling
Pieterse et al, 2011[163]	Department of medical genetics	Clinical geneticists, residents in clinical genetics, genetic counselors	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.
Roshanai et al, 2009[164]	University cancer genetic clinic	Specialist nurse	Included pedigree explanation, Buckman's Breaking Bad News model to inform at-risk relatives, pamphlet, videotape, copies of pedigree, and medical records.
Prior report			
Bowen et al, 2002[57]	Not reported	Genetic counselor or trained health counselor	**Individual genetic counseling**: 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. **Group psychosocial counseling:** 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.
Bowen et al, 2004[62]	Not reported	Genetic counselor or trained health counselor	**Individual genetic counseling**: 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. **Group psychosocial counseling:** 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.
Brain et al, 2002[166]	Not reported	Clinical geneticist and genetic nurse specialist	Breast cancer surveillance, option to enter UK Tamoxifen Prevention Trial, annual surgical followup with surveillance and advice, genetic risk assessment and counseling.
Burke et al, 2000[58]	Unclear	Genetic counselor	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.
Cull et al, 1998[59]	Breast cancer family clinic	Geneticist and breast surgeon	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.
Hopwood et al, 1998[167]	Family history clinics	Unclear	Family history consultation, not otherwise described.
Lerman et al, 1996[168]	Comprehen-sive cancer centers	Genetic counselor	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.

Table 6. Types of Genetic Counseling Provided in Included Studies

Author, year	Setting	Provider of genetic counseling	Components of genetic counseling
Lerman et al, 1999[60]	Hospital and cancer center	Oncology nurses or genetic counselor	**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 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. **Education plus counseling:** 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.
Lobb et al, 2004[169]	Not reported	Clinical geneticists, oncologist, genetic counselors	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.
Watson et al, 1998[171]	Hospitals	Clinical geneticist	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.
Watson et al, 1999[172]	Genetic counseling centers	Clinical geneticists	Not described.

Table 7. Standardized Measures Used to Assess Distress

Measure	Abbreviation	Description
Beck Depression Inventory[334]	BDI	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.
Beck Hopelessness Scale[351]	BHS	A 20-item scale to quantify hopelessness, with scores ranging from 0 to 20 and a score above 9 indicating suicidal ideations.
Body Image after Breast Cancer[333]	BIBC	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.
Body Image Scale[341]	BIS	A 10-item questionnaire for assessing body image changes in patients with cancer.
Brief Symptom Inventory[339]	BSI	A 53-item self-reported psychological symptom scale.
Center for Epidemiologic Studies-Depression[348]	CES-D	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.
Coping Orientation to Problems Experienced Scale[338]	COPE	Covers 14 coping strategies as potential responses to stressors.
Decision Regret Scale[337]	DRS	A 5-item questionnaire to measure dissatisfaction or misgiving after making a medical decision.
DUKE Social Support Questionnaire[345]	DUKE-SSQ	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.
Emotional Approach Coping Scale[350]	None	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.
EuroQoL-5 Dimensions[343]	EQ-5D	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.
General Health Questionnaire[342]	GHQ	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.
Health-Related Quality of Life[330]	HR-QOL	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).
Hospital Anxiety and Depression Scale[335]	HADS	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).
Impact of Events Scale[356]	IES	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).
Lerman Breast Cancer Worry Scale[336]	CWS or LCWS	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.
Medical Coping Modes Questionnaire[349]	MCMQ	A 19-item self-report questionnaire to quantify coping styles into 1 of 4 categories: confrontive, avoidant, resigned, nondominant.

Table 7. Standardized Measures Used to Assess Distress

Measure	Abbreviation	Description
Medical Outcomes Study 36-Item Short Form[344] Swedish Short Term-36 Health Survey[353]	SF-36 or MOS SF-36	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.
Menopause-Specific Quality of Life Questionnaire[346]	MENQOL	A 29-item self-administered questionnaire to assess health-related quality of life postmenopause.
Multidimensional Fatigue Symptom Inventory-Short Form[352]	MFSI-SF	A 30-item questionnaire to measures perceived sleep disturbance.
Pittsburgh Sleep Quality Index[340]	PSQI	A measure of subjective sleep disturbance in clinical populations.
Post-Traumatic Growth Inventory[332]	PTGI	An instrument for assessing positive outcomes reported by persons who have experienced traumatic events.
Sexual Activity Questionnaire[354]	SAQ	A 3-section self-reported questionnaire to assess sexual functioning, including hormonal status, reasons for sexual inactivity, sexual functioning.
State-Trait Anxiety Inventory[331]	STAI	Measures an individual's current anxiety feelings. Scores range from 10 to 40. Scores above 22 indicate high anxiety.
Symptom Checklist-90[347]	SCL-90	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.
Visual Analogue Scale[355]	VAS	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).

Table 8. Prevalence of *BRCA1* and *BRCA2* Mutations in High-Risk Populations

Author, year	Population	Gene	Inclusion criteria	Early-onset	Population-based	High-risk	Ashkenazi Jewish
Breast cancer							
Anglian BCSG, 2000[13]	U.K.	*BRCA1/2*	Population-based series of breast cancer from registry		X		NR
Newman et al, 1998[223]	Caucasian North Carolina	*BRCA1*	Women diagnosed as having first invasive breast cancer between 20 and 74 years		X		NR
Newman et al, 1998[223]	African American North Carolina	*BRCA1*	Women diagnosed as having first invasive breast cancer between 20 and 74 years		X		NR
Anton-Culver et al, 2000[204]	Caucasian Orange County, CA	*BRCA1*	Population-based sample of breast cancer cases		X		No
Anton-Culver et al, 2000[204]	Hispanic Orange County, CA	*BRCA1*	Population-based sample of breast cancer cases		X		No
Newman et al, 1998[223]	African American and Caucasian North Carolina	*BRCA1*	Women diagnosed as having first invasive breast cancer between 20 and 74 years; age 20-39 years	X			NR
Anton-Culver et al, 2000[204]	Total Orange County, CA	*BRCA1*	Population-based series of breast cancer cases; age <40 years	X			Yes/no
Anton-Culver et al, 2000[204]	Total Orange County, CA	*BRCA1*	Population-based series of breast cancer cases; age <40 years	X			Yes/no
Anglian BCSG, 2000[13]	U.K.	*BRCA1/2*	Population-based series of breast cancer from registry; age 35-44 years	X			NR
Anglian BCSG, 2000[13]	U.K.	*BRCA1/2*	Population-based series of breast cancer from registry; age <35 years	X			NR
FitzGerald et al, 1996[208]	Boston, MA	*BRCA1*	Breast cancer diagnosed <30 years	X			No
Peto et al, 1999[16]	U.K.	*BRCA1/2*	1) Women diagnosed with breast cancer <36 years 2) Women diagnosed with breast cancer 36-45 years	X			NR
Malone et al, 2000[220] Same population as Langston et al, 1996[217]	Washington	*BRCA1/2*	1) Women diagnosed with breast cancer <35 years 2) Women diagnosed with breast cancer <45 years with first-degree family history of breast cancer	X			NR
Eccles et al, 1998[207]	U.K.	*BRCA1*	1) Women diagnosed with breast cancer <40 years	X			NR
						X	NR
			2) Women with bilateral breast cancer diagnosed after 39 years 3) Women with a strong family history of breast/ovarian cancer			X	NR
Couch et al, 1997[46]	U.S.	*BRCA1*	1) Women with breast cancer who had a “familial risk factor” for breast cancer			X	No

Table 8. Prevalence of *BRCA1* and *BRCA2* Mutations in High-Risk Populations

Author, year	Population	Gene	Inclusion criteria	Early-onset	Population-based	High-risk	Ashkenazi Jewish
Tommasi et al, 2005[200]	Italy	*BRCA1*	Consecutive series of breast cancer patients plus a positive family history			X	NR
Ovarian cancer							
Janezic et al, 1999[216]	Orange County, CA	*BRCA1*	Population-based series of consecutive ovarian cancer cases		X		No
Stratton et al, 1997[228]	U.K.	*BRCA1*	Women diagnosed with ovarian cancer before age 70 years		X		NR
Anton-Culver et al, 2000[204]	Caucasian Orange County, CA	*BRCA1*	Population-based sample of ovarian cancer cases		X		No
Anton-Culver et al, 2000[204]	Hispanic Orange County, CA	*BRCA1*	Population-based sample of ovarian cancer cases		X		No
Risch et al, 2006[195] Same population as Risch, 2001[225]	Canada Hispanic	*BRCA1/2*	Population-based series of consecutive ovarian cancer		X		No
Risch et al, 2006[195] Same population as Risch, 2001[225]	Canada NonHispanic NonAshkenazi Jewish	*BRCA1/2*	Population-based series of consecutive ovarian cancer		X		No
Risch et al, 2006[195] Same population as Risch, 2001[225]	Total Canada	*BRCA1/2*	Population-based series of consecutive ovarian cancer, age <41 years	X			Yes/no
Gayther et al, 1999[212]	U.K. Familial Ovarian Cancer Registry	*BRCA1/2*	Families with ≥2 cases of ovarian cancer			X	No
Breast and ovarian cancer							
Beristain et al, 2007[174]	Spain	*BRCA1/2*	1) Early-onset breast cancer <40 years	X			NR
			2) Family history of breast and/or ovarian cancer			X	NR
Gayther et al, 1997[211]	UK	*BRCA2*	1) Families with multiple cases of breast cancer 2) Families with multiple cases of ovarian cancer			X	
Frank et al, 2002[47]	Myriad	*BRCA1/2*	Tested by Myriad for full gene			X	No
Weitzel et al, 2005[319]	Hispanic	*BRCA1/2*	Families presenting to the high-risk clinic for testing who were part of the Hereditary Cancer Registry. Had a calculated BRCA mutation probability >5% by any method.			X	No
Konecny et al, 2011[183]	Slovakia	*BRCA1/2*	Families presenting to high-risk clinic based on family history of breast and/or ovarian cancer			X	NR
Seymour et al, 2008[197]	Italy	*BRCA1/2*	Families presenting to high-risk clinic based on family history of breast and/or ovarian cancer			X	NR
Marroni et al, 2004[188]	Italy	*BRCA1/2*	High-risk families presenting for BRCA testing			X	NR
Nanda et al, 2005[193]	Asian	*BRCA1/2*	Families who presented for BRCA testing in high-risk clinics who had ≥2 cases of breast or ovarian			X	No

Table 8. Prevalence of *BRCA1* and *BRCA2* Mutations in High-Risk Populations

Author, year	Population	Gene	Inclusion criteria	Early-onset	Population-based	High-risk	Ashkenazi Jewish
			cancer among FDRs or SDRs				
Nanda et al, 2005[193]	Total NonAshkenazi Jewish	*BRCA1/2*	Families who presented for BRCA testing in high-risk clinics who had ≥2 cases of breast or ovarian cancer among FDRs or SDRs			X	No
Nanda et al, 2005[193]	Caucasian	*BRCA1/2*	Families who presented for BRCA testing in high-risk clinics who had ≥2 cases of breast or ovarian cancer among FDRs or SDRs			X	No
Nanda et al, 2005[193]	African American	*BRCA1/2*	Families who presented for BRCA testing in high-risk clinics who had ≥2 cases of breast or ovarian cancer among FDRs or SDRs			X	No
Nanda et al, 2005[193]	Hispanic	*BRCA1/2*	Families who presented for BRCA testing in high-risk clinics who had ≥2 cases of breast or ovarian cancer among FDRs or SDRs			X	No
Vaziri et al, 2001[202]	U.S.	*BRCA1/2*	Families in the Familial Cancer Registry who had ≥2 cases of breast or ovarian cancer among FDRs			X	NR
Neuhausen et al, 2009[194]	California, Ontario, Australia	*BRCA1/2*	Population-based case probands from cancer registries		X		No
Neuhausen et al, 2009[194]	Philadelphia, New York, Utah, California, Ontario Australia	*BRCA1/2*	Population-based case probands from cancer registries and high-risk families		X	X	No
Neuhausen et al, 2009[194]	Philadelphia, New York, Utah	*BRCA1/2*	Families who presented for BRCA testing in high-risk clinics with a family history of breast and/or ovarian cancer			X	No
Tamboom et al, 2010[199]	Estonia	*BRCA1/2*	Women diagnosed with breast cancer prior to age 45 years	X			NR
Tamboom et al, 2010[199]	Estonia	*BRCA1/2*	Families where the proband was diagnosed with breast or ovarian cancer and at least one relative was diagnosed with these cancers.			X	NR

Author, year	Women tested, *N*	*BRCA1* positive, *n*	*BRCA2* positive, *n*	*BRCA1* or *BRCA2* positive, *n*	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Breast cancer							
Anglian BCSG, 2000[13]	1220	8	16	24	0.6%	1.3%	2.0%
Newman et al, 1998[223]	120	3			2.5%		
Newman et al, 1998[223]	88	0			0.0%		
Anton-Culver et al, 2000[204]	562	9			1.6%		
Anton-Culver et al, 2000[204]	42	0			0.0%		
Newman et al, 1998[223]	43	0			0.0%		

Table 8. Prevalence of *BRCA1* and *BRCA2* Mutations in High-Risk Populations

Author, year	Women tested, *N*	*BRCA1* positive, *n*	*BRCA2* positive, *n*	*BRCA1* or *BRCA2* positive, *n*	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Anton-Culver et al, 2000[204]	41	2			4.8%		
Anton-Culver et al, 2000[204]	17	0			0.0%		
Anglian BCSG, 2000[13]	341	3	4	7	0.8%	1.2%	2.0%
Anglian BCSG, 2000[13]	57	2	4	6	3.5%	7.0%	11%
FitzGerald et al, 1996[208]	26	2			7.7%		
Peto et al, 1999[16]	254	9	6	15	3.5%	2.4%	5.9%
Peto et al, 1999[16]	363	7	8	15	1.9%	2.2%	4.1%
Malone et al, 2000[220]	203	12	7	19	5.9%	3.4%	9.3%
Same population as Langston et al, 1996[217]	235	16	11	27	7.1%	4.9%	12%
	155	10			6.5%		
Eccles et al, 1998[207]	45	0			0.0%		
Eccles et al, 1998[207]	30	8			27%		
Couch et al, 1997[46]	146	21			14%		
Tommasi et al, 2005[200]	100	7			7.0%		
Ovarian cancer							
Janezic et al, 1999[216]	104	2			1.9%		
Stratton et al, 1997[228]	374	13			3.5%		
Anton-Culver et al, 2000[204]	99	4			4.0%		
Anton-Culver et al, 2000[204]	12	0			0.0%		
Risch et al, 2006[195]	15	0	0	0	0.0%	0.0%	0.0%
Same population as Risch, 2001[225]	927	67	52	119	7.2%	5.6%	13%
	157	9	1	10	5.7%	0.6%	6.4%
Gayther et al, 1999[212]	112	40	8	48	36%	7.0%	43%
Breast and ovarian cancer							
Beristain et al, 2007[174]	72	0	0	0	0.0%	0.0%	0.0%
Beristain et al, 2007[174]	164	6	10	16	3.6%	6.1%	9.7%
Gayther et al, 1997[211]	290	64	25	89	22%	8.6%	31%
Frank et al, 2002[47]	6724			1055			16%
Weitzel et al, 2005[319]	110	25	9	34	23%	8.1%	31%
Konecny et al, 2011[183]	104		12			12%	
Konecny et al, 2011[183]	585	85			15%		
Seymour et al, 2008[197]	247			21			8.5%
Marroni et al, 2004[188]	560	80			14%		
Marroni et al, 2004[188]	464		53			11%	
Nanda et al, 2005[193]	2	0	0	0	0.0%	0.0%	0.0%
Nanda et al, 2005[193]	126	31	17	48	25%	13%	38%
Nanda et al, 2005[193]	78	24	12	36	31%	15%	46%
Nanda et al, 2005[193]	43	7	5	12	16%	12%	28%
Nanda et al, 2005[193]	3	0	0	0	0.0%	0.0%	0.0%
Vaziri et al, 2001[202]	104	18	2	20	17.30%	1.9%	19.2%
Neuhausen et al, 2009[194]	NR	NR	NR	NR	4.0%	3.7%	NR

Table 8. Prevalence of *BRCA1* and *BRCA2* Mutations in High-Risk Populations

Author, year	Women tested, *N*	*BRCA1* positive, *n*	*BRCA2* positive, *n*	*BRCA1* or *BRCA2* positive, *n*	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Neuhausen et al, 2009[194]	4084	NR	193	NR	NR	4.7%	NR
Neuhausen et al, 2009[194]	4531	233	NR	NR	5.2%	NR	NR
Neuhausen et al, 2009[194]	NR	NR	NR	NR	9.9%	8.6%	NR
Tamboom et al, 2010[199]	64	4	0	4	6.3%	0.0%	6.3%
Tamboom et al, 2010[199]	47	6	1	7	12.8%	2.1%	14.9%

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

Population	Gene	Cancer type	Prevalence, % (95% CI)	I^2 (p-value)	Studies, *n* (ref)
Early-onset breast or ovarian cancer					
≤35 years	*BRCA1*	B	4.63 (2.47 to 8.52)	NA	5[13, 16, 208, 218, 220]
≤40 years	*BRCA1*	B	4.26 (2.61 to 6.87)	NA	10[13, 16, 174, 195, 204, 207, 208, 218, 220, 223]
≤40 years	*BRCA1*	O	5.17 (2.39 to 9.59)	NR	2[13, 195]
≤45 years	*BRCA1*	B	3.25 (1.72 to 6.06)	NA	11[13, 16, 174, 195, 199, 204, 207, 208, 218, 220, 223]
≤35 years	*BRCA2*	B	3.31 (1.17 to 9.00)	NA	3[13, 16, 220]
≤40 years	*BRCA2*	B	2.90 (1.35 to6.14)	NA	5[13, 16, 174, 195, 220]
≤40 years	*BRCA2*	O	0.64 (0.02 to 3.50)	NR	1[195]
≤45 years	*BRCA2*	B	2.31 (1.11 to 4.77)	NA	6[13, 16, 174, 195, 220]
≤35 years	*BRCA1* & *BRCA2*	B	7.78 (3.99 to 14.63)	NA	5[13, 16, 174, 195, 220]
≤40 years	*BRCA1* & *BRCA2*	B	5.98 (1.87 to17.47)	NA	3[13, 16, 220]
≤40 years	*BRCA1* & *BRCA2*	O	6.37 (3.10 to 11.40)	NR	1[195]
≤45 years	*BRCA1* & *BRCA2*	B	4.63 (1.91 to 10.80	NA	5[13, 16, 195,199, 220]
Selected high-risk cohorts					
	BRCA1	B	1.84 (0.72 to 4.63)	91% (0.190)	4[13, 194, 204, 223]
	BRCA2	B	1.31 (0.67 to 1.95)	NA	1[13]
	BRCA1	O	4.41 (2.47 to 7.74)	70% (0.006)	4[194, 204, 216, 228]
	BRCA2	O	5.61 (4.13 to 7.09)	NA	1[195]
High-risk families					
	BRCA1	B	13.58 (10.09 to 17.07)	86% (<0.001)	11[46, 174, 183, 188, 193, 194, 199, 200, 202, 207, 211]
	BRCA1	O	35.71 (26.92 to 44.51)	NA	1[212]
	BRCA2	B	7.90 (5.30 to 10.50)	73% (0.117)	8[174, 183, 188, 193,194, 199, 202, 211]
	BRCA2	O	7.14 (2.13 to 12.15)	NA	1[212]
	BRCA1 & *BRCA2*	B	19.78 (12.98 to 26.57)	94% (<0.001)	6[47, 174, 193, 197, 199, 211]
	BRCA1 & *BRCA2*	O	42.86 (33.79 to 51.92)	NA	1[212]
Ashkenazi Jewish					
	BRCA1 & *BRCA2*	NA	2.08 (1.28 to 2.88)	89% (<0.001)	4[20, 191, 214, 209]
	BRCA1	NA	1.01 (0.64 to 1.37)	74% (0.004)	5[20, 191, 209, 214, 229]
	BRCA2	NA	1.02 (0.72 to 1.33)	60% (0.028)	5[20, 191, 209, 214, 224]

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

Author, year	Population	Women tested, *N*	*BRCA1* positive, *n*	*BRCA2* positive, *n*	*BRCA1* or *BRCA2* positive, *n*	*BRCA1* mutation frequency	*BRCA2* mutation frequency	*BRCA1* or *BRCA2* mutation frequency
Fodor et al, 1998[209]	Population based (U.S.)	1715	20	18	38	1.2%	1.0%	2.2%
Hartge et al, 1999[214] Struewing et al, 1997[19]	Population based (U.S.)	3742	48	41	89	1.3%	1.1%	2.4%
Metcalfe et al, 2010[191]	Population based (Canada)	2080	10	12	22	0.5%	0.6%	1.1%
Oddoux et al, 1996[224]	Population based (U.S.)	1255		12			0.9%	
Roa et al, 1996[20]	Population based (U.S.)	2717	35			1.3%		
Roa et al, 1996[20]	Population based (U.S.)	2687		37			1.4%	
Roa et al, 1996[20]	Population based (Israel)	403	3			0.7%		
Roa et al, 1996[20]	Population based (Israel)	398		10			2.5%	
Struewing et al, 1995[229]	Population based (U.S.)	327	3			0.9%		
Struewing et al, 1995[229]	Population based (Israel)	369	3			0.8%		

Table 11. Penetrance of BRCA-Related Cancer in BRCA-Positive Women: Single Individual Tested

Author, year	Population or risk group	N	Breast cancer risk			Ovarian cancer risk		
			BRCA1 % (95% CI	*BRCA2* % (95% CI)	*BRCA1* and *BRCA2* % (95% CI)	*BRCA1* % (95% CI)	*BRCA2* % (95% CI)	*BRCA1* and *BRCA2* % (95% CI)
Risk to age 50 years								
Anglian Breast Cancer Study Group, 2000[13]	Cancer registry (U.K.)	8	32 (2 to 62)			11 (1 to74)		
Anglian Breast Cancer Study Group, 2000[13]	Cancer registry (U.K.)	16		18 (2 to 32)			3 (0 to 19)	
Chen et al, 2006[122]	High-risk (U.S.)	283	28 (24 to 34)			13 (9.7 to 17)		
Chen et al, 2006[122]	High-risk (U.S.)	143		23 (19 to29)			4 (2.2 to 6.2)	
Hopper et al, 1999[215]	Cancer registry <40 years (Australia)	18			10 (0 to 24)			
Marroni et al, 2004[188]	High-risk (Italy)	80	27 (20 to 34)			14 (7 to 22)		
Marroni et al, 2004[188]	High-risk (Italy)	53		26 (18 to 34)			3 (0 to 7)	
Risk to age 70 years								
Anglian Breast Cancer Study Group, 2000[13]	Cancer registry (U.K.)	8	47 (7 to 82)			36 (4 to 99)		
Anglian Breast Cancer Study Group, 2000[13]	Cancer registry (U.K.)	16		56 (5 to 80)			10 (1 to 55)	
Antoniou et al, 2002[15]	Cancer registry (U.K.)	Unclear	35.3	50.3		25.9	9.1	
Chen et al, 2006[122]	High-risk (U.S.)	283	46 (39 to 54)			39 (30 to 50)		
Chen et al, 2006[122]	High-risk (U.S.)	143		45 (36 to 51)			22 (14 to 32)	
Hopper et al, 1999[215]	Cancer registry <40 years (Australia)	18			36 (15 to 65)			
Lubinski et al, 2012[187]	Known mutation carriers (26 centers in Canada, U.S., and Poland)— U.S. Results	614			76 (NR)			
Lubinski et al, 2012[187]	Known mutation carriers (26 centers in Canada, U.S., and Poland)— Polish Results	863			57 (NR)			
Marroni et al, 2004[188]	High-risk (Italy)	80	39 (27 to 52)			43 (21 to 66)		
Marroni et al, 2004[188]	High-risk (Italy)	53		44 (29 to 58)			15 (4 to 26)	
Metcalfe et al, 2010[190]	Known mutation carriers (6 countries) 0 FDRs	3011	56	38		39		
Metcalfe et al, 2010[190]	Known mutation carriers (6 countries) 1 FDR	3011	57	46		55		
Metcalfe et al, 2010[190]	Known mutation carriers (6 countries) ≥2 FDRs	3011	72	85		68		

Table 11. Penetrance of BRCA-Related Cancer in BRCA-Positive Women: Single Individual Tested

Author, year	Population or risk group	N	Breast cancer risk			Ovarian cancer risk		
			BRCA1 % (95% CI	*BRCA2* % (95% CI)	*BRCA1* and *BRCA2* % (95% CI)	*BRCA1* % (95% CI)	*BRCA2* % (95% CI)	*BRCA1* and *BRCA2* % (95% CI)
Risk to age 80 years								
Risch et al, 2001[225]	Ovarian cancer registry (Canada)	39	39.1			19.4		
Risch et al, 2001[225]	Ovarian cancer registry (Canada)	21		11.9			6.1	
Risch et al, 2006[195]	Ovarian cancer registry (Canada)	75	90 (77 to 97)			24 (15 to 38)		
Risch et al, 2006[195]	Ovarian cancer registry (Canada)	54		41 (26 to 60)			8.4 (3.9 to 17)	

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

Author, year	Population or risk group	*N*	Breast cancer risk			Ovarian cancer risk		
			BRCA1 % (95% CI)	*BRCA2* % (95% CI)	*BRCA1* and *BRCA2* % (95% CI)	*BRCA1* % (95% CI)	*BRCA2* % (95% CI)	*BRCA1* and *BRCA2* % (95% CI)
Risk to age 50 years								
Al-Mulla et al, 2009[172]	U.K. Exon 2	30	30					
Al-Mulla et al, 2009[172]	U.K. Exon 11	58	80					
Al-Mulla et al, 2009[172]	U.K. Other exons	28	85					
Al-Mulla et al, 2009[172]	U.K. Exon 13	20	92					
Antoniou et al, 2006[173]	French Canadian	25	20 (0 to 45)			1 (0 to 10)		
Antoniou et al, 2006[173]	French Canadian	27		21 (0 to 55)			0.4 (0 to 2)	
Evans et al, 2008[178]	U.K.	223	48 (SE, 0.023)			21 (SE, 0.02)		
Evans et al, 2008[178]	U.K.	162		42 (SE, 0.027)			4 (SE, 0.012)	
Ford et al, 1998[210]	High-risk (BCLC)	32		28 (9 to 44)			0.4 (0 to 1.1)	
Kramer et al, 2005[185]	U.S. Overall	23	0.44 (SE, 0.07)					
Kramer et al, 2005[185]	U.S. With ovaries	23	0.49 (SE, 0.09)					
Milne et al, 2008[192]	Spain	155	35 (15 to 47)			10 (0 to 25)		
Milne et al, 2008[192]	Spain	164		32 (17 to 44)			2 (0 to 9)	
Sutcliffe et al, 2000[230]	Ovarian cancer registry (U.K.) *BRCA 1/2* combined	319			700%			400%
van der Kolk et al, 2010[201]	Netherlands Positive index	111	51 (47 to 54)			21 (18 to 24)		
van der Kolk et al, 2010[201]	Netherlands Positive index	74		46 (41 to 51)			7 (4 to 9)	
Risk to age 70 years								
Antoniou et al, 2006[173]	French Canadian	25	72 (0 to 93)			38 (0 to 78)		
Antoniou et al, 2006[173]	French Canadian	27		75 (0 to 97)			49 (0 to 81)	
Brose et al, 2002[206]	U.S. Age-adjusted risk	147	73 (68 to 78)			41 (36 to 46)		
Evans et al, 2008[178]	U.K.	223	68 (SE, 0.033)			60 (SE, 0.037)		
Evans et al, 2008[178]	U.K.	162		75 (SE, 0.033)			30 (SE, 0.046)	
Ford et al, 1998[210]	High-risk (BCLC)	32		84 (43 to 95)			27 (0 to 47)	
Kramer et al, 2005[185]	U.S. Overall	23	0.76 (SE, 0.08)					
Kramer et al, 2005[185]	U.S. With ovaries	23	0.92 (SE, 0.08)					

