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# Screening for Skin Cancer in Adults: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force

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www.ahrq.gov

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**Prepared by:**
Kaiser Permanente Research Affiliates Evidence-based Practice Center
Group Health Research Institute
Seattle, WA

Kaiser Permanente Center for Health Research
Portland, OR

**Investigators:**
Karen J. Wernli, PhD, MS
Nora B. Henrikson, PhD, MPH
Caitlin C. Morrison, MPH
Matthew Nguyen, MPH
Gaia Pocobelli, PhD
Evelyn P. Whitlock, MD, MPH

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# Structured Abstract

**Background:** Melanoma is the leading cause of skin cancer mortality. Visual skin examination for skin cancer screening could impact disease incidence and mortality in U.S. adults and adolescents.

**Purpose:** We conducted a systematic evidence review of visual skin exam for skin cancer screening in primary care settings to support the U.S. Preventive Services Task Force (USPSTF) in updating its previous recommendation. Our review addressed five key questions in adults and adolescents aged 15 years and older without a prior diagnosis of skin cancer: 1) What is the direct evidence that visual skin cancer screening by primary care provider or dermatologist reduces skin cancer morbidity and mortality, and all-cause-mortality? 2) What are the harms of skin cancer screening and diagnostic follow-up? 3) What are the test characteristics of visual skin cancer screening when performed by primary care providers or dermatologists? 4) Does visual skin cancer screening lead to earlier detection of skin cancer compared with usual care? and 5) What is the association between earlier detection of skin cancer and skin cancer morbidity and mortality, and all-cause mortality?

**Data Sources:** We searched MEDLINE, PubMed, and the Cochrane Collaboration Registry of Controlled Trials for studies published from January 1, 1995 through June 1, 2015. We supplemented searches by examining bibliographies from previous systematic reviews, and retrieved articles and studies included in the previous USPSTF review for potential inclusion. We searched federal agency trial registries for ongoing and unpublished trials.

**Study Selection:** We conducted dual independent review of 12,514 abstracts. We reviewed 453 full text articles, which two reviewers independently evaluated against well-defined inclusion/exclusion criteria and quality rated. Discrepancies were resolved by discussions with a third reviewer and resolved by consensus.

**Data extraction and analysis:** Four investigators abstracted data from 13 studies and 15 articles into evidence tables and a second reviewer checked these data. We qualitatively summarized the evidence for each key question, since data were insufficient in quantity or consistency for meta-analysis.

**Results:** *Key question 1. What is the direct evidence that visual skin cancer screening by a primary care provider or dermatologist reduces skin cancer morbidity and mortality, and all-cause mortality?* One fair-quality ecologic study addressed the impact of physician visual skin cancer exam on melanoma mortality. The Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany, the SCREEN study, conducted in the Schleswig-Holstein region of Germany involved multicomponent intervention: 1) training nondermatologists and dermatologists in skin cancer screening; 2) a media campaign to encourage skin cancer screening in adults aged 20 years and older; and 3) a followup dermatology referral protocol for nondermatologists to refer adults with either suspicious lesions or multiple risk factors for skin cancer. During the one-year intervention period (2003 to 2004), nearly 361,000 adults (19% of the age-eligible adults) were screened with a visual skin cancer exam mainly by nondermatologists. The majority of screenees were women (73.6%), and the

mean age of screenees was 49.7 years (standard deviation 16.2 years). Using a pre-post design comparing melanoma mortality in the population in 1998 to 1999 and 2008 to 2009, the SCREEN program demonstrated a 48 percent reduction in melanoma mortality in the Schleswig-Holstein (intervention) region but no reductions in melanoma mortality were observed in the four neighboring (control) regions without active skin cancer screening program or in Germany as a whole. The reduction in absolute mortality was a decline of 0.8 deaths due to melanoma per 100,000 individuals in the intervention region. As an ecologic study, the results do not provide individual-level data about risk reduction associated with screening, and it is not possible to directly compare changes in mortality among those exposed versus not exposed to skin cancer screening and account for confounding.

*Key question 2. What are the harms of skin cancer screening and diagnostic follow-up?* Two fair-quality studies evaluated the harms of skin cancer screening by assessing biopsy yield and patient satisfaction with shave biopsy results. We found no studies that evaluated harms due to overdiagnosis, procedure-related adverse events or psychosocial harms. The SCREEN study demonstrated variation by screenee age in the number of skin excisions needed to detect one melanoma, squamous cell carcinoma, or basal cell carcinoma. For all cancers detected, fewer excisions were needed to detect one case in older adults aged 65 years or older compared with younger adults. For melanoma, detecting one melanoma in women age 65 years and older required 22 excisions compared with 41 excisions in women aged 20 to 34 years old. Similar patterns were observed in men and other skin cancer types. In a case series of 45 men and women who participated in skin cancer screening and underwent shave biopsy for suspected nonmelanoma skin cancer, 7 percent of patients expressed poor satisfaction with the cosmetic results from shave biopsy after 6 months compared with 16.1 percent of physicians rating the same site as poor.

*Key question 3. What are the test characteristics of visual skin cancer screening when performed by primary care providers vs. dermatologists?* Two fair-quality observational studies reported test characteristics among screening-eligible populations. In the first study, primary care physicians conducted screenings in 16,383 adults in Queensland, Australia. Cancer outcomes were determined by pathology or biopsy reports. False-negative rates were estimated using published literature and population melanoma rates. Within 36 months of the first screening exam, sensitivity for melanoma detection was 40.2 percent (calculated), and specificity was 86.1 percent (95% confidence interval [CI], 85.6% to 86.6%). The positive predictive value for melanoma was 1.4 percent. The second study evaluated the performance of volunteer dermatologists and plastic surgeons who conducted screening in Western Australia among 7,436 adult men and women. At 24 months, sensitivity for melanoma detection was 49.0 percent (95% CI, 34.4 to 63.7%) and the specificity was 97.6 percent (95% CI, 97.2 to 97.9%) with an overall recall rate for of 2.7 percent. The positive predictive value was 11.9 percent (95% CI, 7.8 to 17.2%). Different followup times for cancer outcomes prohibits direct comparison of screening accuracy between the two physician types.

*Key question 4. Does visual skin cancer screening lead to earlier detection of skin cancer compared to usual care?* One fair-quality case-control study from Queensland, Australia, measured the association between whole-body skin exam by a physician in the previous three years among men and women age 20 to 75 years with or without melanoma. Cases (n=3,762)

were diagnosed with first primary melanoma between 2000 and 2003; controls (n=3,824) were randomly selected from electoral rolls according to five-year age categories and sex distribution of the cases. Of controls, 28.3 percent reported receiving a whole-body skin exam by a physician within the previous 3 years compared to 35.3 percent of melanoma cases. In multivariate adjusted models, cases diagnosed with thin melanoma (≤0.75 mm) had a 38 percent higher odds (OR, 1.38 [95% CI, 1.22 to 1.56]) of physician whole-body skin exam in the previous 3 years compared to controls. Further, cases diagnosed with thicker lesions (>0.75 mm) had a 14 percent reduced odds (OR, 0.86 [95% CI, 0.75 to 0.98]) of physician skin exam compared with controls. The thickest melanoma lesion cases (≥3.00 mm) had 40 percent reduced odds of recent physician skin exam compared with controls (OR, 0.60 [95% CI, 0.43 to 0.83]). These results should be confirmed using prospective study design.

*Key question 5. What is the association between earlier detection of skin cancer and skin cancer morbidity and mortality, and all-cause mortality?* Eight fair to good quality studies evaluated lesion thickness or stage associated with melanoma mortality and all-cause mortality. Four of the studies were conducted in U.S. populations, one in Germany, and three in Australia. All eight studies demonstrated a consistent statistically significant relationship between the degree of disease involvement at diagnosis and melanoma mortality, regardless of the characterization of the stage or lesion thickness. Thicker lesions (>4.0mm) were associated with 3.1 to 32.6-fold increased risk of melanoma mortality compared to thinner lesions. Similarly, advanced stage melanomas (stage III or above) were associated with 9.9 to 27.1-fold increased risk of melanoma mortality compared with early stage melanomas. Stage at melanoma detection was associated with statistically significant increase in all-cause mortality among melanoma cases identified from California SEER registries; compared with stage I disease at detection, adjusted hazard of all-cause mortality was 2.26 times higher for stage II (95% CI, 2.14 to 2.39), 4.27 for stage III (95% CI. 3.90 to 4.67) and 10.39 for stage IV (95% CI, 8.96 to 12.00).

**Limitations:** Very few screening studies met our inclusion criteria, and few were conducted within U.S. settings or with clear relevance to U.S. primary care.

**Conclusions:** On a population level, with limited evidence on skin cancer screening, a clear statement cannot be made about the benefit of skin cancer screening for melanoma mortality and all-cause mortality or association with thinner lesions. With few studies to confirm these results, the applicability for widespread skin cancer screening could be limited. Later stage at diagnosis of melanoma is associated with strong effect on melanoma mortality within five years of diagnosis. Future research of skin cancer screening should focus on evaluating the effectiveness of targeted screening in those considered to be at higher risk for skin cancer.

# Abbreviations

| | |
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| AAD | American Academy of Dermatology |
| AAFP | American Academy of Family Physicians |
| ACP | American College of Physicians |
| ACPM | American College of Preventive Medicine |
| AHRQ | Agency for Healthcare Research and Quality |
| AJCC | American Joint Committee on Cancer |
| AK | actinic keratosis |
| BCC | basal cell carcinoma |
| CDC | Centers for Disease Control and Prevention |
| CI | confidence interval |
| CMS | Centers for Medicare and Medicaid Services |
| DNA | deoxyribonucleic acid |
| EPC | Evidence-based Practice Center |
| HR | hazard ratio |
| KQ(s) | key question(s) |
| MD | Maryland |
| mm | millimeter |
| NMSC | non-melanoma skin cancer |
| NR | not reported |
| OR | odds ratio |
| RCT | randomized controlled trial |
| RR | relative risk |
| SCC | squamous cell carcinoma |
| SCREEN | Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany |
| SD | standard deviation |
| SEER | Surveillance, Epidemiology and End Results Program |
| U.S. | United States |
| USPSTF | U.S. Preventive Services Task Force |
| UV | ultraviolet |

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# Chapter 1. Introduction

## Scope and Purpose

This report will be used by the U.S. Preventive Services Task Force (USPSTF) to update the prior review of the effectiveness of skin cancer screening in average risk individuals. In 2009, the USPSTF concluded there was insufficient evidence to assess the balance of benefits and harms of screening for skin cancer by primary care clinicians or by patient skin self-examination (I statement).[1]

## Condition Definition

Skin cancer is among the most common cancers in men and women in the United States.[2] Skin cancer is classified as: 1) non-melanoma skin cancer (NMSC), which includes basal cell and squamous cell cancers, and 2) melanoma skin cancer. NMSC represents the vast majority of skin cancers (>97%) and has very low mortality.[2] Melanoma skin cancer is less common than NMSC but has a higher mortality rate and case-fatality rate.[3] Detection of melanoma is the primary focus of skin cancer screening.

## Prevalence and Burden

### NMSC

Because NMSC is not a reportable cancer to Surveillance, Epidemiology, and End Results (SEER) or state cancer registries, population estimates are based on care visits or skin procedures. An estimated 4.3 million NMSCs were treated in the United States based on U.S. and Australian population statistics.[4] The incidence of NMSC increases with age,[5-7] and is more common in men than in women.[5, 7] Among the Medicare-eligible population, approximately 2.1 million men and women are diagnosed with NMSC annually.[8] With the increasing use of tanning beds, there is growing concern about skin cancer in younger populations. The estimated age-adjusted incidence of basal cell carcinoma in people under age 40 in Olmsted County, Minnesota is 25.9 per 100,000 women and 20.9 per 100,000 men.[9] The incidence of squamous cell carcinoma in the same population was similar between men and women at 3.9/100,000 persons.[9]

The overall incidence of NMSC appears to be increasing over the past few decades; however, this observation could be the result of more evaluations and skin biopsies leading to more diagnoses rather than a true increase in disease in the population.[10]

Mortality statistics are difficult to determine for NMSC, but suggest that the case-fatality rate from NMSC is quite low.[10] From the state of Rhode Island, the age-adjusted NMSC mortality is estimated at 0.91 per 100,000 person years among residents.[11] While mortality is low, the enduring impact of NMSC is reflected at the high recurrence rate at approximately 50 percent.[12]

## Melanoma

Malignant melanoma is the fifth and seventh leading cancer diagnosed in men and women, respectively.[13] In 2015, an estimated 73,870 persons will be diagnosed with melanoma in the United States and 9,940 persons will die from the disease.[13] Over the past nearly 40 years, melanoma incidence rates have increased and mortality rates have remained relatively stable. The increase in melanoma incidence is in part attributed to increasing skin biopsies, which increased 2.5-fold in SEER-Medicare population from 1986 to 2001.[14] Additional biopsies have resulted in increases in early stage melanoma detected, mainly in detection of melanoma in situ.[14]

### Melanoma Incidence

From 1975 to 2011, age-adjusted melanoma incidence rates increased three-fold from 7.9 to 22.7 new cases per 100,000 persons.[3]

*Age*

Melanoma incidence increases with age. During 2007 to 2011, among individuals under age 65 years, the incidence rate was 12.7 cases per 100,000 persons as compared to 81.1 cases per 100,000 persons 65 years and older.[3]

*Sex*

The age-adjusted incidence rate of melanoma was higher in men than women in 2007 to 2011, with 27.7 per 100,000 in men versus 16.7 per 100,000 in women.[3] However, this pattern is not consistent across all ages. Younger women from teens to under age 50 years have higher incidence rates than men.[3]

*Race*

There is variation in melanoma incidence by race. The age-adjusted incidence rate of melanoma was 25.2 cases per 100,000 in whites compared with 1.0 per/100,000 in blacks during 2007 to 2011.[3]

*Stage*

For cases diagnosed from 2004 to 2010, the distribution of stage at diagnosis was: 84 percent localized, 9 percent regional, 4 percent distant, and 4 percent unstaged.[3]

### Melanoma Mortality and Survival

From 1975 to 2011, age-adjusted melanoma mortality rates increased slightly from 2.1 to 2.7 deaths per 100,000.[3] Five-year relative survival among persons diagnosed during 2002 to 2009 was 93% overall.[3]

*Age*

Melanoma mortality rates increase with age. During 2007 to 2011, among individuals under age 65 years, the mortality rate was 1.2 per 100,000 persons as compared to 13.4 per 100,000 persons ≥65 years of age.[3]

*Sex*

Age-adjusted melanoma mortality rates are higher in men than women, 4.1 versus 1.7 deaths per 100,000 persons during 2007 to 2011.[3] Five-year relative survival was 91.1 percent in men and 95.0 percent in women among cases diagnosed during 2004 to 2010.[3]

*Race*

Melanoma mortality rates are greater in whites compared to blacks. During 2007 to 2011, the age-adjusted melanoma mortality rate was 3.1 per 100,000 persons among whites as compared to 0.4 per 100,000 persons among blacks.[3] However, five-year relative survival among individuals diagnosed during 2004 to 2011 was lower in blacks (75.1%) than in whites (92.9%).[3] This difference in relative survival according to race has been attributed to a difference in the distribution of stage at diagnosis: among those diagnosed in 2004 to 2010, 19 percent of blacks were diagnosed with distant or unknown stage of disease as compared to only 7 percent of whites.[3]

*Stage*

For people diagnosed from 2004 to 2010, five-year relative survival by stage was 98.1 percent for localized, 62.6 percent for regional, 16.1 percent for distant, and 78.3 percent for unstaged disease at diagnosis.[3] The vertical depth of melanoma is one of the strongest predictors of patient survival. Fifteen-year patient survival is 93 percent for depth <1 mm, 68 percent for 1 to 4 mm, and 42 percent for >4 mm.[15]

# Etiology and Natural History

## NMSC

NMSC arises from keratinocytes or their precursors.[10] Basal cell carcinoma arises in the lower layers of the epidermis. Squamous cell carcinoma arises in the mid-layer of the epidermis, and can become invasive if left untreated. Actinic keratosis is thought to be the precursor lesion to squamous cell carcinoma and tends to occur in individuals with fair skin and blond or red hair.[2]

Ultraviolet radiation from sun exposure or artificial sources damages DNA and leads to carcinogenesis of both basal and squamous cells.[16]

## Melanoma

Like all cancers, melanoma is described as a process of unregulated clonal growth.[17] Typically melanocytes are found in the border of the epidermis and dermis layer. Melanocytes that grow in a horizontal lentiginuous pattern appear on the skin as a freckle. Clusters of melanocytes can form to develop nevi. Mutations can result in nevi with pleomorphic features (i.e., variable cell and nuclei sizes and shapes) that have the potential to leave the epidermal border to locate in other areas of the skin.[15] The two most common types of melanoma are superficial spreading and nodular melanoma. The vertical depth of the melanoma is directly associated with prognosis. The common locations for melanoma to occur vary in men and women. In men, melanoma is more common on the back and in the head and neck areas. In women, melanoma is more common in the lower extremities, in particular, below the knee.[18]

## Risk Factors

Risk factors for melanoma and NMSC are similar, although there are some risk factors that are mainly associated with melanoma risk.

### Melanoma Only

Risk factors for melanoma are summarized in a recent meta-analysis of observational studies.[19-21]

*Family History of Melanoma*

Pooled estimates suggest a 74 percent increased risk of melanoma with family history of the disease (relative risk [RR], 1.7 [95% confidence interval (CI), 1.4 to 2.1]).[21]

*Dysplastic Nevi*

Increased total number of dysplastic nevi is associated with 6.4-fold increased risk of melanoma (comparing 5 vs. 0 dysplastic nevi: RR, 6.4 [95% CI, 3.8 to 10.3]).[19]

*Multiple Nevi*

The presence of 101 to 120 nevi compared to <15 nevi is associated with 6.9-fold increased risk of melanoma (RR, 6.9 [95% CI, 4.6 to 10.3]).[19]

*Sun Sensitivity*

Having skin that sunburns easily is associated with a 2-fold increased risk of melanoma as compared to having skin that never burns (RR, 2.1 [95% CI, 1.7 to 2.6]).[21] Having natural red hair is associated with a 3.6-fold (RR, 3.6 [95% CI, 2.6 to 5.4]) increased risk of melanoma and natural blond hair with a 2-fold (RR, 2.0 [95% CI, 1.4 to 2.7]) increased risk as compared to having natural dark hair.[21]

*History of Sunburns*

Sunburn history in the highest frequency category is associated with a 2-fold increased risk of melanoma (RR, 2.0 [95% CI, 1.7 to 2.4]).[20]

*Indoor Tanning*

Ever use of tanning beds is associated with a 1.2-fold increased risk of melanoma (RR, 1.2 [95% CI 1.0 to 1.3)[22] and first use at <35 years of age is associated with a 1.8-fold increase in risk (RR, 1.8 [95% CI 1.4 to 2.3]).[23]

*History of NMSC*

A previous history of actinic keratosis, basal cell carcinoma or squamous cell carcinoma is associated with a 4.3-fold increased risk of developing melanoma (RR, 4.3 [95% CI 2.8 to 6.6]).[21]

**NMSC**

Risks of developing basal cell carcinoma and squamous cell carcinoma increase with exposure to ultraviolet radiation, either through sun exposure or use of indoor tanning beds. Similarly to melanoma risk, persons who sunburn easily,[24-26] have natural red or blond hair,[24-26] have sustained a greater frequency of sunburns,[27] and have used indoor tanning beds[22, 28] are at increased risk of developing basal cell carcinoma and squamous cell carcinoma.

## Rationale for Screening

The primary purpose of screening is to detect skin cancers earlier in their clinical course than would happen in usual care, allowing earlier and more effective treatment, and thereby leading to a reduction in skin cancer morbidity and mortality.

## Screening Strategies

Visual skin cancer screening is either a whole or partial body skin examination conducted by a primary care provider or dermatologist. Visual skin cancer screening strategies are focused on the detection of melanoma, but can also detect NMSC.

