JAMA | US Preventive Services Task Force | EVIDENCE REPORT

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

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IMPORTANCE Skin cancer is the most common cancer type and is a major cause of morbidity.

OBJECTIVE To systematically review the benefits and harms of screening for skin cancer to inform the US Preventive Services Task Force.

DATA SOURCES MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from June 1, 2015, through January 7, 2022; surveillance through December 16, 2022.

STUDY SELECTION English-language studies conducted in asymptomatic populations 15 years or older.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently appraised the articles and extracted relevant data from fair- or good-quality studies; results were narratively summarized.

MAIN OUTCOMES AND MEASURES Morbidity; mortality; skin cancer stage, precursor lesions, or lesion thickness at detection; harms of screening.

RESULTS Twenty studies in 29 articles were included (N = 6 053 411). Direct evidence on screening effectiveness was from 3 nonrandomized analyses of 2 population-based skin cancer screening programs in Germany (n = 1 791 615) and suggested no melanoma mortality benefit at the population level over 4 to 10 years' follow-up. Six studies (n = 2 935 513) provided inconsistent evidence on the association between clinician skin examination and lesion thickness or stage at diagnosis. Compared with usual care, routine clinician skin examination was not associated with increased detection of skin cancer or precursor lesions (5 studies) or stage at melanoma detection (3 studies). Evidence on the association between clinician skin examination and lesion thickness at detection was inconsistent (3 studies). Nine studies (n = 1 326 051) found a consistent positive association between more advanced stage at melanoma detection and increasing risk of melanoma-associated and all-cause mortality. Two studies (n = 232) found little to no persistent cosmetic or psychosocial harms associated with screening.

CONCLUSIONS AND RELEVANCE A substantial nonrandomized evidence base suggests a clear association between earlier stage at skin cancer detection and decreased mortality risk. However, nonrandomized studies suggest little to no melanoma mortality benefit associated with skin cancer screening with visual skin examination in adolescents or adults and no association between routine clinician skin examination and earlier stage at melanoma detection. Evidence is inconsistent regarding whether clinician skin examination is associated with thinner melanoma lesions at detection.

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Skin cancer is broadly classified as cutaneous melanoma and keratinocyte carcinoma. Keratinocyte carcinomas comprise the vast majority of all incident skin cancers, with basal cell carcinoma making up about 80% of all incident cases and squamous cell carcinoma making up about 20%.[1] Approximately 1% of all skin cancers are melanoma,[2] but melanoma causes higher skin cancer mortality compared with keratinocyte carcinoma.[3] The degree to which skin cancer has spread before being detected is highly prognostic of survival.[4-6]

In 2016, the US Preventive Services Task Force (USPSTF) concluded that the current evidence was insufficient to assess the balance of benefits and harms of skin cancer screening with clinician visual skin examination in adults (I statement).[7] The purpose of the current systematic evidence review was to update the previous evidence review[8] on the benefits and harms of screening for skin cancer to inform the USPSTF in updating its recommendation.

Methods

Scope of Review

This review addressed 4 a priori–developed key questions (KQs) (**Figure 1**). Methodological details are available in the full evidence report.[10]

Data Sources and Searches

MEDLINE ALL via Ovid, Embase via Elsevier, and the Cochrane Central Register of Controlled Trials via Wiley were searched for relevant English-language articles published between June 1, 2015, and January 7, 2022 (last surveillance on December 16, 2022) (eMethods in the Supplement). Database searches were supplemented by expert suggestions and by scanning reference lists of other relevant systematic reviews.[8] Ongoing surveillance was conducted through article alerts and targeted searches of high–impact-factor journals identified by the USPSTF.[9]

Study Selection

Titles, abstracts, and full-text articles were reviewed by investigators against prespecified eligibility criteria (eTable 1 in the Supplement). Discrepancies were resolved by consensus.

For the effect of screening on health outcomes (KQ1), association between screening and stage at detection (KQ2), and harms of screening (KQ3), the population of interest was asymptomatic individuals 15 years or older who were not under surveillance for skin cancer. Eligible screening was any visual skin examination conducted by a clinician with or without tools to aid examination (eg, dermatoscopy). Studies of patient skin self-examination were excluded because this topic is covered in the 2018 USPSTF evidence review on behavioral counseling for skin cancer prevention.[11] For the association between stage at detection and health outcomes (KQ4), the population of interest was individuals 15 years or older diagnosed with skin cancer. For all KQs, eligible settings were countries categorized as "very high" on the 2019 Human Development Index.[12]

Eligible study designs were randomized clinical trials (RCTs), controlled clinical trials, and nonrandomized studies with a contemporaneous control. For KQ3 only, cohort studies and systematically selected case series were eligible. Outcomes of interest were morbidity and mortality associated with skin cancer, including quality of life, all-cause mortality (KQ1 and KQ4), stage or lesion thickness at detection of skin cancer or precancerous lesion (KQ2), and any harm of skin cancer screening, biopsy, or excision persisting beyond 30 days (KQ3).

The USPSTF's health outcomes of interest were population mortality from skin cancer or all-cause mortality. Measures of relative cancer survival (for example, the proportion of individuals who survive for a given length of time after diagnosis) are commonly used and are clinically important. However, population mortality measures can be less subject to lead time bias and presence of overdiagnosis than relative survival when evaluating early detection programs.[13] Lead time bias is when early detection increases the time that a cancer diagnosis is known, spuriously making survival appear longer. Overdiagnosis is the detection of a cancer through screening that would not otherwise have been diagnosed in a person's lifetime. Overdiagnosis can result in overtreatment that may not benefit the patient.[14]

Data Extraction and Quality Assessment

The quality of each study was independently assessed as "good," "fair," or "poor" by 2 reviewers using USPSTF design-specific quality criteria[9] (eTable 2 in the Supplement). Discordant quality ratings were resolved by consensus. Poor-quality studies were excluded.