Table 12. Penetrance of BRCA-Related Cancer in BRCA-Positive Women: Multiple Individuals Tested

Author, year	Population or risk group	*N*	Breast cancer risk			Ovarian cancer risk		
			BRCA1 **% (95% CI)**	***BRCA2*** **% (95% CI)**	***BRCA1*** **and** ***BRCA2*** **% (95% CI)**	***BRCA1*** **% (95% CI)**	***BRCA2*** **% (95% CI)**	***BRCA1*** **and** ***BRCA2*** **% (95% CI)**
Milne et al, 2008[192]	Spain	155	52 (26 to 69)			22 (0 to 40)		
Milne et al, 2008[192]	Spain	164		47 (29 to 60)			18 (0 to 35)	
Sutcliffe et al, 2000[230]	Ovarian cancer registry (U.K.) *BRCA 1/2* combined	319			11%			12%
van der Kolk et al, 2010[201]	Netherlands Negative index	111	60 (54 to 65)			52 (45 to 58)		
van der Kolk et al, 2010[201]	Netherlands Positive index	111	71 (67 to 76)			59 (53 to 64)		
van der Kolk et al, 2010[201]	Netherlands Negative index	74		78 (69 to 88)			13 (7 to19)	
van der Kolk et al, 2010[201]	Netherlands Positive index	74		87 (82 to 93)			34 (25 to 44)	

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 Penetrance in BRCA-Positive Women in High-Risk Populations

Outcome	Risk age, *y*	Multiple individuals tested			Single individual tested			All studies combined		
		Penetrance, % (95% CI)	I^2 (p-value)	Studies, *n* (ref)	Penetrance, % (95% CI)	I^2 (p-value)	Studies, *n* (ref)	Penetrance, % (95% CI)	I^2 (p-value)	Studies, *n* (ref)
BRCA1										
Breast cancer	50	47 (40 to 53)	60% (0.032)	6[172,173,178,185,192,201]	28 (24 to 32)	0% (0.94)	3[13,122,188]			NA
	70	70 (61 to 79)	83% (<0.001)	6[173,178,185,192,201,206]	46 (40 to 52)	0% (0.60)	5[13,15,122,188,191]			NA
Ovarian cancer	50	14 (3.8 to 23)	94% (<0.001)	4[173,178,192,201]	13 (10 to 16)	0% (0.99)	3[13,122,188]	14 (7 to 20)	89% (<0.001)	7[13,122,173,178,188,192,201]
	70	46 (35 to 57)	85% (<0.001)	5[173,178,192,201,206]	41 (32 to 49)	0% (0.81)	5[13,15,122,188,191]	45 (37 to 52)	65% (0.001)	10[13,15,122,173,178,188,191,192,201,206]
BRCA2										
Breast cancer	50	40 (33 to 46)	57% (0.056)	5[173,178,192,201,210]	23 (19 to 27)	0% (0.63)	3[13,122,188]			NA
	70	71 (59 to 83)	69% (0.012)	5[173,178,192,201,210]	50 (40 to 60)	33% (0.17)	5[13,15,122,188,191]			NA
Ovarian cancer	50	3 (1 to 4)	88% (<0.001)	5[173,178,192,201,210]	4 (2 to 5)	0% (0.88)	3[13,122,188]	3 (1 to 4)	84% (<0.001)	8[13,122,173,178,188,192,201,210]
	70	23 (12 to 34)	67% (0.016)	5[173,178,192,201,210]	17 (11 to 24)	0% (0.52)	4[13,15,122,188]	19 (13 to 25)	45% (0.068)	9[13,15,122,173,178,188,192,201,210]

Abbreviations: CI = confidence interval; NA = not applicable.

Table 14. Penetrance of BRCA-Related Cancer in Women With Uninformative Negative Results

Author, year	Population or risk group	Ascertainment	N	Risk to age, *y*	Breast cancer			Ovarian cancer		
					Cases observed, *n*	Cases expected, *n*	Relative risk (95% CI)	Cases observed, *n*	Cases expected, *n*	Relative risk (95% CI)
Kauff et al, 2005[182]	FDRs in high-risk families who test negative for BRCA	Families with breast cancer but no ovarian cancer	165 families 321 FDRs	85	8	2.46	3.25 (1.4 to 6.4)	1	0.26	3.88 (0.05 to 21.6)
Kauff et al, 2005[182]	SDRs in high-risk families who test negative for BRCA	Families with breast cancer but no ovarian cancer	165 families 262 SDRs	85	4	2.18	1.83 (0.49 to 4.69)	0	0.26	0 (NA to 14.3)
Kauff et al, 2005[182]	Probands in high-risk families who test negative for BRCA	Families with breast cancer but no ovarian cancer	165 families 165 probands	85	7	1.43	4.9 (1.96 to 10.11)	0	0.14	0 (NA to 25.6)
Metcalfe et al, 2009[189]	FDRs in high-risk families who test negative for BRCA	FDRs of breast cancer cases	365 families 1492 women	75	65	16.49	3.94 (3.09 to 5.02)	2	2.34	0.85 (0.23 to 3.12)
Sutcliffe et al, 2000[230]	FDRs and SDRs in high-risk families who test negative for BRCA	Families with ≥2 FDRs with ovarian cancer	56 families 382 relatives	85				4	0.35	11.6 (3.12 to 29.7)
Sutcliffe et al, 2000[230]	FDRs and SDRs in high-risk families who test negative for BRCA	Families with ≥2 FDRs with ovarian cancer	57 families 435 relatives	85	9	2.71	3.32 (1.52 to 6.31)			

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

Author, year	Population or risk group	N	Breast cancer			Ovarian cancer			Genotype	Prospective	Oophorectomy adjustment	Invasive only
			Cases observed, *n*	Cases expected, *n*	Relative risk (95% CI)	Cases observed, *n*	Cases expected, *n*	Relative risk (95% CI)				
Bernholtz, 2012[175]	True negatives Total	307	20	23.8	0.84 (0.51 to 1.30)				Known	Yes	Unknown	Unknown
Domchek, 2010[177]	True negatives FDRs or SDRs	378	2	3.8	0.52 (0.13 to 2.09)	0	0.4	NR	Known	Yes	No	Yes
Domchek, 2010[177]	True negatives FDRs or SDRs	378	2	0.9	2.3 (0.57 to 9.19)				Known	Yes	No	No
Gronwald, 2007[180]	True negatives FDRs	131	2.5	1.2	2 (not given)				54% known; remainder probabilistically assigned	No	No	Unknown
Harvey, 2011[181]	True negatives Total	722	6		1.14 (0.51 to 2.53)				Known	Yes	Yes	Yes
Harvey, 2011[181]	True negatives FDRs and SDRs	442			1.29 (0.58 to 2.88)				Known	Yes	Yes	Yes
Harvey, 2011[181]	True negatives*	424			0.48 (0.12 to 1.93)				Known	Yes	Yes	Yes
Korde, 2011[184]	True negatives FDRs	102			0.66 (0.13 to 1.94)				Known or inferred	Yes	Yes	No
Korde, 2011[184]	True negatives FDRs	102			1.33 (0.49 to 2.91)				Known or inferred	Yes	Yes	No
Korde, 2011[184]	True negatives SDRs	182			0.97 (0.35 to 2.11)				Known or inferred	Yes	Yes	No
Korde, 2011[184]	True negatives TDRs	111			0.69 (0.01 to 3.83)				Known or inferred	Yes	Yes	No
Korde, 2011[184]	True negatives Total	395	10	12	0.75 (0.34 to 1.41)				Known or inferred	Yes	Yes	No
Korde, 2011[184]	True negatives Total	395	10	12	0.82 (0.39 to 1.51)				Known or inferred	Yes	Yes	No
Korde, 2011[184]	True negatives Total	395	10		0.95 (0.45 to 1.74)				Known or inferred	Yes	Yes	No
Kramer, 2005[185]	True negatives Total	353	5		0.65 (0.21 to1.52)				Known or inferred	Yes	Yes	Unknown
Kurian, 2011[186]	True negatives FDRs	NR			0.39 (0.04 to 3.81)				Untested were probabilistically assigned	Unknown	Unknown	No
Rowan, 2007[196]	True negatives FDRs or SDRs	101	3	1	2.9 (1.0 to 8.6)	0	1.7	NR	Known	Yes	Unknown	Yes
Smith, 2007[198]	True negatives Total	258	28	5.3	5.3 (3.5 to 7.7)	4	0.9	4.6 (1.2 to 11.7)	Known	No	No	No
Smith, 2007[198]	True negatives FDRs	184	18	3.6	5 (2.9 to 7.8)				Known	No	No	No

Table 15. Penetrance of BRCA-Related Cancer in Women With True Negative Results

Author, year	Population or risk group	N	Breast cancer			Ovarian cancer			Genotype	Prospective	Oophorectomy adjustment	Invasive only
			Cases observed, *n*	Cases expected, *n*	Relative risk (95% CI)	Cases observed, *n*	Cases expected, *n*	Relative risk (95% CI)				
Smith, 2007[198]	True negatives FDRs	166	13	3.2	4 (2.1 to 6.9)				Known	No	No	No
Smith, 2007[198]	True negatives FDRs	153	3	1.4	2.1 (0.4 to 6.2)				Known	Yes	No	No
van der Kolk, 2010[201]	True negatives FDRs	128	5	2.5	2 (0.7 to 4.7)	0	0.3	0 (0 to 12)	Known	Yes	Yes	No
van der Kolk, 2010[201]	True negatives FDRs	74	4	1.6	2.5 (0.7 to 6.3)	0	0.2	0 (0 to 20.4)	Known	Yes	Yes	No

*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 16. Studies of Distress After Genetic Testing

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

Table 16. Studies of Distress After Genetic Testing

Author, year, quality rating	N, study design	Mutation status	Genetic counseling	Comparison	Measures of distress	Breast cancer worry	Anxiety	Depression
van Dijk et al, 2006[248] 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[250] 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 17. Studies of Test Characteristics of Mammography vs. MRI for Breast Cancer Screening*

Author, year	Risk categories, *n*	Inclusion criteria	Mean age at entry, y (range)	Screening interval	Followup, mo	Mammography vs. MRI		
							Sensitivity, %	Specificity, %
Cortesi et al, 2006[273]	Mutation carrier: 48 High: 674 Intermediate: 257 Slight increase: 346	BRCA carrier Positive FH Male breast cancer Suspected positive FH	42 (20-75) 42 (15-75) 43 (19-67) 40 (18-75)	Varied by risk category and age	Median, 55	Mutation carrier†	50 vs. 100	NR
Leach et al, 2005[274] MARIBS study	*BRCA1*: 39 *BRCA2*: 86 High: 424	*BRCA1* carrier/relative *BRCA2* carrier/relative FH positive/other mutation/syndrome	Median, 40 (31-55)	Annual	Variable, ≥2 scans per woman	*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
Le-Petross et al, 2011[276]	*BRCA1*: 37 *BRCA2*: 36	*BRCA1* carrier/relative *BRCA2* carrier/relative	Median 44 (23-75)	Bi-annual, alternating	Median, 24	*BRCA1/2*	Unable to report§ vs. 92	82 vs. 87
Rijnsburger et al, 2010[278] Dutch MRISC study	*BRCA1*: 422 *BRCA2*: 172 High: 1069 Moderate: 489 Other: 5	*BRCA1* carrier *BRCA2* carrier 30%-50% lifetime risk for BC‖ (high-risk) 15%-30% lifetime risk for BC‖ (moderate-risk) Other mutation carrier	*BRCA1*: 39 *BRCA2*: 40 High risk: 41 Moderate risk: 40	Annual	48	*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

*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 18. Results of Trials of Risk-Reducing Medications: Cancer and Mortality Benefits[115,116]

	Raloxifene vs. tamoxifen		Tamoxifen vs. placebo			Raloxifene vs. placebo		
Outcome	Risk ratio (95% CI)	Events reduced/ increased, *n* (95% CI)*	Risk ratio (95% CI) (Trials, *n*)†	Placebo rate (SE)‡	Events reduced/ increased, *n* (95% CI)*	Risk ratio (95% CI) (Trials, *n*)†	Placebo rate (SE)‡	Events reduced/ increased, *n* (95% CI)*
Invasive breast cancer	1.24 (1.05 to 1.47)§	5 (1 to 9) fewer tamoxifen	0.70 (0.59 to 0.82) (4)	4.70 (1.02)	7 (4 to 12) fewer tamoxifen	0.44 (0.27 to 0.71) (2)	3.19 (0.59)	9 (4 to 4) fewer raloxifene
ER+ invasive breast cancer	0.93 (0.72 to 1.24)‖		0.58 (0.42 to 0.79) (4)	3.67 (0.78)	8 (3 to 13) fewer tamoxifen	0.33 (0.18 to 0.61) (2)	2.45 (0.42)	8 (4 to 12) fewer raloxifene
ER- invasive breast cancer	1.15 (0.75 to 1.77)‖		1.19 (0.92 to 1.55) (4)			1.25 (0.67 to 2.31) (2)		
Noninvasive breast cancer	1.22 (0.95 to 1.59)§		0.85 (0.54 to 1.35)¶ (4)			1.47 (0.75 to 2.91) (2)		
All-cause mortality	0.84 (0.70 to 1.02)§		1.07 (0.90 to 1.27) (4)			0.84 (0.64 to 1.10)** (2)		

*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

Author, year, quality rating	Inclusion criteria	Risk factors Enrolled, *n*	Mean age at surgery, y	Breast cancer incidence Risk estimate (95% CI)	Ovarian cancer incidence Risk estimate (95% CI)	Mortality Risk estimate (95% CI)	Mean followup,* y
Mastectomy							
Surgery vs. no surgery							
Domchek et al, 2010[292] Fair	*BRCA 1/2* carrier No history of salpingo-oophorectomy	*BRCA1* positive n=415†	37	0/43 vs. 19/372 HR NA	NR	NR	2.7
		BRCA2 positive n=245‡	39	0/32 vs. 15/213 HR NA	NR	NR	2.5
Skytte et al, 2011[294] Good	*BRCA1/2* carrier No history of mastectomy or salpingo-oophorectomy	*BRCA1* positive n=201 *BRCA2* positive n=10	NR	3/96 vs. 16/211 HR, 0.39 (0.12 to 1.36)	NR	NR	NR§
Surgery group (observed vs. expected)‖							
Evans et al, 2009[293]¶ NA	Lifetime risk of breast cancer >25%	High-risk *BRCA1/2* positive** n=202	NR	0/307 vs. 21.3 HR NA	NR	NR	7.5
Salpingo-oophorectomy or oophorectomy							
Surgery vs. no surgery							
Domchek et al, 2010[292]¶ Fair	*BRCA1/2* carrier No history of salpingo-oophorectomy	*BRCA1* positive n=1003†	42	14% (32/236) vs. 20% (129/633) HR, 0.63 (0.41 to 0.96)	2% (6/342) vs. 7% (49/661) HR, 0.31 (0.12 to 0.82)	All cause: 2% (8/327) vs. 7% (43/608) HR, 0.52 (0.24 to 1.14)	5.6
		BRCA2 positive n=554‡	46	7% (7/100) vs. 23% (94/401) HR, 0.36 (0.16 to 0.82)	0/123 vs. 14/431 HR NA	All cause: 0/120 vs. 17/403 HR NA	5.8
Kramer et al, 2005[185]†† Fair	*BRCA1*-positive family‡‡; no history of bilateral mastectomy	*BRCA1* positive n=98	NR	18% (6/33) vs. 42% (27/65) HR, 0.38 (0.15 to 0.97)	NR	NR	16.5
		BRCA1 negative n=353	NR	3% (1/34) vs. 1% (4/319) HR NR	NR	NR	16.5
		Undetermined mutation status n=222	NR	0% (0/18) vs. 2.5% (5/204) HR NA	NR	NR	16.5
Surgery group (observed vs. expected)§§							
Olson et al, 2004[296]†† NA	Women with bilateral oophorectomy	High-risk‖ ‖ Surgery <60 years n=55	<60	3/55 vs. 5.4 RR, 0.56 (0.11 to 1.33)	NR	NR	NA
		Surgery <50 years n=41	<50	1/41 vs. 3.9 RR, 0.26 (0.001 to 0.99)	NR	NR	NA
		Moderate risk¶¶ Surgery <60 years n=193	<60	9/193 vs. 10.9 RR, 0.83 (0.38 to 1.44)	NR	NR	NA
		Surgery <50 years n=130	<50	5/130 vs. 7.7 RR, 0.65 (0.21 to 1.32)	NR	NR	NA

Table 19. Studies of Risk-Reducing Surgery

Author, year, quality rating	Inclusion criteria	Risk factors Enrolled, *n*	Mean age at surgery, y	Breast cancer incidence Risk estimate (95% CI)	Ovarian cancer incidence Risk estimate (95% CI)	Mortality Risk estimate (95% CI)	Mean followup,* y
Prior report							
Mastectomy							
Hartmann et al, 1999[290] Hartmann et al, 2001[291] NA	Family history of breast cancer	High risk n=214	42	3/214 vs. 37 expected***; risk reduction, 92% (77% to 98%)	n=2	Breast cancer: 2/214 vs.10 expected***; risk reduction, 81% (31% to 98%)	14 (median)
		Moderate risk n=425		4/425 vs. 37 expected‡‡; risk reduction, 89.5% (p<0.001)	n=0	Breast cancer: 0/425 vs. 10 expected‡‡; risk reduction, 100% (70% to 100%)	
		BRCA1 or *BRCA2* positive††† n=18	41	0/18 vs. 6.1/18 expected‡‡‡; risk reduction, 100% (51% to 100%) 0/18 vs. 4.5/18 expected§§§; risk reduction, 100% (33% to 100%)	NR	NR	13.4 (median)
Oophorectomy (surgery vs. no surgery)							
Struewing et al,1995[229] Poor	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 postoophorectomy 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

Author, year	N (*BRCA1/2*) # of cancer cases	Age at entry, y	Screening interval Followup, y	False-positive rate	False-negative, n	Recall rates	Unneeded* additional exams or imaging Unneeded* biopsy
Kriege et al, 2004[277] Kriege et al, 2006[297] Dutch MRISC study	1909 (14/4) 39 *BRCA1* 45 *BRCA2*	Mean, 40	Annual, same-day Mean, 2.7	n=39 cancers First imaging round (prior mammography): 5.5% vs. 14%; p<0.001 Subsequent imaging rounds: 4.6% vs. 8.2%; p<0.001	n=39 cancers First imaging round (prior mammography): 12 vs. 1 Subsequent imaging rounds: 12 vs. 4	NR	n=45 cancers Exams†: 207 vs. 420 Biopsy: 28% (7/25‡) vs. 43% (24/56‡)
Leach et al, 2005[274] MARIBS study	649 (13/6) 33	Median, 40	Annual, same-day Variable followup, ≥2 scans	NR	NR	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	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
Le-Petross et al, 2011[276]	73 (51/49) 13	Median, 44	Biannual, alternating mammography with MRI Median, 2	15% (11/73) vs. 11% (8/73)	NR	NR	Imaging: 73% (8/11) vs. 50% (4/8) Biopsy: 27% (3/11) vs. 25% (2/8) Imaging plus biopsy: 0% vs. 25% (2/8)

*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

Author, year, quality rating	N, study design	Mutation status	Comparison	Measures of distress	Anxiety	Depression	Sexual activity	Body image	General QOL
Rijnsburger et al, 2004[275] Fair	288; prospective cohort and pre-post	35 *BRCA1/2* mutation positive	A) CBE (n=287) B) CBE + mammography (n=134) C) CBE + MRI (n=109)	SF-36, EQ-5D, VAS, SCL-90	0	NR	NR	NR	0
Spiegel et al, 2011[298] NA	55; pre-post	*BRCA1:* 30/55 (54.5%) *BRCA2:* 25/55 (45.5%)	A) Recall examinations (n=18) B) No recall examinations (n=37)	HADS, WIS	X increase A vs. B*	0	NR	NR	0

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[115,116]

	Raloxifene vs. tamoxifen		Tamoxifen vs. placebo			Raloxifene vs. placebo		
Outcome	Risk ratio (95% CI)	Events reduced/ increased, *n* (95% CI)*	Risk ratio (95% CI) (Trials, *n*)†	Placebo rate (SE)‡	Events reduced/ increased, *n* (95% CI)*	Risk ratio (95% CI) (Trials, *n*)†	Placebo rate (SE)‡	Events reduced/ increased, *n* (95% CI)*
Thromboembolic events§	0.75 (0.60 to 0.93)‖	4 (1 to 7) more tamoxifen	1.93 (1.41 to 2.64) (4)	0.91 (0.19)	4 (2 to 9) more tamoxifen	1.60 (1.15 to 2.23) (2)	2.34 (0.25)	7 (2 to 15) more raloxifene
Deep vein thrombosis	0.72 (0.54 to 0.95)‖	3 (1 to 5) more tamoxifen	1.45 (0.89 to 2.37) (2)			1.91 (0.87 to 4.23) (2)		
Pulmonary embolus	0.80 (0.57 to 1.11)‖		2.69 (1.12 to 6.47) (2)	0.19 (0.07)	2 (0.1 to 6) more tamoxifen	2.19 (0.97 to 4.97) (2)		
Coronary heart disease events	1.10 (0.85 to 1.43)¶		1.00 (0.79 to 1.27) (4)			0.95 (0.84 to 1.06) (2)		
Stroke	0.96 (0.64 to1.43)¶		1.36 (0.89 to 2.08) (4)			0.96 (0.67 to 1.38) (2)		
Endometrial cancer	0.55 (0.36 to 0.83)‖	5 (2 to 9) more tamoxifen	2.13 (1.36 to 3.32) (3)	0.75 (0.15)	4 (1 to 10) more tamoxifen	1.11 (0.65 to 1.89)** (3)		
Cataracts	0.80 (0.72 to 0.95)‖	15 (8 to 22) more tamoxifen	1.25 (0.93 to 1.67)†† (3)			0.93 (0.84 to 1.04) (2)		

*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

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

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

Studies, *n*	Design	Limitations	Consistency	Applicability	Overall quality	Findings
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? **Key Question 3a. What are the potential adverse effects of risk assessment?**						
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	General risk models that predict risk for breast cancer, such as the Gail, are modest predictors for individuals (c-statistic, 0.55 to 0.65). Familial risk models (FHAT, Manchester, RST, PAT, and FHS-7) predict risk for BRCA mutations, are intended to guide referrals to genetic counseling, and have high accuracy (c-statistic, >0.80).
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	Counseling decreased cancer worry, anxiety, and depression; increased the accuracy of risk perception; and decreased intention for mutation testing.
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	Prevalence is 0.2%-0.3% in general populations: 3% women with breast cancer, 6% women with breast cancer onset age ≤40, 10% women with ovarian cancer, and 20% high-risk families; for Ashkenazi Jewish women, 2% in unselected populations and 10% high-risk families. Positive test results indicate risks for breast cancer to age 70 of 46%-70% for *BRCA1* and 50%-71% for *BRCA2*; for ovarian cancer, 41%-46% for *BRCA1* and 17%-23% for *BRCA2*; in Ashkenazi Jewish women, 34% for breast cancer and 21% for ovarian cancer. Uninformative negative test results are associated with increased risk for breast cancer (SIR, 3.81 [95% CI, 3.06 to 4.75]), while true negative results are not (SIR, 1.13 [95% CI, 0.81 to 1.58]); estimates for ovarian cancer were highly heterogeneous.
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	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.

Table 24. Summary of Evidence

Studies, *n*	Design	Limitations	Consistency	Applicability	Overall quality	Findings
Key Question 4. Do interventions reduce the incidence of BRCA-related cancer and mortality in women with increased risk?						
Intensive screening: no effectiveness studies	NA	NA	NA	NA	NA	NA
Risk-reducing medications: systematic review; 6 placebo-controlled trials (4 tamoxifen, 2 raloxifene) and 1 head-to-head trial (STAR)	RCT	No results for BRCA mutation carriers; trials are heterogeneous and data are lacking on doses, duration, and timing of use.	Consistent	Moderate	Good	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.
Risk-reducing surgery: 4 studies of mastectomy and 3 of oophorectomy or salpingo-oophorectomy	Cohort	Comparison groups varied.	Consistent	High	Fair	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%.
Key Question 5. What are the potential adverse effects of interventions to reduce risk for BRCA-related cancer?						
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	Cohort	No RCTs; screening intervals and false-positive calculations varied between studies; some studies lacked within-cohort comparison groups.	Consistent	High	Poor	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.
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	RCT	No results for BRCA mutation carriers; trials are heterogeneous and data on long-term effects are incomplete.	Consistent	High	Good	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.
Risk-reducing surgery: 5 studies of complications, physical effects, or distress	Case-series; before-after studies	Lack of studies; small numbers of participants; no comparison groups.	NA	Low	Poor	Some women experienced physical complications of surgery, had postsurgical symptoms, or changes in body image. Some women had improved anxiety.

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[50]

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 ≤45 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[50]

- 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

Term or Phrase	Definition
BRCA-related cancer	Predominantly breast, ovarian, fallopian tube, and peritoneal
Genetic counseling	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
True negative test	Known confirmed deleterious genetic mutation in relatives, and none detected in the patient
Uninformative negative test	No known deleterious genetic mutations in relatives, and none detected in the patient
Variant of uncertain significance	An abnormality of the *BRCA1* or *BRCA2* gene, but it is not known whether it is associated with an increased risk for cancer
Analytic validity*	Technical test performance measured by analytic sensitivity and specificity, reliability, and assay robustness
Clinical validity*	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
Clinical utility*	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

*Defined by the Centers for Disease Control and Prevention Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group for tests of risk assessment/susceptibility (*Genet Med.* 2009;11:3-14).