Visual inspection is guided by either the ABCDE mnemonic or the ugly duckling perspective. The ABCDE mnemonic[29] is an acronym of characteristics to detect melanoma, and stands for: A) asymmetry (one half of nevus does not match the other half of the nevus); B) border irregularity (edges of nevus are ragged, notched or blurred); C) color (pigmentation of the nevus is not uniform, with variable degrees of tan, brown or black); D) diameter >6 mm; and E) evolving (nevus is changing over time). The ugly duckling approach assess which nevus does not look like the others within a cluster of nevi.[30]

In addition to visual inspection of the skin, dermatologists often use a dermascope, a magnifying device to further inspect the lesion or possibly whole body photography to assess changes in lesions.

Our review focused on clinical visual skin cancer screening by primary care or dermatology and distinct from skin self-examination, as conducted by the patient or partner.

# Treatment Approaches

## Prevention/Intervention

Primary prevention of skin cancer focuses on reducing exposure to sun or UV radiation exposure. Within primary care, physicians can be effective in counseling patients to avoid sun exposure, tanning beds, and provide education on skin cancer risk factors.[31, 32] In an effort to reduce additional UV radiation exposure in adolescents, several U.S. states have initiated legislation to ban the use of tanning beds in persons less than 18 years of age.[33]

## Treatment

Definitive diagnosis of both NMSC and melanoma is through a biopsy including: 1) shave biopsy; 2) punch biopsy; or 3) excisional biopsy. The treatment options vary dependent on the type of skin cancer.

### NMSC

NMSC are removed by either: surgical excision, Mohs micrographic surgery (i.e., tissue is removed in layers until microscopic examination of the layers indicates that the cancer has been completely removed), electrodessication and curettage (i.e., tissue destruction by electric current and removal by scraping with a curette) or cryosurgery (i.e., tissue destruction by freezing).[2] Radiation therapy and certain topical medications might be also be used.[2]

### Melanoma

Primary tumor and surrounding normal tissue are removed and sometimes a sentinel lymph node is biopsied to determine stage.[18] There can be more extensive surgery if the sentinel lymph node is positive.[18] Melanomas with deep invasion or that have spread to lymph nodes might also be treated with immunotherapy, radiation therapy, and/or chemotherapy.[18] Advanced lesion thickness or stage melanoma cases may be treated with palliative surgery, immunotherapy, radiation therapy, and/or chemotherapy.[18]

# Current Clinical Practice in the United States

Dermatologists tend to perform more skin screening exams than family practice physicians or internists,[34] but lack the capacity to offer population screening.[35] Potentially to achieve skin

screening of the general population, there is the two-step screening method with initial review of skin lesions in primary care and referral to dermatology for second review. However, most primary care and general internists report not having sufficient training in skin cancer screening to feel confident in their skills to conduct whole body skin exams on their patients.[36] Hence, skin cancer screening in the United States among primary care physicians remains quite low. Primary care physicians in two counties in Connecticut and Florida indicate that only 31 percent perform skin cancer screening on their adult patients. The primary barrier to screening was physician's lack of confidence in identifying a suspected lesion.[37] While there are several educational interventions to improve knowledge and confidence with skin cancer screening in primary care, few tools have been rigorously tested for measured changes in clinical practice.[38]

Currently, no U.S. professional organizations recommend clinician-performed skin cancer screening, including the American Academy of Family Physicians (AAFP),[39]American College of Preventive Medicine (ACPM),[40] the American Academy of Dermatology (AAD),[41] and the American College of Physicians (ACP).[42] The AAFP cites the 2009 USPSTF report[43] as the basis for their conclusion that there is insufficient evidence to evaluate the balance of benefits and harms of screening.[39] The ACPM, AAD, and ACP do not have current guidance on whether or not to screen. The American Cancer Society has no specific recommendation for skin cancer screening, other than that those persons aged 21 years and older have a cancer-related check-up at their periodic health exam, including possibly an exam for skin cancer.[44] The recommendations from The Community Guide focus on preventing skin cancer through various educational and policy approaches, such as promoting individual behaviors towards sun protection, and target populations in child-care centers, outdoor occupational settings or primary and middle schools.[45]

Despite no current screening guidelines, the AAD[41] has offered free skin cancer screening clinics since 1985 similar to their contemporary SPOTMe® screening campaign[46] and conducted 2.4 million screenings to date.

## Previous USPSTF Recommendations

In 2009, the USPSTF concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening the adult general population by primary care clinicians or by patient skin self-examination for early detection of cutaneous melanoma, basal cell cancer, or squamous cell skin cancer (I statement).[43] The 2009 review found a lack of evidence about the influence of early detection on skin cancer mortality and morbidity and about the magnitude of harms from skin cancer screening.

The 2009 recommendation echoed findings from 2001, in which the USPSTF also concluded there was insufficient evidence to recommend for or against routine skin cancer screening by whole body skin examination for early detection of cutaneous melanoma, basal cell cancer, or squamous cell skin cancer (I statement).[1]

# Chapter 2. Methods

## Scope and Purpose

This systematic review was designed to update the prior 2009 review on the effectiveness of skin cancer screening in average risk individuals. For this review, we adapted the previous analytic framework and key questions (KQs) to address the benefits and harms of primary care screening for skin cancer. Since our review was focused on visual skin cancer screening within primary care settings, skin self-examination was considered outside scope of this review.

## Analytic Framework and Key Questions

Using USPSTF methods (detailed in **Appendix A**), we developed an analytic framework (**Figure 1**) and five KQs:

1. What is the direct evidence that visual skin cancer screening by a primary care provider or dermatologist reduces skin cancer morbidity and mortality, and all-cause mortality?
2. What are the harms of skin cancer screening and diagnostic followup?
3. What are the test characteristics of visual skin cancer screening when performed by primary care providers vs. dermatologists?
4. Does visual skin cancer screening lead to earlier detection of skin cancer compared to usual care?
5. What is the association between earlier detection of skin cancer and skin cancer morbidity and mortality, and all-cause mortality?

## Data Sources and Searches

We designed the review to be an extension of the 2009 systematic review.[47] The literature search for this systematic review covered MEDLINE, PubMed, and the Cochrane Collaboration Registry of Controlled Trials for studies published from January 1, 1995 through June 1, 2015. We worked with a medical librarian to develop our search strategy (**Appendix A, Search Strategy**) and all searches were limited to English language articles. We managed literature search results using version X5 of End Note Library, a bibliographic management software database, and an Access database.

To ensure comprehensiveness, we reviewed the reference lists of included studies, systematic reviews, and meta-analyses to identify relevant articles published before or not identified in our literature searches. We also supplemented our database searches with suggestions from experts and searched Clinicaltrials.gov to identify relevant ongoing trials (**Appendix B**).

All reviewed abstracts and full text articles that might contain references of interest were marked, and references were assessed by the team. Articles identified through reference lists are included in the literature flow diagram (**Appendix A Figure 1**) as "identified through other

sources." Articles that were not already identified in the original search results were evaluated using the inclusion/exclusion criteria described above.

## Study Selection

We developed an *a priori* set of inclusion and exclusion criteria (**Appendix A Table 1**). Two researchers independently reviewed 12,514 unique titles and abstracts to determine if the studies met the inclusion or exclusion criteria for design, population, intervention, and outcomes. We then reviewed the 453 full text potentially relevant articles for inclusion using dual review. We resolved disagreements by consensus and consultation with a third reviewer, if necessary. We excluded articles that did not meet the inclusion criteria, or were rated as poor quality, as described below. Excluded studies are listed in **Appendix C**. Systematic reviews were reviewed to identify potential included articles.

We included studies of asymptomatic adults aged 15 years and older. Included studies were required to be fair to good quality and conducted in countries with a United Nations Human Development Index score of ≥0.9[48] We excluded studies that focused on nonskin cancers; populations under surveillance because of prior skin cancer diagnosis; self- or partner-screening; intermediate or health outcomes relating clinician skin examination to other risk factors (e.g. sun protective behaviors); or measures of doctor-patient relationship quality.

For effectiveness and harms studies (KQ1-4), acceptable screening tests were defined as whole or partial visual skin examination conducted by primary care providers (or related mid-level staff) or dermatologists with or without tools to aid examination (e.g., dermatoscopy, whole body photography). We excluded screening studies that focused on skin examinations in response to patient concerns for suspicious lesions, skin self-screening by individuals or partners, or physician counseling for self-screening. For studies focusing on morbidity and mortality (KQs 1, 5), we reviewed for studies that investigated skin cancer mortality, all-cause mortality, or morbidities associated with any skin cancer (including melanoma in situ, dysplastic nevi, and actinic keratosis), including quality of life. For test characteristic studies (KQ 3), we included studies that assessed cancer outcomes through cancer registry-based systems or pathology/biopsy reports within a defined period postscreening exam, and estimated for false negative rates for melanoma detection in participants that screened negative. For studies on early detection of skin cancer (KQs 4, 5), we included studies that evaluated either American Joint Committee on Cancer (AJCC) stage[49] or Breslow lesion thickness at diagnosis.

We evaluated trials, cohort studies, ecologic studies, and observational studies that reported clinical outcomes, and included case series or case reports for identifications of harms in KQ 2.

## Quality Assessment and Data Abstraction

Two reviewers independently appraised all articles that met the inclusion criteria for this review as good, fair, or poor quality. Appraisal criteria were adapted from the USPSTF design-specific quality criteria (**Appendix A Table 2**). The final quality rating in the evidence tables is based on

a combination of criteria adapted from the USPSTF methods,[50] Dufault 2011[51] and Tu 2008.[52] In general, a good quality study met all criteria well. A fair quality study did not clearly meet at least one criterion but had no known issues that would invalidate its results. Poor quality studies had severe limitations including one or more of the following risks of bias: unclear study population, unclear screening strategy, lack of defined follow-up, and accounting of confounders or reporting of baseline characteristics.

Four researchers extracted data from all included studies rated as fair to good quality into evidence tables. A second reviewer checked the data for accuracy. The reviewers abstracted study characteristics (e.g., population, purpose, exposure, and outcomes), study design elements (e.g., recruitment procedures, inclusion/exclusion criteria, followup duration and attrition), outcomes for screening studies (e.g., true positives, diagnostic yield, positive predictive value), health outcomes (e.g., skin cancer morbidity and mortality) and harms.

## Data Synthesis and Analysis

For the body of evidence defined by the key questions, we created summary evidence tables to capture key study characteristics and sources of heterogeneity (e.g., study quality, sample, geographic location, age and sex). Further, for each key question, we present results summarized qualitatively in the absence of data available to pool across studies.

## Expert Review and Public Comment

A draft research plan that included the analytic framework, KQs, and inclusion criteria was available for public comment from May 15 to June 11, 2014. We made no substantive changes to our review methods based on comments received. A draft version of this report was reviewed by four invited content experts and federal partners from the Centers for Disease Control and Prevention (CDC), Centers for Medicare and Medicaid Services (CMS), National Institutes of Health, the Veterans Administration, and the Military Health Service. Comments received during this process were presented to the USPSTF during its deliberation of the evidence and were addressed in the final version of the report.

## USPSTF Involvement

The authors worked with USPSTF liaisons at key points throughout the review process to refine inclusion criteria, address methodological decisions on applicable evidence, and resolve issues around scope for the final evidence synthesis. The Agency for Healthcare Research and Quality (AHRQ) funded this research under a contract to support USPSTF work. AHRQ staff provided oversight for the project and assisted in external review of the draft evidence synthesis.

# Chapter 3. Results

## Description of Included Studies

Our literature search yielded 12,514 unique abstracts; 453 met the criteria for full-text review (**Appendix A Figure 1**). We included 13 unique studies (k=13) of fair to good quality reported in 15 articles (n=15) that answered one or more of our five key questions as follows: KQ 1 (n=3 articles, k=1 study), KQ 2 (n=3, k=2), KQ 3 (n=2, k=2), KQ 4 (n=1, k=1) and KQ 5 (n=8, k=8) (**Table 1**).

Of the 13 unique studies, most study designs (k=10) were observational cohort studies. The study designs for the remaining 3 studies were case-control, ecologic, and case series. The most relevant included study was the Skin Cancer Research to Provide Evidence for the Effectiveness of Screening (SCREEN) study conducted in the Schleswig-Holstein region of Germany. The SCREEN study provided data on outcomes including mortality (KQ1) and excisions needed to detect one skin cancer (KQ2).

## Included Populations

Of the 13 included studies, five were included for screening questions (KQ1-4) and eight for the association between stage at melanoma detection and skin cancer mortality (KQ5).

In the five screening studies (**Table 2**), four evaluated skin cancer screening in populations and one evaluated skin cancer screening as an exposure using a case-control design. Study population size ranged from 45 to 360,288 individuals. The reported mean age ranged from 32 to 58 years. When reported, the prevalence of more than 1 skin cancer risk factor ranged from 47.7 to 62.4 percent of the populations.

In the eight studies that included the association between stage at melanoma detection and skin cancer mortality, all had a sample size greater than 4,000 individuals. Mean age ranged from 48.3 to 58 years, when reported, and the majority of populations were between 40 to 64 years. One study was conducted in Medicare population. Four studies were conducted with data from the United States, three from Australia, and one from Germany.

## Included Screening Programs

Three different screening programs were described by five articles (**Table 2**).[53-57] The screening interventions were aimed at asymptomatic populations and included screening by primary care physicians only, primary care physicians and other nondermatology specialists, or volunteer dermatologists and plastic surgeons. All screening interventions were multicomponent and included physician education; media campaigns or outreach to encourage individuals to participate in screening; and access to visual skin exams with a medical provider with planned followup for the participants who screen positive. No screening program biopsied lesions at the

time of the first visual exam.

## Quality

We included 4 good and 11 fair quality articles. In general, the limitations for fair quality studies included: response rates for follow-up, study design, outcome assessment, complete data presented, and specifications of model adjustment.

# KQ 1. What Is the Direct Evidence That Visual Screening for Skin Cancer by a Primary Care Provider or Dermatologist Reduces Skin Cancer Morbidity and Mortality and All-Cause Mortality?

## Summary of Results

We identified no trials that assessed skin cancer morbidity or all-cause mortality associated with physician visual skin screening. We identified one fair-quality ecologic study (the SCREEN study) that compared trends in melanoma mortality in the population over 10 years in the Schleswig-Holstein region of Germany, where there was a population-based visual skin cancer screening program compared to melanoma mortality trends in surrounding regions, where there was no population-based skin cancer screening program (**Table 3**).

The SCREEN study introduced a statewide skin cancer screening program in 2003,[54] including multicomponent intervention: 1) training nondermatologists and dermatologists in skin cancer screening; 2) a media campaign to encourage skin cancer screening in adults aged 20 years and older; and 3) a followup dermatology referral protocol for nondermatologists to refer adults with either suspicious lesions or multiple risk factors for skin cancer. During the one-year intervention period (2003 to 2004), nearly 361,000 adults (19% of the age-eligible adults) were screened with a visual skin cancer exam mainly by nondermatologists. The majority of screenees were women (73.6%), and the mean age of screenees was 49.7 years (standard deviation 16.2 years). Changes in melanoma mortality pre- and post-SCREEN intervention were compared to four surrounding geographic regions and Germany as a whole (excluding the intervention region). Between 1998 to 1999 (prescreening) and 2003 to 2004 (screening program initiation), melanoma mortality remained constant in the intervention region and the five comparison regions. Between 1998 to 1999 (prescreening) and 2008 to 2009 (postscreening), age- and sex-adjusted melanoma mortality decreased from 1.7 to 0.9 deaths per 100,000 individuals. The change in melanoma mortality decreased by 48 percent in the SCREEN region, resulting in an overall absolute mortality difference of 0.8 melanoma deaths per 100,000 individuals. By comparison, in the other five regions the absolute change in melanoma mortality remained stable or increased by 0.1 to 0.3 deaths due to melanoma per 100,000 individuals. Percent change in mortality over 10 years increased from 2 to 32 percent. As an ecologic study, the results do not provide individual-level data about risk reduction associated with screening, and it is not possible to directly compare changes in mortality among those exposed versus not exposed to skin cancer screening

and account for confounding. The results should be viewed cautiously.

## Detailed Results: Skin Cancer Screening and Melanoma Mortality

### The SCREEN Program (Germany)

The SCREEN study was conducted to determine the feasibility of a population-based skin cancer screening program in the German primary care health system. Germany had a nationally mandated but previously unorganized early skin cancer detection program.[55] In 1989, analysis of the feasibility of the pilot program and data collection components began. In 2001, pilot intervention activities occurred on a small scale with 200 physicians and 6,000 screened patients in the Schleswig-Holstein region of northern Germany. Pilot activities included physician training sessions, a limited screening program within clinical practice, and public awareness campaigns. The pilot activities helped to draft protocol for full implementation.

Between 2003 and 2004, the SCREEN project implemented population-based skin cancer screening with a component intervention (**Table 2**):

1. Provider education and training. From April 2003 to September 2003, nondermatologists (defined as general practitioners in primary care, obstetricians and gynecologists, and urologists) (n=1,673) and dermatologists (n=116) participated in an 8-hour training course. The course focused on detecting all skin cancers and included training in the epidemiology and etiology of skin cancer, training and practice in standardized whole body visual examination, strategies for actively recruiting patients for screening, and program documentation and referral procedures. All providers were evaluated at the end of training for accuracy in visual diagnosis of skin cancer and demonstrated improvement in knowledge.[55] Training participation rates were 64 percent for nondermatology providers and 98 percent for dermatologists practicing in the region.
2. Public outreach. The intervention encouraged residents of Schleswig-Holstein aged 20 years and older to seek skin cancer screening by a nondermatology physician. Communication channels included health insurers, physicians and mass media campaigns via print, internet, and telephone resources. Outreach efforts provided information about the screening procedure, program eligibility criteria, and how to get screened.
3. Screening procedure. Screening exams were conducted from July 2003 to June 2004. The main screening pathway was a whole body visual skin exam conducted by a nondermatology provider. Referrals to dermatology were made on identification of a suspicious skin lesion or for individuals with risk factors for skin cancer. Alternatively, participants could choose to be initially screened by a dermatologist. Upon documentation of the screening episode using a standardized paper form that included risk factor information, physicians were reimbursed about U.S. $20 per screening exam. From dermatology, all tentative clinical diagnoses were followed by biopsy and histopathologic evaluation. All detected cancers were reported to the state tumor registry.

Neither the surrounding German regions to the east, west, and south, nor Denmark, the country sharing Schleswig-Holstein's northern border, implemented population-based skin cancer screening activities during same timeframe. These areas were used as comparison populations

for melanoma mortality.

*Participation*

Of a total population of 2.8 million, 1.9 million individuals aged 20 years and older comprised the eligible screening population. During the project period, 360,288 people completed visual skin exams, representing 19.1 percent of the eligible population in the region. Screening participation rates varied by age with 20 to 22 percent of adults aged 35 to 69 years participating in screening compared with 14.9 percent of adults over age 70 years. Almost three-quarters of screened participants were women (73.6%).

*Conduct of Screening*

Of initial screening exams, 77.4 percent were conducted by nondermatology providers, and 22.6 percent were conducted dermatologists. Among the 73,710 individuals referred to dermatology after screening by nondermatology providers, 36.8 percent were lost to followup and did not see a dermatology provider for a second clinical exam.

*Skin Lesion Results*

During the SCREEN study period from 2003 to 2004, 1,169 incident melanoma cases were reported to the state cancer registry, 585 of which were detected via the SCREEN study.[54, 55] Of melanomas detected by SCREEN study, 31 percent were melanoma in situ and 69 percent were invasive melanoma diagnoses. The SCREEN study also detected 1,961 basal cell carcinomas, 392 squamous cell carcinomas (including Bowen carcinoma) and 165 other skin cancers.

As anticipated, incidence of melanoma, basal cell carcinoma, squamous cell carcinoma and melanoma in situ all increased statistically significantly by 15 percent to 48 percent during the SCREEN study (**Appendix D Table 3**). Melanoma age-adjusted incidence rates (per 100,000 individuals) in the pre-screening period (2001 to 2003) versus during-screening period (2003 to 2004) increased 27 percent from 14.2 (95% CI, 13.3 to 15.1) to 18.0 (95% CI, 16.6 to 19.4), respectively. Melanoma in situ age-adjusted incidence rates (per 100,000 individuals) increased 48 percent between the pre-screening period versus during-screening period from 5.8 (95% CI, 5.2 to 6.4) to 8.5 (95% CI 7.5 to 9.5). Squamous cell carcinoma age-adjusted incident rates (per 100,000 individuals) in the pre-screening period versus during-screening period were 11.2 (95% CI, 10.6 to 11.8) and 12.9 (95% CI, 12.0 to 13.8), respectively, a 15 percent increase. Basal cell carcinoma age-adjusted incidence rates (per 100,000) increased 29 percent in pre-screening period versus during-screening period from 60.5 (95% CI, 59.0 to 62.1) to 78.4 (95% CI, 75.9 to 80.8).