One investigator extracted data from each included study into standardized evidence tables; a second investigator confirmed accuracy and completeness.

Data Synthesis and Analysis

For each KQ, data were summarized narratively using tables that included details on study design and quality, setting, population, screening program details, outcomes, and harms. When available, results for specific populations (eg, by age, sex, race, and ethnicity) were reported separately. Heterogeneity in outcomes precluded meta-analysis.

The body of evidence for each KQ was summarized in a standardized summary-of-evidence table. The overall strength of evidence for each KQ was assessed based on consistency, precision, reporting bias, and study quality, using the approach described in the *Methods Guide for the Effectiveness and Comparative Effectiveness Reviews*.[15]

Results

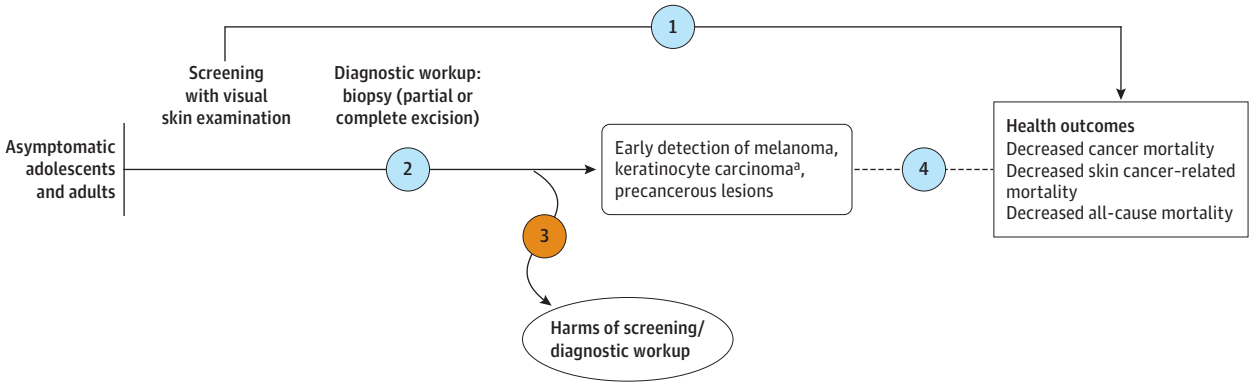
Twenty studies (29 articles) were included, comprising 3 studies from the previous review[16] and 17 new studies, after evaluation of 20 320 abstracts and 522 full-text articles (**Figure 2**). Three studies (10 articles)[17-26] were included for KQ1; 6 studies (7 articles)[27-33] for KQ2; 2 studies (3 articles)[34-36] for KQ3; and 9 studies (9 articles)[37-45] for KQ4 (**Table 1**). Additional details on results and contextual issues are available in the full evidence report.[10]

Benefits of Screening

Key Question 1. What is the effectiveness of routine skin cancer screening with visual skin examination by clinicians in reducing skin cancer morbidity and mortality or all-cause mortality?

No included studies reported all-cause mortality, squamous cell carcinoma mortality, basal cell carcinoma mortality, or skin cancer

Figure 1. Analytic Framework and Key Questions: Skin Cancer Screening



Key questions

1 What is the effectiveness of routine skin cancer screening with visual skin examination by clinicians in reducing skin cancer morbidity and mortality or all-cause mortality?
a. Does the effectiveness of screening vary by subgroup (eg, age, sex, skin type, race and ethnicity, socioeconomic status, or UV exposure)?

2 Does routine skin cancer screening lead to higher rates of detection of precancerous lesions or earlier stage skin cancer compared with usual care (eg, lesion-directed skin examination)?
a. Do rates of earlier skin cancer detection vary by subgroup (eg, age, sex, skin type, race and ethnicity, socioeconomic status, or UV exposure)?

3 What are the harms of skin cancer screening and diagnostic follow-up?
a. Do the harms of screening vary by subgroup (eg, age, sex, skin type, race and ethnicity, socioeconomic status, or UV exposure)?

4 What is the association between detection of precancerous lesions or earlier stage skin cancer and morbidity and mortality due to skin cancer or all-cause mortality?
a. Does this association vary by subgroup (eg, age, sex, skin type, race and ethnicity, socioeconomic status, or UV exposure)?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions (KQs) 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 a relationship between an intermediate outcome and a health outcome that is presumed to describe the natural progression of the disease. Refer to the USPSTF Procedure Manual for interpretation of the analytic framework.[9]

[a] Previously referred to as nonmelanoma skin cancer; includes basal cell carcinoma and squamous cell carcinoma.

morbidity. Three nonrandomized studies of interventions reporting melanoma mortality related to 2 population-based screening programs in Germany[17,19,22,23] met inclusion criteria.