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:
---

1 exp Genetic Counseling/ or Genetic counseling.mp. or genetic counselling.mp. (9041)
2 decision making.mp. or exp Decision Making/ (101487)
3 exp RISK/ (521470)
4 risk$.mp. (946578)
5 exp Breast Neoplasms/ or breast neoplasm$.mp. or Breast cancer$.mp. or exp ovarian neoplasms/ or ovarian cancer$.mp. or ovarian neoplasm$.mp. (159780)
6 1 and (2 or 3 or 4) and 5 (845)

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)

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)

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:
---

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)

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

	Include	Exclude
Population	Asymptomatic adult (age 18 years or older) women with a family history of breast and/or ovarian cancer	Men, children, women with prior history of breast and/or ovarian cancer, no family history of breast and/or ovarian cancer
Interventions	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)	Surveillance, referral practices, testing for polymorphisms
Outcomes	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	Increased detection, predictors of adherence, uptake of screening or risk-reducing interventions
Study types and designs	Randomized, controlled trials; prospective and retrospective cohort studies; case-control studies; cross-sectional studies (for harms); systematic reviews; and meta-analyses	Case reports

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

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]

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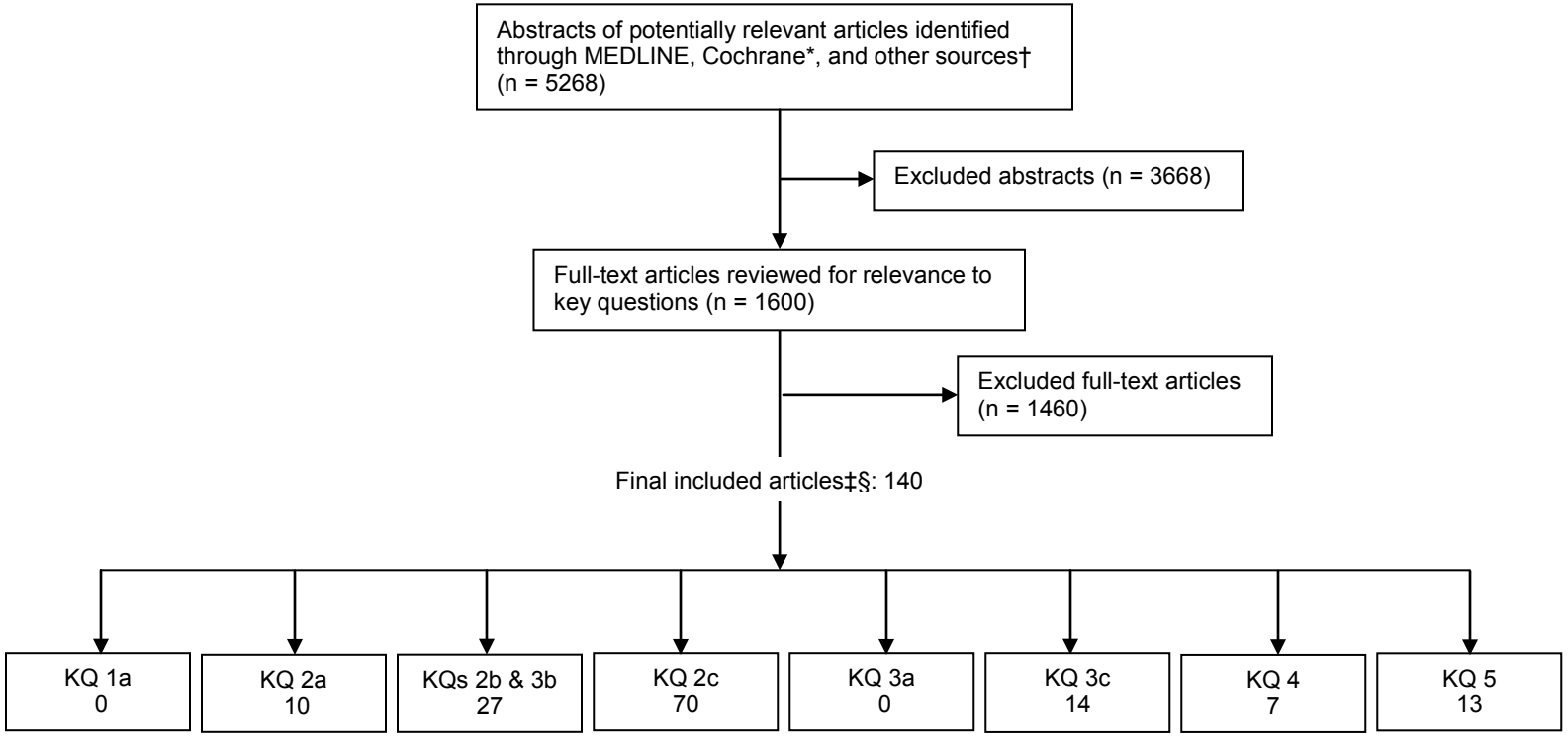
Appendix B5. Literature Flow Diagram



*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

2	Background
3	Wrong population
4	Wrong intervention
5	Wrong publication type
6	Conducted prior to 2004
7	Foreign language study, otherwise included
8	Wrong outcome

Myriad Genetic Laboratories, Inc. http://www.myriadtests.com/index.php. Accessed 25 Oct, 2011
Exclusion code: 2

Ad Hoc Committee on Genetic Counseling of the American Society of Human Genetics. *Am J Hum Genet.* 1975;27:240-242, [PMID: 1124768]
Exclusion code: 2

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Exclusion code: 2

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Exclusion code: 2

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Exclusion code: 2

Appendix C1. Quality Ratings for Randomized, Controlled Trials

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Maintain Comparable Groups?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination
Bloom et al, 2006[151]	Unclear	NR	NR	NR	No	NR	NR	No	Yes
Bowen et al, 2002[57]	Yes	NR	Yes	Yes	Yes	No	No	No	Yes
Bowen et al, 2004[62]	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
Bowen et al, 2006[152]	NR	NR	Yes	Yes	Yes	No	No	No	Yes
Brain et al, 2002[166]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes
Braithwaite et al, 2005[154]	NR	NR	Yes	Yes	Yes	NR	Yes	No	Yes
Burke et al, 2000[58]	Yes	NR	Yes	Yes	Yes	No	No	No	Yes
Cull et al, 1998[59]	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
Cuzick et al, 2007[288] IBIS-I Trial See also Cuzick, 2002[328]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Fisher et al, 2005[284] NSABP P-1 Trial See also Fisher et al, 1998[71]	Yes	Yes	Yes	No	Yes	Unclear	Yes: intervention No: followup	Yes: intervention No: followup	Yes; after unblinding, 32% crossover from placebo to medication
Fry et al, 2003[155]	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
Grady et al, 2008[73] RUTH Trial See also Barrett-Connor et al, 2006[299]	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Helmes et al, 2006[157]	NR	NR	Yes	Yes	Yes	NR	No	No	Yes
Lerman et al, 1996[168]	Yes	NR	Yes	Yes	Yes	Yes	No	No	Yes
Lerman et al, 1999[60]	Yes	NR	Yes	No	Yes	Yes	No	No	Yes
Lippman et al, 2006[288] MORE/CORE Trials See also Cummings et al, 1999[74]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Matloff et al, 2006[160]	No	No	Yes	Yes	Yes	NR	No	No	Yes
Powles et al, 2007[285] Royal Marsden Trial See also Powles et al, 1998[70]	NR	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes; after median of 70 months, 58% still on treatment
Roshanai et al, 2009[164]	Unclear	Yes	Yes	Yes	Yes	NR	Yes	No	Yes

Appendix C1. Quality Ratings for Randomized, Controlled Trials

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Maintain Comparable Groups?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination
Veronesi et al, 2007[287] Italian Randomized Tamoxifen Prevention Trial See also Veronosi et al, 1998[72]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes; 61% completed treatment period
Vogel et al, 2010[289] See also Vogel et al, 2006[329]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes: intervention No: followup	Yes: intervention No: followup	Yes
Watson et al, 1998[170]	Yes	YEs	Yes	Yes	Yes	No	No	No	Yes

Author, Year	Loss to followup differential/high	Intention-to-treat analysis	Post-randomization exclusions	Outcomes Prespecified	Funding source	External validity	Quality rating
Bloom et al, 2006[151]	No	Yes	No	Yes	Grant 4EB-5800, California Breast Cancer Research Program	Population-based from San Francisco area	Poor
Bowen et al, 2002[57]	No	No	No	Yes	National Cancer Institute and National Human Genome Institute (HG01190)	Women in general public with breast cancer	Fair
Bowen et al, 2004[62]	NR	No	No	Yes	National Human Genome Institute, National Cancer Institute, and National Office for Research on Women's Health (HG/CA01190)	Women in Seattle area with lower risk of breast cancer	Fair
Bowen et al, 2006[152]	No	Yes	No	Yes	National Human Genome Research Institute (HG01190)	Ashkenazi Jewish women from large metropolitian area	Fair
Brain et al, 2002[166]	No	Yes	No	Yes	Medical Research Council, National Assembly for Wales, NHS R&D (Wales), and Imperial Cancer Research Fund (Dr. Gray is supported by Tenovus, a cancer charity)	Cancer clinics, Wales	Good
Braithwaite et al, 2005[154]	No	No	No	Yes	CUK (Cancer Research U.K.) (CI345/A169)	Greater London area	Fair

Appendix C1. Quality Ratings for Randomized, Controlled Trials

Author, Year	Loss to followup differential/high	Intention-to-treat analysis	Post-randomization exclusions	Outcomes Prespecified	Funding source	External validity	Quality rating
Burke et al, 2000[58]	No	NR	No	Yes	The National Institutes of Health (HGO1190)	Women in Seattle area with intermediate family history of breast cancer	Fair
Cull et al, 1998[59]	No/Yes	NR	No	Yes	NHS R&D (Cancer) Programme and Imperial Cancer Research Fund	Women from 4 Scottish cancer family clinics	Good
Cuzick et al, 2007[288] IBIS-I Trial See also Cuzick, 2002[328]	Unclear	Yes	No	Yes	CUK; National Health and Medical Research Council Australia	Women at increased risk for breast cancer; general population and clinic recruitment; United Kingdom, Europe, Australia, New Zealand	Fair
Fisher et al, 2005[284] NSABP P-1 Trial See also Fisher et al, 1998[71]	No/Unclear	Yes	No	Yes	National Cancer Institute; U.S. Department of Health and Human Services	Women at increased risk for breast cancer; clinical centers; United States and Canada	Fair
Fry et al, 2003[155]	No/Yes	No	No	Yes	Chief Scientists's Office and Cancer Research U.K.	General population recruitment	Fair
Grady et al, 2008[73] RUTH Trial See also Barrett-Connor et al, 2006[299]	No	Yes	No	Yes	Eli Lilly and Company	Postmenopausal women with history of heart disease or at increased risk of coronary events; multinational sites, including United States	Good
Helmes et al, 2006[157]	No	Yes	No	Yes	National Human Genome Research Institute	Large network of PCPs	Fair
Lerman et al, 1996[168]	No	NR	No	Yes	Public Health Service grants ROICA57767 and K07CAOI604 from the National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services	Georgetown University Medical Center and Washington Hospital Center	Fair
Lerman et al, 1999[60]	No/Yes	NR	No	Yes	National Institutes of Mental Health and National Human Genome Research Institute (MH/HG54435)	Cancer treatment centers	Fair
Lippman et al, 2006[288] MORE/CORE Trials See also Cummings et al, 1999[74]	Unclear	Yes	No	Yes	Costs of publication of this article defrayed in part by payment of page charges; funding source NR	Postmenopausal women with osteoporosis; clinical centers; multinational, including United States	Good

Appendix C1. Quality Ratings for Randomized, Controlled Trials

Author, Year	Loss to followup differential/high	Intention-to-treat analysis	Post-randomization exclusions	Outcomes Prespecified	Funding source	External validity	Quality rating
Matloff et al, 2006[160]	No	No	No	Yes	Susan G. Komen Foundation	General population recruitment	Fair
Powles et al, 2007[285] Royal Marsden Trial See also Powles et al, 1998[70]	Unclear	Yes	No	Yes	National Health Service; CUK	Breast cancer clinics in United Kingdom	Fair
Roshanai et al, 2009[164]	No	No	No	Yes	Swedish Cancer Society	Cancer genetic clinics	Fair
Veronesi et al, 2007[287] Italian Randomized Tamoxifen Prevention Trial See also Veronosi et al, 1998[72]	No	Yes	No	Yes	Italian National Research Council; Italian Foundation for Cancer Research; American-Italian Cancer Foundation; Italian League Against Cancer	Hysterectomized women; general population and clinic recruitment; Italy	Fair
Vogel et al, 2010[289] See also Vogel et al, 2006[329]	No	Yes	No	Yes	National Cancer Institute; U.S. Department of Health and Human Services	Postmenopausal women with increased risk of breast cancer; multiple clinical centers; United States and Canada	Good
Watson et al, 1998[170]	No	Yes	No	Yes	Cancer Research Campaign (Project CP1026)	Women with a family history of breast cancer attending two London genetic clinics	Good

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

Author, Year	Attempt to enroll a random sample or consecutive patients meeting inclusion criteria	Groups comparable at baseline	Used accurate methods for ascertaining exposures, potential confounders, and outcomes	Outcome assessors and/or data analysts blinded to treatment	Report attrition	Appropriate statistical analyses on potential confounders	Important differential or overall high loss to followup	Outcomes prespecified, defined, and ascertained using accurate methods	Quality rating
Domchek et al, 2010[292]	Yes	Not reported	Yes	No	No	Yes	Not reported	Yes	Fair
Foster et al, 2007[238]	Unclear	Not reported	Yes	No	Yes	Yes	No	Yes	Fair
Geirdal et al, 2005[240]	Yes	Yes	Yes	No	Yes	Unclear	No	Yes	Good
Geirdal and Dahl, 2008[239]	Yes	No	Yes	No	Yes	Yes	No	Yes	Good
Hopwood et al, 1998[167]	Unclear	Yes	Yes	No	Yes	Yes	No	Yes	Fair
Julian-Reynier et al, 2011[242]	Unclear	Yes	Yes	No	Yes	Yes	No	Yes	Good
Kinney et al, 2005[243]	No	Not reported	Yes	No	No	Yes	Not reported	Yes	Poor
Kramer et al, 2005[185]	Yes	Not reported	Yes	No	No	Yes	Not reported	Yes	Fair
Lobb et al, 2004[169]	Unclear	Yes	Yes	No	Yes	Yes	No	Yes	Good
Low et al, 2008[244]	Unclear	No	Yes	No	Yes	Yes	Yes	Yes	Fair
Meiser et al, 2002[250]	Unclear	Yes	Yes	No	Yes	Yes	No	Yes	Good
Mikkelsen et al, 2007[161]	Yes	No	Yes	No	Yes	Yes	No	Yes	Fair
Mikkelsen et al, 2009[162]	Yes	No	Yes	No	Yes	Yes	No	Yes	Fair
Reichelt et al, 2004[245]	Yes	Not reported	Yes	No	Yes	Yes	No	Yes	Good
Rijnsburger et al, 2004[275]	No	No	Yes	Unclear: not reported	Yes	Yes	No	Yes	Fair
Skytte et al, 2011[294]	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Good
Struewing et al, 1995[229]	Yes	Not reported	Not reported	No	No	No	Not reported	Yes	Poor
van Dijk et al, 2006[248]	Yes	Not reported	Yes	No	Yes	Yes	No	Yes	Good
Watson et al, 1999[170]	Unclear	Yes	Yes	No	Yes	Yes	No	Yes	Good

Appendix C3. Quality Ratings for Case-Control Studies

Author, year	Did study attempt to enroll all or random sample of cases using predefined criteria?	Were controls derived from the same population as the cases?	Were groups comparable at baseline on key prognostic factors?	Were enrollment rates similar in cases and controls invited to participate?	Did study use accurate methods for identifying outcomes?	Did study use accurate methods for ascertaining exposures and potential confounders?	Did study perform appropriate statistical analyses on potential confounders?	Quality
Armstrong et al, 2005[148]	Yes	No	No	No	Yes	Yes	Yes	Good
Dagan and Shochat, 2009[237] Shochat and Dagan, 2010[248]	Yes	Unclear	Matched	No	Yes	Yes	Yes	Fair

Appendix C4. Quality Rating for Systematic Review

Author, year	Search dates	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	Quality rating
Smerecnik et al, 2009[165]	2000 to 2007	Yes	Yes	Yes	Yes	No	Not reported	No	Not reported	Yes	Fair

Appendix C5. Familial Risk Assessment Models

Ontario Family History Assessment Tool (FHAT)[142]

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

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

Manchester Scoring System[141]

Risk Factor (age of onset for relative in direct lineage)	*BRCA1* Score	*BRCA2* Score
Female breast cancer		
<30	6	5
30-39	4	4
40-49	3	3
50-59	2	2
≥60	1	1
Male breast cancer		
<60	5*	8†
≥60	5*	5†
Ovarian cancer		
<60	8	5
≥60	5	5
Pancreatic cancer	0	1
Prostate cancer		
<60	0	2
≥60	0	1
Total individual genes	**10**	**10**
Total for combined=15		

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)[143]

History of breast or ovarian cancer in the family? If yes, complete checklist.		
Risk Factor	**Breast cancer age ≤50**	**Ovarian cancer at any age**
Yourself		
Mother		
Sister		
Daughter		
Mother's side		
Grandmother		
Aunt		
Father's side		
Grandmother		
Aunt		
≥2 cases of breast cancer after age 50 on the same side of the family		
Male breast cancer at any age in any relative		
Jewish ancestry		

Referral if ≥2 checks in table.

Pedigree Assessment Tool (PAT)[144]

Risk Factor	**Score for every family member with breast or ovarian cancer diagnosis, including 2nd/3rd degree**
Breast cancer at age ≥50	3
Breast cancer at age <50	4
Ovarian cancer at any age	5
Male breast cancer at any age	8
Ashkenazi Jewish heritage	4
Total	

Score ≥8 is the optimal referral threshold.

FHS-7[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.

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Subcategory	Purpose	Study type	N	Country	Population/setting
Current report						
Armstrong et al, 2005[148] Good	Cancer worry Attitudes	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	Case-control	Eligible: NR Enrolled: NR Randomized: NR Analyzed: 408 (217 cases, 191 controls)	U.S.	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
Bennett et al, 2008[150] NA	Psychological	To examine the relationship between measures of anxiety and depression and a number of variables identified to be associated with distress	Before and after	Eligible: 367 Enrolled: 319 Analyzed: 128	U.K.	Women referred for genetic risk assessment to a large Cancer Genetics Service for Wales (CGSW) center
Bennett et al, 2009[149] NA	Cancer worry Psychological	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	Before and after	Eligible: 221 Enrolled: 221 Analyzed: 128	U.K.	Women referred for genetic risk assessment to a large Cancer Genetics Service for Wales (CGSW) center
Bloom et al, 2006[151] Poor	Risk perception Cancer worry Health behaviors	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	RCT	Eligible: NR Enrolled: 163 Randomized: 163 (80 in intervention, 83 in control) Analyzed: 149 (71 in intervention, 78 in control)	U.S.	Sisters of women diagnosed with breast cancer at age ≤50; predominantly Euro-American and well educated; substantial majority receive regular breast cancer screening
Bowen et al, 2006[152] Fair	Risk perception Cancer worry Interest in genetic testing	To test the efficacy of 2 counseling methods in Ashkenazi Jewish women with average or moderately increased risk of breast cancer	RCT	Eligible: 347 Enrolled: 221 Randomized: 221 (68 to psychosocial counseling, 77 to genetic counseling, 75 to control) Analyzed: 96% followup rate	U.S.	Ashkenazi Jewish women from the greater Seattle area; mean age of 47 years; 100% Ashkenazi Jewish

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Subcategory	Purpose	Study type	N	Country	Population/setting
Brain et al, 2011[153] NA	Cancer worry	To provide 6-year followup on women in TRACE study and the predictors of long-term cancer worry, perceived risk, and health behaviors	Before and after	Eligible: 545 Enrolled: 384 Analyzed: 263	U.K.	Women who took part in the TRACE study
Braithwaite et al, 2005[154] Fair	Risk perception	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	RCT	Eligible: 89 Enrolled: 72 Randomized: 72 (38 to GRACE, 34 to clinical nurse specialist) Analyzed: 58	U.K.	Women with a family history of breast cancer recruited through newspaper ads and posters
Fry et al, 2003[155] Fair	Perceived risk Cancer worry	To compare the psychological outcomes of 2 models of breast cancer genetics services	RCT	Eligible:574 Enrolled:373 Analyzed: 244	Scotland	Women referred by GP for breast cancer genetic risk counseling
Gurmankin et al, 2005[156] NA	Risk perception	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	Before and after	Eligible: NR Enrolled: 58 Analyzed: NR	U.S.	New patients at university cancer evaluation program; mean age of 46 years; most were white and had some college education or more
Helmes et al, 2006[157] Fair	Cancer worry Risk perception	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	RCT	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)	U.S.	Physicians network in Washington Mean age, 40.7 years
Hopwood et al, 2004[158] NA	Cancer worry Psychological factors	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	Before and after	Eligible: 271 Enrolled: 256 Analyzed: 234 (1 month), 202 (12 month), 192 (precounsel, 1 and 12 months)	U.K.	Cancer genetic services centers Age range, 49-52 years

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Subcategory	Purpose	Study type	N	Country	Population/setting
Kelly et al, 2008[159] NA	Risk perception	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	Before and after	Eligible: 78 Enrolled: 78 (40 to no personal history of breast cancer, 38 to personal history) Analyzed: NR	U.S.	Women were recruited from the community Mean age, 48.64 years
Matloff et al, 2006[160] Fair	Risk perception	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	RCT	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)	U.S.	Women recruited through advertisements in New Haven, CT
Mikkelsen et al, 2007[161] Fair	Risk perception	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	Prospective cohort	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)	Denmark	Danish women at risk of hereditary breast and ovarian cancer
Mikkelsen et al, 2009[162] Fair	Psychological factors Cancer worry Quality of life changes	To clarify the psychosocial impact of genetic counseling for hereditary breast and ovarian cancer	Prospective cohort	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,	Denmark 2007	Danish women at risk of hereditary breast and ovarian cancer

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Subcategory	Purpose	Study type	N	Country	Population/setting
				and 1070 in group 2)		
Pieterse et al, 2011[163] NA	Risk perception accuracy, correct knowledge, perceived personal control, generalized state anxiety, and cancer-related distress	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	Before and after	Eligible: 204 Enrolled: 77 Randomized: N/A Analyzed: 77	The Netherlands	Women seeking counseling for hereditary cancer at University Medical Center in the Netherlands, surveys exchanged through the mail
Roshanai et al, 2009[164] Fair	Risk perception Psychological factors	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	RCT	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)	Sweden	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)

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Subcategory	Purpose	Study type	N	Country	Population/setting
Prior report						
Bowen et al, 2002[57] Fair	Interest in genetic testing	To test the effects of breast cancer risk on interest in genetic testing in women who have a family history of breast cancer	RCT	Eligible: 561 Enrolled: 357 Randomized: 357 (120 to genetic counseling, 114 to psychosocial group, 123 to delayed counseling) Analyzed: 317 (105 to genetic counseling, 103 to psychosocial, 109 to delayed counseling)	U.S.	Women recruited from the Seattle area; see Bowen et al, 1999. All volunteered after seeing a notice, hearing about the study from a network, or through a relative with cancer
Bowen et al, 2004[62] Fair	Cancer worry Psychological factors Risk perception	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	RCT	Eligible: 561 Enrolled: 354 Randomized: 354 (118 genetic counseling arm, 114 psychosocial counseling arm, 122 delayed intervention arm) Analyzed: 348 (117 genetic counseling arm, 110 psychosocial counseling arm, 121 delayed intervention arm)	U.S.	Recruitment from among family members with breast cancer and through notices in local electronic and print outlets. Recruitment completed in 8 months. Women with a range of actual breast cancer risk levels were included
Brain et al, 2002[166] Good	Psychological factors	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	RCT	Eligible: 1,000 Enrolled: 740 Randomized: 735 (369 control, 366 trial) Analyzed: 653 (315 control, 338 trial)	Wales	Welsh women with family history of breast cancer referred to breast cancer clinic by doctor in 18-month trial period (1996 to 1997). Randomized to trial (n=366) or control group (n=369)
Burke et al, 2000[58] Fair	Cancer worry Risk perception	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	RCT	Eligible: 793 Enrolled: 356 Randomized: 243 (120 to genetic counseling, 123 to control group) Analyzed: 237 (116 to genetic counseling, 121 to control group)	U.S.	Sources for solicitation include women who live within 60 miles of Seattle: 2 studies at Fred Hutchinson Cancer Research Center, an oncologist's practice at University of Washington, mass media announcements

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Subcategory	Purpose	Study type	N	Country	Population/setting
Cull et al, 1998[59] Good	Psychological factors Risk perception	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	RCT	Eligible: 159 Enrolled: 144 Randomized: 128 (66 to video before group, 62 to video after) Analyzed: 95 (53 to video before group, 42 to video after group)	U.K.	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
Hopwood et al, 1998[167] Fair	Psychological factors	To understand psychological support needs for women at high genetic risk for breast cancer	Cohort	Eligible: 176 Enrolled: 174 Analyzed: 158	England	All were consecutive first-time attendees at the Family History Clinics (Manchester, U.K.)
Lerman et al, 1996[168] Fair	Cancer worry Risk perception	To study effect of individualized breast cancer risk counseling	RCT	Eligible: 438 Enrolled: 227 Randomized: 227 (group randomization NR) Analyzed: 200 (90 to risk counseling, 110 to control group)	U.S.	Subjects identified by relatives under treatment for breast cancer at either Fox Chase Cancer Center or Duke Comprehensive Cancer Center
Lerman et al, 1999[60] Fair	Cancer worry Interest in genetic testing	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	RCT	Eligible: 581 Enrolled: 364 Randomized: 364 (group randomization NR) Analyzed: 298 (157 to education only, 141 to education plus counseling)	U.S.	Subjects were recruited from 2 cancer centers (Georgetown University Medical Center or Washington Hospital Center)
Lobb et al, 2004[169] Good	Psychological factors	To examine the effect of different consultant communication styles on a variety of outcomes	Longitudinal	Eligible: NR for unaffected group Enrolled: NR for unaffected group Analyzed: 89	Australia	Women from high-risk breast cancer families attending their first consultation before genetic testing
Watson et al, 1998[171] Good	Cancer worry Psychological factors Risk perception	To look at recall of risk information after genetic counseling and to determine impact of receiving an audiotape of the genetic consultation on level of recall, cancer-related worry, and uptake of risk management methods	RCT	Eligible: 135 Enrolled: 115 Randomized: 115 (60 cases, 55 controls) Analyzed: 107 (56 cases, 51 controls)	U.K.	First-time attendees at the cancer family clinics of 2 London hospitals: Royal Marsden, Sutton and London, and St. George's Hospitals

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Subcategory	Purpose	Study type	N	Country	Population/setting
Watson et al, 1999[170] Good	Psychological factors	To investigate perception of genetic risk and the psychological effects of genetic counseling in women with a family history of breast cancer	Prospective cohort	Eligible: 303 Enrolled: 282 Analyzed: 282	England	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)

Author, year Quality	Demographics	Inclusion/exclusion criteria	Risk level definition
Current report			
Armstrong et al, 2005[148] Good	Cases vs. controls 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%	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	FDR or SDR with a breast or ovarian cancer diagnosis
Bennett et al, 2008[150] NA	Mean age, 43.3 years	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	23% low risk 45% moderate risk 31% high risk
Bennett et al, 2009[149] NA	Mean age, 44.3 years (SD, 10.81; range, 18-76)	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	30/128 (23.4%) at population risk 61/128 (47.7%) at moderate risk 37/128 (28.9%) at high risk
Bloom et al, 2006[151] Poor	Mean age, 47.4 years (SD, 7.2) 77% Euro-American 6.1% African American 9.2% Latina 8.0% Asian/Other	Inclusion: Not reported Exclusion: Prior breast cancer	All had ≥1 FDR (sister) with breast cancer diagnosis at age ≤50

