US Preventive Services Task Force | EVIDENCE REPORT

Screening for Skin Cancer in Adults
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Karen J. Wernli, PhD, MS; Nora B. Henrikson, PhD, MPH; Caitlin C. Morrison, MPH; Matthew Nguyen, MPH; Gaia Pocobelli, PhD; Paula R. Blasi, MPH

IMPORTANCE Skin cancer, primarily melanoma, is a leading cause of morbidity and mortality in the United States.

OBJECTIVE To provide an updated systematic review for the US Preventive Services Task Force regarding clinical skin cancer screening among adults.

DATA SOURCES MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials were searched for relevant studies published from January 1, 1995, through June 1, 2015, with surveillance through February 16, 2016.

STUDY SELECTION English-language studies conducted in asymptomatic populations 15 years and older at general risk for skin cancer.

DATA EXTRACTION AND SYNTHESIS Relevant data were abstracted, and study quality was rated.

MAIN OUTCOMES AND MEASURES Melanoma incidence and mortality, harms from cancer screening, diagnostic accuracy, and stage distribution.

RESULTS No randomized clinical trials were identified. There was limited evidence on the association between skin cancer screening and mortality. A German ecologic study (n = 360 288) found a decrease of 0.8 per 100 000 melanoma deaths in a region with population-based skin cancer screening compared with no change or slight increases in comparison regions. The number of excisions needed to detect 1 skin cancer from clinical visual skin examinations varied by age and sex; for example, 22 for women 65 years or older compared with 41 for women aged 20 to 34 years. In 2 studies of performing visual skin examination, sensitivity to detect melanoma was 40.2% and specificity was 86.1% when conducted by primary care physicians (n = 16 383). Sensitivity was 49.0% and specificity was 97.6% when skin examinations were performed by dermatologists (n = 7436). In a case-control study of melanoma (n = 7586), cases diagnosed with thicker lesions (>0.75 mm) had an odds ratio of 0.86 (95% CI, 0.75-0.98) for receipt of a physician skin examination in the prior 3 years compared with controls. Eight cohort studies (n = 236 485) demonstrated a statistically significant relationship between the degree of disease involvement at diagnosis and melanoma mortality, regardless of the characterization of the stage or lesion thickness. Tumor thickness greater than 4.0 mm was associated with increased melanoma mortality compared with thinner lesions, and late stage at diagnosis was associated with increased all-cause mortality.

CONCLUSIONS AND RELEVANCE Only limited evidence was identified for skin cancer screening, particularly regarding potential benefit of skin cancer screening on melanoma mortality. Future research on skin cancer screening should focus on evaluating the effectiveness of targeted screening in those considered to be at higher risk for skin cancer.

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Author Affiliations: Group Health Research Institute, Kaiser Permanente Research Affiliates Evidence-based Practice Center, Seattle, Washington.

Corresponding Author: Karen J. Wernli, PhD, MS, Group Health Research Institute, Kaiser Permanente Research Affiliates Evidence-based Practice Center, 1730 Minor Ave, Ste 1600, Seattle, WA 98101 (wernli.k@ghc.org).

Skin cancer is among the most common cancers in men and women in the United States,[1] and classified as either nonmelanoma skin cancer (NMSC) (ie, basal cell and squamous cell cancers) or melanoma skin cancer. Although NMSC represents more than 97% of skin cancers,[1] melanoma skin cancer is the primary public health concern with a higher case-fatality rate.[2] Estimates for 2015 were 73 870 people diagnosed with melanoma in the United States and 9940 deaths from their disease.[3]

The rationale for skin cancer screening is to detect skin cancers, particularly melanoma, earlier in their clinical course than would happen in usual care, potentially allowing for earlier and more effective treatment. Primary care physicians or dermatologists can perform visual skin cancer screening of the whole or partial body to detect suspicious lesions for potential biopsy.

In 2009, the US Preventive Services Task Force (USPSTF) concluded that the current evidence was insufficient (I recommendation) to assess the balance of benefits and harms of screening the adult general population by primary care clinicians.[4,5] The purpose of this report was to provide an updated systematic review for the USPSTF regarding clinical skin cancer screening among adults.

Methods

Detailed methods are described in the full report, available at http://www.uspreventiveservicestaskforce.org/Page/Document/final-evidence-review154/skin-cancer-screening2.[6]

Scope of Review

An analytic framework and 5 key questions (KQs) were developed (**Figure 1**). The KQs were designed to identify direct evidence of the benefit of clinical visual skin cancer screening for skin cancer morbidity and mortality (KQ1), the harms and test characteristics of clinical visual skin cancer screening (KQ2 and KQ3), the effectiveness of clinical visual skin cancer screening for early detection of skin cancer (KQ4), and the association between earlier detection of skin cancer and skin cancer morbidity and mortality and all-cause mortality (KQ5).

Data Sources and Searches

MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials were searched for English-language studies published from January 1, 1995, through June 1, 2015. The reference lists were searched from included studies, systematic reviews, and meta-analyses. Suggestions were also sought from experts, and Clinicaltrials.gov was searched to identify relevant ongoing trials.

Since June 2015, we continued to conduct ongoing surveillance through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and therefore the related USPSTF recommendation. The last surveillance was conducted on February 16, 2016, and no new studies were included in the review.