*Melanoma Mortality*

Age- and sex-adjusted melanoma mortality rates in Schleswig-Holstein declined 48 percent in 2008 to 2009 five years after SCREEN study began compared to 1998 to 1999, before the SCREEN study (**Table 3**). From 5 years prescreening (1998 to 1999) to 5 years postscreening (2008 to 2009), melanoma mortality declined by 0.8 melanoma deaths per 100,000 individuals

within the intervention region. Declines in melanoma mortality were not observed in the same time period in regions to the north, south, east or west or in Germany overall (excluding Schleswig-Holstein). During the study period, melanoma mortality changes in other regions were: 2 percent increase in Hamburg (south), 7 percent increase in Lower Saxony (west), 32 percent increase in Mecklenburg-Vorpommern (east), 4 percent increase in Denmark (north), and 10 percent increase in Germany (excluding the intervention region). Melanoma mortality reductions in the intervention region were similar for men and women (**Appendix D Tables 1 and 2**).

As an ecologic study, the results from SCREEN do not provide information about individual risk reduction associated with skin cancer screening, to directly compare changes in mortality among individuals exposed versus not exposed to skin cancer screening and to account for confounding (through randomization or multivariate adjustment), and limits the ability to infer a causal relationship between the SCREEN program and melanoma mortality. The results should be viewed cautiously.

# KQ 2. What Are the Harms of Screening for Skin Cancer and Diagnostic Followup?

## Summary of Results

We assessed harms due to screening including overdiagnosis, psychosocial harms, and procedure-related adverse events. We did not identify any studies that directly reported on procedure-related adverse events or psychosocial harms, such as skin infections or scar revisions in screened populations. Further, we did not identify any studies that specifically identified overdiagnosis in screened populations. We identified two fair quality studies conducted in Germany that assessed the number of excisions needed in detection of one melanoma, basal cell carcinoma, or squamous cell carcinoma (the SCREEN study); and cosmetic acceptance of shave biopsy in a screened population (**Tables 4 and 5**).[54, 58]

The number of excisions needed to detect one melanoma, basal cell carcinoma or squamous cell carcinoma varied by age and sex. For all cancers, fewer excisions were needed to detect a single case in adults aged 65 years or older compared with younger adults. For example, detecting one melanoma in women aged 65 years and older required 22 excisions compared with 41 in women aged 20 to 34 years. Similar patterns were observed in men and other cancer types. In a population of 46 adults who underwent cancer screening subsequent shave biopsy for removal of potential NMSC, 7.1 percent of patients reported their cosmetic results as poor (mean score 1.7 between excellent to good) compared with 16.1 percent of physicians who rated the results as poor (mean score 2.5 between good to fair). Few studies evaluated harms of screening.

## Detailed Results: Harms of Screening for Skin Cancer and Diagnostic Followup

### Excision Rates per Melanoma, Basal Cell, or Squamous Cell Cancer Detected

The fair-quality SCREEN study evaluated the impact of skin cancer screening on overall excisions for melanoma detection by number of melanomas detected (**Table 4**). The study included 15,983 total excisions performed in 360,288 adults screened for skin lesions suspicious for melanoma, squamous cell or basal cell carcinoma. Calculations were based on only one excision per person and one malignant finding per tumor per person.

Comparing men and women, similar numbers of excisions were needed to detect any melanoma (1 per 28 excisions) or any basal cell carcinoma (1 per 9 to 10 excisions). However, 28 additional excisions occurred in women compared to men to detect a single squamous cell carcinoma (56 in women compared with 28 in men). Large differences were seen in diagnostic yield analyzed by age, with younger women and men undergoing more excisions for a lower yield compared to older adults. Compared to women aged 65 years and older, women aged 20 to 34 years experienced 19 additional excisions to detect one melanoma and 134 additional excisions to detect one basal cell carcinoma. The number needed to excise additional squamous cell lesions could not be calculated with the available data in young women. However, 565 additional excisions are needed to detect one squamous cell carcinoma in women aged 35-49 years compared to women over age 65 years. Compared to men aged 65 years and older, men aged 20 to 34 years experienced 24 additional excisions per one melanoma, 898 additional excisions per one squamous cell carcinoma, and 109 additional excisions per one basal cell carcinoma. Based on these excision rates, the estimated false positive rate for melanoma or NMSC can be quite high in a screened population with a younger age-distribution of the population.

### Cosmetic Harms

In one fair-quality study[59] of routine outpatient cancer screening, cosmetic harms were evaluated by 45 patients and a single physician at 6 days and at 6 months after shave biopsy (**Table 5**). Participants were identified during routine skin cancer screening but the study authors did not further describe the screening process. Only patients who underwent razor-blade shave excision for suspected NMSC and did not have subsequent skin cancer were included. In 5 percent of shave sites, delayed healing and infection were postoperatively observed by the physician. Among the 60 percent of patients evaluated at 6 months, physicians reported shave site outcomes, including 52 percent hypopigmentation, 32 percent marginal hyperpigmentation, 23 percent erythema, 7 percent hypertrophic scarring, 4 percent hypotrophic scarring and 13 percent recurrent nevus. At 6 months, the physician and the patients assessed patient outcomes at the excision site based on a four-point physical judgment scale of excellent, good, moderate or poor. The mean patient evaluation score was higher (1.7, between excellent and good) than the mean physician score (2.5 between good and moderate). As such, 7.1 percent of patients expressed poor satisfaction with the cosmetic results from shave biopsy 6 months later, compared with 16.1 percent of their physicians regarding the same lesion removed. The results do not directly assess cosmetic results from excisional biopsies needed for melanoma diagnosis, which are more invasive procedures.

# KQ 3. What Are the Test Characteristics of Visual Screening for Skin Cancer When Performed by Primary Care Providers Versus Dermatologists?

## Summary of Results

We identified two fair quality cohort studies with data on the test characteristics of skin cancer screening performed by primary care physicians or dermatologists in Australia. Skin cancer outcomes were obtained through either cancer registry data[57] or pathology and biopsy reports and an estimate of false negative screen rates (**Table 6**).[56] In the first study in Queensland, Australia, primary care physicians conducted screenings among 16,383 adults. Cancer outcomes were determined by pathology or biopsy reports for positive screens. False-negative rates for melanoma were estimated using prior literature and population melanoma rates. The recall rate was 14.1 percent for those who screened positive and were referred to their usual primary care physicians for followup. Based on melanomas detected within 3 years of the first screen exam, sensitivity for melanoma detection was 40.2 percent (calculated), and specificity was 86.1 percent (95% CI, 85.6 to 86.6%). The positive predictive value for melanoma was 1.4 percent. The second study evaluated the performance of volunteer dermatologists and plastic surgeons who conducted screening 7,436 people in suburban and rural areas in Western Australia. With followup to 24 months for melanoma through cancer registry system, the sensitivity was 49.0 percent (95% CI, 34.4 to 63.7%) and the specificity was 97.6 percent (95% CI, 97.2 to 97.9%) with an overall recall rate for of 2.7 percent. The positive predictive value was 11.9 percent (95% CI, 7.8 to 17.2%). Different followup times for cancer outcomes prohibited direct comparison of screening accuracy between the two physician types.

## Detailed Results: Screening by Primary Care

One fair-quality study of skin cancer screening within nine communities in Queensland, Australia allowed assessment of test characteristics of screening conducted by primary care physicians. The intervention, a pilot study intended to precede a randomized controlled trial, had three components: 1) a community education program; 2) a physician education program including a full-day with dermatology specialists to review skin cancer epidemiology, early diagnosis, management and patient communication aimed at encouraging primary care physicians to offer their patients whole-body skin examinations; and 3) free patient access to skin screening clinics in the intervention regions. Whole body skin examinations were provided by primary care physicians who practiced within the communities and by primary care physicians from outside the community employed by the research study. The research team sent personalized letters to men and women in the community aged 30 to 79 years to encourage participation in skin cancer screening. Positive screens were defined as skin lesion suspected to be cancerous at the screening examination, and people with positive screens were referred to their usual primary care physician for diagnosis and management of the lesion.

Pathology reports from biopsies were used to ascertain cancer outcomes for patients who screened positive. Patients with negative screens were not linked to cancer registry data; instead

negative screening rate for melanoma was estimated using the number of false negative results from the literature[60] and population-based estimates of melanoma incidence. Using a false negative rate of 0.2 percent and an adjusted age distribution for screening participants, an estimated 49 screenees would screen negative but subsequently be diagnosed with melanoma within 3 years of the examination, if the entire sample had been linked to cancer registry data. Because the false-negative rate was estimated only for melanoma and not for all skin cancers, test accuracy for sensitivity and specificity for all skin cancers could not be estimated.

The total sample included 15,343 adults. About 52 percent of the study population was women and the average age of those screened was 46.5 years (standard deviation 16.4). Of those referred for further evaluation, 79.1 percent followed up with their physician.

During the screening program, 33 melanomas (including 13 in situ melanomas), 259 basal cell carcinomas, and 97 squamous cell carcinomas were detected. Other benign skin conditions were also detected. Calculated sensitivity for melanoma of screening exams conducted by primary care physicians for melanoma detection was 40.2 percent [33 melanomas detected within 3 years/(33 melanomas plus 49 estimated false negative melanoma)] and specificity was 86.1 percent (95% CI 85.6 to 86.6). The recall rate was 14.1 percent of all screening exams referred for additional workup among 2,302 individuals. The positive predictive value for melanoma detection among those with a positive screening exam was 1.4 percent, and the overall cancer detection rate was 0.2 percent.

No information was provided on the false negative rate for NMSC so we were not able to calculate sensitivity and specificity. Some study data were available to calculate the positive predictive value for all skin cancer, including melanoma and NMSC in this population, which was 16.9 percent. The cancer detection rate was 2.4 percent.

## Detailed Results: Screening by Dermatologists

From 1994 to 2002, the Lions Cancer Institute offered whole body skin exams to men and women aged 20 years and older in rural and suburban areas of Western Australia. Advertisements in local papers recruited individuals to screening clinics. From 1996, the advertisements directly targeted people with the following eight risk factors: 1) family history of melanoma; 2) five or more moles on the forearm; 3) previous removal of a benign nevus; 4) previous skin cancer; 5) lesion changing in size, color or shape; 6) lesion that does not heal; 7) fair skin that burns rather than tans; and 8) episodes of severe burn as a child. Volunteer dermatologists and plastic surgeons performed the whole body skin exams on patients referring participants to their usual primary care physicians for further evaluation of suspected lesions. All participants regardless of screening outcome were linked to the Lions Cancer Registry for detection of melanoma at 1 and 2 years postscreening exam. Data were only provided for melanoma outcome, and there were no data on all skin cancers or NMSC.

Over the 13 years of the screening program, 9,808 individuals were screened, of whom 7,436 met the study inclusion criteria. About 56 percent of the population were women and 50.6 percent were over age 50 at the time of the screening exam.

There were 33 melanoma lesions diagnosed within 1 year of the screening exam, and 16 additional melanomas diagnosed within 2 years of the screening exam, a total of 49 melanomas. Sensitivity for melanoma at 1 year was 69.7 percent (95% CI 51.3 to 84.4), declining at 2 years to 49.0 percent (95% CI 34.4 to 63.7). Specificity was 97.6 percent (95% CI 97.2 to 97.9). Calculated recall rates for the screening exams was 2.7 percent. The positive predictive value ranged from 11.4 to 11.9 percent for cancers detected within 1 and 2 years, respectively. In this population, the cancer detection rate was 0.31 percent for cancers diagnosed with 1 year and 0.32 percent for cancer diagnosed within 2 years.

# KQ 4. Does Visual Screening for Skin Cancer Lead to Earlier Detection of Skin Cancer Compared With Usual Care?

## Summary of Results

We identified one fair-quality case-control study that measured the association between whole-body skin exams by a physician during the three years before melanoma diagnosis for cases or referent date for controls and risk of invasive melanoma according to lesion thickness at diagnosis (**Table 7**). The study was conducted among 3,762 cases with incident melanoma in Queensland, Australia, and 3,824 controls randomly selected through electoral rolls. Of controls, 28.3 percent reported receiving a clinical skin exam by a physician within 3 years of their reference date compared to 35.3 percent of melanoma cases. In multivariate adjusted models, cases diagnosed with thin melanoma (≤0.75 mm) had a 38 percent higher odds (OR, 1.38 [95% CI, 1.22 to 1.56]) of physician clinical skin exam in previous 3 years compared to controls. Further, cases diagnosed with thicker lesions (>0.75 mm) had a 14 percent reduced odds (OR, 0.86 [95% CI, 0.75 to 0.98]) of recent physician skin exam compared with controls. When thick lesions are further stratified by lesion size, the thickest melanoma lesion cases (≥3.00 mm) had 40 percent reduced odds of recent physician skin exam compared with controls (OR, 0.60 [95% CI, 0.43 to 0.83]). As a case-control study with self-reported exposure, there is the potential for recall bias. Medical record review of patient skin cancer screening history to confirm self-report would strengthen future research.

## Detailed Results: Clinical Screening Exam Within 3 Years of Melanoma Diagnosis

A case-control study in Queensland, Australia, examined melanoma thickness and receipt of a physician clinical skin exam in the 3 years prior to melanoma diagnosis for cases (n=3,762) and controls (n=3,824).[61] Cases were men and women aged 20 to 75 years with a histologically confirmed first primary invasive cutaneous melanoma diagnosed between January 2000 and December 2003, and identified through the Queensland Cancer Registry. Recruitment letters were mailed to cases' treating physicians explaining the research study and seeking permission to contact the patients. After physicians provided permission, cases were invited by letters to participate in the study. Controls were randomly selected from Queensland Electoral Roles matched to five-year age categories and sex distribution of the cases. Controls were also contacted by letter about the study participation.

In telephone interviews, information was obtained on demographics and melanoma risk factors including ethnicity, natural hair color at age 21, eye color, color of skin before tanning, tendency to burn when exposed to sun for an hour without protection, number of moles on the back, childhood sunburn history, and age arriving in Australia. Participation rates in the telephone interviews were 78.0 percent for cases and 50.4 percent for controls.

Among controls, 58 percent of the population was male and 49 percent were between 50-69 years. The frequency of sun exposure factors for controls included: 93 percent with a tendency to burn after sun exposure; 60 percent reported heavy to very heavy average lifetime sun exposure; 19.2 percent with previous diagnosis of NMSC; and 14.5 percent with family history of melanoma in blood relative.

Information on skin cancer screening collected in telephone interviews included self-screening, screening by partners and other lay people, and screening by a doctor, referred to as a clinical skin exam. For cases, screening history was collected only until the time of first awareness of melanoma signs and symptoms for cases. Controls were assigned a reference date to evaluate skin cancer screening exposure. Reference dates were based on the distribution of cases for time from first symptom awareness to date of telephone interview, so the timeframe for recollection would be similar between cases and controls. Clinical skin examinations were determined in telephone interviews with the question: "During the last 3 years before (you believed something was wrong [cases]/referent date [controls]), had a doctor deliberately checked all or nearly all of your whole body for early signs of skin cancer?" The self-reported receipt of screening by cases and controls was not confirmed by medical record review.

However, the question as phrased had been validated in prior work, and test re-test reliability on a sample of the participants one to three months after the interview indicated good agreement for both the cases and the controls.[62]

Of controls, 28.3 percent reported receiving a clinical skin exam by a physician within the 3 years before their reference date compared to 35.3 percent of melanoma cases. When further stratified by lesion thickness, case report of receiving a clinical skin exam declined as lesion thickness increased: 38.7 percent for lesions <0.75 mm, 30.3 percent for lesions 0.76 to 1.49 mm, 28.0 percent of lesions 1.5-2.99 mm, and 22.5 percent of lesions ≥3.00 mm.

Multivariate models adjusted confounders, including age group, sex, education, employment status, marital status, eye color, hair color, skin color, degree of freckling, number of moles on back, age of arrival in Australia, average lifetime sun exposure, family history of melanoma, family history of NMSC, and ethnic status. In multivariate adjusted models, cases diagnosed with thin melanoma lesions (≤0.75 mm) had 38 percent higher odds (95% CI, 1.22 to 1.56) of physician clinical skin exam in the past 3 years compared to controls. Further, cases diagnosed with thicker lesions (>0.75 mm) had 14 percent reduced odds (95% CI, 0.75 to 0.98) of recent physician skin exam compared with controls.

When thick lesions were further stratified by size, the odds of having a clinical skin exam by a physician decreased as thickness increased: 7 percent decreased odds for lesions 0.76 to 1.49 mm (95% CI, 0.79 to 1.10); 17 percent decreased odds for lesions 1.50 to 2.99 mm (95% CI, 0.66 to

1.05); and 40 percent decreased odds for lesions ≥3.0 mm (95% CI, 0.43 to 0.83).

As a case-control study, there is the potential for recall bias due to differential reporting prior physician skin screening examinations from cases compared with controls. However, the potential for cases to recall exam differentially by lesion size seems unlikely. Nonetheless, medical record review of patient skin cancer screening history to confirm self-report would strengthen future research in case-control study designs or through cohort study with clear exposure categories.

# KQ 5. What Is the Association Between Earlier Detection of Skin Cancer and Skin Cancer Morbidity and Mortality and All-Cause Mortality?

## Summary of Results

We identified eight fair or good quality observational studies that included more than 200,000 people. The studies examined the association between either melanoma-specific or all-cause mortality and lesion thickness or stage at diagnosis (either AJCC or SEER stage) (**Tables 8-10**). We identified one good quality study which evaluated cancer stage and all-cause mortality. We did not identify any studies that evaluated lesion thickness or stage at diagnosis associated with skin morbidity.

All studies demonstrated a consistent linear increase in risk of melanoma mortality with increasing tumor thickness or stage, regardless of categorization. Tumor thickness greater than 4.0 mm was associated with a 3.1 to 32.6 increased risk of melanoma mortality compared to thinner lesions in multivariate adjusted models. In the largest study of 68,495 melanoma cases diagnosed from 1992 to 2006 and identified through 13 U.S. SEER registries, each 1.0 mm increase in tumor thickness was associated with a subsequent increase in melanoma mortality. Compared with thin lesions (<1 mm), increased risks of melanoma mortality by thickness were: 2.89 (95% CI, 2.62 to 3.18) for tumors 1.01 to 2.00 mm; 4.69 (95% CI, 4.24 to 5.02) for tumors 2.01 to 4.00 mm; and 5.71 (95% CI, 5.10 to 6.39) for tumors >4.00 mm. Using the same study population and categorizing by SEER summary stage, distant stage was associated with an 18.66-fold increased risk of melanoma mortality compared with localized disease. Finally, results in a cohort of 39,049 residents of California with diagnosis of melanoma demonstrated that late stage at melanoma diagnosis was associated with a 10.4-fold increased risk of all-cause mortality in adjusted hazard ratio (HR) models.

## Detailed Results: Stage at Diagnosis and Melanoma Mortality

Three fair to good quality cohort studies evaluated stage at diagnosis associated with melanoma mortality and also reported measures of risk of melanoma death according to stage at diagnosis using either AJCC or SEER staging (**Table 8**). The three studies had similar consistent, linear results.[63-65] In one study that compared to AJCC stage I , stage II melanoma had 4.96-fold increased relative risk of mortality (95% CI, 4.51 to 5.56); stage III had a 9.99-fold increased

relate risk (95% CI, 8.84 to 11.29); and stage IV had a 27.1-fold increased relative risk (95% CI, 22.4 to 32.8).[64]

Two studies used the SEER staging of local, regional, distant and unknown.[63, 65] One study used in situ melanoma as the referent category. Two study populations potentially overlap but likely minimally. One study evaluated 13 SEER regions from 1992-2006 for all ages. The second study used SEER-Medicare data from 11 SEER regions from 1988 to 2000. Using in situ melanoma as the referent category, hazard ratio of risk of melanoma death was 8.83 (localized), 23.2 (regional), and 94.0 (distant).[63] Using localized stage as the referent category, risk of melanoma death were 3.62 for regional and 18.66 for distant.[65] All estimates in the three studies reached statistical significance.