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Demographics	Inclusion/exclusion criteria	Risk level definition
Bowen et al, 2006[152] 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[153] 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[154] 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[155] 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[156] 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

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Demographics	Inclusion/exclusion criteria	Risk level definition
Helmes et al, 2006[157] Fair	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)	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	14.7% had family history of breast cancer
Hopwood et al, 2004[158] NA	Average across all 5 cancer genetics services: Mean age, 41 years (range, 22-72) 94% Female 2% Ethnic minority	Inclusion: Women seen at a cancer genetics services center Exclusion: Women who had been diagnosed with cancer, age <18 years	NR
Kelly et al, 2008[159] NA	Mean age, 48.64 years (SD, 12.69) 100% Ashkenazi Jewish women	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	≥1 Ashkenazi Jewish grandparent
Matloff et al, 2006[160] Fair	Mean age, 49 years (range, 41-55) 21% Ashkenazi Jewish	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 >10% risk of carrying a mutation	≥1 FDR with breast cancer
Mikkelsen et al, 2007[161] Fair	Median age (years): Counseling: 39 (range, 18-72) Group 1: 56 (range, 28-76) Group 2: 45 (range, 18-75)	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	NR
Mikkelsen et al, 2009[162] Fair	Median age (years): Counseling: 39 (range, 18-72) Group 1: 56 (range, 28-76) Group 2: 45 (range, 18-75)	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	NR

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Demographics	Inclusion/exclusion criteria	Risk level definition
Pieterse et al, 2011[163] NA	Age ≥18 years	Inclusion: Patients sought counseling for hereditary cancer; were first among their 1st- and 2nd-degree relatives to request counseling; were first-time attendees; and age >18 years Exclusion: NR	Seeking counseling for hereditary cancer
Roshanai et al, 2009[164] 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 Exclusion: Suffered from any mental illness	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			
Bowen et al, 2002[57] Fair	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[62] 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

Author, year Quality	Demographics	Inclusion/exclusion criteria	Risk level definition
Brain et al, 2002[166] Good	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)	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	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
Burke et al, 2000[58] Fair	Genetic counseling arm: Average age, 43 years (SD, 12) 94% White Control group arm: Average age, 42 years (SD, 12) 93% White	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	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
Cull et al, 1998[59] Good	Mean age, 39 years (SD, 8)	NR	NR
Hopwood et al, 1998[167] Fair	Mean age, 36.19 years (range, 22.63-46.35)	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	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)

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Demographics	Inclusion/exclusion criteria	Risk level definition
Lerman et al, 1996[168] Fair	18% ages 35-40 years 41% ages 41-49 years 42% age ≥50 years 90% White 10% Black	Inclusion: Women age ≥35 years and a family history of breast cancer Exclusion: A personal history of cancer and younger than age 35 years	≥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
Lerman et al, 1999[60] Fair	24% Black 34% age <40 years 66% age ≥40 years 76% White 41% age <40 years 59% age ≥40 years	Inclusion: Caucasian and African American women with a family history of breast cancer or ovarian cancer Exclusion: Personal history of cancer (except basal cell or squamous cell skin cancer)	≥1 FDR affected with breast cancer and/or ovarian cancer
Lobb et al, 2004[169] Good	Mean age, 38.7 years (range, 19-60)	Inclusion: Women attending their first consultation before genetic testing with no prior testing for or carrier of *BRCA1* or *BRCA2* Exclusion: Unable to give informed consent, age <18 years, showed evidence of severe mental illness, and nonfluent in English	NR
Watson et al, 1998[171] Good	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	Inclusion: 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 Exclusion: NR	NR
Watson et al, 1999[170] Good	Median age, 37 years (range, 19-76)	Inclusion: 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 Exclusion: NR	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

Author, year Quality	Interventions	Measures	Duration of followup
Current report			
Armstrong et al, 2005[148] Good	A) Genetic counseling prior to testing, otherwise not described B) Controls		1999-2003 Not applicable

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Interventions	Measures	Duration of followup
Bennett et al, 2008[150] NA	CGSW referral guidelines and BRCAPRO risk calculation model	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	Year NR 1 week following risk notification
Bennett et al, 2009[149] NA	CGSW referral guidelines and BRCAPRO risk calculation model	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)	Year NR Approximately 5 to 7 weeks
Bloom et al, 2006[151] Poor	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 sreening	1999-2002 6 months
Bowen et al, 2006[152] Fair	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, *BRCA1/2* 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	Year NR 6 months
Brain et al, 2011[153] NA	A) Claus model B) Generalized risk level based on age, reproductive history, and minimal family history	Cancer Worry Scale-Revised (CWS-R, scale 6 to 24) Perceived risk (single item scale, 1 to 5)	Year NR 6 years

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Interventions	Measures	Duration of followup
Braithwaite et al, 2005[154] Fair	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[155] Fair	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 infomative letter; women at moderate/high risk offered appointment at familial breast cancer clinic where a genetics consutant 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 questoinnaires at 4 weeks and 6 months	Cancer Worry Scale (scale 5 to 24) GHQ-30	6 months
Gurmankin et al, 2005[156] NA	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 asses cancer worry	October 2002 to February 2004 1 week

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Interventions	Measures	Duration of followup
	the Life Orientation Test-Revised (0-32 measure of optimism)		
Helmes et al, 2006[157] Fair	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	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	Year NR 3 months
Hopwood et al, 2004[158] NA	A) Genetic counseling, otherwise not described	NSI: 5-response category assement of perceived cancer risk GHQ: 60-item questionnaire to screen individuals for psychiatric disorders	Year NR At 1 month and 1 year following precounseling
Kelly et al, 2008[159] NA	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	CWS: 3-item questionnaire to measure how frequently an individual worries about getting breast cancer	Year NR 6 months
Matloff et al, 2006[160] Fair	A) Counseling session with personalized letter summarizing patient data B) Controls who received no counseling	NSI: Reviewed detailed information about menopause, the risks and benefits of each menopasue therapy option, and a disease risk factor assessment	August 2002 to January 2004 6 months
Mikkelsen et al, 2007[161] Fair	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	IES: 17-item questionnaire to measure an individual's level of distress in relation to a specific event or condition	2003-2004 1 year
Mikkelsen et al, 2009[162] Fair	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	HADS: 14-item self-report scale for the detection of depression and anxiety in hospitalized patients	2003-2004 1 year

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Interventions	Measures	Duration of followup
Pieterse et al, 2011[163] NA	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 (>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	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	24 months (6 months after last counseling session)
Roshanai et al, 2009[164] Fair	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	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	2003-2005 At 2 weeks and at 8 months postcounseling
Prior report			
Bowen et al, 2002[57] Fair	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	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	Years: 6 months

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Interventions	Measures	Duration of followup
Bowen et al, 2004[62] 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[166] 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[58] 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

Author, year Quality	Interventions	Measures	Duration of followup
Cull et al, 1998[59] Good	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	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	Year NR 1 month following clinic consultation
Hopwood et al, 1998[167] Fair	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	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	3, 6, 9, and 12 months following genetic counseling
Lerman et al, 1996[168] Fair	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	IES: 17-item questionnaire to measure an individual's level of distress in relation to a specific event or condition	Year NR 3 months

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Interventions	Measures	Duration of followup
Lerman et al, 1999[60] Fair	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	IES: 17-item questionnaire to measure an individual's level of distress in relation to a specific event or condition	Year NR 1 month
Lobb et al, 2004[169] Good	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	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	4 weeks
Watson et al, 1998[171] Good	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	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	Year NR 6 months

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Interventions	Measures	Duration of followup
Watson et al, 1999[170] Good	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	NSI: Lifetime risk perception assess 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	Years: 12 months

Author, year Quality	Results	Conclusions	Funding source
Current report			
Armstrong et al, 2005[148] Good	<u>Logistic regression model of association between race and use of genetic counseling: OR (95% CI)</u> 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	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.	The American Cancer Clinical Research Training Grant and the Robert Wood Johnson Generalist Physician Faculty Scholar Award

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Results	Conclusions	Funding source
Bennett et al, 2008[150] NA	**Baseline vs. followup after risk assessment** Mean scores (SE) HADS-D: 4.44 (3.77) vs. 4.05 (3.85); NS HADS-A: 8.02 (4.56) vs. 7.03 (4.41); NS IES-I: 13.17 (10.57) vs. 7.76 (8.95); p<0.001 IES-A: 12.19 (10.78) vs. 8.45 (9.61); p<0.01 Perceived health, quality of life (scale, 0 to 100): 76.74 (20.10) vs. 77.96 (17.68); p<0.05 DUKE-SSQ (scale not described): 27.15 (11.93) vs. 24.97 (11.02); p<0.01 **Correlations between key independent variables and HADS-A vs. HADS-D** Age, level or risk assigned, and MCMQ-confrontation were NS IES-I: 0.703 (p<0.01) vs. 0.448 (p<0.01) IES-A: 0.636 (p<0.01) vs. 0.365 (p<0.01) DUKE-SSQ-confidant: 0.364 (p<0.01) vs. 0.493 (p<0.01) DUKE-SSQ-affective: 0.375 (p<0.001) vs. 0.411 (p<0.01 Perceived health: -0.493 (p<0.01) vs. -0.664 (p<0.01) Hopeless about getting cancer: 0.389 (p<0.01) vs. 0.366 (p<0.01) Hopeless about health: 0.374 (p<0.01) vs. 0.197 (p<0.05) Control over getting cancer: -0.372 (p<0.01) vs. 0.175 (NS) MCMQ-avoidance: 0.429 (p<0.001) vs. 0.271 (p<0.01) MCMQ-acceptance-resignation: 0.383 (p<0.01) vs. 0.206 (p<0.05) Neuroticism: 0.265 (p<0.01) vs. 0.193 (p<0.05)	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.	NR
Bennett et al, 2009[149] NA	**Baseline vs. followup after risk assessment** IES-I (estimated from graph) High risk: 12.5 vs. 7.8 (p<0.001) Moderate risk: 12.5 vs. 7.9 (p<0.001) Low risk: 11.8 vs. 8.2 (p<0.001) Between-group differences were NS (p=0.694) IES-A (estimated from graph) High risk: 13.1 vs. 8.3 (p<0.05) Moderate risk: 10.6 vs. 8.9 (p<0.05) Low risk: 10 vs. 11.3 (p<0.05) Between-group differences for low vs. moderate and high risk was significant (p<0.05) **Key variables associated with IES intrusion scores** Cognitive response Control over risk for cancer: -0.279 (p<0.001) Hopelessness about developing cancer: 0.412 (p<0.001) Emotional response to risk information Hopeful: -0.331 (p<0.001) Relieved: -0.278 (p<0.001) Calm: -0.506 (p<0.001)	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.	NR

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Results	Conclusions	Funding source
	Anxious: 0.438 (p<0.001) Social support Confidant support: 0.232 (p<0.01) Affective support: 0.208 (p<0.05) Coping Confrontation: 0.284 (p<0.001) Avoidance: 0.442 (p<0.001) Acceptance-resignation: 0.391 (p<0.001) Variables not associated with IES intrusion scores: age, risk status, and surprised emotional response to risk information Similar results were found for IES avoidance scores		
Bloom et al, 2006[151] Poor	Women overestimated their risk of breast cancer by an average of 25 percentage points; proportion of women underestimating risk was larger in women with perceived lower risk (40%) than those who perceived it as the same (16%), higher (10%), or much higher (5%) than the risk of other women (p=0.009) Women reduced their overestimation more if the initial overestimate was higher (p<0.0001); intervention effect was significant only in women age ≥50 years (p=0.004)	Telephone counseling appears to reduce risk overestimates in women with higher than average risk and to promote healthy behaviors in sisters of women with breast cancer.	Grant 4EB-5800 from the California Breast Cancer Research Program
Bowen et al, 2006[152] Fair	**A vs. B vs. C (results at followup)** Perceived risk (scale, 0% to 100%): 18 (SD, 16) vs. 18 (SD, 16) vs. 32 (SD, 23); p<0.001 for both counseling groups vs. control Cancer worry (scale, 4 to 16): 5.2 (SD, 1.5) vs. 4.9 (SD, 1.1) vs. 6.1 (SD, 1.9); p<0.001 for both counseling groups vs. control Awareness of genetic testing (range from 1=almost nothing to 4=a lot): 2.6 (SD, 0.7) vs. 2.6 (SD, 0.7) vs. 2.2 (SD, 0.7); p<0.001 for both counseling groups vs. control Interest in having genetic testing (range from 1=definitely not to 4=definitely yes): 2.4 (SD, 0.9) vs. 2.4 (SD, 0.9) vs. 2.8 (SD, 0.8); p<0.01 for both counseling groups vs. control Candidacy judgment (range from 1=definitely not to 4=definitely yes): 2.0 (SD, 0.8) vs. 2.0 (SD, 0.8) vs. 2.6 (SD, 0.8); p<0.05 for both counseling groups vs. control Fear of stigma (scale range unclear, higher score indicates higher fear of stigma): 3.4 (SD, 1.1) vs. 3.4 (SD, 1.1) vs. 3.3 (SD, 1.2); no significant difference between groups Access to genetic testing (scale range unclear, higher score indicates more unrestricted access): 3.8 (SD, 1.4) vs. 3.9 (SD, 1.4) vs. 4.3 (SD, 1.4); p<0.05 for both counseling groups vs. control Information flow (scale range unclear, higher score indicates more restrictions on information flow): 2.0 (SD, 1.1) vs. 2.1 (SD, 1.0) vs. 1.9 (SD, 0.9); p<0.05 for both counseling groups vs. control	Counseling, either group or individual, reduced cancer worry, lowered inflated risk perceptions, and decreased interest in genetic testing. Included in Smerecnik 2009 review.	National Human Genome Research Institute grant HG01190

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Results	Conclusions	Funding source
Brain et al, 2011[153] NA	**A vs. B** 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	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.	Wales Office for Research and Development in Health and Social Care
Braithwaite et al, 2005[154] Fair	**A vs. B** 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<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 "very satisfied" with risk information (p<0.01)	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.	Cancer Research U.K. (CUK), grant no. C1345/A169
Fry et al, 2003[155] Fair	**A (standard) vs. B (novel)** 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)	All women experienced a significant reduction in CWS scores, with greatest reductions from baseline to 4 weeks (p<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.	Chief Scientists's Office and Cancer Research U.K.
Gurmankin et al, 2005[156] NA	Mean breast cancer risk perception: 44% Risk perception change from baseline: +17% (p<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)	Patients' breast cancer risk perceptions following risk communication were higher than corresponding actual risk communicated to them (+19% p<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.	The American Cancer Society and a Robert Wood Johnson Faculty Scholar Award

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Results	Conclusions	Funding source
Helmes et al, 2006[157] Fair	**A vs. B vs. C (change from baseline to followup)** Mean risk perception (scale, 0 to 100): -10.29 vs. -8.65 vs. +1.14 (p<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<0.001)	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
Hopwood et al, 2004[158] NA	**Precounseling vs. 1-month followup vs. 12-months followup** 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<0.001)	Cancer distress decreased after counseling and continued to be low 1 year later.	NHS Research and Development Directorate, Programme for Cancer; Project NCP/B42
Kelly et al, 2008[15] NA	**Precounseling vs. postcounseling (ovarian cancer)** 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)	All women underestimated their risk of developing ovarian cancer.	The New Jersey Commission on Cancer Research and the Mid-Atlantic Region Human Genetics Network
Matloff et al, 2006[160] Fair	**A vs. B** 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) **A only** 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)	After counseling, accuracy of perceived risk of breast cancer increased.	Susan G. Komen Foundation
Mikkelsen et al, 2007[161] Fair	**A vs. B vs. C** 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	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

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Results	Conclusions	Funding source
	p=0.07 for A vs. C)		
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
Pieterse et al, 2011[163] NA	Risk perception accuracy: N (%) Precounseling 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.
Roshanai et al, 2009[164] Fair	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<0.01).	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.	The Swedish Cancer Society
Prior report			
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)

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Results	Conclusions	Funding source
Bowen et al, 2004[62] Fair	Women's perceived risk for breast cancer decreased by 50% for the 2 counseling groups relative to control ($p<0.01$). Cancer worry decreased in both counseling groups by 1 scale point ($p<0.05$). 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.	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.	The National Human Genome Institute, the National Cancer Institute, and the National Office for Research on Women's Health (HG/CA01190)
Brain et al, 2002[166] Good	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; $p<0.001$) and moderate risk ($t(443)$, 12.13; $p<0.001$), but not at high risk. Satisfaction: Significantly lower in high-risk group ($p<0.001$). 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.	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.	The Medical Research Council, National Assembly for Wales, NHS R&D (Wales), and Imperial Cancer Research Fund. Dr. Gray is supported by Tenovus, a cancer charity
Burke et al, 2000[58] Fair	Significant differences between counseling and control groups in mean perceived risk of breast cancer ($F=27.9$; $p<0.009$). Significant differences over time in perceived risk for the counseling group ($F=65.9$; $p<0.001$). Interaction between group and time for perceived risk was significant ($F=50.6$; $p<0.001$). 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 ($F=13.41$; $p<0.00001$). 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.	Most participants saw a benefit to counseling and afterward had a more accurate understanding of their risk. Counseling reduced interested in genetic testing.	The National Institutes of Health (HGO1190)

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Results	Conclusions	Funding source
Cull et al, 1998[59] 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[167] 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

Author, year Quality	Results	Conclusions	Funding source
	clinical anxiety or depression.		
Lerman et al, 1996[168] Fair	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.	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.	Public Health Service grants ROICA57767 and K07CAOI604 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services
Lerman et al, 1999[60] Fair	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.	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.	The National Institutes of Mental Health and National Human Genome Research Institute grant MH/HG54435
Lobb et al, 2004[169] Good	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).	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.	The University of Sydney Cancer Research Fund
Watson et al, 1998[171] Good	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	Overall: GHQ-12 scores: For combined groups, median score was 1 (range, 0-11). 36 subjects had a score indicative of psychological morbidity (>3) at baseline and 31 at 1-month and 6-month followup.	NR

Appendix C6. Evidence Table of Genetic Counseling

Author, year Quality	Results	Conclusions	Funding source
	risk) to 9.1 (risk of gene in family). Risk of gene in family, lifetime risk, and risk before age 50 were rated significantly more useful than population risk, risk of no cancer by age 50, and risk of disease over next 5 years. Medical management uptake: No significant correlation between cancer worry change scores and either level of breast clinical exam (p=0.8) or mammography (p=0.8); no difference between cases and controls for rate of self-exam, doctor exam, or mammography at 6-month followup; no difference between groups for other health behaviors unaffected by whether consultation tape was received or not.		
Watson et al, 1999[170] Good	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<0.001). Perception of 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 "frequently or constantly" and 18% worry about breast cancer as a "severe or definite" 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).	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 unrelieved. 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.	The Cancer Research Campaign (CRC project CP1026)

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

provider; RCT = randomized, controlled trial; SD = standard deviation; SDR = second-degree relative; STAI = State-Trait Anxiety Inventory; VA = video after; VAS = Visual Analog Scale; VB = video before.

Appendix C7. Evidence Table of Prevalence of *BRCA1* and *BRCA2* Mutations

Author, year	Data source/ parent study	Setting	Population	Inclusion/exclusion criteria	Country
Prevalence high-risk					
Beristain et al, 2007[174]	NA	NR	Individuals with suspicious personal or family history.	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 <40); 2) patients from families with 2 cases of female breast cancer, 1 diagnosed at age <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.	Basque Country, Spain
Konecny et al, 2011[183]	NA	High-risk clinics	Individuals referred for genetic analysis on the basis of family history.	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 <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 <35 years; 5) the presence of ≥1 case of male breast cancer diagnosed at any age.	Slovakia
Nanda et al, 2005[193]	NA	Genetics clinic	Families presenting to high-risk clinic.	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.	U.S.: University of Chicago, Mayo Clinic, Rush University, UCSF
Neuhausen et al, 2009[194]	Breast Cancer Family Registry	Population and clinic-based family registries	Probands and their families recruited through population and clinic-based registries.	Population-based families from the California Breast CFR recruited case probands <65 years at diagnosis; <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.	U.S., Canada, Australia

Appendix C7. Evidence Table of Prevalence of *BRCA1* and *BRCA2* Mutations

Author, year	Data source/ parent study	Setting	Population	Inclusion/exclusion criteria	Country
Seymour et al, 2008[197]	Cancer Prevention Units in the Forli-Cesena and Ravenna provinces of north-central Italy	Genetics clinic	Women undergoing breast checkups who completed a questionnaire on family history.	Healthy or affected individuals from families meeting 1 of the following criteria: 1) ≥1 relative diagnosed with a) BC at age <36 years, b) BC and OC in the same patient at any age, c) bilateral BC at age <51 years, d) male BC at any age, e) OC of fallopian tube cancer at age <46 years; or 2) a) 2 relatives diagnosed with BC at age <51 years, b) 1 relative with BC at age <51 years and 1 relative with bilateral BC at any age, c) 1 relative with BC at age <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.	Italy
Tamboom et al, 2010[199]	Estonian Cancer Registry	North Estonia Medical Centre's Centre of Oncology and the Hematology and Oncology Clinic of Tartu University Hospital	Early onset, familial, and predictive cases.	Early onset cases were identified if diagnosed with breast cancer <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.	Estonia
Tommasi et al, 2005[200]	Dipartimento Donna of the National Cancer Institute of Bari, Italy	Surgical department	Women with a first diagnosis of breast cancer undergoing surgery.	A preliminary investigation of cancer syndromes was performed by a surgeon and the patients eligible for genetic counseling were referred.	Italy
Vaziri et al, 2001[202]	Familial Cancer Registry of the Cleveland Clinic Foundation	Clinic	Breast and breast-ovarian cancer families recruited through the registry.	An affected proband with ≥2 family members with cancer; 2 of whom must have either breast cancer (<50 years) or ovarian cancer; and ≥1 with breast, ovarian, colon, prostate or pancreatic cancer. Cases must be present in ≥2 generations.	U.S.
Weitzel et al, 2005[319]	City of Hope's Cancer Screening & Prevention Program Network	High-risk clinics; Hereditary Cancer Registry	All patients presenting for genetic cancer risk assessment.	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.	Hispanic; U.S.
Unselected populations (Ashkenazi Jewish)					
Metcalfe et al, 2010[191]	NA	Article published in a national newspaper in May 2008	Ashkenazi or Sephardic Jews.	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.	Ontario, Canada

Appendix C7. Evidence Table of Prevalence of *BRCA1* and *BRCA2* Mutations

Author, year	Study design	Primary risk measure	Comparison group	Family history/risk level definition	N
Prevalence high-risk					
Beristain et al, 2007[174]	Post intervention series	Prevalence	NA	See inclusion/exclusion criteria	236 index cases
Konecny et al, 2011[183]	Post intervention series	Prevalence	NA	See inclusion/exclusion criteria	585 families
Nanda et al, 2005[192]	Post intervention series	Prevalence	NA	NR	155 families
Neuhausen et al, 2009[193]	Post intervention series	Prevalence	NA	See inclusion/exclusion criteria	*BRCA1:* 4531 probands *BRCA2:* 4084 probands 1385 Ashkenazi Jewish probands 1360 individuals
Seymour et al, 2008[191]	Post intervention series	Prevalence	NA	See inclusion/exclusion criteria	363 families 707 individuals
Tamboom et al, 2010[198]	Post intervention series	Prevalence	NA	See inclusion/exclusion criteria	64 early onset 47 familial 33 predictive
Tommasi et al, 2005[199]	Case series	Prevalence	NA	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 <50 years had breast cancer; 3) 1 relative <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 <10%.	100 patients
Vaziri et al, 2001[201]	Post intervention series	Prevalence	NA	See inclusion/exclusion criteria	104 families
Weitzel et al, 2005[320]	Post intervention series	Prevalence	NA	A calculated BRCA mutation probability of ≥5% by any model.	110 probands
Unselected populations (Ashkenazi Jewish)					
Metcalfe et al, 2010[190]	Post intervention series	NA	NA	NR	2080 women

Author, year	Demographics	Participation rate	Genes included	Laboratory methods	Tissue source
Prevalence high-risk					
Beristain et al, 2007[174]	NR	NR	*BRCA1* & *BRCA2*	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.	Blood

Appendix C7. Evidence Table of Prevalence of *BRCA1* and *BRCA2* Mutations

Author, year	Demographics	Participation rate	Genes included	Laboratory methods	Tissue source
Konecny et al, 2011[183]	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	NR	*BRCA1* & *BRCA2*	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.	Blood
Nanda et al, 2005[192]	Race/ethnicity: 50% Caucasian (nonHispanic, nonJewish) 28% African American 19% Ashkenazi Jewish 2% Hispanic 1% Asian	117/160 (73%)	*BRCA1* & *BRCA2*	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.	NR
Neuhausen et al, 2009[193]	Gender: 100% female Age (years) of mutation carriers at diagnosis *BRCA1* vs. *BRCA2* affected: <30: 43 vs. 21 30-39: 193 vs.107 40-49: 168 vs.100 50-59: 51 vs. 65 >60: 19 vs. 28 Unknown: 1 vs. 0 *BRCA2* affected: <30: 21 30-39: 107 40-49: 110 50-59: 65 >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	NR	*BRCA1* & *BRCA2*	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.	Blood and/or buccal samples and tumor tissue
Seymour et al, 2008[196]	100% female Median age at diagnosis: 46.6 years (range: 20 to 80) Race/ethnicity: Italian	NR	*BRCA1* & *BRCA2*	PCR amplification and direct sequencing. Variants were confirmed by resequencing the reverse DNA strand.	Blood

Appendix C7. Evidence Table of Prevalence of *BRCA1* and *BRCA2* Mutations

Author, year	Demographics	Participation rate	Genes included	Laboratory methods	Tissue source
Tamboom et al, 2010[198]	NR	NR	*BRCA1* & *BRCA2*	SSCP-HA followed by direct DNA sequencing and MDE. All mutations were confirmed using PCR.	Blood
Tommasi et al, 2005[199]	100% female Age: NR Race/ethnicity: Italian	NR	*BRCA1*	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.	Blood
Vaziri et al, 2001[201]	NR	NR	*BRCA1* & *BRCA2*	PCR amplification, CSGE, and PTT. Family-specific mutations were amplified and directly sequenced using tissue-derived genomic DNA.	Blood
Weitzel et al, 2005[320]	99% female Mean age at diagnosis: 37 years (for the 89 probands with a cancer diagnosis) Race/ethnicity: 100% Hispanic	98%	*BRCA1*	Full sequencing of exons and flanking intronic sequences by Myriad Genetic Laboratories. 5 specific *BRCA1* rearrangements for assays done after 2001.	NR
Unselected populations (Ashkenazi Jewish)					
Metcalfe et al, 2010[190]	100% female Mean age at enrollment: 49.3 years Race/ethnicity: 1886 (91%) reported 100% Ashkenazi Jewish ancestry 105 (5%) reported 75% Ashkenazi Jewish ancestry (3 grandparents) 56 (3%) reported 50% Ashkenazi Jewish ancestry (2 grandparents) 3 reported 25% Ashkenazi Jewish ancestry (1 grandparent) 17 reported Sephardic Jewish ancestry	NR	*BRCA1* & *BRCA2*	Tested for the 3 Jewish founder *BRCA1* (185delAG and 5382insC) and *BRCA2* (6174delT) mutations. All mutations were confirmed by direct sequencing.	Blood or saliva