Study Selection

Two researchers independently reviewed 12 514 unique titles with abstracts and 453 full-text articles against a priori inclusion and exclusion criteria. We included studies of asymptomatic adults 15 years and older and conducted in countries with a very high (>0.9) Human Development Index (HDI) according to the United Nations.[8] Studies conducted in very high HDI countries are more likely to be applicable to US settings. Randomized clinical trials, observational studies (ie, cohort and case-control studies), and ecologic studies were included for all key questions. Case series or case reports were also included for identification of potential harms due to screening (KQ2). Screening studies were excluded if they focused on skin examinations in response to patient concerns about suspicious lesions or individuals with known skin cancer; skin self-screening by individuals or partners; physician counseling for self-screening; intermediate or health outcomes relating clinician skin examination to other risk factors (eg, sun-protection behaviors); or measures of patient-physician relationship quality (**Figure 2**).

For effectiveness and harms studies, screening tests were defined as whole or partial visual skin examination conducted by primary care physicians or dermatologists with or without tools to aid examination (eg, dermatoscopy, whole-body photography). For studies focusing on morbidity and mortality, studies of skin cancer mortality, all-cause mortality, or morbidities associated with any skin cancer (ie, melanoma in situ, dysplastic nevi, and actinic keratosis), including quality of life, were reviewed. For diagnostic accuracy studies, studies that assessed cancer outcomes through cancer registry–based systems or pathology or biopsy reports within a defined period after receipt of screening and estimated false-negative rates for melanoma detection in participants who screened negative were included. For studies on early detection of skin cancer, studies that evaluated either American Joint Committee on Cancer (AJCC) stage[9] or Breslow lesion thickness at diagnosis were included. Detailed search strategies are listed in the eMethods in the Supplement.

Data Extraction and Quality Assessment

Dual independent critical appraisal of all articles meeting the inclusion criteria was performed. Each study was categorized as good, fair, or poor quality in accordance with USPSTF design-specific quality criteria supplemented with quality criteria for ecologic studies (eTable in the Supplement).[7,10,11] Good- and fair-quality studies were included in the summary of evidence; poor-quality studies were excluded. Key data were extracted on study characteristics, study design elements, outcomes for screening studies, health outcomes, and harms. A second reviewer checked the data for accuracy.

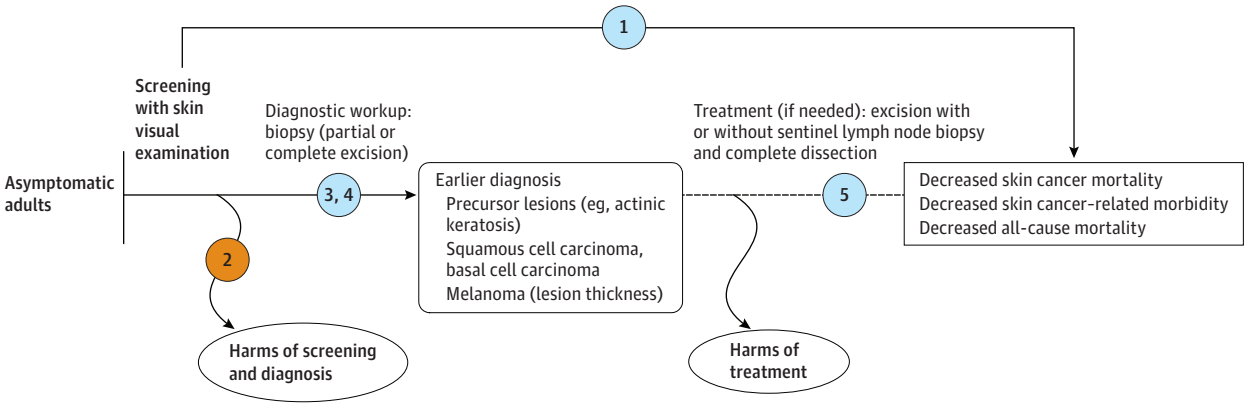
Data Synthesis and Analysis

Summary evidence tables were created to capture study characteristics and sources of heterogeneity (eg, study quality, sample size, geographic location, age, and sex). For each KQ, the number and design of included studies, overall results, consistency of results, limitations of the body of evidence, applicability of findings, and study quality were summarized. Because few studies were included in the review, summary statistics were not derived and meta-analysis was not conducted.

Results

The review included 13 unique fair- or good-quality studies reported in 15 publications (**Table 1**[12-27]). Of the 15 publications, 13 were included for 1 KQ each, and 2 publications were included for 2 KQs.

Figure 1. Analytic Framework and Key Questions



Key questions

1. What is the direct evidence that visual skin cancer screening by a primary care clinician 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 clinicians vs dermatologists?
4. Does visual skin cancer screening lead to earlier detection of skin cancer compared with usual care?
5. What is the association between earlier detection of skin cancer and skin cancer morbidity and mortality and all-cause mortality?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. A dashed line indicates health outcomes that follow an intermediate outcome. Further details are available from the USPSTF procedure manual.[7]

Effectiveness of Skin Cancer Screening

Key Question 1. What is the direct evidence that visual skin cancer screening by a primary care clinician or dermatologist reduces skin cancer morbidity and mortality and all-cause mortality?

No eligible trials assessed skin cancer morbidity or all-cause mortality associated with physician visual skin screening. One fair-quality ecologic study with 3 publications[12-14] compared trends in melanoma mortality over 10 years in northern Germany, where there was a population-based clinical visual skin cancer screening program, with trends in the surrounding regions with no population-based skin cancer screening. The Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany (SCREEN) study launched a population-based skin cancer screening intervention in 2003, which included physician training, a skin cancer public awareness campaign, and referral protocol to dermatology. During the 1-year intervention period (2003-2004), 360 288 adults were screened with a visual skin cancer examination primarily by nondermatologists, representing about 19% of the eligible population. The majority of adults screened were women (73.6%), and the mean (SD) age was 49.7 (16.2) years. Approximately 39% of screened individuals were recommended to follow up with dermatologists but were lost to follow-up and did not return for dermatology review.