## Detailed Results: Lesion Thickness at Diagnosis and Melanoma Mortality

Seven studies using tumor thickness as a main exposure found that the risk of melanoma death increased linearly with increasing tumor thickness at diagnosis (**Table 9**).[63, 65-70] Reference categories ranged from ≤0.25 to ≤1.0 mm. Maximum tumor thickness categories examined ranged from 1.0 to ≥6 mm.

Because of changes in reference category, actual estimates of melanoma mortality varied. In three studies using tumor thickness ≤1.0mm as the reference category, and risk groups consistent with AJCC staging system,[49] HR risk of melanoma death for 1.01 to 2.00 mm ranged from 2.06[63] to 4.13.[68] Risk for tumors 2.01 to 4.00 mm had risks from 3.11[63] to 6.88.[68] Risks associated with >4.0 mm tumors reported in two of the three studies were 5.71[65] and 9.52.[68] In two studies using ≤0.50 mm as the reference category, risk estimates increased with increasing lesion thickness, from 3.9 for tumors 0.76 to 1.0 mm to 23.08 for tumors >6.0 mm.[70] One study used 1 to 1.5mm as the reference category and found incrementally decreasing risk of melanoma mortality for tumors 0.75 to 1.00 mm (RR, 0.55) and tumors ≤0.75 mm (RR, 0.28) and risk increasing to 3.88 for tumors >4.00 mm.[66]

## Detailed Results: Stage at Diagnosis and All-Cause Mortality

We identified one good quality study that evaluated the association of stage at melanoma diagnosis with all-cause mortality (**Table 10**). A study of 39,049 California residents with median age 58.0 years (95% CI 29 to 84 years) diagnosed with melanoma from 1993 to 2003 found increased HR of all-cause mortality associated with increased melanoma stage at detection, with estimates of HR 2.26 for stage II (95% CI, 2.14 to 2.39), HR 4.27 for stage III (95% CI, 3.90 to 4.67), and HR 10.39 for stage IV (95% CI, 8.96 to 12.0) compared to stage I disease.[64]

# Chapter 4. Discussion

## Summary of Evidence

We conducted this systematic review to assist the USPSTF in updating their previous skin cancer screening recommendation.[47] Thirteen (13) unique studies met our inclusion criteria. The prior review did not explicitly evaluate lesion thickness, harms of screening, or the relationship between mortality outcomes and melanoma thickness or stage at diagnosis.

No firm conclusions on skin cancer screening and melanoma mortality can be made from the evidence reviewed. Results from a single population-based ecologic study suggested skin cancer screening may be associated with reductions in population-level melanoma mortality rates, based on pre-intervention versus post-intervention comparisons in one German region with a one year multicomponent skin cancer screening program compared with surrounding regions without the screening program. However, as an ecologic study, the measures of association were drawn from population-level changes in mortality, not individual-level data, which cannot account for confounding or assess comparisons between exposed and non-exposed people. While data demonstrating unchanged or increased melanoma mortality in control regions are promising, the ecologic study design limits assessment of causal inference. Further, the large relative mortality reduction translated to an absolute mortality reduction of 0.8 melanoma deaths per 100,000 people, after screening only 19 percent of the target population. The context of the results must also be considered among: 1) high proportion of younger women screened who are lower risk of melanoma incidence and mortality rather than in older men suggesting a healthy screenee bias; 2) the high proportion of people with suspicious findings without follow-up by dermatology; and 3) the impact of the other components to the screening program including education to the community which cannot be differentiated from visual skin cancer screening. Nonetheless, the results and challenges from the SCREEN study likely reflect real-world population-based screening programs when implemented.

We found limited data on harms of visual screen exams, except for biopsy yields and cosmetic harms. The included evidence suggested that cosmetic results of shave biopsy are acceptable to most adults. Most screen-positive lesions, particularly to detect one malignant melanoma, require additional excisional biopsies as diagnostic workup. When the ratio of excisions required per malignant melanoma identified was evaluated by type of lesion, age, and sex, younger people aged <35 years required about twice as many excisions of suspicious lesion than adults over the age of 64 years. Among young adults, the pretest probability of melanoma is lower than in older adults. Although these data do not clearly define overdiagnosis, they demonstrate a potential excess burden of excisions for nonmalignant lesions in younger people participating in community skin cancer screening programs where the incidence of NMSC and melanoma is lowest.

We were not able to directly compare screening accuracy between dermatology and primary care clinicians, due to differences in time to ascertainment of cancer outcomes that affect screening exam performance measures. Only one study linked participants to cancer registry data, the gold standard for cancer detection, and the only way to assess screen negatives within the population.

Relying on biopsy or pathology reports could have underestimated the number of melanomas detected in the population rather than through cancer registry rates, and the estimation of false negative rates could be an overestimate of the numbers of cancers missed. Nonetheless, whether visual skin cancer examination can detect skin cancer 24 to 36 months from exam might not be a reasonable time frame. Sensitivity is reduced as the length of followup time to observe cancers is extended. Sensitivity was also impacted by the inclusion of both incident melanoma and melanoma in situ in the screen exams conducted by primary care physicians,[56] compared with the inclusion of only invasive melanoma cases included as positive findings in dermatology and plastic surgery examinations.[57] Not impacted by cancer ascertainment followup, recall rates were lower for dermatology providers than primary care physicians, consistent with higher specificity as might be expected for a specialist examination.

Self-report of skin cancer screening within the prior 3 years was associated with reduced risk of thicker melanoma lesions compared with controls with melanoma who did not report skin cancer screening.[61] In the case-control study, cases may have recalled receipt of a recent screening exam differentially than controls without a melanoma diagnosis. To minimize potential recall bias, the study ascertained history of skin screening exams using a well-tested and reliable question documented to have high validity compared with medical record review.[62] The study did not further validate self-report with medical record review. While cases might have recalled their screening history differently than controls, differences within cases are unlikely to have aligned according to according to lesion thickness to produce a spurious trend of decreasing risk with increasing lesion thickness. Data from cohort studies will be important to confirm this finding and its magnitude.

There is consistent evidence that later stage or thicker lesions at melanoma detection is highly related to increased risk of melanoma mortality and may be associated with all-cause mortality.[64] It is unlikely that future research in this area will change the overall conclusions of this body of current evidence based on thickness alone.

## Challenges in Demonstrating Benefits of Visual Screening for Skin Cancer

Despite efforts to conduct true population-based screening, the challenges faced by other countries attempting such programs may be instructive for the United States. First, for population-based screening, the high proportion of well women who received skin cancer screening and represent a group at lower risk of melanoma compared with older men, suggests that healthy screenee bias should be addressed within future skin cancer screening studies. Second, in studies of diagnostic accuracy, the high proportion of individuals with several skin cancer risk factors within the screened populations suggests that the participating population might not represent an average risk population.[53, 71] The need to increase the pre-test probability of melanoma detection is the likely driver of encouraging skin cancer screening participation, but might not reflect the population observed in primary care settings. Hence, further studies should attempt to address inclusion of study populations representing average risk individuals.

Based on the results of the SCREEN study, the German health care system launched a nationwide skin cancer screening program in 2008. Mortality data after the implementation is

important; however, robust data may not be forthcoming.[72] No reports describing a decline in incidence after screening intervention and removal of prevalent disease have been published from the SCREEN study. Further, the only randomized controlled trial to evaluate skin cancer screening began as a pilot study in Queensland, Australia in early 2000s, but a full trial following the pilot was not able to be conducted. At the timing of this report, there are no anticipated results for mortality outcomes from these pilot data.[73]

Both studies of diagnostic accuracy were conducted in Australia, where overall general knowledge of skin protection habits and sun safety is high, and primary care physicians routinely diagnose and manage skin cancer lesions. Physician training in detecting and diagnosing skin cancers in primary care was part of both studies and is likely important for improving performance, whether for screening alone or responding to patient concerns. In a different Australian population presenting for both skin cancer screening and due to concern with skin lesion, sensitivity was statistically significantly different for melanoma detection between general practitioners with and without skin cancer medicine training (60% vs. 29%, $p<0.001$).[74] Specificity was similar for both provider types; however, due to low sensitivity, general practitioners without specific skin cancer training also had lower positive predictive values than those with specialized skin cancer training (18% vs. 25%). Currently, U.S.-based primary care physicians are not confident in their skills to conduct skin cancer screening,[36] and could require additional training to achieve skin cancer screening goals.

Potential harms of skin cancer screening include cosmetic harms, overdiagnosis, overtreatment, and psychosocial harms related to diagnostic workup. The evidence on these harms is very limited. Risk for excision-related harms could be greater in younger people, based on a greater number of excisions required for melanoma or NMSC case detected.[58] For melanoma, excision-related harms are important because the initial management with a biopsy alone is not sufficient for removing the entire lesion. Subsequent excisions are usually necessary for clear margins, even for small lesions, particularly if the first biopsy is a shave or punch biopsy.[75] No identified studies addressed overdiagnosis in a screening setting, but there is potential for overdiagnosis: melanoma incidence has increased 3-fold since 1975 while melanoma mortality has remained stable, suggesting increased detection of clinically insignificant cancers rather than earlier detection of invasive tumors.[14, 76] An important consideration for the 2.1 million Medicare enrollees diagnosed with NMSC annually[8] is the increase in the detection and treatment of basal cell carcinoma in adults that likely has limited impact on life expectancy.[77] Further, patient-relevant definitions and outcomes of melanoma overdiagnosis and overtreatment are not well understood and should be further explored.

The effectiveness of screening depends on effective treatment of identified lesions, and there have been several trends in the surgical treatment of skin cancer. In the late 1990s, clinical practice adopted sentinel lymph node biopsy in the diagnostic work-up of melanoma, even in individuals diagnosed with thin lesions. Based on SEER data (1995 to 2001), the proportion of thin lesions that received sentinel lymph node biopsy statistically significantly increased. The proportion of thin melanomas at <0.69 mm and 0.70 to 1.00 mm with sentinel node biopsy increased from 1.6 and 6.3 percent, respectively, in 1995 to 7.8 and 42.4 percent in 2001.[78] More contemporary biopsy data has not yet been reported, and it is unclear whether the proportion of surgeons using lymph node biopsy has changed. In 2012, the current clinical guidelines from the

American Society for Clinical Oncology and American College of Surgeons recommend sentinel lymph node biopsy for lesions of 1 to 4 mm, but the organizations felt evidence was insufficient to create guidelines for lesions <1.0 mm.[79, 80]

We were unable to describe the proportion of lesions <1.0 mm detected on the trunk or extremities that were treated with Mohs micrographic surgery, which is currently not recommended for basal cell carcinoma, squamous cell carcinoma, lentigo maligna and melanoma in situ on the trunk or extremities. The surgery is only appropriate for particularly large or aggressive types of skin cancer.[81] As part of the AAD Choosing Wisely campaign, clinicians are advised not to treat uncomplicated, NMSC <1.0 mm on the trunk and extremities with Mohs micrographic surgery.[82] Although data on the use of Mohs micrographic surgery for these types of small skin cancers on the trunk or extremities could indicate potential overtreatment of screen-detected skin cancers, we found no relevant published data at the time of this report.

## Future Directions

The balance in favor of screening for skin cancer is likely to be greatest among subgroups of the population that are the most likely to develop fatal melanoma, which is yet to be distinguished. However, several algorithms use melanoma risk factors to qualify risk of melanoma and could have utility for screening programs in identifying individuals who might benefit most from screening.[83-86] The algorithms vary by: whether ascertainment of the risk factor information is meant to be done by a health care provider, whether the target population includes people with a family history of melanoma and/or a history of NMSC; and whether the algorithm has been validated. Most existing algorithms have been developed using only information on melanoma risk among persons of white race.[83-86]

One algorithm intended for use by health care providers during clinical care and developed using data from a large melanoma case-control study estimates 5-year risk of developing melanoma in non-Hispanic white individuals aged 20 to 70 years.[83] The algorithm included demographic information (sex, age, and region of residence), history of blistering sunburn (men)/propensity for skin to become tanned (women), and presence of nevi on the back.[83] The area under the receiver operating characteristic curve – a measure of the accuracy of the algorithm, where 0.5 indicates inability to predict who will and will not develop melanoma[87] – ranged from 0.7 to 0.8 depending on sex and age group.[83] The algorithm was not validated in an external population.[83] There is no evidence to suggest these algorithms have been adopted in U.S. clinical practice. If externally validated, risk assessment tools might lead to research testing a targeted screening approach. As well, similarly to other cancer risk assessment tools, they may provide guidance to individuals on their risk of developing melanoma.

## Review Limitations

Our review focused on the clinical skin examination to screen for skin cancer, and separated out the detection of skin cancer from the individual. The nature of skin cancer makes this review unique. In contrast to breast, colorectal, or lung cancers, where a provider-administered screening modality and access to specialty followup are essential for early detection, individuals

can and do identify concerning lesions on their own skin. Thus, community education about skin cancer and improved access to physician review of suspicious lesions is a critically important part of any skin cancer early detection program. These components have been reviewed by the CDC's The Community Guide.[88] Further, studies conducted outside of primary care, for example workplace, "screening days," or "pigmented lesion clinics" were out of the scope of this review, as were studies of people referred for diagnostic workup but from a source population that could not be defined. For these reasons, the role of physician screening in primary care may appear as isolated in this review.

## Study Limitations and Future Research Needs

The bulk of the literature considered in this review was from international settings, specifically Australia, where skin cancer screening and outcomes have been a research focus and the burden of melanoma is much higher compared to the United States or other countries.[89]

A main limitation of this review is the lack of rigorous studies on skin cancer screening conducted in the United States with an application in primary care or internal medicine settings. Our focus was on fair or good quality studies that met our inclusion criteria. Among U.S. studies, very few had longitudinal followup for cancer outcomes, limiting their applicability. Participants in most screening studies tended to be younger women with a perceived increased risk of skin cancer, even though the incidence of skin cancer is highest in older men.[90]

Further research on skin cancer screening should:

- Conduct followup of sufficient length to assess individual melanoma mortality in screened and unscreened people with ascertainment of cancer outcomes based on registry systems.
- Examine the impact of targeted, risk-based screening versus average risk population screening for clinical effectiveness, and clearly document the risk factors of the screened population for potential self-selection.
- Study the relative impact of primary care-based screening relative to other components of a screening program such as public education and improved access to skin exams.
- Advance knowledge on the potential for overtreatment and overdiagnosis, including the psychosocial consequences, of population based skin cancer screening, to help fully understand the benefits of screening in the context of potential harms.

## Conclusion

On a population level, with limited evidence on skin cancer screening, a clear statement cannot be made about the benefit of skin cancer screening for melanoma mortality and all-cause mortality or association with thinner lesions. With few studies to confirm these results, the applicability for widespread skin cancer screening could be limited. Later stage at diagnosis of melanoma is associated with strong effect on melanoma mortality within five years of diagnosis.

Future research of skin cancer screening should focus on targeted screening in those considered to be at higher risk for skin cancer.

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**Figure 1. Analytic Framework**

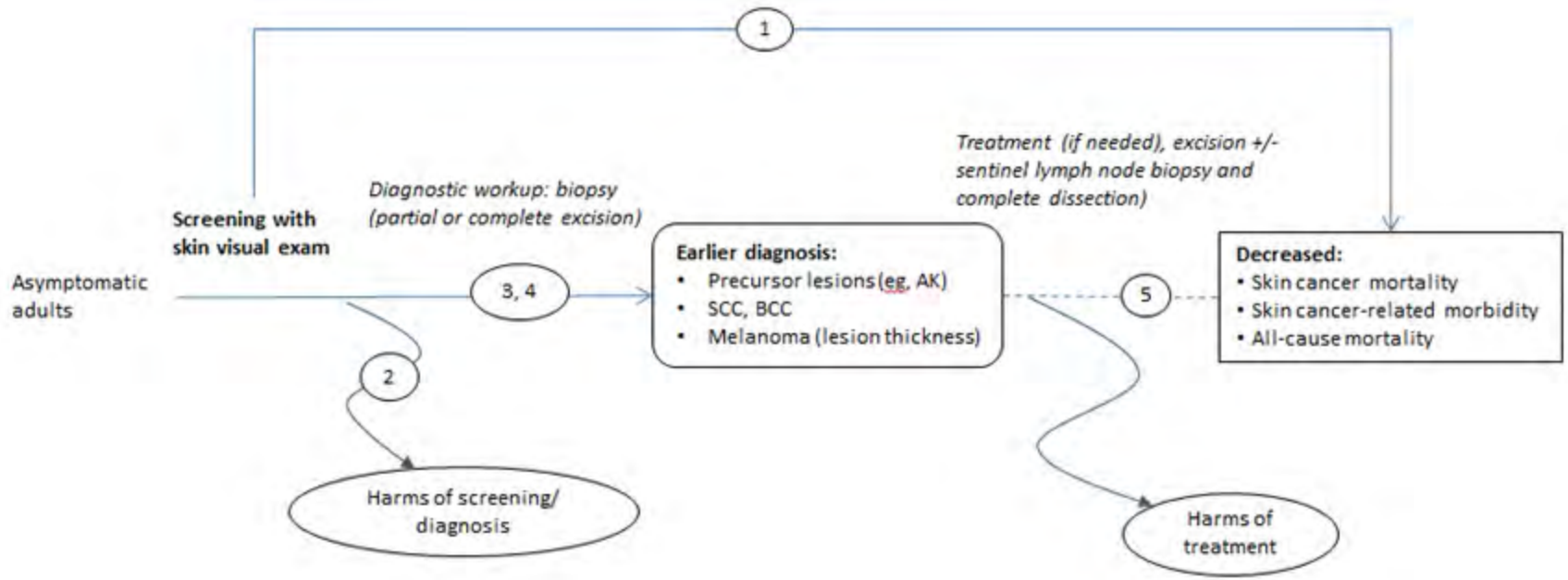

**Table 1. Description of Included Studies for KQs 1 to 5**

| Author, Year Quality | Country | Study Design | N | Population | Mean age, years (SD or range) or category | % female | Dates of data collection | Length of follow-up | KQ |
|---|---|---|---|---|---|---|---|---|---|
| Katalinic, 2012[53] Fair<br>Waldmann, 2012[58] Fair<br>Breitbart, 2012[55] Good<br><br>SCREEN | Germany | Ecologic[53] | 87.46 million | Inhabitants of Germany and Denmark from 1998 to 2009 | NR | 50.9% | 1998-2009 | 5 years after intervention | 1 |
| | | Cohort[55,58] | 360,288 | Residents of Schleswig-Holstein, Germany aged ≥20 years with whole body skin cancer screening exam between July 2003 and June 2004 | 49.7 (16.2) | 73.6% | 2003 -2004 | 12 months | 1,2 |
| Gambichler, 2000[59] Fair | Germany | Case series | 45 | Routine skin cancer screening outpatients not suspected of melanoma with a shave biopsy | 32 (range 15-54) | 51.1% | NR | 6 months after biopsy | 2 |
| Aitken, 2006[56] Fair | Australia | Cohort | 16,383 | Residents in a community-based pilot randomized clinical trial of skin screening program | 46.5 (16.4) | 51.5% | 1998-2001 | Up to 3 years after the initial screening exam | 3 |
| Fritschi, 2006[57] Fair | Australia | Cohort | 7,436 | Adults who attended Lions Cancer Institute weekend mobile screening clinics in rural and suburban locations in Western Australia | <40: 26.2%<br>40-59: 46.2%<br>≥60: 27.6% | 56.0% | 1994-2002 | 2 years after the initial screening exam | 3 |
| Aitken, 2010[61] Fair | Australia | Population-based case-control | 3,762 cases 3,824 controls | Queensland residents aged 20 to 75 years; cases identified from cancer registry and controls selected through stratified random sampling from Queensland Electoral Roll | <40: 16.4%<br>40-69: 69.6%<br>≥70: 14.0%* | 42.4%* | NR | N/A | 4 |
| Marashi-Pour, 2012[68] Good | Australia | Retro-spective cohort study | 52,330 | Cases of cutaneous melanoma from the New South Wales Central Cancer Registry diagnosed between 1988 and 2007 | <40: 14%<br>40-69: 54%<br>≥70: 31 | 42% | 1988-2007 | Follow-up time was calculated from the date of diagnosis until death or end of the study period (December 31, 2007) | 5 |