Author, year	Parts of genes studied	Who was tested?	Results/conclusions	Quality considerations			
				Definition of clinically significant	How was cancer status ascertained?	Confounders	Method
Prevalence high-risk							
Beristain et al, 2007[174]	Exons and intronic boundaries	Proband	16/236 (6.8% of index cases) had mutations	NR	NR	NR	NA
Konecny et al, 2011[183]	Whole coding region	NR	*BRCA1*: 85/585 (15%) families *BRCA2*: 12/104 (12%) families	NR	NR	NR	NA

Appendix C7. Evidence Table of Prevalence of *BRCA1* and *BRCA2* Mutations

Author, year	Parts of genes studied	Who was tested?	Results/conclusions	Quality considerations			
				Definition of clinically significant	How was cancer status ascertained?	Confounders	Method
Nanda et al, 2005[192]	Full sequence	In each family, the individual with the highest probability of being a mutation carrier was tested.	*BRCA1*: 28% -Hispanic: 0% -Asian: 0% -African American: 16% -Caucasian: 31% -Ashkenazi Jewish: 41% *BRCA2*: 16% -Hispanic: 0% -Asian: 0% -African American: 12% -Caucasian: 15% -Ashkenazi Jewish: 28% African Americans were more likely to have sequence variants of unknown significance compared with Caucasian women (44% vs. 12%).	As previously described in Frank et al, 1998.	NR	NR	NA
Neuhausen et al, 2009[193]	Full sequence	Proband and affected family members; Ashkenazi Jewish women for the 3 founder mutations	*BRCA1* vs. *BRCA2* probands Excluding Ashkenazi Jewish: 233/4531 (5.1%) vs. 193/4084 (4.7%)	As defined by the BIC and Myriad Genetic Laboratories.	NR	Age and cancer status were reported.	NA
Seymour et al, 2008[196]	Coding regions and flanking introns	Proband and some relatives	*BRCA1* or *BRCA2*: 21/247 (8.5%) families	NR, although a distinction is made between deleterious and nondeleterious mutations.	Personal and family cancer status was reported by the proband and verified during genetic counseling sessions.	NR	NA
Tamboom et al, 2010[198]	Full sequence	Probands, families, and predictive cases	Early onset vs. familial vs. predictive *BRCA1* 4/64 (6%) vs. 6/47 (13%) vs. 1/33 (3%) *BRCA2* (16 familial cases only) Total: 2/16 (12.5%)	As defined by the BIC database or those which result in a stop codon.	Cancer status was reported by the proband and confirmed in the Estonian Cancer Registry.	Age and cancer status were reported.	NA
Tommasi et al, 2005[199]	Coding region	Proband	*BRCA1*: 7/100 (7%) patients	NR, although a distinction is made between deleterious and nondeleterious mutations.	Cancer status was reported by the proband and updated in genetic counseling.	NR	NA

Appendix C7. Evidence Table of Prevalence of *BRCA1* and *BRCA2* Mutations

Author, year	Parts of genes studied	Who was tested?	Results/conclusions	Quality considerations			
				Definition of clinically significant	How was cancer status ascertained?	Confounders	Method
Vaziri et al, 2001[201]	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[320]	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
Unselected populations (Ashkenazi Jewish)							
Metcalfe et al, 2010[190]	Founder mutations	Individual	Prevalence of mutation: 22/2080 (1.1%) found to have 1 of 3 founder mutations *BRCA1*: 0.5% *BRCA2*: 0.6%	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

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 = mulitplex 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

Author, year	Data source/ parent study	Setting	Population	Inclusion/exclusion criteria
BRCA uncertain or uninformative				
Kauff et al, 2005[182]	Memorial Sloan Kettering Cancer Center	Genetics clinic	BRCA mutation negative site-specific breast cancer kindreds with a living female proband. All probands, 1st-, and 2nd-degree relatives age >18 years at the time that BRCA test results were transmitted to the proband.	Probands 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 <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.
Metcalfe et al, 2009[189]	NA	Genetics clinic	All female FDRs of the breast cancer cases age >18 years at the time the pedigree was drawn.	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.
BRCA true negative				
Bernholtz et al, 2012[175] **[True negative group only]**	Israeli Cancer Registry	Oncogenetics unit, Sheba medical center	Jewish, female mutation carriers and their family members referred for oncogenetic counseling.	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 <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 <50 years. Excluded if nonJewish origin and/or unwillingness to participate.
Domchek et al, 2010[177]	Memorial Sloan Kettering Cancer Center and University of Pennsylvania	Genetics clinic	Women who do not carry a known family mutation in *BRCA1* or *BRCA2*.	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.
Gronwald et al, 2007[180]	NA	18 hospitals in Poland	Women who do not carry a known family mutation in *BRCA1* or *BRCA2.*	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.

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Data source/ parent study	Setting	Population	Inclusion/exclusion criteria
Harvey et al, 2011[181]	Australian Cancer Incidence and Mortality data	1 of 16 family cancer clinics in Australia and New Zealand; Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab)	Women who were blood relatives of mutation carriers who tested negative for the known mutation in their family.	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.
Korde et al, 2011[184]	NCI cohort	NR	Mutation negative women in families with known deleterious *BRCA1/2* mutations.	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.
Kramer et al, 2005[185] **[Mutation Negative Group Only]**	NCI	Families participating in research studies	Self or physician-referred families.	Analysis was restricted to 23 families with a known *BRCA1* mutation out of a larger cohort of 60 HBOC families.
Kurian et al, 2011[186]	BCFR	Population-based cancer registries	Women with incident breast cancer and their female 1st-degree family members, including mothers and full sisters.	Inclusion: Northern California site: Diagnosed with breast cancer at age <65 years through the Greater Bay Area Cancer Registry. Ontario site: Diagnosed at age <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.
Rowan et al, 2007[196]	NA	Familial breast cancer center	Women who do not carry a known family mutation in *BRCA1* or *BRCA2*.	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.

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Data source/ parent study	Setting	Population	Inclusion/exclusion criteria
Smith et al, 2007[198]	M6-ICE Study	Genetics clinic	Women who do not carry a known family mutation in *BRCA1* or *BRCA2*	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.
van der Kolk et al, 2010[201] **[Testing Negative Group Only]**	University Medical Center Groningen	Genetics clinic	Women who do not carry a known family mutation in *BRCA1* or *BRCA2*	Screening is carried out if the family history meets 1 of the following: 1) 1 breast cancer case at age <35 years, 2) 2 breast cancer cases in 1st-degree relatives with 1 case at age <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.
BRCA positive-single				
Chen et al, 2006[122]	Cancer Genetics Network	282 Ashkenazi Jewish families were population-based, the remainder were from genetics clinics	Families presenting to high-risk clinic.	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 >3 diagnoses of breast or ovarian cancer per family. There were 282 Ashkenazi Jewish families recruited at Baylor that were population-based.
Finkelman et al, 2012[179] **[Prospective participants only]**	Prevention and Observation of Surgical End Points (PROSE) Consortium	22 international centers in the PROSE consortium	Jewish and nonJewish women with a confirmed disease-associated *BRCA1/2* mutation.	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.
Lubinski et al, 2012[187]	26 centers in Canda, United States, and Poland	Clinical centers	Unaffected women with a *BRCA1* mutation.	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.
Marroni et al, 2004[188]	NA	Clinical centers	Families receiving BRCA testing.	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.

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Data source/ parent study	Setting	Population	Inclusion/exclusion criteria
Metcalfe et al, 2010[190]	Hereditary Breast Cancer Clinical Study Group	33 centers in 6 countries	Women who were known to be carriers of a deleterious mutation in *BRCA1* or *BRCA2*.	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.
Risch et al, 2006[1895]	Ontario Cancer Registry	Registry for ovarian cancer	All patients diagnosed with invasive and borderline ovarian cancer.	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.
BRCA positive-multi				
Al-Mulla et al, 2009[172]	NA	NR	Patients and their family members in moderate- or high-risk families.	Moderate- or high-risk families.
Antoniou et al, 2006[173]	INHERIT BRCAs	Network of referring physicians	Families with family history suggestive of a genetic component.	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 >18 years and mentally competent.
Evans et al, 2008[178]	NA	Genetics clinic	Families presenting to high-risk clinic.	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.
Kramer et al, 2005[185] **[Mutation Carrier Group Only]**	NCI	Families participating in research studies	Self- or physician-referred families.	Analysis was restricted to 23 families with a known *BRCA1* mutation out of a larger cohort of 60 HBOC families.

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Data source/ parent study	Setting	Population	Inclusion/exclusion criteria
Milne et al, 2008[192]	NA	Genetics clinic	Families testing positive for deleterious mutations in *BRCA1* or *BRCA2*.	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.
van der Kolk et al, 2010[201] **[Mutation Carriers Group Only]**	University Medical Center Groningen	Genetics clinic	Families presenting to high-risk clinic.	Screening is carried out if the family history meets 1 of the following inclusion criteria: 1) 1 breast cancer case at age <35 years, 2) 2 breast cancer cases in FDRs with 1 case at age <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.

Author, year	Country	Study design	Primary risk measure	Comparison group	Family history/ risk level definition	N
BRCA uncertain or uninformative						
Kauff et al, 2005[182]	U.S.	Retrospective cohort study	SIR	Age-specific cancer incidence rates from the SEER program.	See inclusion/exclusion criteria. Family history was collected via questionnaire sent to the proband.	165 probands 583 FDRS or SDR
Metcalfe et al, 2009[189]	Ontario, British Columbia	Retrospective cohort study	Cumulative incidence SIR	Expected rates for Ontario and British Columbia were obtained from the registry data recorded in "Cancer Incidence in Five Continents (Volume VII)."	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.	365 families 874 breast cancers at baseline 1492 FDRs who did not have breast cancer at baseline
BRCA true negative						
Bernholtz et al, 2012[235] **[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[177]	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

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Country	Study design	Primary risk measure	Comparison group	Family history/ risk level definition	N
Gronwald et al, 2007[180]	Poland	Cohort Families: penetrance	OR	Expected number of breast cancer cases was determined for Poland from the "Cancer Incidence in Five Continents (Volume VIII)," using age-specific estimates.	NR	188 families 261 sisters (140 received genetic testing)
Harvey et al, 2011[181]	Australia	Prospective	SIR	Australian Cancer Incidence and Mortality data	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.	722 mutation-negative women
Korde et al, 2011[184]	U.S.	Cohort Families: penetrance	Observed to expected risk ratio	Age-, race-, and calendar time-specific expected number of breast cancer cases were derived from the SEER 2009 Cancer Registry.	Degree of relatedness to closest relative with known BRCA mutation (1st, 2nd, or 3rd-degree). Adjustment for intact ovaries vs. oophorectomy age category.	395 women 28 families
Kramer et al, 2005[185] **[Mutation Negative Group Only]**	U.S.	Post intervention series	Cumulative risk	NA	NR	23 families 673 females total 353 were *BRCA1* mutation negative for the known family mutation
Kurian et al, 2011[186]	Melbourne and Sydney, Australia, Ontario, Canada, and Northern California, U.S.	Cohort Families: penetrance	Risk ratio, HR	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.	NR	Probands: Australia (n=799) Canada (n=1034) U.S. (n=1214) FDRs: approximately 9,000

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Country	Study design	Primary risk measure	Comparison group	Family history/ risk level definition	N
Rowan et al, 2007[195]	Ontario, Canada	Cohort Families: penetrance	SIR	The expected number was estimated from the age-specific breast cancer rates for the Ontario population from 1993 to 1997 ("Cancer Incidences in Five Continents")	NR	104 subjects 64 families
Smith et al, 2007[197]	Manchester and Birmingham, England	Cohort Families: penetrance	SIR	Expected numbers were calculated using incidence rates for the period 1975 to 2004 from the North Western Cancer Registry, using age-, sex-, and calendar period-specific estimates.	NR	277 families 258 individuals tested negative for the family mutation (28 with breast cancer, 4 with ovarian cancer)
van der Kolk et al, 2010[201] **[Testing Negative Group Only]**	Netherlands	Cohort Families: penetrance	SIR	Dutch cancer registries	NR	185 families 111 segregating *BRCA1* 74 segregating *BRCA2* 1188 women total 128 noncarriers for *BRCA1* 74 noncarriers for *BRCA2*
BRCA positive-single						
Chen et al, 2006[122]	U.S.	Post intervention series	Age-specific cumulative risk; RR	To estimate the hazard of breast or ovarian cancer in noncarriers, age-conditional probabilities from SEER were used.	NR	676 Ashkenazi Jewish families 1272 families of other ethnicities 1948 counselees had genetic testing performed (1 from each pedigree)
Finkelman et al, 2012[179] **[Prospective participants only]**	U.S.	Prospective	HR	NA	NR	2362 BC analyses (1874 nonJewish vs. 488 Jewish) 3787 OC analyses (3034 nonJewish vs. 753 Jewish)

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Country	Study design	Primary risk measure	Comparison group	Family history/ risk level definition	N
Lubinski et al, 2012[187]	Canada, U.S., and Poland	Prospective	Cumulative incidence, HR, age-specific cancer and incidence rates	North American cohort	NR	1477 women 614 North America 863 Poland
Marroni et al, 2004[188]	Italy	Post intervention series	Cumulative incidence	Cancer registry data	NR	568 families 80 segregating *BRCA1* 52 segregating *BRCA2* 435 not segregating a BRCA mutation
Metcalfe et al, 2010[220]	Canada, U.S., Poland, Austria, Italy, France	Post intervention series	Penetrance	NA	A) ≥1 FDR or SDR with breast or ovarian cancer, b) no FDR or SDR with these cancers.	3011 women
Risch et al, 2006[1895]	Ontario, Canada	Case series	Cumulative incidence	NA	NR	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
BRCA positive-multi						
Al-Mulla et al, 2009[172]	Yorkshire and Humberside, U.K.	Post intervention series	Cumulative incidence, HR	NA	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.	241 patients and their family members 131 families 219 subjects with available clinical and mutation data
Antoniou et al, 2006[173]	French Canadian	Post intervention series	Cumulative risk	NA	NR	191 families 25 families segregating *BRCA1* 27 families segregating *BRCA2*

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

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

Author, year	Demographics	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied
BRCA uncertain or uninformative						
Kauff et al, 2005[182]	Mean age: 51.6 years 100% female 67% Ashkenazi Jewish ancestry Followup: Mean, 40.6 months (range, 15.3 to 82.4 months)	165/207 (80%)	*BRCA1* & *BRCA2*	NR	NR	NR
Metcalfe et al, 2009[189]	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)	NR	*BRCA1* & *BRCA2*	Methods changed over time and between centers but used a combination of PTT, DGGE, dHPLC, and direct sequencing	NR	All coding regions

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Demographics	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied
BRCA true negative						
Bernholtz et al, 2012[235] **[True negative group only]**	100% female Mean age at testing: 43.0 years (SD, 13.0; range, 19.7 to 92.8) Mean age at diagnosis: 54.1 years (SD, 12.9; range, 48.1 to 60.1) Mean age at diagnosis, *BRCA1*: 55.5 (SD, 12.5) Mean age at diagnosis, *BRCA2*: 54.7 (SD, 15.35) Race/ethnicity: Ashkenazi Jewish Median followup time: 7.2 years	NR	*BRCA1 & BRCA2*	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.	NR	Mutant alleles of founder mutations and full sequence for all others
Domchek et al, 2010[177]	100% female 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	378/405 (93%)	*BRCA1* & *BRCA2*	Direct sequencing. Individuals of Ashkenazi Jewish descent were also tested for the 3 founder mutations in *BRCA1* (185delAG, 5382insC) and *BRCA2* (6174delT).	NR	Family mutation
Gronwald et al, 2007[180]	100% female Mean age: NR Race/ethnicity: Polish	188/198 (95%) families	*BRCA1*	See Lubinski et al 2006 reference.	NR	Family mutation
Harvey et al, 2011[181]	100% female 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)	NR	*BRCA1 & BRCA2*	NR	Blood	NR
Korde et al, 2011[184]	100% female Mean age at cohort entry: 31.3 years Race/ethnicity: NR	395/415 (95%)	*BRCA1* & *BRCA2*	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 descendents of an individual who tested negative).	NR	Family mutation

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Demographics	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied
Kramer et al, 2005[185] **[Mutation 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[186]	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. Ontario and U.S.: Complete gene. Australia: Exon and flanking introns, or founder mutations, or full gene.
Rowan et al, 2007[195]	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

Author, year	Demographics	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied
Smith et al, 2007[197]	100% female Median age: 50 years (range, 23 to 87) Race/ethnicity: NR	NR	*BRCA1* & *BRCA2*	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.	Blood	Family mutation
van der Kolk et al, 2010[201] **[Testing Negative Group Only]**	NR	NR	*BRCA1* & *BRCA2*	Denaturing gradient gel electrophoresis, the protein truncation test, direct sequencing, and multiplex ligation-dependent probe amplification.	NR	NR
BRCA positive-single						
Chen et al, 2006[122]	2.7% male Mean age: 52.8 years Race/ethnicity: 35% Ashkenazi Jewish	NR	*BRCA1* & *BRCA2*	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).	NR	NR
Finkelman et al, 2012[179] **[Prospective participants only]**	NonJewish vs. Jewish 100% female Mean age at ascertainment, BC: 39.1 (range, 2.0 to 89.3) vs. 42.7 (range, 10.2 to 90.4) Mean age at ascertainment, OC: 41.5 (range, 2.0 to 89.3) vs. 45.1 (range, 10.2 to 90.4) Race/ethnicity: NR Mean followup time, BC: 5.2 (range, 0.0 to 33.3) vs. 4.7 (range, 0.0 to 33.1) Mean followup time, OC: 5.6 (range, 0.0 to 33.3) vs. 5.0 (range, 0.0 vs. 33.1)	NR	*BRCA1* & *BRCA2*	NR	NR	NR

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Demographics	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied
Lubinski et al, 2012[187]	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 followup time: 4.8 (range, 0 to 14.9) vs. 4.0 (range, 0 to 10	NR	*BRCA1*	NR	NR	NR
Marroni et al, 2004[188]	100% female Age: NR Race/ethnicity: NA (Italian)	NR	*BRCA1* & *BRCA2*	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.	NR	NR
Metcalfe et al, 2010[220]	NR	NR	*BRCA1* & *BRCA2*	NR	NR	NR
Risch et al, 2006[1895]	100% female Mean age: NR Race/ethnicity: 44% British Isles 28% Mixed European 11% French Canadian 17% Other	1171/2338 (50%) eligible subjects	*BRCA1* & *BRCA2*	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.	Blood	Coding exons and exon-intron boundaries.
BRCA positive-multi						
Al-Mulla et al, 2009[172]	40 (18%) males 179 (82%) females Mean age: 47.7 years Race/ethnicity: NR	NR	*BRCA1* & *BRCA2*	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	Blood	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.
Antoniou et al, 2006[173]	NR	NR	*BRCA1* & *BRCA2*	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	Blood	Full sequence

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Demographics	Participation rate	Genes included	Laboratory methods	Tissue source	Parts of genes studied
Evans et al, 2008[178]	100% female Age: NR Race/ethnicity: NR	NR	*BRCA1* & *BRCA2*	A whole gene test, including a test for large deletions.	NR	NR
Kramer et al, 2005[185] **[Mutation Carrier 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
Milne et al, 2008[191]	NR	NR	*BRCA1* & *BRCA2*	A range of methods.	NR	NR
van der Kolk et al, 2010[201] **[Mutation Carriers Group Only]**	NR	NR	*BRCA1* & *BRCA2*	Denaturing gradient gel electrophoresis, the protein truncation test, direct sequencing, and multiplex ligation-dependent probe amplification.	NR	NR

Author, year	Who was tested?	Results/conclusions	Quality considerations			
			Definition of clinically significant	How was cancer status ascertained?	Confounders	Method
BRCA uncertain or uninformative						
Kauff et al, 2005[182]	Proband	Observed vs. expected BC: 19 vs. 6.07; SIR, 3.13 (95% CI, 1.88 to 4.89); p<0.001 OC: 1 vs. 0.66; SIR, 1.52 (95% CI, 0.02 to 8.46); p=0.48	NR	Cancer status was reported by the proband by questionnaire.	Collected data included age and cancer status. Not reported whether prophylactic surgery or vital status were collected.	NA
Metcalfe et al, 2009[189]	≥1 woman affected with breast cancer was tested in each family	BC: SIR, 3.9 (95% CI, 3.1 to 5.0); p<0.0001 OC: SIR, 0.85 (95% CI, 0.23 to 3.12); p=0.82	NR	Cancer status was reported by the proband and other family members by telephone interview.	Collected data included age, cancer status, prophylactic surgery, and vital status.	NA

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Who was tested?	Results/conclusions	Quality considerations			
			Definition of clinically significant	How was cancer status ascertained?	Confounders	Method
BRCA true negative						
Bernholtz et al, 2012[235] **[True negative group only]**	All mutation carrying families and 1318 female individuals genotyped for mutation carriers from within the 884 families.	Observed in study vs. expected in Israeli population BC: 20 vs. 23.8; SIR, 0.84 (95% CI, 0.51 to 1.30) BC <50 years: 9 vs. 6.4; SIR, 1.41 (95% CI, 0.64 to 2.67) BC >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).	NR	NR	Information was collected on age and cancer status. It is not clear if information was available on prophylactic surgery and vital status.	NA
Domchek et al, 2010[177]	All subjects were tested for the known mutation in the family.	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	NR	Cancer status was obtained by personal report or from a family member.	Information was collected on age, cancer status, vital status, and prophylactic surgery. DCIS and invasive cancer were reported separately.	NA
Gronwald et al, 2007[180]	140/261 (54%) of sisters received direct testing. Genotypes are assigned probabilistically for untested women, adjusted for cancer status and vital status.	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	NR	It is not reported how cancer status was determined.	Not reported if information was collected on prophylactic surgery. Did not distinguish between DCIS and invasive breast cancer.	NA

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Who was tested?	Results/conclusions	Quality considerations			
			Definition of clinically significant	How was cancer status ascertained?	Confounders	Method
Harvey et al, 2011[181]	Unaffected mutation negative women coming from families with known mutations.	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)	NR	Cancer status was verified by pathology reports.	Information was collected on age, cancer status, prophylactic surgery, and vital status.	NA
Korde et al, 2011[184]	All subjects tested, or genotype was available by direct inference.	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)	NR	Cancer status was obtained from the subject or a family member by questionnaire. All cancer diagnoses were confirmed by review of the pathology reports.	Information was collected on age, cancer status, vital status, and prophylactic surgery. Did not distinguish between DCIS and invasive breast cancer.	NA
Kramer et al, 2005[185] **[Mutation Negative Group Only]**	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.	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)	NR	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.	Information was collected on prophylactic surgery, age, cancer status, and vital status.	NA

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Who was tested?	Results/conclusions	Quality considerations			
			Definition of clinically significant	How was cancer status ascertained?	Confounders	Method
Kurian et al, 2011[186]	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.	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)	Mutations were classified as deleterious if they were protein-truncating, missense, or slice-site mutations as defined by the Breast Cancer Information Core.	It is not clear how family cancer status information was collected or verified.	It is not clear whether information was collected on prophylactic surgery or vital status. Did not distinguish between DCIS and invasive breast cancer.	NA
Rowan et al, 2007[195]	All subjects tested.	Observed vs. expected BC: 3 vs. 1.0; SIR, 2.9 (95% CI, 1.0 to 8.6) OC: 0 vs. NR	NR	Personal cancer history was collected by survey.	It is not clear whether information was collected on prophylactic surgery. Did not distinguish between DCIS and invasive breast cancer.	NA
Smith et al, 2007[197]	Multiple members of each family were tested. Untested individuals had genotypes assigned probabilistically based on age and cancer status.	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) All 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 negativ e 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.	NR	Cancer status was reported by a family member and confirmed by means of hospital or pathology records, regional cancer registries, or death certification.	Information was collected on age, cancer status, vital status, and prophylactic surgery. Did not distinguish between DCIS and invasive breast cancer.	NA

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Who was tested?	Results/conclusions	Quality considerations			
			Definition of clinically significant	How was cancer status ascertained?	Confounders	Method
van der Kolk et al, 2010[201] **[Testing Negative Group Only]**	Probands and some family members. Noncarriers were defined as women who tested negative for a known familial mutation in either *BRCA1* or *BRCA2*.	Observed vs. expected BC in *BRCA1* group: 5 vs. 2.5; age- and period-adjusted SIR, 2.0 (95% CI, 0.7 to 4.7) OC in *BRCA1* group: 0 vs. 0.3; age- and period-adjusted SIR, 0 (95% CI, 0 to 12) BC in *BRCA2* group: 4 vs. 1.6; age- and period-adjusted SIR, 2.5 (95% CI, 0.7 to 6.3) OC in *BRCA2* group: 0 vs. 0.2; age- and period-adjusted SIR, 0 (95% CI, 0 to 20.4)	NR	Cancer status was reported by the family. Cancer cases were confirmed by hospital or pathology records or else through a first degree family member.	DCIS was included as breast cancer. Information was collected on age, cancer status, vital status, and prophylactic surgery.	NA
BRCA positive-single						
Chen et al, 2006[122]	Proband	*BRCA1* carriers vs. *BRCA2* 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)	NR	NR	It is not clear if information was collected on prophylactic surgery or vital status.	The retrospective likelihood approach was used.
Finkelman et al, 2012[179] **[Prospective participants only]**	Proband	BC vs. OC *BRCA1*, 185delAG (ref nonCJM): HR, 1.23 (95% CI, 0.87 to 1.73) vs. 0.97 (95% CI, 0.58 to 1.63) *BRCA1*, 5382insC (ref nonCJM): HR, 1.53 (95% CI, 0.96 to 2.45) vs. 0.61 (95% CI, 0.27 vs. 1.38) *BRCA2*, 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).	NR	NR	Information was collected on prophylactic surgery, age, cancer status, and vital status.	Cumulative incidence of cancer based on method adapted from Antoniou et al, 2003.

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Who was tested?	Results/conclusions	Quality considerations			
			Definition of clinically significant	How was cancer status ascertained?	Confounders	Method
Lubinski et al, 2012[187]	Proband	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).	NR	Cancer status was reported by the proband and 70% were confirmed with pathology reports.	Information was collected on prophylactic surgery, age, cancer status, and vital status.	Theoretical penetrance curves up to age 70, for age-specific cancer rates calculated based on 5-year intervals.
Marroni et al, 2004[188]	Probands. Not reported if other family members tested.	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)	NR	Cancer status was reported by family members for FDRs and SDRs of the proband.	It is not clear if information was collected on prophylactic surgery	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

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Who was tested?	Results/conclusions	Quality considerations			
			Definition of clinically significant	How was cancer status ascertained?	Confounders	Method
						(MCMC) method implemented in BRCAPRO.
Metcalfe et al, 2010[220]	Proband	0 FDRs vs. 1 FDR vs. ≥2 FDRs diagnosed with BC at age ≤50 years *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%	NR	Cancer status was reported by the proband.	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

Author, year	Who was tested?	Results/conclusions	Quality considerations			
			Definition of clinically significant	How was cancer status ascertained?	Confounders	Method
Risch et al, 2006[1895]	Proband	*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)	Founder mutations; shortened, non-functional proteins; substitutions producing premature termination codons; mutations reported previously as documented in the BIC database or elsewhere.	Investigators reviewed pathology reports to determine eligibility for the proband. Family history information was reported by the proband through telephone interview.	It is not clear if information was collected on prophylactic surgery	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.
BRCA positive-multi						
Al-Mulla et al, 2009[172]	Probands and their family members.	Median age at onset for BC (years) 185delAG mutation in exon 2: 55 4184delTCAA mutation in exon 11: 47 Exon 13 duplication: 41	NR	Not clear.	Information was collected on age, cancer status, and vital status.	Cox proportional hazards regression adjusting for clustering within families using robust standard errors by the method of Lin and Wei.