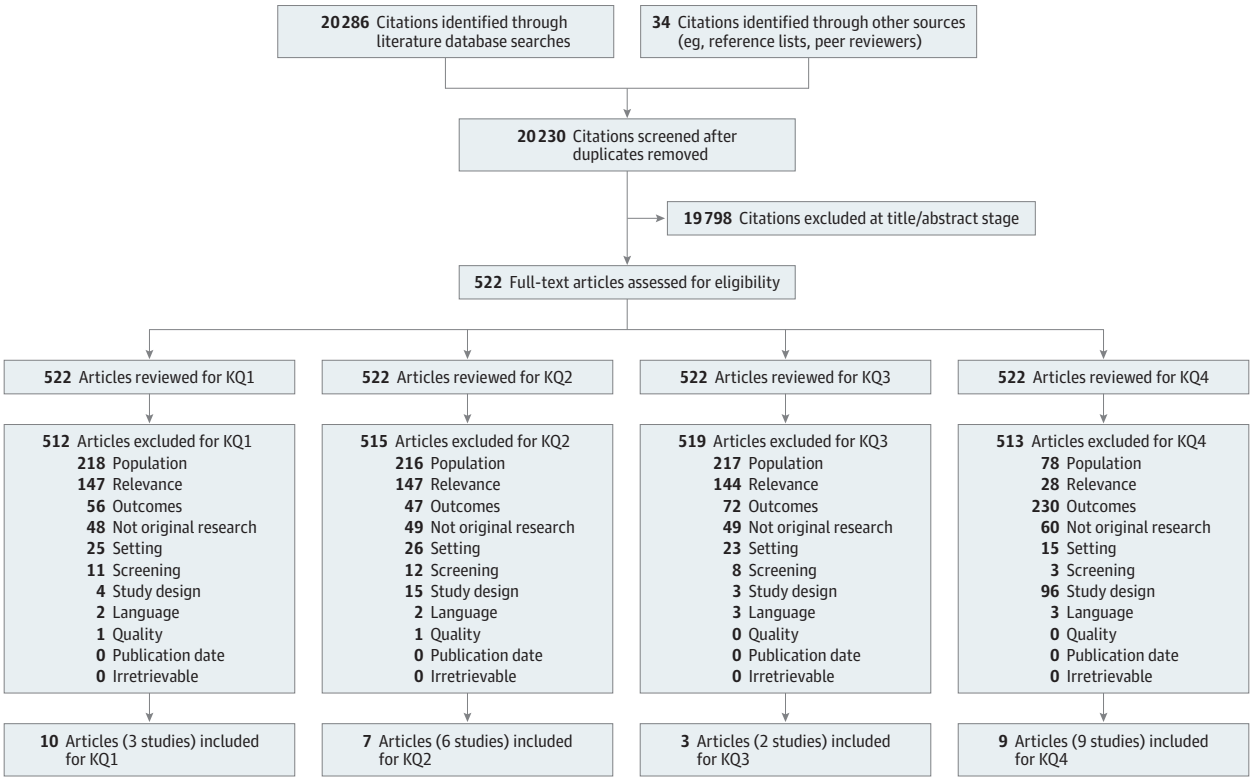
The first screening program was the Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany (SCREEN) skin cancer screening pilot, conducted in the Schleswig-Holstein state in northern Germany between 2003-2004.[23] During the 12-month pilot, 360 288 people received clinician visual skin examination. The screened population had a mean age of 49.7 years, and 73.6% were women. Nearly half of participants had at least 1 risk factor for melanoma.[18] Data on other specific population subgroups (eg, patient characteristics such as skin type or race, ethnicity, or both) were not reported.

In a nonrandomized ecologic analysis with 10-year follow-up of the SCREEN program, age-adjusted population melanoma mortality in the SCREEN region compared with the remaining German population suggested no mortality benefit associated with routine skin cancer screening.[23] As reported in the previous evidence review,[16] 5-year follow-up data from the SCREEN pilot study[24] suggested a 49% lower mortality in the screening region compared with the surrounding regions at 5 years' follow-up (2003-2004 program; evaluation through 2009). However, 10-year follow-up data indicated that the previously reported mortality benefit appeared to attenuate over time (**Figure 3**). The SCREEN region's age-standardized melanoma mortality rate fluctuated but overall was similar to Germany's fairly stable melanoma mortality rate between 1998 and 2010 (between 1.9 and 2.1 per 100 000).[23]

Following the SCREEN pilot,[24] Germany implemented nationwide routine skin cancer screening by primary care clinicians or dermatologists for all statutory health insurance enrollees 35 years or older. The implementation was not designed as an evaluation study and thus did not include a comparison group.[46]

Two nonrandomized studies reported melanoma mortality data related to the German national skin cancer screening program.[17,19,23] The first study, which was the only one to include analyses of individual-level data, included enrollees in a health insurance plan that administers German national statutory health insurance.[19] The sample, who were enrollees 35 years or older between 2010-2016 (n = 1 431 327), had a mean age of 63.9 years and 55.7% were female; race, ethnicity, and skin type were not reported. The study

Figure 2. Literature Search Flow Diagram: Skin Cancer Screening



All eligible full-text articles could be reviewed for more than 1 key question (KQ). Reasons for exclusion: Population: Study not conducted in an included population. Relevance: Study not relevant to screening for skin cancer. Outcomes: Study did not have relevant outcomes or had incomplete outcomes. Not original research: Study not original research. Setting: Study not conducted in a country relevant to US practice (those categorized as "very high" on the 2019 United Nations Human Development Index).[12] Screening: Study used an ineligible screening modality. Study design: Study did not use an included design. Language: Publication not in English. Quality: Study was poor quality. Publication date: Primary results published prior to included date range. Irretrievable: Publication not available or accessible.

team analyzed data from persons with incident melanoma diagnosed during 2013-2016 with no history of melanoma in the previous 3 years (n = 2475). People with documented skin cancer screening as identified through billing codes in the 2 years before diagnosis were considered to have received screening. The observation period was 4 years.