**Table 1. Description of Included Studies for KQs 1 to 5**

| Author, Year Quality | Country | Study Design | N | Population | Mean age, years (SD or range) or category | % female | Dates of data collection | Length of follow-up | KQ |
|---|---|---|---|---|---|---|---|---|---|
| Pollack, 2011[65] Good | U.S. | Retro-spective cohort study | 68,495 | Cases of melanoma (excluding in situ disease) in the 13 SEER registries in individuals aged >15 years with no previous cancer diagnosis | <40: 19.5%<br>40-64: 48.9%<br>≥65: 31.5% | 45.1% | 1992-2006 | First primary melanoma cases diagnosed from 1992 to 2001. Followed up through 2006. | 5 |
| Reyes-Ortiz, 2006[63] Fair | U.S. | Retro-spective cohort study | 23,068 | 23,068 Medicare beneficiaries age ≥65 residing in one of 11 SEER regions, diagnosed with melanoma between 1988 and 1999, and ethnicity information complete | <39: 0%<br>40-64: 0%<br>≥65: 100% | 40.0% | 1988-1999 | Survival defined as the period between diagnosis and death from melanoma. Censored at death from other causes or December 31, 2000. Follow-up through December 31, 2000. | 5 |
| Leiter, 2004[70] Fair | Germany | Retro-spective cohort study | 12,728 | People with thin incident primary invasive melanoma between 1976 and 2000 in the German-based Central Malignant Melanoma Registry | 50 (15.7) | 58.6% | 1976-2000 | Data obtained from the Central Malignant Melanoma registry. Patients were examined every 3 to 6 months for 10 years. All patients included had a follow-up time of at least 3 months and at most 10 years. | 5 |
| Luke, 2003[67] Fair | Australia | Retro-spective cohort study | 9,519 | Residents of the state of South Australia diagnosed with invasive cutaneous melanoma | <39: 21%<br>40-69: 53%<br>≥70: 26% | 49.9% | 1980-2000 | 1994 to 2000 diagnostic period identified through cancer registry; dates censored at death from other causes or December 31, 2000 | 5 |
| Zell, 2008[64] Good | U.S. | Retro-spective cohort study | 39,049 | Incident patient cases of cutaneous melanoma reported between 1993 to 2003 in the California Cancer Registry[†] | 58[‡] (95% CI: 29.0 to 84.0) | 43.1% | 1993-2003 | Hospital registrars contacted cases annually and CCR staff annually reviewed death certificates. The last date of follow-up was either date of death or the last date of contact. | 5 |

**Table 1. Description of Included Studies for KQs 1 to 5**

| Author, Year Quality | Country | Study Design | N | Population | Mean age, years (SD or range) or category | % female | Dates of data collection | Length of follow-up | KQ |
|---|---|---|---|---|---|---|---|---|---|
| Owen, 2001[66] Fair | U.S. | Retro-spective cohort study | 4,560 | Registered patients at the Duke University Melanoma Clinic who began treatment at Duke within 3 months before or after excision of a primary melanoma (in situ excluded) | 48.3 (14.2)§ | 45.5% | 1970-1995 | Patients registered at Duke University Melanoma clinic between January 1, 1970 and December 31, 1995. Follow-up was limited to 10 years by censoring all observations for patients still alive at 10 years after surgery (also death from other causes and LTFU resulted in censoring). | 5 |
| Green 2012[69] Fair | Australia | Retro-spective cohort study | 26,736 | Queensland residents with a single thin invasive melanoma (≤1.00 mm) diagnosed between 1982 and 2006 | 52.7 (range: 15 to 89) | 46.4% | 1982-2006 | Minimum 1 year follow-up (survival assessed up to December 31, 2007). Average length of follow-up not reported. | 5 |

All numbers in italics represent calculated numbers.
*These data refer to control participants only.
†California cancer registry is part of SEER.
‡Median age.
§Mean age at surgery.

**Abbreviations:** SD = standard deviation, KQ = key question, NR = not reported, N/A = not applicable, SEER = Surveillance, Epidemiology and End Results Program, CCR = California Cancer Registry, LTFU = lost to followup, mm = millimeter(s).

**Table 2. Description of Screening Interventions of Included Studies (KQs 1–4)**

| Author, Year<br>Quality<br>Location | Target population | N | % female<br>Mean age (SD) | Skin cancer risk factors | Provider | Setting and skin cancer screening program | Follow-up of identified lesions |
|---|---|---|---|---|---|---|---|
| Katalinic, 2012[53]<br>Fair (KQ 1)<br><br>Waldmann, 2012[58]<br>Fair (KQs 1, 2)<br><br>Breitbart, 2012[55]<br>Good (KQs 1, 2)<br><br>SCREEN study<br>Germany | Residents of Schleswig-Holstein Germany<br>1998-2009 | 360,288 | 73.6%<br>49.7 (16.2) | NR<br>Among people with referral to dermatology, report of skin conditions included:<br>Multiple melanocytic nevi: 9.8%<br>Clinically atypical nevi: 9.0%<br>UV-damaged skin: 4.8%<br>Actinic keratosis: 2.1% | Nondermatologist and dermatologists | 1. Physician education (training of 64.0% nondermatologist and 98.3% dermatologists who practice in this region).<br>2. Public awareness campaign<br>3. Whole body skin exam conducted by nondermatologist and dermatologists | Referred to dermatologist |
| Gambichler, 2000[59]<br>KQ2<br>Fair<br><br>Germany | Patients undergoing shave excision biopsy for suspicion of NMSC | 45 | 51.1%<br>32 (15-54) | NR | Dermatologists | Routine outpatient skin cancer screening (not further specified) followed by razor blade shave excision | Assessed by physician after 6 months |
| Aitken, 2006[56]<br>Fair (KQ3)<br><br>Australia | 9 intervention communities<br>All primary care patients (adult) | 16,383 | 51.5%<br>46.5 (16.4) | ≥1 risk factor*: 47.7% | Primary care physicians | 1. Physician education<br>2. Community education program<br>3. Free access screening clinics for whole body skin exam excluding areas covered by underwear | Referred to personal primary care physician; people not completing referral sent a reminder at 2 and 5 months |
| Fritschi, 2006[57]<br>Fair (KQ3)<br><br>Australia | Residents in rural and suburban locations, Western Australia | 7,436 | 56.0%<br><40: 26.2%<br>40-59: 46.2%<br>≥60: 27.6% | 0 to 2 risk factors†: 37.7%<br>3 to 5: 55.8%<br>6 to 8: 6.6% | Dermatologists and plastic surgeons | 1. Earned media providing education on 8 risk factors and number to call for appointment<br>2. Mobile clinic staffed by physician volunteers<br>3. Whole body skin exam | Referred to primary care physician. Cancer outcomes were ascertained from national cancer registry as gold standard. |

*Fair skin, a tendency to burn after 1 hour of sun exposure, or more than 10 moles on the body.
†Risk factors included: family history of melanoma, five or more moles on the forearms, previous removal of benign nevi, previous skin cancer, a lesion that is changing in size, color or shape, a lesion that does not heal, fair skin that burns rather than tans, and episodes of severe sunburn as a child.

**Abbreviations:** KQ(s) = key question(s), SD = standard deviation, NR = not reported, UV = ultraviolet, NMSC = non-melanoma skin cancer.

**Table 3. Melanoma Mortality Associated With Visual Skin Cancer Screening (KQ 1)**

| Katalinic, 2012[53] | Total population 2009 (millions) | Pre-screening 1998-1999 Melanoma deaths (N) | Pre-screening 1998-1999 WASR (95% CI) | Screening program 2003-2004 Melanoma deaths (N) | Screening program 2003-2004 WASR (95% CI) | Post-screening 2008-2009 Melanoma deaths (N) | Post-screening 2008-2009 WASR (95% CI) | Absolute change in WASR from 1998-1999 to 2008-2009 | % change in mortality rate 1998-1999 to 2008-2009 |
|---|---|---|---|---|---|---|---|---|---|
| **Intervention region:** Schleswig-Holstein (360,288 people screened) | 2.83 | 86 | 1.7 (1.4-2.0) | 82 | 1.4 (1.2-1.6) | 50 | 0.9 (0.7-1.1) | -0.8 | -48% |
| **Comparison regions** | | | | | | | | | |
| South: Hamburg | 1.78 | 41 | 1.2 (0.9-1.5) | 52 | 1.5 (1.2 - 1.8) | 46 | 1.2 (1.0-1.5) | 0 | +2% |
| West: Lower-Saxony | 7.94 | 224 | 1.4 (1.3-1.6) | 239 | 1.5 (1.3 - 1.6) | 253 | 1.5 (1.4-1.7) | +0.1 | +7% |
| East: Mecklenburg-Vorpommern | 1.66 | 32 | 1.0 (0.8-1.3) | 43 | 1.3 (1.0 - 1.6) | 50 | 1.3 (1.0-1.6) | +0.3 | +32% |
| North: Denmark | 5.53 | 203 | 2.3 (2.0-2.5) | 221 | 2.3 (2.0 - 2.5) | 252 | 2.5 (2.2-2.7) | +0.2 | +4% |
| Germany* | 79.1 | 1,940 | 1.3 (1.3-1.4) | 2,213 | 1.4 (1.3 - 1.4) | 2,529 | 1.4 (1.4-1.5) | +0.1 | +10% |

*Excludes Schleswig-Holstein region.

**Abbreviations:** KQ = key question, CI = confidence interval, WASR = world age-standardized morality rate per 100,000.

**Table 4. Number of Excisions Needed to Detect One Case of Melanoma or Squamous or Basal Cell Carcinoma (KQ 2)**

| Number of excisions needed to detect 1 case | Melanoma | Squamous cell carcinoma | Basal cell carcinoma |
|---|---|---|---|
| Waldmann, 2012[58]<br>Fair<br>Germany | | | |
| Overall | 28 | 41 | 9 |
| **Female** | | | |
| Age, years | | | |
| 20-34 | 41 | N/A | 138 |
| 35-49 | 30 | 579 | 34 |
| 50-64 | 24 | 72 | 8 |
| ≥65 | 22 | 14 | 4 |
| **Total** | **28** | **56** | **10** |
| **Male** | | | |
| Age, years | | | |
| 20-34 | 52 | 926 | 116 |
| 35-49 | 55 | 435 | 35 |
| 50-64 | 22 | 48 | 7 |
| ≥65 | 20 | 12 | 4 |
| **Total** | **28** | **28** | **7** |

**Abbreviations:** KQ = key question, N/A = not applicable.

**Table 5. Measured Cosmetic Harms From Participating in Screening and Diagnostic Workup (KQ 2)**

| Study | N | Procedure and provider type | Harms assessment | Reported harms |
|---|---|---|---|---|
| Gambichler, 2000[59] Fair Germany | 45 patients who had been identified by skin cancer screening with 77 nevi and received biopsy | Deep shave excision with razor blade biopsy | Assessed by physician* and patient on a 4-point scale 6 months after excision (1=excellent, 4=poor) | Physician-reported poor: 16.1%; mean score, 2.5<br>Patient-reported poor: 7.1%; mean score, 1.7 |

*Cosmetic harms defined as: erythemia, hyperpigmentation, hypopigmentation, hypertrophic scarring, and hypotrophic scaring.

**Abbreviation:** KQ = key question.

**Table 6. Diagnostic Accuracy of Primary Care Providers and Dermatologists for Diagnosing Melanoma Through Visual Skin Examination (KQ 3)**

| Study, year Quality | Who performed screening? | Comparison/gold standard | Follow-up (months) | Sensitivity (95% CI)* | Specificity (95% CI)* | Recall rate† | PPV (95% CI)*‡ | Cancer detection rate | Cancer rate |
|---|---|---|---|---|---|---|---|---|---|
| Fritschi, 2006[57] Fair Australia | Volunteer dermatologist or plastic surgeons | Cancer diagnosis in regional cancer registry within 2 years of screening | 12 mo melanoma | 69.7% (51.3 to 84.4) | 97.6% (97.2 to 97.9) | *2.7%* | 11.4 (7.4-16.7) | *0.3%* | *0.4%* |
| | | | 24 mo melanoma | 49.0% (34.4 to 63.7) | 97.6% (97.2 to 97.9) | *2.7%* | 11.9 (7.8-17.2) | *0.3%* | *0.7%* |
| Aitken, 2006[56] Fair Australia | Primary care physicians | For positive screen: pathology and biopsy reports | 36 mo – melanoma only | *40.2%* | 86.1% (85.6 to 86.6) | 14.1% | *1.4%* | *0.2%* | *0.5%* |
| | | Estimated the number of false-negatives based on prior literature[60] and Queensland melanoma incidence rates | 36 mo – any skin cancer | *Cannot be calculated* | *Cannot be calculated* | 14.1% | *16.9%* | *2.4%* | *Cannot be calculated* |

Values that are italicized were calculated using available data from the study results.
*Confidence intervals reported for measures calculated by study authors.
†Recall rate = the number of skin exams that resulted in a recommendation for followup with a dermatologist divided by the number of screened individuals; the recall rate is the same regardless whether followup is 1 or 2 years.
‡Skin cancer diagnosis among those recalled for further examination.

**Abbreviations:** KQ = key question, CI = confidence interval, PPV = positive predictive value, mo = month.

**Table 7. Association Between Physician Clinical Skin Examination and Lesion Thickness at Melanoma Detection (KQ 4)**

| Study | Total N | Study population | Exposure | Main analysis and adjusted confounders | Main result OR (95% CI) |
|---|---|---|---|---|---|
| Aitken, 2010[61] Fair Queensland, Australia | Controls: 3,824<br>Cases: 3,762 | **Controls:** randomly selected from Queensland Electoral Rolls, based on 5 year groups and sex distribution of cases<br><br>**Cases:** men and women aged 20-75 years with histologically confirmed primary melanoma diagnosed between January 2000 and December 2003 | During the last 3 years before [you first believed something was wrong (cases)/reference date (controls)] had a doctor deliberately checked all or nearly all of your whole body for early signs of skin cancer? | Logistic regression adjusted for age group, sex, education, employment status, marital status, eye color, hair color, skin color, degree of freckling, number of moles on back, age of arrival in Australia, average lifetime sun exposure, family history of melanoma, family history of non-melanoma skin cancer and ethnic status | Controls: Referent<br><br>Lesion thickness (in mm)<br>≤0.75: 1.38 (1.22-1.56)<br>>0.75: 0.86 (0.75-0.98)<br><br>Stratification of thicker lesions<br>0.76-1.49: 0.93 (0.79-1.10)<br>1.50-2.99: 0.83 (0.66-1.05)<br>≥3.00: 0.60 (0.43-0.83) |

**Abbreviations:** KQ = key question, OR = odds ratio, CI = confidence interval, mm = millimeters.

**Table 8. Association Between Stage at Melanoma Diagnosis and Melanoma-Related Mortality (KQ 5)**

| Study, year<br>Quality<br>Country | N | % Female<br>Age (years) | Stage distribution | Melanoma deaths (n) | Primary analysis | Confounders for adjustment | Melanoma-related mortality<br>Adjusted HR (95% CI) |
|---|---|---|---|---|---|---|---|
| Pollack, 2011[65]<br>Good<br>U.S. (13 SEER regions)<br><br>1992-2006 | 68,495 | 45.1% female<br><br><40: (19.5%)<br>40-64: (48.9%)<br>≥65: (31.5%) | Localized: 82.5%<br>Regional: 10.8%<br>Distant: 3.3%<br>Unstaged: 3.5% | NR | Cox regression restricted to 5 year followup after diagnosis | Stratified on histologic subtype and anatomic site and adjusted for sex, age at diagnosis, race/ethnicity, stage, and depth. | Localized: Referent<br>Regional: 3.62 (3.35, 3.91)<br>Distant: 18.66 (16.54, 21.06) |
| Zell, 2008[64]<br>Good<br>U.S. (California)<br><br>1993-2003 | 39,049 | 43.1% female<br><br>Median age 58 (95% CI: 29.0, 84.0) | Stage: IA: 58.7%<br>IB: 21.0%<br>IIA: 8.6%<br>IIB: 5.0%<br>IIC: 1.2%<br>IIIB: 13.1%<br>IIIC: 1.7%<br>IV: 0.7% | 2,842 | Cox proportional hazard ratios | Age, sex, race/ethnicity, AJCC stage, histologic subtype, anatomic tumor site, tumor ulceration, SES quintile. radiation therapy, chemotherapy and immunotherapy. | I: Referent<br>II: 4.96 (4.51, 5.56)<br>III: 9.99 (8.84, 11.29)<br>IV: 27.1 (22.4, 32.8) |
| Reyes-Ortiz, 2006[63]<br>Fair<br>U.S. (11 SEER regions)<br><br>1988-2000 | 23,068 | 40.0% female<br><br><39: 0 (0%)<br>40-64: 0 (0%)<br>≥65: (100%) | In situ: 32.8%<br>Localized: 45.7%<br>Regional: 8.5%<br>Distant: 3.0%<br>Unknown: 10.0% | NR | Kaplan-Meier product limit. Cox proportional hazards | Census tract median income, race/ethnicity, age, sex, marital status, years of diagnosis (1988-1993, 1994-1999), stage, tumor thickness, histology, site, and comorbidity (Charlson score of 0, 1, 2+) | In situ: Referent<br>Localized: 8.83 (6.0, 12.9)<br>Regional: 23.2 (15.7, 34.3)<br>Distant: 94.0 (63.3, 139.5)<br>Unknown: 19.1(13.1, 27.8) |

**Abbreviations:** KQ = key question, HR = hazard ratio, CI = confidence interval, SEER = Surveillance, Epidemiology and End Results Program, NR = not reported, AJCC = American Joint Committee on Cancer, SES = socioeconomic status.