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Who was tested?	Results/conclusions	Quality considerations			
			Definition of clinically significant	How was cancer status ascertained?	Confounders	Method
Antoniou et al, 2006[173]	Families were included that had ≥1 mutation carrier identified and ≥1 further family member had DNA testing after the mutation carrier was identified.	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)	NR	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.	It was not reported whether prophylactic surgery was collected.	Penetrance parameters were estimated by maximum likelihood using a modified segregation analysis implemented in MENDEL.
Evans et al, 2008[178]	Index case and some family members. Testing is offered to all blood relatives. Where possible, all affected women with breast/ovarian cancer are tested.	*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).	NR	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.	Information was collected on age, cancer status, prophylactic surgery, and vital status. DCIS was included as breast cancer.	Penetrance analysis was performed by including all mutation positive individuals and appropriate numbers of untested FDRs on a proportional basis.
Kramer et al, 2005[185] **[Mutation Carrier Group Only]**	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.	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)	NR	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.	Information was collected on prophylactic surgery, age, cancer status, and vital status.	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

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Who was tested?	Results/conclusions	Quality considerations			
			Definition of clinically significant	How was cancer status ascertained?	Confounders	Method
						event. A Cox proportional hazards model incorporated oophorectomy as a time-dependent covariate to estimate the effect oophorectomy on the incidence of breast cancer. To provide estimate of the absolute risk of breast cancer by age in mutation carriers, oophorectomy was treated as time-fixed covariate as defined at the beginning of a given age interval. Followup time was divided into 10 year intervals. A competing risks model (with death as the competing risk) was then used to estimate the 10 year cumulative incidence.
Milne et al,	Probands and ≥1	*BRCA1*	Deleterious if	Cancer status was	Information was	Penetrance

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Who was tested?	Results/conclusions	Quality considerations			
			Definition of clinically significant	How was cancer status ascertained?	Confounders	Method
2008[191]	family member were tested.	Penetrance to age 70: 52% (95% CI, 26 to 69) for BC and 22% (95% CI, 0 to 40) for OC *BRCA2* Cumulative risk to age 70: 47% (95% CI, 29 to 60) for BC and 18% (95% CI, 0 to 35) for OC	they a) were classified as "clinically important" 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 consequen-ces; 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.	collected on age, cancer status, prophylactic surgery, and vital status.	parameters were estimated by maximum likelihood using a modified segregation analysis implemented in MENDEL.

Appendix C8. Evidence Table of Penetrance of BRCA-Related Cancer

Author, year	Who was tested?	Results/conclusions	Quality considerations			
			Definition of clinically significant	How was cancer status ascertained?	Confounders	Method
			pathogenicity			
van der Kolk et al, 2010[201] **[Mutation Carriers Group Only]**	Probands and some family members. Obligate carriers were defined if a child as well as a parent or sibling carried a BRCA mutation.	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)	NR	Cancer status was reported by the family. Cancer cases were confirmed by hospital or pathology records or else through a first degree family member.	DCIS was included as breast cancer. Information was collected on age, cancer status, vital status, and prophylactic surgery.	Cumulative incidence was estimated using Kaplan-Meier survival analysis.

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

Author, year Quality	Subcategory	Purpose	Study type	N	Country	Population/Setting
Current report						
Arver et al, 2004[235] NA	Psychological	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.	Before and after	Eligible: NR Enrolled: 66 Analyzed: 63 at week 1 and 2 months, 61 at 6 months, 59 at 12 months	Sweden	Clinical Genetic Unit, Karolinska University Hospital, Stockholm
Dagan and Shochat, 2009[236] Fair Same population as Shochat and Dagan, 2010[247]	Psychological Cancer worry	To investigate the association between *BRCA1/2* status and HR-QOL in Ashkenazi asymptomatic women.	Case-control	Eligible: 152 (39 carriers, 77 noncarriers, 36 controls) Enrolled: 73 (17 carriers, 20 noncarriers, 36 controls) Analyzed: 73 (17 carriers, 20 noncarriers, 36 controls)	Israel	Rambam Health Care Campus oncogenetic clinic
Ertmanski et al, 2009[237] NA	Psychological	To predict which women might suffer from abnormally high levels of anxiety and depression after receiving a positive genetic test result.	Before and after	Eligible: NR Analyzed: 56	Poland	Women seeking genetic testing at cancer genetics center in Poland. Women who tested positive for BRCA were included in analysis.
Foster et al, 2007[238] Fair	Cancer worry	To assess long-term impact of genetic testing for breast/ovarian cancer predisposition in a clinical cohort.	Prospective cohort	Eligible: NR Analyzed: 154	U.K.	Recruited from 9 U.K. centers between 1997 and 2000
Geirdal et al, 2005[240] Good Same population as Geirdal and Dahl, 2008[239]	Psychological	To explore psychological distress in women at risk of FBOC and HNPCC cancer and without access to genetic testing, and to compare them with mutation carriers and with healthy women from the general population.	Prospective cohort	Eligible: 10,321 (253 FBOC, 10,000 normal controls, 68 *BRCA1* mutation carriers) Enrolled: 10,244 (176 FBOC, 10,000 normal controls, 68 *BRCA1* mutation carriers) Analyzed: 10,244 (176 FBOC, 10,000 normal controls, 68 *BRCA1* mutation carriers)	Norway	Section for Genetic Counseling, Department of Cancer Genetics, The Norwegian Radium Hospital
Geirdal and Dahl, 2008[239] Good Same population as Geirdal et al, 2005[240]	Psychological	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.	Prospective cohort	Eligible: 333 (253 FBOC, 80 *BRCA1* mutation carriers) Enrolled: 242 (174 FBOC, 68 *BRCA1* mutation carriers) Analyzed: 242 (174 FBOC, 68 *BRCA1* mutation carriers)	Norway	Section for Genetic Counseling, Department of Cancer Genetics, The Norwegian Radium Hospital

Appendix C9. Evidence Table of Distress After Genetic Testing

Author, year Quality	Subcategory	Purpose	Study type	N	Country	Population/Setting
Graves et al, 2012[241] NA	Psychological	To examine long-term psychosocial outcomes in a large U.S. sample.	Case-series	Eligible: 655 Enrolled: 464 Analyzed: 107 (unaffected)	U.S.	Women at the Lombardi Comprehensive Cancer Center Familial Cancer Registry
Julian-Reynier et al, 2011[242] Good	Risk perception	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.	Prospective cohort	Eligible: 331 Analyzed: 246	France	French Cancer Genetic Network
Kinney et al, 2005[243] Poor	Psychological	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.	Prospective cohort	Eligible: NR Analyzed: 52	U.S.	Members of a high-risk African American kindred that was identified previously with the *BRCA1* mutation
Low et al, 2008[244] Fair	Psychological	To examine the relationship between mutation carrier status, personal cancer history, and the potential positive impact of genetic testing.	Prospective cohort	Eligible: NR Analyzed: 47	U.S.	UCLA Familial Cancer Registry and Genetic Evaluation Program
Metcalfe et al, 2012[249] NA	Psychological	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 postive BRCA mutation result.	Before and after	Eligible: 22 Enrolled: 19 Analyzed: 17	Canada	Jewish women responding to a newspaper ad
Reichelt et al, 2004[245] Good	Psychological	To examine the short-term psychological impact of receiving definite results concerning *BRCA1* mutation status in a clinical setting.	Prospective cohort	Eligible: 301 Enrolled: 244 Analyzed: 209	Norway	Unit of Medical Genetics, The Norwegian Radium Hospital
Reichelt et al, 2008[246] NA	Psychological	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.	Before and after	Eligible: NR Analyzed: 181	Norway	Section for Hereditary Cancer, Department of Medical Genetics, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway

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Author, year Quality	Subcategory	Purpose	Study type	N	Country	Population/Setting
Shochat and Dagan, 2010[247] Fair Same population as Dagan and Schochat,2009[236]	Insomnia	To investigate the association between positive genetic diagnosis for *BRCA1/2* founder mutations and symptoms of insomnia in Ashkenazi asymptomatic women.	Case-control	Eligible: 152 (39 carriers, 77 noncarriers, 36 controls) Enrolled: 73 (17 carriers, 20 noncarriers, 36 controls) Analyzed: 73 (17 carriers, 20 noncarriers, 36 controls)	Israel	Rambam Health Care Campus oncogenetic clinic between 1996 and 2006
van Dijk et al, 2006[248] Good	Cancer worry	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.	Prospective cohort	Eligible: NR Enrolled: 133 Analyzed: 132	The Netherlands	Department of Clinical Genetics in Leiden or Rotterdam between 1995 and 2002, in families where a BRCA mutation was already detected
Prior report						
Meiser et al, 2002[250] Good	Psychological	To study the psychological adjustment of women who have undergone testing for *BRCA1/2* breast and ovarian cancer susceptibility.	Prospective cohort	Eligible: NR Enrolled: 143 (30 carriers, 60 noncarriers, and 53 controls) Analyzed: 140 (30 carriers, 59 noncarriers, and 51 controls)	Australia	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

Author, year Quality	Demographics	Inclusion/Exclusion criteria	Risk level definition	Mutation status	Measures
Current report					
Arver et al, 2004[235] NA	Mean age of 40.5 years (SD 11.1)	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 Exclusion: Individuals with cancer and men	Women with a 50% or 25% risk of being gene carriers	BRCA carriers and noncarriers	Hospital Anxiety and Depression Scale (HADS, each subscale 0 to 21) Swedish SF-36 Health Survey (SF-36, scale NR)
Dagan and Shochat, 2009[236] Fair Same population as Shochat and Dagan, 2010[247]	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)	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	FDR and/or SDR with breast or ovarian cancer and/or relative with other cancer	BRCA carriers and noncarriers	Health-Related Quality of Life (HR-QOL, scale NR) Cancer Related Worry (CRW, scale NR) The Brief Symptom Inventory (BSI, scale NR)

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Author, year Quality	Demographics	Inclusion/Exclusion criteria	Risk level definition	Mutation status	Measures
Ertmanski et al, 2009[237] NA	NR for women without breast cancer	Inclusion: Women who tested positive for BRCA mutation and completed both baseline and followup measures Exclusion: NR	Positive family history of early onset breast or ovarian cancer	BRCA positive	State-Trait Anxiety Inventory (STAI, scale 1 to 10) Impact of Events Scale (IES, scale 0 to 75)
Foster et al, 2007[238] Fair	Median age 42 years (range: 23-72)	Inclusion: Unaffected by cancer and from families with a *BRCA1/2* mutation identified in an affected blood relative Exclusion: NR	50% risk of inheriting a *BRCA1/2* mutation, this was lower if intervening relative had died	BRCA carriers and noncarriers	General Health Questionnaire (GHQ-28, scale 0 to 28) Cancer worry scale-revised (CWS-R, scale 6 to 24)
Geirdal et al, 2005[240] Good Same population as Geirdal and Dahl, 2008[239]	Mean age (years): FBOC: 40.5 (SD 9.7) *BRCA1* carriers: 42.0 (SD 10.6) Controls: 42.5 (SD 10.9)	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	Family history of ≥2 FDRs (or SDR though males) with early onset (<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	BRCA positive FBOC, mutation status unknown	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)
Geirdal and Dahl, 2008[239] Good Same population as Geirdal et al, 2005[240]	Mean age (years): FBOC: 40.5 (SD 9.7) *BRCA1* carriers: 42.0 (SD 10.6)	Inclusion: FBOC: Women age ≥18 years, had been to genetic counseling at Section for Genetic Counseling *BRCA1* positive: Women age ≥18 years, had been to genetic counseling and testing 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	Family history of ≥2 FDRs (or SDRs though males) with early onset (<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	BRCA positive FBOC, mutation status unknown	Hospital Anxiety and Depression Scale (HADS, anxiety subscale 0 to 21) Coping Orientation to Problems Experienced Scale (COPE, scale varied for each coping strategy)
Graves et al, 2012[241] NA	NR for women without breast cancer	Inclusion: Women ages 25 to 75 years, received *BRCA1/2* test results, and were at least 3 years postdisclosure at the time of the study Exclusion: Not reported	NR	47/107(43.9%) BRCA positive 60/107 (56.1%) BRCA true negative	Impact of Events Scale (IES, scale 0 to 75) State-Trait Anxiety Inventory (STAI, scale 20 to 80)
Julian-Reynier et al, 2011[242] Good	Mean age (years) Carriers: 37.2 Noncarriers: 41.7	Inclusion: *BRCA1/2* mutation carriers and noncarriers in the same families Exclusion: NR	*BRCA1/2* mutation carriers or members of families where a mutation was identified	101/246 (41%) *BRCA1/2*	Perception of personal risk of cancer (6-point Likert scale) Preventive health behaviors

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Author, year Quality	Demographics	Inclusion/Exclusion criteria	Risk level definition	Mutation status	Measures
Kinney et al, 2005[243] 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, 2008[244] 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, 2012[249] 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, 2004[245] 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, 2008[246] 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)

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Author, year Quality	Demographics	Inclusion/Exclusion criteria	Risk level definition	Mutation status	Measures
Shochat and Dagan, 2010[247] Fair Same population as Dagan and Schochat,2009[236]	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)	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	FDR and/or SDR with breast or ovarian cancer and/or relative with other cancer	BRCA carriers and noncarriers	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)
van Dijk et al, 2006[248] Good	NR for women without breast cancer	Inclusion: Women from a family with a previously detected BRCA mutation, age ≥18 years, and had not previously received genetic counseling elsewhere Exclusion: NR	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) <30% personal risk estimate for low risk and 2) ≥30% personal risk estimate for high-risk	BRCA positive, true negative, and uninformative results	Impact of Events Scale (IES, scale 0 to 75) Breast cancer worry question of "During the last 2 weeks, how often did you worry about developing breast cancer?" (Likert scale ranging from 1=almost never to 4=almost all the time)
Prior report					
Meiser et al, 2002[250] Good	Mean age of 40 years (SD 11.1)	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	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	BRCA carriers and noncarriers	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)

Appendix C9. Evidence Table of Distress After Genetic Testing

Author, year Quality	Duration of followup	Results	Conclusions	Funding source
Current report				
Arver et al, 2004[235] NA	1995-1999 At 1 week, 2, 6, and 12 months	**Pretest vs. 1 week posttest vs. 2 months posttest vs. 6 months posttest vs. 1 year posttest** Mean on psychological scale HADS-A (estimated from graph): 5.6 vs. 4.6 vs. 4.0 vs. 4.0 vs. 4.2; p<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	Anxiety went down over time, however depression and QOL were not affected. The results were not separated out by carriers and noncarriers though.	King Gustav V's Jubilee Fund and the Swedish Cancer Society
Dagan and Shochat, 2009[236] Fair Same population as Shochat and Dagan, 2010[247]	January 2006-November 2007 Mean followup of 8.0 years (SD 1.9)	**Carriers (n=17) vs. noncarriers (n=20) vs. controls (n=36)** 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	Carriers had higher QOL distress regarding role limitation due to emotional problems and physical problems compared to noncarriers and controls.	NR
Ertmanski et al, 2009[237] NA	January 2005-December 2007 At 1 month and 1 year	**Pretest vs. 1 month posttest vs. 1 year posttest** 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	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.	Polish Ministry of Science and Higher Education grant number 2 PO5 D 129 29
Foster et al, 2007[238] Fair	1997-2000 3 years	**Carriers (n=53) vs. noncarriers (n=101)** 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	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.	Award C1226/A137 from Cancer Research U.K.

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Author, year Quality	Duration of followup	Results	Conclusions	Funding source
Geirdal et al, 2005[240] Good Same population as Geirdal and Dahl, 2008[239]	January 2000-December 2001	**FBOC (n=176) vs. carriers (n=68) vs. controls (n=10,000)** Mean differences on psychological scales (SD) HADS-D: 2.4 (2.9) vs. 1.7 (2.4) vs. 3.2 (2.9); p<0.05 FBOC vs. carriers HADS-A: 5.2 (3.8) vs. 4.2 (3.6) vs. 4.5 (3.5); p<0.05 FBOC vs. carriers GHQ-28: 3.3 (5.4) vs. 2.3 (4.0) vs. NR; p<0.05 FBOC vs. carriers IES-I: 10.2 (8.7) vs. 9.8 (7.6) vs. NR; p=NS IES-A: 8.3 (7.9) vs. 8.4 (7.6) vs. NR; p=NS BHS: 3.7 (2.5) vs. 3.8 (2.6) vs. NR; p=NS	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.	Norwegian Foundation for Health and Rehabilitation, National Council for Mental Health, Norway, and a donation from Edith Kongshe, Oslo
Geirdal and Dahl, 2008[239] Good Same population as Geirdal et al, 2005[240]	January 2000-December 2001	**FBOC (n=174) vs. carriers (n=68)** Mean HADS-A: 5.3 (SD, 3.9) vs. 4.2 (SD, 3.6); p=0.04 Prevalence of HADS-defined anxiety: 24% vs. 24%; p=NS Mean (SD) on subscales of COPE with significant differences, higher scores=strategy used more often Active coping: 10.2 (3.2) vs. 8.7 (3.2); p=0.002 Planning: 9.1 (3.5) vs. 7.9 (3.7); p=0.01 Suppression of competing activities: 6.7 (2.7) vs. 5.2 (2.3); p<0.001 Focus on and venting of emotions: 8.1 (3.6) vs. 6.2 (2.7); p<0.001 Seeking instrumental support: 10.2 (3.6) vs. 7.4 (3.1); p<0.001 Seeking emotional support: 9.4 (3.3) vs. 7.9 (2.7); p=0.003 Acceptance: 12.4 (3.1) vs. 13.3 (2.9); p=0.01 Mental disengagement: 6.7 (2.8) vs. 6.0 (2.2); p=0.03 NS COPE subscales: positive reinterpretation and growth, restraint coping, denial, behavioral disengagement, turning to religion, and use of humor	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* mutations 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.	Norwegian Foundation for Health and Rehabilitation, National Council for Mental Health, Norway, and a donation from Edith Kongshe, Oslo
Graves et al, 2012[241] NA	Years NR Median of 5 years posttest	**Logistic regression bivariate analysis (statistically significant associations)** 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)** Genetic testing distress 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 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 Positive experiences 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	Among unaffected women, *BRCA1/2* carriers reported higher genetic testing distress and lower positive experiences compared with *BRCA1/2* true negatives.	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

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Author, year Quality	Duration of followup	Results	Conclusions	Funding source
		true negative) accounted for an additional 6% of variance in positive experiences; p=0.008		
Julian-Reynier et al, 2011[242] Good	2000-2006 5 years	**Carriers (n=101) vs. noncarriers (n=145)** Change from before test result to after test result of those who perceived personal risk as high Breast cancer risk: +18% vs. -47%; p=0.016 for carriers change and p<0.001 for noncarriers change Ovarian cancer risk: +20% vs. -27%; p=0.007 for carriers change and p<0.001 for noncarriers change	Carriers perception of risk increased after receiving genetic test results, while noncarriers perception of risk decreased.	Institute National du Cancer
Kinney et al, 2005[243] Poor	Year NR 4 month	Noncarriers unaffected with breast cancer decreased anxiety from baseline to 1 month followup; p=0.001, data not shown	Noncarriers anxiety went down after receiving genetic test results.	National Human Genome Research Institute, National Institute of Nursing Research and the National Cancer Institute
Low et al, 2008[244] Fair	September 1998-Fall 2003 Average of 20.9 months	**Carriers (n=7) vs. noncarriers (n=40)** Mean on psychological scale (SE) PTGI total score (estimated from graph): 14 vs. 22; p=NR IES-R at 1-month posttest: 5.83 (2.47) vs. 1.37 (0.10); p<0.05 Approach coping score: 2.32 (0.18) vs. 2.37 (0.14); p=NS	Women with BRCA positive mutations reported greater distress after testing than noncarriers, but did not report differences in positive life changes.	STOP CANCER Research Career Development Award
Metcalfe et al, 2012[249] NA	Years NR 2 years	**Pretest vs. 1 year posttest vs. 2 years posttest** Mean IES-I (SD): 1.1 (1.9) vs. 10.9 (8.6) vs. 6.9 (6.2); p=0.02 Mean IES-A (SD): 4.1 (8.7) vs. 12.9 (8.2) vs. 10.4 (9.4); NS Mean IES-total (SD): 5.2 (10.5) vs. 23.8 (14.5) vs. 17.2 (14.5); p=0.05 **2 years posttest clinical distress levels** 2/19 (11%) severe distress (score ≥44) 4/19 (21%) moderate distress (score 26-43) 7/19 (37%) mild distress (score 9-25) 6/19 (32%) subclinical distress (score <9)	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	NR
Reichelt et al, 2004[245] Good	September 1997-October 1999 6 weeks	**Carriers (n=141) vs. noncarriers (n=68)** Mean on psychological scales (SD) at followup; all p=NS IES-I: 9.8 (7.6) vs. 9.3 (8.0) IES-A: 8.4 (7.6) vs. 7.6 (7.4) HADS-A: 4.2 (3.6) vs. 4.1 (3.9) HADS-D: 1.7 (2.4) vs. 2.3 (2.7) GHQ-28: 2.3 (4.0) vs. 2.4 (4.5) BHS: 3.8 (2.6) vs. 4.0 (2.8) **Tested (n=244) vs. not tested (n=57)** Mean on psychological scales (SD) at baseline IES-I (subscale 0 to 35): 8.8 (7.5) vs. 8.9 (7.3); p=NS IES-A (subscale 0 to 40): 8.0 (7.1) vs. 7.7 (7.3); p=NS	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.	A grant from the Norwegian Research Council

Appendix C9. Evidence Table of Distress After Genetic Testing

Author, year Quality	Duration of followup	Results	Conclusions	Funding source
		HADS-A (subscale 0 to 21): 4.4 (3.8) vs. 4.1 (3.2); p=NS HADS-D (subscale 0 to 21): 2.0 (2.6) vs. 1.3 (1.8); p<0.05 GHQ (scale 0 to 84): 2.5 (4.2) vs. 2.0 (3.2); p=NS BHS (scale 0 to 20): 4.0 (2.7) vs. 3.7 (2.1); p=NS		
Reichelt et al, 2008[246] NA	September 1997-October 1999 At 6 weeks and 8 months	**Pretest vs. 6 weeks posttest vs. 18 months posttest** Mean psychological scales (SD) HADS: 6.6 (6.1) vs. 6.2 (6.1) vs. 6.9 (6.9); p=NS IES-I: 9.3 (7.8) vs. 9.0 (7.8) vs. 8.7 (7.9); p=NS	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.	Norwegian Research Council grant number 115586/320
Shochat and Dagan, 2010[247] Fair Same population as Dagan and Schochat, 2009[236]	January 2006-November 2007 Mean followup of 8.0 years (SD 1.9)	**Carriers (n=17) vs. noncarriers (n=20) vs. controls (n=36)** Reported sleep problems (PSQI >5): 53% vs. 20% vs. 28%; p=0.03 for carriers vs. other groups <u>Mean on sleep measures (SD)</u> 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 <u>Correlations between PSQI total score and other measures</u> 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 <u>Linear regression model predictors of PSQI total score (poor sleep quality)</u> 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<0.001	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.	NR

Appendix C9. Evidence Table of Distress After Genetic Testing

Author, year Quality	Duration of followup	Results	Conclusions	Funding source
van Dijk et al, 2006[248] Good	1998-2002 At 1 and 7 months	**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<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<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<0.05 for positive group vs. other groups and p<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<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<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<0.05 for positive group vs. other groups	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.	The Dutch Cancer Society Grant number UL 98-1740

Appendix C9. Evidence Table of Distress After Genetic Testing

Author, year Quality	Duration of followup	Results	Conclusions	Funding source
Prior report				
Meiser et al, 2002[250] 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.

Appendix C10. Evidence Table of Intensive Screening Interventions

Author, year Quality	Design	Purpose	Population/ setting	Inclusion/exclusion criteria	Risk level definitions
Breast cancer					
Cortesi et al, 2006[273] NA Modena Study Group for Familial Breast and Ovarian Cancer participants	Prospective cohort (Expected incidence ratio derived from registry data)	To describe the results of an intensive surveillance program and document effectiveness of the program in selecting individuals at risk of breast cancer	Italy Women with increased risk of breast cancer	Inclusion Women age >18 years with *BRCA1/2* mutations discovered through genetic testing or increased risk for breast cancer relative to the general population based on Gail model, Claus tables, and modified BRCAPro model (adapted to the Italian population) and study defined criteria: ≥3 relatives diagnosed with breast or ovarian cancer in 2 different generations; ≥1 of these 3 relatives must be FDR of 1 of the other 2, in case of male interposition, a relationship of different degree is allowed; ≥1 breast cancer diagnosed at age <35 years regardless of family history; ≥1 breast cancer and 1 ovarian cancer in the same woman, regardless of family history; ≥1 male breast cancer, regardless of family history; 1 sporadic breast cancer or ovarian cancer Exclusion Women with symptoms suggestive of breast cancer; women with a personal history of breast cancer	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 <40 years or with bilateral breast cancer; breast cancer diagnosed at age <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.
Leach, 2005[274] NAMARIBS study	Prospective cohort, one-arm	To compare contrast enhanced MRI with mammography for breast cancer screening in women genetically predisposed to breast cancer	U.K. Women attending 1 of 22 participating centers in the U.K. with increased breast cancer risk	Inclusion Asymptomatic women ages 35 to 49 years fulfilling 1 of the following: 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. Aim was to include women whose affected FDRs had ≥60% chance of being a *BRCA1/2* mutation carrier or women with an annual risk of at least 0.9%. Exclusion Women with previous breast cancer, those with any cancer such that prognosis was <5 years, participants who had predictive genetic testing during study and whose results were negative, women who developed cancer during study period.	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.

Appendix C10. Evidence Table of Intensive Screening Interventions

Author, year Quality	Design	Purpose	Population/ setting	Inclusion/exclusion criteria	Risk level definitions
Le-Petross et al, 2011[276] NA	Retrospective analysis of prospective cohort, one-arm	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	United States Women at increased genetic risk of breast cancer at single institution	Inclusion 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. Exclusion Women with history of breast cancer, who had calculated lifetime risk of breast cancer >20%, or who did not undergo a screening MRI, women who used chemoprevention or underwent bilateral prophylactic mastectomy, those with metastatic disease, undergoing treatment, or high BMI preventing MRI, women lost to followup, or died during original trial.	Based on BRCA status.
Rijnsburger et al, 2010[278] See also Kriege et al, 2004[277] NA Dutch MRISC study	Prospective cohort (Registry data/data from another prospective study used for cancer characteristics comparison)	To evaluate the long-term results of the Dutch MRI Screening (MRISC) study, including separate analyses of *BRCA1/2* mutation carriers and survival results	The Netherlands Women with increased familial or genetic predisposition for breast cancer attending academic and/or cancer centers at 6 sites	Inclusion 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). Exclusion Women with symptoms suggestive of breast cancer or who had a personal history of breast cancer; women proven not to have a mutation in a family with a proven mutation.	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.
Ovarian Cancer					
Hermsen et al, 2007[281] NA	Prospective cohort, one-arm (staging compared to 2 external comparison groups; unscreened family members with cancer, combined data from multiple studies)	To assess efficacy of annual gynecological screening, accounting for compliance to protocol	The Netherlands Women with BRCA mutation screened at 6 University Family Cancer Clinics	Inclusion Women with *BRCA1/2* mutation screened at 1 of participating centers. Exclusion Women with symptoms at first visit, who had only 1 visit, or who were found to have cancer at first screening visit.	Based on BRCA status.