Of 325 melanoma deaths, a higher proportion was observed in the unscreened group compared with the screened group (154 deaths, 22.8% of the unscreened group; 171 deaths, 9.5% of the screened group; unadjusted hazard ratio [HR], 0.37 [95% CI, 0.30-0.46]; $P < .05$) (**Table 2**).[19] On adjustment for age, sex, comorbidity, health-seeking behavior (estimated by receipt of flu vaccine), personal history of melanoma, and stage categories (estimated by documented melanoma metastasis or receipt of systemic anticancer therapy), the association was attenuated but remained statistically significant (adjusted HR, 0.62 [95% CI, 0.48-0.80]; $P < .05$). Sensitivity analyses to assess lead time bias similarly attenuated both unadjusted (HR, 0.50 [95% CI not reported]; $P < .05$) and adjusted estimates (adjusted HR, 0.75 [95% CI not reported]; not significant).

The second study was a nonrandomized ecologic analysis of melanoma mortality rates in Germany and surrounding countries during the first 5 years of the German national screening program, which screened approximately 3 million individuals.[17,22] This study compared melanoma mortality rates before and after the implementation of the screening program in Germany and 22 other European countries without screening programs. The unadjusted mean annual melanoma mortality rate per 100 000 paradoxically increased between the baseline period (2000-2007; before the German screening program began in 2008) and the follow-up period (2008-2012) in both Germany and the other European countries (point estimates not reported).[22]

Three publications from the 2 German screening programs reported age- and sex-specific melanoma mortality.[17,22,23] Across these analyses, there was no evidence of a population-level melanoma mortality benefit to screening in age- or sex-specific population groups.

Association Between Screening and Stage at Detection

Key Question 2. Does routine skin cancer screening lead to higher rates of detection of precancerous lesions or earlier stage skin cancer compared to usual care (for example, lesion-directed skin examination)?

Six nonrandomized studies with data on approximately 2.9 million individuals evaluated visual skin examinations conducted by primary care physicians or dermatologists and compared outcomes

Table 1. Characteristics of Included Studies

Characteristic	No. of studies			No. of people analyzed[c]
	Reporting benefits or harms of skin cancer screening with visual skin examination (KQ1, KQ2, KQ3)[a]	Reporting association between stage at detection and skin cancer mortality (KQ4)[b]	Total	
KQ				
1: Effectiveness of screening on health outcomes	3	0	3	1 791 615[d]
2: Effectiveness on screening on stage/thickness at detection	6	0	6	2 935 513
3: Harms of screening	2	0	2	232
4: Association between stage/thickness at detection and health outcomes	0	9	9	1 326 051
Study design				
Randomized	0	0	0	0
Nonrandomized	11	9	20	6 053 411
Controlled, experimental[e]	0	0	0	0
Controlled, nonexperimental	11	9	20	6 053 411
Case-control	1	0	1	7586
Cohort	8	9	17	5 685 537
Ecologic	2	0	2	360 288
New studies since 2016 systematic review	8	9	17	5 685 492
Rated as good quality	2	3	5	2 249 411
Country				
US	2	6	8	1 865 198
Germany	6	0	6	3 814 127
Other European countries[f]	2	2	4	337 521
Australia	1	1	2	36 565
Population characteristics reported				
Age	10	9	19	6 053 224
Sex	11	9	20	6 053 411
Race and/or ethnicity	3	6	9[g]	1 872 784
Skin type	2	0	2[h]	9568
History of previous skin cancer screening	3	0	3	9755
Family history of skin cancer	4	0	4	370 043
Previous skin cancer	5	2	7	1 927 654
Other skin cancer risk factors[i]	3	1	4	370 357
Skin cancer screening context				
National/regional screening program	5	0	5	3 814 082
Time-limited screening event	2	0	2	309 661
Physician-focused decision support	2	0	2	595 986
Clinical practice/usual care	2	0	2	7631
Skin cancers of interest				
Melanoma only	3	9	12	3 360 763
Keratinocyte carcinoma only	0	0	0	0
Both melanoma and keratinocyte carcinoma	7	0	7	2 692 603
Other	1[j]	0	1[j]	45
Outcomes reported for specific population groups				
Age	5	4	9	1 901 829
Sex	4	2	6	811 043
Race and ethnicity	0	3	3	708 814

Abbreviation: KQ, key question.

[a] Among asymptomatic adolescents and adults 15 years or older not already under surveillance for skin cancer.

[b] Among adolescents and adults 15 or older diagnosed with skin cancer. All studies included for KQ4 focused on melanoma; no included studies contributed data for keratinocyte cancer mortality.

[c] N refers to sum of each individual study population and does not account for overlapping populations (from Surveillance, Epidemiology, and End Results data, for example) for KQ4 studies.

[d] N = not reported in 1 study; n = 1 791 615 in the other 2 studies.

[e] Controlled clinical trials or nonrandomized clinical trials.

[f] Includes Belgium, Italy, Norway, and Sweden.

[g] Eight of 9 studies reporting race, ethnicity, or both were based in the US; 1 was based in Australia.