Between 1998 to 1999 (prescreening) and 2008 to 2009 (post-screening), age- and sex-adjusted melanoma mortality decreased by 48% in the intervention region, from 1.7 deaths (95% CI, 1.4-2.0) to 0.9 deaths (95% CI, 0.7-1.1) per 100 000 persons, representing an overall absolute mortality difference of 0.8 melanoma deaths per 100 000 persons (**Table 2**). Over the same period in the 5 comparison regions, melanoma mortality remained stable or increased by 0.1 to 0.3 deaths per 100 000 persons, representing increases of 2% to 32%.

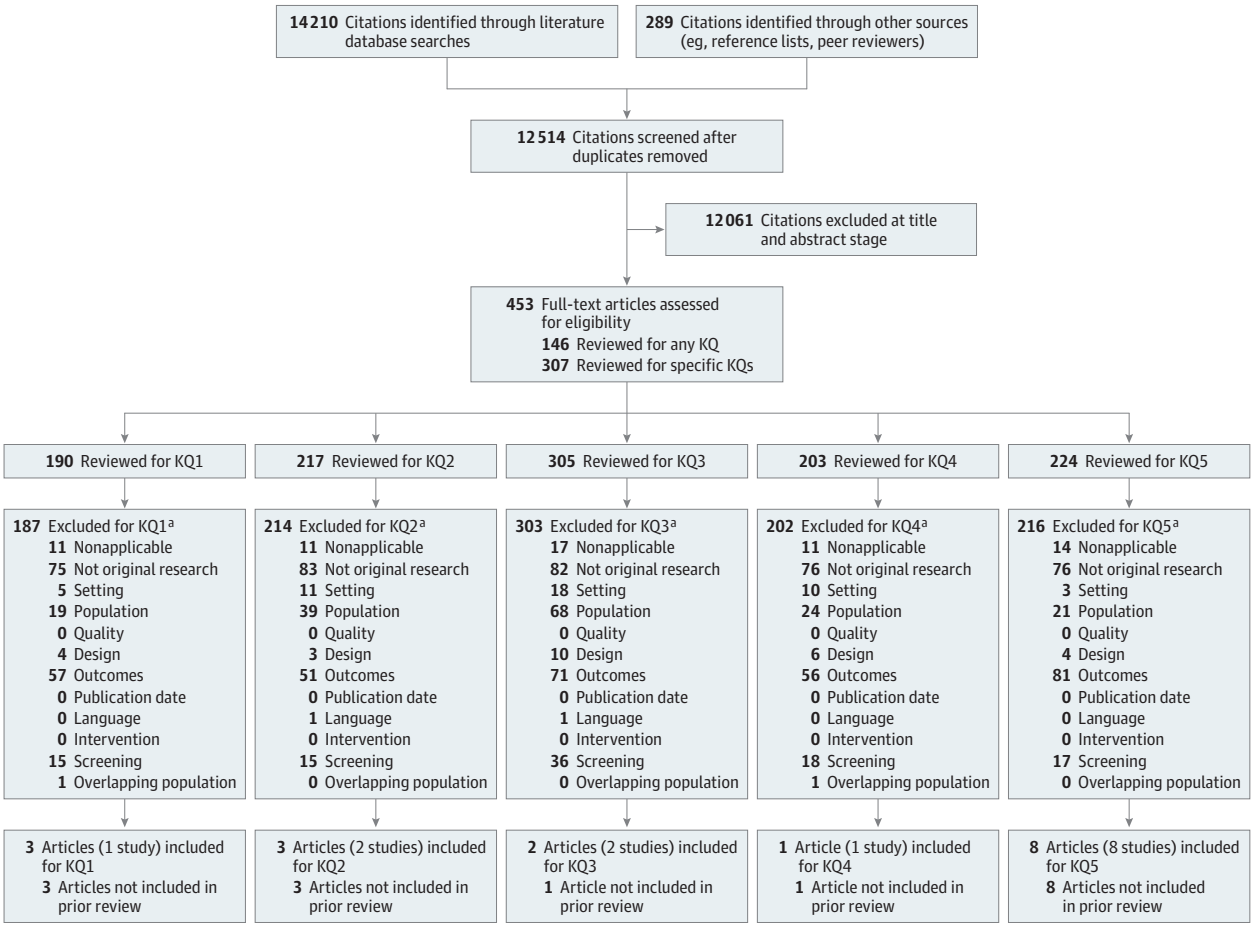
Harms of Skin Cancer Screening

Key Question 2. What are the harms of skin cancer screening and diagnostic follow-up?

Two fair-quality studies with 3 articles, conducted in Germany, assessed the number of excisions needed for the detection of 1 melanoma, basal cell carcinoma, or squamous cell carcinoma in the SCREEN study and the cosmetic acceptance of shave biopsy in a screened population (Table 2).[13-15]

In a population of 360 288 adults, the number of excisions needed to detect 1 melanoma, basal cell carcinoma, or squamous cell carcinoma varied by age and sex.[13] Fewer excisions were needed to detect a single case of skin cancer in adults 65 years or older compared with younger adults. Detecting 1 melanoma in women 65 years

Figure 2. Literature Search Flow Diagram



[a] Details about reasons for exclusion are as follows. Nonapplicable: Study aim not applicable. Not original research: Study was not original research. Setting: Study was not conducted in a setting or country relevant to US primary care. Population: Study was not conducted in a population of asymptomatic adults 15 years and older. Quality: Study did not meet criteria for fair or good quality (ie, it was poor quality). Design: Study did not use an included design. Outcomes: Study did not have relevant outcomes or had incomplete outcomes. Publication date: Study did not meet publication date criteria. Language: Study was published in a non-English language. Intervention: Study used an excluded intervention approach. Screening: Study used an excluded screening approach. Overlapping population: Study population overlapped with 1 or more studies included for this key question (KQ).

and older required 22 excisions compared with 41 in women aged 20 to 34 years. Similar patterns were observed in men and across the other types of skin cancer.

In a population of 45 adults who underwent shave biopsy after screening for removal of potential NMSC, patients reported their cosmetic results as poor for 7.1% of shave sites (mean score, 1.7, between excellent to good) compared with a physician who rated the results as poor for 16.1% of shave sites (mean score, 2.5, between good to fair).[15]

Screening Diagnostic Accuracy

Key Question 3. What are the test characteristics of visual screening for skin cancer when performed by primary care clinicians vs dermatologists?

Two fair-quality cohort studies conducted in Australia evaluated test characteristics of skin cancer screening performed by primary care physicians or dermatologists (Table 2). In Queensland, Australia, primary care physicians conducted screenings among 16 383 adults.[16] Cancer outcomes were determined by pathology or biopsy reports for positive screens. The study did not follow up participants with negative screen results, so the exact number of true-negative and false-negative findings was unknown. Therefore, false-negative rates for melanoma were estimated using prior literature in a population screened for skin cancer and melanoma rates for the Queensland population. The recall rate was 14.1% for those who screened positive and were referred to their usual primary care physicians for follow-up. Although the study did not report sensitivity for melanoma detection, sensitivity could be calculated using an estimated false-negative rate. Based on melanomas detected within 3 years of the first screen examination, sensitivity for melanoma detection was calculated as 40.2%, and specificity was 86.1% (95% CI, 85.6%-86.6%).

The second study evaluated the performance of volunteer dermatologists and plastic surgeons who conducted screening of 7436 people in suburban and rural areas in Western Australia.[17] With follow-up to 24 months for melanoma through a cancer registry

Table 1. Description of Included Publications

Source	Quality[a]	Country	Study Design	No. of Participants	Population	Age, y	Female, No. (%)	Dates of Data Collection	Length of Follow-up
Key Question 1									
Katalinic et al,[12] 2012 (SCREEN)	Fair	Germany	Ecologic	87.46 million[b]	Residents of Germany and Denmark	NR	44.53 million (50.9)[b]	1998-2009	Five years after intervention
Key Questions 1 and 2									
Waldmann et al,[13] 2012	Fair	Germany	Cohort	360 288	Residents of Schleswig-Holstein, Germany, aged ≥20 y with whole-body skin cancer screening examination	Mean (SD): 49.7 (16.2)	265 306 (73.6)	2003-2004	Twelve months
Breitbart et al,[14] 2012 (SCREEN)	Good								
Key Question 2									
Gambichler et al,[15] 2000	Fair	Germany	Case series	45	Routine skin cancer screening outpatients not suspected of melanoma with a shave biopsy	Mean (range): 32 (15-54)	23 (51.1)	NR	Six months after biopsy
Key Question 3									
Aitken et al,[16] 2006	Fair	Australia	Cohort	16 383	Residents in a community-based pilot randomized clinical trial of a skin screening program	Mean (SD): 46.5 (16.4)	8438 (51.5)	1998-2001	Up to 3 years after initial screening examination
Fritschi et al,[17] 2006	Fair	Australia	Cohort	7436	Adults who attended Lions Cancer Institute weekend mobile screening clinics in rural and suburban locations in Western Australia	No. (%): <40: 1948 (26.2) 40-59: 3437 (46.2) ≥60: 2051 (27.6)	4163 (56.0)	1994-2002	Two years after initial screening examination
Key Question 4									
Aitken et al,[18] 2010	Fair	Australia	Population-based case-control	3762 cases 3824 controls	Queensland residents aged 20-75 y; cases identified from cancer registry and controls selected through stratified random sampling from Queensland Electoral Roll	No. (%): <40: 629 (16.4) 40-69: 2660 (69.6) ≥70: 535 (14.0)[c]	1621 (42.4)[c]	NR	NA
Key Question 5									
Marashi-Pour et al,[19] 2012	Good	Australia	Retrospective cohort study	52 330	Cases of cutaneous melanoma from the New South Wales Central Cancer Registry	No. (%): <40: 7813 (14.9) 40-69: 28 132 (53.8) ≥70: 16 374 (31.3)	21 982 (42.0)	1988-2007	Follow-up time calculated from date of diagnosis until death or end of study period (December 31, 2007)
Green et al,[20] 2012	Fair	Australia	Retrospective cohort study	26 736	Queensland residents with a single thin invasive melanoma (≤1.00 mm) diagnosed	Mean (range): 52.7 (15-89)	12 408 (46.4)	1982-2007	Minimum 1 year follow-up. (Survival assessed up to December 31, 2007.) Average length of follow-up not reported.

(continued)

Table 1. Description of Included Publications (continued)

Source	Quality[a]	Country	Study Design	No. of Participants	Population	Age, y	Female, No. (%)	Dates of Data Collection	Length of Follow-up
Pollack et al,[21] 2011	Good	United States	Retrospective cohort study	68 495	Cases of melanoma (excluding in situ disease) in the 13 SEER registries in individuals aged >15 y with no previous cancer diagnosis	No. (%): <40: 13 383 (19.5) 40-64: 33 526 (48.9) ≥65: 21 586 (31.5)	30 869 (45.1)	1992-2006	First primary melanoma cases diagnosed from 1992 to 2001. Followed up through 2006.
Zell et al,[22] 2008	Good	United States	Retrospective cohort study	39 049	Incident cases of cutaneous melanoma reported to the California Cancer Registry[d]	Median (95% CI): 58 (29.0-84.0)	16 819 (43.1)	1993-2003	Hospital registrars contacted cases annually and CCR staff annually reviewed death certificates. Last date of follow-up was either date of death or last date of contact.
Reyes-Ortiz et al,[23] 2006	Fair	United States	Retrospective cohort study	23 068	23 068 Medicare beneficiaries aged ≥65 y residing in 1 of 11 SEER regions, diagnosed with melanoma and with complete ethnicity information	No. (%): ≥65: 23 068 (100)	9225 (40.0)	1988-2000	Survival defined as period between diagnosis and death from melanoma. Censored at death from other causes or December 31, 2000.
Leiter et al,[24] 2004	Fair	Germany	Retrospective cohort study	12 728	Persons with thin incident primary invasive melanoma in the German-based Central Malignant Melanoma Registry	50 (15.7)	7458 (58.6)	1976-2000	Data obtained from Central Malignant Melanoma registry. Patients were examined every 3-6 mo for 10 y. All patients included had follow-up time of >3 mo and >10 y.
Luke et al,[25] 2003	Fair	Australia	Retrospective cohort study	9519	Residents of the state of South Australia diagnosed with invasive cutaneous melanoma	No. (%): <39: 1999 (21.0) 40-69: 5015 (52.6) ≥70: 2505 (26.3)	4751 (49.9)	1980-2000	1994-2000 diagnostic period identified through cancer registry; dates censored at death from other causes or December 31, 2000.
Owen et al,[26] 2001	Fair	United States	Retrospective cohort study	4560	Registered patients at the Duke University Melanoma Clinic who began treatment at Duke within 3 mo before or after excision of a primary melanoma (in situ excluded)	Mean (SD): 48.3 (14.2)[e]	2075 (45.5)	1970-1995	Patients registered at Duke University Melanoma clinic January 1, 1970, to December 31, 1995. Follow-up limited to 10 y by censoring all observations for patients still alive at 10 y after surgery (also death from other causes and loss to follow-up resulted in censoring).

Abbreviations: CCR, California Cancer Registry; NA, not applicable; NR, not reported; SCREEN, Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany; SEER, Surveillance, Epidemiology, and End Results Program.

[a] Quality assessed using criteria developed by the US Preventive Services Task Force.[27]

[b] Calculated.

[c] These data refer to control participants only.

[d] California cancer registry is part of SEER.

[e] Mean age at surgery.

Table 2. Summary of Findings by Study

Source	Summary of Findings
Key Question 1	
Katalinic et al,[12] 2012 Waldmann et al,[13] 2012 Breitbart et al,[14] 2012 (SCREEN)	Between prescreening (1998-1999) and postscreening (2008-2009), melanoma mortality in the intervention region decreased from 1.7 (95% CI, 1.4-2.0) to 0.9 (95% CI, 0.7-1.1) deaths per 100 000 persons. There were no mortality reductions observed in the surrounding comparison areas.
Key Question 2	
Waldmann et al,[13] 2012 Breitbart et al,[14] 2012 (SCREEN)	The number of excisions needed to detect skin cancer varied by age and sex. Detecting 1 melanoma in women aged ≥65 y required 22 excisions compared with 41 in women aged 20-34 y. Similar patterns were observed in men and across other skin cancer types.
Gambichler et al,[15] 2000	Six months after shave biopsy for removal of potential NMSC, patients reported cosmetic outcomes as poor for 7.1% of shave sites compared with 16.1% of physician assessment.
Key Question 3	
Aitken et al,[16] 2006	With primary care physicians conducting screenings, specificity for melanoma detection was 86.1% (95% CI, 85.6%-86.6%) at 36-mo follow-up. The study did not report sensitivity, but by using the study's estimated false-negative rates, sensitivity was calculated at 40.2%.
Fritschi et al,[17] 2006	With dermatologists and plastic surgeons conducting screenings, specificity for melanoma detection was 97.6% (95% CI, 97.2%-97.9%) and sensitivity was 49.0% (95% CI, 34.4%-63.7%) at 24-mo follow-up.
Key Question 4	
Aitken et al,[18] 2010	Overall 28.3% of controls reported receiving a clinical skin exam in the previous 3 y compared with 35.3% of melanoma cases. Compared with controls, the OR for receiving a recent clinical skin exam was 1.38 (95% CI, 1.22-1.56) among cases with thin melanoma lesions (≤0.75 mm) and 0.86 (95% CI, 0.75-0.98) among cases with thicker lesions (>0.75 mm).
Key Question 5	
Marashi-Pour et al,[19] 2012	Using a Breslow lesion thickness of ≤1.0 mm as referent, adjusted HR (95% CI) for melanoma-related mortality was as follows: 4.13 (3.74-4.56) for lesion thicknesses of 1.01-2.0 mm 6.88 (6.18-7.65) for lesion thicknesses of 2.01-4.0 mm 9.52 (8.42-10.77) for lesion thicknesses of ≥4.01 mm
Green et al,[20] 2012	Using a Breslow lesion thickness of <0.25 mm as referent, adjusted HR (95% CI) for melanoma-related mortality was as follows: 1.14 (0.7-1.7) for lesion thicknesses of 0.25-0.49 mm 1.84 (1.2-2.9) for lesion thicknesses of 0.50-0.74 mm 4.33 (2.8-6.8) for lesion thicknesses of 0.75-1.00 mm
Pollack et al,[21] 2011	Using a Breslow lesion thickness of ≤1.0 mm as referent, adjusted HR (95% CI) for melanoma-related mortality was as follows: 2.89 (2.62-3.18) for lesion thicknesses of 1.01-2.0 mm 4.69 (4.24-5.02) for lesion thicknesses of 2.01-4.0 mm 5.71 (5.10-6.39) for lesion thicknesses of >4.0 mm
Zell et al,[22] 2008	Using AJCC stage I melanoma as referent, adjusted HR (95% CI) for melanoma-related mortality was as follows: 4.96 (4.51-5.56) for stage II melanoma 9.99 (8.84-11.29) for stage III melanoma 27.1 (22.4-32.8) for stage IV melanoma
Reyes-Ortiz et al,[23] 2006	Using SEER staging with in situ melanoma as referent, adjusted HR (95% CI) for melanoma-related mortality was as follows: 8.83 (6.0-12.9) for localized melanoma 23.2 (15.7-34.3) for regional melanoma 94.0 (63.3-139.5) for distant melanoma 19.1 (13.1-27.8) for unknown staging
Leiter et al,[24] 2004	Using a Breslow lesion thickness of ≤0.50 mm as referent, adjusted RR (95% CI) for melanoma-related mortality was as follows: 1.9 (1.2-2.9) for lesion thicknesses of 0.51-0.75 mm 3.9 (2.6-5.8) for lesion thicknesses of 0.76-1.00 mm
Luke et al,[25]2003	Using a Breslow lesion thickness of ≤0.50 mm as referent, adjusted HR (95% CI) for melanoma-related mortality was as follows: 2.81 (1.81-4.35) for lesion thicknesses of 0.51-1.00 mm 6.18 (3.75-10.20) for lesion thicknesses of 1.01-1.50 mm 8.53 (5.05-14.43) for lesion thicknesses of 1.51-2.00 mm 13.89 (8.16-23.64) for lesion thicknesses of 2.01-2.50 mm 15.44 (8.90-26.80) for lesion thicknesses of 2.51-3.00 mm 20.74 (11.83-36.34) for lesion thicknesses of 3.01-3.50 mm 27.39 (15.71-47.73) for lesion thicknesses of 3.51-4.00 mm 32.62 (18.78-56.63) for lesion thicknesses of 4.01-4.50 mm 21.09 (11.38-39.09) for lesion thicknesses of 4.51-5.00 mm 22.1 (10.62-45.99) for lesion thicknesses of 5.01-5.50 mm 33.99 (18.13-63.73) for lesion thicknesses of 5.51-6.00 mm 23.08 (12.70-41.95) for lesion thicknesses of ≥6.01 mm
Owen et al,[26] 2001	Using a Breslow lesion thickness of 1.0-1.5 mm as referent, adjusted RR (95% CI) for melanoma-related mortality was as follows: 0.28 (0.17-0.44) for lesion thicknesses ≤0.75 mm 0.55 (0.4-0.76) for lesion thicknesses of 0.75-1.0 mm 1.93 (1.6-2.34) for lesion thicknesses of 1.5-3.0 mm 3.02 (2.37-3.86) for lesion thicknesses of 3.0-4.0 mm 3.88 (3.12-4.83) for lesion thicknesses of >4.0 mm

Abbreviations: SCREEN, Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany; SEER, Surveillance, Epidemiology, and End Results Program.

system for screen-positive and screen-negative results, the sensitivity was 49.0% (95% CI, 34.4%-63.7%) and the specificity was 97.6% (95% CI, 97.2%-97.9%) with an overall recall rate of 2.7%. The screening accuracy of dermatology and primary care clinicians could not be directly compared because of differences in time to ascertainment of cancer outcomes that affect screening examination performance measures.

Skin Cancer Screening and Early Detection

Key Question 4. Does visual skin cancer screening lead to earlier detection of skin cancer compared with usual care?

One fair-quality case-control study[18] measured the association between whole-body skin examinations by a physician during the 3 years before melanoma diagnosis and risk of invasive melanoma according to lesion thickness at diagnosis (Table 2). The study was conducted among 3762 cases with incident melanoma in Queensland, Australia, and 3824 controls randomly selected through electoral rolls and given a referent date. Of controls, 28.3% reported receiving a skin examination within 3 years of their reference date compared with 35.3% of melanoma cases. When stratified by lesion thickness, prevalence of report of receiving a clinical skin examination declined as lesion thickness increased: 38.7% for lesions less than 0.75 mm, 30.3% for lesions 0.76 to 1.49 mm, 28.0% for lesions 1.5 to 2.99 mm, and 22.5% for lesions 3.00 mm or larger. In multivariable-adjusted models, cases diagnosed with thin melanoma (≤0.75 mm) had an odds ratio (OR) of 1.38 (95% CI, 1.22-1.56) for physician skin examination in the previous 3 years compared with controls. Cases diagnosed with thicker lesions (>0.75 mm) had an OR of 0.86 (95% CI, 0.75-.98) for recent physician skin examination compared with controls. The subgroup of cases with the thickest melanoma lesions (≥3.00 mm) had an OR of 0.60 (95% CI, 0.43-0.83) for recent physician skin examination compared with controls.

Early Detection and Morbidity and Mortality

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- or good-quality observational studies were included with a total population of 236 485 (Table 2). These studies examined the association between either melanoma-specific or all-cause mortality and lesion thickness or stage at diagnosis (either AJCC or SEER [US Surveillance, Epidemiology, and End Results Program] stage) at diagnosis. One good-quality study evaluated cancer stage and all-cause mortality.

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 increased melanoma mortality compared with thinner lesions in multivariable-adjusted models (hazard ratios [HRs] ranging from 3.17; 95% CI, 2.56-3.92, to 32.62; 95% CI, 18.78-56.63). In the largest study, with 68 495 melanoma cases diagnosed from 1992 to 2006 identified through 13 SEER registries, greater tumor thickness was associated with higher melanoma mortality. Compared with thin lesions (<1.0 mm), HRs for melanoma mortality by thickness were 2.89 (95% CI, 2.62-3.18) for tumors 1.01 to 2.00 mm, 4.69 (95% CI, 4.24-5.02) for tumors 2.01 to 4.00 mm, and 5.71 (95% CI, 5.10-6.39) for tumors larger than 4.00 mm. Using the same study population and categorizing by SEER summary stage, distant stage was associated with increased melanoma mortality compared with localized disease. In a cohort study of 39 049 residents of California who were diagnosed with melanoma, late stage at diagnosis was associated with increased all-cause mortality in adjusted models (HR, 10.39; 95% CI, 8.96-12.0).

Discussion

A substantial body of evidence consistently suggests that later stage and increasing skin lesion thickness at melanoma detection is associated with increased melanoma and all-cause mortality risk (**Table 3**). However, the evidence for an association between skin cancer screening and melanoma mortality is limited (Table 3). One population-based ecologic study found that visual skin examination by physicians was associated with a small reduction in absolute differences in population-level melanoma mortality. However, study design limits assessment of the intervention in the absence of a comparison population or more robust control of confounding. In addition, newly published follow-up research has suggested that the decline in melanoma mortality was transient, and melanoma mortality has returned to prescreening levels.[28]

Skin cancer screening could be accompanied by psychosocial harms, cosmetic harms, or overdiagnosis (ie, the diagnosis of disease that will not cause symptoms or death in a person's expected lifetime). For melanoma, biopsy alone is not usually sufficient for removing even small lesions, and subsequent excisions are often necessary for clear margins, particularly after shave or punch biopsy.[29] One study found cosmetic results of shave biopsy were acceptable to adults with suspected but not confirmed NMSC.[15] Detecting 1 case of skin cancer in younger age groups requires significantly more excisions than in older groups,[13] which suggests a potential excess burden of diagnostic workup in younger people, who experience the lowest incidence of NMSC and melanoma.

The potential for overdiagnosis of skin cancer is substantial. Since 1986, melanoma incidence rates have increased, but mortality rates have remained relatively stable. The increase is in part attributed to increasing skin biopsy rates, which increased from 2847 to 7222 per 100 000 individuals in the SEER Medicare population from 1986-2001.[30] Biopsies have resulted in increased detection of early-stage melanoma, mainly melanoma in situ.[30] These data suggest potential increased detection of clinically insignificant cancers rather than earlier detection of invasive tumors, in the absence of changes in mortality.[30,31] The 2.1 million Medicare enrollees diagnosed with NMSC annually[32] face increasing detection and treatment of basal cell carcinoma that likely has limited effect on life expectancy.[33] No studies meeting the inclusion criteria assessed overdiagnosis of clinical visual skin cancer screening.

The 2 included studies on diagnostic accuracy were conducted in Australia, where knowledge of skin protection habits and sun safety is high. Because of the relatively high prevalence of melanoma in Australia, primary care physicians routinely diagnose and manage skin cancer.[34] Physician training in detecting and diagnosing skin cancers was part of both studies and is likely important for improving performance, for both screening and responding to patient concerns. In the United States, some primary care physicians may not be fully confident in their skills to conduct skin cancer

Table 3. Overall Summary of Evidence by Key Question

No. of Studies	No. of Observations	Population	Study Design	Summary of Findings, Consistency	Major Limitations	Applicability	Overall Quality
Key Question 1: Effectiveness of Skin Cancer Screening[a]							
1 Study (3 articles)	360 288	Residents of Schleswig-Holstein Germany ≥20 y with whole-body skin cancer screening exam between July 2003 and June 2004	Ecologic (1 study)	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. Consistency could not be assessed because only 1 study was included.	In the main study, an ecologic study design permitted only population-level analysis of mortality rates compared with those in the surrounding areas, not individual-level data. In the absence of comparison of individual-level data, the study was not able to address confounding and participant screening bias. 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.	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 eligible) had a high proportion of younger women screened, who are at low risk for melanoma.	Fair
Key Question 2: Harms of Skin Cancer Screening[b]							
2 Studies (3 articles)	360 333	Routine skin cancer screening outpatients in Germany	Cohort (1 study) Case series (1 study)	The number of excisions needed to detect 1 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% of patients viewed their scar outcomes poorly at 6 mo after biopsy. Consistency was low because different harms were assessed in each study and 1 per outcome.	Data from the SCREEN study presented the false-positive rates and number of excisions needed to detect 1 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.	The SCREEN data suggest potential for very high number of false-positive results that could be relevant to other screening programs. Patient-reported data on cosmetic harms is important.	Fair
Key Question 3: Screening Diagnostic Accuracy[c]							
2 Studies (2 articles)	23 819	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	Cohort (2 studies)	Sensitivity to detect melanoma was 40.2% and specificity was 86.1% when conducted by primary care physicians and cancer outcomes were assessed within 3 years. Sensitivity was 49.0% and specificity 97.6% when skin examinations were performed by dermatologists and cancer outcomes were assessed within 2 years. Recall rate was 14.1% for primary care and 2.7% for dermatologists. Melanoma detection rates were under 1% in both studies. Consistency was low because different follow-up times prohibit direct comparison of studies.	An Australian cohort study assessed performance of dermatologists in a mobile screening program. An unrelated cohort study, also Australian, assessed performance of primary care clinicians. Missed cancers were detected through registry and medical records linkages, but ascertainment bias is likely due to differential follow-up time periods.	These results may not apply to US settings.	Fair

(continued)

Table 3. Overall Summary of Evidence by Key Question (continued)

No. of Studies	No. of Observations	Population	Study Design	Summary of Findings, Consistency	Major Limitations	Applicability	Overall Quality
Key Question 4: Skin Cancer Screening and Early Detection[d]							
1 Study (1 article)	7586	Queensland residents aged 20-75 y; cases identified from cancer registry and controls selected through stratified random sampling from Queensland Electoral Roll	Case-control (1 study)	28.3% of controls reported receiving a clinical skin exam in the previous 3 y compared with 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. Consistency could not be assessed because only 1 study was included.	One Australian case-control study compared receipt of physician whole-body skin exam in the previous 3 y and the association of melanoma thickness (in cases) with physician skin exam. Potential for recall bias.	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 multimodal skin cancer early-detection programs.	Fair
Key Question 5: Early Detection and Morbidity and Mortality[e]							
8 Studies (8 articles)	236 485	Cases of melanoma identified through registries in Australia, Germany, and the United States	Observational cohort study (8 studies)	All studies demonstrated a consistent linear increase in risk of melanoma mortality with increasing tumor thickness or stage. Tumor thickness >4.0 mm was associated with a 3.1-32.6 increased risk of melanoma mortality compared with thinner lesions in multivariable adjusted models. Consistency among studies was high.	Three good-quality and 5 fair-quality observational studies included >200 000 people with melanoma in the United States, 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.	The association of melanoma or all-cause mortality with earlier stage or lesion thickness at detection is relevant to screening programs.	Good

Abbreviations: exam, examination; KQ, key question; NMSC, nonmelanoma skin cancer; SCREEN, Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany.

[a] KQ1: What is the direct evidence that visual screening for skin cancer by a primary care clinician or dermatologist reduces skin cancer morbidity and mortality and all-cause mortality?

[b] KQ2: What are the harms of screening for skin cancer and diagnostic follow-up?

[c] KQ3: What are the test characteristics of visual screening for skin cancer when performed by primary care clinicians vs dermatologists?

[d] KQ4: Does visual screening for skin cancer lead to earlier detection of skin cancer compared with usual care?

[e] KQ5: What is the association between earlier detection of skin cancer and skin cancer morbidity and mortality and all-cause mortality?

screening[35] and could require additional training to achieve skin cancer screening goals.

The benefits of skin cancer screening may be greatest among subgroups most likely to develop fatal melanoma. 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.[36-39] However, none have been externally validated, and they are generally based on risk in people of white race.[36-39] No evidence was identified to suggest these algorithms have been adopted in US clinical practice. If externally validated, risk assessment tools might lead to evaluating a targeted screening approach.

One of the main limitations of this report is that the majority of the eligible evidence was from international settings, especially Australia and Germany, where skin cancer screening and outcomes have been a focus of research, and the burden of melanoma is much higher compared with that in the United States or other countries.[40]

Another limitation of this review is that it focused on physician-initiated visual skin examinations. Population-based skin cancer screening does not exist in isolation, because most skin cancer screening programs are conducted along with community education and media programs. Currently, the US Community Preventive Services Task Force recommends skin cancer prevention and education interventions in child care centers, outdoor occupational and recreational settings, and primary and middle school settings, as well as multicomponent community-wide interventions for improving sun-protection behaviors.[41-45] The USPSTF recommends primary care-based counseling on UV exposure reduction for people aged 10 to 24 years with fair skin.[46] The review also excluded studies conducted outside of primary care settings, such as workplace-based screening programs or pigmented lesion clinics, because these interventions are aimed primarily at enhancing access to physician review of patient-identified lesions and likely do not represent screening populations.

The body of evidence for skin cancer screening would be improved with prospective studies of both universal and risk-based screening strategies with sufficient follow-up time (at least 12 months postexamination) to assess individual-level melanoma outcomes in screened and unscreened people. Researchers conducting skin cancer screening studies should be aware of the effect of healthy participant bias and assess comprehensive data on the skin cancer risk factors of study participants. In instances of multicomponent skin cancer reduction strategies, assessment of the relative effect of each component, including visual skin examination performed by physicians independent of media campaigns, would be beneficial. Advancement of knowledge on potential overdiagnosis and overtreatment associated with population-based skin cancer screening would help distinguish benefits of screening from potential harms.

Conclusions

Only limited evidence was identified for skin cancer screening, particularly regarding potential benefit of skin cancer screening on melanoma mortality. Future research on skin cancer screening should focus on evaluating the effectiveness of targeted screening in those considered to be at higher risk for skin cancer.

ARTICLE INFORMATION

Author Contributions: Dr Wernli had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Wernli, Henrikson, Morrison, Nguyen.
Acquisition, analysis, or interpretation of data: Wernli, Henrikson, Morrison, Nguyen, Pocobelli, Blasi.
Drafting of the manuscript: Wernli, Henrikson, Morrison, Nguyen, Pocobelli.
Critical revision of the manuscript for important intellectual content: Wernli, Henrikson, Morrison, Nguyen, Pocobelli, Blasi.
Statistical analysis: Wernli, Henrikson.
Obtained funding: Wernli.
Administrative, technical, or material support: Wernli, Morrison, Nguyen, Pocobelli, Blasi.
Study supervision: Wernli.

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