Author, year Quality	N	Baseline Demographics	Screening method and interval	Scoring criteria

Appendix C10. Evidence Table of Intensive Screening Interventions

Author, year Quality	N	Baseline Demographics	Screening method and interval	Scoring criteria
Breast cancer				
Cortesi et al, 2006[273] NA Modena Study Group for Familial Breast and Ovarian Cancer participants	1325 enrolled 48 mutation carriers (37 *BRCA1* and 11 *BRCA2*) 674 high risk 257 intermediate risk 346 slightly increased risk	Mean age at surveillance (range), years Carrier: 42 (20-75) High-risk: 42 (15-75) Intermediate risk: 43 (19-67) Slightly increased risk: 40 (18-75)	From 1994 to September 2000 all women underwent: A) Mammography B) Ultrasonography C) CBE D) Transvaginal ultrasound and serum CA 125 levels Testing interval varied by assessed risk (see below). From October 2000 mutation carrier surveillance modified to include: E) CE MRI BRCA risk: Started at age 25 with annual mammography and MRI, biannual CBE and ultrasound plus transvaginal ultrasound and serum CA 125 levels. High risk: Started at age 30 with mammography every 2 years until age 36 and then annually, biannual CBE and ultrasound plus annual transvaginal ultrasound and serum CA 125 levels. Intermediate risk: Started at age 30 with mammography every 2 years until age 40 and then annually, biannual CBE and ultrasound plus annual transvaginal ultrasound and serum CA 125 levels. Slightly increased risk: Started at age 30 with 1 mammogram < 40 years, then every 18 to 24 months, and annual CBE and ultrasound. 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.	
Leach, 2005[274] NAMARIBS study	649 analyzed 82 (13%) with known *BRCA1* mutation 38 (6%) with known *BRCA2* mutation	Median age at entry, years: 40 (range, 31-55; only 1 woman age >50 years)	All women underwent: A) Annual mammography from age 35 years (or younger if FDR developed cancer at age <35 years) B) Annual CE MRI 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.	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.

Appendix C10. Evidence Table of Intensive Screening Interventions

Author, year Quality	N	Baseline Demographics	Screening method and interval	Scoring criteria
Le-Petross et al, 2011[276] NA	321 screened 73 analyzed (37 [51%] *BRCA1*, 36 [49%] *BRCA2*)	Median age at entry, years: 44 (range, 23-75) Mean age at diagnosis, years: 51 (range, 43-64)	All women underwent CBE every 6 months plus: A) Mammography every 6 months alternating with B) MRI every 6 months Note: Ultrasound used to evaluate abnormal screen findings, biopsy as required.	BIRADS
Rijnsburger et al, 2010[278] See also Kriege et al, 2004[277] NA Dutch MRISC study	2275 enrolled 2157 analyzed (422 *BRCA1*, 172 *BRCA2*, 5 other mutation, 1069 high risk, 489 moderate risk)	Mean age at entry, years: Cohort: 40.1 (range, 19-75) *BRCA1*: 38.7 *BRCA2*: 40.0 High risk: 40.8 Moderate risk: 40.0	All women underwent: A) Biannual CBE B) Annual mammography C) Annual contrast enhanced MRI Note: Both imaging investigations performed on same day or time period when possible, between day 5 and 15 of menstrual cycle. Note: When 1 of the examinations reported "probably benign finding" or "need additional imaging evaluation" (BI-RADS 3 or 0), further investigation undertaken by ultrasonography. Malignancy diagnosis based on histological findings.	BIRADS
Ovarian Cancer				
Hermsen et al, 2007[281] NA	883 (683 *BRCA1*, 200 *BRCA2*) 459 for analysis of screening/ compliance (data available for all screen visits)	Median age, years: *BRCA1*: 40 (range, 21-76) *BRCA2*: 44 (range, 25-77)	All women underwent: A) Annual serum CA-125 measurement B) Annual TVUS Starting at age 35 years or 5 years earlier than youngest diagnosed ovarian cancer in the family Note: Biannual screens were done in some centers during the study period, but this was not systematically adopted.	CA-125: >35kU1-1 abnormal if resulted in extra screen visit or diagnostic operation. TVUS: Abnormal or normal.

Author, year Quality	Duration/ Followup	Outcome: Test characteristics	Cancer incidence
Breast Cancer			
Cortesi et al, 2006[273] NA Modena Study Group for Familial Breast and Ovarian Cancer participants	1992-2005 Median, 55 months (range, 1-151 months)	44 breast cancers detected; 64% (n=28) invasive, 36% (n=16) DCIS 36 screen-detected Carriers: n=5 cancers (4 invasive, 1 DCIS) High risk: n=23 (14 invasive, 9 DCIS) Intermediate risk: n=11 (8 invasive, 3 DCIS) Slightly increased risk: n=5 (2 invasive, 3 DCIS) <u>Sensitivity, A vs. B vs. A+B vs. E</u> All: 78% (28/36) vs. 50% (18/36) vs. 97% (35/36) vs. 100% (4/4) Carriers: 50% (2/4) vs. 75% (3/4) vs. 75% (3/4) vs. 100% (4/4) High risk: 90% (19/21) vs. 52% (11/21) vs. 100% (21/21) Intermediate risk: 50% (4/8) vs. 450% (4/8) vs. 100% (8/8) Slightly increased risk: 100% (3/3) vs. 0% (0/3) vs. 100% (3/3)	Breast cancer incidence in study population vs. expected incidence All: SIR, 4.9 (95% CI, 1.6-7.6), p<0.001 Carriers: SIR, 20.3 (95% CI, 3.1-83.9), p<0.001 High-risk: SIR, 4.5 (95% CI, 1.5-8.3), p<0.001 Intermediate risk: SIR, 7.0 (95% CI, 2.0-17.1), p=0.0018 Slightly increased risk: SIR not significantly increased 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 >85 years; observed women-years at risk were multiplied by expected cancer incidence to estimate total number of cancers expected.

Appendix C10. Evidence Table of Intensive Screening Interventions

Author, year Quality	Duration/ Followup	Outcome: Test characteristics	Cancer incidence
Leach, 2005[274] 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 40% (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<0.0001 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

Author, year Quality	Duration/ Followup	Outcome: Test characteristics	Cancer incidence
		Excluding 6 DCIS cases: 31% (15-51) vs. 86% (68-96), p=0.0009 A plus B: 97% (82-100) Any cancer, excluding *BRCA1* carriers/relatives: 50% (28-72) vs. 68% (45-86), p=0.45 Any cancer, excluding *BRCA2* carriers/relatives: 35% (16-57) vs. 87% (66-97) A plus B: 96% (78-100) Specificity (95% CI), A vs. B All cancers: 94% (92-95) vs. 81% (79-83), p<0.0001	
Le-Petross et al, 2011[276] NA	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	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) 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	13 cancers detected (10 invasive, 3 DCIS) in 11 patients 5/13 cancers detected on first screening cycle (likely prevalent), 8/13 incident cancers 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
Rijnsburger et al, 2010[278] See also Kriege et al, 2004[277] NA Dutch MRISC study	1999-2006 Median, 4.9 years; mean, 4.0 years (range, 0.1 to 6.3 years); followup post diagnosis for mortality Relapse: Median, 5.0 years (range, 1.7-8.4 years)	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 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	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

Appendix C10. Evidence Table of Intensive Screening Interventions

Author, year Quality	Duration/ Followup	Outcome: Test characteristics	Cancer incidence
		Mutation (any breast cancer) *BRCA1*: 13% (2.8-34) vs. 25% (9.8-47) vs. 67% (45-84), p=0.0129 for B vs. C *BRCA2*: 7.7% (0.2-36) vs. 62% (33-86) vs. 69% (39-91), p=1.0 for B vs. C Risk group (any breast cancer) High: 32% (13-56) vs. 46% (24-68) vs. 77% (55-92) Moderate: 33% (9.9-65) vs. 47% (21-73) vs. 67% (38-88) *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. Specificity (95% CI), A vs. B vs. C Any breast cancer: 98% (97.5-98.2) vs. 95 (94.0-95.1) vs. 90 (88.9-90.4) Mutation (any breast cancer) *BRCA1*: 97% (95.7-97.9) vs. 95% (93.0-95.9) vs. 91% (89.1-92.6) *BRCA2*: 98% (96.4-99.4) vs. 94% (90.9-96.0) vs. 92% (88.7-94.5) Risk group (any breast cancer) High: 98% (97.7-98.7) vs. 95% (93.8-95.3) vs. 89% (87.9-90.1) Moderate: 98% (96.9-98.6) vs. 95% (93.5-95.9) vs. 90% (87.8-91.0) PPV (95% CI), A vs. B vs. C Any breast cancer: 10% (5.7-17) vs. 8.5% (5.8-12) vs. 7.7% (5.8-9.9) Mutation (any breast cancer) *BRCA1*: 8.8% (1.8-24) vs. 9.5% (3.6-20) vs. 14% (8.5-22) *BRCA2*: 14% (0.4-58) vs. 26% (12-45) vs. 23% (11-39) Risk group (any breast cancer) High: 9.8% (3.7-20) vs. 5.3% (2.6-9.5) vs. 4.5% (2.6-7.1) Moderate: 12% (3.4-28) vs. 8.5% (3.5-17) vs. 6.2% (3.0-11)	
Ovarian Cancer			
Hermsen et al, 2007[281] NA	1993-2005 1473 person-years	15 cancers diagnosed in cohort Based on 459 women with data on each visit: 7 cancers diagnosed (2 prevalent, 2 interval, 3 incident) Sensitivity (95% CI), A vs. B vs. A+B All cancers: 42% (14-70) vs. 25% (1-50) vs. 42% (14-70) Excluding occult cancers: 71% (38-100) vs. 43% (6-80) vs. 71% (38-100) Specificity (95% CI), A vs. B vs. A+B All cancers: 99% for all (CI range, 98-100) Excluding occult cancers: 99% for all (CI range, 98-100) PPV (95% CI), A vs. B vs. A+B All cancers: 33% (9-57) vs. 20% (0-40) vs. 23% (5-40) Excluding occult cancers: 33% (9-57) vs. 20% (0-40) vs. 23% (5-40) NPV (95% CI), A vs. B vs. A+B All cancers: 99% (99-100) for all	10 cancers diagnosed during followup 5 screen-detected 6.5 cases expected Based on 459 women with data on each visit: 7 cancers diagnosed (2 prevalent, 2 interval, 3 incident) SIR (95% CI) Overall: 1.5 (0.7-2.8) *BRCA1*: 1.7 (0.8-3.1) *BRCA2*: unable to estimate, no event observed Optimally screened women-years (interval between screen visits <13 months): 1.6 (0.5-3.6) 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

Appendix C10. Evidence Table of Intensive Screening Interventions

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

Author, year Quality	Outcome: Cancer characteristics Interval cancers	Outcome: Disease-free survival Mortality	Conclusions	Funding source
Breast Cancer				
Cortesi et al, 2006[273] NA Modena Study Group for Familial Breast and Ovarian Cancer participants	Staging: 61% (n=17) stage I; 25% (n=7) stage II; 7% (n=2) stage III; 7% (n=2) stage IV Size: 29% (n=8) <10 mm in diameter; 36% (n=10) were 10-15 mm in diameter; 32% (n=9) >15 mm in diameter; 1 was inflammatory breast cancer Nodal status: 36% (n=10) node positive 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 DCIS: Screening sensitivity for DCIS increased with age; low rate (65%) in women <50 years; high rate (93%) in oldest age group	Post treatment, 4 recurrences and 3 deaths (2 for disease progression, 1 from heart failure). Actuarial 5 year survival rate was 93%.	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.	Italian consortium for Hereditary Breast and Ovarian Cancer; COFIN-MURST 2003-2005; Faondazione Cassa di Risparmio di Modena; Associazione Angela Serra per la ricerca sul Cancro
Leach, 2005[274] NAMARIBS study	Grade: 10% (3/29) grade 1; 24% (7/29) grade 2; (66%) 19/29 grade 3 Size: 38% (11/29) were <10 mm in greatest dimension; 14% (4/29) were 10-14 mm in greatest dimension; 17% (5/29) were 15-19 mm; 31% (9/29) were ≥20 mm in greatest dimension; average tumor size = 15 mm Nodal status: 81% (21/26) cancers node-negative Interval cancers: n=2 (1 considered benign on MRI and 1 considered benign on mammography; method of detection NR)	NR	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.	Grant from U.K. Medical Research Council; MRI cost paid from subvention funding for research from U.K. National Health Service
Le-Petross et al, 2011[276] NA	Size on MRI: Mean, 14 mm (range, 1-30 mm) Nodal status: 9% (1/11) women node-positive Interval cancers: n=0	NR	Screening women at increased genetic risk of breast cancer by alternating mammography with MRI every 6 months has a higher cancer yield than	NR

Appendix C10. Evidence Table of Intensive Screening Interventions

Author, year Quality	Outcome: Cancer characteristics Interval cancers	Outcome: Disease-free survival Mortality	Conclusions	Funding source
			studies that screened using both modalities at the same time point.	
Rijnsburger et al, 2010[278] See also Kriege et al, 2004[277] NA Dutch MRISC study	<u>Characteristics of detected breast cancer (includes 78 screen-detected cancers and 11 interval cancers)</u> 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 Histology: 29% (21/72) grade 1, 32% (23/72) grade 2, 39% (28/72) grade 3; p1<0.001, p2=0.15 p1=overall comparison between subgroups p2=comparison between *BRCA1* and *BRCA2* Note: Age at diagnosis, number of interval cancers, and estrogen and progesterone receptor status significantly different between subgroups <u>Number of interval cancers (total, invasive, DCIS)</u> *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 <u>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)</u> Number of DCIS: 6 vs. 120 vs. 0 Invasive tumor size ≤1 cm: 19/44 vs. 193/1380 vs. 5/45; p<0.001 vs. control 1, p<0.04 vs. control 2 Nodal status negative: 28/44 vs. 657/1380 vs. 17/45; p<0.001 vs. control 1, p=0.001 vs. control 2 Histological grade 1: 19/44 vs. 99/1380 vs. 4/45; p<0.001 vs. control 1, p=0.01 vs. control 2 Note: Control 1 = National Cancer Registry data of women with breast cancer diagnosed in 1998; Control 2 = participants diagnosed with breast cancer between 1996 and 2002 participating in a prospective study of gene mutation.	<u>Disease-free and overall survival in 89 patients</u> 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%) *BRCA1* and 1/16 (6.3%) *BRCA2* 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	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

Appendix C10. Evidence Table of Intensive Screening Interventions

Author, year Quality	Outcome: Cancer characteristics Interval cancers	Outcome: Disease-free survival Mortality	Conclusions	Funding source
Ovarian Cancer				
Hermsen et al, 2007[281] NA	Stage: 80% (8/10) stage III/IV (4/5 incident, 4/5 interval cancers) vs. 77% (20/26) in unscreened family members with cancer Interval cancers: n=5	After mean followup of 28 months from diagnosis: 3/15 cases died of ovarian cancer	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.	Biocare Foundation

*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

Trial Quality	Design	Purpose	Intervention	Country/population/ setting	Inclusion/exclusion criteria
Tamoxifen vs. placebo					
IBIS-I[287] Fair See also Cuzick 2002[328]	RCT	To report the updated analysis of IBIS-I, focusing on the period after active treatment was completed	Oral tamoxifen 20 mg/day or placebo Groups directly compared, no expected incidence rates but baseline risk assessed using complex model for 10-year risk of ≥5%	United Kingdom (60% of participants), Europe, Australia, and New Zealand (37% of participants) Women at increased risk of breast cancer Recruited from family history clinics, relatives of women with breast cancer, breast screening centers, general practitioners, and the media	Inclusion 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. Exclusion Women with any previous invasive breast cancer, aside from nonmelanoma skin cancer, previous deep vein thrombosis or pulmonary embolism, current users of anticoagulants, or those wishing to become pregnant.
NSABP P-1[284] Fair See also Fisher et al, 1998[71]	RCT	To update the findings from the NSABP P-1 Trial after 7 years of followup	Oral tamoxifen 20 mg/day vs. placebo Note: 2 groups compared directly, no expected incidence rates	United States and Canada Women at increased risk for breast cancer Recruited through 133 clinical centers	Inclusion 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. Exclusion Women who had taken hormone replacement therapy, oral contraception, or androgens within 3 months of randomization; history of DVT or pulmonary embolism.

Appendix C11. Evidence Table of Risk-Reducing Medications

Trial Quality	Design	Purpose	Intervention	Country/population/ setting	Inclusion/exclusion criteria
Royal Marsden[285] Fair See also Powles et al, 1998[70]	RCT	To identify any long-term prevention of breast cancer associated with tamoxifen treatment after 20 years of followup of the Royal Marsden trial	Oral tamoxifen 20 mg/day or placebo Note: 2 groups compared directly, no expected incidence rates	United Kingdom Women at increased risk of breast cancer Recruited from breast clinics at Royal Marsden Hospital	Inclusion 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 <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.
Italian Randomized Tamoxifen Prevention[286] Fair See also Veronesi et al, 1998[72]	RCT	To update the results of the Italian Randomized Tamoxifen Prevention Trial after 11 years of followup, focusing on the occurrence of breast cancer	Oral tamoxifen 20 mg/day vs. placebo Note: 2 groups compared directly, no expected incidence rates	Italy (97% of patients), South America, Greece Healthy women at average risk for breast cancer Recruited via national advertising and through gynecologists	Inclusion Healthy women ages 35 to 70 years who had a hysterectomy for reasons other than neoplasm. Exclusion Women with severe concurrent illness or history of cardiac disease, endometriosis, and suspected or certain previous DVT.
Raloxifene vs. placebo					
RUTH[73] Good See also Barrett-Connor et al, 2006[299]	RCT	To provide further details about breast cancer incidence by tumor characteristics, duration of treatment, and subgroup in the RUTH trial	Oral raloxifene 60 mg/day vs. placebo Note: 2 groups compared directly, no expected incidence rates (5-year risk of invasive breast cancer at baseline based on Gail model)	Multinational Postmenopausal women at increased risk of coronary events Recruited through 177 sites in 26 countries, including the U.S.	Inclusion 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 <5 years; chronic liver or renal disease; recent use of oral or transdermal estrogens or current use of sex hormones or SERMs.

Appendix C11. Evidence Table of Risk-Reducing Medications

Trial Quality	Design	Purpose	Intervention	Country/population/ setting	Inclusion/exclusion criteria
MORE and CORE[288] Good See also Cummings et al, 1999[74]	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					
STAR[289] Good See also Vogel et al, 2006[329]	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

Trial Quality	Assignment/attrition	Demographics	Surveillance	Duration/follow up
Tamoxifen vs. placebo				
IBIS-I[287] Fair See also Cuzick 2002[328]	Tamoxifen vs. placebo 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	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.	5 years of treatment Median followup was 95.6 months
NSABP P-1[284] Fair See also Fisher et al, 1998[71]	Tamoxifen vs. placebo 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 Note: withdrawal rate between year 6 and 7 of followup was higher in the placebo vs. tamoxifen group, resulting in different amounts of information for groups during this period	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%)	NR	5 years of treatment Mean followup was 6.2 years
Royal Marsden[285] Fair See also Powles et al, 1998[70]	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 Note: self-reported compliance was 8% less in the tamoxifen arm vs. placebo (p=0.002); difference seen at 1 year and remained constant over treatment period	Tamoxifen vs. placebo Median age, years (range): 47 (31-70) vs. 47 (30-70) Age <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	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.	8 years of treatment Median followup was 158 months

Appendix C11. Evidence Table of Risk-Reducing Medications

Trial Quality	Assignment/attrition	Demographics	Surveillance	Duration/follow up
Italian Randomized Tamoxifen Prevention[286] Fair See also Veronesi et al, 1998[72]	Tamoxifen vs. placebo 13,419 recruited 4,989 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	Median age at entry: 51 years FDRs with breast cancer, n: None: 2359 (87%) vs. 2407 (89%) ≥1: 341 (13%) vs. 301 (11%) Note: no differences between groups on any baseline characteristics	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.	Mean duration of treatment, 4.2 years Mean followup, 9.1 years (cancers other than breast endpoint) 11.2 years (breast cancer endpoint)
Raloxifene vs. placebo				
RUTH[73] Good See also Barrett-Connor et al, 2006[299]	Raloxifene vs. placebo 10,101 enrolled and randomized: 5044 vs. 5057 Completed 5 years of followup: 4060 (80%) vs. 3979 (79%) Note: 71% of placebo and 70% of raloxifene group took 70% of study medication based on pill counts	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%) Note: no differences between groups on any baseline characteristics Note: Unable to determine number without family history per group because of missing values not accounted for	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.	Median exposure to drug was 5.05 years Median followup, 5.6 years (analysis of data collected before February 2006)
MORE and CORE[288] Good See also Cummings et al, 1999[74]	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	Characteristics at beginning of MORE Age ≥65 years, n (%): 4621/7705; 2563 (60%) of combined raloxifene groups; 1550 (60%) of placebo group Age <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 Note: no significant differences between groups at baseline in MORE or CORE	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.	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)

Appendix C11. Evidence Table of Risk-Reducing Medications

Trial Quality	Assignment/attrition	Demographics	Surveillance	Duration/follow up
Tamoxifen vs. raloxifene				
STAR[289] Good See also Vogel et al, 2006[329]	184,460 screened; 88,092 excluded for breast cancer risk <1.7% 96,368 had breast cancer risk ≥1.7%; 20,616 consented to screening for medical eligibility 20,168 met eligibility criteria; 421 did not want to participate 19,747 randomized; 9872 assigned to tamoxifen; 9875 assigned to raloxifene 19,471 original analysis (274 lost to followup; 146 in tamoxifen group, 128 in raloxifene group; 2 excluded for bilateral mastectomy prior to randomization) 19,490 update analysis; 9736 in tamoxifen group; 9754 in raloxifene group (followup collected on 20 women missing from original; 1 excluded due to breast cancer diagnosis before randomization) 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	Characteristics at entry of women included in the STAR update analysis Mean age, years: 58.5 (SD 7.4) Age distribution: 9% <50 years; 50% ages 50-59 years; 32% ages 60-69 years; 8.8% age ≥70 years FDRs with breast cancer, n (%); tamoxifen vs. raloxifene: None: 2838 (29) vs. 2791 (27) 1: 5046 (52) vs. 5135 (53) 2: 1532 (16) vs. 1561 (16) ≥3: 320 (3.3) vs. 267 (2.7)	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.	Mean duration of treatment was 43.5 months (SD, 20.7) for tamoxifen group and 46.8 months (SD, 20.0) for raloxifene group Median followup, 81 months (analysis cutoff March 2009)

Trial Quality	Results	Conclusions	Funding source
Tamoxifen vs. placebo			
IBIS-I[287] Fair See also Cuzick 2002[328]	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)	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.	Cancer Research United Kingdom; National Health and Medical Research Council Australia

Appendix C11. Evidence Table of Risk-Reducing Medications

Trial Quality	Results	Conclusions	Funding source
NSABP P-1[284] Fair See also Fisher et al, 1998[71]	Tamoxifen vs. placebo 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)	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	National Cancer Institute; U.S. Department of Health and Human Services
Royal Marsden[285] Fair See also Powles et al, 1998[70]	Tamoxifen vs. placebo 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	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	National Health Service; Cancer Research U.K.
Italian Randomized Tamoxifen Prevention[286] Fair See also Veronesi et al, 1998[72]	Tamoxifen vs. placebo 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)	In women with ≥1 FDR with breast cancer, more breast cancer observed in tamoxifen arm than in placebo arm; not statistically significant difference	Italian National Research Council; Italian Foundation for Cancer Research; American-Italian Cancer Foundation; Italian League Against Cancer
Raloxifene vs. placebo			
RUTH[73] Good See also Barrett-Connor et al, 2006[299]	Raloxifene vs. placebo 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	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	Eli Lilly and Company

Appendix C11. Evidence Table of Risk-Reducing Medications

Trial Quality	Results	Conclusions	Funding source
MORE and CORE[288] Good See also Cummings et al, 1999[74]	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			
STAR[289] Good See also Vogel et al, 2006[329]	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 Raloxifen Trial.