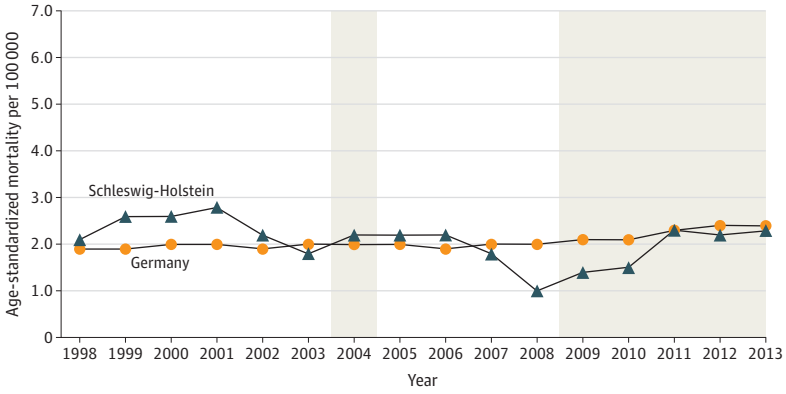
[h] The 2 studies reporting skin type were based in Belgium and Australia.

[i] Includes actinic keratosis; nevi; social risk factors.

[j] 1 study focused exclusively on macular melanocytic nevi.

between groups receiving routine skin cancer screening or usual care.[27-31,33] One of the 6 studies was conducted in the US[32]; the remainder took place in Europe and Australia. Study populations ranged from 497 to 34 295 persons with skin cancer or precursor lesions. Outcomes assessed included precursor lesion detection (2 studies),[28,30] stage at melanoma detection (3 studies),[31-33] and stage at keratinocyte carcinoma detection (1 study).[31] Three studies reported thickness at melanoma detection,[27,28,32] and 1 study

Figure 3. Ecologic Trends in Melanoma Mortality, Overall Population, Schleswig-Holstein vs Germany, 1998-2013[23]



Based on data from ecologic analysis by Katalinic et al, 2015.[23] SCREEN indicates Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany. Shaded regions indicate periods of active screening for the Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany (SCREEN) program (July 2003-June 2004) and the German national screening program (July 2008 onward).

reported the odds of having received a clinical skin examination in people with and without skin cancer.[27]

Outcome measures included American Joint Committee on Cancer stages I through IV; summary stages (local, regional, advanced); melanoma in situ; and melanoma thickness. Studies varied regarding whether they included melanoma in situ and in how they defined categories of melanoma thickness. Skin cancer examination programs were heterogeneous in both intervention and comparison group selection. Two publications used data from the German national skin cancer screening program and compared people with and without documented skin cancer screening.[31,33] Two time-limited regional skin cancer screening events also were included. One compared participants in a community-based screening program conducted in Trento, Italy, in 2001-2004 with the general population of the same city through 2013.[28] The other compared 2 Belgian communities conducting single 4- to 5-day skin cancer screening events: one where people were invited to receive whole-body examination and one where people were invited to have suspicious skin lesions examined.[30] The single US-based study was a physician-focused decision support intervention and did not include direct outreach to patients.[32] Last, a case-control study conducted in Australia identified cases among people with incident melanoma (n = 3762) and matched controls (n = 3824) and assessed self-reported whole-body physician skin examination during the previous 3 years.[27]

Screening populations were broadly defined as adult populations and were majority female. Only the US-based study reported race, ethnicity, or both for the screened group (88.4% White).[32] Only the Belgian study reported skin cancer risk factors, which included distributions of Fitzpatrick skin phenotype, nevus count, and family and personal skin cancer history.[30]

In total, 53 329 skin cancer or precursor lesions were detected (n = 11 182 melanomas, 41 686 keratinocyte carcinomas, and 461 precursor lesions). Demographic characteristics of those with detected lesions were reported in 3 studies[28,32,33]; 2 reported age and sex distribution,[28,33] and 1 noted that 99.2% of melanomas were diagnosed in non-Hispanic White patients.[32] Skin cancer risk factors were not reported.

Stage at Melanoma Detection

Findings were inconsistent across the 3 included studies reporting data on stage at melanoma detection. Neither of the 2 German studies reporting stage at invasive melanoma detection[31,33] (ie, excluding melanoma in situ) found an association between skin cancer screening and stage at melanoma detection.

In 2 studies reporting in situ melanoma at detection, findings were inconsistent. In the German study using American Joint Committee on Cancer stage categories (n = 1536 melanoma cases), there was no association between screening and detection of in situ melanoma,[31] while in the US-based study (n = 994 melanoma cases), in situ melanoma made up a larger proportion of cases in the screened group compared with the unscreened group (48.3% of all melanomas detected at in situ stage in screened group vs 34.6% in unscreened group; adjusted HR, 2.6 [95% CI, 2.1-3.1]; $P < .001$).[32]

Thickness at Melanoma Detection

Findings were inconsistent between 3 studies reporting data on melanoma thickness at detection.[27,28,32] In the US-based study, there was a higher adjusted HR in the screened group of detection at thickness 1 mm or less (adjusted HR, 1.8 [95% CI, 1.5-2.2]; $P < .001$), but not for the greater than 1 mm category (adjusted HR, 1.0 [95% CI, 0.7-1.3]; $P = .75$).[32] In the Italian study, the proportion of melanomas detected at less than 1 mm thickness was similar between groups (70.4% in the screened group and 57.7% in the usual care group, $P = .24$) but was higher for screen-detected melanomas detected at thickness less than 2 mm (92.6% of in the screened group and 75.9% of melanomas in the usual care group, $P = .043$).[28]

In the Australian case-control study the odds of having had a clinical skin examination by a physician decreased as thickness increased, from 7% decreased odds for lesions 0.76 to 1.49 mm (95% CI, 0.79-1.10) to 40% decreased odds for lesions 3.0 mm or greater (95% CI, 0.43-0.83).[27]

Keratinocyte Carcinoma Stage at Detection

One study using data from the German national skin cancer screening program reported stage at keratinocyte carcinoma detection

Table 2. Melanoma Mortality for First-Onset Melanoma 2013-2016 Among Screened Enrollees in AOK Plus Health Insurer in Saxony, Germany (KQ1)[a]

	Total No.	No. (%)		ARR in melanoma mortality for screening participants (95% CI)	Unadjusted HR (95% CI)[b,c]		Adjusted HR (95% CI)[b,c]	
		Screened	Unscreened		Melanoma mortality	Lead time bias correction	Melanoma mortality	Lead time bias correction
AOK Plus population	1 431 327	688 708 (48.1)	742 619 (51.9)	13.3% (NR)	0.37 (0.30-0.46)[e]	0.50 (NR)[e]	0.62 (0.48-0.80)[e]	0.75 (NR)
Incident melanoma[d]	2475	1801 (72.8)	674 (27.2)					
Melanoma deaths	325	171 (9.5)	154 (22.8)					

Abbreviations: ARR, absolute risk reduction; HR, hazard ratio; KQ, key question; NR, not reported.

[a] Data are from Datzmann et al, 2022.[19]

[b] Hazard ratios for dying within the observation period; screening participation within 2 years before diagnosis vs no screening participation.

[c] Adjusted for age group (3 age categories, not reported); sex; year of diagnosis; education; systemic anticancer therapy; history of nonmelanoma skin cancer; influenza vaccination in the year before the initial melanoma diagnosis; colorectal, prostate, and breast cancer screening within 3 years prior to diagnosis; health checkup (from age 35 years onward) within the 2 years prior to diagnosis; 22 Elixhauser comorbidities; stroke, ischemic heart disease and heart failure in last 3 months; 5 strata for type or timing of metastasis.

[d] First onset, 2013-2016.

[e] $P < .05$.

(n = 10 844 keratinocyte carcinoma cases).[31] This study found similar distributions of keratinocyte carcinoma stage in each group; 99.9% of keratinocyte carcinoma cases were detected at stage I/II in the screened group compared with 99.8% in the unscreened group.

Precursor Lesion Detection

In the Belgian study, rates of actinic keratoses and atypical nevi were similar in both groups: actinic keratoses was detected in 7.9% of the total body examination group and 7.8% of the lesion-directed examination group ($P = .90$). Atypical nevi were detected in 15.1% of the total body examination group and 17.3% of the lesion-directed group ($P = .33$).[30]

Harms of Skin Cancer Screening

Key Question 3. What are the harms of skin cancer screening and diagnostic follow-up?

The review identified 2 small fair-quality nonrandomized studies that addressed the harms of skin cancer screening. One was conducted in Germany (n = 45)[34] and assessed cosmetic acceptance of shave biopsy in a screened population at a 6-month follow-up; lesions suspected of melanoma were excluded. The other was conducted in the US (n = 187)[35,36] and assessed psychological well-being at 5 and 8 months after screening.

In the German study, 27 patients rated 7% (4/56) of shave sites as having poor cosmetic outcomes at 6-month follow-up (median score, 1.5 [interquartile range, 1-2]; excellent to good).[34] In the US-based study of adults who underwent skin cancer screening by trained primary care clinicians (n = 187), participants scored within the normal range on measures of anxiety and depression at 5- and 8-month follow-up assessments.[35,36]

Association Between Stage at Detection and Health Outcomes

Key Question 4. What is the association between detection of precancerous lesions or earlier stage skin cancer and morbidity and mortality due to skin cancer or all-cause mortality?

Nine fair- or good-quality nonrandomized studies with data collected between 1975 and 2016 (n = 1 326 051) reported on the association between stage at diagnosis and mortality.[37-41,43-45] All 9 studies were newly identified since the prior recommendation, and the 6 US-based studies had overlapping populations. Seven studies (n = 1 037 610) reported the association between stage at diagnosis and melanoma mortality,[37,38,40-44] and 3 studies[39,44,45] (n = 473 660) reported the association between the stage at diagnosis and all-cause mortality. No included studies evaluated the association between stage at diagnosis and skin cancer morbidity or keratinocyte carcinoma mortality.

Studies used large databases with patient information from the US (SEER [Surveillance, Epidemiology, and End Results] program, National Cancer Database), Australia (Queensland Cancer Registry), Norway (data from the Norwegian Malignant Melanoma Registry matched with data from other sources), and Sweden (Swedish Cancer Registry). The 6 US-based studies used data collected between 1975 and 2016 (median data collection period, 22 years [range, 11-41 years]). Other studies used data collected between 2003-2005 in Sweden,[45] 2008-2012 in Norway,[43] and 1995-2008 in Australia.[40]

The weighted average age across all included studies was 59.0 years, and 45.4% of all participants were female. All 6 US-based studies provided information on participants' race, ethnicity, or both.[37-39,41,42,44] Most participants in these studies (96.0%) were White; 0.2% were American Indian or Alaska Native, 0.8% were Asian American or Pacific Islander, 0.7% were Black, and 3.0% were of Hispanic ethnicity. Participants' personal, family, or environmental risk factors for skin cancer were rarely reported.