**Table 9. Association Between Breslow Lesion Thickness of Melanoma at Diagnosis and Melanoma Mortality (KQ 5)**

| Study, year<br>Quality<br>Country | N | % Female<br>Age | Distribution of Breslow thickness (mm) at detection | Melanoma deaths (n) | Primary analysis | Confounders for adjustment | Melanoma-related mortality<br>Adjusted HR* (95% CI) |
|---|---|---|---|---|---|---|---|
| Marashi-Pour, 2012[68]<br>Good<br>Australia<br><br>1988-2007 | 52,330 | 42% female<br><br><40: 7,813 (15%)<br>40-69: 28,132 (54%)<br>≥70: 16,374 (31%)<br>Missing: 11 (0%) | ≤1: 61%<br>1.01-2: 16%<br>2.01-4: 10%<br>≥4.01: 6%<br>Missing: 7% | 5,291 melanoma deaths (13,581 from all causes) | Fine and Gray competing risk regression with backward modeling | Sex, age at diagnosis, histological type, body site, year and season of diagnosis, tumor thickness, and degree of spread at diagnosis | ≤1.0mm: Referent<br>1.01-2.0mm: 4.13 (3.74-4.56)<br>2.01-4.0mm: 6.88 (6.18-7.65)<br>≥4.01mm: 9.52 (8.42-10.77)<br>Missing: 6.37 (5.57-7.29) |
| Green, 2012[69]<br>Fair<br>Australia<br><br>1982-2006 | 26,736 | 46.4% female<br><br>Mean age 52.7 | <0.25: 2,372 (8.9%)<br>0.25-0.49: 11,552 (43.2%)<br>0.50-0.74: 8,366 (31.3%)<br>0.75-1.00: 4,446 (16.6%) | Total: 592<br><0.25: 24 (4.1%)<br>0.25-0.49: 127 (21.5%)<br>0.50-0.74: 174 (29.4%)<br>0.75-1.00: 267 (45.1%) | Multivariate Cox proportional hazard models | Year, sex, time after diagnosis, sex*time after diagnosis (interaction), age group, site, level, morphology | <0.25: Referent<br>0.25-0.49: 1.14 (0.7-1.7)<br>0.50-0.74: 1.84 (1.2-2.9)<br>0.75-1.00: 4.33 (2.8-6.8) |
| Pollack, 2011[65]<br>Good<br>U.S. (13 SEER regions)<br><br>1992-2006 | 68,495 | 45.1% female<br><br><40: (19.5%)<br>40-64: (48.9%)<br>≥65y: (31.5%) | 0.01-1.00: 59.8%<br>1.01-2.00: 13.9%<br>2.01-4.00: 7.6%<br>>4: 4.3%<br>Unknown: 13.7%<br>No tumor found: 0.7% | NR | Cox regression restricted to 5 year follow-up. 56,886 cases out of 68,495 in multivariate analyses (missing data) | Stratified on histologic subtype and anatomic site. Adjusted for sex, age at diagnosis, race/ethnicity, stage, and depth. | ≤1.0 mm: Referent<br>1.01mm-2.0mm: 2.89 (2.62-3.18)<br>2.01mm-4.0mm: 4.69 (4.24-5.02)<br>>4.0mm: 5.71 (5.10-6.39)<br>No tumor found: 3.03 (1.98-4.64) |
| Reyes-Ortiz, 2006[63]<br>Fair<br>U.S. (11 SEER regions)<br><br>1988-1999 to 2000 | 23,068 | 40% female<br><br><39: 0 (0%)<br>40-64: 0 (0%)<br>≥65: 23,068 (100%) | <1.00: 30.7%<br>1.01-2.00: 8.8%<br>2.01-4.00: 6.6%<br>>4.00: 3.9%<br>Unknown: 50.0% | NR | Kaplan-Meier product limit. Cox proportional hazards | Census tract median income, race/ethnicity, age, sex, marital status, years of diagnosis (1988-1993, 1994-1999), stage, tumor thickness, histology, site, and comorbidity (Charlson score of 0, 1, 2+) | ≤1.00mm: Referent<br>1.01-2.0mm: 2.06 (1.69-2.50)<br>2.01-4.0mm: 3.11 (2.57-3.76)<br>>4.0mm: 3.17 (2.56-3.92)<br>Unknown: 2.05 (1.70-2.47) |
| Leiter, 2004[70]<br>Fair<br>Germany<br><br>1976-2000 | 12,728 | 59% female<br><br>Mean age 50 (SD 15.7) | ≤0.25: 8.4%<br>0.26-0.50: 36.3%<br>0.51-0.75: 29.7%<br>0.76-1.00: 25.6% | 162 | Multivariate Cox proportional hazard models | Adjusted by age, sex, Breslow's tumor thickness, Clark's level of invasion, ulceration, regression, histologic subtypes, and body sites | ≤0.50: Referent<br>0.51-0.75: 1.9 (1.2-2.9)<br>0.76-1.00: 3.9 (2.6-5.8) |

**Table 9. Association Between Breslow Lesion Thickness of Melanoma at Diagnosis and Melanoma Mortality (KQ 5)**

| Study, year<br>Quality<br>Country | N | % Female<br>Age | Distribution of Breslow thickness (mm) at detection | Melanoma deaths (n) | Primary analysis | Confounders for adjustment | Melanoma-related mortality<br>Adjusted HR* (95% CI) |
|---|---|---|---|---|---|---|---|
| Luke, 2003[67†]<br>Fair<br>Australia<br><br>1980-2000 | 9,519 | 50% female<br><br><39: 1,999 (21%)<br>40-69: 5,015 (53%)<br>≥70: 2,505 (26%) | ≤0.50: 35.1%<br>0.51-1.00: 31.8%<br>1.01-1.50: 11.1%<br>1.51-2.00: 5.9%<br>2.01-2.50: 3.9%<br>2.51-3.00: 2.7%<br>3.01-3.50: 1.9%<br>3.51-4.00: 1.8%<br>4.01-4.50: 1.9%<br>4.51-5.00: 1.2%<br>5.01-5.50: 0.5%<br>5.51-6.00: 0.8%<br>6.01+: 1.4% | NR | Cox proportional hazard regression (relative risk of case fatality) | Diagnostic period, Breslow thickness, Clark level, body site, age at diagnosis, and sex | ≤0.50: Referent<br>0.51-1.00: 2.81 (1.81-4.35)<br>1.01-1.50: 6.18 (3.75-10.20)<br>1.51-2.00: 8.53 (5.05-14.43)<br>2.01-2.50: 13.89 (8.16-23.64)<br>2.51-3.00: 15.44 (8.90-26.80)<br>3.01-3.50: 20.74 (11.83-36.34)<br>3.51-4.00: 27.39 (15.71-47.73)<br>4.01-4.50: 32.62 (18.78-56.63)<br>4.51-5.00: 21.09 (11.38-39.09)<br>5.01-5.50: 22.1 (10.62-45.99)<br>5.51-6.00: 33.99 (18.13-63.73)<br>≥6.01: 23.08 (12.70-41.95) |
| Owen, 2001[66]<br>Fair<br>U.S.<br><br>1970-1995 | 4,560 | 46% female<br><br>Mean age at surgery: 48.3 (14.2) | <0.75: 10.5%<br>0.75-1.0: 13.2%<br>1.0-1.5: 26.1%<br>1.5-3.0: 32.8%<br>3.0-4.0: 7.3%<br>>4.0: 10.0% | 867 | Cox proportional hazards | Age, sex, and site of primary lesion | ≤0.75 mm: 0.28 (0.17-0.44)<br>0.75-1.0 mm: 0.55 (0.4-0.76)<br>1.0-1.5 mm: Referent<br>1.5-3.0 mm: 1.93 (1.6-2.34)<br>3.0-4.0 mm: 3.02 (2.37-3.86)<br>>4.0 mm: 3.88 (3.12-4.83) |

*Leiter 2004 and Owen 2001 reported relative risks (RR), not hazard ratios (HR).
†Missing data n= 1103; percentages based off of n = 8,416.

**Abbreviations:** KQ = key question, HR = hazard ratio, CI = confidence interval, SEER = Surveillance, Epidemiology and End Results Program, NR = not reported, SD = standard deviation.

**Table 10. Association Between Melanoma AJCC Stage and All-Cause Mortality (KQ 5)**

| Study, year<br>Quality<br>Country | Dates of data collection | N | Age<br>Percent female | All-cause deaths | Primary analysis | Adjustment variables | All-cause mortality HR (95% CI) |
|---|---|---|---|---|---|---|---|
| Zell, 2008[64]<br>Good<br>California, U.S. | 1993-2003 | 39,049 | Median: 58 years (95% CI: 29.0-84.0)<br>43.1% | 6,706 | Cox proportional hazard ratio | Age, sex, race/ethnicity, AJCC stage, histologic subtype, anatomic tumor site, surgery stage, SES quintile, radiation therapy, chemotherapy and immunotherapy. | I: Referent<br>II: HR, 2.26 (95% CI, 2.14-2.39)<br>III: HR, 4.27 (95% CI 3.9-4.67)<br>IV: HR, 10.39 (95% CI, 8.96-12.0) |

**Abbreviations:** AJCC = American Joint Committee on Cancer, KQ = key question, HR = hazard ratio, CI = confidence interval, SES = socioeconomic status.

**Table 11. Summary of Evidence**

| Key question | Population | No. of studies (k), no. of observations (n) | Design | Major limitations | Consistency | Applicability | Overall quality | Summary of findings |
|---|---|---|---|---|---|---|---|---|
| KQ 1. What is the direct evidence that visual screening for skin cancer by a primary care provider or dermatologist reduces skin cancer morbidity and mortality and all-cause mortality? | Residents of Schleswig-Holstein Germany ≥20 years with whole body skin cancer screening exam between July 2003 and June 2004 | K=1 study (3 articles) n=360,288 | Ecologic (1) | In the main study, an ecologic study design permitted only population-level analysis of mortality rates compared to those in the surrounding areas, not individual-level data. Two related publications using observational designs described skin cancer incidence after the screening program and participation in the program. The physician screening component was part of a multimodal screening program involving physician education, dermatologist referral for screen-detected lesions, public outreach, and access to physician review of patient-identified suspicious lesions. | N/A (1 study included) | The screening program made considerable efforts to be truly population-based and screen the entire adult population in the study area. However, the screened population (19% of total) had 2 to10% self-reporting risk factors, likely representing a self-selected population. | Fair | In the SCREEN study in Germany, melanoma mortality decreased 48% from 1.7 to 0.9 melanoma deaths per 100,000 individuals 5 years after the screening program. Absolute reduction was 0.8 melanoma deaths per 100,000 individuals. There were no mortality reductions in the surrounding geographic areas. |

**Table 11. Summary of Evidence**

| Key question | Population | No. of studies (k), no. of observations (n) | Design | Major limitations | Consistency | Applicability | Overall quality | Summary of findings |
|---|---|---|---|---|---|---|---|---|
| KQ 2. What are the harms of screening for skin cancer and diagnostic followup? | Routine skin cancer screening outpatients in Germany | K=2 (4 articles) n=360,333 | Cohort (1), Case series (1) | Data from the SCREEN study presented the false positive rates and number of excisions needed to detect one melanoma during the screening program. Overdiagnosis could not be assessed directly. A small study of 45 people assessed the acceptability of cosmetic scars from shave biopsy for suspected NMSC, which is not the major approach to melanomas | Low (different harms assessed in each study and one per outcome) | The SCREEN data suggest potential for very high number of false positives that could be relevant to other screening programs. Patient-reported data on cosmetic harms is important. | Fair | The number of excisions needed to detect one skin cancer varied by age and sex. Fewer excisions were needed to detect a single case in older adults and in men. After shave biopsy for removal of potential NMSC detected through cancer screening, 7% percent of patients viewed their scar outcomes poorly at 6 months after biopsy |
| KQ 3. What are the test characteristics of visual screening for skin cancer when performed by primary care providers versus dermatologists? | Australian residents who either participated in a community based pilot randomized clinical trial of skin screening program or attended Lions Cancer Institute weekend mobile screening clinics in rural and suburban locations in Western Australia. | K=2 (2 articles) n=23,819 | Cohort (2) | An Australian cohort study assessed performance of dermatologists in a mobile screening program. An unrelated cohort study, also Australian, assessed performance of primary care providers. Missed cancers were detected through registry and medical records linkages, but ascertainment bias is likely due to differential followup time periods. | Low (follow-up times prohibit direct comparison of studies) | These results may not apply to U.S. settings. | Fair | Sensitivity for melanoma detection was 40.2% at 36 months for primary care providers and 49.0% at 24 months for dermatologists. Specificity was 86.1% at 36 months for primary care providers and 97.6% at 24 months for dermatologists. Recall rate was 14.1% for primary care and 2.7% for dermatologists. Melanoma detection rates were under 1 percent in both studies |

**Table 11. Summary of Evidence**

| Key question | Population | No. of studies (k), no. of observations (n) | Design | Major limitations | Consistency | Applicability | Overall quality | Summary of findings |
|---|---|---|---|---|---|---|---|---|
| KQ 4. Does visual screening for skin cancer lead to earlier detection of skin cancer compared with usual care? | Queensland residents between 20 and 75 years; cases identified from cancer registry and controls selected through stratified random sampling from Queensland Electoral Roll | K=1 (1 article) n=7,586 | Case control (1) | One Australian case-control study compared receipt of physician whole-body skin exam in the previous 3 years and the association of melanoma thickness (in cases) with physician skin exam. Potential for recall bias, potential for spectrum bias, exaggerating effect sizes found. | N/A (1 study included) | The ability of physician skin exam to detect lesions earlier than through usual care or self-identification is important to establishing an effect of physician screening in the context of multi-modal skin cancer early detection programs. | Fair | 28.3% of controls reported receiving a clinical skin exam in the previous 3 years compared to 35.3% of melanoma cases. Cases with thin melanoma lesions (≤0.75 mm) had 38% higher odds of clinical skin exam than controls. Cases with thicker lesions (>0.75 mm) had 14% reduced odds of recent physician skin exam compared with controls. |
| KQ 5. What is the association between earlier detection of skin cancer and skin cancer morbidity and mortality and all-cause mortality? | Cases of melanoma identified through registries in Australia, Germany and the U.S. | K=8 (8 articles) n= 236,485 | Observ-ational (8) | Three good quality and five fair quality observational studies included more than 200,000 people with melanoma in the US, Germany, and Australia. The studies examined the association between melanoma-specific mortality and lesion thickness or stage at diagnosis. One of the good quality studies also assessed all-cause mortality and stage at diagnosis. | High | The association of melanoma or all-cause mortality with earlier stage or lesion thickness at detection is relevant to screening programs. | Good | All studies demonstrated a consistent linear increase in risk of melanoma mortality with increasing tumor thickness or stage. Tumor thickness greater than 4.0 mm was associated with a 3.1 to 32.6 increased risk of melanoma mortality compared to thinner lesions in multivariate adjusted models. |

**Abbreviations:** KQ = key question, N/A = not applicable, SCREEN = Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany, NMSC = non-melanoma skin cancer, mm = millimeter(s).

# Search Strategy

| Sources Searched | Number of items 1995-present |
|---|---|
| *MEDLINE* | 10,611 |
| *PUBMED* | 260 |
| *Cochrane Central Register of Controlled Clinical Trials* | 716 |

Key:
/ = MeSH subject heading
$ = truncation
* = truncation
? = wildcard
ab = word in abstract
ae = adverse effects
adj# = adjacent within x number of words
near/# = adjacent within x number of words
kw = keyword
mo = mortality
su = surgery
ti = word in title

**Cochrane Central Register of Controlled Clinical Trials**
Issue 6 of 12, June 2014

#1 (skin or derm* or cutaneous or epithelial or epithelium or epiderm*):ti,ab,kw near/3 (cancer* or neoplasm* or carcinoma* or tumor* or tumour* or malignan* or lesion* or metasta* or dysplas*):ti,ab,kw #2 melanoma*:ti,ab,kw
#3 (naevoid or nevoid):ti,ab,kw near/3 syndrome*:ti,ab,kw
#4 (dysplastic or malignant):ti,ab,kw near/2 (nevus or naevus or nevi or naevi):ti,ab,kw
#5 "Hutchinson's Melanotic Freckle":ti,ab,kw
#6 "lentigo maligna":ti,ab,kw
#7 basal:ti,ab,kw next cell:ti,ab,kw next (carcinoma* or neoplasm* or carcinoma* or tumor* or tumour* or malignan* or lesion* or metasta* or epithelioma*):ti,ab,kw
#8 (basocellular* or basosquamous):ti,ab,kw next carcinoma*:ti,ab,kw
#9 squamous:ti,ab,kw next cell:ti,ab,kw next (carcinoma* or neoplasm* or carcinoma* or tumor* or tumour* or malignan* or lesion* or metasta* or epithelioma*):ti,ab,kw
#10 merkel:ti,ab,kw next cell:ti,ab,kw next (carcinoma* or neoplasm* or carcinoma* or tumor* or tumour* or malignan* or lesion* or metasta* or epithelioma*):ti,ab,kw
#11 "actinic keratosis":ti,ab,kw
#12 bowen*:ti,ab,kw next disease:ti,ab,kw
#13 cutaneous:ti,ab,kw near/2 lymphoma*:ti,ab,kw
#14 {or, #1-`#13}
#15 screen*:ti,ab,kw
#16 (skin or body or physical):ti,ab,kw near/3 (exam* or inspect*):ti,ab,kw
#17 (dermoscop* or dermatoscop*):ti,ab,kw
#18 visual*:ti,ab,kw next inspect*:ti,ab,kw
#19 photography:ti,ab,kw
#20 {or #15-#19}

#21 #14 and #20 Publication Year from 1995 to 2014, in Trials
#22 (biopsy* or biopsies or biopsied):ti,ab,kw
#23 (excise* or excision*):ti,ab,kw
#24 rebiops*:ti,ab,kw
#25 #22 or #23 or #24
#26 (harm or harms or harmful or harmed):ti,ab,kw
#27 (death or deaths):ti,ab,kw
#28 (adverse or negative or unintended):ti,ab,kw next (effect* or event* or outcome* or reaction*):ti,ab,kw
#29 complication*:ti,ab,kw
#30 side:ti,ab,kw next effect*:ti,ab,kw
#31 safety:ti,ab,kw
#32 false:ti,ab,kw next negative*:ti,ab,kw
#33 misdiagnos*:ti,ab,kw
#34 overdiagnos*:ti,ab,kw
#35 (unneeded or unnecessary):ti,ab,kw near/5 (treat* or therap* or surg* or procedure*):ti,ab,kw
#36 label*:ti,ab,kw
#37 psychological:ti,ab,kw next effect*:ti,ab,kw
#38 (cicatrix or scar*):ti,ab,kw
#39 {or #26-#38}
#40 #14 and #25 and #39 Publication Year from 1995 to 2014, in Trials
#41 (detect* or diagnos* or biops*):ti,ab,kw near/5 stage:ti,ab,kw
#42 (late* or distant or advanced or end):ti,ab,kw next stage:ti,ab,kw
#43 (early or earlier):ti,ab,kw next (diagnos* or detect* or discovery or findings):ti,ab,kw
#44 #41 or #42 or #43
#45 #14 and #44 Publication Year from 1995 to 2014, in Trials
#46 (surger* or surgical):ti
#47 curettage:ti,ab,kw
#48 dessicat*:ti,ab,kw
#49 electrodessicat*:ti,ab,kw
#50 cryosurg*:ti,ab,kw
#51 "laser ablation":ti,ab,kw
#52 mohs:ti,ab,kw
#53 metastasectom*:ti,ab,kw
#54 lymphadenectom*:ti,ab,kw
#55 ("lymph node" or "lymph nodes" or lymphoid):ti,ab,kw near/3 (remov* or dissect* or resect*):ti,ab,kw
#56 {or #46-#55}
#57 (lymphedema or lymphoedema):ti,ab,kw
#58 (surg* or postsurg* or post-surg*):ti,ab,kw near/2 infect*:ti,ab,kw
#59 {or #26-#31, #38, #57-#58}
#60 #14 and #56 and #59 Publication Year from 1995 to 2014, in Trials 1
#61 #21 or #40 or #45 or #60

**MEDLINE** search strategy

Database: Ovid MEDLINE(R) <1946 to July Week 3 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <July 24, 2014>, Ovid MEDLINE(R) Daily Update <July 24, 2014>

## Appendix A. Detailed Methods

Search Strategy:

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1 Skin Neoplasms/
2 Melanoma/
3 Melanoma, Amelanotic/
4 Nevus/
5 Dysplastic Nevus Syndrome/
6 Hutchinson's Melanotic Freckle/
7 Carcinoma, Basal Cell/
8 Carcinoma, Squamous Cell/
9 Carcinoma, Merkel Cell/
10 Neoplasms, Basal Cell/
11 Neoplasms, Squamous Cell/
12 "Neoplasms, Adnexal and Skin Appendage"/
13 Actinic keratosis/
14 Bowen disease/
15 Lymphoma, T-Cell, Cutaneous/
16 ((skin or derm$ or cutaneous or epithelial or epithelium or epiderm$) adj3 (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or dysplas$)).ti.
17 melanoma$.ti.
18 ((naevoid or nevoid) adj3 syndrome$).ti.
19 ((dysplastic or malignant) adj2 (nevus or naevus or nevi or naevi)).ti.
20 Hutchinson$ Melanotic Freckle.ti.
21 lentigo maligna.ti.
22 (basal cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti.
23 ((basocellular$ or basosquamous) adj carcinoma$).ti.
24 (squamous cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti.
25 (merkel cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti.
26 actinic keratosis.ti.
27 bowen$ disease.ti.
28 (cutaneous adj2 lymphoma$).ti.
29 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30 ((skin or derm$ or cutaneous or epithelial or epithelium or epiderm$) adj3 (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or dysplas$)).ti,ab.
31 melanoma$.ti,ab.
32 ((naevoid or nevoid) adj3 syndrome$).ti,ab.
33 ((dysplastic or malignant) adj2 (nevus or naevus or nevi or naevi)).ti,ab.
34 Hutchinson$ Melanotic Freckle.ti,ab.
35 lentigo maligna.ti,ab.
36 (basal cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti,ab.
37 ((basocellular$ or basosquamous) adj carcinoma$).ti,ab.
38 (squamous cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti,ab.