Appendix C12. Evidence Table of Risk-Reducing Surgery

Author, year Quality	Design	Purpose	Sample size	Population/setting	Demographics
Salpingo-oophorectomy or oophorectomy vs. no oophorectomy					
Domchek et al, 2010[292] Fair	Prospective cohort	To assess the relationship of RRM or RRSO with cancer outcomes.	Eligible: 2482 Analyzed: 1458 with no prior breast cancer (935 *BRCA1*, 523 *BRCA2*)	1974-2008 U.K., Europe, and North America Women from 22 centers in the PROSE consortium	NR
Kramer et al, 2005[185] Fair Note: only oophorectomy performed	Prospective cohort	To assess whether population differences in oophorectomy prevalence might significantly influence breast cancer penetrance estimates in *BRCA1* mutation families.	Eligible: 673 (98 *BRCA1* positive, 23 from *BRCA1* families)	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	NR Mean, 2.7 cases of breast cancer and 3.0 cases of ovarian cancer per family diagnosed before ascertainment
Olson et al, 2004[296] NA Note: only oophorectomy performed	Retrospective cohort	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.	Eligible: 851 Analyzed: 634	1970-1994 U.S./review of Mayo Clinic Surgical Index Followup survey completed by patient or surrogates (if patient deceased)	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
Mastectomy vs. no mastectomy					
Domchek et al, 2010[292] Fair	Prospective cohort	To assess the relationship of RRM or RRSO with cancer outcomes.	Eligible: 2482 Analyzed: 1458 with no prior breast cancer (935 *BRCA1*, 523 *BRCA2*)	1974-2008 U.K., Europe, and North America Women from 22 centers in the PROSE consortium	NR
Evans et al, 2009[293] NA	Prospective cohort	To assess effectiveness of risk-reducing surgery in women at high risk of breast cancer, including carriers and noncarriers of *BRCA1/2* mutation.	Eligible: 550 Enrolled: 314 women with no prior breast cancer	1987-1992 Europe Multidisciplinary family history clinics established at 10 centers	Mean age of women undergoing mastectomy at Manchester site, years: 41 (range, 21-60) Age range at all sites, years: 21-72

Appendix C12. Evidence Table of Risk-Reducing Surgery

Author, year Quality	Design	Purpose	Sample size	Population/setting	Demographics
Skytte et al, 2011[294] Good	Prospective cohort	To compare incidence of breast cancer after RRM in healthy BRCA mutation carriers versus nonoperated mutation carriers and background population.	Eligible: 307 with mutation (201 *BRCA1*, 106 *BRCA2*)	January 1996-February 2008 Denmark Women from clinical genetics departments at multiple sites with mutation status diagnosed	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 <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
Prior Report					
Mastectomy					
Hartmann et al, 1999[290]	Retrospective cohort	To define the effect of RRM on incidence of breast cancer and risk of death from breast cancer	Eligible: 639 Analyzed: 639	1960-1993 U.S.; Mayo Clinic medical records of women who underwent RRM	Mean age at surgery, 42 (range, 18-79)
Hartmann et al, 2001[291]	Retrospective cohort	To report the effect of RRM on breast cancer risk in *BRCA1/2* carriers identified from a high-risk cohort	18 *BRCA1/2*	*BRCA1/2* mutation carriers undergoing RRM and enrolled as high-risk participants in prior study (Hartmann 1999)	Mean age at surgery, 41 (range, 20-75)
Oophorectomy					
Struewing et al, 1995[229]	Prospective cohort	To determine the incidence of post-oophorectomy carcinomatosis and quatify the effectiveness of risk-reducing surgery	Eligible: 16 families Analyzed: 12 families (390 1st-degree relatives of breast or ovarian cancer cases)	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.	NR

Appendix C12. Evidence Table of Risk-Reducing Surgery

Author, year Quality	Inclusion/exclusion criteria	Risk definition	Followup
Salpingo-oophorectomy or oophorectomy vs. no oophorectomy			
Domchek et al, 2010[292] Fair	Inclusion Women with *BRCA1/2* mutations, no prior ovarian cancer, no salpingo-oophorectomy at time of ascertainment, and minimum 6 months followup. Exclusion 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.	BRCA status	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. **Oophorectomy & breast cancer outcomes:** *BRCA1* followed mean 4.7 years to censoring *BRCA2* followed mean 4.7 years to censoring **Oophorectomy & ovarian cancer outcomes:** *BRCA1* followed mean 5.6 years to censoring *BRCA2* followed mean 5.8 years to censoring
Kramer et al, 2005[185] Fair Note: only oophorectomy performed	Inclusion 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. Exclusion Breast cancer diagnosed before family ascertainment and families with variants of uncertain significance.	BRCA status	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
Olson et al, 2004[296] NA Note: only oophorectomy performed	Inclusion Women age <60 years with bilateral oophorectomy during study dates. Exclusion 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.	High risk ≥1 1st-degree relative with breast cancer at age <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	N/A
Mastectomy vs. no mastectomy			
Domchek et al, 2010[292] Fair	Inclusion Women with *BRCA1/2* mutations, no prior ovarian cancer, no salpingo-oophorectomy at time of ascertainment, and minimum 6 months followup. Exclusion 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.	BRCA status	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. **Mastectomy & breast cancer outcomes:** *BRCA1* followed mean 2.7 years to censoring *BRCA2* followed mean 2.5 years to censoring

Appendix C12. Evidence Table of Risk-Reducing Surgery

Author, year Quality	Inclusion/exclusion criteria	Risk definition	Followup
Evans et al, 2009[293] NA	Inclusion 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 *BRCA1/2* carriers only. Exclusion NR	Lifetime risk of breast cancer >25% based on family history with or without mutation status or diagnosis of breast cancer in contralateral breast	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
Skytte et al, 2011[294] Good	Inclusion *BRCA1/2* mutation positive and women who did not have mastectomy or salpingo-oophorectomy prior to study. Exclusion Diagnosis of breast or ovarian cancer before BRCA testing and women who opted for risk-reducing surgery before receiving test result.	BRCA status	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
Prior Report			
Mastectomy			
Hartmann et al, 1999[290]	Inclusion Women with a family history of breast cancer who had bilateral RRM Exclusion Breast cancer detected in surgically treated breast; surgery for augmentation of reduction High-risk comparison group inclusion Sisters of high-risk subjects were recruited to the study	High risk ≥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 ≥2 with ovarian cancer; ≥3 2nd- or 3rd-degree relatives with breast cancer; 1 1st-degree relative with bilateral breast cancer; breast cancer in male family members Moderate risk Women who did not meet these criteria	Median, 14 years; with a minimum of 2 years for 99% of the subjects.
Hartmann et al, 2001[291]	Inclusion Women with *BRCA1/2* mutations who had bilateral RRM mastectomy	BRCA status	13.1 years

Appendix C12. Evidence Table of Risk-Reducing Surgery

Author, year Quality	Inclusion/exclusion criteria	Risk definition	Followup
Oophorectomy			
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

Author, year Quality	Results	Conclusions	Funding source
Salpingo-oophorectomy or oophorectomy vs. no oophorectomy			
Domchek et al, 2010[292] Fair	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. 223/1034 (22%); HR, 0.54 (95% CI, 0.37-0.79) *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. 60/1011 (5.9%); HR, 0.45 (95% CI, 0.21-0.95) *BRCA1*: 8/327 (2.4%) 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. 22/973 (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. 24/975 (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

Author, year Quality	Results	Conclusions	Funding source
Kramer et al, 2005[185] Fair Note: only oophorectomy performed	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[296] NA Note: only oophorectomy performed	Expected vs. observed number of cancer cases <u>Age of surgery <60 years</u> 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) <u>Age of surgery <50 years</u> 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) <u>Age of surgery <60 years and premenopausal before surgery</u> 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) <u>Age of surgery <50 years and premenopausal before surgery</u> 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
Mastectomy vs. no mastectomy			
Domchek et al, 2010[292] Fair	Number of cancer cases in women with no history of breast cancer; surgery vs. no surgery <u>Risk-reducing mastectomy and risk of first occurrence of breast cancer</u> 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

Author, year Quality	Results	Conclusions	Funding source
Evans et al, 2009[293] NA	Manchester (mastectomy vs. no mastectomy): RRM: 179 vs. 0 Breast cancers expected based on life tables: 12.12 vs. 20.8 Cancers diagnosed: 0 vs. 21 All sites: RRM: 307 per Table 2 (314 per text [p. 256]) Expected cancers: 21.30 Cancers diagnosed: 0	Risk-reducing surgery is highly effective	NR
Skytte et al, 2011[294] Good	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 "no mastectomy" 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)	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	NR
Prior Report			
Mastectomy			
Hartmann et al, 1999[290]	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<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).	In women with high risk of breast cancer on the basis of family history, RRM can significantly reduce the incidence of breast cancer	U.S. Department of Defense; National Cancer Insitute; Donaldson Charitable Trust
Hartmann et al, 2001[291]	Risk Reduction: Easton model (a high-penetrance model), 6.1 cases were expected; Struewing 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 Struewing model (95% CI, 15.6-99.6 and CI, 54.1-100).	Risk-reducing mastectomy is associated with a substantial reduction in the incidence of breast cancer in known *BRCA1/2* mutation	NR

Appendix C12. Evidence Table of Risk-Reducing Surgery

Author, year Quality	Results	Conclusions	Funding source
		carriers	
Oophorectomy			
Struewing et al, 1995[229]	Surgery vs. no surgery *Preliminary Analysis from National Cancer Insititute only* <u>Ovarian cancer incidence</u> 1st-degree relative: 2/44 vs. 8/346 2nd-degree relative: 0 vs. 1 Note: Incidence includes post-oophorectomy ovarian carcinomatosis <u>Breast cancer incidence</u> 1st-degree relative: 3/44 vs. 14/346 2nd-degree relative: 0 vs. 3	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	NR

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

Author, year Quality	Subcategory	Study design	Country/population/ setting	Inclusion/exclusion criteria	Risk level definition
Breast cancer screening					
Kriege et al, 2004[277] NA Dutch MRISC study	Physical harms of increased screening	Prospective cohort (breast cancer characteristics compared to registry data and women with breast cancer from another prospective cohort study)	The Netherlands Women with increased familial or genetic predisposition for breast cancer attending academic and/or cancer centers at 6 sites	Inclusion Cumulative lifetime risk of breast cancer >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	Cumulative lifetime risk of breast cancer >15% due to genetic or familial predisposition according to modified Claus tables
Kriege et al, 2006[297] NA Dutch MRISC study	Physical harms of increased screening	Prospective cohort (breast cancer characteristics compared to registry data and women with breast cancer from another prospective cohort study)	The Netherlands Women with increased familial or genetic predisposition for breast cancer attending academic and/or cancer centers at 6 sites	Inclusion Cumulative lifetime risk of breast cancer >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	Cumulative lifetime risk of breast cancer >15% due to genetic or familial predisposition according to modified Claus tables
Leach et al, 2005[274] NAMARIBS study	Physical harms of increased screening	Prospective cohort, one-arm	U.K. Women attending 1 of 22 participating centers in the U.K. with increased breast cancer risk	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 <5 years, participants who had predictive genetic testing during study and whose results were negative, women who developed cancer during study period	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

Appendix C13. Evidence Table of Harms of Intensive Screening

Author, year Quality	Subcategory	Study design	Country/population/ setting	Inclusion/exclusion criteria	Risk level definition
Le-Petross et al, 2011[276] NA	Physical harms of increased screening	Retrospective analysis of prospective cohort study, one-arm	U.S. Women at increased genetic risk of breast cancer at single institution	Inclusion 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 Exclusion Women with history of breast cancer, who had calculated lifetime risk of breast cancer >20%, or who did not undergo a screening MRI, women who used chemoprevention or underwent bilateral prophylactic mastectomy, those with metastatic disease, undergoing treatment, or high BMI preventing MRI, women lost to followup, or died during original trial	Based on BRCA status or FDR of BRCA mutation carrier
Ovarian cancer screening					
Hermsen et al, 2007[281] NA	Physical harms of increased screening	Prospective cohort, one-arm (Staging compared to 2 external comparison groups; unscreened family members with cancer, combined data from multiple studies)	The Netherlands Women with BRCA mutation screened at 6 University Family Cancer Clinics	Inclusion Women with *BRCA1/2* mutation screened at 1 of participating centers Exclusion Women with symptoms at first visit, who had only 1 visit, or who were found to have cancer at first screening visit	Based on BRCA status
Prior report					
Bourne et al, 1993[279] NA	Physical harms of increased screening	Prospective cohort, one-arm	U.K. Self-referred asymptomatic women with a close relative diagnosed with ovarian cancer	Inclusion Women age ≥25 years with ≥1 close relatives who had developed ovarian cancer; symptomless	Based on pedigree/pattern of inheritance

Appendix C13. Evidence Table of Harms of Intensive Screening

Author, year Quality	N	Demographics	Duration/followup	Screening method and interval
Breast cancer screening				
Kriege et al, 2004[277] NA Dutch MRISC study	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	Mean age at entry, years: 40 (range, 19-72)	1999-2003 Median, 2.9 years (mean, 2.7; range, 0.1-3.9 years)	A) Biannual CBE B) Annual mammography C) Annual contrast enhanced MRI Note: When 1 of the examinations reported as "probably benign finding" or "need additional imaging evaluation" (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 "suspicious abnormality" or "highly suggestive of malignancy" (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
Kriege et al, 2006[297] NA Dutch MRISC study	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	Mean age at entry, years: 40 (range, 19-72)	1999-2003 Median, 2.9 years (mean, 2.7; range, 0.1-3.9 years)	A) Biannual CBE B) Annual mammography C) Annual contrast enhanced MRI Note: When 1 of the examinations reported as "probably benign finding" or "need additional imaging evaluation" (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 "suspicious abnormality" or "highly suggestive of malignancy" (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
Leach et al, 2005[274] NAMARIBS study	649 n=82 (13%) with known *BRCA1* mutation n=38 (6%) with known *BRCA2* mutation	Median age at entry, years: 40 (range, 31-55; only 1 woman age >50 years)	Study recruitment 1997-2003 Variable screening episodes per individual but screening continued until each women had ≥2 annual scans (in 2004)	A) Annual mammography from age 35 years (or younger if FDR developed cancer at age <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)
Le-Petross et al, 2011[276] NA	Screened: 321 Analyzed: 73 (37 [51%] *BRCA1*, 36 [49%] *BRCA2*)	Median age at entry, years: 44 (range, 23-75)	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)	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

Appendix C13. Evidence Table of Harms of Intensive Screening

Author, year Quality	N	Demographics	Duration/followup	Screening method and interval
Ovarian cancer screening				
Hermsen et al, 2007[281] NA	883 n=683 *BRCA1*, 200 *BRCA2* 459 for analysis of screening/compliance (data available for all screening visits)	Median age, years: *BRCA1*: 40 (range, 21-76) *BRCA2*: 44 (range, 25-77)	1993-2005 1473 person-years	A) Annual serum CA-125 measurement B) Annual TVUS Starting at age 35 years or 5 years earlier than youngest diagnosed ovarian cancer in the family Note: Biannual screens were done in some centers during the study period, but this was not systematically adopted
Prior report				
Bourne et al, 1993[279] NA	1601	Mean age, years: 47 (range, 17-79)	Unclear duration 4 years	TVUS ± color flow imaging§ (screening interval NR)

Author, year Quality	Results	Funding source
Breast cancer screening		
Kriege et al, 2004[277] NA Dutch MRISC study	Based on 45 cancers, B vs. C: <u>Additional investigations:</u> 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†)	Grant from Dutch Health Insurance Council
Kriege et al, 2006[297] NA Dutch MRISC study	Imaging rounds of 39 evaluable invasive breast cancers, B vs. C: <u>First imaging round, with prior mammography</u> False positive rate (%): 5.5 vs. 14.0; P<0.001 False negatives (n): 12 vs. 1 <u>Subsequent imaging rounds</u> False positive rate (%): 4.6 vs. 8.2; p<0.001 False negatives (n): 12 vs. 4	Grant from Dutch Health Insurance Council
Leach et al, 2005[274] NAMARIBS study	Based on 33 screen-detected cancers: <u>Recall rates, A vs. B</u> 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 <u>Additional diagnostic procedures in 245 women without cancer:</u> 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	Grant from U.K. Medical Research Council; MRI cost paid from subvention funding for research from U.K. National Health Service

Appendix C13. Evidence Table of Harms of Intensive Screening

Author, year Quality	Results	Funding source
	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 PPV of diagnostic surgical biopsy=56% 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 Preoperative diagnosis of cancer made in 24/33 (73%) of screen-detected cancers	
Le-Petross et al, 2011[276] NA	13 cancers in 11 women (12 on screen, 1 on prophylatic mastectomy) 20/73 women underwent biopsy, 11 cancers diagnosed by biopsy in 10 women Overall biopsy yield for MRI was 50% (10/20) <u>False positive, A vs. B</u> 11/73 (15%) vs. 8/73 (11%) Required further imaging: 8 vs. 4 Required biopsy: 3 vs. 2 Required imaging plus biopsy: 0 vs. 2	NR
Ovarian cancer screening		
Hermsen et al, 2007[281] NA	15 cancers diagnosed in cohort 10 cancers diagnosed during followup 5 screen-detected <u>Based on 459 women with data on each visit</u>: 7 cancers diagnosed (2 prevalent, 2 interval, 3 incident) 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 <u>Benign‡ diagnostic surgery, A vs. B</u> 67% (4/6) vs. 100% (9/9) A+B: 55% (6/11) 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	NIHR Biomedical Research Centre at Central Manchester Foundation Trust
Prior report		
Bourne et al, 1993[279] NA	11 cancers diagnosed (6 screen-detected, 5 interval) 3.8% (61/1601) with positive screening result, referral to surgery False-positive cases: 55/61 referred cases (cancer detected in 6/61 referred cases) False-positive rate: 3.4% (95% CI, 2.6-4.5 [55/1595]) <u>Addition of color flow imaging and criterion of morphological score ≥5 or pulsatility index <1:</u> Retrospective addition (applied to positive ultrasound results) = 15 false-positive cases Prospective addition (applied at the time of ultrasound exam) = 6 false-positive cases Note: 43% of women had only 1 TVUS (prevalent screen)	NR

*Additional investigation included ultrasound ± fine needle biopsy, or repeat mammography, or repeat MRI.
†Women with BIRAD score ≥3 on mammography or MRI.
‡Surgery for final benign diagnosis.
§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

Author, year Quality	Subcategory	Purpose	Study type	N	Country	Population/ Setting	Demographics
Brandberg et al, 2008[302] Brandberg et al, 2012[304] NA	Sexual functioning Psychological	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.	Before and after	Eligible: NR Enrolled: 90 Analyzed: 65	Sweden	Karolinska University Hospital	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%)
Finch et al, 2011[306] NA	Sexual functioning	To examine the impact of RRSO on menopausal symptoms and sexual functioning in women who carry a *BRCA1/2* mutation.	Case-series	Eligible: NR Enrolled: 67	Canada	University Health Network	Not reported separately for women without breast cancer
Gahm et al, 2010[303] NA	Sexual functioning QOL Pain	To analyze the physical effects and to report effects on sexual functioning and health-related quality of life at least 2 years after RRM.	Cross-sectional	Eligible: NR Enrolled: 1784 (59 with RRM and 1725 included as reference sample)	Sweden	Karolinska University Hospital	Mean age of 40 years (range, 25-65)
Metcalfe et al, 2004[301] NA	Sexual functioning Psychological	To assess psychosocial functioning in a population-based series of women who have previously undergone RRM in a specified time period.	Case-series	Eligible: 122 Enrolled: 75 Analyzed: 60	Canada	Ontario hospitals in the Central East Health Information Partnership	Mean age of 43.5 years (SD, 7.8) at time of surgery and 47.8 years (SD, 8.6) at time of questionnaire
Rijnsburger et al, 2004[275] Fair	QOL	To describe the short-term effects of screening for breast cancer in high-risk women on health-related quality of life.	Prospective cohort Before and after	Eligible: 529 Enrolled: 329 Analyzed: 288	The Netherlands	MRI Screening Study conducted at 6 family cancer centers	Mean age of 40.9 years (SD, 8.9)
Spiegel et al, 2011[298] NA	Psychological	To compare women with recall examinations following MRI to those without recall examinations on breast cancer worry and anxiety.	Before and after	Eligible: 221 Enrolled: 134 Analyzed: 55	Canada	Women participating in an MRI screening trial	Mean age of 45 years (range, 25-60)
Wasteson et al, 2011[305] NA	Risk perception Psychological	To evaluate the long-term physical and psychological consequences of RRM in after 10 years.	Case-series	Eligible: NR Enrolled: 15 Analyzed: 13	Sweden	Women at Karolinska University Hospital enrolled in retrospective study	Mean age of 45 years (range: 40-57)

Appendix C14. Evidence Table of Psychological and Sexual Functioning Harms of Interventions

Author, year Quality	Inclusion/Exclusion criteria	Risk level definition	Mutation status	Measures	Interventions
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 (scale NR)	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

Author, year Quality	Inclusion/Exclusion criteria	Risk level definition	Mutation status	Measures	Interventions
Rijnsburger et al, 2004[275] Fair	Inclusion: Women already under intensive surveillance and women who came for the first time to the clinic Exclusion: Women with evident symptoms suspicious for breast cancer or previous breast cancer	Risk category 1: *BRCA1/2* mutation carriers (50%-85% cumulative lifetime risk) Risk category 2: 30%-50% cumulative lifetime risk Risk category 3: 15%-30% cumulative lifetime risk	35 were *BRCA1/2* mutation positive	Medical Outcomes Study 36-Item Short Form (SF-36, subscales 0 to 100) EuroQoL-5 Dimensions (EQ-5D, scale 0-1) Visual Analogue Scale (VAS, scale 0 to 100) Symptom Checklist-90 (SCL-90, scale 12-60)	A) CBE (n=287) B) CBE + mammography (n=134) C) CBE + MRI (n=109)
Spiegel et al, 2011[298] NA	Inclusion: Women participating in MRI screening trial who agreed to participate Exclusion: NR	All were mutation carriers	30/55 (54.5%) *BRCA1* 25/55 (45.5%) *BRCA2*	Hospital Anxiety and Depression Scale (HADS, subscales 0 to 21) Breast Cancer Worry Interference Scale (WIS, scores 7 to 35)	All received annual mammography, MRI, and ultrasound and semiannual CBE A) Women with recall exams (n=18) B) Women without recall exams (n=37)
Wasteson et al, 2011[305] NA	Inclusion: Women enrolled in previous retrospective study of RRM with reconstruction, agreed to participate 10 years later Exclusion: NR	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	3/13 (23.1%) BRCA positive by 10 year followup	Semistructured interviews focused on experiences related to RRM with reconstruction	RRM with reconstruction

Author, year Quality	Duration of followup	Results	Conclusions	Funding source
Brandberg et al, 2008[302] Brandberg et al, 2012[304] NA	October 1997 to December 2005 1 year	**Before RRM vs. 6 months after RRM vs. 1 year after RRM** Mean scales (SE) HADS-A: 5.59 (0.55) vs. 3.80 (0.55) vs. 3.83 (0.52); p=0.0004 HADS-D: 2.53 (0.39) vs. 1.93 (0.31) vs. 1.98 (0.36); p=NS SAQ, pleasure subscale: 12.82 (0.62) vs. 12.21 (0.66) vs. 11.18 (0.56); p=0.005 SAQ, discomfort subscale: 0.56 (0.15) vs. 0.53 (0.20) vs. 0.81 (0.19); p=NS SAQ, habit subscale: 0.94 (0.06) vs. 0.82 (0.08) vs. 0.82 (0.08); p=NS Bodily pain as reported by SF-36: 81.0 (2.98) vs. 80.7 (2.84) vs. 82.6 (3.29); p=NS	Anxiety decreased after surgery, while sexual pleasure increased. All other measures did not change over time.	Swedish Cancer Society, Swedish Association for Cancer and Traffic Victims, and Stockholm County Council

Appendix C14. Evidence Table of Psychological and Sexual Functioning Harms of Interventions

Author, year Quality	Duration of followup	Results	Conclusions	Funding source
		NS difference over time on any portion of impact on areas of life measures, any portion of BIS, and any subscales of SF-36.		
Finch et al, 2011[306] NA	October 2002 to June 2008 1 year	Women experienced a significant worsening of vasomotor symptoms ($p<0.01$) and a decrease in sexual function ($p<0.05$)	Women had worse vasomotor symptoms and decrease in sexual functioning.	Toronto Fashion Show, Kristi Piia Callum Memorial Fellowship in Ovarian Cancer Research, and University of Toronto Open Fellowship
Gahm et al, 2010[303] NA	2004-2006 Mean followup of 29 months (range, 24-49)	A vs. B **Mean SF-36 subscales (estimated from graph)** Physical functioning: 94 vs. 89; p=NS Role functioning: 86 vs. 85; p=NS Bodily pain: 87 vs. 72; p=0.002 General health: 79 vs. 77; p=NS Vitality: 68 vs. 68; p=NS Social functioning: 90 vs. 89; p=NS Role emotional: 80 vs. 85; p=NS Mental health: 80 vs. 80; p=NS **Pain and discomfort questionnaire responses after RRM** 38/55 (69%) pain in breasts 20/55 (36%) pain affected sleep 12/55 (22%) pain affected daily activities 39/55 (71%) discomfort in breasts 48/55 (87%) pain or discomfort in breasts 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) Pain or discomfort not related with negative effects in sexual outcomes ($p>0.05$ for both) **Postoperative complications** 11/59 (18.6%) had infections 3/59 (5.1%) required implant extraction 4/59 (6.8%) had hematoma 2/59 (3.4%) required acute operative evacuation 2/59 (3.4%) had revision of flap necrosis 35/59 (59%) had corrective surgical procedures 24/59 (41%) had procedure involving implant pockets **Sexuality questionnaire responses after RRM** 25/55 (45%) totally lost sexual sensations 22/55 (40%) substantially impaired sexual sensations 38/55 (69%) negative change in sexual importance of breasts 41/55 (75%) negative change in sexual enjoyment of breasts 32/55 (58.2%) no change in sexual intercourse Sexual attractiveness changes varied substantially	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.	None

Appendix C14. Evidence Table of Psychological and Sexual Functioning Harms of Interventions

Author, year Quality	Duration of followup	Results	Conclusions	Funding source
		Regret scale responses after RRM 52/55 (94.5%) agreed the decision was right 51/55 (92.7%) would make the same decision again 48/55 (87.3%) said it was a wise decision		
Metcalfe et al, 2004[301] NA	January 1991 to June 2000 Mean time between surgery and questionnaire of 52.2 months (SD, 32.3)	97% were satisfied or extremely satisfied with decision to have RRM **Mean scales (SD) for whole group after RRM** 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 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 Sexual activity, pleasure: 12.25 (4.72) Sexual activity, discomfort: 1.97 (2.13) Sexual activity, habit: 1.22 (0.66) 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) **Age <50 years vs. ≥50 years** Mean scales (SD) IES-I: 9.07 (8.57) vs. 6.31 (6.10); p=NS IES-A: 8.61 (9.03) vs. 9.38 (6.85); p=NS Sexual activity, pleasure: 12.75 (4.70) vs. 10.25 (4.56); p=NS Sexual activity, discomfort: 1.78 (2.12) vs. 2.88 (2.03); p=NS Sexual activity, habit: 1.18 (0.64) vs. 1.42 (0.79); p=NS BIBC, vulnerability: 2.38 (0.80) vs. 2.60 (0.87); p=NS BIBC, body concerns: 3.12 (1.03) vs. 2.99 (0.86); p=NS BIBC, body stigma: 2.27 (0.91) vs. 2.52 (0.81); p=NS BIBC, transparency: 2.26 (0.86) vs. 1.97 (0.46); p=NS **Postsurgical symptoms** 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) 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.	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.	NR

Appendix C14. Evidence Table of Psychological and Sexual Functioning Harms of Interventions

Author, year Quality	Duration of followup	Results	Conclusions	Funding source
Rijnsburger et al, 2004[275] Fair	2000-2002 1-4 weeks after screening	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 **Before screening (T0) vs. day of screening (T1) vs. after screening (T2)** Mean VAS: 81.9 vs. 79.0 vs. 80.7; p<0.01 T0 vs. T1 and p<0.05 T1 vs. T2 **Before screening vs. after screening (A, B, and C groups combined) vs. reference group (Dutch general population)** Mean on SF-36 subscales; p=NS for before and after screening Physical functioning: 89.9 vs. 89.4 vs. 86.3; p<0.01 for reference group vs. before screening Role-physical: 85.7 vs. 84.1 vs. 77.6; p<0.01 for reference group vs. before screening Bodily pain: 82.4 vs. 83.0 vs. 72.8; p<0.01 for reference group vs. before screening General health perceptions: 76.4 vs. 77.3 vs. 72.2; p<0.01 for reference group vs. before screening Vitality: 67.1 vs. 68.9 vs. 64.8; p=NS Social functioning: 87.7 vs. 87.9 vs. 83.5; p<0.01 for reference group vs. before screening Role-emotional: 85.2 vs. 88.1 vs. 80.1; p<0.05 for reference group vs. before screening Mental health: 76.8 vs. 77.7 vs. 74.4; p<0.05 for reference group vs. before screening Mean SCL-90: 17.5 vs. 17.1 vs. 18.7; p<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<0.01 for reference group vs. before screening	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.	Health Care Insurance Board, the Netherlands
Spiegel et al, 2011[298] NA	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

Author, year Quality	Duration of followup	Results	Conclusions	Funding source
Wasteson et al, 2011[305] NA	Years NR Median, 10 years (range, 9-12)	**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	Most women stated positive affects 10 years after RRM with reconstruction.	NR

Abbreviations: BIBC = 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.