More advanced stage at detection was consistently and positively associated with increased risk of mortality in 3 studies (n = 407 133) reporting melanoma-specific mortality and 3 studies (n = 473 660) reporting all-cause mortality. For example, in 1 US-based study (n = 185 219), adjusted HRs for melanoma mortality were 5.8 (95% CI, 5.3-6.3) for localized, 31.5 (95% CI, 28.9-34.2) for regional, and 169.6 (95% CI, 154.2-186.6) for distant-stage disease compared with in situ disease at detection, and the risk for all-cause mortality was adjusted HR 1.5 (95% CI, 1.5-1.5) for localized, 3.9 (95% CI, 3.8-4.1) for regional, and 15.8 (95% CI, 14.9-16.7) for distant disease, compared with in situ melanoma at detection.[44]

In 2 studies (n = 135 490), melanoma mortality risk was higher for males than for females.[38,40] Three studies (n = 708 814) found a higher melanoma mortality risk among Asian American, Black, Hispanic, Native American, or Pacific Islander adults compared with White adults.[37,41,42]

No included studies addressed keratinocyte carcinoma mortality by stage at detection or evaluated the association between stage at detection and skin cancer morbidity.

Discussion

This systematic review was conducted to support the USPSTF in updating its 2016 recommendation on skin cancer screening. Overall, the findings align with the results of the 2016 systematic review, adding data from 17 new studies. **Table 3** shows a summary of the evidence for each KQ.

All direct evidence on the benefits of screening comes from nonrandomized analyses of population-based skin cancer screening programs in Germany.[17,19,22,23] Since the previous recommendation,[7] longer follow-up data for mortality has been published for the SCREEN skin cancer screening pilot, as well as new data evaluating Germany's national skin cancer screening program. Together, these data suggested little to no melanoma mortality benefit associated with routine skin cancer screening. Individual-level data available in 1 nonrandomized study suggested a potential mortality benefit associated with skin cancer screening in the German program that was attenuated on multivariable analyses and analyses of potential lead time bias.[19] Limited data on melanoma mortality rates in specific population groups were available.

The body of evidence offers at best inconsistent evidence regarding a benefit of visual skin examination in stage or lesion thickness at detection. However, these findings should not be interpreted as evidence of no benefit and also should be interpreted in light of the potential for overdiagnosis in skin cancer, particularly for detection of in situ melanoma and melanoma less than 1 mm in thickness.[47] The overall strength of evidence is high for the association between stage at detection and both melanoma-specific and all-cause mortality. The current review, which focused on measures of population mortality, is consistent with the substantial body of literature establishing stage at melanoma diagnosis as a primary prognostic indicator of melanoma survival[48,49] and adds limited information on specific population groups.

Little evidence was available about the benefits of skin cancer screening for keratinocyte carcinomas of the skin, which are prevalent and can result in morbidity and mortality. Four included studies suggest no association between routine clinician skin examination and stage at keratinocyte carcinoma detection, but the overall strength of evidence is low. There was no evidence about the association between stage at keratinocyte carcinoma detection and skin cancer or all-cause mortality.

Given the small number of studies conducted among screened populations, the included body of evidence is insufficient to fully assess psychosocial or cosmetic harms of skin cancer screening. Based on included evidence from 2 very small studies,[34,36] one examining cosmetic harms and the other examining psychosocial harms from screening, there is little to no evidence of persistent harms associated with screening. These findings are consistent with those from studies conducted in unscreened populations, suggesting minimal persistent patient-reported harms up to 6 months after skin cancer surgery.[50-52] This review found no studies directly examining skin cancer overdiagnosis—or its potential consequence, overtreatment—although both remain potential harms of skin cancer screening.

Limitations

The lack of individual-level or trial data on the effectiveness of skin cancer screening is a primary limitation of the literature. Because no national organizations recommend routine skin cancer screening by clinicians, and because large trials of skin cancer screening may not be feasible, the evidence identified in this review represents the best evidence currently available. Little data on specific population groups were available; this may represent a missed opportunity to provide evidence about risk-based skin cancer screening approaches. There was very limited evidence about the effectiveness and harms of screening for keratinocyte cancers. Studies of the association between clinician skin examination and stage at skin cancer detection were heterogeneous in that they were conducted in varying settings and used a variety of skin examination procedures and comparison groups. This heterogeneity limited interpretation across studies.

In the absence of randomized studies, the body of evidence from nonrandomized studies would be strengthened by data on benefits and harms of risk-based screening in specific population subgroups based on known risk factors such as age, sex, skin type, or UV exposure or in groups stratified using validated risk assessment tools; data on screening benefits and harms for specific melanoma subtypes; and by individual-level analyses of mortality outcomes in persons with screen-detected melanoma compared with those with melanoma detected through usual care or lesion-directed examination. Evidence on potential overdiagnosis and subsequent overtreatment of early-stage skin cancer also would be beneficial. Applicability to US settings is difficult to assess, particularly with respect to specific population groups (eg, race or ethnicity) and health system differences.

Table 3. Summary of Evidence by Key Question

No. of studies	Summary of findings	Consistency and precision	Overall strength of evidence	Body of evidence limitations	Applicability
KQ1: Benefits of skin cancer screening					
Melanoma: 3 nonrandomized studies (n = NR in 1 study; n = 1 791 615 in 2 studies)	Melanoma mortality: Based on nonrandomized and ecologic evidence, limited to no mortality benefit to population-based skin cancer screening programs at 4- to 10-y follow-up compared with no screening All-cause mortality: NA (no studies)	Melanoma mortality: consistent, imprecise	Low for limited to no mortality benefit	No randomized study designs Ecologic design limits individual-level analyses Little information about clinical, socioeconomic, or behavioral risk factors Potential lead time and healthy screenee bias	European population with universal health insurance and subsidized clinician skin examination No US data
Keratinocyte carcinoma: no studies	NA	NA	Insufficient		
KQ2: Association between skin cancer screening and stage or lesion thickness at detection					
Melanoma: 6 nonrandomized studies (n = 2 947 595)	Routine clinician skin examination not associated with earlier stage at detection of invasive melanoma compared with usual care (2 studies) Inconsistent evidence whether clinician skin examination is associated with increased detection of in situ melanoma compared with usual care (2 studies) or melanoma at either <1 mm or <2 mm thickness compared with usual care (3 studies)	Reasonably consistent, imprecise	Moderate for no association between screening and stage at invasive melanoma detection Low for inconsistent evidence for association between screening and thinner lesions at detection or detection of in situ melanoma	Lack of information on clinical, biological, or socioeconomic risk factors in included populations Heterogeneous comparison groups and screening interventions Potential for selection bias in screening program participation (both patients and clinicians) Limited data on specific population groups	Five of 6 included studies conducted outside of US The single US study was applicable to US primary care insured populations receiving care in large academic medical centers Populations predominantly White race or European ancestry
Keratinocyte carcinoma: 4 nonrandomized studies (n = 2 332 128)	Routine clinician skin examination not associated with either increased detection or stage at detection of keratinocyte carcinoma (4 studies)	Reasonably consistent, imprecise	Low for no association between routine clinician skin examination and either keratinocyte carcinoma detection or stage at keratinocyte carcinoma detection		
Skin cancer precursor lesions: 2 nonrandomized studies (n = 309 661)	Routine clinician skin examination not associated with increased detection of skin cancer precursor lesions (actinic keratosis or dysplastic nevi) compared with usual care (2 studies)	Reasonably consistent, imprecise	Low for no association between routine clinician skin examination and precursor lesion detection		
KQ3: Harms of skin cancer screening					
Cosmetic harms: 1 nonrandomized study (n = 45)	27 Patients rated 7% (4/56) of shave biopsy sites as having poor cosmetic outcomes at 6-mo follow-up	Reasonably consistent, imprecise	Insufficient for minimal persistent harms of screening	Small body of evidence for screened populations Heterogeneous outcomes	People receiving routine screening in US and Germany
Psychological harms: 1 nonrandomized study (n = 187)	Adults who underwent skin cancer screening scored within the normal range on measures of anxiety and depression and reported none to minimal psychological harms of screening at 5- and 8-mo follow-up assessment	Reasonably consistent, imprecise			

(continued)

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

No. of studies	Summary of findings	Consistency and precision	Overall strength of evidence	Body of evidence limitations	Applicability
KQ4: Association between stage at detection and health outcomes					
Melanoma: 9 nonrandomized studies (n = 1 326 051[a])	Melanoma mortality: Progression of melanoma stage at detection is positively associated with increasing risk of melanoma mortality Compared with in situ melanoma at detection, adjusted HRs for melanoma mortality were 5.8 (95% CI, 5.3-6.3) for localized, 31.5 (95% CI, 28.9-34.2) for regional, and 169.6 (95% CI, 154.2-186.6) for distant-stage disease in 1 US study (n = 185 219) Melanoma mortality risk higher among American Indian or Alaska Native, Asian or Pacific Islander, Black, and Hispanic adults with AJCC stage I melanoma and SEER localized stages compared with White adults at the same stages All-cause mortality: Progression of melanoma stage, for both SEER summary stage and AJCC stages, at detection positively associated with increasing risk of all-cause mortality	Melanoma mortality: Reasonably consistent, reasonably precise All-cause mortality: Reasonably consistent, reasonably precise	High for association between stage at detection and melanoma and all-cause mortality	Generally well-conducted nonrandomized studies of large cancer registry data Heterogeneous risk measures and choice of referent groups Primary quality concerns are incompleteness and potential inaccuracy of retrospectively collected data	Populations of the US, Australia, Sweden, and Norway with melanoma diagnosis
Keratinocyte carcinoma: no studies	NA	NA	NA		

Abbreviations: AJCC, American Joint Committee on Cancer; HR, Hazard ratio; KQ, Key Question; NA, not applicable; NR, not reported; RR, relative risk; SEER, Surveillance, Epidemiology, and End Results Program.

[a] N refers to sum of each individual study population and does not account for overlapping populations (from SEER data, for example).

Conclusions

A substantial nonrandomized evidence base suggests a clear association between earlier stage at skin cancer detection and decreased mortality risk. However, nonrandomized studies suggest little to no melanoma mortality benefit associated with skin cancer screening with visual skin examination in adolescents or adults and no association between routine clinician skin examination and earlier stage at melanoma detection. Evidence is inconsistent regarding whether clinician skin examination is associated with thinner melanoma lesions at detection.

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Author Contributions: Dr Henrikson 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.
Concept and design: Henrikson, Ivlev, Blasi, Nguyen, Lin.
Acquisition, analysis, or interpretation of data: Henrikson, Ivlev, Blasi, Nguyen, Senger, Perdue.
Drafting of the manuscript: Henrikson, Ivlev, Blasi, Nguyen.
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