39 (merkel cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti,ab.
40 actinic keratosis.ti,ab.
41 bowen$ disease.ti,ab.
42 (cutaneous adj2 lymphoma$).ti,ab.
43 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44 limit 43 to ("in data review" or in process or "pubmed not medline")
45 29 or 44
46 Mass screening/
47 Early detection of Cancer/
48 (screen$ or detect$).ti,ab.
49 46 or 47 or 48
50 Physical Examination/
51 Dermoscopy/
52 Photography/
53 ((skin or body or physical) adj3 (exam$ or inspect$)).ti,ab.
54 visual$ inspect$.ti,ab.
55 dermoscop$.ti,ab.
56 dermatoscop$.ti,ab.
57 photography.ti,ab.
58 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
59 45 and 49 and 58
60 screen$.ti.
61 45 and 60
62 59 or 61
63 limit 62 to (english language and yr="1995 -Current")
64 remove duplicates from 63
65 Biopsy/
66 Biopsy, Needle/
67 Biopsy, Large-Core Needle/
68 Sentinel Lymph Node Biopsy/
69 (biopsy$ or biopsies or biopsied).ti,ab.
70 (excise* or excision$).ti,ab.
71 rebiopsy.ti,ab.
72 65 or 66 or 67 or 68 or 69 or 70 or 71
73 (harm or harms or harmful or harmed).ti,ab.
74 (adverse effects or mortality).fs.
75 Mortality/
76 Morbidity/
77 death/
78 (death or deaths).ti,ab.
79 ((adverse or negative or unintended) adj (effect$ or event$ or outcome$ or reaction$)).ti,ab.
80 complication$.ti,ab.
81 side effect$.ti,ab.
82 safety.ti,ab.
83 false negative$.ti,ab.
84 misdiagnos$.ti,ab.
85 overdiagnos$.ti,ab.

86 ((unneeded or unnecessary) adj5 (treat$ or therap$ or surg$ or procedure$)).ti,ab.
87 label$.ti,ab.
88 psychological effect$.ti,ab.
89 Cicatrix/
90 (cicatrix or scar$).ti,ab.
91 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or
90
92 45 and 72 and 91
93 limit 92 to (english language and yr="1995 -Current")
94 remove duplicates from 93
95 Neoplasm Staging/
96 ((detect$ or diagnos$ or biops$) adj5 stage).ti,ab.
97 ((late$ or distant or advanced or end) adj stage).ti,ab.
98 ((early or earlier) adj (diagnos$ or detect$ or discovery or findings)).ti,ab.
99 95 or 96 or 97 or 98
100 Registries/
101 Survival Analysis/
102 SEER program/
103 Morbidity/
104 Mortality/
105 Death/
106 mo.fs.
107 (registr$ or register$).ti,ab.
108 SEER.ti,ab.
109 "Surveillance epidemiology and end results".ti,ab.
110 morbidit$.ti,ab.
111 mortalit$.ti,ab.
112 (death or deaths).ti,ab.
113 survival.ti,ab.
114 110 or 111 or 112 or 113
115 limit 114 to ("in data review" or in process or "pubmed not medline")
116 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 115
117 45 and 99 and 116
118 limit 117 to (english language and yr="1995 -Current")
119 remove duplicates from 118
120 Dermatologic Surgical Procedures/ ]
121 Curettage/
122 Dessication/
123 Cryosurgery/
124 Laser Therapy/
125 Mohs Surgery/
126 Lymph Node Excision/
127 (surger$ or surgical).ti.
128 curettage.ti,ab.
129 dessicat$.ti,ab.
130 electrodessicat$.ti,ab.
131 cryosurg$.ti,ab.
132 laser ablation.ti,ab.

133 mohs.ti,ab.
134 metastasectom$.ti,ab.
135 lymphadenectom$.ti,ab.
136 ((lymph node$ or lymphoid) adj3 (remov$ or dissect$ or resect$)).ti,ab.
137 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136
138 limit 137 to ("in data review" or in process or "pubmed not medline")
139 120 or 121 or 122 or 123 or 124 or 125 or 126 or 138
140 45 and 139
141 Skin Neoplasms/su
142 Melanoma/su
143 Melanoma, Amelanotic/su
144 Nevus/su
145 Dysplastic Nevus Syndrome/su
146 Hutchinson's Melanotic Freckle/su
147 Carcinoma, Basal Cell/su
148 Carcinoma, Squamous Cell/su
149 Carcinoma, Merkel Cell/su
150 Neoplasms, Basal Cell/su
151 Neoplasms, Squamous Cell/su
152 "Neoplasms, Adnexal and Skin Appendage"/su
153 Actinic keratosis/su
154 Bowen disease/su
155 Lymphoma, T-Cell, Cutaneous/su
156 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155
157 Lymphedema/
158 Lymph?edema.ti,ab.
159 Surgical wound infection/
160 ((surg$ or postsurg$ or post-surg$) adj2 infect$).ti,ab.
161 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 89 or 90 or 157 or 158 or 159 or 160
162 156 and 161
163 limit 162 to (english language and yr="1995 -Current")
164 64 or 94 or 119 or 163
165 Animal/ not (Animal/ and Human/)
166 164 not 165
167 (oral or tongue or larynx or laryng$ or hypolaryng$ or oropharyng$ or pharynx or pharyng$ or esophag$ or oesophag$ or gastric or ovary or ovaries or ovarian or cervical or cervix or endometrium or endometrial or lung or breast or ocular or vulva$ or anus or anal or mucosal).ti.
168 166 not 167

**PubMed** search strategy [publisher-supplied references only]

| Search | Query |
|---|---|
| #62 | Search **(((#61) AND publisher[sb]) AND English[Language]) AND ("1995"[Date - Publication] : "3000"[Date - Publication])** |
| #61 | Search **#12 AND #60** |
| #60 | Search **#17 OR #34 OR #44 OR #59** |
| #59 | Search **#55 AND #58** |

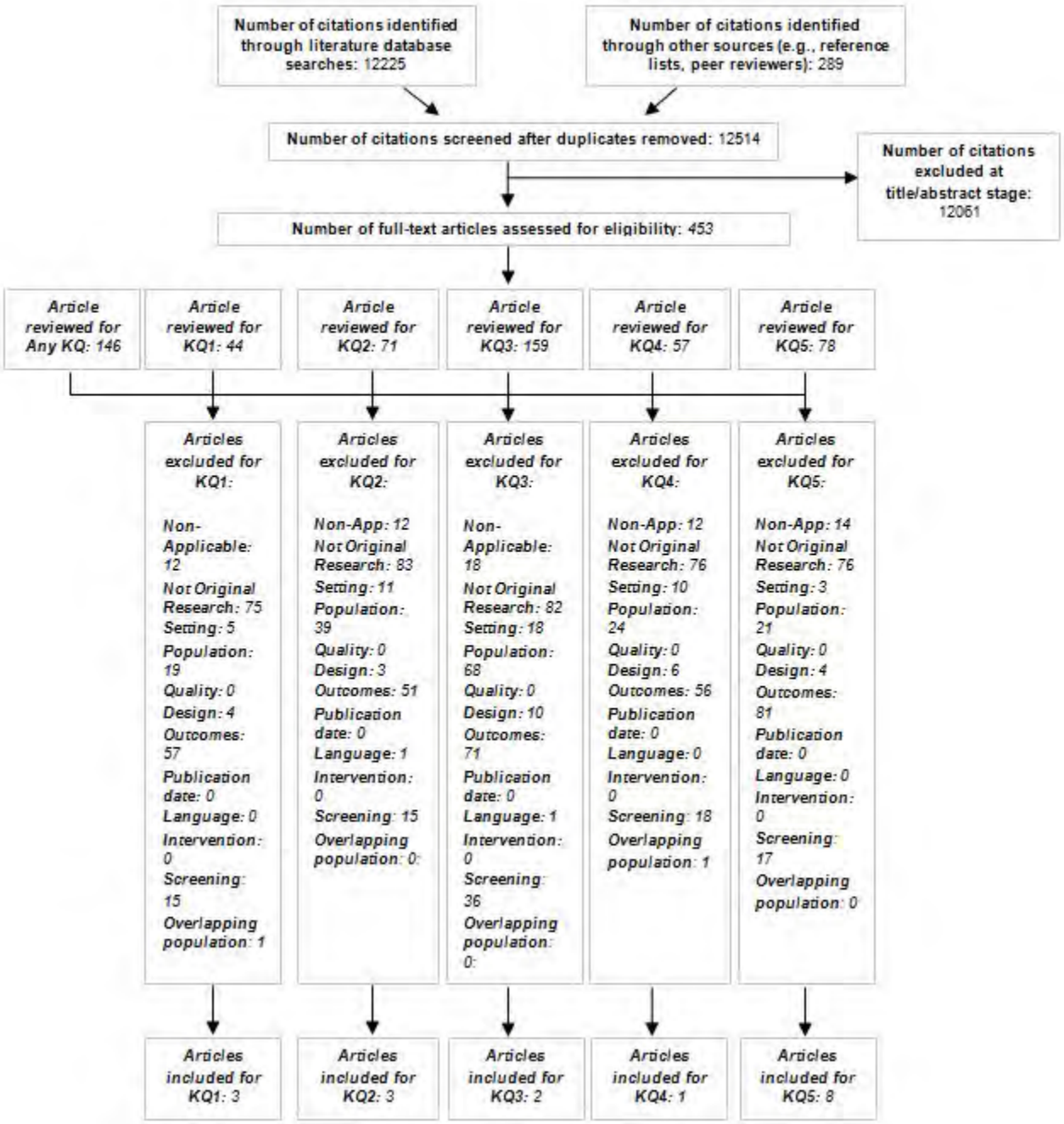
## Appendix A. Detailed Methods

| Search | Query |
|---|---|
| #58 | Search **#22 OR #23 OR #24 OR #25 OR #26 OR #32 OR #56 OR #57** |
| #57 | Search **(surg*[tiab] OR postsurg*[tiab] OR post surg*[tiab]) AND infect*[tiab]** |
| #56 | Search **lymphedema[tiab] OR lymphoedema[tiab]** |
| #55 | Search **#45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54** |
| #54 | Search (**lymph node*[tiab] OR lymphoid[tiab]) AND (remov*[tiab] OR dissect*[tiab] OR resect*[tiab])** |
| #53 | Search **lymphadenectomy*[tiab]** |
| #52 | Search **metastasectom*[tiab]** |
| #51 | Search **mohs[tiab]** |
| #50 | Search **laser ablation[tiab]** |
| #49 | Search **cryosurg*[tiab]** |
| #48 | Search **electrodessicat*[tiab]** |
| #47 | Search **dessicat*[tiab]** |
| #46 | Search **curettage[tiab]** |
| #45 | Search **surger*[ti] OR surgical[ti]** |
| #44 | Search **#38 AND #43** |
| #43 | Search **#39 OR #40 OR #41 OR #42** |
| #42 | Search **survival[tiab]** |
| #41 | Search **morbidity[tiab] OR mortality[tiab] OR death[tiab] OR deaths[tiab]** |
| #40 | Search **SEER[tiab] OR surveillance epidemiology[tiab]** |
| #39 | Search **registr*[tiab] OR register*[tiab]** |
| #38 | Search **#35 OR #36 OR #37** |
| #37 | Search **early diagnos*[tiab] OR early detection[tiab] OR earlier diagnos*[tiab] OR earlier detection[tiab] OR diagnosed earl*[tiab] OR detected earl*[tiab]** |
| #36 | Search **late stage[tiab] OR distant stage[tiab]** |
| #35 | Search **(detect*[tiab] OR diagnos*[tiab] OR biops*[tiab]) AND stage[tiab]** |
| #34 | Search **#21 AND #33** |
| #33 | Search **#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32** |
| #32 | Search **scar*[tiab] OR cixatrix[tiab]** |
| #31 | Search **psychological effect*[tiab]** |
| #30 | Search **label*[tiab]** |
| #29 | Search **((unneeded[tiab] OR unnecessary[tiab]) AND (treat*[tiab] OR therap*[tiab] OR surg*[tiab] OR procedure*[tiab]))** |
| #28 | Search **misdiagnos*[tiab] OR overdiagnos*[tiab]** |
| #27 | Search **false negative[tiab]** |
| #26 | Search **safety[tiab]** |
| #25 | Search **side effect*[tiab]** |
| #24 | Search **complication*[tiab]** |

## Appendix A. Detailed Methods

| Search | Query |
|---|---|
| #23 | Search **adverse effect*[tiab] OR adverse event*[tiab] OR adverse outcome*[tiab] OR adverse reaction*[tiab]** |
| #22 | Search **death[tiab] OR deaths[tiab] OR harm[tiab] OR harms[tiab] OR harmful[tiab] OR harmed[tiab]** |
| #21 | Search **#18 OR #19 OR #20** |
| #20 | Search **rebiopsy[tiab]** |
| #19 | Search **excise*[tiab] OR excision*[tiab]** |
| #18 | Search **biopsy*[tiab] OR biopsies[tiab] OR biopsied[tiab]** |
| #17 | Search **#13 OR #14 OR #15 OR #16** |
| #16 | Search **dermoscop*[tiab] OR dermatoscop*[tiab] OR photography[tiab]** |
| #15 | Search **visual inspect*[tiab] OR visually inspect[tiab]** |
| #14 | Search **skin exam*[tiab] OR body exam*[tiab] OR physical exam*[tiab]** |
| #13 | Search **screen*[tiab]** |
| #12 | Search **#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11** |
| #11 | Search **cutaneous[ti] AND lymphoma*[ti]** |
| #10 | Search **bowen disease[ti]** |
| #9 | Search **actinic keratosis[ti]** |
| #8 | Search **basocellular carcinoma*[ti] OR basosquamous carcinoma*[ti]** |
| #7 | Search **(basal[ti] OR squamous[ti] OR merkel[ti]) AND (cancer*[ti] OR neoplasm*[ti] OR carcinoma*[ti] OR tumor*[ti] OR tumour*[ti] OR malignan[ti] OR lesion[ti] OR metasta*[ti] OR epithelioma*[ti])** |
| #6 | Search **"lentigo maligna"[ti]** |
| #5 | Search **"hutchinson's melanotic freckle"[ti]** |
| #4 | Search **(dysplastic[ti] or malignant[ti]) AND (nevus[ti] OR naevus[ti] OR nevi[ti] OR naevi[ti])** |
| #3 | Search **(naevoid[ti] or nevoid[ti]) AND syndrome*[ti]** |
| #2 | Search **melanoma*[ti]** |
| #1 | Search **(skin[ti] or derm*[ti] or cutaneous[ti] or epithelial[ti] or epiderm*[ti]) AND (cancer*[ti] or neoplasm*[ti] or carcinoma*[ti] or tumor*[ti] or tumour*[ti] or malignan*[ti] or lesion*[ti] or metasta*[ti])** |

**Appendix A Figure 1. Literature Flow Diagram**



**Appendix A Table 1. Inclusion and Exclusion Criteria**

| | Include | Exclude |
|---|---|---|
| **Population** | Asymptomatic adults age 15 years and older | • Persons younger than age 15 years<br>• People already under surveillance for skin cancer due to previous skin or other cancer |
| **Settings** | Primary care-relevant, countries with a United Nations Human Development Index score of ≥0.9 | |
| **Screening tests** | Total or partial visual skin examination conducted by primary care providers or dermatologists with or without tools to aid examination (for example but not limited to, dermatoscopy; whole body photography) | • Diagnostic skin examinations in response to patient concern<br>• Skin self-screening by individuals or partners<br>• Physician counseling for self-screening |
| **Comparison** | **KQs 1, 2:** No visual skin examination<br><br>**KQ 3:** Biopsy<br><br>**KQ 4:** Usual care<br><br>**KQ 5:** Stage at detection | |
| **Outcomes** | **KQs 1, 5**: Morbidity associated with any skin cancer (including melanoma in situ, dysplastic nevi, actinic keratosis) including quality of life; skin cancer mortality; or all-cause mortality<br><br>**KQ 2:** Any harm from screening, biopsy, or excision including over-diagnosis, psychosocial harms, or procedure-related adverse events<br><br>**KQ 3:** Sensitivity, specificity, positive predictive value, false positive, false negative, cancer detection rates<br><br>**KQ 4:** Lesion thickness or stage at diagnosis | Non-skin location<br><br>Intermediate or health outcomes relating clinician skin examination to other risk behaviors (e.g., self-screening, sun protective behaviors) or measures of doctor-patient relationship quality |
| **Study design** | Fair- to good-quality studies published since January 1, 1995 to March 31, 2015.<br><br>Systematic reviews (of included study designs); randomized, controlled trials; selected well-designed controlled clinical trials; observational studies including cohort and case-control studies; ecologic studies<br><br>**KQs 2:** Same as above and including harms of screening case series | Poor-quality studies with a fatal flaw; studies outside of the publication window; case reports and case series (except as noted for KQs 2 and 6); decision analyses |

**Appendix A Table 2. Quality Assessment Criteria**

| Study Design | Adapted Quality Criteria |
|---|---|
| Randomized controlled trials, adapted from the USPSTF methods[50] | • Valid random assignment?<br>• Was allocation concealed?<br>• Was eligibility criteria specified?<br>• Were groups similar at baseline?<br>• Were measurements equal, valid and reliable?<br>• Was there intervention fidelity?<br>• Was there adequate adherence to the intervention?<br>• Were outcome assessors blinded?<br>• Was there acceptable followup?<br>• Were the statistical methods acceptable?<br>• Was the handling of missing data appropriate?<br>• Was there evidence of selective reporting of outcomes?<br>• Was the device calibration and/or maintenance reported? |
| Ecologic studies adapted from Dufault 2011[51] and Tu 2008[52] | • A priori information: is the identified ecological relationship between the exposure and the outcomes biologically plausible and consistent which what is already known about a given topic at an individual subject level?<br>• Adequate sample size<br>• Level of aggregation appropriate / are the subjects in the ecologic study representative of the group, place or population of interest?<br>• Level of inference (individual, ecologic, unclear)<br>• Pre-specification of ecologic units<br>• Classification of primary outcomes; were the exposure and outcome variables measured and defined in a similar or same way across the different populations or groups that are being studied?<br>• Analytic methodology: would it be practical to conduct alternative ways of studying the same question? Or was the ecologic study the only alternative?<br>• Validity of regression<br>• Use of covariates; have the data been collected on important confounding variables that might also explain the exposure-outcome relationship and have they been statistically adjusted for? If data are not available on key factors, is it reasonable to assume that heir prevalence is similar in the different groups or populations being compared?<br>• Discussion of cross-level bias / have the investigators interpreted their data with appropriate caveats? Did they acknowledge the possibility of an ecological fallacy? Were alternative explanations for the association between the exposure and outcomes considered by the investigators?<br>• Have the study data been collected at multiple levels? If yes, was multilevel modeling considered or used for analyzing the data? |

## Appendix B. Ongoing Studies

We identified 4potentially relevant ongoing randomized controlled clinical trials through four registries: ClinicalTrials.gov (http://clinicaltrials.gov), Current Controlled Trials (http://www.controlled-trials.com), Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au) and the World Health Organization's International Clinical Trials Registry Platform (http://www.who.int/ictrp). We restricted our searches to "skin cancer" AND screening.

Four studies regarding skin cancer screening were identified from ClinicalTrials.gov. These four studies focused on skin cancer screening efficacy and range from not yet recruiting to recently completed. Two of the studies[91, 92] focus on training and education for physicians regarding skin cancer screening. Of these two screening education projects the Skin Cancer Screening Education Study (SCSES) just began recruitment in February 2015. In addition to the two skin cancer screening education trials there are two other potentially relevant ongoing studies: One study addresses the attitudes and barriers[93] to skin cancer screening in an academic dermatology clinic and depending on the demographics of the population, may not be considered included (those in dermatologist waiting room may not represent asymptomatic population). The beach based controlled trial[94] represents an evaluation of a skin cancer and education program delivered at beaches. This intervention also includes skin cancer prevention education and therefore, depending on the actual methods may not contain the relevant population.

We also used NIH Research portfolio online reporting tools (RePORTer)[95] to identify ongoing projects that are currently funded through NIH. From RePORTer we found one potentially relevant currently funded work on skin cancer screening. Comparative Assessments of **screening** Strategies for Melanoma (5R21CA182241) led by Dr. Sandra J. Lee at the Dana-Farber Cancer Institute, Harvard Medical School. The proposal is centered around research problems arising in the early detection of malignant melanoma with an emphasis on sex-based differences in the early diagnosis of melanoma. The principal research areas include: (i) Investigate the natural history of melanoma and develop stochastic models for early detection of melanoma, (ii) Evaluate the mortality benefit of potential screening programs in the general and high-risk populations, (iii) Establish a pilot database of individuals at high-risk of developing melanoma and evaluate the factors associated with the risk of developing melanoma and of fatal melanoma.

During our bridge search and expert review two additional screening efforts were brought to our attention. These include one US based training program for increasing effectiveness of primary care provider screening.[96] This web-based training program aims to increase appropriate diagnosis and management of skin cancer screening. The second screening effort that would be of interest to future research is a French screening campaign.[31]This cluster randomized controlled trial was a targeted melanoma prevention intervention. This particular paper focused on patient prevention behavior, there may be relevant data from future papers that pertain to effectiveness of skin cancer screening by primary care physicians.

## Appendix C. Excluded Studies

| Code | Reason for Exclusion |
|---|---|
| E1 | Not English |
| E2 | Not original research in a peer-reviewed journal |
| E3 | Publication date not 1995-present |
| E4 | Ineligible SETTING (a) non-generalizable to primary care; (b) low HDI country |
| E5 | Ineligible POPULATION |
| E6 | Ineligible OUTCOMES |
| E7 | Ineligible screening strategy |
| E8 | Ineligible treatment |
| E9 | Ineligible study design |
| E10 | Study rated as poor quality |
| E11 | Overlapping study population |
| E12 | N/A |

**Abbreviations:** HDI = Human Development Index, N/A = not applicable.


1. Screening for melanoma. Med Lett Drugs Ther. 2011;53-1372:72. PMID: 21897350. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
2. Do I need an annual skin check to screen for cancer? Mayo Clin Womens Healthsource. 2009;13-6:8. PMID: 19415051. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
3. New tools aid in diagnosing and detecting skin cancer in earliest stages. Dermatol Nurs. 2009;21-4:222-3. PMID: 19691242. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
4. Early detection of melanoma plus regular skin exams is vital for beating disease. Dermatol Nurs. 2009;21-6:363-4. PMID: 20102024. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
5. How to decrease morbidity and mortality of skin cancer: primary prevention of skin cancer/screening of skin cancer. Report of a workshop held under the auspices of the Society of Dermatological Prevention (ADP e.V.), Commission of Early Detection and Prevention of Skin Cancer. 11 May 1994, Hamburg, Germany. Eur J Cancer Prev. 1996;5-4:297-9. PMID: 8894567. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
6. Abbas Q, Celebi ME, Fondon I. Computer-aided pattern classification system for dermoscopy images. Skin Res Technol. 2012;18-3:278-89. PMID: 22093020. **KQ3E9.**
7. Abbas Q, Garcia IF, Emre Celebi M et al. Unified approach for lesion border detection based on mixture modeling and local entropy thresholding. Skin Res Technol. 2013;19-3:314-9. PMID: 23573804. **KQ3E9.**
8. Abbas Q, Garcia IF, Rashid M. Automatic skin tumour border detection for digital dermoscopy using a new digital image analysis scheme. Br J Biomed Sci. 2010;67-4:177-83. PMID: 21294444. **KQ3E4.**
9. Affleck AG, Varma S. A case of do-it-yourself Mohs' surgery using bloodroot obtained from the internet. Br J Dermatol. 2007;157-5:1078-9. PMID: 17854372. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
10. Aitken JF, Elwood JM, Lowe JB et al. A randomised trial of population screening for melanoma. J Med Screen. 2002;9-1:33-7. PMID: 11943795. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
11. Aitken JF, Youl PH, Janda M et al. Increase in skin cancer screening during a community-based randomized intervention trial. Int J Cancer. 2006;118-4:1010-6. PMID: 16152577. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E6.**
12. Alam M, Ratner D. Cutaneous squamous-cell carcinoma. N Engl J Med. 2001;344-13:975-83. PMID: 11274625. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
13. Aldridge RB, Naysmith L, Ooi ET et al. The importance of a full clinical examination: assessment of index lesions referred to a skin cancer clinic without a total body skin examination would miss one in three melanomas. Acta Derm Venereol. 2013;93-6:689-92. PMID: 23695107. **KQ2E5, KQ3E5.**
14. Altamura D, Menzies SW, Argenziano G et al. Dermatoscopy of basal cell carcinoma: morphologic variability of global and local features and accuracy of diagnosis. J Am Acad Dermatol. 2010;62-1:67-75. PMID: 19828209. **KQ3E7.**

15. Amrock SM, Meydani A. Trends and disparities in total-body skin examination: evaluating the National Health Interview Survey, 2000-2010. JAMA Dermatol. 2013;149-3:363-4. PMID: 23552730. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E6.**
16. Andersson AP, Dahlstrom KK, Drzewiecki KT. Prognosis of thin cutaneous head and neck melanoma (<1mm). Eur J Surg Oncol. 1996;22-1:55-7. PMID: 8846868. **KQ5E6.**
17. Andersson TM, Eriksson H, Hansson J et al. Estimating the cure proportion of malignant melanoma, an alternative approach to assess long term survival: a population-based study. Cancer Epidemiol. 2014;38-1:93-9. PMID: 24447700. **KQ5E6.**
18. Andreeva VA, Cockburn MG. Cutaneous melanoma and other skin cancer screening among Hispanics in the United States: a review of the evidence, disparities, and need for expanding the intervention and research agendas. Arch Dermatol. 2011;147-6:743-5. PMID: 21690545. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E6.**
19. Annessi G, Bono R, Sampogna F et al. Sensitivity, specificity, and diagnostic accuracy of three dermoscopic algorithmic methods in the diagnosis of doubtful melanocytic lesions: the importance of light brown structureless areas in differentiating atypical melanocytic nevi from thin melanomas. J Am Acad Dermatol. 2007;56-5:759-67. PMID: 17316894. **KQ3E7.**
20. Anzai S, Anan T, Kai Y et al. Skin cancer screening on a fishing island and in an inland agricultural area of Japan. J Dermatol. 2005;32-11:875-82. PMID: 16361747. **KQ1E6, KQ2E6, KQ3E9, KQ4E9, KQ5E6.**
21. Argenziano G, Puig S, Zalaudek I et al. Dermoscopy improves accuracy of primary care physicians to triage lesions suggestive of skin cancer. J Clin Oncol. 2006;24-12:1877-82. PMID: 16622262. **KQ3E7.**
22. Argenziano G, Zalaudek I, Hofmann-Wellenhof R et al. Total body skin examination for skin cancer screening in patients with focused symptoms. J Am Acad Dermatol. 2012;66-2:212-9. PMID: 21757257. **KQ1E5, KQ2E5, KQ3E5, KQ4E5, KQ5E5.**
23. Augustin M, Stadler R, Reusch M et al. Skin cancer screening in Germany - perception by the public. J Dtsch Dermatol Ges. 2012;10-1:42-9. PMID: 21923730. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E6.**
24. Austin JR, Byers RM, Brown WD et al. Influence of biopsy on the prognosis of cutaneous melanoma of the head and neck. Head Neck. 1996;18-2:107-17. PMID: 8647675. **KQ2E5.**
25. Averbook BJ, Fu P, Rao JS et al. A long-term analysis of 1018 patients with melanoma by classic Cox regression and tree-structured survival analysis at a major referral center: Implications on the future of cancer staging. Surgery. 2002;132-4:589-602; discussion 602-4. PMID: 12407342. **KQ5E6.**
26. Averbook BJ, Lee SJ, Delman KA et al. Pediatric melanoma: analysis of an international registry. Cancer. 2013;119-22:4012-9. PMID: 24022819. **KQ5E6.**
27. Averbook BJ, Russo LJ, Mansour EG. A long-term analysis of 620 patients with malignant melanoma at a major referral center. Surgery. 1998;124-4:746-55; discussion 755-6. PMID: 9780997. **KQ5E6.**
28. Azzarello LM, Jacobsen PB. Factors influencing participation in cutaneous screening among individuals with a family history of melanoma. J Am Acad Dermatol. 2007;56-3:398-406. PMID: 17184873. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E6.**
29. Baade P, Coory M. Trends in melanoma mortality in Australia: 1950-2002 and their implications for melanoma control. Aust N Z J Public Health. 2005;29-4:383-6. PMID: 16222938. **KQ1E13.**
30. Baade P, Meng X, Youlden D et al. Time trends and latitudinal differences in melanoma thickness distribution in Australia, 1990-2006. Int J Cancer. 2012;130-1:170-8. PMID: 21344376. **KQ4E7.**
31. Badertscher N, Meier M, Rosemann T et al. The role of skin self-examination at the Swiss skin cancer day. BMC Health Serv Res. 2014;14:581. PMID: 25408258. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7.**
32. Baehner FL, Li R, Jenkins T et al. The impact of primary melanoma thickness and microscopic tumor burden in sentinel lymph nodes on melanoma patient survival. Ann Surg Oncol. 2012;19-3:1034-42. PMID: 21989664. **KQ5E7.**

33. Bafounta ML, Beauchet A, Aegerter P et al. Is dermoscopy (epiluminescence microscopy) useful for the diagnosis of melanoma? Results of a meta-analysis using techniques adapted to the evaluation of diagnostic tests. Arch Dermatol. 2001;137-10:1343-50. PMID: 11594860. **KQ3E13.**
34. Balch CM, Soong SJ, Gershenwald JE et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol. 2001;19-16:3622-34. PMID: 11504744. **KQ5E6.**
35. Balch CM, Soong SJ, Smith T et al. Long-term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1-4 mm melanomas. Ann Surg Oncol. 2001;8-2:101-8. PMID: 11258773. **KQ2E5, KQ5E6.**
36. Balch CM, Soong S, Ross MI et al. Long-term results of a multi-institutional randomized trial comparing prognostic factors and surgical results for intermediate thickness melanomas (1.0 to 4.0 mm). Intergroup Melanoma Surgical Trial. Ann Surg Oncol. 2000;7-2:87-97. PMID: 10761786. **KQ5E6.**
37. Baldwin BT, Cherpelis BS, Sondak V et al. Sentinel lymph node biopsy in melanoma: Facts and controversies. Clin Dermatol. 2010;28-3:319-23. PMID: 20541686. **KQ2E2, KQ6.**
38. Bambara M, Magnano M, Castelli G et al. 0109 Study on diseases of the skin in an industrial population of a petrochemical site in Sicily. Occup Environ Med. 2014:A74. PMID: 25018467. **KQ1E6.**
39. Banky JP, Kelly JW, English DR et al. Incidence of new and changed nevi and melanomas detected using baseline images and dermoscopy in patients at high risk for melanoma. Arch Dermatol. 2005;141-8:998-1006. PMID: 16103329. **KQ1E7.**
40. Barzegari M, Ghaninezhad H, Mansoori P et al. Computer-aided dermoscopy for diagnosis of melanoma. BMC Dermatol. 2005;5:8. PMID: 16000171. **KQ3E4.**
41. Barzilai DA, Cooper KD, Neuhauser D et al. Geographic and patient variation in receipt of surveillance procedures after local excision of cutaneous melanoma. J Invest Dermatol. 2004;122-2:246-55. PMID: 15009702. **KQ2E5.**
42. Bataille V. Early detection of melanoma improves survival. Practitioner. 2009;253-1722:29-32, 3. PMID: 19938560. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
43. Bauer AM. Current trends of surgical management of head and neck carcinomas. Nurs Clin North Am. 2001;36-3:501-6, x. PMID: 11532664. **KQ2E2.**
44. Bauer P, Cristofolini P, Boi S et al. Digital epiluminescence microscopy: usefulness in the differential diagnosis of cutaneous pigmentary lesions. A statistical comparison between visual and computer inspection. Melanoma Res. 2000;10-4:345-9. PMID: 10985668. **KQ3E13.**
45. Bello DM, Chou JF, Panageas KS et al. Prognosis of acral melanoma: a series of 281 patients. Ann Surg Oncol. 2013;20-11:3618-25. PMID: 23838913. **KQ5E6.**
46. Benelli C, Roscetti E, Pozzo VD et al. The dermoscopic versus the clinical diagnosis of melanoma. Eur J Dermatol. 1999;9-6:470-6. PMID: 10491506. **KQ1E5, KQ2E5, KQ3E5, KQ4E5, KQ5E5.**
47. Bennassar A, Ishioka P, Vilalta A. Surgical treatment of primary melanoma. Dermatol Ther. 2012;25-5:432-42. PMID: 23046022. **KQ2E7.**
48. Ben-Porat L, Panageas KS, Hanlon C et al. Estimates of stage-specific survival are altered by changes in the 2002 American Joint Committee on Cancer staging system for melanoma. Cancer. 2006;106-1:163-71. PMID: 16331596. **KQ5E6.**
49. Berwick M, Armstrong BK, Ben-Porat L et al. Sun exposure and mortality from melanoma. J Natl Cancer Inst. 2005;97-3:195-9. PMID: 15687362. **KQ1E7, KQ2E5, KQ3E5, KQ4E6, KQ5E7.**
50. Beyeler M, Dummer R. Cutaneous melanoma: uncommon presentations. Clin Dermatol. 2005;23-6:587-92. PMID: 16325067. **KQ1E9, KQ2E6, KQ3E9, KQ4E9, KQ5E9.**
51. Bhattacharyya N, Nayak VK. Survival outcomes for second primary head and neck cancer: a matched analysis. Otolaryngol Head Neck Surg. 2005;132-1:63-8. PMID: 15632911. **KQ1E5, KQ2E5, KQ3E5, KQ4E5, KQ5E5.**
52. Boi S, Cristofolini M, Micciolo R et al. Incidence and mortality data from cutaneous melanoma in Trentino: registry-based study. J Cutan Med Surg. 2008;12-2:59-63. PMID: 18346401. **KQ1E7.**

53. Bong JL, Perkins W. Shave excision of benign facial melanocytic naevi: a patient's satisfaction survey. Dermatol Surg. 2003;29-3:227-9. PMID: 12614413. **KQ2E5.**
54. Bono A, Bartoli C, Cascinelli N et al. Melanoma detection. A prospective study comparing diagnosis with the naked eye, dermatoscopy and telespectrophotometry. Dermatology. 2002;205-4:362-6. PMID: 12444332. **KQ3E5.**
55. Bono A, Ferrari A. Early diagnosis remains the most reliable way to cure children with melanoma. Pediatr Blood Cancer. 2005;45-3:355; author reply 356. PMID: 15809990. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
56. Bono A, Tolomio E, Trincone S et al. Micro-melanoma detection: a clinical study on 206 consecutive cases of pigmented skin lesions with a diameter < or = 3 mm. Br J Dermatol. 2006;155-3:570-3. PMID: 16911283. **KQ3E7.**
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## Appendix C. Excluded Studies


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## Appendix C. Excluded Studies


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## Appendix C. Excluded Studies


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**Appendix D Table 1. Melanoma Mortality Associated With Visual Skin Cancer Screening in Men (KQ 1)**

| Katalinic, 2012[53] Fair | Total population 2009 (millions) | Pre-screening 1998-1999 Melanoma deaths (n) | Pre-screening 1998-1999 WASR (95% CI) | Screening program 2003-2004 Melanoma deaths (n) | Screening program 2003-2004 WASR (95% CI) | Post-screening 2008-2009 Melanoma deaths (n) | Post-screening 2008-2009 WASR (95% CI) |
|---|---|---|---|---|---|---|---|
| **Intervention region:** Schleswig-Holstein (360,288 people screened) | 1.39 | 42 | 1.9 (1.5-2.4) | 43 | 1.6 (1.2-1.9) | 28 | 1.0 (0.7-1.3) |
| **Comparison regions** | | | | | | | |
| South: Hamburg | 0.87 | 19 | 1.3 (0.9-1.8) | 29 | 2.0 (1.5-2.5) | 24 | 1.4 (1.0-1.8) |
| West: Lower-Saxony | 3.90 | 112 | 1.7 (1.5-1.9) | 123 | 1.8 (1.5-2.0) | 151 | 2.0 (1.8-2.3) |
| East: Mecklenburg-Vorpommern | 0.82 | 15 | 1.1 (0.7-1.5) | 23 | 1.6 (1.1-2.2) | 28 | 1.6 (1.2-2.1) |
| North: Denmark | 2.74 | 117 | 2.9 (2.4-3.3) | 118 | 2.7 (2.4-3.1) | 150 | 3.2 (2.8-3.5) |
| Germany* | 38.8 | 1,000 | 1.6 (1.6-1.7) | 1,229 | 1.8 (1.7-1.9) | 1,382 | 1.8 (1.7-1.9) |

*Excludes Schleswig-Holstein region.

**Abbreviations:** KQ = key question, WASR = world age-standardized morality rate per 100,000; CI = confidence interval.

**Appendix D Table 2. Melanoma Mortality Associated With Visual Skin Cancer Screening in Women (KQ 2)**

| Katalinic, 2012[53] Fair | Total population 2009 (millions) | Pre-screening 1998-1999 Melanoma deaths (n) | Pre-screening 1998-1999 WASR (95% CI) | Screening program 2003-2004 Melanoma deaths (n) | Screening program 2003-2004 WASR (95% CI) | Post-screening 2008-2009 Melanoma deaths (n) | Post-screening 2008-2009 WASR (95% CI) |
|---|---|---|---|---|---|---|---|
| **Intervention region:** Schleswig-Holstein (360,288 people screened) | 1.44 | 45 | 1.4 (1.1-1.8) | 39 | 1.3 (0.9-1.6) | 22 | 0.7 (0.5-1.0) |
| **Comparison regions** | | | | | | | |
| South: Hamburg | 0.91 | 22 | 1.2 (0.8-1.6) | 23 | 1.1 (0.7-1.4) | 23 | 1.1 (0.7-1.5) |
| West: Lower-Saxony | 4.04 | 112 | 1.3 (1.1-1.4) | 116 | 1.2 (1.0-1.4) | 102 | 1.1 (0.9-1.3) |
| East: Mecklenburg-Vorpommern | 0.84 | 17 | 0.8 (0.5-1.2) | 20 | 1.0 (0.6-1.3) | 23 | 1.1 (0.7-1.5) |
| North: Denmark | 2.79 | 86 | 1.8 (1.5-2.1) | 103 | 1.8 (1.5-2.1) | 103 | 1.9 (1.6-2.1) |
| Germany* | 40.3 | 940 | 1.1 (1.0-1.1) | 984 | 1.1 (1.0-1.1) | 1,148 | 1.2 (1.1-1.2) |

*Excludes Schleswig-Holstein region.

**Abbreviations:** KQ = key question, WASR = world age-standardized morality rate per 100,000; CI = confidence interval.

**Appendix D Table 3. Impact of Screening on Detection of Melanoma in Situ, Squamous Cell Carcinoma, and Basal Cell Carcinoma**

| Study Year Quality Location | N screened | Age-adjusted incidence rates per 100,000 (95% CI) | In situ melanoma | Malignant melanoma | In situ SCC | SCC | BCC |
|---|---|---|---|---|---|---|---|
| **Breitbart 2012**[55] Good Schleswig-Holstein, Germany | 360,288 | Baseline (2001-2003) | 5.8 (5.2-6.4) | 14.2 (13.3-15.1) | 6.7 (6.3-7.2) | 11.2 (10.6-11.8) | 60.5 (59.0-62.1) |
| | | SCREEN (2003-2004) | 8.5 (7.5-9.5) | 18.0 (16.6-19.4) | 8.8 (8.1-9.6) | 12.9 (12.0-13.8 | 78.4 (75.9-80.8) |
| | | % change | 48% increase | 27% increase | 31% increase | 15% increase | 29% increase |

**Abbreviations:** CI = confidence interval, SCC = squamous cell carcinoma, BCC = basal cell carcinoma, SCREEN = Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany.