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Screening for Skin Cancer: An Evidence Update for the U.S. Preventive Services Task Force

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Structured Abstract

Objective: We conducted this review to support the United States Preventive Services Task Force (USPSTF) in updating its 2016 recommendation on screening for skin cancer. The objective was to review benefits and harms of routine skin cancer screening in asymptomatic screening populations aged ≥15 years.

Data Sources: We searched MEDLINE ALL via Ovid, Embase via Elsevier, and the Cochrane Central Register of Controlled Trials via Wiley. We updated the search used in the 2016 systematic review on January 12, 2021, and we ran a bridge search on January 7, 2022. A research librarian developed and executed the search strategy. Studies included in the prior review to support the 2016 recommendation and studies referenced in recently published reviews were also considered for inclusion.

Study Selection: We reviewed 20,320 abstracts and 522 full-text articles against prespecified inclusion criteria. Eligible studies were English-language randomized controlled trials (RCTs), controlled clinical trials, nonrandomized studies with contemporaneous controls reporting morbidity or mortality associated with skin cancer, or all-cause mortality, stage or lesion thickness at detection of skin cancer or precancerous lesions, and harms of skin cancer screening. At least two investigators independently critically appraised all studies. Data were extracted by one investigator and checked for accuracy by a second.

Data Analysis: We extracted relevant study details and outcomes from fair- or good-quality studies. We provided narrative synthesis of results and used summary tables to facilitate comparisons across studies. The overall strength of evidence was graded as high, moderate, low, or insufficient based on criteria adapted from the Evidence-based Practice Center (EPC) Program.

Results: We included three studies (10 articles, n=NR in one study; 1,791,615 in the other two) on the direct benefits of skin cancer screening and two studies (3 articles, n=232) on persistent harms of skin cancer screening. We included six studies (7 articles, n=2,947,595) on the association between routine clinician skin examination and stage or lesion thickness at skin cancer detection. We included nine studies (9 articles, n=1,326,051) on the association between stage at skin cancer detection and melanoma or all-cause mortality. Seventeen studies were newly identified in this update.

Direct evidence on effectiveness of skin cancer screening. Three non-randomized studies (one good-quality; two fair-quality) evaluated the association between melanoma mortality and skin cancer screening over 4 to 10 years followup. At 10-years of followup of the Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany (SCREEN) study, population melanoma mortality rates in the SCREEN region compared to the rest of Germany suggest no mortality benefit to routine skin cancer screening. Similarly, at 5-year followup of the German National Screening Program, no mortality benefit was observed based on national population statistics. One non-randomized study of melanoma mortality in individuals with documented skin cancer screening provided through German statutory health insurance found an absolute decrease in mortality suggesting a screening benefit at four-year

followup, but this difference was attenuated on multivariate analysis and adjustment for lead time bias. No included studies reported all-cause mortality, skin squamous cell carcinoma mortality, basal cell carcinoma mortality, or skin cancer morbidity.

Harms. Evidence on the persistent psychosocial or cosmetic harms of screening was minimal. In a fair-quality study conducted in Germany (n=45), 27 patients rated 7 percent (4 out of 56) of shave biopsy sites having poor cosmetic outcomes at 6-month followup. A fair-quality United States study (n=187) that assessed psychological wellbeing at 5 and 8 months after skin cancer examination by trained primary care providers found that participants scored within the normal range on measures of anxiety and depression, with none to minimal psychological impacts of screening. Overdiagnosis and subsequent overtreatment of early-stage melanoma is a potential harm of skin cancer screening based on population incidence rates, but no direct evidence was available.

Indirect evidence: association between routine clinician skin examination and stage or thickness at skin cancer detection. Based on data from four fair-quality evaluations of three skin cancer screening programs (n=2,344,210), and one good-quality physician-focused skin examination initiative (n=595,799), routine clinician skin examination is not associated with increased detection of keratinocyte carcinoma, melanoma, or skin cancer precursor lesions compared to usual care or lesion-directed examination. Similarly, routine skin examination is not associated with stage at detection for invasive melanoma. Evidence is inconsistent on whether clinician skin examination is associated with higher detection of *in situ* melanoma based on two studies (n=2,530 melanoma cases), or with thinner lesions (<1mm or <2mm) at melanoma detection based on three studies (n=6,133 melanoma cases).

Indirect evidence: association between stage at skin cancer detection and melanoma mortality or all-cause mortality. Three nonrandomized studies (two good-quality, one fair-quality; n=407,133) reported melanoma-specific mortality, and three nonrandomized studies (one good-quality, 2 fair-quality; n=473,660) reported all-cause mortality. Later stage at detection was consistently associated with increased risk of melanoma mortality. Compared to *in situ* disease at detection, adjusted hazard ratios for melanoma mortality were 5.8 (95% CI, 5.3 to 6.3) for localized, 31.5 (95% CI, 28.9 to 34.2) for regional, and 169.6 (95% CI, 154.2 to 186.6) for distant stage in one U.S.-based study (n=185,219). Two studies using localized stage at detection as the referent group found a similar pattern of increasing melanoma mortality risk with increasing stage. No included studies evaluated the association between stage at diagnosis and skin cancer morbidity.

In two nonrandomized studies (1 good-quality, 1 fair-quality; n=135,490), melanoma mortality was higher for males than for females. Three studies with overlapping populations (n=708,814) examined melanoma mortality risk for specific racial and ethnic groups. One study found similar odds of melanoma mortality risk for White and Black persons within each stage at detection. In two other studies with overlapping populations, melanoma mortality risk was higher among Black, Asian American, Native American, Pacific Islanders (AANAPI), and Hispanic adults with melanoma AJCC Stage I and SEER localized stages compared to White adults. In one of these studies, the risk for melanoma mortality among Hispanic persons with regional or distant melanoma stage was also higher than among White adults.

Regarding all-cause mortality, the same pattern was observed over three large nonrandomized studies. In one study (n=185,219), the risk for all-cause mortality was adjHR 1.5 (95% CI, 1.5 to 1.5) for localized, 3.9 (95% CI, 3.8 to 4.1) for regional, 15.8 (95% CI, 14.9 to 16.7) for distant disease, compared to *in situ* melanoma at detection.

No included studies addressed keratinocyte carcinoma mortality by stage at detection.

Limitations: The body of evidence for benefits and harms of screening is small and derived from nonrandomized studies primarily conducted outside of the United States. The applicability to United States primary care settings might be low.

Conclusions: A substantial observational evidence base suggests a clear association between earlier stage at skin cancer detection and decreased mortality risk. However, ecological studies suggest no melanoma mortality benefit associated with skin cancer screening in adolescents or adults in regions with implemented routine screening compared to regions without routine screening. Nonrandomized evidence suggests no association between routine clinician skin examination and earlier stage at melanoma detection; evidence is inconsistent on whether clinician skin examination is associated with thinner melanoma lesions at detection. There is little direct evidence on harms of screening, however; other than overdiagnosis and overtreatment, there are few hypothesized serious harms.

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Chapter 1. Introduction

Condition Definition

Skin cancer is the abnormal growth of cells in skin tissue and is broadly classified as cutaneous melanoma and keratinocyte carcinoma (KC, previously referred to as nonmelanoma skin cancer). Cutaneous melanoma arises from pigment-producing cells called melanocytes in the epidermis, the outermost skin layer. Melanoma is less common than KC but is more likely to grow and spread.[1, 2] Noncutaneous (nonskin) melanoma develops from melanocytes in other areas of the body (e.g., the eye in ocular melanoma, mucosal surfaces in mucosal melanoma).[3]

This review's scope is limited to cutaneous melanoma, hereafter described as "melanoma," and KC. KC includes squamous cell carcinoma and basal cell carcinoma. Squamous cell carcinoma of the skin (SCC) can develop in the skin or in other parts of the body, such as the squamous mucosal epithelium. SCC of the skin is the only type of SCC addressed in this report. Basal cell carcinoma (BCC) develops in basal cells in the lower epidermis. Precursor lesions that may develop into skin cancer include actinic keratosis and atypical or dysplastic nevi; however, many dysplastic nevi never develop into melanoma and melanoma can develop *de novo* without arising from pre-existing nevi.[4]

Melanoma progression is described using two main staging conventions (**Table 1**). The Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute's staging convention describes three summary stages: localized (limited to skin tissue); regional (spread to lymph nodes); and distant (spread or metastasis to other parts of the body). Localized skin cancers may be further described in terms of thickness or depth, terms that describe how deep into the skin tissue the cancer has grown. The second staging system, developed and updated by the American Joint Committee on Cancer (AJCC, a program of the American College of Surgeons), is a histopathologic system that establishes standardized, clinically meaningful categories of tumor (T) thickness, ulceration, and mitotic rate; lymph node involvement (N); and metastasis (M) to assign Stage I, II, III, or IV (**Table 1**). The AJCC system was developed as a tool for assessing prognosis and guiding care. The current version (8th edition, implemented in 2018) is based on analysis of survival data from an international cohort (n=43,792) of persons diagnosed with melanoma since 1998.[5]

Prevalence and Burden

KCs comprise the vast majority (99%) of all incident skin cancers, with BCC making up about 80 percent of all incident cases and SCC making up about 20 percent.[6]

KCs are not required to be reported to cancer registries in the United States, so precise epidemiological estimates are not available. Based on Medicare and national survey data, a 2015 study estimated that 5.4 million KC cases were diagnosed among 3.3 million people in the United States population in 2012.[7] The incidence of KC increases with age and is more common in males than in females.[8-10] KC incidence appears to be increasing in recent decades,[7] possibly

related to increased exposure to ultraviolet radiation (UVR), increased detection, and increased longevity. Reliable estimates of KC mortality are not available, but death from KC is relatively uncommon (e.g., 0.32/100,000 for SCC-specific and 0.14 for BCC-specific mortality among Rhode Island residents between 1985 and 1987).[11] An emerging body of evidence suggests that the currently known SCC-related mortality rate is underestimated.[12]

Approximately one percent of all skin cancers are melanoma.[13] Melanoma causes the most skin cancer mortality compared to KC, with 7,990 melanoma deaths expected in the United States in 2023.[14] Melanoma incidence has been increasing consistently since 1975, with an average increase of 1.4 percent each year from 2009–2018. The increase in melanoma incidence has been attributed to increased UVR exposure[15] and increased detection.[16] There will be an estimated 97,610 new cases of melanoma in the United States in 2023 (22.9 per 100,000 persons).[14] Melanoma accounts for 5.2 percent of all new cancer cases in the U.S.[17] and is the fifth leading cancer in terms of incidence (new cases) in males and females.[18]

Although melanoma incidence has been steadily increasing over the past four decades, survival rates have remained stable over the same time period and have even begun improving in recent years (**Figure 1**).[18] According to United States SEER data, age-adjusted melanoma incidence rates increased on average 1.2 percent each year between 2010 and 2019.[14] An analysis of SEER data from 1975-2017 found that melanoma *in situ* incidence has increased more rapidly than that of invasive melanoma.[19] According to 2012–2018 SEER data, 5-year survival for melanoma ranges from 99.5 percent for localized stage disease to 31.9 percent for distant stage disease.[14] Age-adjusted death rates have decreased on average 3.3 percent each year between 2011 and 2020.[14, 19]

Incidence and mortality of melanoma increases with age, and is highest in males and in White persons (**Table 2**).[14, 20, 21] Melanoma incidence is lower in Black persons, but less likely to be diagnosed at early stage, when treatment works best. The percentage of new skin cancer cases diagnosed at a local stage is lower in Black persons (50.6%) and Asian/Pacific Islanders (64.2%), compared to White persons (78.1%).[22] The 5-year relative survival rate for those diagnosed at a local stage also is lower in Black persons (88.5%; 95% CI, 78.9% to 93.9%) and Asian/Pacific Islanders (89.7%; 95% CI, 84.8% to 93.1%) than in white persons (99.1%; 95% CI, 98.7% to 99.3%).[23] Notably, skin cancer has primarily been studied in persons with light skin, which may contribute to disparities in diagnosis, care, and treatment. Clinical presentation (e.g., melanoma subtype, location of lesion) of skin cancer can differ in people with darker skin tones.[24, 25] Other factors that may contribute to disparities in skin cancer outcomes include socioeconomic status, insurance status, place of residence, and access to care.[26]

Etiology and Natural History

BCC develops from the basal layer of the epidermis. SCC on the other hand arises from keratinocytes in the mid-layer of the epidermis. Unlike BCCs, which rarely metastasize, a small proportion (estimated metastatic rate 1.9%–4.9%) of SCCs metastasize in the absence of treatment.[27-29] The most common location of melanoma and KC is skin that has been exposed to the sun; however, skin cancer on nonexposed skin is more likely to develop in Black, Asian, and

native Hawaiian persons.[30] SCC commonly appears on the face, ears, neck, lips, and back of hands, whereas BCC is especially prevalent on the head and neck.[31]

Melanomas develop through the unregulated growth of melanocytes, melanin-producing cells found between the epidermal and dermal layers of the skin. Melanocytes may grow in a horizontal lentiginous pattern to appear on the skin as a freckle, and clusters of melanocytes may develop into nevi. Melanomas have metastatic potential when they infiltrate the dermis and begin a vertical growth phase into deeper skin layers.

There are four major histologic subtypes of melanoma skin cancer: 1) superficial spreading; 2) lentigo maligna; 3) acral lentiginous; and 4) nodular. Of these, superficial spreading and nodular melanomas are the most common subtypes,[32] though incidence of lentigo maligna has been increasing in recent years.[33, 34] Nodular melanomas begin their vertical growth phase immediately, whereas other types may take decades.[35, 36] Ten-year relative survival rates are lowest for nodular (61.5%) and acral lentiginous melanoma (69.9%) compared with superficial spreading (96.5%) and lentigo maligna melanoma (99.4%).[33] Acral lentiginous melanoma (ALM), which occurs on the palms of hands, soles of feet, fingers, toes, and nail units, is the least common melanoma subtype.[37] Incidence of ALM is highest in Hispanic white persons followed by non-Hispanic white persons;[38] however, among Black populations, ALM is the most frequently occurring melanoma subtype.[37]

The degree to which melanoma has spread at detection is highly prognostic of survival, making skin cancer a candidate for population screening programs. Melanoma thickness and ulceration are the primary prognostic indicators of survival in early stage disease,[39] and depth of vertical growth is directly related to prognosis.[39-41] Both the AJCC and SEER staging systems recognize this and include clinically meaningful categories of thickness in early stage disease, as well as lymph node involvement and metastasis for more advanced stages (**Table 1**). In addition, the systematic review supporting the United States Preventive Services Taskforce's (USPSTF) 2016 recommendation on skin cancer screening identified eight nonrandomized studies that examined the association between either melanoma-specific or all-cause mortality and lesion thickness or stage at diagnosis.[42] All studies demonstrated a consistent linear increase in risk of melanoma mortality with increasing tumor thickness or stage.[43]

Risk Factors

The epidemiology and risk factors for skin cancer, especially for melanoma, are well-characterized. Exposure to UVR is the major environmental risk factor for all types of skin cancer in exposed skin.[44, 45] The World Health Organization's International Agency for Research on Cancer has classified UVR, UVR-emitting devices, solar radiation, and indoor tanning devices as carcinogenic to humans with sufficient evidence linking their use to melanoma and other skin cancers.[46]

Sunlight is the primary source of UVR exposure. Melanoma risk is associated with intense intermittent sun exposure and a frequent history of sunburn is associated with a 2-fold increased

risk of melanoma.[47] Cumulative sun exposure, such as long-term outdoor occupational exposure, appears to increase KC risk, but not risk of melanoma.[47, 48]

Another important source of UVR exposure, especially in adolescents, is the use of indoor tanning beds, which is associated with both KC and melanoma. Ever use of tanning beds is associated with a 1.7-fold increased risk of SCC,[49] a 1.3-fold increased risk of BCC,[49] and a 1.2-fold increased risk of melanoma.[49, 50] Associations with indoor tanning are stronger for persons with a younger age at exposure (1.8-fold increased melanoma risk for <35 years compared to ≥35 years at first exposure).[51]

Increased age, as well as male sex are associated with increased risk of skin cancer incidence and mortality. Epidemiological studies have shown that melanoma incidence and mortality rapidly increase with age, with the mean age at diagnosis being 65 years.[14] Melanoma incidence during 2015–2019 was 6.6 cases per 100,000 persons aged <50 years, 36.7 cases per 100,000 persons aged 50 to 64 years, and 88.5 cases per 100,000 persons in adults aged ≥65 years (**Table 2**). Mortality rates mirror this trend, showing that during 2015–2019 persons from these age groups had adjusted rates of 0.4, 3.0, and 11.3 deaths per 100,000 persons (**Table 2**).[20] Data consistently show that males are at a higher risk of melanoma incidence and mortality compared to females (**Table 2**). Age-adjusted melanoma incidence during 2015–2019 was reported as 27.6 per 100,000 in males and 17.0 per 100,000 in females.[14] However, this sex-specific difference is not consistent across all ages. Younger females, particularly those aged 15–39 years, had modestly higher incidence rates than their male counterparts, likely related to higher use of tanning and tanning beds among females. The highest rates were observed in older males aged ≥65 years (137.3 per 100,000) and nearly tripled those of similarly aged females (52.4 per 100,000);[52] this may reflect a combination of behavioral risk factors and tendency for thicker skin in males.[53] Although 5-year survival is similar for males and females, age-adjusted melanoma mortality rates are higher in males, with 3.2 and 1.4 deaths per 100,000, respectively. The difference in age-adjusted melanoma mortality increases with age and increases faster in males (**Table 2**).[52]

As estimated according to socially constructed race and ethnicity categories, melanoma incidence is highest among White persons (38.6 per 100,000 persons in males; 25.5 per 100,000 persons in females) (**Table 2**). Melanoma incidence is lower among American Indian/Alaska Native persons (8.7 per 100,000) and persons of Hispanic ethnicity (any race; 4.6 per 100,000) (**Table 2**). Black persons have the lowest rates of melanoma (1.0 per 100,000).[21] The incidence of melanoma varies in persons with different skin phenotypes—type I (sun-unexposed skin color is white and always burns, not tans) through VI (sun-unexposed skin color is dark brown to black and never burns, always tans) according to the Fitzpatrick Skin Phototype Classification.[54] The higher melanoma incidence seen in White persons, compared with other races and ethnicities, could be due to fair skin being susceptible to sunburning more easily.[55] In addition, having light-colored eyes and red or blond hair are associated with an increased risk of skin cancer, and these traits are more common in White persons.[56-58] Natural red hair and natural blond hair confer a 3.6-fold and 2-fold increase in melanoma risk, respectively, compared to naturally dark hair.[58] Emerging evidence suggests no to weak association between UV exposure and melanoma incidence in skin of color (broadly defined as any race or ethnicity other than non-Hispanic White, Fitzpatrick skin types IV through VI, or tanning ability of rarely or never burns).[59]

Other melanoma risk factors include an increase in the number of nevi, or moles, on the skin (especially moles that are atypical).[55, 60] Number of typical nevi is associated with an increased risk of melanoma in a dose-response manner.[61, 62] Atypical nevi also confer risk in a dose-response relationship with number, with a 1.5-fold increased risk associated with a single atypical nevus and a more than 6-fold increased risk associated with five atypical nevi compared to none.[55]

Persons with a previous history of KC have been shown to have an increased risk of developing melanoma,[63] and a history of melanoma is associated with an increased risk of developing a second primary melanoma.[64, 65]

Melanoma has a genetic component, as measured by both family history[66, 67] and by polygenic heritable factors such as skin type, nevus count, hair color, and eye color.[68, 69] Pooled estimates suggest that family history of the disease increases melanoma risk 1.7-fold.[58] Other hereditary components account for <7 to 10 percent of melanomas.[66, 67] Additionally, persons with familial atypical multiple mole and melanoma (FAMMM) syndrome have a high lifetime risk of developing melanoma, and those with basal cell nevus syndrome develop multiple BCCs at an early age. Three large U.S.-based cohort studies found evidence that persons with a family history of melanoma skin cancer have 74 percent increased risk of melanoma (HR, 1.74 [95% CI, 1.45 to 2.09]), a 22 percent increased risk of SCC (HR, 1.22 [95% CI, 1.06 to 1.40]), and a 27 percent increased risk of BCC (HR, 1.27 [95% CI, 1.12 to 1.44]) compared to those without a family history.[70] Hereditary melanoma is most commonly attributed to a mutation in *CDKN2A/p16*. Other commonly cited melanoma hereditary genes include *CDKN2A/AFR, CDK4, TERT, MITF, BAP1, POT1*.[71] In addition to FAMMM syndrome, several rare genetic conditions confer increased skin cancer risk.[69, 72] For example, xeroderma pigmentosum impairs the ability to repair UVR-induced DNA damage and increases the risk of both KC and melanoma at an early age.[73] Albinism is characterized by hypopigmentation and confers an increased risk of KC.

Screening, Diagnosis, and Treatment

The rationale for screening for skin cancer is to detect skin cancers earlier in their clinical course than would happen without screening, allowing earlier and more effective treatment and thereby leading to a reduction in skin cancer morbidity and mortality. Visual skin cancer screening is either a whole or partial body skin examination conducted by a clinician to detect suspicious skin lesions. Clinicians are trained in the detection and diagnosis of skin cancer using mnemonics such as the ABCDE mnemonic[74] to identify characteristics of skin lesions that may signify melanoma (asymmetry, border irregularity, color, diameter, and evolution over time). Another approach to skin cancer screening is the "ugly duckling" sign. In this approach, the clinician identifies pigmented lesions which look different than the other nevi in a given patient.[75] In addition to visual inspection of the skin with the naked eye, dermatologists often use a magnifying device called a dermatoscope (also called a dermascope or dermoscope) to further inspect the lesion. The use of dermoscopy by primary care providers is increasing, particularly in Australia.[76-78]

A definitive diagnosis of both KC and melanoma is through biopsy, including partial biopsy (for KC) and deep shave/saucerization biopsy, punch excision, or elliptical excision (for melanoma).[79] Some lesions can be removed at the time of examination, or individuals with suspicious lesions may be referred to a dermatologist for virtual or in-person consultation.

Treatment

KC is removed by either surgical excision, Mohs micrographic surgery (i.e., tissue is removed in layers until the microscopic examination of the layers indicates that cancer has been completely removed), or electrodesiccation and curettage (i.e., tissue destruction by electric current and removal by scraping with a curette).[80] Photodynamic therapy (i.e., combined use of a photosensitizing agent with light) is mainly used to treat superficial KC.[81, 82] Radiation therapy or topical medications might also be used.

For melanoma, the primary tumor and surrounding normal tissue are surgically removed, possibly with sentinel lymph node biopsy to determine stage. More extensive surgery (e.g., complete lymph node dissection) may be conducted if the sentinel lymph node is positive. Unresectable melanoma (e.g., stage III-IV) may be treated with palliative surgery, immunotherapy, radiation therapy, chemotherapy, or a combination.[83]

Since 2011, major advancements in the development of immunotherapies and targeted therapies have changed how advanced melanoma is treated. These treatments are now considered the standard of care and are used as the first line treatment because of improved survival and are associated with fewer side effects than traditional approaches.[79, 84-86] Immunotherapies and targeted therapies fall mainly into two groups based on their primary targets: those that inhibit the mitogen-activated kinase pathway in tumors with BRAFV600 (known as MAPK or BRAF inhibitors), and those that inhibit various checkpoints involved in the activation of the immune system (known as checkpoint inhibitors). The U.S. Food and Drug Administration (FDA) has approved a number of immunotherapies for the treatment of advanced and metastatic melanoma, including the checkpoint inhibitors ipilimumab (a monoclonal antibody that targets CTLA-4), nivolumab (a monoclonal antibody that targets PD-1), vemurafenib (a BRAF inhibitor), and pembrolizumab (a PD-1 inhibitor), as well as talimogene laherparepvec (TVEC).[84, 86, 87]

Current Clinical Practice

The majority of melanomas (67%–75%) are initially detected by patients or their spouses (i.e., lesion-directed examination), not clinician exam.[88, 89] Current practice for persons who are not under surveillance for skin cancer typically involves lesion-directed examination. In lesion-directed examination, a clinician examines a lesion identified incidentally or by a patient. Persons with known elevated skin cancer risk (e.g., personal history of melanoma, multiple nevi) may be under routine surveillance and receive more frequent skin examinations.

Dermatologists are more likely to report more skin examinations performed than family practice clinicians or internists (552 [81.3%] dermatologists versus 333 [59.6%] family practice clinicians versus 243 [56.4%] internists).[90] It is unclear how many of these screenings are performed in

persons with elevated risk for skin cancer versus how many were in persons with an average risk for skin cancer.

Primary care clinicians in two counties in Connecticut and Florida indicate that only 31 percent perform skin cancer screening on their adult patients; the primary barrier was clinician lack of confidence in identifying a suspicious lesion.[91, 92] While there are several educational interventions to improve knowledge of and confidence in skin cancer screening in primary care, few tools have been rigorously tested for measured changes in clinical practice.[93, 94]

The use of virtual care (e.g., telehealth, telemedicine) has rapidly increased since the beginning of 2020 as a response to the COVID-19 pandemic.[95] Evidence suggests that telehealth may improve access to care, improve patient and provider satisfaction, and reduce costs for both health systems and some patients, with the promise of delivering clinical outcomes similar to those from in-person care for some conditions and health needs.[96] Telehealth in primary care and teledermatology (i.e., dermatology services over distance, or distance and time) is being used to evaluate patients' individual risk for skin cancer, facilitate skin cancer screening and early diagnosis, and provide behavioral counseling.[96-98]

Current Screening Recommendations

Currently, no professional organizations in the United States recommend clinician-performed population-based skin cancer screening (**Appendix B**). The American Academy of Family Physicians cites the 2016 USPSTF recommendation[99] as the basis for its conclusion that there is insufficient evidence to evaluate the balance of benefits and harms of screening. The American College of Physicians, however, does not have current guidance on whether or not to screen. The American Cancer Society (ACS) has no specific recommendation for skin cancer screening, but highlights the importance of knowing one's own skin and provides instructions on performing skin self-examination.[100, 101] The American Academy of Dermatology (AAD) similarly encourages regular skin self-examination in asymptomatic persons with no history of skin cancer. Also, AAD states that persons should seek advice from their health provider on the frequency of self-exam.[102] The AAD has offered free skin cancer screening clinics since 1985, similar to its contemporary SPOTMe® screening campaign.[103]

A nationwide skin cancer screening program was implemented in Germany in 2008, following the results of the Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany (SCREEN) study.[104] Other than Germany, routine screening is not recommended by professional organizations in other countries, including the United Kingdom, The Netherlands, and Australia.

Previous USPSTF Recommendation

In 2016, the USPSTF concluded that the current evidence was insufficient to assess the balance of benefits and harms of visual skin examination by a clinician to screen for skin cancer in adults (I statement).[99] This statement applied to asymptomatic adults who did not have a history of

premalignant or malignant skin lesions. Patients with suspicious skin lesions or those already under surveillance because of a high risk of skin cancer, such as those with a familial syndrome, were outside the scope of the recommendation statement. The 2016 recommendation does not mention immunosuppressed patients or other groups at high-risk of developing skin cancer.

The USPSTF addressed counseling for skin cancer prevention, including skin self-examination, in the evidence review supporting its 2018 recommendation statement.[48] In 2018, the USPSTF recommended skin cancer prevention counseling for young adults, adolescents, children, and parents of young children (B recommendation) and for adults older than 24 years with fair skin types (C recommendation). The USPSTF concluded the current evidence was insufficient to assess the balance of benefits and harms of counseling adults about skin self-examination for skin cancer prevention (I statement).[105]

Chapter 2. Methods

Scope and Purpose

This systematic review provides updated evidence regarding the effectiveness of routine skin cancer screening by a clinician in reducing skin cancer morbidity and mortality, as well as the harms of screening. In addition, this review addresses whether routine screening leads to higher rates of detection of precancerous lesions or earlier stage skin cancer, as well as the association of earlier detection and morbidity/mortality from skin cancer or all-cause mortality. The USPSTF will use this evidence review to update their 2016 recommendation[99] on screening for skin cancer.

Key Questions and Analytic Framework

The analytic framework is presented in **Figure 2**.

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 subgroups (for example, age, sex, skin type, race/ethnicity, socioeconomic status, or ultraviolet [UV] exposure)?
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)?
   a. Do rates of earlier skin cancer detection vary by subgroups (for example, age, sex, skin type, race/ethnicity, socioeconomic status, or UV exposure)?
3. What are the harms of skin cancer screening and diagnostic followup?
   a. Do the harms of screening vary by subgroups (for example, age, sex, skin type, race/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 subgroups (for example, age, sex, skin type, race/ethnicity, socioeconomic status, UV exposure)?

Data Sources and Searches

We searched the following databases for English-language literature: MEDLINE ALL via Ovid, Embase via Elsevier, and the Cochrane Central Register of Controlled Trials via Wiley. We updated the search used in the 2016 systematic review on January 12, 2021, and we ran a bridge search on January 7, 2022. A research librarian developed and executed the search, which was peer-reviewed by a second research librarian (**Appendix A**). We also reviewed all included

studies from the prior review,[106] which identified studies prior to 2015. We then supplemented our database searches with expert suggestions and by reviewing reference lists from other recent relevant systematic reviews.[107-115] We also searched ClinicalTrials.gov for ongoing screening trials. We imported the literature from these sources directly into EndNote X7 (Thomson Reuters, New York, NY).

Study Selection

A total of 20,320 abstracts were reviewed. Initial identification of low-relevance abstracts was conducted using keywords relating to exclusion criteria. This identified 10,115 citations that were reviewed by a single investigator. The remaining 10,205 abstracts were dual-reviewed by independent reviewers against a priori specified inclusion criteria using an online platform (DistillerSR). The team then reviewed 522 full-text articles (**Appendix A Figure 1**) against specified inclusion criteria (**Appendix A Table 1**). We resolved discrepancies through consensus and consultation with a third investigator.

For screening key questions (KQs 1, 2, 3), the population of interest was asymptomatic adolescents and adults aged 15 years or older with or without a family history of melanoma. We excluded studies focused solely on persons already under surveillance for skin cancer (e.g., because of previous skin cancer, genetic syndromes associated with increased skin cancer risk, or conditions associated with a suppressed immune system). We included studies of any visual skin examination conducted by a clinician with or without tools to aid examination (e.g., dermatoscopy; whole-body photography). We excluded studies of patient skin self-examination as this topic is covered in the 2018 evidence review[48] on behavioral counseling for skin cancer prevention. For KQ1, we excluded studies focused exclusively on lesion-directed diagnostic skin examination (e.g., in response to patient concern). For KQ1 and KQ2, we excluded studies conducted exclusively in specialty care settings, such as dermatology or plastic surgery.

For KQ4 (the association between stage at detection and health outcomes), the population of interest was adolescents and adults age 15 and older diagnosed with skin cancer. Since lesion thickness is used in determining skin cancer stage, the primary exposure of interest for KQ4 was stage at detection. Specifically, we included studies reporting measures of association between mortality outcomes (excluding relative survival measures such as 5-year survival) and stage at detection using either AJCC or SEER staging (**Table 1**). To identify and focus on the strongest available evidence within a large literature base of nonrandomized studies, we included population-based studies with data collected across multiple sites. We excluded studies that did not report data on stage at detection (e.g., those that only reported lesion thickness, depth, or Clark levels), that compared grouped stages only (e.g., Stage I+II vs. Stage III+IV) or sub-stages only (e.g., IIA vs. IIB vs. IIC), or that were limited to a single body part or cancer subtype. Where included studies reported thickness, we also abstracted and reported those data.

Included study designs were randomized controlled trials (RCTs) and controlled clinical trials. Also, anticipating limited to no data from randomized trials, we included nonrandomized studies with a contemporaneous control for all key questions. For KQ3 only, we additionally included large screening registry or database nonrandomized studies, cohort studies, and systematically

selected case series. Outcomes of interest were morbidity or mortality associated with skin cancer, including quality of life, skin cancer mortality, or 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, including psychosocial harms and procedure-related adverse events (KQ3).

For all key questions, we limited studies to those conducted in primary care-relevant settings and in countries categorized as "Very High" in the 2019 Human Development Index.[116] We included only studies that published their results in English because of resource constraints. We excluded studies that were not original research (e.g., editorials, opinion pieces, and narrative reviews) and studies that were not peer-reviewed (e.g., conference abstracts).

Quality Assessment and Data Abstraction

At least two reviewers independently critically appraised all articles that met the inclusion criteria based on the Newcastle Ottawa Scales for nonrandomized studies[117] and the USPSTF's design-specific quality criteria for trials (**Appendix A Table 2**). We rated articles as good, fair, or poor quality. In general, a good-quality study met all criteria. A fair-quality study did not meet, or it was unclear whether it met, at least one criterion, but also had no known important limitations that could invalidate its results. A poor-quality study had a single fatal flaw or multiple important limitations. We excluded all poor-quality studies from this review. Disagreements about critical appraisal were resolved by consensus and, if needed, consultation with a third independent reviewer.

One reviewer extracted key elements of included studies into standardized evidence tables in DistillerSR (Evidence Partners, Ottawa, Canada). A second reviewer checked the data for accuracy. Evidence tables were tailored for each key question. Tables generally included details on: study design/quality, setting and population (e.g., country, inclusion criteria, age, sex, race and/or ethnicity, skin type), screening exam/protocol (e.g., who administered, how administered), length of followup, and outcomes (e.g., skin cancer morbidity or mortality, all-cause mortality, stage or lesion thickness at detection, harms of screening).

Data Synthesis and Analysis

We synthesized results by KQ. We used a standardized summary of evidence table to summarize the overall strength of evidence for each KQ. This table included the number and design of included studies, summary of results, consistency or precision of results, reporting bias, summary of study quality, limitations of the body of evidence, and applicability of the findings. We also assessed the potential for population overlap between studies. For population-based studies with substantially overlapping patient populations (e.g., SEER data from identical time periods) and the same outcomes presented, we used studies with the largest sample size and the most extended followup.

Because of the limited number of studies and the population heterogeneity, we provided a

narrative synthesis of results and used summary tables to facilitate comparisons across studies. Heterogeneity in outcomes precluded pooling or meta-analysis.

Grading the Strength of the Body of Evidence

We graded the strength of the overall body of evidence for each KQ. We adapted the Evidence-based Practice Center (EPC) approach,[118] which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[119] Our method explicitly addresses four of the five EPC-required domains: consistency (similarity of effect direction and size), precision (degree of certainty around an estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or selective analysis reporting), and study quality (i.e., study limitations). We did not address the fifth required domain—directness—as it is implied in the structure of the KQs (i.e., pertains to whether the evidence links the interventions directly to a health outcome).

Consistency was rated as reasonably consistent, inconsistent, or not applicable (e.g., single study). Precision was rated as reasonably precise, imprecise, or not applicable (e.g., no evidence). The body-of-evidence limitations reflect potential reporting bias, study quality, and other important restrictions in answering the overall KQ (e.g., lack of replication of interventions, nonreporting of outcomes important to patients).

We graded the overall strength of evidence as high, moderate, or low. "High" indicates high confidence that the evidence reflects the true effect, and that further research is very unlikely to change our confidence in the estimate of effects. "Moderate" indicates moderate confidence that the evidence reflects the true effect, and that further research may change our confidence in the estimate of effect and may change the estimate. "Low" indicates low confidence that the evidence reflects the true effect, and that further research is likely to change our confidence in the estimate of effect and is likely to change the estimate. A grade of "insufficient" indicates that evidence is either unavailable or does not permit estimation of an effect. We developed our overall strength-of-evidence grade based on consensus discussion involving at least two reviewers.

Expert Review and Public Comment

The draft Research Plan was posted on the USPSTF website for public comment from January 7, 2021, to February 3, 2021. In response to public comment, the USPSTF clarified the wording of KQs 2 and 4 to more clearly delineate precancerous lesions from early-stage skin cancer; clarified that the exclusion of "lesion-directed diagnostic skin examination (e.g., in response to patient concern)" applies to KQ1 only; added race/ethnicity and socioeconomic status as additional examples of subpopulations that will be examined for each KQ; and added KQ4a to assess whether the association varies by subgroups. The USPSTF made no other substantive changes that altered the scope of the review.

A draft version of this report was reviewed by invited content experts and federal partners, who are listed in the acknowledgements. Comments received during this process were presented to the USPSTF during its deliberation of the evidence and, subsequently, addressed in this version of the report.

USPSTF and AHRQ Involvement

The authors worked with USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework and key questions and to resolve issues around scope for the final evidence synthesis.

AHRQ staff provided oversight for the project, coordinated systematic review, reviewed the draft report, and assisted in an external review of the draft evidence synthesis.

Chapter 3. Results

Literature Search

We reviewed 20,320 abstracts and assessed 522 full-text articles for inclusion (**Appendix A Figure 1**). For KQ1, we included three studies (10 articles);[104, 120-128] for KQ2, we included six studies (7 articles);[129-135] KQ3 was comprised of two studies (3 articles);[136-138] and KQ4 included nine studies (9 articles).[139-147]

Seventeen studies were newly identified in this update.[121, 124, 130, 132-135, 138-147]

A list of included studies and a list of excluded studies with reasons for exclusion are available in **Appendix C** and **Appendix D**, respectively. We determined all included studies were of fair or good quality (**Appendix A Table 2**).

KQ1. 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? Does the Effectiveness of Screening Vary by Subgroups (e.g., Age, Sex, Skin Type, Race/Ethnicity, Socioeconomic Status, or UV Exposure)?

Summary of Results

Based on ecologic data and non-randomized study data from three evaluations of two related screening programs in Germany, the included evidence (both screening programs rated fair quality) does not suggest a melanoma mortality benefit at the population level over 4 to 10 years' followup after screening (n=NR in one study; 1,791,615 in the other two). At ten-year followup of the Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany (SCREEN) pilot, melanoma mortality in the SCREEN region compared to the rest of Germany does not support an ongoing mortality benefit to routine skin cancer screening.[125] Similarly, at 5-year followup of the German National Screening Program, no mortality benefit was observed based on national population statistics. Rather, increases in mortality, not decreases, were observed for multiple European countries, including Germany.[124]

One non-randomized study (n=1,431,327) of melanoma mortality in individuals with documented skin cancer screening provided through German statutory health insurance found an absolute decrease in mortality suggesting a screening benefit at four-year followup, but this difference was attenuated on multivariate analysis and adjustment for lead time bias.[121] No included studies reported all-cause mortality, SCC mortality, BCC mortality, or skin cancer morbidity.

Three included publications from the two German screening programs reported age- and sex-specific melanoma mortality. Similar to the results reported in the main study populations, across these analyses, there was no evidence of a melanoma mortality benefit to screening at the population level.

Detailed Results

Overview of Included Studies

Publications using data from two population-based screening programs in Germany met inclusion criteria (**Tables 3 and 4**). The first fair-quality study, also included in the previous review, was the SCREEN skin cancer screening pilot, which was conducted in the Schleswig-Holstein state in northern Germany from 2003–2004 (n=360,288 screened). Ten-year followup data on melanoma mortality from this program is included in this report.[125] The second screening program is the German national skin cancer screening program, implemented in 2008, which includes skin cancer screening covered through statutory health insurance following the promising 5-year mortality data observed in the SCREEN program.[126] One evaluation used a nonrandomized design (n=1,431,327) to examine administrative data from a German health insurance company with documented skin cancer screening as provided through the German skin cancer screening program.[121] Another evaluation (2 publications) reporting melanoma mortality rates in Germany and surrounding countries during the first 5 years of the screening program, which included approximately 3 million screened individuals, also met inclusion criteria.[120, 124] All but one included publication used ecologic analyses to examine melanoma mortality rates in screened geographic areas compared to areas without population screening programs.

Subgroup data (KQ1a) on melanoma mortality by age and sex is provided for both Germany and for the SCREEN program. One study analyzed the annual percent change (APC) in melanoma mortality by sex and age in Germany compared to eight other European countries in order to estimate the impact of the German skin cancer screening program on melanoma mortality by age and sex subgroups.[120]

Summary of Included Screening Programs

SCREEN (Germany) (2003–2004)[104, 122, 125, 126, 128]

The SCREEN study was conducted to determine the feasibility of a population-based skin cancer screening program in the German primary care health system[104] (**Table 4**). In 2001, pilot intervention activities occurred on a small scale with 200 physicians and 6,000 screened patients in the Schleswig-Holstein state of northern Germany. Between 2003 and 2004, following the pilot, the SCREEN project implemented population-based skin cancer screening in Schleswig-Holstein. All residents aged 20 years or more and insured with national statutory health insurance were eligible to participate. The screening program included three main components:

1. <u>Provider education and training</u>. In 2003, nondermatologists (general practitioners in primary care, obstetricians and gynecologists, and urologists; n=1,673) and dermatologists (n=116) participated in an 8-hour training course focused on detecting skin cancer. Content 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.[104] Training participation rates were 64 percent for nondermatology providers and 98 percent for dermatologists in the region.
2. <u>Public outreach</u>. An outreach campaign encouraged residents of Schleswig-Holstein aged 20 years and older to seek skin cancer screening by a nondermatology physician through the program. Communication channels included health insurers, physicians, and print, digital, and telephone mass media campaigns.
3. <u>Clinician skin exam</u>. Screening exams were conducted from July 2003 to June 2004 via whole-body visual skin exam conducted by a nondermatology provider, although dermatologists also participated in the program and conducted initial screenings. Suspicious lesions were either referred to dermatology or handled by the screening dermatologist. Physicians were reimbursed about $20 USD per screening exam. All tentative clinical diagnoses were followed by biopsy and histopathologic evaluation. Approximately three quarters (77.4%) of screening exams were conducted by nondermatology providers, and 22.6 percent were conducted by 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.[104] All confirmed skin cancers were reported to the state tumor registry.

German National Screening Program (2008–2013)[120, 124, 135, 148, 149]

Following the completion of the SCREEN study,[126] Germany implemented a nationwide routine skin cancer screening covered by statutory health insurance (**Table 4**). The implementation was not designed as a research study and did not include a comparison group; though a 5-year evaluation was required.[149] Screening included a total skin exam by either a participating primary care clinician or a participating dermatologist. Participating providers completed a standardized 8-hour training program similar to that used in the SCREEN study. Topics included benefits and risks of early screening; etiology of skin cancer and risk factors; training in implementing the screening program; patient communication; and discussion of case examples.[123, 150] Screening included a visual examination of all visible skin and mucous membranes (oral, vaginal, anal) and was offered free of charge to all enrollees aged 35 years or older. Screening physicians were reimbursed for screenings.[149] During 2008–2009, screenings were conducted approximately equally by general practitioners or dermatologists.[148]

In Germany, health insurance is mandatory, and the administration of health insurance is implemented by non-governmental insurance companies.[151] Documentation of clinician skin cancer screening, a reimbursable service for clinicians, is noted in individual health records through billing codes.

Population Summary

SCREEN Program

Of a total population of 2.8 million in the Schleswig-Holstein region, 1.9 million individuals aged 20 years and older comprised the eligible screening population (**Table 5**). During the project period, 360,288 people received clinician 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.

Among screened participants, the mean age was 49.7 years. Almost three-quarters of screened participants were females (73.6%). Nearly half of participants were judged to have at least one risk factor for melanoma based on family history of melanoma (6.1%), personal history of melanoma (1642 people, 2.6%), presence of atypical nevi (51.9%), multiple melanocytic nevi (56.2%) or congenital moles (20.9%). Other risk factors included UV-damaged skin (72.0%); actinic keratosis (31.2%), personal history of KC (16.9%); X-ray damaged skin (2.6%) or immunosuppression (2.7%).[104] Data on other specific population subgroups (e.g., race and/or ethnicity) was not reported.

German National Screening Program

The total number of screened residents from the study period 2008–2013 is not reported in the included studies. However, an earlier publication describing the German program estimated that the population enrolled in the German health insurance plan DAK-Gesundheit was approximately 6.1 million members in an 18-month period in 2008–2009; in that time period approximately 920,000 people received screening.[148]

Characteristics of the screened population were not consistently reported. The German population during the screening period 2008–2012 was 51.2 percent female with a mean age of 43 years (including all ages) (**Table 5**).[135] During that period, the mean quarterly screening participation was 30.8 percent, with screening participation significantly higher in females (age- and federal state- adjusted participation rates were 29.7% for males and 31.9% for females).[148] Screening participation was highest in people over age 65, with state-adjusted rates among males between the ages 65 and 79 exceeding 40 percent.[148]

The good quality nonrandomized study by Datzmann and colleagues included enrollees in AOK PLUS, a health insurance plan that administers German national statutory health insurance and insures approximately 25 million people.[121] The included sample was enrollees 35 years or older between 2010-2016 (n=1,431,327). The sample was mean age 63.9 years and 55.7% female. Neither race and ethnicity nor skin type was reported. Overall the screened and unscreened groups were similar, except for receipt of systemic therapy within 30 days (11.6% in screened vs 21.8% in unscreened group), suggesting a stage shift associated with screening. The study team identified all prevalent cases of melanoma during the study period (n=4,552) and limited their analysis to incident melanoma cases diagnosed during 2013-2016 with no evidence of melanoma in the previous 3 years (n=2475). People with documented skin cancer screening as identified

through billing codes in the previous two years before diagnosis were considered to have received the screening intervention. The observation period was four years.

The outcome of interest was melanoma mortality. The team measured both the absolute risk difference as a difference in numbers of deaths during the observation period. They also conducted multivariable modeling and estimated both unadjusted and adjusted hazard ratios. Adjustment variables included age, sex, comorbidity, health-seeking behavior (estimated by receipt of flu vaccine), personal history of melanoma; and approximated stage categories of documented metastasis or receipt of systemic anticancer therapy. They also conducted sensitivity analyses to assess the potential for lead time bias by removing patients with survival of less than 360 days. Lead time bias associated with screening is when survival can appear longer because of detection, not because of intervention.[152]

Quality

For this key question, two included studies were rated fair quality and the Datzmann study was rated as good quality. Followup time was sufficient to observe skin cancer incidence and mortality over time, screening procedures were well described, populations were clearly defined, sources of outcome data were strong (use of national and regional health statistics), and sample sizes were large.

Quality concerns were primarily related to the known limitations of ecologic studies,[153-155] including the lack of controlled intervention (e.g., selection bias with voluntary screening programs) and the lack of individual-level data on screening participants, including–importantly– previous screening participation and the presence of skin cancer risk factors. There is adequate biologic plausibility for an effect of screening to be observed at the population level, and the included studies' followup times are sufficient to observe melanoma mortality. However, the included studies can neither directly compare individual-level changes in mortality among people receiving versus not receiving skin cancer screening, nor account for confounding through randomization or adjustment for environmental factors or socioeconomic, risk factor, or demographic variables. As such, our ability to infer a causal relationship between skin cancer screening and melanoma mortality is limited and should be viewed cautiously.

Another potential quality concern has been raised in a related study, where the authors examined the cause of death statistics for Schleswig-Holstein during the years of the SCREEN program evaluation (2007–2010), which overlaps with the years the mortality benefit was observed (2004–2009).[126] They concluded that potential for misclassification existed during that time period, when an unusually high number of deaths were coded as "malignancies of ill-defined, secondary, and unspecified sites" (ICD-10 codes C76–C80) and an unusually low number of deaths were coded as due to malignant melanoma. They argue that this change would be sufficient to explain the mortality benefit observed in those years.[156]

Detailed Results by Outcome

No included studies reported all-cause mortality, SCC mortality, or BCC mortality.

Melanoma Mortality in the SCREEN Program

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.[104] Of these 585, 31 percent were melanoma *in situ* and 69 percent were invasive melanoma. The SCREEN study also detected 1,961 basal cell carcinomas, 392 SCC and 165 other skin cancers.

Incidence of melanoma, BCC, SCC, and melanoma *in situ* increased during the SCREEN pilot (**Figures 3 and 4**). Melanoma age-adjusted incidence rates (per 100,000 individuals) increased 27 percent from 14.2 (95% CI, 13.3 to 15.1) during 2001–2003 to 18.0 (95% CI, 16.6 to 19.4) during the active screening period (2003–2004). Similarly, melanoma *in situ* age-adjusted incidence rates (per 100,000 individuals) increased 48 percent between the pre-screening period versus during-screening period. SCC age-adjusted incidence 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. BCC age-adjusted incidence rates (per 100,000) increased 29 percent in the prescreening 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).[104]

In the previous evidence review,[106] included data from the SCREEN study[126] suggested a 49 percent mortality reduction in the screening region compared to the surrounding regions at 5 years of followup from the end of the program (2003–2004 program; evaluation through 2009). However, updated data with longer followup to 2013 suggests that the mortality improvement previously reported appears to attenuate over time (**Table 6, Figure 5**). It should be noted that Germany as a whole had a fairly stable melanoma mortality rate between 1998 and 2010 (between 1.9 and 2.1 per 100,000), with a marginal increase between 2011 and 2013 (2.2 to 2.3 per 100,000). The SCREEN region's age-standardized mortality rate fluctuated more: higher than Germany's overall rate in the years preceding the SCREEN program (1998–2002); similar to Germany's overall rate during the SCREEN program (2003–2004); and decreasing to below the German rate around 2008–2010 when compared to Germany as a whole.[125] An additional analysis conducted of observed versus expected melanoma mortality in the SCREEN region (state of Schleswig-Holstein, northern Germany) compared to the state of Saarland (western Germany) from 2003–2008 found that observed melanoma deaths in the SCREEN region were lower than would be expected (age- and sex- adjusted standardized mortality rate 0.59, 95% CI, 0.40 to 0.83) (**Table 7**).[157] This is consistent with the 49 percent mortality rate reported in earlier publications.[126]

Melanoma Mortality in the German Screening Program

Based on German incidence rates used as the comparator in the 10-year followup of the SCREEN program, age-standardized melanoma incidence rates increased markedly at the time when the German national program was introduced. Age-standardized melanoma incidence rates increased from between 14.0 and 14.9 per 100,000 during 2003–2007, to between 17.7 and 18.2 per 100,000 during 2008–2011.

An evaluation of the German national program examined change in incident melanoma diagnoses based on hospital discharges. The multivariable fixed effects model suggested an

association of the German program with increased diagnoses in the unadjusted model (coefficient 0.276, SE 0.02, p<0.001). Although this effect was attenuated with the addition of covariates (coefficient 0.181, SE 0.02, p<0.001), an independent association of the screening program with new diagnoses appeared to remain. This finding suggests that the German program was effective in increasing new skin cancer diagnoses after 2008, while not in the surrounding European countries.[124]

Two included studies reported data on melanoma mortality in Germany related to the implementation of national skin cancer screening.[120, 121, 125] The first, a study by Datzmann and colleagues, observed a total of 325 melanoma deaths during the 4-year observation period, and found a higher proportion of melanoma deaths in the unscreened group compared to the screened group (171 deaths, 9.5% of the screened group; 154 deaths, 22.8% of the unscreened group; unadjusted HR 0.37, p<0.05) (**Table 8**).[121] On adjusted analyses, the association was attenuated but remained statistically significant (adjHR 0.62, p<0.05). The sensitivity analyses to assess potential lead time bias were similarly attenuated on both unadjusted (HR 0.50, p<0.05) and adjusted estimates (adjHR 0.75, NS).

A separate analysis of melanoma mortality from 2000 to 2012 between Germany and 22 other European countries found that the unadjusted mean annual melanoma mortality rate per 100,000 increased, not decreased, between the time period 2000–2007 (before the German national skin cancer screening program began in 2008) and 2008–2012 (**Table 9**). Although point estimates were not reported, similar increasing melanoma mortality trends were observed in many of the other European countries.[124] This evidence suggests that there is no observable benefit to national skin cancer screening.

Adjusted mortality rates were not provided, but the authors fit a multivariable fixed effects model using a hypothetical control group comprised of the included 22 European countries (excluding Germany) to estimate the screening program impact on melanoma mortality (**Table 10**). This model included population-level demographic variables (age, sex, physician density, education), and accounts for the years in Germany in which the SCREEN program took place (2003–2004) using dummy variables.[124] There was an association between mortality and the German program in the unadjusted model (coefficient 0.242, p<0.01), but with the addition of covariates there was no significant independent relationship between the screening program and mortality (coefficient 0.077, not significant). The authors concluded there was no significant overall effect of the German skin cancer screening program on melanoma mortality.[124]

Specific Population Results (KQ1a)

Three included publications from the two German screening programs reported age- and sex-specific melanoma mortality.[120, 124, 125] Data on race and/or ethnicity-specific or other specific populations was not reported.

In the SCREEN study, mortality rates were lower in females than males throughout the followup period (**Figure 6**). Female mortality rates for Schleswig-Holstein dipped below that of Germany in 2005 (the year after the SCREEN pilot ended) and then again in 2007–2010. No statistical tests of significance were reported. Female mortality rates appeared fairly steady, fluctuating

between 0.9 and 2.2 melanoma deaths per 100,000 for Schleswig-Holstein and 1.5 and 1.7 per 100,000 for Germany (**Table 6**).[125] Similar to the trend among females, for males the mortality rate was fairly steady, varying between 2.3 and 3 per 100,000 for Germany. The rate for Schleswig-Holstein males varied the most, with one dip in mortality in 2003 (the first year of the SCREEN program) and the lowest mortality observed in 2008 (1.1 per 100,000), then increasing steadily thereafter. Mortality rates increased in 2005 (just at the end of the SCREEN program) and appeared to be increasing toward the last 3 years of the followup period, approaching that of Germany as a whole (**Table 6**).[125]

The German National Screening Program publications reported findings on the impact of age on melanoma mortality. Although the fixed effects multivariable model in the Kaiser and colleagues study's model did not support an overall impact of the screening program, the proportion of the population over the age of 65 years did appear independently linked to improved mortality (coefficient 0.094, SE 0.03, p<0.001) (data not shown).[124]

The fluctuation in melanoma mortality reported in the SCREEN program appeared primarily in people aged 65 years or over (**Table 11**). Melanoma mortality rates were highest in both males and females in this age group, in both the SCREEN region and in Germany as a whole (**Figures 7 and 8**). In females aged 65 years or over, the mortality rate in the SCREEN region was highest in 2001 (13.2 per 100,000, two years before the SCREEN program began) and lowest in 2008–2009 (3.8 per 100,000; five years after the SCREEN program), increasing thereafter.[125] Similarly to females, in males aged 65 years or older, the mortality rate in the SCREEN region was also highest in 2001 (17.7 per 100,000; two years before the SCREEN program began), decreased to its lowest point in 2009 (5.7 per 100,000, 5 years after the end of the SCREEN program), then steadily increased to approach the German national mortality rate by the end of the followup period.[125] Additionally, in both males and females, melanoma mortality was similar in both the SCREEN region and in Germany by the end of the followup period in all age groups.[125]

In the analysis of the annual percent change in melanoma mortality in Germany compared to eight other European countries, there was little evidence of differential annual percent change in melanoma mortality in either males or females that could be attributable to the German program (**Table 9**).[120] Overall, in males, all countries except the Czech Republic saw a slight annual increase in melanoma mortality between 1980 and 2012. However, for the period 2008–2012 (the German program began 2008), the annual percent change was flat for all countries, including Germany.[120] For females in Germany, there was no significant annual percentage change for either the entire period 1980–2012 or the screening program period 2008–2012. Other countries saw more annual fluctuations in the percent change in female melanoma mortality over the longer observation period. The annual percent change among females remained flat for all countries, including Germany, for 2008–2012.[120]

Annual percent change in mortality data were only reported for both sex and age for the entire period 1980–2012. These data suggest that several countries, including Germany, observed a significant increase in melanoma mortality in males aged 60–74 years (Germany 1.4 APC, 95% CI, 0.6 to 2.1) and 75 years and older (Germany's was 1.6 APC, 95% CI, 1.1 to 2.1) compared to males under age 60 years. Germany's annual percentage change increase was smaller in the two age groups of males aged 60–74 years and 75 years or more compared to other countries

observing a significant increase in the annual percent change.[120] For females, a similar pattern was observed (Germany: age 60–74 APC -0.4, 95% CI -0.8 to 0; age 75+ APC 1.0, 95% CI 0.8 to 1.3), although the annual percent change increases were smaller than for males.[120]

KQ2. Does Routine Skin Cancer Screening Lead to Higher Rates of Detection of Precancerous Lesions or Earlier Stage Skin Cancer Compared to Usual Care (e.g., Lesion-Directed Skin Examination)? Do Rates of Earlier Skin Cancer Detection Vary by Subgroups (e.g., Age, Sex, Skin Type, Race/Ethnicity, Socioeconomic Status, or UV Exposure)?

Summary of Results

Based on nonrandomized observational data from four evaluations of three skin cancer screening programs (all fair-quality, n=2,344,210),[130, 132, 133, 135] and one good-quality physician-focused skin cancer examination initiative (n=595,799),[134] routine clinician skin examination does not appear to be associated with increased detection of KC, melanoma, or skin cancer precursor lesions compared to usual care or lesion-directed examination.

Three studies reporting heterogeneous categories of stage at detection suggested a similar lack of association between screening and stage at melanoma detection. Routine clinician skin examination was not associated with earlier detection in two studies, one using AJCC stage categories of melanoma *in situ*, stage I/II, and stage III/IV[133] and the other using SEER-comparable stages (presence of lymph node and distant metastasis).[135] However, in another study, the distribution of melanoma *in situ* at detection favored the screened group.[134]

There is mixed evidence on the association between clinician skin examination and lesion thickness at detection based on three nonrandomized studies reporting clinically relevant lesion thickness categories, with one study suggesting no association with lesions <1mm at detection but some association for lesions <2mm at detection,[130] and one study finding association for lesions <1mm only and not for lesions thicker than 1mm.[134] The third, a case-control study, found higher odds of having received a clinician skin examination in people with melanomas detected at <0.75mm thickness compared to unaffected controls, but not for thicker lesions; though people with lesions ≥3.00mm had significantly lower odds of having received an examination compared to controls.[129]

Detailed Results

Overview of Included Studies

Per our inclusion criteria, all studies included evaluations of visual skin examinations conducted by primary care physicians or dermatologists and compared precursor lesion detection or stage at

skin cancer detection between groups receiving either routine skin cancer screening or usual care.

Six nonrandomized studies with data on approximately 2.9 million individuals and 53,329 skin cancer or precursor lesions met inclusion criteria (**Tables 3-5**),[129-133, 135] one of which was carried forward from the previous review.[129] One of the six studies was conducted in the United States.[134] Study populations ranged from 497 to 34,295 skin cancer or precursor lesion cases. The outcomes assessed included precursor lesions (2 studies),[130, 132] stage at melanoma detection (3 studies),[133-135] and stage at KC detection (1 study).[133] Three studies reported thickness at melanoma detection,[129, 130, 134] and one study reported the odds of having received a clinical skin examination in people with and without skin cancer.[129]

We included four studies that reported analyses of three skin cancer examination programs that included outreach to patients. These three programs varied in their implementation and comparison group composition (**Tables 3 and 4**). Two included publications used data from the German National Skin Cancer Screening Program to compare people with skin cancer who had documented skin cancer screening to those without documented screening.[133, 135] One study compared skin cancer detection in people who had participated in a community-based screening program conducted in Trento, Italy, in 2001–2004 to skin cancer detection in the general population of the same city through 2013.[130] Lastly, a study conducted in Belgium compared skin cancer detection in two communities where different public outreach strategies were used for single 4- to 5-day screening events: in one community, people were invited to receive whole body examination; in the other community, people were invited to have suspicious skin lesions examined.[132] Screening participation rates were reported for two studies and were overall quite low: 12.4 percent in the German screening program;[135] and 17.9 percent in the total body screening group in Belgium compared to 3.3 percent for the lesion directed screening group in the Belgian study.[132]

The intervention in the U.S.-based study was a physician-focused decision support intervention and did not include direct outreach to patients.[134] In this quality improvement initiative in academic primary care clinics, full-body skin examination was added to the list of preventive care recommendations in the electronic health record of patients aged 35 years or older. Primary care physicians were offered training in diagnosing skin cancer and encouraged to participate in the initiative by medical center leadership.[131, 134]

Finally, a case-control study conducted in Queensland, Australia, identified cases among those with incident melanoma (n=3,762) and matched unaffected controls randomly selected through electoral rolls (n=3,824). The authors measured the association between self-reported whole-body physician skin examination during the three years before either the melanoma diagnosis for cases or referent date for controls and assessed the odds of having received a clinician skin exam within strata of melanoma lesion thickness at diagnosis.[129]

Population Summary

Screening population sizes were not always reported, but when reported they ranged from 1,328 to 533,393 in screened groups and 248 to 1,489,074 for unscreened/usual care groups (**Table 5**).

The largest population was for the German National Screening Program,[135] and the smallest was for the Belgian study.[132] In total, 53,329 detected skin cancer or precursor lesions were reported in this included body of evidence (n=11,182 melanoma cases; 41,686 KC cases, and 461 precursor lesion cases).

Overall, the intended screening populations were broadly defined adult populations (**Table 5**). The Italian study also included adolescents aged 15 years and older (mean age 40.2 years, range 15–84 years).[130] The screening populations were majority female, except for the Australian case-control study,[129] which used age- and sex-matching to select control participants. The sex distribution of the case group was not reported, whereas the control group was 57 percent male.[129] Only the U.S.-based study reported race and/or ethnicity for the screened group (88.4% White).[134]

Only the Belgian study reported measures of socioeconomic status, reporting the highest education level attained for both study groups.[132] There was a statistically significant different distribution of educational categories between groups, with the total body exam (screening) group trending slightly toward a lower educational level than the lesion-directed screening group (45.8% with no more than a high school education in the total body exam group compared to 38.9% in the lesion-directed screening group; p<0.01 for trend).[132]

Only one study reported skin cancer risk factors for screening populations.[132] In the Belgian study, distributions of Fitzpatrick skin type and nevus count were similar between the study groups (e.g., nevus counts of less than 25 were observed in 57.1% of the total body exam screening group and 58.0% of the lesion-directed exam group; p=0.96 for trend).[132] Family history of skin cancer was also reported at similar frequencies between the two groups (10.7% of total body exam screening group and 13.1% of lesion directed exam group, p=0.17).[132] Additionally, personal history of skin cancer was reported in similar small proportions of both study groups (2.4% in the total body exam screening group and 2.0% in the lesion directed exam group; p=0.84).

Demographic characteristics of detected cases were reported for three studies.[130, 134, 135] Two of these reported age and sex distributions of detected cases,[130, 135] and one noted that 99.2% of melanomas were diagnosed in patients who identified their race as Non-Hispanic White.[134] Risk factor characteristics were not reported for any detected case populations.

Quality

The single U.S.-based study was rated as good quality,[134] and the five other nonrandomized studies were rated as fair quality.[129, 130, 132, 133, 135] Quality concerns included unclear reporting of demographic and risk factors of study groups, unclear reporting of completeness of data and outcome assessment methods, handling of missing data, and the use of self-reported data for outcomes. In addition, one of the publications using German national screening data used a previously-published algorithm for estimating stage at melanoma detection from claims data, rather than direct observation of medical records, which could introduce misclassification errors.[133] Staging conventions, stage categories, and melanoma thickness categories were

heterogeneous across studies. None of the studies reported adjusting for lead time bias when reporting KQ2-relevant outcomes.

In the U.S.-based study, screened and unscreened groups were overall similar in age, sex, and insurance status, but some statistically significant differences were observed between screened and unscreened populations. The screened population was reported to be somewhat older (median age 60 years vs. 57 years, p<0.001), and race and/or ethnicity differed between groups (e.g., 6.8% of the screened population was Black, compared to 7.2% of the unscreened population, p<0.001).[134] Further, insurance coverage appeared more generous in the screened population compared with the unscreened population (3.0% Medicaid in the screened group compared to 6.3% in the unscreened group; p<0.001). Outcomes, however, were adjusted for age, sex, and insurance status.[134]

Detailed Results

Melanoma

Melanoma detection rates. Five included publications reported data on overall melanoma detection rates associated with routine screening in three European skin cancer screening programs and in one United States health system-based skin cancer screening initiative (**Table 12**).[130, 132-135] Across all three European programs, overall melanoma detection rates were similar between screened populations compared to usual care or lesion-directed examination populations. One evaluation of the German program using AOK PLUS data from 2005-2012 found melanoma detection rates were similar in the group receiving routine screening (0.31% case detection rate) compared to those receiving usual care (0.13% case detection rate).[135] A separate evaluation of the German program reported numbers of skin cancers detected but did not provide sufficient data to calculate the difference in detection rates.[133] In the Belgian study, melanoma case detection rates were 0.5 percent in the total body exam group vs. 0.4 percent in the lesion-detected exam group, p=0.87.[132] In the Italian screening program, the melanoma detection rate was 0.4 percent in both the screened group (initial screening and during the followup period after screening) and in the unscreened group.[130] In the U.S.-based study, melanoma detection rates were higher in the group with documented skin exam compared to the group without (0.25% in screened group, 0.14% in unscreened group; p<0.001).[134]

Stage at melanoma detection. The three studies reporting data on stage at melanoma detection used heterogeneous stage categories (**Table 13, Appendix E Figure 3**). Two of these were analyses of German national screening program data. One analysis used AJCC stage categories, including *in situ* melanoma,[133] and one analysis reported lymph node and distant metastases at detection.[135] The U.S.-based study reported distributions of *in situ* versus various thickness categories of invasive melanoma.[134]

Findings were inconsistent between two studies including *in situ* melanoma at detection. In the German study using AJCC stage categories (n=1536 melanoma cases), there was no association between screening and detection of *in situ* melanoma.[133] In the U.S.-based study (n=994 melanoma cases), *in situ* melanoma made up a larger proportion of cases in the screened group compared to the unscreened group (48.3% of all melanomas detected at *in situ* stage in screened

group vs 34.6% in unscreened group, adjusted hazard ratio [adjHR], 2.6 [95% CI, 2.1 to 3.1]; p<0.001).[134]

Findings were more consistent across two studies reporting stage at invasive melanoma only (i.e., excluding melanoma *in situ*); neither study found an association between skin cancer screening and stage at invasive melanoma detection. In the German study using AJCC stage categories (n=1536 melanoma cases), there was no difference between screened and unscreened groups at AJCC combined stages I/II, or combined stages III/IV at detection.[133] In the German study using AOK PLUS data from 2005-2012 (n=3504 melanoma cases), lymph node metastasis and distant metastasis were observed at similar rates between screened and unscreened groups. For example, lymph node metastases at detection were similarly detected in persons with documented whole-body screening (5.9%), and those without such documentation (8.5 percent).[135]

Thickness at melanoma detection. Findings were inconsistent between three studies reporting data on heterogeneous categories of melanoma thickness at detection from three countries: the United States, Italy, and Australia (**Table 13, Appendix E Figure 4**).[129, 130, 134] In the U.S.-based study, there was a higher adjusted hazard ratio in the screened group of detection at thickness ≤1mm (AJCC 7th edition sub-category T1) (adjHR1.8, 95% CI, 1.5 to 2.2; p<0.001), but not in the greater than 1mm category (AJCC sub-category T2-T4) (adjHR 1.0, NS).[134] In the Italian study of routine screening compared to usual care, the proportion of melanomas detected at <1mm thickness was similar between groups (70.4% in the screened group and 57.7% in the usual care group, p=0.242), but was higher for screen-detected melanomas detected at <2mm thickness
(AJCC sub-category T3-T4; 92.6% of in the screened group and 75.9% of melanomas in the usual care group, p=0.043).[130]

In the Australian case-control study, 28.3 percent (1083 out of 3,824) of controls reported receiving a clinical skin exam by a physician within the previous 3 years compared to 35.3 percent (1328 out of 3,762) of melanoma cases. The odds of having had a clinical skin exam by a physician decreased as thickness increased in an inverse linear pattern: 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).[129]

Keratinocyte Cancer

Keratinocyte skin cancer detection. Four included studies provided data on KC rates associated with routine screening from three screening programs (**Table 12**).[130, 132, 133, 135] Two of these used data from Germany during the German National Screening Program at different periods. One found a similar KC detection rate in the screened population compared to those who were unscreened (2.5% vs 1.2%, RR [95% CI] 2.16 [2.11 to 2.21]).[135] The other German study found similar numbers of KC cases in both screened and unscreened groups.[133] The Belgian study, a comparison of total body exam compared to lesion-detected exam as a result of community skin examination events in two neighboring communities, reported similar detection rates of both BCC and SCC in both the total body exam group compared to the lesion-directed exam group (BCC 1.8% detection rate vs 2.8%, p=0.28; SCC 0.1% vs 0%, p=0.99).[132] The

Italian study only reported BCC (12 [0.3%]) and SCC (1 [0.03%]) identified in the screening population making comparisons to the unscreened population impossible.[130]

Keratinocyte skin cancer stage at detection. Only a single study reported the stage of KC detection (**Table 13, Appendix E Figure 1**). In the German program (n=10,844 KC cases), similar distributions of KC stage in each group were reported (99.9% of KC cases detected at stage I/II in screened group; 99.8% in unscreened group).[133]

Precursor lesion detection. Two studies – the Belgian study of one-time total body examination compared to one-time lesion-directed examination, and the Italian study of total body examination compared with no screening – reported rates of detection of skin cancer precursor lesions (**Table 12, Appendix E Figure 2**).[130, 132] In the Belgian study, rates of actinic keratoses and atypical nevi were similar in both groups. Actinic keratoses was detected in 7.9 percent of the total body exam group and 7.8 percent of the lesion-directed exam group (p=0.90). Atypical nevi were detected at 15.1 percent of the total body exam group and 17.3 percent of the lesion-directed group (p=0.33).[132] As was the case with the KC data, in the Italian study the number of dysplastic nevi were only reported in the screening population (11 out of 3635 [0.3%]) and not the unscreened population.[130]

Specific Population Results (KQ2a)

No studies reported KC detection rates or KC stage at detection comparisons stratified by specific population groups.

The Australian case-control study (n=7,586), reported age- and sex-specific adjusted odds of having reported a clinical skin exam by a physician in melanoma cases according to increasing thickness compared to controls (**Table 14**).[129] The odds of having received a clinical skin exam followed similar patterns as the main result for age and sex subgroups, with thinner melanomas associated with higher odds of having received a clinical skin exam. Males with the thinnest melanomas (0.01mm to 0.75mm) were more likely to have received a clinical skin exam (adjOR 1.54, p<0.01), while males with the thickest melanomas (≥ 3mm) were less likely to have received a clinical exam (adjOR 0.62, p<0.05). The trend was present but not statistically significant among females.[129] Within both age strata (age 20-49 and age 50-74, males and females combined) the highest odds of having received a clinical skin exam were observed for people with the thinnest melanomas (0.01mm–0.75mm), while people with the thickest melanomas (≥3mm) had the lowest odds of clinical skin exam.[129]

The Italian study reported melanoma detection and thickness by sex and age in the screening population (n=3,635) (**Table 14**).[130] During the initial screening period, the majority of those with melanoma <1mm thick were females (7 of 10), whereas the majority of those with melanoma >1mm thick were males (3 of 4). This pattern was mirrored in the followup period (n=3,618).

The U.S.-based study reported melanoma detection rates and thickness at detection among those age 65 and older (**Table 15**). Findings were similar to those in the full study population. For example, melanoma detection rates were higher in the screened population (0.33%) compared to

the unscreened population (0.21%; adjHR 1.6 [95% CI, 1.3 to 2.0]; p<0.001). In addition, *in situ* melanomas made up a larger proportion of melanoma cases in the screened group (45.8%) compared with the unscreened group (38.5%; adjHR 1.9 [95% CI, 1.4 to 2.6]; p<0.001). There was a higher adjusted hazard ratio in the screened group for detection at thickness ≤1mm (adjHR 1.9 [95% CI, 1.3 to 2.6]; p<0.001) but not for thickness >1mm (adjHR 1.0 [95% CI, 0.7 to 1.6]; p=0.90).[134]

KQ3. What Are the Harms of Skin Cancer Screening and Diagnostic Followup? Do the Harms of Screening Vary by Subgroups (e.g., Age, Sex, Skin Type, Race/Ethnicity, Socioeconomic Status, or UV Exposure)?

Summary of Results

We identified only two small fair-quality nonrandomized studies that explicitly addressed the harms of skin cancer screening. One was conducted in Germany (n=45)[136] and assessed cosmetic acceptance of shave biopsy in a screened population at 6-month followup; lesions suspected of melanoma were excluded. The other was conducted in the United States (n=187)[137, 138] and assessed psychological wellbeing at 5 and 8 months after screening.

In the German study, 27 patients rated 7 percent (4 out of 56) of shave sites as having poor cosmetic outcomes at 6-month followup (median score 1.5, IQR [1–2], excellent to good). In the U.S.-based study of adults who underwent skin cancer screening by trained primary care providers (n=187), participants at 5- and 8-month followup assessment scored within the normal range on measures of anxiety, depression, or none to minimal psychological impacts of screening.

Detailed Results

Overview of Included Studies

Two fair-quality nonrandomized studies[136, 138] (n=232) met inclusion criteria, one of which was brought forward from the previous review (**Tables 3–5**).[136] One German study examined the cosmetic harms of shave biopsy excision.[136] The other study set in the United States reported on the potential psychological harms[137, 138] of skin cancer screening. The U.S. study was an evaluation of the same physician-focused decision support intervention that was included for KQ2[134] and was newly identified since the previous review. No included studies for KQ1 reported harms data. No included studies reported on procedure-related adverse events beyond 30 days (e.g., scar revisions) in screened populations.

One small study was conducted in Germany (n=45) in 2000 (**Table 16**).[136] This study assessed patient-reported cosmetic acceptance of deep shave excisions at 6-months of followup after excision. Only razor blade excisions of macular melanocytic nevi less than 15 mm in diameter were included in this study; lesions suspected of melanoma were excluded. Participants were

identified during routine skin cancer screening before the implementation of the German National Screening Program.

The other study was conducted in a United States academic medical center (n=187)[137, 138] (**Table 17**). Primary care providers who had completed an online training program for detecting and diagnosing skin cancer conducted skin cancer screenings. This study used various scales to estimate patient-reported psychological harms (e.g., anxiety, depression, physical and social consequences) and health-related quality of life at 5 and 8 months after screening. The study compared results between two screened patient groups—patients classified as those with "full body exam" and those with "partial body exam." Another comparison examined psychological indicators among patients who underwent biopsy following screening and those without biopsy at 5 months after screening. Although only people with skin cancer screening documented in their electronic medical record were included, group allocation was based on patients' self-reported screening and experience (i.e., recall of screening, the level of undress, and body parts examined).

Population Summary

The German study included persons aged 15–54 years (mean age 32 years);[136] the other study included adults aged 35 years and older (**Table 5**).[138] An estimated 44.4 percent of total participants in both studies were females.

In the U.S.-based study,[137, 138] 89.8 percent of participants were White, and 5.3 percent were Black. In this study, 20.9 percent of participants had a personal history of skin cancer, 58.6 percent had a family history of melanoma, and 40.1 percent had received previous skin exams.

Quality

Both included studies for this key question were rated fair quality. Both were nonrandomized cross-sectional studies with a very small number of participants and no unscreened comparator group. In the German study,[136] only 60 percent (27 out of 45) of recruited persons evaluated cosmetic outcomes of the shave sites. The results do not assess cosmetic results from excisional biopsies needed for melanoma diagnosis, which are more invasive procedures. Further, this study reports the number of shave sites, rather than the number of patients dissatisfied with the shave sites' appearance. The U.S.-based study[137, 138] did not assess for psychological or quality of life outcomes at baseline. The authors compared outcomes between two groups of patients based on the patients' recall of whether part of their body was examined or whether their whole body was examined for skin cancer five months prior to completing the survey.

Detailed Results by Outcome

A fair-quality study of routine outpatient cancer screening (n=45 patients, 56 deep shave excisions) assessed patients' perceptions of the cosmetic acceptance of deep shave excisions of macular melanocytic nevi with the razor blade technique at 6-months of followup (**Table 16**).[136] Patients used a four-point scale (1=excellent, 2=good, 3=moderate, or 4=poor) to evaluate cosmetic outcomes with no prespecified judgment criteria. The median patient evaluation score

was similar (1.5) and IQR [1–2] (excellent to good). Patients judged 7 percent (4 of 56) of shave sites as having poor cosmetic outcomes, 4 percent (2) as moderate outcomes, 39 percent (22) as good outcomes, and 50 percent (28) as excellent outcomes.

A fair-quality study[137, 138] estimated the potential for psychological harms and health-related quality of life after skin cancer screening among 187 adults at 5-months of followup and 126 (67.4% of 187) at 8-months of followup (**Table 17**). This study also estimated the potential for psychological harms associated with skin biopsy among 186 patients at 5-months following skin cancer screening.[137] This study assessed patients' anxiety and depression with the Hospital Anxiety and Depression rating scale (HADS), general anxiety with the Spielberger State-Trait Anxiety Index—form 6 (STAI-6), positive and negative psychological impacts of screening with the Psychological Consequences Questionnaire (PCQ), and health-related quality of life with the 12-Item Short-Form Health Survey (SF-12).

Participants had undergone skin cancer screening and were classified as having "full body examined" or only "partial body exam." Participants in both groups scored within the normal range on various scales, with no indication of anxiety, depression, or other negative psychological impacts from screening at 5- and 8-month followup assessment.[138] Participants with skin biopsy (n=23) and without biopsy (n=163) also scored within the normal range on psychological scales. Overall, there were no meaningful differences in psychological indicators between biopsied and non-biopsied patients.[137]

Specific Population Results (KQ3a)

We did not identify evidence on the potential harms of screening for specific populations.

KQ4. 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? Does This Association Vary by Subgroups (e.g., Age, Sex, Skin Type, Race/Ethnicity, Socioeconomic Status, or UV Exposure)?

Summary of Results

In three included nonrandomized studies (two good-quality, one fair-quality; n=407,133) reporting melanoma-specific mortality and three nonrandomized studies (one good-quality, two fair-quality; n=473,660) reporting all-cause mortality, progression of stage at detection was consistently and positively associated with increased risk of melanoma mortality. Risk estimates varied according to referent groups used. Compared to *in situ* disease at detection, adjusted hazard ratios for melanoma mortality were 5.8 (95% CI, 5.3 to 6.3) for localized, 31.5 (95% CI, 28.9 to 34.2) for regional, and 169.6 (95% CI, 154.2 to 186.6) for distant stage in one U.S.-based

study (n=185,219).[146] Two studies using localized stage at detection as the referent group found a similar pattern of increasing melanoma mortality risk with increasing stage.

In two studies (one good-quality, one fair-quality; n=135,490), melanoma mortality was higher for males than for females. Three studies (n=708,814) that examined melanoma mortality risk with respect to racial and ethnic groups found a higher risk among Black, Hispanic, and Asian American, Native American or Pacific Islander (AANAPI) adults compared with White adults. One of these found similar odds of melanoma mortality risk for White and Black persons within each stage of detection. In the other two studies with overlapping populations, melanoma mortality risk was higher among Black, Hispanic, and AANAPI adults with melanoma AJCC Stage I and SEER localized stages compared to White adults. One of these studies also demonstrated a higher risk of melanoma mortality among Hispanic persons with regional or distant melanoma stages compared with White adults.

Regarding all-cause mortality, the same pattern was observed over three large nonrandomized studies using varying referent groups. In one study (n=185,219), the risk for all-cause mortality was adjHR 1.5 (95% CI, 1.5 to 1.5) for localized, 3.9 (95% CI, 3.8 to 4.1) for regional, and 15.8 (95% CI, 14.9 to 16.7) for distant disease, compared to *in situ* melanoma at detection.

No included studies addressed KC mortality by stage at detection. We did not identify studies that evaluated the association between stage at diagnosis and skin cancer morbidity.

Detailed Results

Overview of Included Studies

A total of nine fair- or good-quality nonrandomized studies with data collected between 1975 and 2016 (n=1,326,051) were included[139-143, 145-147] (**Tables 18–23**). All nine studies were newly identified since the prior recommendation; however, some studies had overlapping populations. Seven studies (n=1,037,610) reported the association between stage at diagnosis and melanoma mortality,[139, 140, 142-146] and three studies[141, 146, 147] (n=473,660) reported the association between the stage of melanoma at diagnosis and all-cause mortality in adults. No included studies evaluated the association between stage at diagnosis and skin cancer morbidity. No studies contributed data for KC mortality.

No studies included in the 2016 review were carried forward for this KQ due to the change in our inclusion criteria to focus on stage at detection rather than independently on melanoma thickness, which is included in the AJCC staging criteria.

Population Summary

Studies used large databases with patient information from the United States (SEER, 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 six U.S.-based studies used the SEER and National Cancer Database data collected between 1975 and 2016 (median data collection period 22 [range 11 to 41] years) with

the longest period in the U.S.-based Qian 2021[144] study. Studies not conducted in the United States used data that were collected between 2003–2005 in Sweden,[147] 2008–2012 in Norway,[145] and 1995–2008 in Australia.[142]

Although the patient populations across the included United States studies overlap, these studies differed in the outcomes they presented (i.e., all-cause mortality, melanoma-specific mortality), melanoma staging systems they used (AJCC or SEER), referent stages the authors used to estimate the risk of melanoma mortality, and subgroup analysis (**Table 18**).

The weighted average age across all included studies was 59.0 years. Across included studies, 45.4 percent of all participants were female. All six U.S.-based studies provided information on participants' race and/or ethnicity.[139-141, 143, 144, 146] Most participants in these studies (96.0%) were white, 0.7% were Black, 0.8% were Asian American or Pacific Islanders, 0.2% were American Indian or Alaska Natives, and 3.0% of participants were of Hispanic ethnicity. Participants' personal, family, or environmental risk factors for skin cancer were rarely reported.

Quality

Among the nine included studies, six[139-141, 143, 144, 147] were rated fair- and three[142, 145, 146] were rated good-quality nonrandomized studies. The included studies used large national-level databases with the data systematically collected over many decades (i.e., SEER, Swedish Cancer Registry, Queensland Cancer Registry [Australia], Norwegian Malignant Melanoma Registry). The followup time was sufficient to observe mortality.

Quality concerns were primarily related to the limitations of nonrandomized studies using retrospectively collected data, which include the incompleteness and inaccuracy of the collected data, incompleteness of individual-level data, and unreported handling of missing data. For example, miscoding and missing data in the SEER database resulted in a restaging of a large number of diagnoses.[158, 159] In addition, the included studies either did not report how they handled missing data or reported omitting missing data from their analyses.

Detailed Results by Outcome

Melanoma Mortality and Stage at Diagnosis

Overall, seven fair- and good-quality studies reported an association between the stage of melanoma at diagnosis and melanoma mortality using either the AJCC or SEER stages (**Table 19**).[139, 140, 142-146] Four studies contributed data only for specific populations (see **Specific Population Results** subsection).[139, 140, 142, 144]

All three studies[143, 145, 146] with estimates across all participants demonstrated a consistent and statistically significant increase in the risk of melanoma mortality with disease progression. Two large U.S.-based studies using SEER staging with overlapping populations used different referent categories.[143, 146] A good-quality Ward-Peterson 2016 study (n=185,219) compared the risk for melanoma mortality at localized, regional, and distant melanoma with *in situ* melanoma diagnosed between 1982 and 2011.[146] Using *in situ* melanoma as the reference category, the

adjusted HR of risk for melanoma mortality was 5.8 (95% CI, 5.3 to 6.3) for localized, 31.5 (95% CI, 28.9 to 34.2) for regional, and 169.6 (95% CI, 154.2 to 186.6) for distant stages. The fair-quality Mahendraraj 2017 study (n=213,827) also demonstrated a statistically significantly increased risk of melanoma mortality at regional (OR, 3.8 [95% CI, 3.5 to 4.1]) and distant (OR, 7.5 [95% CI, 6.3 to 8.9]) stages compared to the reference group of local disease.[143] Another smaller study using SEER staging of 8,087 Norwegian adults demonstrated a trend similar to the U.S. studies—increasing risk for melanoma mortality within disease progression. Using the localized stage as the reference category, the adjusted risk of melanoma mortality was adjHR 4.00 (95% CI, 3.26 to 4.90) for regional disease and 16.82 (95% CI, 12.88 to 21.95) for distant disease.[145]

All-Cause Mortality and Stage at Diagnosis

Two fair-quality studies and one good-quality study (n=473,660) reported an association between the stage of melanoma at diagnosis and all-cause mortality in adults (**Table 20**). The studies used the AJCC,[141] SEER,[146] and tumor, node, metastasis (TNM)[147] sub-stages.

Two U.S.-based studies with overlapping populations (Farrow 2020 and Ward-Peterson 2016) used different staging systems. The Farrow 2020 study (n=268,668)[141] used the AJCC's stage IV as a referent stage and demonstrated that the risk for all-cause mortality was statistically significantly lower in patients with earlier stages. The risk of all-cause mortality was 62 percent lower in persons with stage III (adjHR, 0.38 [95% CI, 0.36 to 0.40]), 81 percent lower among those with stage II (adjHR, 0.19 [95% CI, 0.18 to 0.20]), and 91 percent lower in persons diagnosed with stage I (adjHR, 0.09 (95% CI, 0.08 to 0.10]), compared to persons diagnosed with stage IV melanoma between 2004 and 2015. The Ward-Peterson 2016 study used the SEER stages of *in situ*, localized, regional, and distant melanoma for adults diagnosed between 1982 and 2011. This study demonstrated similar results—disease progression is statistically significantly associated with a higher risk of all-cause mortality. In this study, the risk of all-cause mortality was 50 percent higher in persons with the localized stage (adjHR, 1.5 [95% CI, 1.5 to 1.5]), 290 percent higher in persons with the regional stage (adjHR, 3.9 [95% CI, 3.8 to 4.1]), and 1,480 percent higher among persons diagnosed with distant melanoma (adjHR, 15.8 [95% CI, 14.9 to 16.7]), compared with the reference group of *in situ* melanoma.

A third study[147] using TNM sub-staging of 19,773 Swedish adults found an increased risk of all-cause mortality within each T, N, and M stages. For example, the risk for all-cause mortality was statistically significantly higher among persons diagnosed with T4b (adjHR, 5.90 [95% CI, 5.17 to 6.74]) compared to those diagnosed with T1a, higher in persons diagnosed with N+ (adjHR, 2.24 [95% CI, 1.82 to 2.75]) compared to those with N0, and higher in those with M+ (adjHR, 3.17 [95% CI, 2.40 to 4.19]) compared to patients with the M0 substage.

Mortality and Lesion Thickness at Diagnosis

Lesion thickness at diagnosis was not an exposure of interest for this review, as the association of increasing tumor thickness and melanoma mortality was previously established by the systematic review to support the 2016 recommendation.[106] Two included studies (n=27,860)[145, 147] also reported the association between melanoma thickness and risk for either all-cause or

melanoma mortality. Consistent with the prior review, both studies showed an increased risk for either all-cause or melanoma mortality with increasing melanoma thickness at diagnosis.

In the Zheng 2020 study (n=19,773), the risk for all-cause mortality was higher among persons diagnosed with T4a (adjHR, 4.37 [95% CI, 3.72 to 5.13]) compared to those diagnosed with T1a.[147] In the Robsahm 2018 study (n=8,087), the risk for melanoma mortality was also statistically significantly higher among persons diagnosed with T4 (adjHR 9.68 [95% CI, 7.06 to 13.28]) compared to persons diagnosed with T1.[145]

Specific Population Results (KQ4a)

Three overlapping studies provided estimates of melanoma mortality risk stratified by race and/or ethnicity (**Table 21**). The Dawes 2016 study (n=96,953) used AJCC stages and White persons as a reference group to estimate the risk for melanoma mortality among Black, AANAPI, and Hispanic persons diagnosed with melanoma between 1992 and 2009.[139] This study demonstrated that Black persons, compared to White persons, had a statistically significantly higher risk of melanoma mortality at stages I (HR, 3.04 [95% CI, 2.34 to 3.95]) and III (HR, 1.86 [95% CI, 1.21 to 2.87]), but not at stages II (HR, 1.34 [95% CI, 0.92 to 1.95]) and IV (HR, 1.03 [95% CI, 0.68 to 1.57]). Additionally, the risk for melanoma mortality was statistically significantly higher among Black, AANAPI, and Hispanic adults aged 25–49, 50–74, and ≥75 years with melanoma stage I compared with White adults. Among pediatric patients and young adults aged 0–24 years, Black (HR, 9.50 [95% CI, 1.23 to 73.62]) and Hispanic (HR, 3.75 [95% CI, 1.22 to 11.56]) patients with stage II melanoma had a higher risk for melanoma mortality than White patients. The Qian 2021 study[144] (n=398,034) used SEER stages and White persons as a reference group to estimate the risk for melanoma mortality among Black, Asian or Pacific Islanders (API), American Indian or Alaska Native (AIAN), and Hispanic persons diagnosed with melanoma between 1975 and 2016 (**Table 22**). This study, which provided similar risk estimates as the Dawes 2016 study,[139] demonstrated that Black, Hispanic, API and AIAN persons diagnosed with localized melanoma between 2010 and 2016 had a statistically significantly higher risk (HRs) of melanoma mortality compared with White persons diagnosed at the same stage. This study also found that Hispanic individuals diagnosed with regional and distant melanoma between 2010 and 2016 had a higher risk of melanoma mortality compared with White persons at the same stages. The Mahendraraj 2017 study[143] (n=213,827) used SEER stages to estimate melanoma mortality risk for White (n=212,721) and Black (n=1,106) persons diagnosed with melanoma between 1988 and 2011. Overall, 19,207 (9.0%) of White and 241 (21.8%) of Black persons died of melanoma during the observation period. The risk for melanoma mortality was statistically significantly higher among persons with regional and distant stages for both White and Black persons than the reference group of localized disease (**Table 21**).

Two studies (n=135,490) compared the difference in the risk of melanoma mortality between females and males by stage (**Table 23**). The U.S.-based Enninga 2017 study[140] (n=106,511) used SEER stages to compare the risk for melanoma mortality among females and males diagnosed with melanoma between 1992 and 2011. The age-adjusted risk of melanoma mortality among males was higher at the localized (adjHR 1.59, [95% CI 1.49 to 1.70]), regional (adjHR 1.37, [95% CI 1.28 to 1.47]), and distant (adjHR 1.10, [95% CI 1.01 to 1.20]) stages than among

female patients. The higher risk for melanoma mortality for males persisted across all age categories (i.e., 18–45, 46–54, and ≥55) for persons with the localized and regional stages; however, the difference between males and females with distant disease for the same age groups was not statistically significant. The Australian Khosrotehrani 2015 study[142] (n=28,979) compared the risk for melanoma mortality at different AJCC stages among females and males by stage. The data for AJCC stages III and IV were combined due to the small number of persons diagnosed with these stages. In this study, the risk of melanoma mortality for females of any age (15–45 years, 46–59 years, and ≥60 years) was 36 percent lower (adjOR, 0.64 [95% CI, 0.51 to 0.82]) at stage I and 29 percent lower (adjOR, 0.71 [95% CI, 0.58 to 0.87]) at stage II compared with male patients. There was no statistically significant difference in the risk of melanoma mortality between females and males with the combined III and IV stages (adjOR, 0.70 [95% CI, 0.44 to 1.10]). Female patients with stage II and aged 15–45 and those with any stage aged ≥60 years also had a statistically significantly lower risk of melanoma mortality compared with male patients.

Chapter 4. Discussion

Summary of Evidence

We conducted this systematic review to support the USPSTF in updating their 2016 recommendation on skin cancer screening. This review assessed the effectiveness and harms of routine screening with clinician visual skin examination and the associations between screening and stage or thickness at detection and between stage at skin cancer detection and melanoma and all-cause mortality. Since the previous review,[106] we have included 17 new studies. Among them are two new studies reporting on the national skin cancer screening program in Germany (KQ1);[124] five new studies comparing stage or lesion thickness at detection between routine skin examination compared to usual care (KQ2);[129, 131-133, 135] nine new studies assessing the association between stage at skin cancer detection and mortality (KQ4);[139-143, 145-147] and one new study providing data on the potential psychosocial harms of screening (KQ3).[138] Overall, our findings align with the results of the 2016 systematic review. A summary of the evidence for each key question is shown in **Table 24** and summarized below.

Melanoma

Direct Evidence of Benefits of Clinician Visual Skin Examination

All direct evidence on screening effectiveness comes from nonrandomized analyses of population-based skin cancer screening programs in Germany.[120, 121, 124, 125] Since the previous review, longer followup data for mortality has been published for the SCREEN skin cancer screening program—a regional pilot screening program included in the previous review—adding non-overlapping national skin cancer mortality data following the introduction of a national skin cancer screening program and one analysis of melanoma mortality using German health insurance claims data.

Population-level mortality statistics alone suggest no melanoma mortality benefit associated with routine skin cancer screening in German regions offering routine screening compared to regions without routine screening programs. Individual-level data available in one included study suggests a potential mortality benefit associated with skin cancer screening in the German program that was attenuated on multivariable analyses and sensitivity analyses to assess lead time bias.[121] However, despite a well-conducted study, several limitations remain in this observational analysis, including potential healthy screenee bias, lead time bias, and inability to assess overdiagnosis. Limited data on melanoma mortality rates in specific population groups were available. There was some evidence of reduced mortality in screened persons over age 65, in particular, for males. However, these results should be considered hypothesis-generating, given the limitations of the included study designs.

Our findings about the lack of available evidence are consistent with a 2019 Cochrane Collaboration systematic review,[160] which included only randomized trials of screening in people without suspected melanoma. Primary outcomes were total mortality, melanoma overdiagnosis,

quality of life, and psychosocial consequences. The review reported on two trials of skin cancer screening. One trial's main outcome was increasing skin self-examination, and the other was a pilot study that never led to a randomized trial. Neither study reported on any of the review's primary outcomes; nor did they report melanoma mortality or other outcomes of interest for our review. Neither study was included in our review.

Our conclusions are limited substantially by the lack of randomized studies and by the limitations of ecologic study designs, including the inability to conduct individual level analyses of screening benefit, such as screening program participation and impacts in specific population groups. Applicability to U.S. settings is difficult to assess, particularly with respect to specific population groups (e.g., race or ethnicity) and health system differences. Thus, we find an overall low strength of evidence for no to limited melanoma mortality benefit.

Indirect Evidence on the Potential Benefits of Skin Cancer Screening

Given the lack of direct evidence on the benefits of skin cancer screening, the USPSTF is interested in evidence along the indirect pathway through which skin cancer screening could result in improved mortality and morbidity. This indirect evidence includes two questions: whether visual skin examination by a clinician is associated with thinner lesions or earlier stage at detection compared to usual care, and whether early stage at detection is associated with lower melanoma and all-cause mortality.

Association Between Clinician Skin Exam and Lesion Thickness or Stage at Diagnosis

Based on three studies reporting detection of *in situ* melanoma or stage at invasive melanoma detection and three studies reporting thickness at melanoma detection in screened populations, the body of evidence is inconsistent.

Based on two analyses of German screening program data, there is no evidence of an indirect screening benefit through earlier stage at invasive melanoma detection. The body of evidence is less consistent with respect to *in situ* melanoma and thickness at melanoma detection. In a study of routine clinician skin examination conducted as part of a U.S.-based clinical decision support initiative, the proportion of *in situ* melanomas (versus invasive melanoma of any stage) was higher in the group receiving skin examination (48.3% of total melanomas detected *in situ* in screened group vs. 34.6% in unscreened group, adjHR 2.6 [95% CI, 2.1 to 3.1]; p<0.001).[134] However, an analysis of German National Screening Program data found similar rates of *in situ* melanoma detection in both screened and unscreened groups.[133]

Findings also were inconsistent for the association between skin exam and melanoma thickness. Across three studies reporting melanoma detection of lesions <2 mm (AJCC Stage IB–IIA) or <1 mm thickness (AJCC Stage IA and IB), no clear association or estimation of magnitude of effect was apparent. While one Australian study suggested a pattern of thinner melanoma lesions associated with skin examination and, conversely, thicker lesions associated with lack of skin exam; this was not supported in the other two studies, which both found inconsistent evidence between heterogenous thickness categories. Together the three studies do not provide consistent

evidence about which thickness categories (e.g., the thinnest lesions) might be associated with a screening benefit.

Several limitations of these studies should be noted. Stage and thickness categories were heterogeneous, limiting pooled analyses and direct comparisons across studies. In addition to small numbers of melanoma cases in several studies, delivery of skin examination varied widely, including community-based skin examination events, a national population screening program, a physician-focused initiative with no patient involvement, and a case control study measuring patient self-report of skin examination. Community-based and physician-focused events, in particular, likely include a mix of lesion-directed (i.e., patient-detected) and asymptomatic population-based screening, which could dilute any association between true population screening and stage or thickness at detection. Further, skin examination in these studies was conducted by a mix of dermatologists and primary care clinicians; as discussed below (see **Test Performance Considerations and Potential for Overdiagnosis and Overtreatment**) accuracy of clinician visual skin examination appears similar between primary care or specialist clinicians, but the total number needed to biopsy to diagnose one melanoma may be higher compared to dermatologists.

Taken together, the body of evidence on invasive melanoma stage at detection, *in situ* melanoma at detection, and melanoma thickness at detection offers inconsistent indirect evidence at best of a benefit of visual skin examination through earlier stage at detection or detection of thinner lesions. Given their inconsistency, 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 <1 mm in thickness. The overall strength of evidence is low for inconsistent evidence about visual skin examination and detection of thinner melanoma or *in situ* melanoma at detection.

Association Between Stage at Diagnosis and Melanoma or All-Cause Mortality

Our review found across nine nonrandomized studies that there is a strong, consistent positive association between advancing stage at melanoma detection and increasing melanoma mortality and all-cause mortality risk. Specific relative risk estimates varied with the choice of referent group (*in situ* melanoma versus localized stage at detection), risk measure, adjustment variables, and staging system used (AJCC or SEER summary stage), but the positive relationship was the same across studies. These findings should be viewed as confirmatory of the substantial body of literature establishing stage at melanoma diagnosis—which for early stage primarily refers to lesion thickness—as a primary prognostic indicator of melanoma survival. The AJCC melanoma staging system is updated based on survival analyses of a large (>46,000) international cohort of persons with melanoma,[5, 161] and reflects clinically relevant categories of lesion thickness, nodal involvement, and metastasis based on their prognostic relationship to melanoma survival considering current treatment options.[5] Our review adds measures of mortality, rather than relative survival, and limited information on specific population groups. One large U.S.-based study[144 162] found that melanoma mortality risk was lower for White persons with localized melanoma than for Black, Hispanic, API, and AIAN persons with the same stage. Overall, this body of evidence has a high strength of evidence and underscores the widely accepted and well-

studied notion that early detection and treatment of melanoma is associated with improved mortality outcomes.

Keratinocyte Cancers

No direct evidence was available in the included studies about the benefits of skin cancer screening for keratinocyte cancers of the skin. Four included studies suggest that routine clinician skin examination was not associated with either increased detection or stage at detection of keratinocyte skin cancer (overall strength of evidence is low). No evidence was available in the included studies about the association between stage at KC detection and skin cancer or all-cause mortality.

Harms of Skin Cancer Screening

Direct evidence on harms of skin cancer screening continues to be sparse. Hypothesized harms from screening include cosmetic harms (e.g., scarring) from diagnostic workup, psychosocial harms (e.g., worry) from the screening process, and overdiagnosis and overtreatment. Based on included evidence from two small studies,[136, 138] one examining cosmetic harms and the other psychosocial harms from screening, there is little to no evidence of persistent harms associated with screening. These findings are consistent with studies conducted in unscreened populations suggesting minimal persistent patient-reported harms from skin cancer surgery at up to 6 months after surgery.[163-165] Overall, given the small number of studies focused on screened populations, the included body of evidence is insufficient to fully assess psychosocial or cosmetic harms of skin cancer screening.

Our review found no studies directly examining overdiagnosis or overtreatment harms from skin cancer screening, although this remains a potential harm of skin cancer screening (see **Potential for Overdiagnosis and Overtreatment**).

Contextual Considerations

Risk Assessment Tools in Primary Care

Given the clear link between early detection of melanoma and mortality, identification of individuals at risk of skin cancer could benefit clinical practice through the development of validated risk assessment tools. Multiple risk assessment tools have been developed, typically using established risk factors for melanoma (e.g., fair skin, increased number of nevi, family history of melanoma, polygenic risk). Polygenic risk scores for skin cancer risk prediction may show promise, but these are early in development, and none have been externally validated.[166-168]

A 2020 systematic review aimed to evaluate published risk assessment models for melanoma and concluded that there is a lack of consensus across models, most of which have not been externally validated. There was substantial heterogeneity in risk factor selection, methods, and validation,[169] prohibiting direct comparisons between models. Only six of 40 included studies

validated their findings using external datasets. One study validated their findings using multiple external datasets (Western Australian Melanoma Study, Leeds Melanoma Case-Control Study, the Epigene-QSkin Study, and the Swedish Women's Lifestyle and Health Cohort Study),[170] while the other five used a single external data set for validation. This demonstrates a need for more validation studies of existing models, focusing on external validation using multiple data sources, before these models are ready for clinical use.

Test Performance Considerations

In most cancer screening, a device or test (e.g., mammography) is used to visualize cancers that might not be detected otherwise, and a patient receives diagnostic workup and followup care subsequent to the screening visit. Assessment of test performance is typically limited to the qualities of the device or test. However, clinician visual skin examination uses clinical judgment and is not the only way to visualize concerning lesions, as people can self-examine their own skin. Treatment can often be completed with lesion removal at the time of detection, conflating assessment of the screening and diagnostic workup processes. Thus, traditional measures of test performance (e.g., sensitivity, specificity, false positives) may be less interpretable for skin cancer than with other cancer screening tests. But as an ideal screening test, visual skin examination would accurately identify and triage all malignant lesions and minimize unnecessary biopsy of false positives. Influencing factors might include training or subspecialty of the screening clinician; the use of assistive tools during visual examination (e.g., dermoscopy or confocal microscopy); asynchronous vs. in-person clinician review of lesions; and use of artificial intelligence apps.

Primary Care vs. Subspecialist Setting/Screening

Few studies have examined the test accuracy of a visual screening inspection in primary care, and even fewer have examined the accuracy of initial skin examination in persons without self-identified lesions. These studies are often limited by their small size, uncertain or high risk of bias, and low applicability to a general screening population. A 2018 review[113] conducted by the Cochrane Skin Cancer Diagnostic Test Accuracy Group examined the diagnostic accuracy of visual skin examination for diagnosing cutaneous melanoma. Setting (primary, secondary, specialist) was not associated with statistically significant differences in the accuracy of visual skin inspection and across 39 datasets and various types of skin examinations (i.e., first examination; diagnosis of a previously identified suspicious lesion). Similarly, the relative diagnostic odds ratio of secondary care or a specialist clinic compared to primary care was 1.51 (95% CI, 0.32 to 7.09). The use of a named diagnostic algorithm (e.g., ABCDE) compared with no reported algorithm did not improve accuracy (relative diagnostic odds ratio 1.03 [95% CI, 0.25 to 4.34]).

The 2018 review[113] identified no studies of true population-based screening with visual exam but did include three studies prospectively recruiting primary care patients seeking review of suspicious lesions (lesion-directed screening). These studies were conducted outside the United States in Italy, England, and Australia. Only one[171] of the three studies reported patient characteristics; patients were primarily men (64%), White (94%), and aged 45 years or younger (55%). Among these primary care patients with suspicious lesions, there were a total of 1339

lesions and 55 melanomas. Individual study estimates for sensitivity to detect melanoma varied widely (ranging from 0.34 to 1.0). Pooled sensitivity to detect melanoma was high, though this estimate was imprecise (sensitivity 0.924, 95% CI, 0.262 to 0.998). Pooled specificity was 0.797 (95% CI, 0.737 to 0.847), suggesting a potential opportunity for training to improve diagnostic abilities. With these pooled estimates, if a clinician saw 1000 suspicious lesions where 90 were melanoma, 83 would correctly be identified as melanoma (**Figure 9**). But 185 lesions would incorrectly screen positive and be unnecessarily subject to biopsy.

Clinician visual skin examination by either primary care or specialist clinicians can detect and diagnose most melanomas; additional training in melanoma diagnosis may further enhance these skills. A 2021 review of 31 training programs for primary care physicians found that training can improve melanoma diagnosis (e.g., improved confidence, decrease in dermatologist referral for ultimately benign lesions, and improved benign/malignant ratio of referred lesions) although trainees may require refresher or booster training material for a sustained effect.[172]

Use of Magnifying Tools During Visual Skin Examination

Magnifying tools, such as dermoscopy or confocal microscopy, might also help improve accuracy further. A related systematic review[173] found that two of three studies conducted among primary care patients with suspicious lesions also compared visual inspection alone to visual inspection plus dermoscopy. In both studies, visual inspection plus dermoscopy improved the test accuracy to detect melanoma. In one study,[78] both sensitivity (0.53 vs 0.38) and specificity (0.89 vs 0.85) improved, but the confidence intervals overlapped. In the second study,[174] sensitivity was the same for both screening approaches (1.0), but specificity was higher when a dermoscope was added (0.90 vs 0.73).

Reflectance confocal microscopy alone or in addition to dermoscopy to detect melanoma and atypical intraepidermal melanocytic variants may further enhance accuracy, but is typically limited to specialty settings.[175]

In-Person Screening vs. Asynchronous or Virtual Visual Skin Examination

In-person visual skin examination appears more accurate than asynchronous lesion review. The Cochrane systematic review also examined how in-person visual examination compared to asynchronous clinician review of images. Across 39 datasets, in-person visual examinations (28 datasets) to detect melanomas had much higher accuracy compared to only asynchronous clinician review of clinical images (11 datasets) (relative diagnostic odds ratio 8.54; 95% CI, 2.89 to 25.3).[113]

Additional Test Performance Considerations

Teledermatology includes dermatologist examination of digital images asynchronously or via live video consultation and appears to have high sensitivity with mixed specificity. A systematic review[176] completed by the Cochrane Skin Cancer Diagnostic Test Accuracy Group identified 22 teledermatology test accuracy studies; 16 of these examined test accuracy and six studies

examined the referral accuracy. Four studies reported a pooled sensitivity of 0.949 (95% CI, 0.901 to 0.974) and pooled specificity of 0.843 (95% CI, 0.485 to 0.968).

Another related systematic review[177] examined the accuracy of five different smartphone applications to detect melanoma or atypical intraepidermal melanocytic variants, which could help improve access to dermatology review of patient-identified suspicious lesions. Two studies were identified; one examined the accuracy of an application where a dermatologist assessed the images and three artificial intelligence-based applications and the other study examined one artificial intelligence-based application. Together these studies examined 332 lesions and 86 melanomas. Accuracy of the four AI-based applications varied widely: sensitivity ranged from 0.07 (95% CI, 0.02 to 0.16) to 0.98 (95% CI, 0.90 to 1.00) and specificity from 0.30 (95% CI, 0.22 to 0.40) to 0.94 (95% CI, 0.87 to 0.97). The accuracy of the application storing images to be reviewed by a dermatologist reported a sensitivity of 0.73 (95% CI, 0.52 to 0.88) and a specificity of 0.83 (95% CI, 0.75 to 0.89).

Potential for Overdiagnosis and Overtreatment

Overdiagnosis generally refers to the detection of a condition that would not have caused illness in the absence of detection. Overdiagnosis in cancer screening is defined as the detection of a (histologically confirmed) cancer through screening that would not otherwise have been diagnosed in a person's lifetime had screening not been done. Overtreatment is a potential consequence of overdiagnosis, and is defined as treatment provided after identification of incidental findings of uncertain significance, overdetection of precancerous lesions, or overdiagnosis or misdiagnosis of cancer and that may not benefit the patient.[178]

Direct measurement of overdiagnosis is not possible but may be explored indirectly using long term trial data or population data. Unexplained increasing excess incidence of skin cancer can indicate the presence of overdiagnosis, though the excess-incidence approach can result in overestimates of overdiagnosis.[178, 179] Concern about melanoma overdiagnosis was first raised in the 1990s, following observations[16, 180-182] of a trend that continues divergence between increasing melanoma incidence and a relatively flat melanoma mortality rate. Based on SEER data, in the United States, the annual incidence of melanoma increased from 7.9 to 25.3 per 100,000 individuals between 1975 and 2018, while mortality remained stable (death rates per 100,000 were 2.07 in 1975 and 2.01 in 2018) (**Figure 1**). Melanomas diagnosed at early stages (*in situ* and lesions less than <1 mm thickness[183]) are the main contributors to the increased incidence.[19]

Potential explanations of increasing incidence of melanoma include an aging population; increased UV exposure via increased sun exposure and tanning bed behavior; changes in histopathologic criteria that result in higher sensitivity; better reporting of melanoma; and increased diagnostic scrutiny.[183, 184] Increased diagnostic scrutiny could indicate overdiagnosis, especially in the absence of improved health outcomes, as is demonstrated in the case of melanoma.

Neither the 2016 USPSTF skin cancer screening evidence review,[106] nor a 2019 review of the effects of skin cancer screening commissioned by the Cochrane collaboration, found trial data on

overdiagnosis[160] associated with patient-, caregiver-, or provider-directed screening. The included studies in our review reveal little new information about potential overdiagnosis, limited to estimates of increased incidence from population data without accompanying evidence of a mortality benefit. After the introduction of the German program in 2008, skin cancer incidence rose sharply for both melanoma and KC (**Figures 3, 4, and 10; Appendix E Table 1**).[135] As measured by skin cancer-related hospital discharges as a proxy for incidence, a similar increase did not appear in surrounding European countries during the same period.[124] This suggests that skin cancer screening could potentially result in overdiagnosis of skin cancer without evidence of improved mortality, but no direct evidence was available.

Overtreatment of skin cancer could be estimated by measures of unnecessary excisions or lesion removal. One of these measures is the number needed to biopsy (NNB), if a skin lesion is inappropriately classified as malignant and sent to biopsy. This misclassification can be related to clinician training or inappropriate clinical guidelines. For skin cancer, however, interpretation of these measures is complicated since lesion removal, followed by biopsy, can serve as the complete treatment. In a systematic review of 46 studies of 455,496 biopsied tumors and 29,257 biopsied melanomas, the weighted mean number needed to biopsy (NNB) for a diagnosis of cutaneous melanoma was 14.8 (ranging from 2.2–30.5) for any health care providers, 14.6 for Australian primary care practitioners, 13.2 for U.S.-based dermatologists and advanced practice professionals, and 7.5 for dermatologists in all studies (confidence intervals not reported).[185] In another meta-analysis of 36 observational studies and 398,549 biopsies, the NNB was estimated to be 9.71 (95% CI, 7.72 to 12.29, I^2=99.7%) across all specialties. The NNB was estimated to be 22.62 (95% CI, 12.95 to 40.10; k=6, I^2= 99.8%) for primary care practitioners, to be 9.60 (95% CI, 6.97 to 13.41; k=14, I^2=98.0%) for dermatologists, and to be 5.85 (95% CI, 4.24 to 8.27; k=12, I^2=97.6%) for dermatologists with a subspecialty in pigmented lesions.[186] However, the authors acknowledged that specialists may have a lower NNB than primary care providers because specialists see a higher proportion of high-risk patients.[186]

One observational study (not included in our review) used Australian national data to examine excess lifetime risk of melanoma in 2012 compared to 1982 to estimate melanoma overdiagnosis.[187] The excess incidence approach in this study assumed the same diagnostic intensity in 1982 and 2012. For women, this study found that the absolute lifetime risk of melanoma diagnoses, including *in situ*, increased by 5.1 percent, and the risk for invasive melanoma increased by 0.7 percent from 1982 to 2012. Among women, the estimated overdiagnosis of melanoma detected at any stage, including *in situ*, was 53.7 percent (95% CI, 51.3% to 56.1%) with 10,492 cancer diagnoses and 5,634 (95% CI, 5,386 to 5,882) overdiagnosed melanomas in 2012. Overdiagnosis of invasive melanoma was estimated to be 15.2 percent (95% CI, 11.4% to 19.0%) with 5,088 diagnoses and 744 (95% CI, 580 to 968) cases of overdiagnosed melanoma.

Another observational study assessed dermatology visits and skin surgeries among patients of PCPs who did and did not undergo training in diagnosing skin cancer as part of the U.S.-based physician-focused decision support intervention included for KQ2 and KQ3. In the group with the highest percentage of trained providers, there was a 79% increase in melanoma diagnoses (95% confidence interval, 15% to 138%) and no substantial increase in skin surgeries or dermatology visits in any group at 6.5 months follow up.[188]

Serious Harms of Skin Cancer Treatment

Mohs micrographic surgery is a planned procedure for treatment of skin cancer, particularly KC. It occurs separately from screening and is generally associated with a low risk of serious adverse events. A multicenter prospective cohort study of 23 medical centers found that out of 20,821 Mohs procedures, 179 adverse events were reported, for an adverse event rate of less than 1 percent (0.72%).[189] Serious harms that have been reported due to Mohs procedures and wide local excision include infection, functional loss, and superficial skin necrosis.[189, 190] Serious harms from other surgical treatments such as excision, and electrodesiccation and curettage are rare, but include scarring or disfigurement, nerve damage, persistent pain or sensitivity at the surgical site, and infection.[191-194]

Topical treatments, such as 5-flurouracil and imiquimod creams, are commonly used to treat superficial KC or actinic keratosis when surgical excision is not optimal or desired by the patient.[79, 195] Serious harms from these treatments include severe stomach pain, vomiting, and blistering of the treated skin, as well as burning, crusting, erythema, permanent hypopigmentation, erosion, rash, and pain at the treatment site.[196-198] These effects have been reported to peak at approximately 6 weeks of treatment but can persist up to 2 years.[196] Additionally, flu-like symptoms such as nausea, fever, fatigue, and muscle weakness have been associated with both treatments. Photodynamic therapy (i.e., a combined use of a drug [photosensitizing agent] along with the light) is mainly used to treat superficial KC. Serious side effects from this therapy are extremely rare.[199]

Serious harms from radiation therapy and chemotherapy have been well documented, and include hair loss, permanent pigment changes, dermal fibrosis, peripheral neuropathy, and memory loss.[79, 85, 200-203] These conditions typically resolve once treatment is completed; however, some patients may continue to experience lasting effects.

Serious side effects of immunotherapies have been reported in approximately 10 to 55 percent of patients.[84, 203] For immune checkpoint inhibitors these include dermatitis, colitis, pruritus, vitiligo, skin eruptions, extreme fatigue, the aggravation of existing autoimmune conditions, and in rare instances, death.[79, 84, 85, 203] Reported side effects from BRAF/MAPK inhibitors include severe ultraviolet A-induced photosensitivity, painful palmoplantar keratosis, hair loss, thickening of the skin of the palms/feet, the development of cutaneous SCC, and dermatitis.[79, 204] More than 90 percent of those on BRAF monotherapies experience adverse events and approximately 40 percent of those on checkpoint inhibitors will experience autoimmune skin conditions.[79] Approximately 25 percent of patients experience persistent symptoms.[204, 205] Reported adverse events associated with treatment with TVEC include nausea, fatigue, flu-like illness, and cellulitis.[84] Immunotherapy treatment, used in combination or alongside more traditional therapies, continues to be the focus of active research.

Ongoing Trials

According to ClinicalTrials.gov, as of April 2022, six trials relevant to skin cancer screening in adults are ongoing. However, none of these trials evaluate the benefits and harms of population-based skin cancer screening (**Appendix F**).

Limitations of Approach

This review focuses on the benefits and harms of routine clinician visual skin examination in adolescents and adults without self-identified skin lesions of concern. Preventive counseling to encourage sun protection behaviors and patient or partner skin self-examination are not included here and are addressed in another USPSTF recommendation statement.[99] Similarly, clinician review of patient-identified concerning skin lesions (frequently called "screening" in the literature) was out of scope. To provide the best available evidence on skin cancer screening effectiveness, we included ecologic study designs, which have inherent limitations that would likely not be included in the presence of more robust study designs. Further, we excluded screening programs that did not primarily include clinician skin examination, limiting our ability to comment on technology-based forms of skin examination.

Our review is limited to harms explicitly related to screening, biopsy, or excision in screened populations, and may have missed relevant data in other populations (e.g., persons seeking diagnostic workup of suspicious lesions). This may have narrowly limited the assessment of cosmetic harms of shave biopsy/diagnostic workup. Further, we limited our review to studies of persistent harms beyond 30 days, which precludes our ability to comment on patient-reported harms before, during, and immediately after screening.

We limited our assessment of the association between stage at detection and health outcomes to mortality outcomes, excluding relative survival outcomes (e.g., 5-year survival). This focused our review on the health outcomes important to the USPSTF, but in so doing we may have missed relevant information, particularly on survival outcomes in specific population groups.

Test performance considerations and potential overdiagnosis related to skin cancer screening are considered contextually in this review, not through systematically reviewed key questions.

Limitations of the Literature

The lack of direct individual-level or trial data on the effectiveness of skin cancer screening is a primary limitation of the literature. Since no national organizations recommend routine skin cancer screening by clinicians, and since large trials of skin cancer screening may not be feasible and none are underway, the included evidence from Germany currently represents the best evidence available. Little data on specific population groups was available and may represent a missed opportunity to provide evidence about risk-based skin cancer screening approaches. There was very limited information about the effectiveness and harms of screening for

keratinocyte cancers. This is not surprising, since keratinocyte cancers are not reportable diseases to cancer registries.

Included studies of the association of stage at detection and skin cancer mortality tended to use summary stage categories rather than the AJCC staging system, limiting assessment of substages, particularly lesion thickness, in early-stage melanoma. Included studies of the association between clinician skin exam and earlier detection of skin cancers described heterogeneous settings, skin examination procedures, and comparison groups.

Future Research Needs

The highest quality evidence for direct effectiveness of skin cancer screening would come from randomized controlled trials. However, these trials may not be feasible. The body of evidence from non-randomized 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, UV exposure, or 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 to those with melanoma detected through usual care or lesion-directed examination. Evidence on potential overdiagnosis and subsequent overtreatment of early-stage skin cancer would also be beneficial.

Conclusion

A substantial observational evidence base suggests a clear association between earlier stage at skin cancer detection and decreased mortality risk. However, nonrandomized studies suggest no melanoma mortality benefit associated with skin cancer screening in adolescents or adults in regions with implemented routine screening compared to regions without routine screening, and limited evidence for potential benefit from one nonrandomized study. Nonrandomized evidence suggests no association between routine clinician skin examination and earlier stage at melanoma detection; evidence is inconsistent on whether clinician skin examination is associated with thinner melanoma lesions at detection. There is little direct evidence on harms of screening, however; other than overdiagnosis and overtreatment, there are few hypothesized persistent serious harms.

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Figure 1. Incidence and Mortality Trends, Melanoma Skin Cancer, United States, SEER 2000-2019
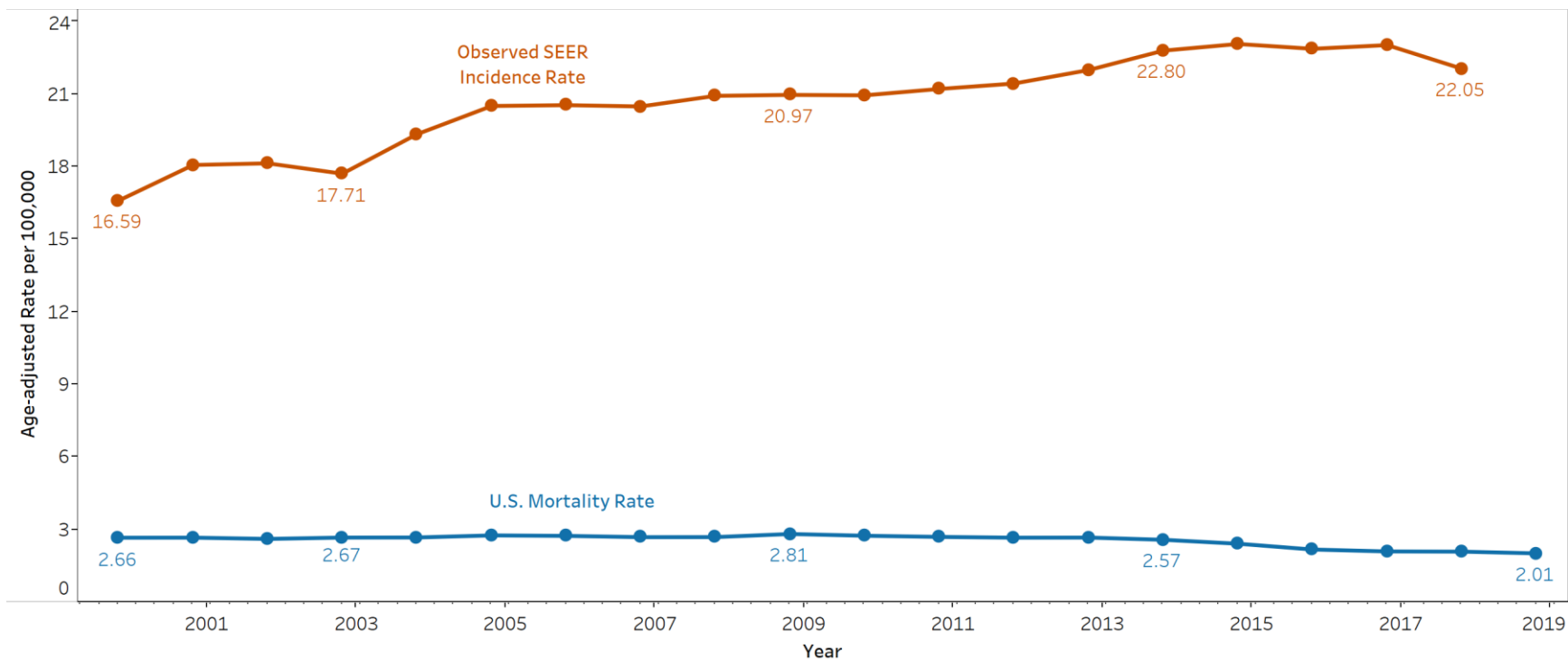
Accessed 11/30/2021

Figure 2. Analytic Framework
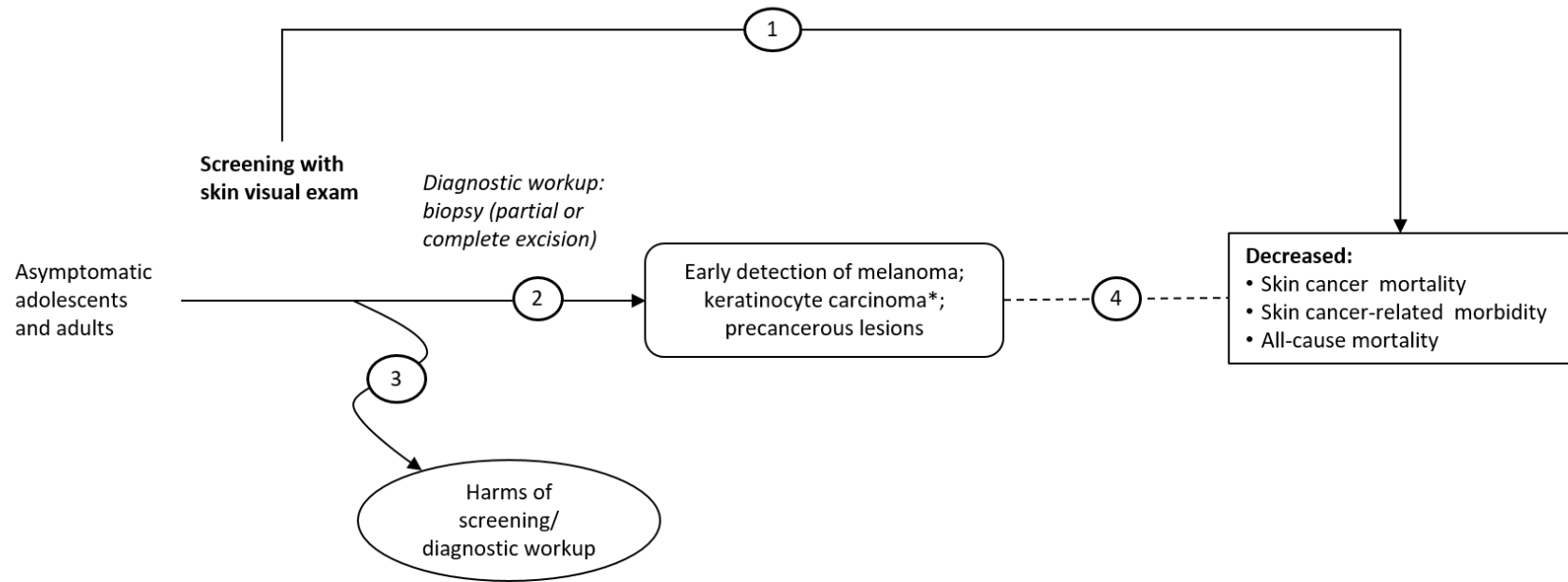
*Previously referred to as nonmelanoma skin cancer; includes basal cell carcinoma and squamous cell carcinoma.

Figure 3. Incidence of BCC, SCC, and Melanoma Before and After Implementation of National Screening Programs, Germany[124]
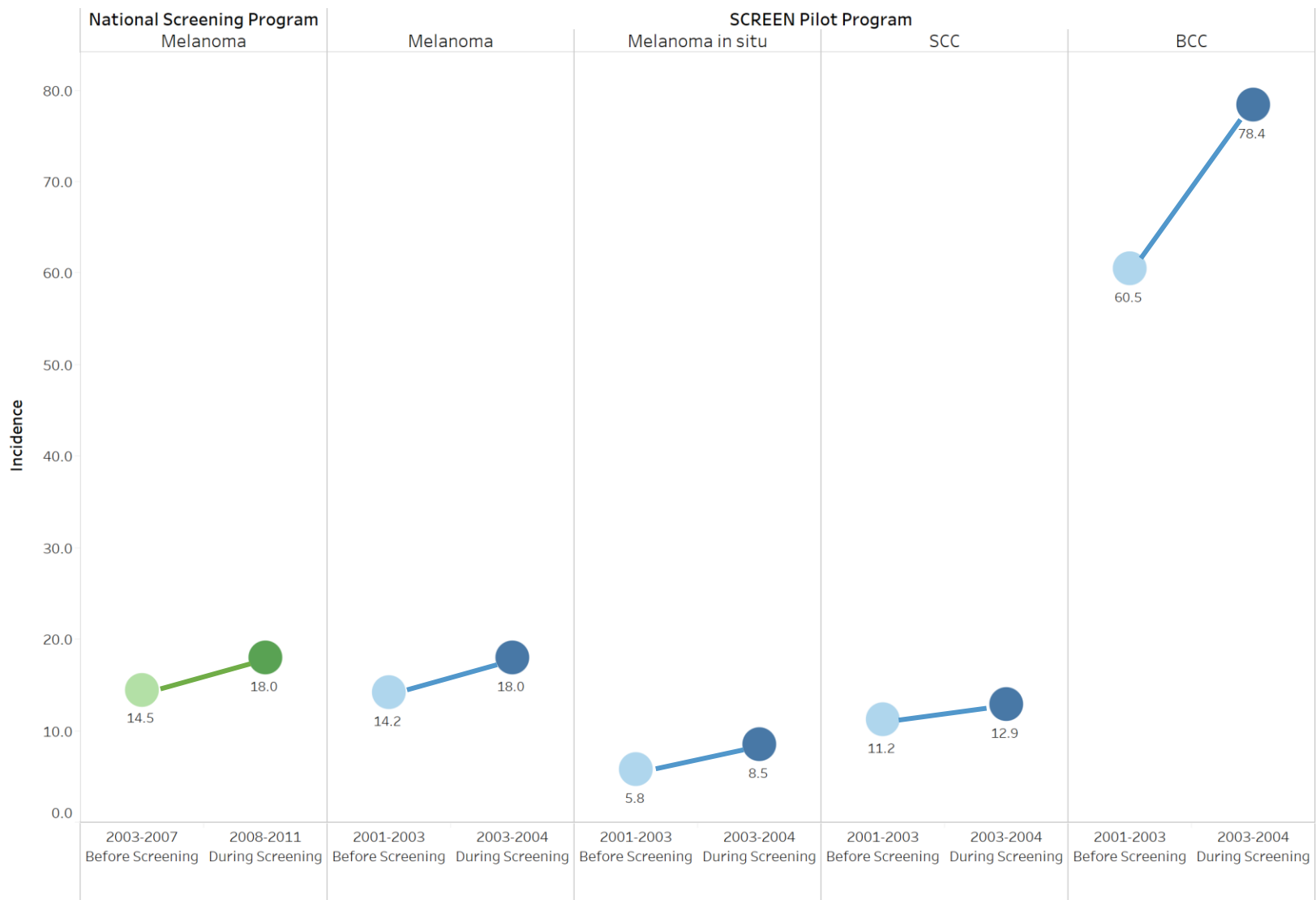
Figure 4. Age-Standardized Annual Incidence for Melanoma and Keratinocyte Skin Cancer Before and After the Initiation of the German National Screening Program[135]
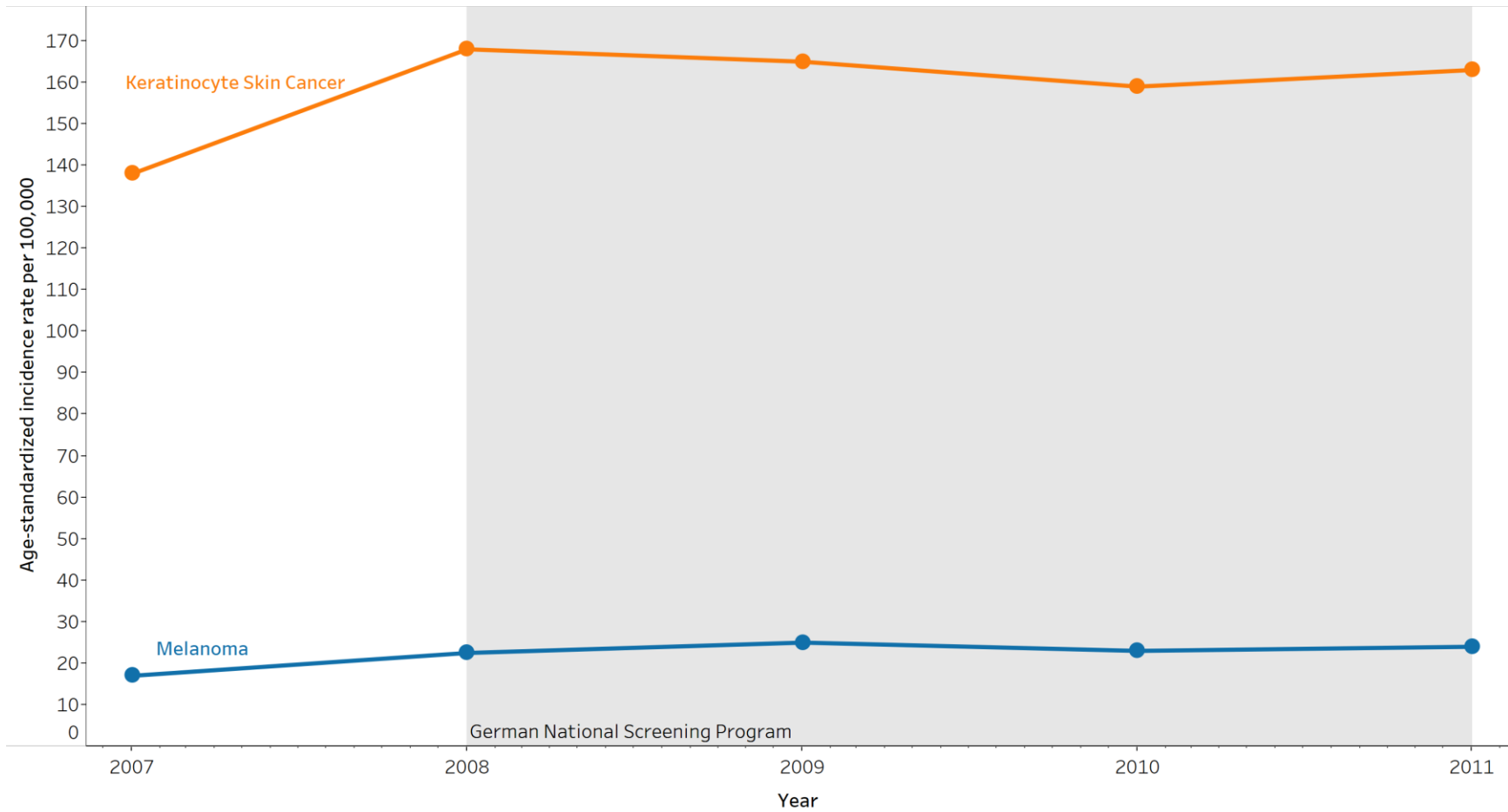
Figure 5. Melanoma Mortality, Overall Population, Schleswig-Holstein vs. Germany, 1998-2013[124] (In table form in Table 6)
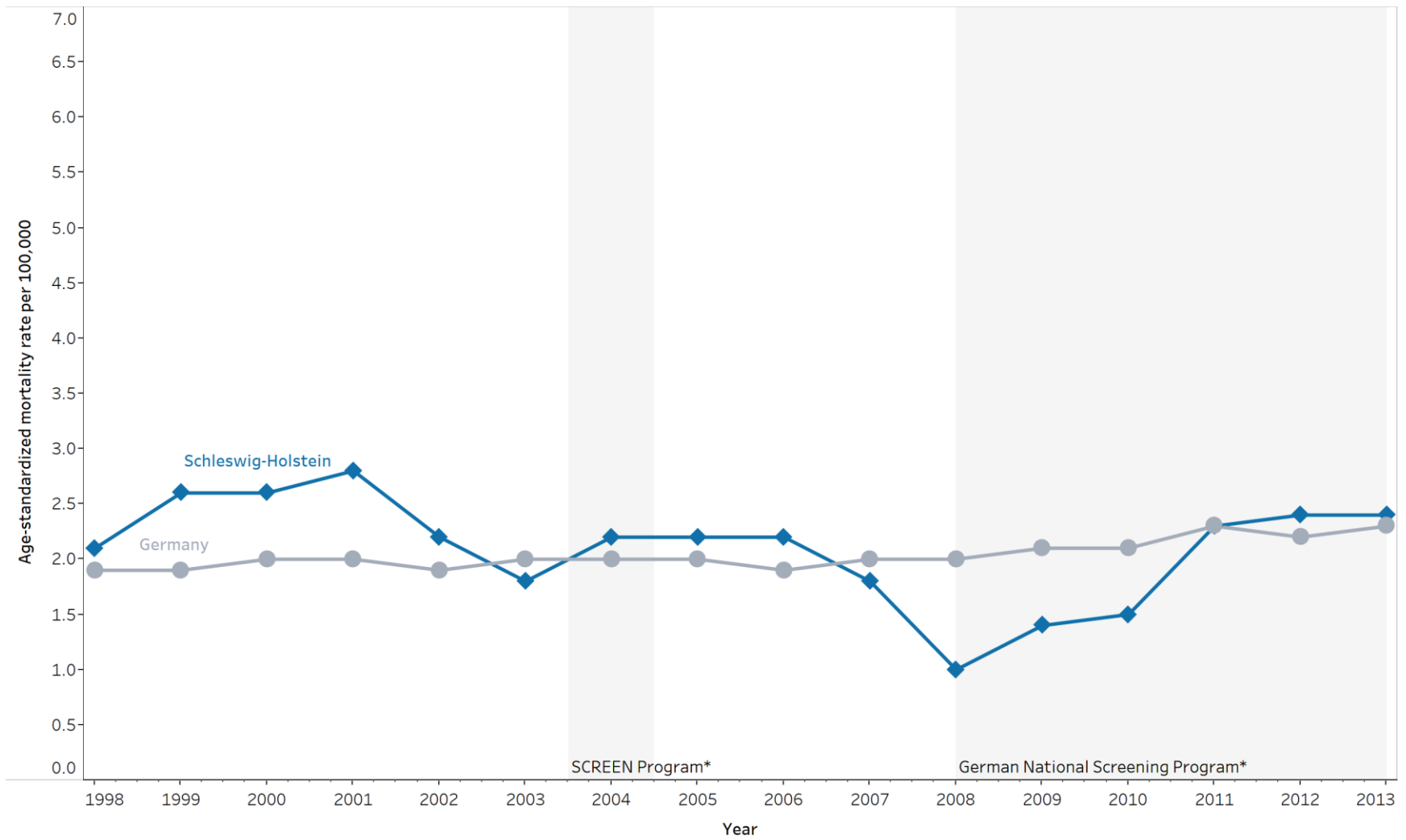
* Period of active screening

Figure 6. Melanoma Mortality, Males and Females, Schleswig-Holstein vs. Germany, 1998-2013[124] (In table form in Table 6)
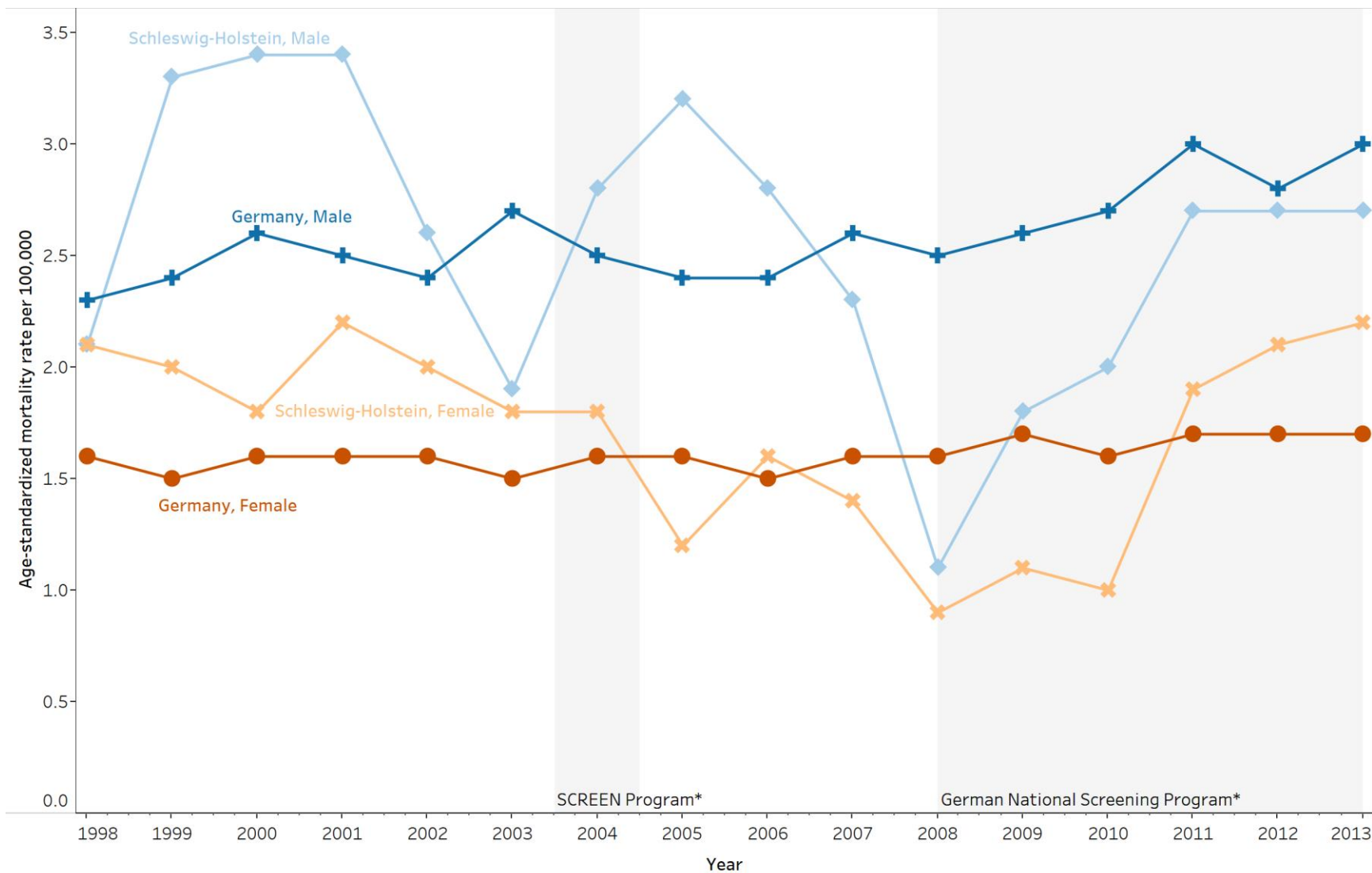
* Period of active screening

Figure 7. Melanoma Mortality, Males by Age Group, Schleswig-Holstein vs. Germany, 1998-2013[124] (In table form in Table 11)

* Period of active screening

Figure 8. Melanoma Mortality, Females by Age Group, Schleswig-Holstein vs. Germany, 1998-2013[124] (In table form in Table 11)
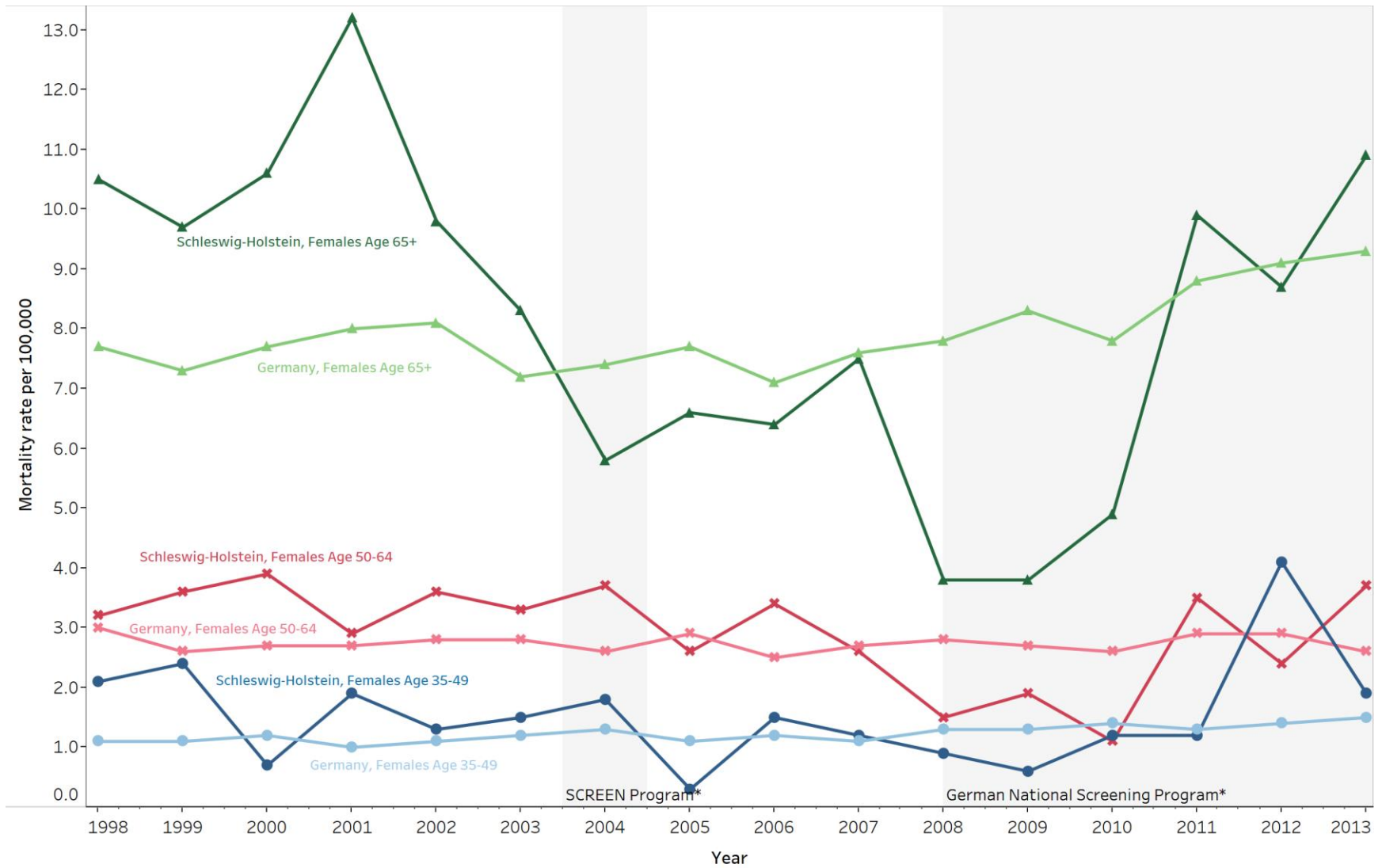
* Period of active screening

Figure 9. Pictogram Depicting the Test Performance of Visual Inspection for Hypothetical 1,000 Lesions[113]

Screened with Visual Inspection

Screen Positive

269 lesions screen positive, 83 of which are melanoma

Screen Negative

732 lesions screen negative, 7 of which are melanoma

1000 lesions are visually inspected, 90 of which are melanoma

■ Melanoma
■ Noncancerous
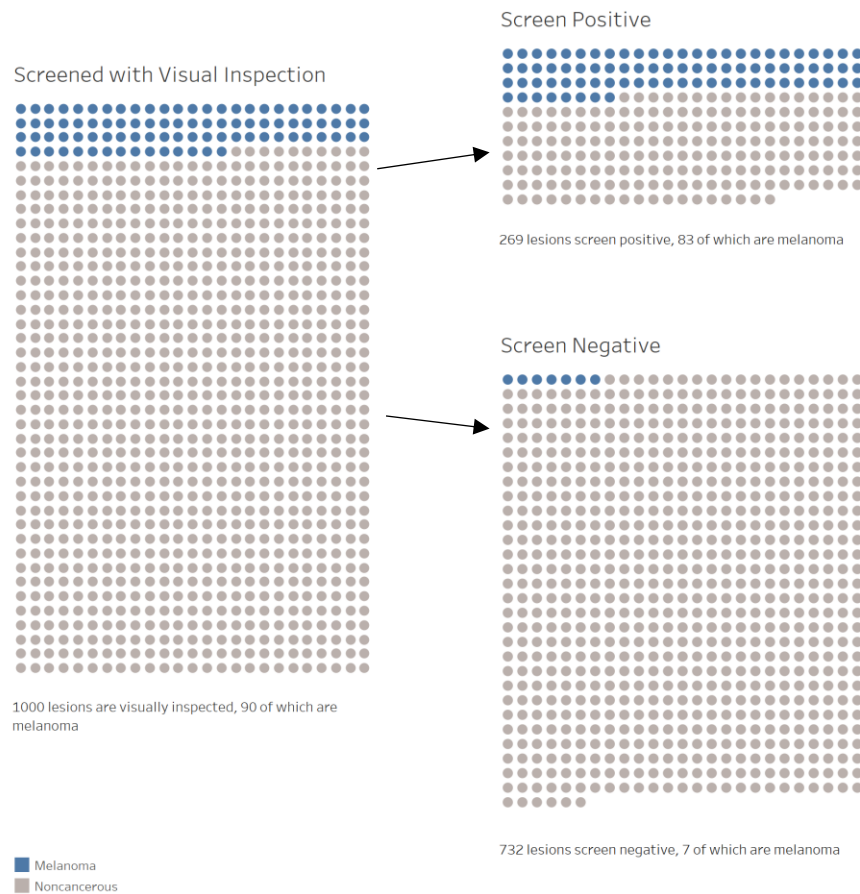
Pictogram depicting hypothetical: The pooled sensitivity to detect melanoma was 0.924 (95% CI, 0.262 to 0.998) and specificity was 0.797 (95% CI, 0.737 to 0.847). While the pooled sensitivity for visual inspection is quite high, with only three studies, the estimate was imprecise and individual estimates varied widely (ranging from 0.34 to 1.0). The ideal screening test would maximize sensitivity, identifying all patients with cancer, but also minimize the false positives who would be subject to unnecessary workup. With these pooled estimates, if a physician saw 1,000 suspicious lesions where 90 were melanoma, 83 would correctly be identified as melanoma (Figure). But 185 lesions would incorrectly screen positive and be unnecessarily subject to further workup (i.e., biopsy).

Figure 10. Melanoma Incidence and Mortality, Overall Population, Schleswig-Holstein vs. Germany, 1998–2013[124]
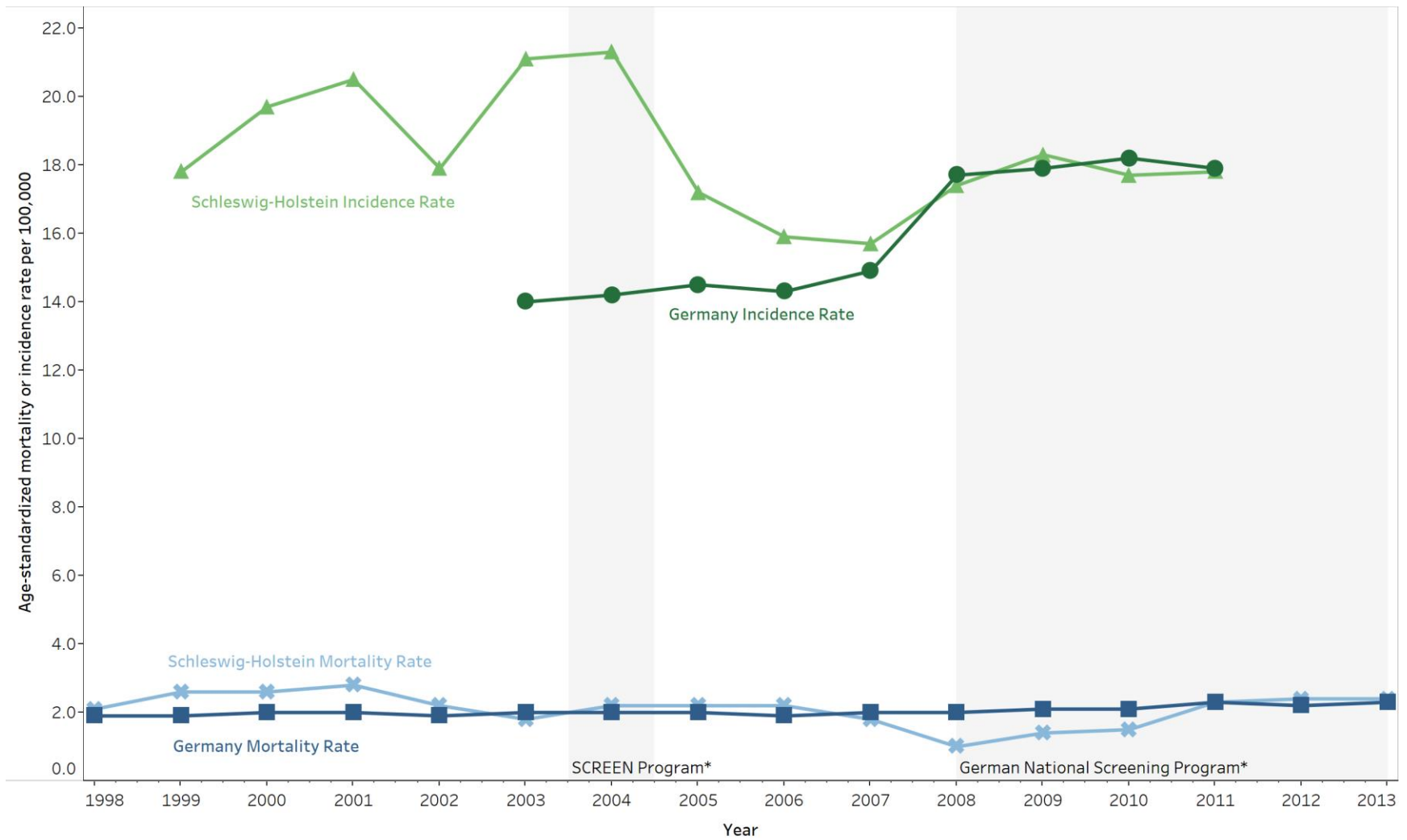
* Period of active screening

Table 1. Comparison of AJCC (7th Edition) and SEER Staging Systems Used in the Included Studies

AJCC 7 Stage[207, 208]*	AJCC 7 Tumor Thickness			AJCC 7 Node		AJCC 7 Metastasis		SEER Stage[161]	SEER Thickness/Depth (Clark's level of invasion)
0	Tis	Melanoma in situ		N0	No melanoma in lymph nodes	M0	No metastasis found	In situ	In situ (I)
IA	T1a	≤1.0mm	No ulceration and mitosis <1/mm^2	N0		M0		Localized	≤0.75 mm (II) 0.76–1.50 mm (III) >1.5 mm (IV)
IB	T1b	≤1.0mm	with ulceration or mitoses ≥1/mm^2	N0		M0			
	T2a	1.01–2.0mm	without ulceration	N0		M0			
IIA	T2b	1.01–2.0mm	with ulceration	N0		M0			
	T3a	2.01–4.0mm	without ulceration	N0		M0			
IIB	T3b	2.01–4.0mm	with ulceration	N0		M0			
	T4a	>4.0mm	without ulceration	N0		M0			
IIC	T4b	>4.0mm	with ulceration	N0		M0			
III	Any T			N1	Melanoma in 1 lymph node	M0		Regional	Direct extension: Thru entire dermis (V); satellite nodules ≤2 cm from primary site Lymph node: spread to regional lymph nodes
				N2	Melanoma in 2-3 lymph nodes	M0			
				N3	Melanoma in 4 or more lymph nodes	M0			
IV	Any T			Any N		M1	Metastasis to in skin, subcutaneous tissue, or distant lymph nodes (M1a); lung (M1b); or other distant organs (M1c)	Distant	Metastasis to cartilage, bone, muscle, or metastatic (generalized) skin lesions or organs

*This table describes the AJCC 7th edition criteria because the included studies in this review use that version. In the 8th edition, published in 2017, T1a is defined as nonulcerated melanomas <0.8 mm in thickness, and T1b is defined as melanomas from 0.8 to 1.0 mm in thickness regardless of ulceration status and ulcerated melanomas less than 0.8 mm in thickness.[5]

Abbreviations: AJCC=American Joint Committee on Cancer; cm=Centimeter; mm=millimeter; SEER=Surveillance, Epidemiology, and End Results Program.

Table 2. Melanoma of the Skin, 5-Year Age-Adjusted Incidence and Mortality Rates, per 100,000, SEER, 2015-2019*[14, 52]

Race/ethnicity	Males Incidence	Males Mortality	Females Incidence	Females Mortality
All Races (includes Hispanic)	27.6	3.2	17.0	1.4
Hispanic (any race)	4.6	0.9	4.5	0.5
American Indian/Alaska Native (non-Hispanic)	8.7	1.0	8.3	0.6
Asian/Pacific Islander (non-Hispanic)	1.4	0.3	1.2	0.3
Black (non-Hispanic)	1.0	0.4	0.9	0.3
White (non-Hispanic)	38.6	4.0	25.5	1.8
Age-Specific Data				
<50 years	5.4	0.4	7.9	0.3
50–64 years	42.5	4.0	31.3	2.0
≥65 years	137.3	17.9	52.4	6.6

*All stages.

Table 3. Study Characteristics of Included Studies (KQs 1-3)

Key Question	Author, Year Study or Program Name Quality	Country	N	Study Design	Intended screening population	Length of Followup
KQ1: 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?	Datzmann, 2022[121] German national skin cancer screening program Good	Germany	1,431,327	Nonrandomized study	Adults age 35 and older who were enrolled in AOK PLUS (a statutory health insurer in Saxony, Germany) between 2010 and 2016	4 years
	Kaiser, 2018[124] Boniol, 2015[120] German national skin cancer screening program Fair	Germany	NR	Nonrandomized study (Ecologic)	Enrollees in German statutory health insurance (90% of German population) Age 35 years and over	Kaiser 2000–2013 Boniol 1980–2012
	Katalinic, 2015[104, 122, 125, 126, 128] Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany (SCREEN) Fair	Germany	360,288 screened	Nonrandomized study (Ecologic)	Resident of Schleswig-Holstein region; age 20 or older; insured with German statutory health insurance	Katalinic 2012[126]: 1998–2009 Katalinic 2015[125]: 1998–2013 Eisemann 2018[122]: 2003–2008
KQ2: Does routine skin cancer screening lead to higher rates of detection of precancerous lesions or earlier stage skin cancer compared to usual care (e.g., lesion-directed skin examination)?	Krensel, 2020[133] German National Screening Program Fair	Germany	Total study population=NR Total skin cancer cases included for KQ2 analysis= 12,082	Nonrandomized study	All enrollees in Barmer (a provider of national statutory health insurance) who were age 35 years and older with an incident diagnosis of cutaneous melanoma, nonmelanoma skin cancer, and preliminary stages of skin cancer.	2013–2016 Eligible participants had to have continuous enrollment from 8 quarters before (preobservation period) until 4 quarters after (followup period) incident diagnosis.
	Matsumoto, 2022[131, 134] INFORMED (INternet curriculum FOR Melanoma Early Detection) Good	US	Total study population= 595,799 Total skin cancer cases included for KQ2 analysis=994	Nonrandomized study	Patients age 35 and older who saw a UPMC-employed primary care physician for an office visit from 2014 to 2018. Patients were considered "screened" if they had a documented full body skin examination by a PCP or skin cancer screening visit with a clinician during the study period.	Median 3 years

Table 3. Study Characteristics of Included Studies (KQs 1-3)

Key Question	Author, Year Study or Program Name Quality	Country	N	Study Design	Intended screening population	Length of Followup
	Hoorens, 2016[132] Fair	Belgium	Total study population= 1,982 Total skin cancer cases included for KQ2 analysis=47	Nonrandomized study	Residents of two communities (Wichelen and Nevele) in East Flanders, Belgium, age 18 and older	NR (appears to be immediately after screening, 2014)
	Trautmann, 2016[135] German National Screening Program Fair	Germany (Saxony)	Total study population= 2,022,467 Total skin cancer cases included for KQ2 analyses= 34,295	Nonrandomized study	All persons insured by AOK PLUS (a provider of national statutory health insurance) with incident melanoma or nonmelanoma skin cancer	NR (used administrative healthcare data from 2005–2012)
	Cristofolini, 2015[130] Fair	Italy	Total study population= 307,679 Total skin cancer cases included for KQ2 analyses= 1,390*	Nonrandomized study	All residents of Trento province (comparison group) as well as all residents who participated in free whole-body skin examination of pigmented lesions offered by Trento branch of the Italian League Against Cancer (screening group)	Median 10 years
	Aitken, 2010[129] Fair	Australia	Total study population= 7,586 Total skin cancer cases included for KQ2 analyses= 3,762	Nonrandomized study	Queensland residents age 20–75 diagnosed with histologically confirmed first primary invasive cutaneous melanoma between January 1, 2000, and December 31, 2003	3 years
KQ3: What are the harms of skin cancer screening and diagnostic followup?	Risica, 2018[137, 138] Fair	US	187	Nonrandomized study	UPMC patients that completed a mailed survey who were ≥35 years of age and were indicated in the EMR of having a visit where a skin cancer screen was done in two selected PCP practices	8 months

Table 3. Study Characteristics of Included Studies (KQs 1-3)

Key Question	Author, Year Study or Program Name Quality	Country	N	Study Design	Intended screening population	Length of Followup
	Gambichler, 2000[136] Fair	Germany	45	Nonrandomized study	Patient undergoing routine skin cancer screening in the outpatient setting with macular melanocytic nevi of less than 15 mm	6 months

*Number of keratinocyte cancers not reported for comparison group of Trento population.

Abbreviations: KQ=Key question; mm=millimeter; NR=Not reported; PCP=Primary care provider; UPMC=University of Pittsburgh Medical Center; EMR=electronic medical record; US=United States.

Table 4. Intervention Characteristics, Included Studies (KQs 1-3)

Key Question	Author, Year Study Name Quality	Country	Providers Conducting Screening	Screening Intervention Description	Comparison Group Description	Frequency of Screening	Followup Protocol of Identified Lesions
KQ1: 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?	Datzmann, 2022[121] German national skin cancer screening program Good	Germany	Primary care physician or dermatologist	Whole body skin examination included examination of the entire body surface and all visible mucous membranes (oral, genital, and anal).[149] Adults age ≥35 years enrolled in German statutory health insurance are eligible for asymptomatic screening. Program began 2008.	Enrollees with first-onset melanoma diagnosed 2013–2016 who did not participate in the screening program	Once every 2 years	Primary care–identified lesions referred to dermatology Dermatologist-identified lesions followed up by identifying dermatologist[149]
	Kaiser, 2018[124] Boniol, 2015[120] German national skin cancer screening program Fair	Germany	Primary care physician or dermatologist	Whole body skin examination included examination of the entire body surface and all visible mucous membranes (oral, genital, and anal).[149] Screening was free of charge to screenees as part of German statutory health insurance. Program began 2008. Enrollees encouraged to have suspicious lesions checked as early as possible.	No comparison group established by screening program. Ecologic comparisons: Other European countries (22 countries)*[124] Surrounding countries (8 countries)†[120]	Once every 2 years	Primary care–identified lesions referred to dermatology Dermatologist-identified lesions followed up by identifying dermatologist[149]
	Katalinic, 2015[104, 122, 125, 126] Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany (SCREEN) Fair	Germany	Dermatologists and non-dermatologists	Pilot study in a single state (Schleswig-Holstein) 2003–2004. Components: 1) training nondermatologists and dermatologists in skin cancer screening; 2) media campaign to encourage skin cancer screening in adults age 20 years and older; 3) full body skin examination	Germany (including SH region),[104, 122, 125, 126] Germany (excluding intervention region),[122] Saarland region, Germany,[126] Four adjoining regions to intervention region‡[126]	Single screening	Referred to dermatologist

Table 4. Intervention Characteristics, Included Studies (KQs 1-3)

Key Question	Author, Year Study Name Quality	Country	Providers Conducting Screening	Screening Intervention Description	Comparison Group Description	Frequency of Screening	Followup Protocol of Identified Lesions
KQ2: Does routine skin cancer screening lead to higher rates of detection of precancerous lesions or earlier stage skin cancer compared to usual care?	Krensel, 2020[133] German National Screening Program Fair	Germany	NR	Routine skin cancer screening per German national screening program guidance within any quarter of the year in which the excision took place*	No documentation of routine skin cancer screening within any quarter of year in which excision took place	NR	Biopsy or excision to verify diagnoses
	Matsumoto, 2022[131, 134] INFORMED (INternet curriculum FOR Melanoma Early Detection) Good	US	Primary care physician	Electronic health record was modified to include full-body skin examination as a preventive service recommendation for patients age 35 years and older; program promoted by health system leadership to primary care physicians; physician training via validated web-based skin cancer identification training tool Years: 2014–2018	Did not receive screening during study period (2014–2018)	NR	Biopsy or referral to dermatologist for further evaluation through routine standard-of-care practice
	Hoorens, 2016[132] Fair	Belgium	Dermatologist	Total body screening residents received personal invite to 5-day TBE event held in 2014. Lesion-directed screening residents received personal invite to 4-day event offering review of suspicious lesions. For both groups, screening was performed by trained physicians using both naked-eye inspection and dermoscopy. For lesion-directed screening group, a total body examination was offered to all participants at the end of the lesion screening.	Lesion-directed screening using visual inspection and dermoscopy followed by optional total body examination	Single screening	In the case of a suspicious lesion, a second opinion was obtained. Suspicious lesions were photographed, and the patient received a referral letter for their PCP or dermatologist

Table 4. Intervention Characteristics, Included Studies (KQs 1-3)

Key Question	Author, Year Study Name Quality	Country	Providers Conducting Screening	Screening Intervention Description	Comparison Group Description	Frequency of Screening	Followup Protocol of Identified Lesions
	Trautmann, 2016[135] German National Screening Program Fair	Germany (Saxony)	PCP and dermatologists	Evidence in administrative data of routine skin cancer screening per German national screening program guidance‖	Comparison group consisted of persons without documentation of skin cancer screening	NR	NR
	Cristofolini, 2015[130] Fair	Italy	Dermatologist	Public awareness campaign offering education about skin cancer and free whole-body skin examinations. Whole-body skin examinations involved the following: patients undressed and had all skin examined by the same trained dermatologist, with a dermatoscopic check of lesions. Patients with suspect lesions were sent to surgery for excision and histological examination. Dates of screening Jan 2001–December 2004, program sponsored by nonprofit cancer prevention advocacy group.	General population of Trento, Italy	NR	Sent to surgery for excision and histological examination
	Aitken, 2010[129] Fair	Australia	Physician (not further specified)	Clinical skin examination was determined retrospectively by asking: "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?" For cases, this clinical skin examination did not include the initial examination by a doctor as part of the diagnostic process, unless this was a whole-body clinical skin examination of an asymptomatic patient (i.e., a skin screening examination)	Control group also asked about receipt of clinical skin examination in 3 years prior to reference date	NR	NA

Table 4. Intervention Characteristics, Included Studies (KQs 1-3)

Key Question	Author, Year Study Name Quality	Country	Providers Conducting Screening	Screening Intervention Description	Comparison Group Description	Frequency of Screening	Followup Protocol of Identified Lesions
KQ3: What are the harms of skin cancer screening and diagnostic followup?	Risica, 2018[137, 138] Fair	US	Primary care physician	Full-body visual skin examination by a UPMC PCP. UPMC melanoma screening program background: UPMC PCPs were invited to take part of the Internal Curriculum for Melanoma Early Detection (INFORMED) online training program to improve early detection of melanoma and keratinocyte carcinomas. INFORMED is a validated web-based training for detection of skin cancers, particularly melanoma. "Thoroughly screened" patients are those who self-reported being screened and being completely undressed ("with or without undergarments") and had at least 2 of 3 body parts (back, abdomen, calves) examined.	"Not thoroughly screened" patients were those who did not indicate having whole body screened for skin cancer, did not disrobe, or have 2 of 3 body parts examined	Single screening	Some patients reported undergoing skin biopsies following screening
	Gambichler, 2000[136] Fair	Germany	NR	Routine skin cancer screening in the outpatient setting	NR	NR	NR

*Austria, Belgium, Bulgaria, Switzerland, Czech Republic, Denmark, Spain, Finland, France, Croatia, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, and Slovakia.
†Czech Republic, Poland, Denmark, Austria, Belgium, France, The Netherlands, and Switzerland.
‡Denmark; German federal states of Mecklenburg-Vorpommern, Hamburg, and Lower Saxony.
∥AOK PLUS covers 51% of inhabitants in the German state of Saxony.

Abbreviations: EHR=Electronic health record; KQ=Key question; NR=Not reported; PCP=Primary care physician; UPMC=University of Pittsburgh Medical Center; US=United States.

Table 5. Population Characteristics, Included Studies (KQs 1-4)

Key Question	Author, Year Study Name Quality	Country	N	Population Description	Mean Age, yrs	Female, %	Race/ Ethnicity, %	Hx of Previous SC Screening, n (%)	Family History of Skin Cancer, n (%) Previous Skin Cancer, n (%)	Other Risk Factors
KQ1: 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?	Datzmann, 2022[121] German national skin cancer screening program Good	Germany	1,431,327	Adults age 35 years and older who were enrolled in AOK PLUS (a statutory health insurer in Saxony, Germany) between 2010 and 2016	63.9	55.7	NR	NR	NR Melanoma in previous 3 years: 0 (0%) Other previous melanoma or KC: NR	NR

Table 5. Population Characteristics, Included Studies (KQs 1-4)

Key Question	Author, Year Study Name Quality	Country	N	Population Description	Mean Age, yrs	Female, %	Race/ Ethnicity, %	Hx of Previous SC Screening, n (%)	Family History of Skin Cancer, n (%) Previous Skin Cancer, n (%)	Other Risk Factors
	Kaiser, 2018[120, 124] German national skin cancer screening program Fair	Germany	NR	National statutory health insurance enrollees (90% of German population) Excluding residents of Schleswig-Holstein region Age 35 years and older	Percent of population age ≥65: Screening group: mean 19.4, SD 2.2 Comparison group (Europe): mean 17.4, SD 3.1	Ratio of males to females: 0.96, SD 0.01	NR	NR	NR	Medical doctor density per 100,000 inhabitants: Screening group: mean 366.41, SD 63.35 Comparison group (Europe): mean 366.16, SD 109.08 GDP per capita (Euros): Screening group: mean 28,269.05. SD 8834.7 Comparison group (Europe): mean 23,585.02, SD 10,090.5 Percent with tertiary education§: Screening group: Mean 26.18, SD 4.57 Comparison group (Europe): Mean 20.83, SD 8.35 Employment rates (%): Screening group: 74.84, SD 3.65 Comparison group (Europe): 68.63, SD 6.26

Table 5. Population Characteristics, Included Studies (KQs 1-4)

Key Question	Author, Year Study Name Quality	Country	N	Population Description	Mean Age, yrs	Female, %	Race/ Ethnicity, %	Hx of Previous SC Screening, n (%)	Family History of Skin Cancer, n (%) Previous Skin Cancer, n (%)	Other Risk Factors
	Katalinic, 2015[104, 122, 125, 126] Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany (SCREEN) Fair	Germany	360,288 screened	Residents of Schleswig-Holstein region; age 20 years or older; insured with German statutory health insurance	49.7	73.6	NR	NR	First-degree relative with malignant melanoma: 3,831 (6.1) Personal history of malignant melanoma: 1,642 (2.6) Personal history of KC: 4,063 (16.9)	Actinic keratosis, n (%): 7,490 (31.2) Multiple melanocytic nevi, n (%): 35,160 (56.2) Clinically atypical nevi, n (%): 32,468 (51.9) Congenital moles, n (%): 13,071 (20.9) UV-damaged skin, n (%): 17,301 (72.0) X-ray damaged skin n (%): 638 (2.6) Immunosuppression: n (%): 658 (2.7)
KQ2: Does routine skin cancer screening lead to higher rates of detection of precancerous lesions or earlier stage skin cancer compared to usual care?	Aitken, 2010[129] Fair	Australia	Total study population =7,586 Total skin cancer cases included for KQ2 analyses =3,762	Queensland residents age 20-75 years diagnosed with histologically confirmed first primary invasive cutaneous melanoma (not including acral lentiginous melanoma) between Jan 1, 2000 and Dec 31, 2003	Overall NR; 20–39: 16.4% 40–49:20.4% 50–59:26.2% 60+: 37.0%	42.4	UK: 67.3 European: 9.3 Other: 23.2	28.3% reported having had a clinical skin examination within 3 years before reference date 35.3% reported having had a clinical skin examination within 3 years before melanoma first noticed	Family Hx of melanoma†: 553 (14.5%) Family Hx of KC†: 826 (21.6%) Previous diagnosis of KC*†: 734 (19.2)	NR

Table 5. Population Characteristics, Included Studies (KQs 1-4)

Key Question	Author, Year Study Name Quality	Country	N	Population Description	Mean Age, yrs	Female, %	Race/ Ethnicity, %	Hx of Previous SC Screening, n (%)	Family History of Skin Cancer, n (%) Previous Skin Cancer, n (%)	Other Risk Factors
	Cristofolini, 2015[130] Fair	Italy	Total study population =307,679 Total skin cancer cases included for KQ2 analyses =1,390[††]	Residents of Trento, Italy, who participated in free whole-body skin screening program between Jan 2001 and Dec 2004	40.2	52.6	NR	NR	NR	NR
	Matsumoto, 2022[131, 134] INFORMED (INternet curriculum FOR Melanoma Early Detection) Good	US	Total study population =595,799 Total skin cancer cases included for KQ2 analysis= 994	Patients age 35 years and older who saw a UPMC-employed primary care physician for an office visit from 2014–2018	57	55.9	Non-Hispanic White: 84.0 White, ethnicity unknown: 3.9 Hispanic White: 0.5 Black: 7.9 Asian: 1.5 AIAN: 0.1 Pacific Islander: 0.04 Not reported: 2.0	NR	NR	NR

Table 5. Population Characteristics, Included Studies (KQs 1-4)

Key Question	Author, Year Study Name Quality	Country	N	Population Description	Mean Age, yrs	Female, %	Race/ Ethnicity, %	Hx of Previous SC Screening, n (%)	Family History of Skin Cancer, n (%) Previous Skin Cancer, n (%)	Other Risk Factors
	Hoorens, 2016[132] Fair	Belgium	Total study population =1,982 Total skin cancer cases included for KQ2 analysis= 47	Residents of two communities (Wichelen and Nevele) in East Flanders, Belgium, age 18 years and older	51.5	56.2	NR	At least 1 previous skin check: 38.2%	Family Hx of SC: 220 (11.1) Personal Hx of SC: 46 (2.3)	N (%) Presence of actinic keratosis: 152 (7.8) Solar lentigines: 1,264 (65.3) Atypical nevi: 298 (15.4)
	Krensel, 2020[133] Fair	Germany	Total study population =NR Total skin cancer cases included for KQ2 analysis= 12,380	Enrollees in health insurance company; age 35 years and older with incident diagnosis of cutaneous melanoma, KC, and preliminary stages of skin cancer who had undergone routine skin cancer screening within the quarter of the year in which the excision took place or the previous quarter	69.0	56.4	NR	NR	NR	NR

Table 5. Population Characteristics, Included Studies (KQs 1-4)

Key Question	Author, Year Study Name Quality	Country	N	Population Description	Mean Age, yrs	Female, %	Race/ Ethnicity, %	Hx of Previous SC Screening, n (%)	Family History of Skin Cancer, n (%) Previous Skin Cancer, n (%)	Other Risk Factors
	Trautmann, 2016[135] German National Screening Program Fair	Germany	Total study population = 2,022,467 Total skin cancer cases included for KQ2 analyses =34,295	All persons continuously insured by AOK PLUS from Jan 1, 2005, to Dec 31, 2012, or death. AOK PLUS is a large German health insurance company covering 51% of inhabitants of the German state of Saxony.	46.5	53.6	NR	NR	NR	NR
KQ3: What are the harms of skin cancer screening and diagnostic followup?	Gambichler, 2000[136] Fair	Germany	45	Individuals aged 15–54 years, from the outpatient setting who underwent routine skin cancer screening who were prospectively recruited after clinical and epiluminescence microscopic investigation. Only those with macular melanocytic nevi with diameter of less than 15 mm were included.	32	51.0	NR	NR	NR	NR

Table 5. Population Characteristics, Included Studies (KQs 1-4)

Key Question	Author, Year Study Name Quality	Country	N	Population Description	Mean Age, yrs	Female, %	Race/ Ethnicity, %	Hx of Previous SC Screening, n (%)	Family History of Skin Cancer, n (%) Previous Skin Cancer, n (%)	Other Risk Factors
	Risica, 2018[137, 138] Fair	US	187	UPMC: ≥35 years of age; having documentation of a visit where a skin cancer screen was done in two selected PCP practices	NR	42.8	White: 89.8 Black: 5.3 Other: 4.8	75 (40.1)	Family Hx of melanoma: 109 (58.6) Personal Hx of SC: 39 (20.9)	NR
KQ4: 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?	Dawes 2016[139] Fair	US	96,953	Individuals diagnosed with melanoma between 1992 and 2009 with the data in SEER database Data collected: 1992–2009	Mean: NR 47% age 50 to 74 years (range, 0 to >74 years)	45.3	White: 94.8 Black: 0.5 AANAPI: 1.3 Hispanic: 3.4¶	NR	NR	NR
	Enninga, 2017[140] Fair	US	106,511	Adults diagnosed with melanoma between 1992 and 2011 with the data in SEER database Data collected: 1992–2011 (followup for deaths was until 2012)	Mean: 59.1‖ 18–45: 28.1 46–54: 18.9 ≥55: 53.0	44.8	White: 95.5 Black: 0.5 Asian or PI: 0.9 AI/AN: 0.2 Unknown: 2.9 Hispanic: 3.2	NR	NR 0% for previous melanoma*	NR

Table 5. Population Characteristics, Included Studies (KQs 1-4)

Key Question	Author, Year Study Name Quality	Country	N	Population Description	Mean Age, yrs	Female, %	Race/ Ethnicity, %	Hx of Previous SC Screening, n (%)	Family History of Skin Cancer, n (%) Previous Skin Cancer, n (%)	Other Risk Factors
	Farrow, 2020[141] Fair	US	268,668	Adults age ≥18 years diagnosed with melanoma classified according to pathologic AJCC stage I–IV between 2004 and 2015 in the National Cancer Database Data collected: 2004–2015	61[‡]	42.4	White: 98.7 Black: 0.6 Other: 0.7	NR	NR	NR
	Khosrotehrani, 2015[142] Good	Australia	28,979	Histologically verified incident cases of first primary invasive melanomas diagnosed from 1995 to 2008 among people age 15–89 years in Queensland Cancer Registry and SEER database Data collected: 1995–2008 (melanoma-specific deaths were ascertained up to 2010)	Mean: 56.1[‖] 15–45: 27.5% 46–59: 28.1% 60–89: 44.5%	43.3	NR	NR	NR	NR

Table 5. Population Characteristics, Included Studies (KQs 1-4)

Key Question	Author, Year Study Name Quality	Country	N	Population Description	Mean Age, yrs	Female, %	Race/ Ethnicity, %	Hx of Previous SC Screening, n (%)	Family History of Skin Cancer, n (%) Previous Skin Cancer, n (%)	Other Risk Factors
	Mahendraraj, 2017[143] Fair	US	213,827	Patients of the White or Black** race with cutaneous melanoma from the SEER database from 1988–2011 Data collected: 1988–2011	Entire population: 58.9‖ White: 58.9 Black: 60.5	M:F White: 1.33 Black: 1	White: 99.5 Black: 0.5	NR	NR	NR
	Qian, 2021[144] Fair	US	398,034	Adults with cutaneous (95.7%), mucosal (1.2%), and uveal (3.1%) melanoma diagnosed between 1975 and 2016	60.1‖	43.0	White: 95.40 Black: 0.57 Asian or PI: 0.73 AI/AN: 0.20 Hispanic: 3.09	NR	NR	NR
	Robsahm, 2018[145] Good	Norway	8,087	Individuals, age 2 to 98 years, with a first primary invasive melanoma diagnosis in the period 2008–2012 Data collected: 2008–2012 (followup for deaths was until 2015)	60.5‖ 64‡	50.1	NR	NR	NR	Urban-rural area, n (%) Urban: 3,846 (47.6%) Rural: 4,241 (52.4%)

Table 5. Population Characteristics, Included Studies (KQs 1-4)

Key Question	Author, Year Study Name Quality	Country	N	Population Description	Mean Age, yrs	Female, %	Race/ Ethnicity, %	Hx of Previous SC Screening, n (%)	Family History of Skin Cancer, n (%) Previous Skin Cancer, n (%)	Other Risk Factors
	Ward-Peterson, 2016[146] Good	US	185,219	Adults age ≥18 years diagnosed with primary cutaneous melanoma from 1982 to 2011 Data collected: 1982–2011	Mean: 57.2[∥] <30: 6.0% 30–39: 13.8% 40–49: 18.1% 50–59: 19.4% 60–69: 18.5% ≥70: 24.3%	43.0	Non-Hispanic White: 91.7 Hispanic Black: 1.7 Hispanic: 2.5 Other: 1.2 Missing race data: 2.9	NR	NR	NR
	Zheng, 2020[147] Fair KQ4	Sweden	19,773	Patients in Swedish Cancer Registry who were diagnosed with first melanoma classified according to TNM staging system and who had tumor thickness data available Data collected: 2003–2015	Mean: 65.3[∥] ≤50:27.0% 51–60:17.9% 61–70:22.9% 71–80:19.2% 81–90:11.0% ≥91:20.1%	50.9	NR	NR	NR 0% for previous melanoma*	NR

*Those with previous melanoma were excluded.
†Denominator=3,824.
‡Median.
§WHO definition: university or higher.
∥Calculated, weighted mean.
¶Categories are mutually exclusive; Hispanic persons were excluded from other groups, regardless of race.
**Study defined as African American and Caucasian.
††Number of keratinocyte cancers not reported for comparison group of Trento population.

Abbreviations: AANAPI=Asian American/Native American/Pacific Islander; PI=Pacific Islander; AI/AN=American Indian/Alaska Native; AJCC=American Joint Committee on Cancer; Dec=December; GDP=Gross domestic product; Hx=History; Jan=January; KQ=Key question; Mm=Millimeter; NR=Not reported; PCP=Primary care physician; SC=Skin cancer; SD=Standard deviation; SEER=Surveillance, Epidemiology, and End Results program; TNM=Tumor size and spread to nearby tissue, tumor spread to nearby lymph nodes, metastases; UK=United Kingdom; UPMC=University of Pittsburgh Medical Center; US=United States; UV=Ultraviolet.

Table 6. Age-Standardized Melanoma Mortality per 100,000, SCREEN Study Region and Germany, 1998-2013, Total and by Sex (KQ1, KQ1a, depicted graphically also in Figures 5 and 6)[125]

Katalinic, 2015 Fair	Schleswig-Holstein* Age-standardized mortality rate per 100,000	Schleswig-Holstein* Number of melanoma deaths	Germany† Age-standardized mortality rate per 100,000	Germany† Number of melanoma deaths	Schleswig-Holstein* Age-standardized mortality rate per 100,000	Schleswig-Holstein* Number of melanoma deaths	Germany† Age-standardized mortality rate per 100,000	Germany† Number of melanoma deaths	Schleswig-Holstein* Age-standardized mortality rate per 100,000	Schleswig-Holstein* Number of melanoma deaths	Germany† Age-standardized mortality rate per 100,000	Germany† Number of melanoma deaths
Year	Total	Total	Total	Total	Female	Female	Female	Female	Male	Male	Male	Male
1998	2.1	77	1.9	2,030	2.1	45	1.6	1,004	2.1	32	2.3	1,026
1999	2.6	95	1.9	2,021	2	44	1.5	964	3.3	51	2.4	1,057
2000	2.6	97	2	2,178	1.8	43	1.6	1,017	3.4	54	2.6	1,161
2001	2.8	109	2	2,217	2.2	52	1.6	1,046	3.4	57	2.5	1,171
2002	2.2	88	1.9	2,210	2	45	1.6	1,073	2.6	43	2.4	1,137
2003	1.8‡	76‡	2	2,295	1.8‡	41‡	1.5	1,009	1.9‡	35‡	2.7	1,286
2004	2.2‡	87‡	2	2,293	1.8‡	37‡	1.6	1,037	2.8‡	50‡	2.5	1,256
2005	2.2	86	2	2,327	1.2	29	1.6	1,089	3.2	57	2.4	1,238
2006	2.2	88	1.9	2,287	1.6	35	1.5	1,021	2.8	53	2.4	1,266
2007	1.8	78	2	2,467	1.4	36	1.6	1,099	2.3	42	2.6	1,368
2008	1§	44§	2	2,500	0.9§	21§	1.6	1,135	1.1§	23§	2.5	1,365
2009	1.4§	55§	2.1	2,657	1.1§	22§	1.7	1,203	1.8§	33§	2.6	1,454
2010	1.5§	64§	2.1	2,711	1§	24§	1.6	1,143	2§	40§	2.7	1,568
2011	2.3§	104§	2.3	2,921	1.9§	49§	1.7	1,212	2.7§	55§	3	1,709
2012	2.4§	105§	2.2	2,875	2.1§	50§	1.7	1,248	2.7§	55§	2.8	1,627
2013	2.4§	112§	2.3	3,042	2.2§	55§	1.7	1,255	2.7§	57§	3	1,787

*SCREEN study region.
†Germany data includes Schleswig-Holstein.
‡Years of SCREEN skin cancer screening program (2003–2004).
§Years of German national skin cancer screening (2008–2013).

Table 7. Observed vs. Expected Mortality, SCREEN Study Region and Saarland Region, Germany, 2003–2008 (KQ1)[122]

Eisemann, 2018 Fair	N	Followup period	Person years analyzed	Incident melanoma cases	Observed deaths, age- and sex-adjusted	Observed mortality rate per 100,000 (age- and sex-adjusted)	Expected deaths, adjusted for age, sex, and population size	Standardized mortality rate, age- and sex-adjusted (95% CI)
SCREEN participants (Schleswig-Holstein region)*	360,196	July 2003–December 2008	1,981,078	1,472	31	1.56	52.7	0.59 (0.40, 0.83)
Saarland region†	~1 million	July 2003–December 2008	5,763,767	1,026	111	1.93	52.7	0.59 (0.40, 0.83)

*Routine skin cancer offered through SCREEN study 2003–2004.
†No routine skin cancer offered in this region until 2008.

Abbreviations: CI=Confidence interval; KQ=Key question.

Table 8. Melanoma Mortality for First-Onset Melanoma 2013–2016 Among Screened Enrollees in AOK Plus Health Insurer in Saxony, Germany

Datzmann, 2022[121] Good	Total N	Screened N (%)	Unscreened N (%)	ARR in melanoma mortality for screening participants	Unadjusted HR[†] for melanoma mortality	Unadjusted HR[†], lead time bias correction	Adjusted HR[†§] for melanoma mortality	Adjusted HR[†§], lead time bias correction
AOK Plus population	1,431,327	688,708 (48.1)	742,619 (51.9)	13.3%	0.37[‡]	0.50[‡]	0.62[‡]	0.75
Incident melanoma*	2,475	1,801 (72.8)	674 (27.2)					
Melanoma deaths	325	171 (9.5)	154 (22.8)					

*First onset 2013–2016.
†Hazard ratios for dying within the observation period; screening participation within 2 years before diagnosis vs. no screening participation.
‡p<0.05.
§Adjusted for age group (three); 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, ischaemic heart disease and heart failure in last 3 months; five strata for type/timing of metastasis.

Abbreviations: ARR=absolute risk reduction; HR=hazard ratio.

Table 9. Melanoma Mortality Overall and by Sex and Age Group; Germany and Surrounding Countries, 1980–2012[120]

Boniol, 2015 Fair	Annual percent change (95% CI) All ages 1980–2012	All ages 2008–2012*	Age less than 60 years; 1980–2012	Age 60–74 years; 1980–2012	Age 75 years and older; 1980–2012
Men					
Germany	0.44 (0.26 to 0.62)‡	2.57 (−0.10 to 5.24)	−0.9 (−1.2 to −0.7)¶	1.4 (0.6 to 2.1)**	1.6 (1.1 to 2.1)**
Czech Republic†	−0.55 (−0.91 to −0.20)‡	0.65 (−4.57 to 5.88)	−2.8 (−3.5 to −2.1)¶	−0.3 (−0.9 to 0.4)	2.1 (1.4 to 2.8)**
Poland	2.70 (2.43 to 2.97)‡	1.19 (−0.64 to 3.01)	−0.4 (−1.6 to 0.7)	3.1 (2.7 to 3.5)**	5.6 (4.9 to 6.2)**
Denmark§	0.60 (0.17 to 1.03)‡	−1.70 (−7.51 to 4.11)	−1.2 (−1.8 to −0.6)¶	1.6 (0.9 to 2.2)**	2.8 (1.6 to 4.1)**
Austria	0.84 (0.40 to 1.28)‡	−0.06 (−1.17 to 1.04)	−0.9 (−1.5 to −0.3)¶	1.1 (0.5 to 1.7)**	1.5 (−0.3 to 3.3)
Belgium‖	2.10 (1.77 to 2.60)‡	−2.74 (−7.18 to 1.71)	2.2 (1.5 to 3.0)**	2.3 (1.7 to 2.9)**	1.7 (0.8 to 2.7)**
France‖	2.20 (2.03 to 2.37)‡	1.96 (−1.60 to 5.51)	1.1 (0.9 to 1.4)**	2.2 (1.7 to 2.6)**	3.4 (2.9 to 3.9)**
The Netherlands	2.54 (2.31 to 2.76)‡	1.04 (−3.34 to 5.42)	1.2 (0.8 to 1.5)**	3.9 (3.5 to 4.4)**	3.9 (3.2 to 4.7)**
Switzerland‖	0.33 (−0.06 to 0.72)	4.28 (−3.85 to 12.4)	−1.3 (−2.1 to −0.6)¶	0.6 (−0.0 to 1.2)	0.1 (−1.6 to 1.9)
Women					
Germany	−0.15 (−0.30 to 0.00)	0.02 (−1.79 to 1.82)	0.3 (−0.2 to 0.8)	−0.4 (−0.8 to −0.0)¶	1.0 (0.8 to 1.3)**
Czech Republic†	−0.90 (−1.41 to −0.39)‡	−0.25 (−4.40 to 3.90)	−2.2 (−3.0 to −1.4)¶	−0.4 (−1.1 to 0.3)	6.4 (−2.0 to 15.5)
Poland	1.62 (1.28 to 1.97)‡	1.28 (−0.85 to 3.42)	−0.5 (−1.0 to −0.0)¶	2.0 (1.7 to 2.4)**	3.5 (3.1 to 4.0)**
Denmark§	−0.11 (−0.64 to 0.41)	−1.70 (−9.61 to 6.21)	−1.7 (−2.5 to −0.8)¶	0.6 (−0.2 to 1.3)	2.0 (1.4 to 2.6)**
Austria	0.29 (−0.11 to 0.69)	2.17 (−7.11 to 11.5)	−0.4 (−1.0 to 0.3)	0.3 (−0.3 to 0.9)	−0.5 (−2.1 to 1.1)
Belgium‖	2.22 (1.74 to 2.84)‡	−1.17 (−5.74 to 3.41)	1.0 (0.1 to 2.0)**	0.8 (−0.6 to 2.3)	2.2 (1.4 to 3.0)**
France‖	1.23 (0.97 to 1.49)‡	2.64 (−9.63 to 14.9)	0.5 (0.1 to 0.9)**	0.4 (−0.7 to 1.4)	2.2 (1.8 to 2.6)**
The Netherlands	1.79 (1.48 to 2.10)‡	−0.82 (−6.33 to 4.69)	1.2 (0.8 to 1.6)**	2.3 (1.7 to 2.9)**	2.8 (2.4 to 3.3)**
Switzerland‖	−0.37 (−0.78 to 0.04)	−1.21 (−3.11 to 0.69)	−1.4 (−2.0 to −0.8)¶	0.2 (−0.5 to 0.9)	0.1 (−0.7 to 0.9)

*German national screening program began in 2008.
†Years of reporting for the Czech Republic: 1986–2012.
‡Significant trends.
§Years of reporting for Denmark: 1980–2011.
‖Years of reporting for Belgium, France, and Switzerland: 1980–2010.
¶Statistically significant decrease in melanoma mortality.
**Statistically significant increase in melanoma mortality.

Table 10. Unadjusted Melanoma Mortality Rate per 100,000 Before and After Implementation of National Skin Cancer Screening, Germany, 2000–2012 (KQ1)

Study	Country	N in group	Number of deaths (2000–2012)	Unadjusted melanoma mortality rate per 100,0000[†], mean (2000–2007)	Unadjusted melanoma mortality rate per 100,0000[†], mean (2008–2012[‡])
Kaiser 2018[124] Fair	Germany (excluding Schlesweig-Holstein)*	NR	NR	2.733	3.429
	Europe (excluding Germany)[§]	NR	NR	2.841	3.155

*SCREEN skin cancer screening program was conducted in Schleswig-Holstein region 2003–2004.
[†]ICD-10 C43.
[‡]National German skin cancer screening implemented in 2008.
[§]22 European countries: Austria, Belgium, Bulgaria, Switzerland, Czech Republics, Germany, Denmark, Spain, Finland, France, Croatia, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, and Slovakia (Eurostat data).

Abbreviations: KQ=Key question; NR=Not reported.

Table 11. Unadjusted Melanoma Mortality Rates per 100,000, Germany and Schleswig-Holstein, by Age Group and Sex (KQ1a depicted graphically also in Figures 7 and 8)[125]

Katalinic, 2015 Fair	Schleswig-Holstein	Germany	Schleswig-Holstein	Germany	Schleswig-Holstein	Germany	Schleswig-Holstein	Germany	Schleswig-Holstein	Germany	Schleswig-Holstein	Germany
	Male	Male	Male	Male	Male	Male	Female	Female	Female	Female	Female	Female
Year	35 to 49	35 to 49	50 to 64	50 to 64	65+	65+	35 to 49	35 to 49	50 to 64	50 to 64	65+	65+
1998	1.7	1.5	4.3	4	9.1	10.5	2.1	1.1	3.2	3	10.5	7.7
1999	3.3	1.6	6.7	4.2	12.3	10.3	2.4	1.1	3.6	2.6	9.7	7.3
2000	2.9	1.6	7.8	4.6	11.8	11.1	0.7	1.2	3.9	2.7	10.6	7.7
2001	1.9	1.6	6.4	4.4	17.7	11.3	1.9	1	2.9	2.7	13.2	8
2002	1.2	1.4	3.6	4.2	12.7	10.9	1.3	1.1	3.6	2.8	9.8	8.1
2003	0.3*	1.6	4.0*	4.7	11.1*	12	1.5*	1.2	3.3*	2.8	8.3*	7.2
2004	1.2*	1.4	6.3*	4.3	13.3*	11.8	1.8*	1.3	3.7*	2.6	5.8*	7.4
2005	2.6	1.3	5.6	4.2	13.9	11.3	0.3	1.1	2.6	2.9	6.6	7.7
2006	1.7	1.4	6.5	4.1	12	11.4	1.5	1.2	3.4	2.5	6.4	7.1
2007	1.1	1.5	5.4	4.5	9.6	11.9	1.2	1.1	2.6	2.7	7.5	7.6
2008	0.6†	1.5†	1.5†	3.9†	6.2†	12.1†	0.9†	1.3†	1.5†	2.8†	3.8†	7.8†
2009	1.5†	1.3 †	5†	4.3†	5.7†	13†	0.6†	1.3†	1.9†	2.7†	3.8†	8.3†
2010	1.5†	1.6 †	3.7†	4.4†	9†	13.8†	1.2†	1.4†	1.1†	2.6†	4.9†	7.8†
2011	2.5†	1.7 †	3.6†	4.6†	14†	16.5†	1.2†	1.3†	3.5†	2.9†	9.9†	8.8†
2012	1.6†	1.3 †	5.3†	4.4†	12.6†	15.8†	4.1†	1.4†	2.4†	2.9†	8.7†	9.1†
2013	1.3†	1.5 †	5.1†	4.5†	13.5†	17.3†	1.9†	1.5†	3.7†	2.6†	10.9†	9.3†

*Years in which skin cancer screening (pilot project in Schleswig-Holstein or national skin cancer screening) was performed.
†Years of German national skin cancer screening (2008–2013).

Table 12. Skin Cancer or Precursor Lesion Detection Rates, Screened vs. Unscreened (KQ2)

Study, year Quality Country	Population Description	Participation Rate in Screening Program, %	Screening Population, N	Type of Skin Cancer or Precursor Lesion	Total Detected in the Screened Population, n (%)	Total Detected in the Comparison Population, n (%)	Between Group Difference
Cristofolini, 2015[130] Fair Italy	Screening: Residents of Trento, Italy, who participated in free whole-body skin screening program between January 2001 and Dec 2004; participants were followed until 2013 (excluding those with a history of melanoma) No routine screening: Residents of Trento, Italy 2005–2017 (excluding people with previous melanoma diagnosis)	NR	Routine screening: 3,635 (initial screening group); 3,618 (followup period) No routine screening: 307,679	Melanoma	Screening group: 15 (0.4) Followup period: 14 (0.4)	1,362 (0.4)*	NR
				BCC, SCC	Screening group: BCC: 12 (0.3) SCC: 1 (0.03)	NR	
				Dysplastic nevi	Dysplastic nevi: 11 (0.3)	NR	
Matsumoto, 2022[131, 134] Good US	Primary care patients age ≥35 years with office visit in 2014–2018 Routine screening: EHR documentation of full body skin examination during study period No routine screening: no EHR documentation of full body skin examination during study period	NR	Routine screening: 144,851 No routine screening: 450,948	Melanoma	356 (0.25) Age-sex adjusted incidence per 100,000 person-years (95% CI): 65.3 (57.9-73.7)	638 (0.14) Age-sex adjusted incidence per 100,000 person-years (95% CI): 42.2 (39.0-45.6)	AdjHR (95% CI): 1.8 (1.6-2.1); p<0.001‖

Table 12. Skin Cancer or Precursor Lesion Detection Rates, Screened vs. Unscreened (KQ2)

Study, year Quality Country	Population Description	Participation Rate in Screening Program, %	Screening Population, N	Type of Skin Cancer or Precursor Lesion	Total Detected in the Screened Population, n (%)	Total Detected in the Comparison Population, n (%)	Between Group Difference
Hoorens, 2016[132] Fair Belgium	Routine screening: participants receiving single TBE during 5-day screening event No routine screening: participants in lesion-directed 4-day examination event	Routine screening: 17.9 No routing screening: 3.3	Routine screening: 1,668 No routine screening: 248	All skin cancer	39 (2.3)	8 (3.2)	Screened minus Unscreened (95% CI): -0.89 (-3.96 to 0.90); p=0.40
				Melanoma	8 (0.5)	1 (0.4)	Screened minus Unscreened (95% CI): 0.08 (-1.78 to 0.65); p=0.87
				BCC	30 (1.8)	7 (2.8)	Screened minus Unscreened (95% CI): -1.02 (-3.96 to 0.61); p=0.28
				SCC or Bowen disease	1 (0.1)	0 (0)	Screened minus Unscreened (95% CI): 0.06 (-1.47 to 0.34); p=0.99
				Actinic keratosis	130 (7.9)	22 (7.8)	NR, p=0.90
				Atypical nevi	249 (15.1)	49 (17.3)	NR, p=0.33
Krensel, 2020[133] Fair Germany	German national skin cancer screening program 2013–2016	NR	NR	Melanoma	815 (NR)	721 (NR)*	NR
				NMSC/KC†	5,378 (NR)	5,466 (NR)	
Trautmann, 2016[135] Fair Germany	German national skin cancer screening program 2005–2012 (Saxony)	12.4	Screened: 533,393 Unscreened: 1,489,074	Melanoma	1,668 (0.3)	1,836 (0.1)	RR (95% CI): 2.50 (2.34 to 2.67)§
				NMSC	13,535 (2.5)	17,256 (1.2)	RR (95% CI): 2.16 (2.11 to 2.21)§

*No routine screening.
†Nonmelanoma skin cancer/keratinocyte cancer (includes squamous cell carcinoma and basal cell carcinoma).
‡Adjusted for age, sex, race/ethnicity, and insurance status.
§Calculated; unadjusted.
║Cox proportional hazard ratio, adjusted for age, sex, and White race

Abbreviations: Adj=Adjusted; BCC=Basal cell carcinoma; CI=Confidence interval; KC=Keratinocyte carcinoma; KQ=Key question; NMSC=Nonmelanoma skin cancer; NR=Not reported; RR=Relative risk; SCC=Squamous cell carcinoma; TBE=Total body examination.

Table 13. Stage or Thickness at Melanoma or KC Detection, Screened vs. No Routine Skin Cancer Screening (KQ2)

Study, year Quality Country	Population description	Type of skin cancer	Cases detected, N	Stage or thickness at detection*	Routine skin cancer screening n (% of cases); 95% CI	No routine skin cancer screening n (% of cases); 95% CI	Between group difference
Aitken 2010[129] Fair Australia	Cases: Queensland residents age 20–75 years diagnosed with histologically confirmed first primary invasive cutaneous melanoma[§§] between Jan 1, 2000 and Dec 31, 2003 Controls: Adults selected from Queensland Electoral Roll using stratified random sampling based on 5-year age groups and sex distribution of cases (excluding those with confirmed melanoma diagnoses)	Melanoma	3,762	0.01 to 0.75 mm[‖‖]	2049 (54.5)	NR	adjOR of clinical skin examination in 3 years prior to noticing lesion (95% CI)[††,‡‡] 1.38 (1.22 to 1.56) [Control reference group]
				0.76 to 1.49 mm	1017 (27.0)	NR	adjOR, 0.93 (0.79 to 1.10)
				1.50 to 2.99 mm	443 (11.8)	NR	adjOR, 0.83 (0.66 to 1.05)
				≥3.00 mm	253 (6.7)	NR	adjOR, 0.60 (0.43 to 0.83)
				≤0.75 mm	NR	NR	adjOR, 1.38 (1.22 to 1.56)
				>0.75 mm	NR	NR	adjOR, 0.86 (0.75 to 0.98)
Cristofolini, 2015[130] Fair Italy	Screening: Residents of Trento, Italy, who participated in free whole-body skin screening program between January 2001 and Dec 2004; followup participants were followed until 2013 (those with a history of melanoma were excluded from this group) No routine screening: Residents	Melanoma	1,389	In situ (screening period)	1 person of 15 (6.7%)	NR	NR
				>1 mm (screening period)	4/14=28.6%	NR	NR
				Mean (screening period)	0.87 mm (median: 0.52 mm)	NR	NR
				<1 mm (screening + followup)	19/27=70.4%	786 (57.7)	Unadjusted difference between combined screening groups and unscreened group, p=0.242
				<2 mm (screening + followup)	25/27=92.6%	1,034 (75.9)	Unadjusted difference between combined screening groups and unscreened group, p=0.043
				In situ (followup screening group[¶])	0/13=0%	NR	NR

Table 13. Stage or Thickness at Melanoma or KC Detection, Screened vs. No Routine Skin Cancer Screening (KQ2)

Study, year Quality Country	Population description	Type of skin cancer	Cases detected, N	Stage or thickness at detection*	Routine skin cancer screening n (% of cases); 95% CI	No routine skin cancer screening n (% of cases); 95% CI	Between group difference
	of Trento, Italy 2005–2017 (excluding people with previous melanoma diagnosis)			<1 mm (followup screening group¶)	9/13=69.2%	NR	NR
				>1 mm (followup screening group¶)	4/13=30.8%	NR	NR
				Mean (followup screening group¶)	0.83 mm (median 0.60 mm)	NR	NR
Matsumoto, 2022[131] Good US	Primary care patients age ≥35 years diagnosed with melanoma following office visit in 2014–2018	Melanoma	Total: 994 Screened: 356 Unscreened: 638	In situ	172 (48.3)	221 (34.6)	AdjHR (95% CI): 2.6 (2.1-3.1); p<0.001¶¶
				≤1 mm	132 (37.1)	238 (37.3)	AdjHR (95% CI): 1.8 (1.5-2.2); p<0.001¶¶
				>1 mm	52 (14.6)	179 (28.1)	AdjHR (95% CI): 1.0 (0.7-1.3); p=0.75¶¶
				>2 mm	28 (7.9)	101 (15.8)	AdjHR (95% CI): 0.9 (0.6-1.4); p=0.61)¶¶
				>4 mm	12 (3.4)	51 (8.0)	AdjHR (95% CI): 0.8 (0.4-1.4); p=0.38¶¶
Krensel, 2020[133]† Fair Germany	German national skin cancer screening program 2013-2016	Melanoma	1,536	In situ	10 (1.23); NR	In situ: 10 (1.43); NR	Screening – no screening (%): 0 (-0.20)
				Stage I/II:	799 (98.04); NR	707 (98.09); NR	Screening – no screening (%): 92 (-0.05)
				Stage III/IV:	6 (0.74); NR	3 (0.48); NR	Screening – no screening (%): 3 (0.26)
		KC	10,844	In situ	4 (0.07); NR	10 (0.18); NR	Screening – no screening (%): -6 (-0.10)
				Stage I/II	5373 (99.91); NR	5454 (99.77); NR	Screening – no screening (%): -81 (0.13)
				Stage III/IV	1 (0.02); NR	3 (0.05); NR	Screening – no screening (%): -2 (-0.03)
Trautmann, 2016[135] Fair Germany	German national skin cancer screening program 2005–2012 (State of Saxony)	Melanoma	3,504	Lymph node metastasis	98 (5.9); ~3.4% to ~9.6%‡	156 (8.5%); ~5.7%, ~10.4%‡	NS
				Distant metastasis	25 (1.5); ~0.4% to ~3.4%‡	64 (3.5) ~1.3%, ~7.8%‡	NS‡

* Author-reported stage/thickness data categories.
† Uses TNM / AJCC staging system to report on melanoma and KC stage at detection. This information was calculated using an algorithm used in other publications for estimating stage from claims data.
‡ Estimated from the graphic representation of confidence intervals (point estimates of confidence intervals not reported).
§ Cases excluded due to missing information.
‖ Adjusted for age, sex, race/ethnicity, and insurance status.

Table 13. Stage or Thickness at Melanoma or KC Detection, Screened vs. No Routine Skin Cancer Screening (KQ2)

¶ Data available on n=13/14 people.
**Sampling for this study included all cases in registry with thick (≥0.75 mm) melanoma and a 60% sample of cases with thinner melanoma (<0.75 mm).
††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 nonmelanoma skin cancer, and ethnicity.
‡‡Ascertained via self-report.
§§Does not include acral lentiginous melanoma.
‖‖Thickness categories comparable to thickness/depth categories used in SEER summary staging, localized stage (≤0.75 mm (II) 0.76–1.50 mm (III) >1.5 mm (IV), See Table 1.
¶¶Cox proportional hazard ratio, adjusted for age, sex, and White race.

Abbreviations: Adj=Adjusted; CI=Confidence interval; Dec=December; EHR=Electronic health record; Jan=January; KC=Keratinocyte carcinoma; KQ=Key question; Mm=millimeter; NR=Not reported; NS=Not significant; OR=Odds ratio.

Table 14. Stage or Thickness at Melanoma Detection, Specific Populations, Routine Clinician Skin Examination Compared to Usual Care or No Screening (KQ2a)

Study, year Quality	Population N	Type of skin cancer or precursor lesion	Subgroup	Stage at detection*, n (% of cases); 95% CI Routine skin cancer screening	Stage at detection*, n (% of cases); 95% CI No routine skin cancer screening	Between group difference
Aitken 2010[129] Fair	Cases: 3,762 Controls: 3,824	Melanoma	Sex	NR	NR	Melanoma thickness at detection: adjOR of clinical skin examination in 3 years prior to noticing lesion (95% CI)[†‡] Males 0.01 to 0.75 mm: 1.54 (1.31 to 1.82), p<0.01 0.76 to 1.49 mm: 0.96 (0.78 to 1.19), NS 1.50 to 2.99 mm: 0.85 (0.63 to 1.15), NS ≥3.00 mm: 0.62 (0.42 to 0.91), P<0.05 Females 0.01 to 0.75 mm: 1.20 (0.99 to 1.45), NS 0.76 to 1.49 mm: 0.90 (0.70 to 1.16), NS 1.50 to 2.99 mm: 0.79 (0.54 to 1.16), NS ≥3.00 mm: 0.55 (0.29 to 1.03), NS
			Age	NR	NR	Melanoma thickness at detection adjOR of clinical skin examination in 3 years prior to noticing lesion (95% CI)[†‡] Age 20–49 yrs 0.01 to 0.75 mm: 1.32 (1.08 to 1.62), p<0.05 0.76 to 1.49 mm: 0.98 (0.76 to 1.27), NS 1.50 to 2.99 mm: 0.67 (0.41 to 1.07), NS ≥3.00 mm: 0.48 (0.22 to 1.06), NS Age 50–74 yrs 0.01 to 0.75 mm: 1.43 (1.22 to 1.67), p<0.01 0.76 to 1.49 mm: 0.91 (0.74 to 1.12), NS 1.50 to 2.99 mm: 0.90 (0.68 to 1.18), NS ≥3.00 mm: 0.62 (0.43 to 0.89) p<0.05

Table 14. Stage or Thickness at Melanoma Detection, Specific Populations, Routine Clinician Skin Examination Compared to Usual Care or No Screening (KQ2a)

Study, year Quality	Population N	Type of skin cancer or precursor lesion	Subgroup	Stage at detection*, n (% of cases); 95% CI Routine skin cancer screening	Stage at detection*, n (% of cases); 95% CI No routine skin cancer screening	Between group difference
Cristofolini, 2015[130] Fair	Routine screening: 3,635 (screening group); 3,618 (followup screening group) No routine screening: 307,679	Melanoma	Sex	Screening group: Male: 9/15=60% Female: 6/15=40% Followup screening group: Male: 5/14=35.7% Female: 9/14=64.3% **Breslow thickness** Screening group: *Mean thickness* Female: 0.65 mm (median 0.52 mm) Male: 1.15 mm (median 0.825 mm) Thickness <1 mm: 10/14=71.4% (3 male, 7 female) Thickness >1 mm: 4/14=28.6% (3 male, 1 female) Followup screening group: *Mean thickness* Female: 0.61 mm (median 0.45 mm) Male: 1.19 mm (median 1.10 mm) Thickness <1 mm: 9/13=69.2% (2 male, 7 female) Thickness >1 mm: 4/13=30.8% (3 male, 1 female)	NR	NR

* Author-reported stage/thickness data categories.
† 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 nonmelanoma skin cancer, and ethnicity.
‡ Ascertained via self-report.

Abbreviations: Adj=Adjusted; CI=Confidence intervals; KQ=Key question; NR=Not reported; NS=Not significant; Mm=millimeter; OR=Odds ratio.

Table 15. Melanoma Detection Rates and Thickness at Melanoma Detection, Population Age ≤65, Screening Compared to No Screening (KQ2a)

Study, year Quality	Population N	Melanoma detected in screened population; N (%)	Melanoma detected in unscreened population; N (%)	Between group difference; adjHR (95% CI)*; p-value	Stage at detection	Screened group; n (% of cases)	Unscreened group; n (% of cases)	Between group difference; adjHR (95% CI)*; p-value
Matsumoto, 2022[131, 134] Good US	Age ≥65 years screened: 47,603 Age ≥65 years unscreened: 127,777	155 (0.33) Adj incidence per 100,000 person-years (95% CI): 98.7 (83.2–117.2)†	270 (0.21) Adj incidence per 100,000 person years (95% CI): 66.5 (58.7–75.3)†	1.6 (1.3-2.0); p<0.001	In situ	71 (45.8)	104 (38.5)	1.9 (1.4–2.6); p<0.001
					≤1 mm	56 (36.1)	83 (30.7)	1.9 (1.3–2.6); p<0.001
					>1 mm	28 (18.1)	83 (30.7)	1.0 (0.7–1.6); p=0.90
					>2 mm	16 (10 .3)	60 (22.2)	0.8 (0.5–1.4); p=0.42
					>4 mm	5 (3.2)	33 (12.2)	0.5 (0.2–1.2); p=0.11

*Cox proportional hazard ratio, adjusted for age, sex, and White race.
†Adjusted for age and sex.

Table 16. Cosmetic Harms of Routine Skin Cancer Screening or Diagnostic Workup (KQ3)

Study, year Quality Country	Population	Procedure and Provider Type	Harms Assessment	Reported Harms
Gambichler, 2000[136] Fair Germany	45 patients (51% women) with a mean age of 32 years who had been identified by skin cancer screening with 77 nevi and received biopsy; 25 patients and 56 shave sites were examined for cosmetic harms at 6-month followup	Deep shave excision with razor blade biopsy	Assessed on a 4-point scale 6 months after excision (scale: 1=excellent, 2=good, 3=moderate, 4=poor)	Patients: median score=1.5, (IQR 1–2, excellent to good)[†] 7.1% (4 of 56) shave sites were rated as having poor cosmetic outcomes

[†]Calculated.

Abbreviations: KQ=key question. IQR=interquartile range.

Table 17. Psychological Measures and Quality of Life Among Individuals Who Reported Full-Body Skin Cancer Screening and Those Who Reported Partial Body Examination (KQ3)

Study, Year Quality	Measure	Construct	Scoring range	Interpretation	5-month followup result, median (range), *p*	8-month followup result, median (range), *p*
Risica, 2018[137, 138] Fair	Hospital Anxiety and Depression scale (HADS-A)	Anxiety	0 to 21	<8 No depression or anxiety 8–10 Mild 11–14 Moderate 15–21 Severe	Full body exam*: 3.5 (0–15) Partial body exam†: 4 (0–18) *p*=0.9	Full body exam*: 3 (0–14) Partial body exam†: 4 (0–16) *p*=0.6
	Hospital Anxiety and Depression scale (HADS-D)	Depression	0 to 21	For anxiety and depression separately.	Full body exam*: 1 (0–20) Partial body exam†: 2 (0–15) *p*=0.1	Full body exam*: 1 (0–19) Partial body exam†: 2 (0–12) *p*=0.3
	Spielberger State-Trait Anxiety Index – form 6 (STAI-6)	Anxiety	20 to 80	Higher score indicates greater disease severity. In research, individuals with >44 points are often referred to as being highly anxious.	Full body exam*: 23.3 (20–70) Partial body exam†: 26.7 (20–80) *p*=0.6	Full body exam*: 23.3 (20–80) Partial body exam†: 23.3 (20–63.7) *p*=0.6
	Psychological Consequences Questionnaire (PCQ)	Negative emotional consequences	0 to 15	Higher score indicates greater distress from screening.	Full body exam*: 0 (0–9) Partial body exam†: 0 (0–8) *p*=0.5	Full body exam*: 0 (0–10) Partial body exam†: 0 (0–11) *p*=0.8
		Negative physical consequences	0 to 12	Higher score indicates greater distress from screening.	Full body exam*: 0 (0–5) Partial body exam†: 0 (0–4) *p*=0.3	Full body exam*: 0 (0–8) Partial body exam†: 0 (0–10) *p*=0.8
		Negative social consequences	0 to 9	Higher score indicates greater distress from screening.	Full body exam*: 0 (0–8) Partial body exam†: 0 (0–6) *p*=0.7	Full body exam*: 0 (0–7) Partial body exam†: 0 (0–9) *p*=0.8
		Positive emotional consequences	0 to 15	Higher score indicates greater positive effect from screening.	Full body exam*: 6 (0–15) Partial body exam†: 4 (0–15) *p*=0.0002	Full body exam*: 7 (0–15) Partial body exam†: 6 (0–15) *p*=0.6
		Positive physical consequences	0 to 9	Higher score indicates greater positive effect from screening.	Full body exam*: 0 (0–9) Partial body exam†: 0 (0–9) *p*=0.4	Full body exam*: 0 (0–9) Partial body exam†: 0 (0–9) *p*=0.9
		Positive social consequences	0 to 6	Higher score indicates greater positive effect from screening.	Full body exam*: 0 (0–6) Partial body exam†: 0 (0–6) *p*=0.5	Full body exam*: 0 (0–6) Partial body exam†: 0 (0–6) *p*=0.8

Table 17. Psychological Measures and Quality of Life Among Individuals Who Reported Full-Body Skin Cancer Screening and Those Who Reported Partial Body Examination (KQ3)

Study, Year Quality	Measure	Construct	Scoring range	Interpretation	5-month followup result, median (range), *p*	8-month followup result, median (range), *p*
	12-Item Short Form Health Survey, Physical Component Summary (SF-12 PCS)	Health-related Quality of life: physical component	0 to 100	The US population average is 50 points. Higher scores indicate better-perceived health.	Full body exam*: 40.6 (30.9–47.3) Partial body exam†: 40.5 (31.4–48.7) *p*=0.7	Full body exam*: 41.0 (4.0) Partial body exam†: 40.4 (3.8) *p*=0.4
	12-Item Short Form Health Survey, Mental Component Summary (SF-12 MCS)	Health-related Quality of life: mental component	0 to 100	The US population average is 50 points. Higher scores indicate better-perceived health.	Full body exam*: 49.3 (36.9–56.6) Partial body exam†: 49.1 (28.5–60.5) *p*=0.4	Full body exam*: 49.2 (28.6–56.9) Partial body exam†: 49.5 (35.5–59.2) *p*=0.02

*Full body examination defined as patients reporting that they had their skin thoroughly examined by their PCP (based on questions that included if screening was performed, the level of undress, and whether certain body parts were examined).
†Partial body examination defined as patients reporting that they did not have their whole body screened by their PCP, did not disrobe, or did not have certain body parts examined.

Abbreviations: KQ=Key Question; PCP=Primary care physician; US=United States.

Table 18. Study Characteristics, Included Studies (KQ4)

Study, Year Quality Country	Population	N	Data source Years of data collection Staging system	Measure of risk	Adjustment variables	Outcomes assessed (melanoma mortality, all-cause mortality)	Summary of analyses for KQ4 Referent group	Specific population group for KQ4a
Dawes, 2016[139] Fair US	Adults diagnosed with primary cutaneous melanoma	96,953	SEER-13 registry database 1992–2009 AJCC	HR	None	Melanoma mortality	NR	1. Race group by stage I–IV (White vs. Black). Referent group: White persons, within each stage strata. 2. Race/ethnicity group (White, AANAPI, Black, Hispanic) by age group (0–24 years, 25–49 years, 50–74 years, ≥75 years). Referent group: White persons, within each stage strata.

Table 18. Study Characteristics, Included Studies (KQ4)

Study, Year Quality Country	Population	N	Data source Years of data collection Staging system	Measure of risk	Adjustment variables	Outcomes assessed (melanoma mortality, all-cause mortality)	Summary of analyses for KQ4 Referent group	Specific population group for KQ4a
Enninga, 2017[209] Fair US	Adults age ≥18 years with primary cutaneous melanoma	106,511	SEER-13 registry database 1992–2011 (followup for deaths was until 2012) SEER	HR	Age (main analysis only)	Melanoma mortality	NR	1. Analyses stratified by stage at diagnosis (females vs. males). Referent group: female persons, within each stage strata. 2. Females vs. males, stratified analysis by stage and age group (18–45 years, 46–54 years, ≥55 years). Referent group: female persons, within each stage strata.

Table 18. Study Characteristics, Included Studies (KQ4)

Study, Year Quality Country	Population	N	Data source Years of data collection Staging system	Measure of risk	Adjustment variables	Outcomes assessed (melanoma mortality, all-cause mortality)	Summary of analyses for KQ4 Referent group	Specific population group for KQ4a
Farrow, 2020[141] Fair US	Adults age ≥18 years with melanoma	268,668	National Cancer Database 2004–2015 AJCC	Adjusted HR	Age, sex, race, insurance coverage, income, education, and CD score, tumor characteristics (stage, location, margin positivity), and facility characteristics (academic vs. comprehensive community vs. community hospital, facility location)	All-cause mortality	Risk estimates by stage at diagnosis (Stages I–IV) Referent group: Stage IV	NR

Table 18. Study Characteristics, Included Studies (KQ4)

Study, Year Quality Country	Population	N	Data source Years of data collection Staging system	Measure of risk	Adjustment variables	Outcomes assessed (melanoma mortality, all-cause mortality)	Summary of analyses for KQ4 Referent group	Specific population group for KQ4a
Khosrotehrani, 2015[‡142] Good Australia	Individuals age 15–89 years with primary melanoma	28,979	Queensland Cancer Registry (Australia) 1995–2008 (melanoma-specific deaths were ascertained up to 2010) AJCC	OR	Age, sex, body site, thickness of primary tumor, ulceration, nodal spread, metastasis	Melanoma mortality	NR	1. Analyses stratified by stage at diagnosis (males vs. females). Referent group: male persons, within each stage strata. 2. Males vs. females, stratified analysis by stage and age group (15–45 years, 46–59 years, ≥60 years). Referent group: male persons, within each stage strata.
Mahendraraj, 2017[143] Fair US	White and Black adults diagnosed with cutaneous melanoma	213,827	SEER registry database* 1988–2011 SEER	OR	Age, gender, ethnicity, geographic region, tumor histology, site, depth, stage, grade, lymph node status, presence of ulceration, type of treatment received	Melanoma mortality	Multivariable risk estimates by stage at diagnosis (localized, regional, and distant). Referent group: Localized stage	Multivariable risk estimates provided for White and Black persons independently[†]. Referent group: Localized stage.

Table 18. Study Characteristics, Included Studies (KQ4)

Study, Year Quality Country	Population	N	Data source Years of data collection Staging system	Measure of risk	Adjustment variables	Outcomes assessed (melanoma mortality, all-cause mortality)	Summary of analyses for KQ4 Referent group	Specific population group for KQ4a
Qian, 2021[144] Fair US	Adults with cutaneous (95.7%), mucosal (1.2%), and uveal (3.1%) melanoma diagnosed between 1975 and 2016	398,034	SEER registry database 1975–2016 (data analysis was stratified by years of data collection: 1975–1999; 2000–2009; 2010–2016)	HR	Age, gender, primary site, histologic subtype, and stage	Melanoma mortality	NR	1. Race/ethnicity group (Hispanic, Black, API, AIAN) by stage (localized, regional, distant) Referent group: White persons, within each stage strata. 2. Race/ethnicity group (Hispanic, Black, API, AIAN) by stage (localized, regional, distant) for age ≥65 years Referent group: White persons, within each stage strata.

Table 18. Study Characteristics, Included Studies (KQ4)

Study, Year Quality Country	Population	N	Data source Years of data collection Staging system	Measure of risk	Adjustment variables	Outcomes assessed (melanoma mortality, all-cause mortality)	Summary of analyses for KQ4 Referent group	Specific population group for KQ4a
Robsahm, 2018[145] Good Norway	Individuals age 2–98 years diagnosed with primary melanoma	8,087	Norwegian Malignant Melanoma Registry, which is part of the Cancer Registry of Norway 2008–2012 (followup for deaths was until 2015) SEER	HR	Age, sex, anatomic site, melanoma subtype, T-stage, ulceration, second primary melanoma	Melanoma mortality	Risk estimates by stage at diagnosis (localized, regional, and distant). Referent group: Localized stage	NR
Ward-Peterson-2016[146] Good US	Adults age ≥18 diagnosed with primary cutaneous melanoma	185,219	SEER registry database 1982–2011 SEER	HR	Age, sex, decade of diagnosis, site at diagnosis, stage at diagnosis	Melanoma mortality All-cause mortality	Risk estimates by stage at diagnosis (in situ, localized, regional, and distant). Referent group: In situ melanoma	NR

Table 18. Study Characteristics, Included Studies (KQ4)

Study, Year Quality Country	Population	N	Data source Years of data collection Staging system	Measure of risk	Adjustment variables	Outcomes assessed (melanoma mortality, all-cause mortality)	Summary of analyses for KQ4 Referent group	Specific population group for KQ4a
Zheng, 2020[147] Fair Sweden	Adults diagnosed with first melanoma	19,773	Swedish Cancer Registry 2003–2015 Tumor (T), node (N), and metastasis (M) components of AJCC	HR	Age, gender, year of diagnosis, tumor thickness, ulceration and histology, locoregional and distant metastasis, diagnosis of second primary cancer	All-cause mortality	Stratified risk estimated within T (primary tumor), N (regional lymph nodes) and M (distant metastasis) components. Referent groups: T: T1a (≤1.0 mm with no ulceration or mitosis) N: N0 M: M0	NR

*The SEER registries pulled from include: Alaska Native Tumor Registry, Arizona Indians, Cherokee Nation, Connecticut, Detroit, Georgia Center for Cancer Statistics, Greater Bay Area Cancer Registry, Greater California, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Jersey, New Mexico, Seattle-Puget Sound, and Utah.
†Authors refer to the analyzed groups as Caucasian and African American persons.
‡Additionally, this study used the SEER data collected between 1995 and 2010 to compare the risk (ORs) for melanoma mortality between females and males at I, II, and combined III and IV AJCC stages (n=57,402). For this review, we did not analyze the US data/estimates as another included study (Enninga, 2017)[140] used HRs to compare the risk in these two groups with the data collected over a longer period—1992 to 2011 (n=106,511).

Abbreviations: AANAPI=Asian American/Native American/Pacific Islander; AJCC=American Joint Committee on Cancer; CD=Charlson-Deyo; HR=Hazard ratio; KQ=Key Question; NR=Not reported; OR=Odds ratio; SEER=Surveillance, Epidemiology, and End Results Program; US=United States.

Table 19. Melanoma Stage at Diagnosis and Melanoma Mortality (KQ4)

Author, Year Quality	Years of data collection Country	Study N	Mean age, years	Female, %	Race/ Ethnicity, %	History of skin cancer screening, %	Summary stage, SEER	Stage distribution at diagnosis, %	Melanoma deaths, n	Risk of melanoma mortality
Mahendraraj, 2017[210] Fair	1988–2011 US	213,827	Entire population: 58.9‖ White: 58.9 Black: 60.5	43.0	White: 99.5 Black: 0.5 Other/Mixed: 0	Hx of SC: NR Family Hx of SC: NR	Localized	82.4	NR	Referent group
							Regional	9.5	NR	OR‡, 3.8 (95% CI, 3.5 to 4.1)
							Distant	3.8	NR	OR‡, 7.5 (95% CI, 6.3 to 8.9)
							Unstaged	4.3	NR	--
Robsahm, 2018[145] Good	2008–2012 (followup for deaths was until 2015) Norway	8,087	60.5‖ 64 (median)	50.1	NR	NR	Local	91.8	438	Referent group
							Regional	5.0	156	adjHR†, 4.00 (95% CI, 3.26 to 4.90)
							Distant	3.2	159	adjHR†, 16.82 (95% CI, 12.88 to 21.95)
Ward-Peterson, 2016[146] Good	1982–2011 US	185,219	Mean: 57.2‖	43.0	White: 91.7 Black: 1.7 Other/Mixed: NR	Hx of SC: NR Family Hx of SC: NR	In situ	32.8	NR	Referent group
							Localized	56.8	NR	adjHR*, 5.8 (95% CI, 5.3 to 6.3)
							Regional	7.9	NR	adjHR*, 31.5 (95% CI, 28.9 to 34.2)
							Distant	2.5	NR	adjHR*, 169.6 (95% CI, 154.2 to 186.6)

*Adjusted for age, gender, decade of diagnosis, site at diagnosis, and stage at diagnosis.
†Adjusted for sex, age, anatomic site, melanoma subtype, T-stage, ulceration, and second primary melanoma.
‡Unadjusted.
‖Calculated, weighted mean.

Abbreviations: Adj=Adjusted; CI=Confidence interval; HR=Hazard ratio; Hx=History; KQ=Key Question; NR=Not reported; OR=Odds ratio; SC=Skin cancer; SD=Standard deviation; SEER=Surveillance, Epidemiology, and End Results Program; US=United States.

Table 20. Melanoma Stage at Diagnosis and All-Cause Mortality (KQ4)

Author, Year (Study) Quality	Data Collection Country	Study N	Mean Age, years	Female, %	Race/Ethnicity, % Hx of SC, %	Stage	Stage Distribution at Diagnosis, %	All-Cause Mortality, n	All-Cause Mortality adjHR, 95% CI
Farrow, 2020[140]	2004–2015	268,668	61*	42.4	White: 98.7	I	8.3	NR	0.09 (0.08 to 0.10)[†]
					Black: 0.6	II	43.4	NR	0.19 (0.18 to 0.20)[†]
					Other/mixed race: NR	II	36.6	NR	0.38 (0.36 to 0.40)[†]
Fair	US					IV	11.7	NR	Referent group
					Hx of SC: NR Family Hx of SC: NR				
Ward-Peterson, 2016[146]	1982–2011	185,219	57.2	43.0	White: 91.7 Black: 1.7	In situ	32.8	NR	Referent group
	US				Other/mixed race: NR	Localized	56.8	NR	1.5 (1.5 to 1.5)[‡]
						Regional	7.9	NR	3.9 (3.8 to 4.1)[‡]
Good					Hx of SC: NR Family Hx of SC: NR	Distant	2.5	NR	15.8 (14.9 to 16.7)[‡]
Zheng, 2020[147]	2003–2015	19,773	65.3	50.9	White: NR	Total	NR	3,182 (calculated)	NA
					Black: NR	T1a	48.0	664	Referent group
					Other/mixed race: NR	T1b	7.8	127	1.44 (1.20 to 1.73)[§]
Fair	Sweden					T2a	16.3	349	1.46 (1.28 to 1.66)[§]
					Hx of melanoma: 0	T2b	3.9	142	2.38 (1.98 to 2.86)[§]
					Family Hx of SC: NR	T3a	7.3	369	2.71 (2.36 to 3.11)[§]
						T3b	5.9	425	3.71 (3.23 to 4.27)[§]
						T4a	3.6	313	4.37 (3.72 to 5.13)[§]
						T4b	7.3	793	5.90 (5.17 to 6.74)[§]
						N0[‖]	71.2	1,700	Referent group
						Nx[‖]	26.3	1,225	1.29 (1.11 to 1.50)[§]
						N+[‖]	2.5	257	2.24 (1.82 to 2.75)[§]
						M0[¶]	69.2	1,661	Referent group
						Mx[¶]	29.9	1,395	0.92 (0.79 to 1.07)[§]
						M+[¶]	0.9	126	3.17 (2.40 to 4.19)[§]

*Median.
[†]Adjusted for age, gender, race, insurance coverage, income, education, and CD score, tumor characteristics (stage, location, margin positivity), and facility characteristics (academic vs. comprehensive community vs. community hospital, facility location).
[‡]Adjusted for age, gender, decade of diagnosis, site at diagnosis, stage at diagnosis.
[§]Adjusted for age, gender, year of diagnosis, tumor thickness, ulceration and histology, locoregional and distant metastasis, diagnosis of second primary cancer.
[‖]Locoregional metastasis to lymph nodes.
[¶]Distant metastasis.

Abbreviations: Adj=Adjusted; CD=Charlson-Deyo; CI=Confidence interval; HR=Hazard ratio; Hx=History; KQ=Key Question; NR=Not reported; SC=Skin cancer; US=United States.

Table 21. Melanoma Stage at Diagnosis and Melanoma Mortality, by Race and/or Ethnicity (KQ4a)

Author, Year Quality	Data Collection Country	Study N	Race/Ethnicity Group	Age Group, years	Stage, SEER and AJCC	Stage Distribution at Diagnosis, %	Melanoma Deaths, n	Risk of Melanoma Mortality
Mahendraraj, 2017[143] Fair	1988-2011 US	213,827	White	All ages (mean 58.8 [SD 17.12])	Local	82.5	19,207	Referent group
					Regional	9.5		OR, 3.0 (95% CI, 2.8 to 3.2)
					Distant	3.7		OR, 4.7 (95% CI, 4.0 to 5.4)
					Unstaged	4.3		--
			Black	All ages (mean 60.5 [SD 18.16])	Local	56.3	241	Referent group
					Regional	21.9		OR, 4.3 (95% CI, 2.5 to 7.3)
					Distant	14.3		OR, 3.7 (95% CI, 1.3 to 10.5)
					Unstaged	7.5		--
Dawes 2016[139] Fair	1992–2009 US	96,953	White	All ages (≥0)	I	75.97	NR	Referent group
					II	12.93		
					III	6.65		
					IV	4.45		
			Black	All ages (≥0)	I	52.68	NR	HR, 3.04 (95% CI, 2.34 to 3.95)*
					II	22.82		HR, 1.34 (95% CI, 0.92 to 1.95)
					III	13.42		HR, 1.86 (95% CI, 1.21 to 2.87)
					IV	11.07		HR, 1.03 (95% CI, 0.68 to 1.57)
				0 to 24	I	--	NR	HR, 5.80 (0.79 to 42.34)*
					II	--		HR, 9.50 (1.23 to 73.62)
					III	--		HR, 1.34e-8 (0.0 to Inf.)
					IV	--		HR, 3.62e-8 (0.0 to Inf.)
				25 to 49	I	--	NR	HR, 2.98 (1.33 to 6.65)*
					II	--		HR, 1.52 (0.49 to 4.72)
					III	--		HR, 2.36 (1.05 to 5.30)
					IV	--		HR, 2.18 (1.13 to 4.22)
				50 to 74	I	--	NR	HR, 2.76 (1.83 to 4.15)*
					II	--		HR, 1.33 (0.81 to 2.19)
					III	--		HR, 1.71 (0.85 to 3.44)
					IV	--		HR, 0.94 (0.47 to 1.89)
				≥75	I	--	NR	HR, 2.36 (1.60 to 3.47)*
					II	--		HR, 1.45 (0.72 to 2.90)
					III	--		HR, 1.23 (0.58 to 2.60)
					IV	--		HR, 0.79 (0.33 to 1.91)
			AANAPI	All ages (≥0)	I	61.17	NR	NR
					II	16.48		
					III	12.13		
					IV	10.22		
				0–24	I	--	NR	HR, 2.52 (0.61 to 10.46)*
					II	--		HR, 5.15e-7 (0.0 to Inf.)
					III	--		HR, 1.33e-8 (0.0 to Inf.)

Table 21. Melanoma Stage at Diagnosis and Melanoma Mortality, by Race and/or Ethnicity (KQ4a)

Author, Year Quality	Data Collection Country	Study N	Race/Ethnicity Group	Age Group, years	Stage, SEER and AJCC	Stage Distribution at Diagnosis, %	Melanoma Deaths, n	Risk of Melanoma Mortality
					IV	--		HR, 2.01 (0.47 to 8.57)
				25-49	I	--	NR	HR, 2.70 (1.73 to 4.21)*
					II	--		HR, 0.71 (0.26 to 1.90)
					III	--		HR, 1.11 (0.53 to 2.35)
					IV	--		HR, 1.22 (0.71 to 2.07)
				50–74	I	--	NR	HR, 2.59 (2.02 to 3.33)*
					II	--		HR, 1.48 (0.97 to 2.2)
					III	--		HR, 1.57 (0.99 to 2.47)
					IV	--		HR, 1.13 (0.78 to 1.65)
				≥75	I	--	NR	HR, 1.51 (1.11 to 2.06)*
					II	--		HR, 0.85 (0.52 to 1.40)
					III	--		HR, 1.34 (0.79 to 2.30)
					IV	--		HR, 1.15 (0.68 to 1.78)
			Hispanic	All ages (≥0)	I	69.17	NR	NR
					II	15.33		
					III	9.36		
					IV	6.14		
				0–24	I	--	NR	HR, 1.71 (0.61 to 4.81)*
					II	--		HR, 3.75 (1.22 to 11.56)
					III	--		HR, 1.35e-8 (0.0 to Inf.)
					IV	--		HR, 0.79 (0.27 to 2.27)
				25–49	I	--	NR	HR, 1.94 (1.53 to 2.46)*
					II	--		HR, 1.70 (1.19 to 2.42)
					III	--		HR, 0.82 (0.52 to 1.29)
					IV	--		HR, 0.53 (0.31 to 0.90)
				50–74	I	--	NR	HR, 1.99 (1.69 to 2.34)*
					II	--		HR, 1.31 (0.99 to 1.74)
					III	--		HR, 1.16 (0.82 to 1.63)
					IV	--		HR, 1.04 (0.79 to 1.37)
				≥75	I	--	NR	HR, 1.28 (1.06 to 1.56)*
					II	--		HR, 1.16 (0.83 to 1.63)
					III	--		HR, 1.49 (0.85 to 2.60)
					IV	--		HR, 1.04 (0.61 to 1.78)

*White=Referent group.

Abbreviations: AANAPI=Asian American/Native American/Pacific Islander; Adj=Adjusted; AJCC=American Joint Committee on Cancer; CI=Confidence interval; HR=Hazard ratio; KQ=Key Question; NR=Not reported; OR=Odds ratio; SD=Standard deviation; SEER=Surveillance, Epidemiology, and End Results Program; US=United States.

Table 22. Melanoma Stage at Diagnosis and Melanoma Mortality, by Race and/or Ethnicity (KQ4a) From Qian 2021 Study (n=398,034)*

Author, Year Quality Country	Age Group	Race/Ethnicity Group	Stage, SEER	Stage Distribution at Diagnosis, %	Risk of Melanoma Mortality, adj HR (95% CI) 1975–2000 n=85,609 (all ages)	Risk of Melanoma Mortality, adj HR (95% CI) 2000–2009 n=164,192 (all ages)	Risk of Melanoma Mortality, adj HR (95% CI) 2010–2016 n=148,233 (all ages)
Qian, 2021 Fair US	All ages (n=398,034)	White	Localized	77.1	Referent group	Referent group	Referent group
			Regional	8.8			
			Distant	3.8			
		Hispanic†	Localized	66.5	1.05 (0.90-1.24)	1.44 (1.26-1.66)	1.54 (1.21-1.96)
			Regional	14.2	1.01 (0.83-1.22)	1.32 (1.17-1.49)	1.56 (1.30-1.87)
			Distant	6.8	0.83 (0.66-1.05)	1.06 (0.92-1.23)	1.17 (0.99-1.38)
		Black†	Localized	51.1	1.49 (1.12-1.98)	1.92 (1.44-2.57)	4.08 (2.70-6.16)
			Regional	20.5	1.62 (1.22-2.15)	1.49 (1.19-1.86)	1.74 (1.24-2.45)
			Distant	13.6	1.33 (1.00-1.76)	0.78 (0.60-1.01)	1.01 (0.74-1.39)
		Asian or Pacific Islander†	Localized	58.6	1.19 (0.90-1.58)	1.46 (1.09-1.94)	2.19 (1.41-3.40)
			Regional	18.2	1.17 (0.88-1.56)	1.26 (1.02-1.56)	1.28 (0.85-1.93)
			Distant	10.4	1.18 (0.86-1.62)	1.03 (0.81-1.32)	1.68 (1.27-2.23)
		American Indian or Alaska Native†	Localized	69.2	0.79 (0.42-1.46)	1.20 (0.68-2.12)	2.14 (1.02-4.50)
			Regional	12.9	2.30 (1.27-4.16)	1.19 (0.75-1.90)	2.86 (1.66-4.94)
			Distant	5.7	1.25 (0.59-2.62)	0.64 (0.31-1.35)	0.77 (0.37-1.61)
	Age ≥65 (n=162,456)	White	Localized	NR	Referent group	Referent group	Referent group
			Regional	NR			
			Distant	NR			
		Hispanic†	Localized	NR	0.94 (0.68-1.29)	1.54 (1.11-2.14)	1.49 (1.01-2.22)
			Regional	NR	1.11 (0.80-1.53)	1.45 (0.86-2.45)	1.76 (1.06-2.94)
			Distant	NR	1.22 (0.82-1.81)	0.92 (0.80-1.06)	1.24 (0.005-318.2)
		Black†	Localized	NR	1.28 (0.81-2.02)	1.54 (0.37-6.42)	4.19 (1.91-9.19)
			Regional	NR	1.39 (0.93-2.08)	1.53 (0.15-15.3)	1.71 (0.31-9.30)
			Distant	NR	1.55 (1.03-2.33)	0.81 (0.68-0.97)	1.21 (0.74-2.00)
		Asian or Pacific Islander†	Localized	NR	1.26 (0.78-2.04)	1.36 (0.1-17.73)	1.24 (0-17225.3)
			Regional	NR	1.57 (1.06-2.30)	1.31 (0.61-2.81)	1.48 (0.02-143.3)
			Distant	NR	1.31 (0.85-2.03)	1.16 (0.58-2.33)	1.68 (0.48-5.89)
		American Indian or Alaska Native†	Localized	NR	0.99 (0.32-3.08)	1.14 (0.28-4.70)	1.85 (0.38-8.99)
			Regional	NR	2.82 (1.17-6.80)	1.65 (0.57-4.79)	1.96 (0.17-22.74)
			Distant	NR	NR	NR	NR

*Number of melanoma deaths not reported.
†White=Referent group.

Abbreviations: AANAPI=Asian American/Native American/Pacific Islander; Adj=Adjusted; AJCC=American Joint Committee on Cancer; CI=Confidence interval; HR=Hazard ratio; KQ=Key Question; NR=Not reported; OR=Odds ratio; SD=Standard deviation; SEER=Surveillance, Epidemiology, and End Results Program; US=United States.

Table 23. Melanoma Stage at Diagnosis and Melanoma Mortality, Sex and Age Group (KQ4a)

Author, Year (Study) Quality	Data Collection Country	Study N	Sex	Age Group, years	Stage, SEER and AJCC	Stage Distribution at Diagnosis, %	Melanoma Deaths, n	Risk of Melanoma Mortality
Enninga, 2017[140] Fair	1992–2011 (followup for deaths was until 2012) US	106,511	Females	≥18	Localized	85.9	1,423	Referent group
					Regional	8.5	1,195	
					Distant	2.5	791	
					Unstaged	3.0	--	
			Males	≥18	Localized	81.4	2,856	adjHR, 1.59 (95% CI, 1.49 to 1.70)*
					Regional	11.1	2,444	adjHR, 1.37 (95% CI, 1.28 to 1.47)*
					Distant	4.2	1,706	adjHR, 1.10 (95% CI, 1.01 to 1.20)*
					Unstaged	3.3	--	--
				18–45	Localized	--	--	HR, 2.05 (95% CI,1.79 to 2.35)
					Regional	--		HR, 1.65 (95% CI, 1.42 to 1.92)
					Distant	--		HR, 1.14 (95% CI, 0.93 to 1.38)
				46–54	Localized	--	--	HR, 1.89 (95% CI, 1.62 to 2.20)
					Regional	--		HR, 1.40 (95% CI, 1.18 to 1.66)
					Distant	--		HR, 1.07 (95% CI, 0.86 to 1.33)
				≥55	Localized	--	--	HR, 1.42 (95% CI, 1.30 to 1.54)
					Regional	--		HR, 1.25 (95% CI, 1.14 to 1.36)
					Distant	--		HR, 1.09 (95% CI, 0.99 to 1.21)
Khosrotehrani, 2015[142] Good	1995–2008 (melanoma-specific deaths were ascertained up to 2010) Australia	28,979	Males	≥15	I	87	--	Referent group
					II	12		
					III, IV	1		
					Unknown	5		
			Females	≥15	I	83	1,712 for the entire study population	adjOR[†], 0.64 (95% CI, 0.51 to 0.82)
					II	16		adjOR[†], 0.71 (95% CI, 0.58 to 0.87)
					III, IV	1		adjOR[†], 0.70 (95% CI, 0.44 to 1.10)
					Unknown	6		--
				15–45	I	--	--	adjOR[†], 0.80 (95% CI, 0.51 to 1.17)
					II	--		adjOR[†], 0.56 (95% CI, 0.33 to 0.98)
					III, IV	--		adjOR[†], 0.88 (95% CI, 0.30 to 2.58)

Table 23. Melanoma Stage at Diagnosis and Melanoma Mortality, Sex and Age Group (KQ4a)

Author, Year (Study) Quality	Data Collection Country	Study N	Sex	Age Group, years	Stage, SEER and AJCC	Stage Distribution at Diagnosis, %	Melanoma Deaths, n	Risk of Melanoma Mortality
				46–59	I	--	--	adjOR[†], 0.81 (95% CI, 0.53 to 1.23)
					II	--		adjOR[†], 0.95 (95% CI, 0.61 to 1.49)
					III, IV	--		adjOR[†], 1.76 (95% CI, 0.66 to 3.80)
				≥60	I	--	--	adjOR[†], 0.43 (95% CI, 0.30 to 0.63)
					II	--		adjOR[†], 0.70 (95% CI, 0.55 to 0.89)
					III, IV	--		adjOR[†], 0.46 (95% CI, 0.24 to 0.87)

*Male:Female (Female=Referent category), adjusted for age.
[†]Female:Male (Male=Referent category); adjusted for sex, age, body site and thickness of the primary tumor, ulceration, nodal spread, and metastasis.

Abbreviations: Adj=Adjusted; AJCC=American Joint Committee on Cancer; CI=Confidence interval; HR=Hazard ratio; KQ=Key Question; OR=Odds ratio; SEER=Surveillance, Epidemiology, and End Results Program; US=United States.

Table 24. Summary of Evidence Table

Key Question	Studies (K) Observations (N) Study Design	Summary of Findings	Consistency and Precision	Overall Strength of Evidence	Body of Evidence Limitations	Applicability
KQ1. 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? KQ1a. Does the effectiveness of screening vary by subgroups?	K=3 (1 good-quality, 2 fair-quality) N: NR in one study; 1,791,615 in the other two studies **Melanoma:** K=3 (1 good-quality, 2 fair-quality), n=NR in one study; 1,791,615 in the other two studies **KC:** No studies Nonrandomized study (ecologic)	**Melanoma mortality:** Based on nonrandomized and ecologic evidence, limited to no mortality benefit to population-based skin cancer screening programs at 4- to 10-year followup compared to no screening **All-cause mortality:** No studies **KC:** No studies	**Melanoma mortality:** Consistent, imprecise **KC:** NA	**Melanoma:** Low for limited to no mortality benefit **KC:** Insufficient	Ecologic design limits individual level analyses Little information about clinical, socioeconomic, or behavioral risk factors in included populations Potential lead time and healthy screenee bias Use of population statistics for outcome assessment Trial evidence with mortality outcomes unlikely	European population with universal health insurance and subsidized clinician skin examination. No US data.

Table 24. Summary of Evidence Table

| KQ2. Does routine skin cancer screening lead to higher rates of detection of precancerous lesions or earlier stage skin cancer compared to usual care? KQ2a. Do rates of earlier skin cancer detection vary by subgroups? | **Melanoma:** K=6 (1 good-quality, 5 fair-quality), n=2,947,595 **KC:** K=4 (all fair-quality), n=2,332,128 **Skin cancer precursor lesions:** K=2 (both fair-quality), n=309,661 Nonrandomized studies | **Melanoma:** Routine clinician skin examination is not associated with earlier stage at detection of invasive melanoma compared to usual care (2 studies) Inconsistent evidence on whether clinician skin examination is associated with increased detection of *in situ* melanoma compared to usual care (2 studies) Inconsistent evidence on whether clinician skin examination is associated with increased detection of melanoma at either <1 mm or <2 mm thickness compared to usual care (3 studies) **KC:** Routine clinician skin examination is not associated with either increased detection or stage at detection of KC (4 studies) **Skin cancer precursor lesions:** Routine clinician skin examination is not associated with increased detection of skin cancer precursor lesions (actinic keratosis or dysplastic nevi) compared to usual care (2 studies) | Reasonably consistent, imprecise | **Melanoma:** 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 **KC:** Low for no association between routine clinician skin examination and either KC detection or stage at KC detection **Skin cancer precursor lesions:** Low for no association between routine clinician skin examination and precursor lesion detection | 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 conducted outside of the 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 |

Table 24. Summary of Evidence Table

Key Question	Studies (K) Observations (N) Study Design	Summary of Findings	Consistency and Precision	Overall Strength of Evidence	Body of Evidence Limitations	Applicability
KQ3. What are the harms of skin cancer screening and diagnostic followup? KQ3a. Do the harms of screening vary by subgroups?	Cosmetic harms K=1 (fair-quality) n=45 Psychological harms K=1 (fair-quality) n=187 KQ3a: No studies included Nonrandomized studies	**Cosmetic harms:** 27 patients rated 7% (4 out of 56) of shave biopsy sites having poor cosmetic outcomes at 6-month followup **Psychological harms:** US-based study of adults who underwent skin cancer screening by trained primary care providers, participants at 5- and 8-month followup assessment scored within the normal range on measures of anxiety and depression; and reported none to minimal psychological harms of screening	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

Table 24. Summary of Evidence Table

Key Question	Studies (K) Observations (N) Study Design	Summary of Findings	Consistency and Precision	Overall Strength of Evidence	Body of Evidence Limitations	Applicability
KQ4. 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? KQ4a. Does this association vary by subgroups?	**Melanoma:** K=9 (3 good-quality, 6 fair-quality), n=1,326,051* **KC:** No included studies Nonrandomized studies	**Melanoma mortality:** Progression of melanoma stage at detection was strongly, positively associated with increasing risk of melanoma mortality Compared to *in situ* melanoma at detection, adjHRs for melanoma mortality were 5.8 (95% CI, 5.3 to 6.3) for localized, 31.5 (95% CI, 28.9 to 34.2) for regional, and 169.6 (95% CI, 154.2 to 186.6) for distant stage in one US study (n=185,219) Melanoma mortality risk is higher among Black, API, AIAN, and Hispanic adults with melanoma AJCC stage I and SEER localized stages compared to White adults at the same stages. **All-cause mortality:** Progression of melanoma stage, for both SEER summary stage and AJCC stages, at detection was positively associated with increasing risk of all-cause mortality	**Melanoma mortality, all-cause mortality:** Reasonably consistent, reasonably precise **KC:** NA	**Melanoma:** High for association between stage at detection and melanoma and all-cause mortality **KC:** NA	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

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

Table 24. Summary of Evidence Table

Abbreviations: AANAPI=Asian American/Native American/Pacific Islander; API=Asian or Pacific Islander; AIAN=American Indian or Alaska Native; Adj=Adjusted; AJCC=American Joint Committee on Cancer; CI=Confidence interval; HR=Hazard ratio; KC=Keratinocyte carcinoma; KQ=Key Question; NR=Not reported; RR=Relative risk; SEER=Surveillance, Epidemiology, and End Results Program; US=United States.

Appendix A. Literature Search Strategies for Primary Literature

Bridge searches
MEDLINE via Ovid:
Database: Ovid MEDLINE(R) ALL <1946 to January 06, 2022>
Search Strategy:
----
1   Skin Neoplasms/ (129409)
2   Melanoma/ (90728)
3   Melanoma, Amelanotic/ (652)
4   Nevus/ (6301)
5   Dysplastic Nevus Syndrome/ (1136)
6   Hutchinson's Melanotic Freckle/ (744)
7   Carcinoma, Basal Cell/ (17897)
8   Carcinoma, Squamous Cell/ (135127)
9   Carcinoma, Merkel Cell/ (2824)
10   Neoplasms, Basal Cell/ (647)
11   Neoplasms, Squamous Cell/ (1685)
12   "Neoplasms, Adnexal and Skin Appendage"/ (339)
13   Actinic keratosis/ (2315)
14   Bowen disease/ (1949)
15   Lymphoma, T-Cell, Cutaneous/ (3697)
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$)).ti. (52939)
17   melanoma$.ti. (76077)
18   ((naevoid or nevoid) adj3 syndrome$).ti. (49)
19   ((dysplastic or malignant) adj2 (nevus or naevus or nevi or naevi)).ti. (836)
20   Hutchinson$ Melanotic Freckle.ti. (11)
21   lentigo maligna.ti. (558)
22   (basal cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti. (7894)
23   ((basocellular$ or basosquamous) adj carcinoma$).ti. (117)
24   (squamous cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti. (52500)
25   (merkel cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti. (2746)
26   actinic keratosis.ti. (1164)
27   bowen$ disease.ti. (1119)
28   (cutaneous adj2 lymphoma$).ti. (1006)
29   or/1-28 (363896)
30   ((skin or derm$ 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$)).ti,ab. (175444)
31   melanoma$.ti,ab. (126484)
32   ((naevoid or nevoid) adj3 syndrome$).ti,ab. (152)
33   ((dysplastic or malignant) adj2 (nevus or naevus or nevi or naevi)).ti,ab. (2138)
34   Hutchinson$ Melanotic Freckle.ti,ab. (35)
35   lentigo maligna.ti,ab. (1188)

36 (basal cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti,ab. (15572)
37 ((basocellular$ or basosquamous) adj carcinoma$).ti,ab. (241)
38 (squamous cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti,ab. (112585)
39 (merkel cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti,ab. (3680)
40 actinic keratosis.ti,ab. (2541)
41 bowen$ disease.ti,ab. (2167)
42 (cutaneous adj2 lymphoma$).ti,ab. (2494)
43 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (391209)
44 limit 43 to ("in data review" or in process or "pubmed not medline") (42473)
45 29 or 44 [skin cancer terms] (385494)
46 Mass screening/ (111499)
47 Early detection of Cancer/ (31666)
48 (screen$ or detect$).ti,ab. (3208953)
49 46 or 47 or 48 [screening terms] (3240300)
50 Physical Examination/ (42354)
51 Dermoscopy/ (5296)
52 Photography/ (27041)
53 ((skin or body or physical) adj3 (exam$ or inspect$)).ti,ab. (92934)
54 visual$ inspect$.ti,ab. (9509)
55 dermoscop$.ti,ab. (5313)
56 dermatoscop$.ti,ab. (1225)
57 photography.ti,ab. (15973)
58 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 [exam terms] (180612)
59 45 and 49 and 58 (2490)
60 screen$.ti. (194784)
61 45 and 60 (2089)
62 59 or 61 (4307)
63 limit 62 to (english language and yr="2015 -Current") (1676)
64 remove duplicates from 63 (1673)
65 Biopsy/ (183099)
66 Biopsy, Needle/ (49569)
67 Biopsy, Large-Core Needle/ (2178)
68 Sentinel Lymph Node Biopsy/ (12226)
69 (biopsy$ or biopsies or biopsied).ti,ab. (426788)
70 (excise* or excision$).ti,ab. (183198)
71 Rebiops$.ti,ab. (752)
72 65 or 66 or 67 or 68 or 69 or 70 or 71 [biopsy] (700929)
73 (harm or harms or harmful or harmed).ti,ab. (137516)
74 (adverse effects or mortality).fs. (2379318)
75 Mortality/ or Morbidity/ (77303)
76 death/ (18760)
77 (death or deaths).ti,ab. (909617)

78   "Drug-Related Side Effects and Adverse Reactions"/ or Long Term Adverse Effects/ (35776)

79   ((adverse or negative or unintended) adj (effect$ or event$ or outcome$ or reaction$)).ti,ab. (484749)

80   complication$.ti,ab. (1005513)

81   side effect$.ti,ab. (271474)

82   safety.ti,ab. (586254)

83   false negative$.ti,ab. (36032)

84   misdiagnos$.ti,ab. (38092)

85   overdiagnos$.ti,ab. (4523)

86   ((unneeded or unnecessary) adj5 (treat$ or therap$ or surg$ or procedure$)).ti,ab. (14620)

87   label$.ti,ab. (565965)

88   psychological effect$.ti,ab. (4699)

89   Cicatrix/ (24030)

90   (cicatrix or scar$).ti,ab. (187490)

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 [harms] (5315254)

92   45 and 72 and 91 (13066)

93   limit 92 to (english language and yr="2015 -Current") (4063)

94   remove duplicates from 93 (4058)

95   Neoplasm Staging/ (186206)

96   ((detect$ or diagnos$ or biops$) adj5 stage).ti,ab. (45586)

97   ((late$ or distant or advanced or end) adj stage).ti,ab. (137365)

98   ((early or earlier) adj (diagnos$ or detect$ or discovery or findings)).ti,ab. (178249)

99   95 or 96 or 97 or 98 [staging] (512692)

100   Registries/ (101512)

101   Survival Analysis/ (143501)

102   SEER program/ (9043)

103   Morbidity/ (32372)

104   Mortality/ (48301)

105   Death/ (18760)

106   mo.fs. (621324)

107   (registr$ or register$).ti,ab. (469949)

108   SEER.ti,ab. (9016)

109   "Surveillance epidemiology and end results".ti,ab. (11568)

110   morbidit$.ti,ab. (431528)

111   mortalit$.ti,ab. (868291)

112   (death or deaths).ti,ab. (909617)

113   survival.ti,ab. (1052085)

114   110 or 111 or 112 or 113 (2531644)

115   limit 114 to ("in data review" or in process or "pubmed not medline") (283788)

116   100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 115 [registries morbidity] (1479421)

117   45 and 99 and 116 (12827)

118   limit 117 to (english language and yr="2015 -Current") (4435)

119   remove duplicates from 118 (4430)

Appendix A. Literature Search Strategies for Primary Literature

120   Dermatologic Surgical Procedures/ (7326)
121   Curettage/ (4588)
122   Dessication/ (7746)
123   Cryosurgery/ (13662)
124   Laser Therapy/ (39419)
125   Mohs Surgery/ (3651)
126   Lymph Node Excision/ (35762)
127   (surger$ or surgical).ti. (664277)
128   curettage.ti,ab. (12149)
129   dessicat$.ti,ab. (289)
130   electrodessicat$.ti,ab. (138)
131   cryosurg$.ti,ab. (4153)
132   laser ablation.ti,ab. (8326)
133   mohs.ti,ab. (3829)
134   metastasectom$.ti,ab. (2544)
135   lymphadenectom$.ti,ab. (18578)
136   ((lymph node$ or lymphoid) adj3 (remov$ or dissect$ or resect$)).ti,ab. (28082)
137   127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 (727329)
138   limit 137 to ("in data review" or in process or "pubmed not medline") (72745)
139   120 or 121 or 122 or 123 or 124 or 125 or 126 or 138 (182804)
140   45 and 139 (14973)
141   Skin Neoplasms/su (17958)
142   Melanoma/su (10396)
143   Melanoma, Amelanotic/su (128)
144   Nevus/su (587)
145   Dysplastic Nevus Syndrome/su (95)
146   Hutchinson's Melanotic Freckle/su (248)
147   Carcinoma, Basal Cell/su (5135)
148   Carcinoma, Squamous Cell/su (27490)
149   Carcinoma, Merkel Cell/su (494)
150   Neoplasms, Basal Cell/su (59)
151   Neoplasms, Squamous Cell/su (227)
152   "Neoplasms, Adnexal and Skin Appendage"/su (80)
153   Actinic keratosis/su (73)
154   Bowen disease/su (254)
155   Lymphoma, T-Cell, Cutaneous/su (49)
156   140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 [skin cancer surgery] (55498)
157   Lymphedema/ (9779)
158   Lymph?edema.ti,ab. (10882)
159   Surgical wound infection/ (38685)
160   ((surg$ or postsurg$ or post-surg$) adj2 infect$).ti,ab. (22073)
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 [harms lymphedema surgery outcomes] (4788906)
162   156 and 161 (18891)
163   limit 162 to (english language and yr="2015 -Current") (4281)

164   64 or 94 or 119 or 163 (12204)
165   Animal/ not (Animal/ and Human/) (4905488)
166   164 not 165 (12092)
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. (1550547)
168   166 not 167 (7672)

Cochrane Central Register of Controlled Clinical Trials (CENTRAL) via Wiley:
Date Run: 07/01/2022 20:49:50
#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   9428
#2   melanoma*:ti,ab,kw   5929
#3   (naevoid or nevoid):ti,ab,kw near/3 syndrome*:ti,ab,kw   0
#4   (dysplastic or malignant):ti,ab,kw near/2 (nevus or naevus or nevi or naevi):ti,ab,kw
        40
#5   "Hutchinson's Melanotic Freckle":ti,ab,kw   8
#6   "lentigo maligna":ti,ab,kw   33
#7   basal:ti,ab,kw next cell:ti,ab,kw next (carcinoma* or neoplasm* or cancer* or tumor* or tumour* or malignan* or lesion* or metasta* or epithelioma*):ti,ab,kw   1035
#8   (basocellular* or basosquamous):ti,ab,kw next carcinoma*:ti,ab,kw   6
#9   squamous:ti,ab,kw next cell:ti,ab,kw next (carcinoma* or neoplasm* or cancer* or tumor* or tumour* or malignan* or lesion* or metasta* or epithelioma*):ti,ab,kw 6777
#10   merkel:ti,ab,kw next cell:ti,ab,kw next (carcinoma* or neoplasm* or cancer* or tumor* or tumour* or malignan* or lesion* or metasta* or epithelioma*):ti,ab,kw 88
#11   "actinic keratosis":ti,ab,kw   814
#12   bowen*:ti,ab,kw next disease:ti,ab,kw   111
#13   cutaneous:ti,ab,kw near/2 lymphoma*:ti,ab,kw   37
#14   {or #1-#13}   20514
#15   screen*:ti,ab,kw   82568
#16   (skin or body or physical):ti,ab,kw near/3 (exam* or inspect*):ti,ab,kw   18448
#17   (dermoscop* or dermatoscop*):ti,ab,kw   349
#18   visual*:ti,ab,kw next inspect*:ti,ab,kw   790
#19   photography:ti,ab,kw 3866
#20   {or #15-#19}   100455
#21   #14 and #20 with Publication Year from 2015 to present, in Trials 935
#22   (biopsy* or biopsies or biopsied):ti,ab,kw   33249
#23   (excise* or excision*):ti,ab,kw   7371
#24   rebiops*:ti,ab,kw   167
#25   #22 or #23 or #24   39569
#26   (harm or harms or harmful or harmed):ti,ab,kw   13354
#27   (death or deaths):ti,ab,kw   80022
#28   (adverse or negative or unintended):ti,ab,kw next (effect* or event* or outcome* or reaction*):ti,ab,kw   280044

#29   complication*:ti,ab,kw   198035
#30   side:ti,ab,kw next effect*:ti,ab,kw   150014
#31   safety:ti,ab,kw 258866
#32   false:ti,ab,kw next negative*:ti,ab,kw 1607
#33   misdiagnos*:ti,ab,kw 462
#34   overdiagnos*:ti,ab,kw 392
#35   (unneeded or unnecessary):ti,ab,kw near/5 (treat* or therap* or surg* or
procedure*):ti,ab,kw 948
#36   label*:ti,ab,kw 78015
#37   psychological:ti,ab,kw next effect*:ti,ab,kw 794
#38   (cicatrix or scar*):ti,ab,kw   13001
#39   {or #26-#38} 693560
#40   #14 and #25 and #39 with Publication Year from 2015 to present, in Trials 761
#41   (detect* or diagnos* or biops*):ti,ab,kw near/5 stage:ti,ab,kw   4134
#42   (late* or distant or advanced or end):ti,ab,kw next stage:ti,ab,kw   11264
#43   (early or earlier):ti,ab,kw next (diagnos* or detect* or discovery or findings):ti,ab,kw
       6960
#44   #41 or #42 or #43   21418
#45   #14 and #44 with Publication Year from 2015 to present, in Trials 557
#46   (surger* or surgical):ti 76330
#47   curettage:ti,ab,kw   1685
#48   dessicat*:ti,ab,kw   7
#49   electrodessicat*:ti,ab,kw   15
#50   cryosurg*:ti,ab,kw   540
#51   "laser ablation":ti,ab,kw   600
#52   mohs:ti,ab,kw 260
#53   metastasectom*:ti,ab,kw   183
#54   lymphadenectom*:ti,ab,kw   1782
#55   ("lymph node" or "lymph nodes" or lymphoid):ti,ab,kw near/3 (remov* or dissect* or
resect*):ti,ab,kw   3615
#56   {or #46-#55} 82689
#57   (lymphedema or lymphoedema):ti,ab,kw   1519
#58   (surg* or postsurg* or post-surg*):ti,ab,kw near/2 infect*:ti,ab,kw 7719
#59   (#26 or #27 or #28 or #29 or #30 or #31 or #38 or #57 or #58)   667482
#60   #14 and #56 and #59 with Publication Year from 2015 to present, in Trials 498
#61   #21 or #40 or #45 or #60   2291

Date limit line:
#62   #21 or #40 or #45 or #60 with Cochrane Library publication date from Jan 2021 to
present 357

Embase via Elsevier:
#1. 'skin cancer'/exp OR 'skin tumor'/de OR 'melanoma'/de OR 'benign skin tumor'/exp OR
'actinic keratosis'/de   329,895

Appendix A. Literature Search Strategies for Primary Literature

#2. ((skin OR derm* OR cutaneous OR epithelial OR epithelium OR epiderm*) NEAR/3 (cancer* OR neoplas* OR carcinoma* OR tumo*r* OR malignan* OR lesion* OR metasta* OR dysplas*)):ti,ab   245,169

#3. melanoma*:ti,ab   179,108

#4. ((naevoid OR nevoid) NEAR/3 syndrome*):ti,ab   191

#5. ((dysplastic OR malignant) NEAR/2 (nevus OR naevus OR nevi OR naevi)):ti,ab   2,753

#6. hutchinson*:ti,ab AND 'melanotic freckle':ti,ab   61

#7. 'lentigo maligna':ti,ab   1,715

#8. ('basal cell' NEAR/1 (cancer* OR neoplas* OR carcinoma* OR tumo*r* OR malignan* OR lesion* OR metasta* OR epithelioma*)):ti,ab   21,605

#9. ((basocellular* OR basosquamous) NEAR/1 carcinoma*):ti,ab   375

#10. ('merkel cell' NEAR/1 (cancer* OR neoplas* OR carcinoma* OR tumo*r* OR malignan* OR lesion* OR metasta* OR epithelioma*)):ti,ab   5,309

#11. 'actinic keratosis':ti,ab   3,695

#12. 'bowen* disease':ti,ab   2,797

#13. (cutaneous NEAR/2 lymphoma*):ti,ab   3,733

#14. #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   553,819

#15. 'mass screening'/de OR 'cancer screening'/de OR 'early cancer diagnosis'/de   154,924

#16. screen*:ti,ab OR detect*:ti,ab   4,178,597

#17. #15 OR #16   4,217,374

#18. 'physical examination'/de OR 'skin examination'/exp OR 'photography'/exp   515,079

#19. ((skin OR body OR physical) NEAR/3 (exam* OR inspect*)):ti,ab   161,831

#20. 'visual* inspect*':ti,ab   13,775

#21. dermoscop*:ti,ab   6,929

#22. dermatoscop*:ti,ab   1,842

#23. photography:ti,ab   20,361

#24. #18 OR #19 OR #20 OR #21 OR #22 OR #23   612,334

#25. #14 AND #17 AND #24   8,084

#26. screen*:ti   259,234

#27. #14 AND #26   3,017

#28. #25 OR #27   10,603

#29. 'biopsy'/de OR 'skin examination'/exp OR 'large core needle biopsy'/de OR 'sentinel lymph node biopsy'/de   399,688

#30. biopsy*:ti,ab OR biopsies:ti,ab OR biopsied:ti,ab   694,052

#31. excise*:ti,ab OR excision*:ti,ab   243,059

#32. rebiops*:ti,ab   2,910

#33. #29 OR #30 OR #31 OR #32   1,108,202

#34. harm:ti,ab OR harms:ti,ab OR harmful:ti,ab OR harmed:ti,ab   176,555

#35. 'mortality'/de OR 'cancer mortality'/de OR 'surgical mortality'/de OR 'death'/de OR 'morbidity'/de OR 'adverse event'/exp OR 'side effect'/exp   2,249,034

#36. death:ti,ab OR deaths:ti,ab   1,307,735

#37. ((adverse OR negative OR unintended) NEAR/1 (effect* OR event* OR outcome* OR reaction*)):ti,ab   742,638

#38. complication*:ti,ab   1,490,258

#39. 'side effect*':ti,ab   402,017
#40. safety:ti,ab   904,820
#41. 'false negative*':ti,ab   50,380
#42. misdiagnos*:ti,ab   55,381
#43. overdiagnos*:ti,ab   7,917
#44. ((unneeded OR unnecessary) NEAR/5 (treat* OR therap* OR surg* OR procedure*)):ti,ab
22,509
#45. label*:ti,ab   720,613
#46. 'psychological effect*':ti,ab   5,894
#47. 'scar'/exp   85,856
#48. cicatrix:ti,ab OR scar*:ti,ab   255,035
#49. #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44
OR #45 OR #46 OR #47 OR #48   6,344,805
#50. #14 AND #33 AND #49   23,410
#51. 'tumor classification'/exp   498,822
#52. ((detect* OR diagnos* OR biops*) NEAR/5 stage):ti,ab   78,925
#53. ((late* OR distant OR advanced OR end) NEAR/1 stage):ti,ab   206,326
#54. ((early OR earlier) NEAR/1 (diagnos* OR detect* OR discovery OR findings)):ti,ab
282,585
#55. #51 OR #52 OR #53 OR #54   978,055
#56. 'register'/de OR 'cancer registry'/exp OR 'survival analysis'/de   187,332
#57. 'mortality'/de OR 'cancer mortality'/de OR 'surgical mortality'/de OR 'death'/de OR
'morbidity'/de   1,384,498
#58. registr*:ti,ab OR register*:ti,ab   650,353
#59. seer:ti,ab   17,108
#60. 'surveillance epidemiology and end results':ti,ab   16,793
#61. morbidit*:ti,ab   655,879
#62. mortalit*:ti,ab   1,280,224
#63. death:ti,ab OR deaths:ti,ab   1,307,735
#64. survival:ti,ab   1,561,919
#65. #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64   4,449,378
#66. #14 AND #55 AND #65   23,560
#67. 'skin surgery'/de OR 'curettage'/de OR 'desiccation'/de OR 'cryosurgery'/de OR 'low level
laser therapy'/de OR 'mohs micrographic surgery'/de OR 'lymph node dissection'/de
147,891
#68. surger*:ti OR surgical:ti   834,877
#69. curettage:ti,ab   15,473
#70. dessicat*:ti,ab   361
#71. electrodessicat*:ti,ab   231
#72. cryosurg*:ti,ab   5,275
#73. 'laser ablation':ti,ab   9,484
#74. mohs:ti,ab   4,701
#75. metastasectom*:ti,ab   3,920
#76. lymphadenectom*:ti,ab   29,224
#77. (('lymph node*' OR lymphoid) NEAR/3 (remov* OR dissect* OR resect*)):ti,ab
44,056

#78. #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 1,002,439

#79. #14 AND #78   30,464

#80. 'skin cancer'/exp/dm_su OR 'skin tumor'/dm_su OR 'melanoma'/dm_su OR 'benign skin tumor'/exp/dm_su OR 'actinic keratosis'/dm_su   35,388

#81. #79 OR #80   54,550

#82. 'lymphedema'/de   19,168

#83. lymph*edema:ti,ab   15,762

#84. 'surgical infection'/de   56,782

#85. ((surg* OR postsurg* OR 'post surg*') NEAR/2 infect*):ti,ab   32,076

#86. #49 OR #82 OR #83 OR #84 OR #85   6,390,209

#87. #81 AND #86   15,203

#88. #28 OR #50 OR #66 OR #87   61,359

#89. #88 NOT (('animal model'/exp OR 'animal experiment'/exp OR 'nonhuman'/de OR 'animal'/exp) NOT 'human'/de)   59,748

#90. oral:ti OR tongue:ti OR larynx:ti OR laryng*:ti OR hypolaryng*:ti OR oropharyng*:ti OR pharynx:ti OR pharyng*:ti OR esophag*:ti OR oesophag*:ti OR gastric:ti OR ovary:ti OR ovaries:ti OR ovarian:ti OR cervical:ti OR cervix:ti OR endometrium:ti OR endometrial:ti OR lung:ti OR breast:ti OR ocular:ti OR vulva*:ti OR anus:ti OR anal:ti OR mucosal:ti   2,043,498

#91. #89 NOT #90   48,492

#92. 'clinical trial'/de OR 'controlled clinical trial'/de OR 'randomized controlled trial'/exp OR 'randomization'/exp OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de   1,745,764

#93. 'meta analysis'/exp OR 'meta analysis (topic)'/de   277,275

#94. 'intermethod comparison'/de OR 'double blind procedure'/de   470,348

#95. 'clinical trial*':ti,ab OR 'controlled trial*':ti,ab OR random*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR trial:ti OR placebo:ti,ab   2,463,628

#96. compare:ti OR compared:ti OR comparison:ti   576,882

#97. (evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)   2,420,992

#98. (open NEXT/1 label):ti,ab   93,410

#99. ((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab 253,841

#100.(parallel NEXT/1 group*):ti,ab   28,650

#101.crossover:ti,ab OR 'cross over':ti,ab   114,247

#102.((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab   405,885

#103.assigned:ti,ab OR allocated:ti,ab   435,414

#104.(controlled NEAR/8 (study OR design OR trial)):ti,ab   404,226

#105.volunteer:ti,ab OR volunteers:ti,ab   264,587

#106.#92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105   6,142,879

#107.'controlled study'/exp   8,776,888

#108.'longitudinal study'/exp OR 'prospective study'/de OR 'retrospective study'/de   1,998,477

#109.'cohort analysis'/de OR 'follow up'/de   2,394,342

Appendix A. Literature Search Strategies for Primary Literature

#110.'observational study'/de   258,002
#111.'correlational study'/de   52,279
#112.'family study'/de   26,087
#113.'case control*':ti,ab   187,623
#114.cohort:ti,ab   1,105,924
#115.longitudinal:ti,ab   381,034
#116.'follow up':ti,ab OR followup:ti,ab   1,751,006
#117.prospective*:ti,ab   1,210,350
#118.'comparison group*':ti,ab OR 'control group*':ti,ab   757,393
#119.observational:ti,ab   339,743
#120.retrospective*:ti,ab   1,455,587
#121.database*:ti,ab   798,285
#122.nonrandomi*:ti,ab   39,615
#123.population*:ti,ab   2,608,255
#124.epidemiologic*:ti,ab   345,127
#125.'cross sectional':ti,ab   558,465
#126.#107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125 14,329,834
#127.#106 OR #126   16,342,576
#128.#91 AND #127   30,081
#129.#91 AND #127 AND [english]/lim AND [2015-2022]/py   15,132

Date limit line:
#130.#91 AND #127 AND [english]/lim AND [2015-2022]/py AND [12-01-2021]/sd   3,570

Original searches

MEDLINE via Ovid:
Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to January 08, 2021>
Search Strategy:
----
1   Skin Neoplasms/ (122639)
2   Melanoma/ (85810)
3   Melanoma, Amelanotic/ (611)
4   Nevus/ (6097)
5   Dysplastic Nevus Syndrome/ (1116)
6   Hutchinson's Melanotic Freckle/ (680)
7   Carcinoma, Basal Cell/ (17171)
8   Carcinoma, Squamous Cell/ (130801)
9   Carcinoma, Merkel Cell/ (2599)
10   Neoplasms, Basal Cell/ (622)
11   Neoplasms, Squamous Cell/ (1654)
12   "Neoplasms, Adnexal and Skin Appendage"/ (307)

Appendix A. Literature Search Strategies for Primary Literature

13   Actinic keratosis/ (2109)
14   Bowen disease/ (1899)
15   Lymphoma, T-Cell, Cutaneous/ (3465)
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$)).ti. (50559)
17   melanoma$.ti. (72435)
18   ((naevoid or nevoid) adj3 syndrome$).ti. (49)
19   ((dysplastic or malignant) adj2 (nevus or naevus or nevi or naevi)).ti. (829)
20   Hutchinson$ Melanotic Freckle.ti. (11)
21   lentigo maligna.ti. (538)
22   (basal cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti. (7564)
23   ((basocellular$ or basosquamous) adj carcinoma$).ti. (111)
24   (squamous cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti. (48326)
25   (merkel cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti. (2577)
26   actinic keratosis.ti. (1074)
27   bowen$ disease.ti. (1096)
28   (cutaneous adj2 lymphoma$).ti. (948)
29   or/1-28 (348146)
30   ((skin or derm$ 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$)).ti,ab. (167103)
31   melanoma$.ti,ab. (120189)
32   ((naevoid or nevoid) adj3 syndrome$).ti,ab. (148)
33   ((dysplastic or malignant) adj2 (nevus or naevus or nevi or naevi)).ti,ab. (2095)
34   Hutchinson$ Melanotic Freckle.ti,ab. (33)
35   lentigo maligna.ti,ab. (1138)
36   (basal cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti,ab. (14905)
37   ((basocellular$ or basosquamous) adj carcinoma$).ti,ab. (227)
38   (squamous cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti,ab. (105191)
39   (merkel cell adj (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$ or lesion$ or metasta$ or epithelioma$)).ti,ab. (3438)
40   actinic keratosis.ti,ab. (2382)
41   bowen$ disease.ti,ab. (2112)
42   (cutaneous adj2 lymphoma$).ti,ab. (2353)
43   30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (370760)
44   limit 43 to ("in data review" or in process or "pubmed not medline") (43213)
45   29 or 44 [skin cancer terms] (370216)
46   Mass screening/ (105601)
47   Early detection of Cancer/ (26804)
48   (screen$ or detect$).ti,ab. (3009872)
49   46 or 47 or 48 [screening terms] (3040274)

Appendix A. Literature Search Strategies for Primary Literature

50   Physical Examination/ (41203)
51   Dermoscopy/ (4707)
52   Photography/ (26210)
53   ((skin or body or physical) adj3 (exam$ or inspect$)).ti,ab. (87690)
54   visual$ inspect$.ti,ab. (8796)
55   dermoscop$.ti,ab. (4728)
56   dermatoscop$.ti,ab. (1128)
57   photography.ti,ab. (15108)
58   50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 [exam terms] (171739)
59   45 and 49 and 58 (2329)
60   screen$.ti. (182363)
61   45 and 60 (1990)
62   59 or 61 (4056)
63   limit 62 to (english language and yr="2015 -Current") (1430)
64   remove duplicates from 63 (1414)
65   Biopsy/ (176527)
66   Biopsy, Needle/ (49302)
67   Biopsy, Large-Core Needle/ (1821)
68   Sentinel Lymph Node Biopsy/ (11353)
69   (biopsy$ or biopsies or biopsied).ti,ab. (406321)
70   (excise* or excision$).ti,ab. (175778)
71   Rebiops$.ti,ab. (711)
72   65 or 66 or 67 or 68 or 69 or 70 or 71 [biopsy] (671651)
73   (harm or harms or harmful or harmed).ti,ab. (123766)
74   (adverse effects or mortality).fs. (2255171)
75   Mortality/ or Morbidity/ (72919)
76   death/ (17846)
77   (death or deaths).ti,ab. (846009)
78   "Drug-Related Side Effects and Adverse Reactions"/ or Long Term Adverse Effects/ (33489)
79   ((adverse or negative or unintended) adj (effect$ or event$ or outcome$ or reaction$)).ti,ab. (441798)
80   complication$.ti,ab. (938978)
81   side effect$.ti,ab. (255697)
82   safety.ti,ab. (531682)
83   false negative$.ti,ab. (34148)
84   misdiagnos$.ti,ab. (34921)
85   overdiagnos$.ti,ab. (4189)
86   ((unneeded or unnecessary) adj5 (treat$ or therap$ or surg$ or procedure$)).ti,ab. (13635)
87   label$.ti,ab. (542702)
88   psychological effect$.ti,ab. (4193)
89   Cicatrix/ (22736)
90   (cicatrix or scar$).ti,ab. (171218)
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 [harms] (4990117)
92   45 and 72 and 91 (12442)

93   limit 92 to (english language and yr="2015 -Current") (3444)
94   remove duplicates from 93 (3413)
95   Neoplasm Staging/ (177140)
96   ((detect$ or diagnos$ or biops$) adj5 stage).ti,ab. (41929)
97   ((late$ or distant or advanced or end) adj stage).ti,ab. (128088)
98   ((early or earlier) adj (diagnos$ or detect$ or discovery or findings)).ti,ab. (164256)
99   95 or 96 or 97 or 98 [staging] (479381)
100   Registries/ (92863)
101   Survival Analysis/ (137979)
102   SEER program/ (8047)
103   Morbidity/ (30677)
104   Mortality/ (45548)
105   Death/ (17846)
106   mo.fs. (591252)
107   (registr$ or register$).ti,ab. (421847)
108   SEER.ti,ab. (7869)
109   "Surveillance epidemiology and end results".ti,ab. (10223)
110   morbidit$.ti,ab. (403380)
111   mortalit$.ti,ab. (797285)
112   (death or deaths).ti,ab. (846009)
113   survival.ti,ab. (979037)
114   110 or 111 or 112 or 113 (2350010)
115   limit 114 to ("in data review" or in process or "pubmed not medline") (290125)
116   100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 115 [registries morbidity] (1401438)
117   45 and 99 and 116 (12258)
118   limit 117 to (english language and yr="2015 -Current") (3864)
119   remove duplicates from 118 (3830)
120   Dermatologic Surgical Procedures/ (7074)
121   Curettage/ (4446)
122   Dessication/ (7297)
123   Cryosurgery/ (13148)
124   Laser Therapy/ (38148)
125   Mohs Surgery/ (3246)
126   Lymph Node Excision/ (33723)
127   (surger$ or surgical).ti. (631566)
128   curettage.ti,ab. (11639)
129   dessicat$.ti,ab. (287)
130   electrodessicat$.ti,ab. (127)
131   cryosurg$.ti,ab. (4106)
132   laser ablation.ti,ab. (7776)
133   mohs.ti,ab. (3519)
134   metastasectom$.ti,ab. (2358)
135   lymphadenectom$.ti,ab. (17730)
136   ((lymph node$ or lymphoid) adj3 (remov$ or dissect$ or resect$)).ti,ab. (26158)
137   127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 (691169)

138   limit 137 to ("in data review" or in process or "pubmed not medline") (74054)
139   120 or 121 or 122 or 123 or 124 or 125 or 126 or 138 (179096)
140   45 and 139 (14309)
141   Skin Neoplasms/su (17070)
142   Melanoma/su (10021)
143   Melanoma, Amelanotic/su (125)
144   Nevus/su (576)
145   Dysplastic Nevus Syndrome/su (92)
146   Hutchinson's Melanotic Freckle/su (223)
147   Carcinoma, Basal Cell/su (4921)
148   Carcinoma, Squamous Cell/su (26692)
149   Carcinoma, Merkel Cell/su (465)
150   Neoplasms, Basal Cell/su (58)
151   Neoplasms, Squamous Cell/su (227)
152   "Neoplasms, Adnexal and Skin Appendage"/su (75)
153   Actinic keratosis/su (68)
154   Bowen disease/su (249)
155   Lymphoma, T-Cell, Cutaneous/su (48)
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 [skin cancer surgery] (53576)
157   Lymphedema/ (9233)
158   Lymph?edema.ti,ab. (10159)
159   Surgical wound infection/ (36984)
160   ((surg$ or postsurg$ or post-surg$) adj2 infect$).ti,ab. (20180)
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 [harms lymphedema surgery outcomes] (4484893)
162   156 and 161 (18243)
163   limit 162 to (english language and yr="2015 -Current") (3643)
164   64 or 94 or 119 or 163 (10392)
165   Animal/ not (Animal/ and Human/) (4741836)
166   164 not 165 (10302)
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. (1473595)
168   166 not 167 (6505)

Cochrane Central Register of Controlled Clinical Trials (CENTRAL) via Wiley:
Date Run: 12/01/2021 22:56:53

#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   8659
#2   melanoma*:ti,ab,kw   5471
#3   (naevoid or nevoid):ti,ab,kw near/3 syndrome*:ti,ab,kw   0

#4	(dysplastic or malignant):ti,ab,kw near/2 (nevus or naevus or nevi or naevi):ti,ab,kw
	38
#5	"Hutchinson's Melanotic Freckle":ti,ab,kw	8
#6	"lentigo maligna":ti,ab,kw	28
#7	basal:ti,ab,kw next cell:ti,ab,kw next (carcinoma* or neoplasm* or cancer* or tumor* or tumour* or malignan* or lesion* or metasta* or epithelioma*):ti,ab,kw	966
#8	(basocellular* or basosquamous):ti,ab,kw next carcinoma*:ti,ab,kw	5
#9	squamous:ti,ab,kw next cell:ti,ab,kw next (carcinoma* or neoplasm* or cancer* or tumor* or tumour* or malignan* or lesion* or metasta* or epithelioma*):ti,ab,kw 6265
#10	merkel:ti,ab,kw next cell:ti,ab,kw next (carcinoma* or neoplasm* or cancer* or tumor* or tumour* or malignan* or lesion* or metasta* or epithelioma*):ti,ab,kw 74
#11	"actinic keratosis":ti,ab,kw	746
#12	bowen*:ti,ab,kw next disease:ti,ab,kw	106
#13	cutaneous:ti,ab,kw near/2 lymphoma*:ti,ab,kw	33
#14	{or #1-#13}	18926
#15	screen*:ti,ab,kw	73849
#16	(skin or body or physical):ti,ab,kw near/3 (exam* or inspect*):ti,ab,kw	16935
#17	(dermoscop* or dermatoscop*):ti,ab,kw	267
#18	visual*:ti,ab,kw next inspect*:ti,ab,kw	712
#19	photography:ti,ab,kw	3469
#20	{or #15-#19}	90240
#21	#14 and #20 with Publication Year from 2015 to 2021, in Trials	769
#22	(biopsy* or biopsies or biopsied):ti,ab,kw	30879
#23	(excise* or excision*):ti,ab,kw	6815
#24	rebiops*:ti,ab,kw	158
#25	#22 or #23 or #24	36717
#26	(harm or harms or harmful or harmed):ti,ab,kw	12063
#27	(death or deaths):ti,ab,kw	72613
#28	(adverse or negative or unintended):ti,ab,kw next (effect* or event* or outcome* or reaction*):ti,ab,kw	259695
#29	complication*:ti,ab,kw	184994
#30	side:ti,ab,kw next effect*:ti,ab,kw	141964
#31	safety:ti,ab,kw 237359
#32	false:ti,ab,kw next negative*:ti,ab,kw 1496
#33	misdiagnos*:ti,ab,kw	401
#34	overdiagnos*:ti,ab,kw 367
#35	(unneeded or unnecessary):ti,ab,kw near/5 (treat* or therap* or surg* or procedure*):ti,ab,kw	865
#36	label*:ti,ab,kw 69921
#37	psychological:ti,ab,kw next effect*:ti,ab,kw	718
#38	(cicatrix or scar*):ti,ab,kw	11624
#39	{or #26-#38}	642600
#40	#14 and #25 and #39 with Publication Year from 2015 to 2021, in Trials	648
#41	(detect* or diagnos* or biops*):ti,ab,kw near/5 stage:ti,ab,kw	3664
#42	(late* or distant or advanced or end):ti,ab,kw next stage:ti,ab,kw	10187

#43   (early or earlier):ti,ab,kw next (diagnos* or detect* or discovery or findings):ti,ab,kw
       6228
#44   #41 or #42 or #43   19252
#45   #14 and #44 with Publication Year from 2015 to 2021, in Trials   468
#46   (surger* or surgical):ti70496
#47   curettage:ti,ab,kw   1581
#48   dessicat*:ti,ab,kw   7
#49   electrodessicat*:ti,ab,kw   14
#50   cryosurg*:ti,ab,kw   501
#51   "laser ablation":ti,ab,kw   565
#52   mohs:ti,ab,kw 236
#53   metastasectom*:ti,ab,kw   166
#54   lymphadenectom*:ti,ab,kw   1665
#55   ("lymph node" or "lymph nodes" or lymphoid):ti,ab,kw near/3 (remov* or dissect* or
resect*):ti,ab,kw   3310
#56   {or #46-#55} 76395
#57   (lymphedema or lymphoedema):ti,ab,kw   1383
#58   (surg* or postsurg* or post-surg*):ti,ab,kw near/2 infect*:ti,ab,kw 7208
#59   (#26 or #27 or #28 or #29 or #30 or #31 or #38 or #57 or #58)   619181
#60   #14 and #56 and #59 with Publication Year from 2015 to 2021, in Trials   422
#61   #21 or #40 or #45 or #60   1924

Embase via Elsevier:
#1   'skin cancer'/exp OR 'skin tumor'/de OR 'melanoma'/de OR 'benign skin tumor'/exp OR
'actinic keratosis'/de   311543
#2   ((skin OR derm* OR cutaneous OR epithelial OR epithelium OR epiderm*) NEAR/3
(cancer* OR neoplas* OR carcinoma* OR tumo*r* OR malignan* OR lesion* OR metasta* OR
dysplas*)):ti,ab   230750
#3   melanoma*:ti,ab   168357
#4   ((naevoid OR nevoid) NEAR/3 syndrome*):ti,ab   184
#5   ((dysplastic OR malignant) NEAR/2 (nevus OR naevus OR nevi OR naevi)):ti,ab 2679
#6   hutchinson*:ti,ab AND 'melanotic freckle':ti,ab   59
#7   'lentigo maligna':ti,ab 1617
#8   ('basal cell' NEAR/1 (cancer* OR neoplas* OR carcinoma* OR tumo*r* OR malignan*
OR lesion* OR metasta* OR epithelioma*)):ti,ab   20348
#9   ((basocellular* OR basosquamous) NEAR/1 carcinoma*):ti,ab   351
#10   ('merkel cell' NEAR/1 (cancer* OR neoplas* OR carcinoma* OR tumo*r* OR malignan*
OR lesion* OR metasta* OR epithelioma*)):ti,ab   4952
#11   'actinic keratosis':ti,ab 3427
#12   'bowen* disease':ti,ab 459
#13   (cutaneous NEAR/2 lymphoma*):ti,ab   3460
#14   #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   521590
#15   'mass screening'/de OR 'cancer screening'/de OR 'early cancer diagnosis'/de   145301
#16   screen*:ti,ab OR detect*:ti,ab 3915915
#17   #15 OR #16   3952938

#18   'physical examination'/de OR 'skin examination'/exp OR 'photography'/exp482345
#19   ((skin OR body OR physical) NEAR/3 (exam* OR inspect*)):ti,ab 150389
#20   'visual* inspect*':ti,ab 12778
#21   dermoscop*:ti,ab   5809
#22   dermatoscop*:ti,ab   1604
#23   photography:ti,ab   19103
#24   #18 OR #19 OR #20 OR #21 OR #22 OR #23   574221
#25   #14 AND #17 AND #24   7368
#26   screen*:ti   242957
#27   #14 AND #26 2812
#28   #25 OR #27   9711
#29   'biopsy'/de OR 'skin examination'/exp OR 'large core needle biopsy'/de OR 'sentinel lymph node biopsy'/de   384845
#30   biopsy*:ti,ab OR biopsies:ti,ab OR biopsied:ti,ab   651428
#31   excise*:ti,ab OR excision*:ti,ab   231449
#32   rebiops*:ti,ab 2750
#33   #29 OR #30 OR #31 OR #32 1046723
#34   harm:ti,ab OR harms:ti,ab OR harmful:ti,ab OR harmed:ti,ab   160662
#35   'mortality'/de OR 'cancer mortality'/de OR 'surgical mortality'/de OR 'death'/de OR 'morbidity'/de OR 'adverse event'/exp OR 'side effect'/exp   2123561
#36   death:ti,ab OR deaths:ti,ab   1212813
#37   ((adverse OR negative OR unintended) NEAR/1 (effect* OR event* OR outcome* OR reaction*)):ti,ab   674739
#38   complication*:ti,ab   1385663
#39   'side effect*':ti,ab   377930
#40   safety:ti,ab   820849
#41   'false negative*':ti,ab 47860
#42   misdiagnos*:ti,ab   50580
#43   overdiagnos*:ti,ab   7413
#44   ((unneeded OR unnecessary) NEAR/5 (treat* OR therap* OR surg* OR procedure*)):ti,ab   20835
#45   label*:ti,ab   686568
#46   'psychological effect*':ti,ab   5318
#47   'scar'/exp   80154
#48   cicatrix:ti,ab OR scar*:ti,ab   233525
#49   #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48   5918605
#50   #14 AND #33 AND #49   21318
#51   'tumor classification'/exp   451299
#52   ((detect* OR diagnos* OR biops*) NEAR/5 stage):ti,ab   71924
#53   ((late* OR distant OR advanced OR end) NEAR/1 stage):ti,ab   191408
#54   ((early OR earlier) NEAR/1 (diagnos* OR detect* OR discovery OR findings)):ti,ab   261028
#55   #51 OR #52 OR #53 OR #54 897182
#56   'register'/de OR 'cancer registry'/exp OR 'survival analysis'/de   174263

#57   'mortality'/de OR 'cancer mortality'/de OR 'surgical mortality'/de OR 'death'/de OR 'morbidity'/de 1318853
#58   registr*:ti,ab OR register*:ti,ab   586613
#59   seer:ti,ab   15195
#60   'surveillance epidemiology and end results':ti,ab   14942
#61   morbidit*:ti,ab610389
#62   mortalit*:ti,ab 1172638
#63   death:ti,ab OR deaths:ti,ab   1213072
#64   survival:ti,ab   1446387
#65   #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64   4118283
#66   #14 AND #55 AND #65   21012
#67   'skin surgery'/de OR 'curettage'/de OR 'desiccation'/de OR 'cryosurgery'/de OR 'low level laser therapy'/de OR 'mohs micrographic surgery'/de OR 'lymph node dissection'/de   138543
#68   surger*:ti OR surgical:ti   791912
#69   curettage:ti,ab 14735
#70   dessicat*:ti,ab 357
#71   electrodessicat*:ti,ab 205
#72   cryosurg*:ti,ab   5187
#73   'laser ablation':ti,ab   8863
#74   mohs:ti,ab   4639
#75   metastasectom*:ti,ab 3647
#76   lymphadenectom*:ti,ab   27719
#77   (('lymph node*' OR lymphoid) NEAR/3 (remov* OR dissect* OR resect*)):ti,ab   41167
#78   #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77
        949269
#79   #14 AND #78 28544
#80   'skin cancer'/exp/dm_su OR 'skin tumor'/dm_su OR 'melanoma'/dm_su OR 'benign skin tumor'/exp/dm_su OR 'actinic keratosis'/dm_su   33743
#81   #79 OR #80   51615
#82   'lymphedema'/de   17948
#83   lymph*edema:ti,ab   14626
#84   'surgical infection'/de 51938
#85   ((surg* OR postsurg* OR 'post surg*') NEAR/2 infect*):ti,ab   29238
#86   #49 OR #82 OR #83 OR #84 OR #85   5962061
#87   #81 AND #86 14163
#88   #28 OR #50 OR #66 OR #87 55786
#89   #88 NOT (('animal model'/exp OR 'animal experiment'/exp OR 'nonhuman'/de OR 'animal'/exp) NOT 'human'/de)   54299
#90   oral:ti OR tongue:ti OR larynx:ti OR laryng*:ti OR hypolaryng*:ti OR oropharyng*:ti OR pharynx:ti OR pharyng*:ti OR esophag*:ti OR oesophag*:ti OR gastric:ti OR ovary:ti OR ovaries:ti OR ovarian:ti OR cervical:ti OR cervix:ti OR endometrium:ti OR endometrial:ti OR lung:ti OR breast:ti OR ocular:ti OR vulva*:ti OR anus:ti OR anal:ti OR mucosal:ti
        1937404
#91   #89 NOT #90 43991

Appendix A. Literature Search Strategies for Primary Literature

#92   'clinical trial'/de OR 'controlled clinical trial'/de OR 'randomized controlled trial'/exp OR 'randomization'/exp OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de 1658355

#93   'meta analysis'/exp OR 'meta analysis (topic)'/de   244255

#94   'intermethod comparison'/de OR 'double blind procedure'/de   447271

#95   'clinical trial*':ti,ab OR 'controlled trial*':ti,ab OR random*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR trial:ti OR placebo:ti,ab   2279186

#96   compare:ti OR compared:ti OR comparison:ti   549307

#97   (evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)   2225824

#98   (open NEXT/1 label):ti,ab   83963

#99   ((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab   241386

#100   (parallel NEXT/1 group*):ti,ab   26720

#101   crossover:ti,ab OR 'cross over':ti,ab   108903

#102   ((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab   380281

#103   assigned:ti,ab OR allocated:ti,ab   405667

#104   (controlled NEAR/8 (study OR design OR trial)):ti,ab   374271

#105   volunteer:ti,ab OR volunteers:ti,ab   254381

#106   #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105   5739562

#107   'controlled study'/exp 8088576

#108   'longitudinal study'/exp OR 'prospective study'/de OR 'retrospective study'/de   1746197

#109   'cohort analysis'/de OR 'follow up'/de 2140477

#110   'observational study'/de   218946

#111   'correlational study'/de   46791

#112   'family study'/de   25940

#113   'case control*':ti,ab   167936

#114   cohort:ti,ab   977729

#115   longitudinal:ti,ab   347885

#116   'follow up':ti,ab OR followup:ti,ab   1620158

#117   prospective*:ti,ab   1120812

#118   'comparison group*':ti,ab OR 'control group*':ti,ab   707155

#119   observational:ti,ab   297638

#120   retrospective*:ti,ab   1306243

#121   database*:ti,ab 705193

#122   nonrandomi*:ti,ab   36131

#123   population*:ti,ab   2419527

#124   epidemiologic*:ti,ab   326244

#125   'cross sectional':ti,ab   494182

#126   #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125   13289912
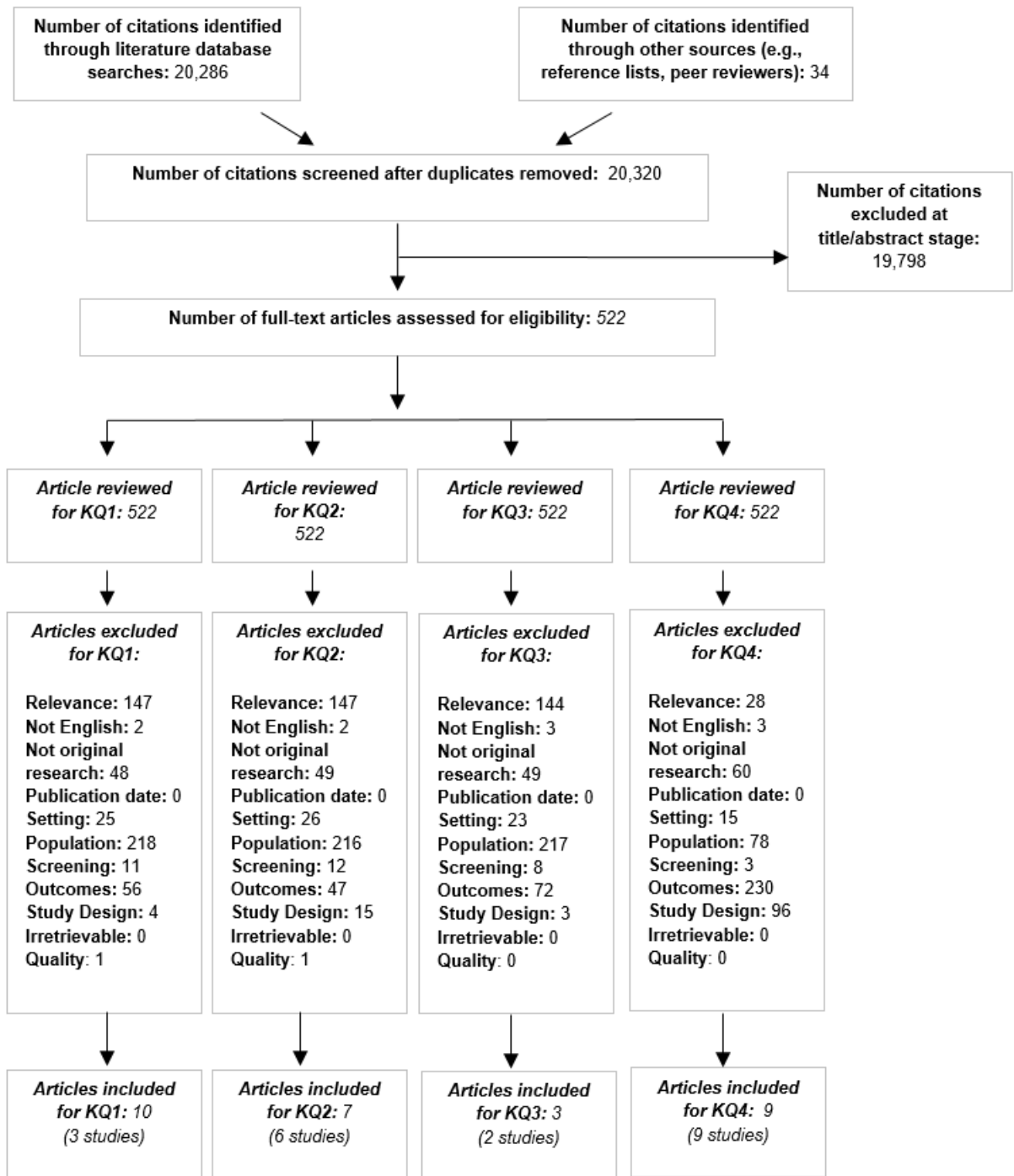
#127   #106 OR #126 15226253
#128   #91 AND #127   26927
#129   #91 AND #127 AND [english]/lim AND [2015-2021]/py   11982

Appendix A Figure 1. Literature Flow Diagram


```
┌─────────────────────────────┐          ┌─────────────────────────────┐
│ Number of citations identified│          │ Number of citations identified│
│ through literature database  │          │ through other sources (e.g.,  │
│ searches: 20,286             │          │ reference lists, peer reviewers): 34 │
└─────────────────────────────┘          └─────────────────────────────┘
                    ↓                          ↓
        ┌─────────────────────────────────────────────┐      ┌─────────────────┐
        │ Number of citations screened after duplicates │      │ Number of citations │
        │ removed: 20,320                              │  →   │ excluded at       │
        └─────────────────────────────────────────────┘      │ title/abstract stage: │
                              ↓                               │ 19,798            │
        ┌─────────────────────────────────────────────┐      └─────────────────┘
        │ Number of full-text articles assessed for     │
        │ eligibility: 522                             │
        └─────────────────────────────────────────────┘
```

Article reviewed for KQ1: 522	Article reviewed for KQ2: 522	Article reviewed for KQ3: 522	Article reviewed for KQ4: 522
Articles excluded for KQ1: Relevance: 147 Not English: 2 Not original research: 48 Publication date: 0 Setting: 25 Population: 218 Screening: 11 Outcomes: 56 Study Design: 4 Irretrievable: 0 Quality: 1	**Articles excluded for KQ2:** Relevance: 147 Not English: 2 Not original research: 49 Publication date: 0 Setting: 26 Population: 216 Screening: 12 Outcomes: 47 Study Design: 15 Irretrievable: 0 Quality: 1	**Articles excluded for KQ3:** Relevance: 144 Not English: 3 Not original research: 49 Publication date: 0 Setting: 23 Population: 217 Screening: 8 Outcomes: 72 Study Design: 3 Irretrievable: 0 Quality: 0	**Articles excluded for KQ4:** Relevance: 28 Not English: 3 Not original research: 60 Publication date: 0 Setting: 15 Population: 78 Screening: 3 Outcomes: 230 Study Design: 96 Irretrievable: 0 Quality: 0
Articles included for KQ1: 10 (3 studies)	Articles included for KQ2: 7 (6 studies)	Articles included for KQ3: 3 (2 studies)	Articles included for KQ4: 9 (9 studies)

Abbreviation: KQ = Key question.

Appendix A Table 1. Inclusion and Exclusion Criteria

	Include	**Exclude**
Population	KQs 1-3: Asymptomatic adolescents and adults age 15 years and older with or without a family history of melanoma KQ4: Adolescents and adults age 15 years and older diagnosed with skin cancer	Individuals younger than age 15 years KQs 1-3: Individuals under surveillance for skin cancer (e.g. previous skin cancer; genetic syndromes associated with increased skin cancer risk; conditions associated with suppressed immune system) KQ4: Overlapping population with already included study (contains duplicative data)
Settings	Primary care–relevant settings In-person or virtual settings Countries categorized as "Very High" on the 2019 Human Development Index (as defined by the United Nations)[1]	KQ1, KQ2: Conducted exclusively in specialty care settings (for example, dermatology, plastic surgery)
Screening tests	Total or partial visual skin examination conducted by a clinician with or without tools to aid examination (for example but not limited to, dermatoscopy; whole body photography)	KQ1: Lesion-directed diagnostic skin examination (e.g. in response to patient concern) Skin self-exam or behavioral counseling by clinician for self-exam
Comparison	KQ1: No visual skin examination KQ2: Usual care (e.g. lesion-directed examination) KQ4: Stage or thickness at detection (precancerous lesions or skin cancer)	
Outcomes	KQ1, KQ4: Morbidity or mortality associated with skin cancer, including quality of life; skin cancer mortality; or all-cause mortality KQ2: Stage or lesion thickness at detection of skin cancer or precancerous lesion. KQ3: Any persistent harm (beyond 30 days) from screening, biopsy, or excision; including psychosocial harms and procedure-related adverse events	KQ1, KQ2, KQ4: Non-skin location, Merkel cell carcinoma Risk reduction behaviors (e.g., skin self-exam, sun protective behaviors) or measures of doctor-patient relationship quality Outcomes not stratified by skin cancer type (melanoma vs. non-melanoma skin cancers) KQ4: -Reports relative survival data only (no mortality data) -Reports risk as a continuous estimate only (e.g., single HR / risk estimate for association) -Reports results in graphical format only

Appendix A Table 1. Inclusion and Exclusion Criteria

	Include	**Exclude**
Study design	All KQs: Fair- and good-quality studies KQ1, KQ2, KQ4: Randomized, controlled trials; controlled clinical trials; nonrandomized studies with a contemporaneous control KQ3: Randomized, controlled trials; controlled clinical trials; large screening registry or database nonrandomized studies; cohort studies; and systematically selected case series *Note: KQ4 studies must use AJCC (any version) or SEER staging criteria*	All KQs: Poor-quality studies KQ1, KQ2: Decision analyses KQ3: Case studies KQ4: - Studies taking place at single site or institution - Studies reporting only Breslow depth, thickness, T-stages, or Clark levels - Studies comparing grouped stages (e.g., I+II vs. III+IV) or sub-stages (e.g., Ia vs. Ib vs. Ic vs. Id) - Studies limited to a single body part (e.g., lip, outer ear) or cancer sub-type (e.g., acral melanoma)
Publication type	Original, peer-reviewed research	Not original research (e.g., editorials, opinion pieces, narrative reviews) Not peer-reviewed research (e.g., conference abstracts)

Abbreviations: AJCC = American Joint Committee on Cancer; KQ = Key question; HR = Hazard ratio; SEER = Surveillance, Epidemiology, and End Results Program

Appendix A Table 2. Quality Assessment Criteria

Study Design	Quality criteria
Nonrandomized studies (e.g., prospective cohort studies), adapted from the Newcastle-Ottawa Scale (NOS)[2]	**Bias arising in randomization process or due to confounding** • Balance in baseline characteristics • No baseline confounding • No time-varying confounding **Bias in selecting participants into the study** • No evidence of biased selection of sample • Start of followup and start of intervention coincide **Bias due to departures form intended interventions** • Participant intervention status is clearly and explicitly defined and measured • Classification of intervention status is unaffected by knowledge of the outcome or risk of the outcome **Bias in classifying interventions** • Fidelity to intervention protocol • Participants were analyzed as originally allocated **Bias from missing data** • Outcome data are reasonably complete and comparable between groups • Confounding variables that are controlled for in analysis are reasonably complete • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of biased use of inferential statistics **Bias in reporting results selectively** • No evidence that the measures, analyses, or subgroup analyses are selectively reported
Randomized clinical trials, adapted from U.S. Preventive Services Task Force Manual[3]	**Bias arising in the randomization process or due to confounding** • Valid random assignment/random sequence generation method used • Allocation concealed • Balance in baseline characteristics **Bias in selecting participants into the study** • CCT only: No evidence of biased selection of sample **Bias due to departures from intended interventions** • Fidelity to the intervention protocol • Low risk of contamination between groups • Participants were analyzed as originally allocated **Bias from missing data** • No, or minimal, post-randomization exclusions • Outcome data are reasonably complete and comparable between groups • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of biased use of inferential statistics **Bias in reporting results selectively** • No evidence that the measures, analyses, or subgroup analyses are selectively reported

Appendix B. Recommendations of Others

Country	Organization	Year	Recommendation
United States	American Cancer Society (ACS)[4, 5]	2020, Accessed	Recommend cancer-related check-ups for persons aged >20 years by having periodic health exams and counseling, including skin cancer. The ACS suggests that approximately 10% of all people with melanoma have a family history of the disease and that this population get regular skin exams by a dermatologist and perform self-exams monthly.
	American Academy of Family Physicians (AAFP)	2016	AAFP agrees with the USPSTF's recommendations on skin cancer screening and provides no separate recommendations.
	American Academy of Dermatology (AAD)[6]	2020, Accessed	Provides a language that encourages regular self-exams in asymptomatic persons with no history of skin cancer. Also, the AAD states that persons should seek advice from their health providers on the frequency of self-exam.
Australia and New Zealand	Cancer Council Australia (CCA)[7]; endorsed by the Australasian College of Dermatologists	2019	General population: screening is not recommended due to insufficient evidence that screening reduces mortality. However, the CCA states that persons should consult their health provider if they notice any change in their skin. High-risk persons: CCA encourages total body photography and dermatoscopy every 6 months in persons with a high-risk for skin cancer (defined as having fair skin, light eye color, light or red hair, multiple nevi, compromised immune system, personal/family history of any skin cancer).
	Royal Australian College of General Practitioners (RACGP)[8]	2018	General population: screening is not recommended due to insufficient evidence that screening reduces mortality. Recommended opportunistic screening in persons with an increased risk for skin cancer (based on family history, skin type, actinic damage, history of KC, and high levels of exposure and episodes of sunburn in childhood). High-risk persons: RACGP encourages self-exams in persons with a high-risk (i.e., either with a history of melanoma or >5 atypical nevi) for skin cancer every 3 months and clinical examination every 6 months.
	Australian Skin and Skin Cancer Research Center Melanoma Screening Summit[9]	2019	General population: There is currently insufficient evidence to support systematic screening in the general population. High-risk persons: More research is needed on how risk-based population stratification tools could improve the balance of benefits and harms of opportunistic screening.
Germany	Federal Joint Committee[10]	2008	Nationwide skin cancer screening program: Routine screening is offered to adults aged ≥35 with health insurance every two years.

Appendix B. Recommendations of Others

Country	Organization	Year	Recommendation
The Netherlands	Dutch Working Group on Melanoma[11]	2013	General population: Routine screening is not recommended. Increased risk: Annual exams are recommended for persons with ≥5 atypical nevi or with ≥100 banal nevi. High-risk persons: In persons with a high-risk due to genetic factors: Screening of the skin once or twice per year by a dermatologist.
United Kingdom	British Association of Dermatologists[12]	2010	Increased risk for skin cancer: Recommended self-exam and monitoring by a health provider.

Appendix C. Included Studies

Below is a list of included studies and their ancillary publications (indented below main results publication):

Key Question 1

1. Datzmann T, Schoffer O, Meier F, Seidler A, Schmitt, J. Are patients benefiting from participation in the German skin cancer screening programme? A large cohort study based on administrative data. Br J Dermatol. 2022;186(1):69-77. PMID: 34289097.

2. Kaiser M, Schiller J, Schreckenberger C. The effectiveness of a population-based skin cancer screening program: evidence from Germany. European Journal of Health Economics. 2018;193:355-367. PMID: 28353004.

   o Boniol M, Autier P, Gandini S. Melanoma mortality following skin cancer screening in Germany. BMJ Open. 2015;59:e008158. PMID: 26373399.

   o Geller AC, Greinert R, Sinclair C, Weinstock MA, Aitken J, Boniol M, Capellaro M, Dore JF, Elwood M, Fletcher SW, Gallagher R, Gandini S, Halpern AC, Katalinic A, Lucas R, Marghoob AA, Nolte S, Schuz J, Tucker MA, Volkmer B, Breitbart E. A nationwide population-based skin cancer screening in Germany: proceedings of the first meeting of the International Task Force on Skin Cancer Screening and Prevention (September 24 and 25, 2009). Cancer Epidemiol. 2010;343:355-8. PMID: 20381443.

   o Kornek T, Schafer I, Reusch M, Blome C, Herberger K, Beikert FC, Augustin M. Routine skin cancer screening in Germany: four years of experience from the dermatologists' perspective. Dermatology. 2012;225(4):289-93. PMID: 23295723.

3. Katalinic A, Eisemann N, Waldmann A. Skin Cancer Screening in Germany. Documenting Melanoma Incidence and Mortality From 2008 to 2013. Dtsch Arztebl Int. 2015;11238:629-34. PMID: 26429634.

   o Breitbart EW, Waldmann A, Nolte S, Capellaro M, Greinert R, Volkmer B, Katalinic A. Systematic skin cancer screening in Northern Germany. J Am Acad Dermatol. 2012;662:201-11. PMID: 22074699.

   o Eisemann N, Waldmann A, Holleczek B, Katalinic A. Observed and Expected Mortality in the German Skin Cancer Screening Pilot Project Screen. J Med Screen. 2018;253:166-168.

   o Katalinic A,Waldmann A, Weinstock MA, Geller AC, Eisemann N, Greinert R, Volkmer B, Breitbart E. Does skin cancer screening save lives?: an observational study comparing trends in melanoma mortality in regions with and without screening. Cancer. 2012;11821:5395-402. PMID: 22517033.

   o Stang A, Jöckel KH. Does Skin Cancer Screening Save Lives? A Detailed Analysis of Mortality Time Trends in Schleswig-Holstein and Germany. Cancer. 2016;1223:432-7. PMID: 26480048.

Key Question 2

4. Aitken JF, Elwood M, Baade PD, Youl P, English D. Clinical whole-body skin examination reduces the incidence of thick melanomas. Int J Cancer. 2010;1262:450-8. PMID: 19609948.

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Key Question 4

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Appendix C. Included Studies

18. Ward-Peterson M, Acuña JM, Alkhalifah MK, Nasiri AM, Al-Akeel ES, Alkhaldi TM, Dawari SA, Aldaham SA. Association between Race/Ethnicity and Survival of Melanoma Patients in the United States over 3 Decades. Medicine (Baltimore). 2016;95(17):e3315. PMID: 27124020.

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20. Qian Y, Johannet P, Sawyers A, Yu, J, Osman, I, Zhong, J. The ongoing racial disparities in melanoma: An analysis of the Surveillance, Epidemiology, and End Results database (1975-2016). J Am Acad Dermatol. 2021;84(6):1585-93. PMID: 32861710.

E Codes
E1. Not relevant
E2. Not English
E3. Not original research
E4. Publication date (published 2014 or earlier – doesn't apply to studies carried forward from prior review)

Ineligible SETTING
    E5a. Exclusively specialty care setting (dermatology, plastic surgery, etc.)
    E5b. Not "very high HDI" country
    E5c. Other ineligible setting

Ineligible POPULATION
    E6a. Younger than age 15
    E6b. (KQ1-3): Already under surveillance for skin cancer (due to previous skin cancer, genetic syndrome, immunosuppression, etc.)
    E6c. Other ineligible population
    E6d. Overlapping population; contains duplicative data

Ineligible SCREENING
    E7a. Lesion-directed diagnostic skin exam (in response to patient concern)
    E7b. Other ineligible screening (e.g., skin self-exam, behavioral counseling by clinician for self-exam, biomarkers, consumer smartphone apps)

Ineligible OUTCOMES
    E8a. Incomplete study / protocol only
    E8b. Other ineligible outcomes

Ineligible STUDY DESIGN
    E9a. (KQ 1, 2, 4): No comparison group
    E9b. Other ineligible design

E10. Irretrievable
E11. Poor QUALITY

1.   2-cm versus 4-cm surgical excision margin for thick (>2 mm) primary malignant melanoma: long-term follow-up of a multicenter randomized trial. European journal of surgical oncology. 2020;462:e15-e16. PMID: CN-02137007. **E6c, E8b, E6c, E6c.**

2.   Abdel-Rahman O Evaluation of the eighth American Joint Committee on Cancer staging system for malignant melanoma of the skin. Future Oncology. 2018;145:471-481. PMID: 29322826. **E1, E9b, E1, E1.**

3.   Afshar N, Dashti S G, Thursfield V, Farrugia H, Giles G G, Milne R L, English D R Do age at diagnosis, tumour thickness and tumour site explain sex differences in melanoma survival? a sequential causal mediation analysis using cancer registry data. Journal of Global Oncology. 2018;4:33s. **E1, E3, E1, E1.**

4.   Aitken J F, Janda M, Elwood M, Youl P H, Ring I T, Lowe J B Clinical outcomes from skin screening clinics within a community-based melanoma screening program. J Am Acad Dermatol. 2006;541:105-14. PMID: 16384764. **E8b, E6c, E8b, E8b**.

5.   Aitken J F, Youlden D R, Baade P D, Soyer H P, Green A C, Smithers B M Generational shift in melanoma incidence and mortality in Queensland, Australia, 1995-2014. International Journal of Cancer. 2018;1428:1528-1535. PMID: 29105744. **E1, E8b, E1, E1.**

6.   20109 ~ Ajmal S, Comissiong D, Barsky M, Vezeridis M P, Miner T J Surgical treatment of melanoma in elderly: Do we follow NCCN guidelines?. Annals of Surgical Oncology. 2015;221:S123. **E6b, E8b, E6b, E6b.**

7.   Akufo-Tetteh E, Wong C, Black L, Harris A Stripping down to the bare facts: The importance of full-skin examination in the diagnosis of malignant melanoma. British Journal of Dermatology. 2015;173:35. **E8b, E8b, E9a, E8b.**

8.   Al-Himdani S, Naderi N, Whitaker I S, Jones N W An 18-year Study of Malignant Melanoma in Childhood and Adolescence. Plastic and Reconstructive Surgery - Global Open. 2019;78:e2338. PMID: 31592003. **E6c, E8b, E6c, E6c.**

9.   Ali Z, Todd P M Total body skin examination increases squamous cell carcinoma detection: a retrospective cohort study. Clinical & Experimental Dermatology. 2020;451:86-88. PMID: 31120587. **E5a, E5a, E5a, E5a.**

10. Allais B S, Beatson M, Wang H, Shahbazi S, Bijelic L, Jang S, Venna S Five-Year Survival in Patients with Nodular and Superficial Spreading Melanomas in the US Population. Journal of the American Academy of Dermatology. 2020;;. **E6b, E8b, E6b, E6b.**

11. Al-Qurayshi Z, Sullivan C B, Schwalje A, Walsh J, Bayon R, Tufano R, Kandil E Presentation and Outcomes of Elderly Patients Undergoing Head and Neck Surgeries: A National Perspective. Otolaryngology - Head and Neck Surgery (United States). 2020;1632:335-343. **E6c, E6c, E6c, E6c.**

12. Amber K T, Ledon J A, Savas J A, Dusseault S K, Nouri K Visual identification of skin cancer in beachgoers: A need for improved education on non-melanoma skin cancer in the general population and melanoma in the African-American population. International Journal of Dermatology. 2015;543:e85-e87. **E1, E1, E1, E1.**

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14. Anastasiadou Z, Schafer I, Siebert J, Gunther W, Reusch M, Augustin M Participation and

health care provision of statutory skin cancer screening in Germany - a secondary data analysis. Journal of the European Academy of Dermatology & Venereology. 2016;303:424-7. PMID: 26856813. **E8b, E8a, E8b, E8b.**

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17. Anderson A M, Matsumoto M, Saul M I, Secrest A M, Ferris L K Accuracy of Skin Cancer Diagnosis by Physician Assistants Compared With Dermatologists in a Large Health Care System. JAMA Dermatology. 2018;1545:569-573. PMID: 29710082. **E8b, E6c, E9b, E8b.**

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20. Arnold-Bruning F S, Blaschke T, Kramer K, Lademann J, Thiede G, Fluhr J W, Patzelt A, Meinke M C Application of parelectric spectroscopy to detect skin cancer-A pilot study. Skin Research & Technology.

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Manrique-Silva E, Quaglino P, Tonella L, Jaka A, Richarz N, Rodríguez-Peralto J L, Ortiz P, Boada A, Ribero S, Nagore E, Malvehy J, Puig S Differences in cutaneous melanoma survival between the 7th and 8th edition of the American Joint Committee on Cancer (AJCC). A multicentric population-based study. European Journal of Cancer. 2021;145:29-37. **E1, E9b, E1, E1.**

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from melanoma in Germany 1997-2013. Melanoma Research. 2020;:386-395. **E6c, E8b, E6c, E6c.**

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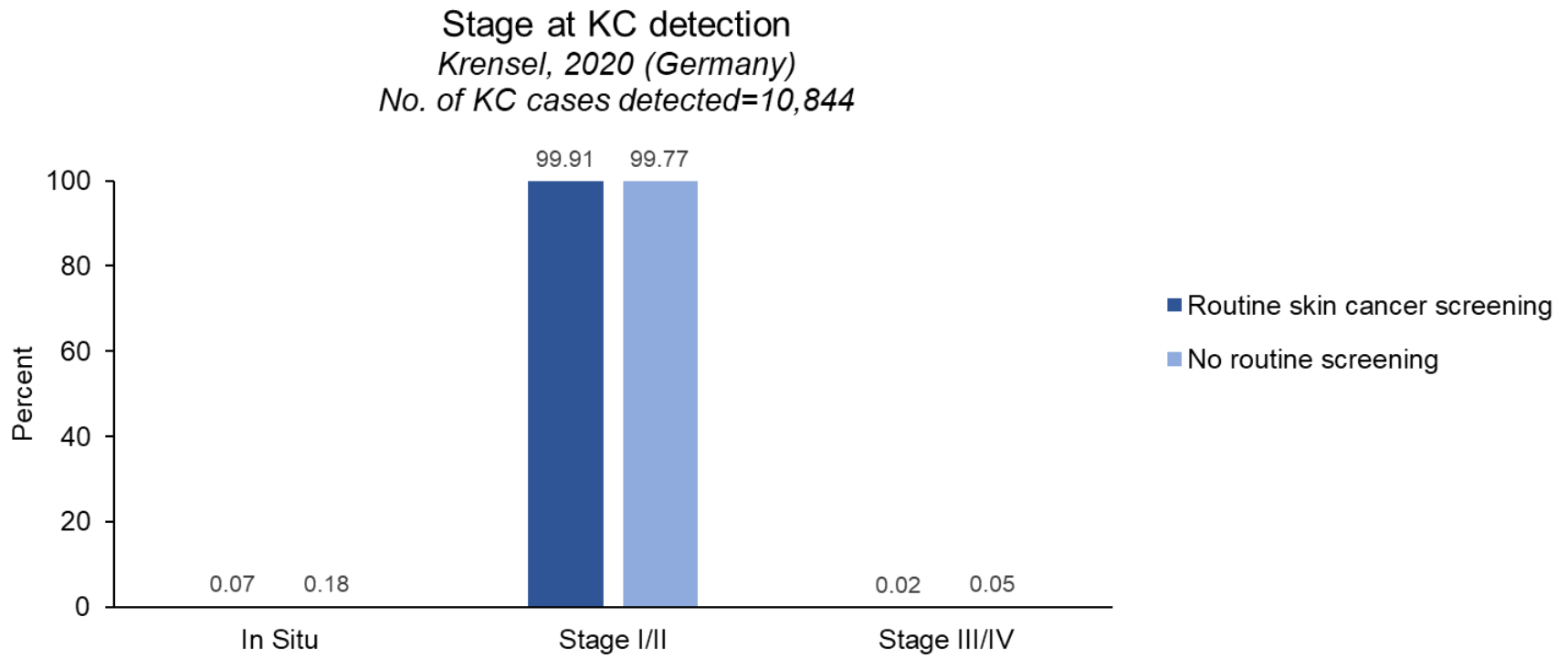
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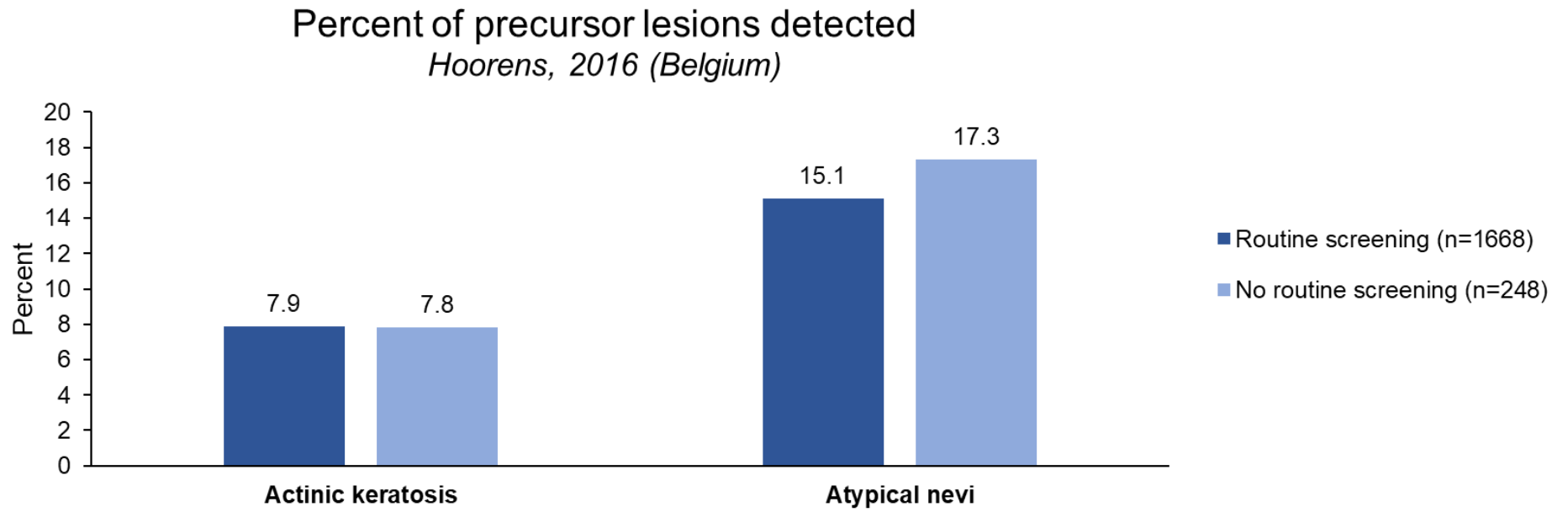
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Stage at KC detection
Krensel, 2020 (Germany)
No. of KC cases detected=10,844

Percent of precursor lesions detected
Hoorens, 2016 (Belgium)

Legend:
- Routine screening (n=1668)
- No routine screening (n=248)

Actinic keratosis: 7.9 (Routine screening), 7.8 (No routine screening)
Atypical nevi: 15.1 (Routine screening), 17.3 (No routine screening)

Appendix E Figure 3. Stage at Melanoma Detection, Screened vs. No Routine Skin Cancer Screening (KQ2)[13, 15, 16]

Stage at melanoma detection
Matsumoto 2022 (US)

Stage at melanoma detection
Krensel, 2020 (Germany)

Stage at melanoma detection
Trautmann, 2016 (Germany)

AdjHR (95% CI): 2.6 (2.1-3.1); p<0.001

■ Routine skin cancer screening
■ No routine screening

Melanoma thickness at detection
Aitken, 2010 (Australia)
No. of melanoma cases=3,762

Thickness	adjOR* (95% CI)
0.01-0.75 mm: 54.5	adjOR* 1.38 (95% CI, 1.22-1.56)
0.76-1.49 mm: 27	adjOR* 0.93 (95% CI, 0.79-1.10)
1.50-2.99 mm: 11.8	adjOR* 0.83 (95% CI, 0.66-1.05)
3.00+ mm: 6.7	adjOR* 0.60 (95% CI, 0.43-0.83)

*adjOR of clinical skin exam in previous 3 years

Melanoma thickness at detection
Cristofolini, 2015 (Italy)
No. of melanoma cases=1,389

Thickness	Routine screening	No routine screening
<1.00 mm	70.4	57.7
<2.00 mm	92.6	75.9

Melanoma thickness at detection
Matsumoto 2022 (US)
No. of melanoma cases=994

Thickness	Routine screening	No routine screening
Thin invasive ≤1mm	37.1	37.3
>1mm	14.6	28.1

AdjHR (95% CI): 1.8 (1.5-2.2); p<0.001

AdjHR (95% CI): 1.0 (0.7-1.3); p=0.75

■ Routine skin cancer screening
■ No routine screening

	Schleswig-Holstein*	Schleswig-Holstein*	Germany†	Germany†	Schleswig-Holstein*	Schleswig-Holstein*	Germany†	Germany†	Schleswig-Holstein*	Schleswig-Holstein*	Germany†	Germany†
	Age-standardized incidence rate per 100,000	Incidence	Age-standardized incidence rate per 100,000	Incidence	Age-standardized incidence rate per 100,000	Incidence	Age-standardized incidence rate per 100,000	Incidence	Age-standardized incidence rate per 100,000	Incidence	Age-standardized incidence rate per 100,000	Incidence
Year	Total	Total	Total	Total	Female	Female	Female	Female	Male	Male	Male	Male
1998	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
1999	17.8	590	NR	NR	19.1	334	NR	NR	16.5	256	NR	NR
2000	19.7	657	NR	NR	18.8	333	NR	NR	20.6	324	NR	NR
2001	20.5	695	NR	NR	22	388	NR	NR	18.9	307	NR	NR
2002	17.9	609	NR	NR	18.8	334	NR	NR	17	275	NR	NR
2003	21.1‡	718‡	14	13,992	24‡	409‡	14.3	7,483	18.3‡	309‡	13.6	6,508
2004	21.3‡	736‡	14.2	14,428	22.1‡	394‡	13.9	7,418	20.4‡	342‡	14.4	7,010
2005	17.2	632	14.5	14,966	17.2	332	14.4	7,727	17.3	300	14.6	7,240
2006	15.9	591	14.3	14,987	15.7	303	14.2	7,702	16.2	288	14.4	7,285
2007	15.7	590	14.9	15,740	16.2	314	14.9	8,068	15.3	276	14.9	7,673
2008	17.4§	661§	17.7§	18,852§	19§	367§	17§	8,068§	15.9§	294§	18.3§	9,547§
2009	18.3§	683§	17.9§	19,253§	18.5§	339§	17.2§	9,305§	18.1§	344§	18.6§	9,882§
2010	17.7§	682§	18.2§	19,605§	18.3§	349§	18§	9,371§	17.1§	333§	18.4§	9,852§
2011	17.8§	701§	17.9§	19,646§	18.7§	365§	17.6§	9,753§	16.9§	336§	18.2§	9,875§
2012§	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2013§	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

*SCREEN study region.
†Germany data includes Schleswig-Holstein.
‡Years of SCREEN skin cancer screening program (2003–2004).
§Years of German national skin cancer screening (2008–2013).

Appendix References

According to ClinicalTrials.gov there are 6 trials on skin cancer screening in adults that are either: recruiting, not yet recruiting, active, or complete with no results available. They are described in the table below by expected completion date.

Identifier	Study Name	Location	Sponsor	Planned N	Study design	Intervention	Relevant Outcomes	Estimated completion	2022 Status
NCT02902822	Tele-dermatology of Skin Cancer in a Cohort of Local Health Authority Employees in the Province of Bergamo	Italy	Centro Studi Gised, Italy	461 patients	Randomized clinical trial	Web-based / smartphone app allowing patients to send photos of suspicious lesions	Skin cancer incidence	May 2019	Complete; no results available
NCT02352428	Skin Cancer Screening Education Study (SCSES)	Canada	Association of Dermatological Prevention, Germany	200 physicians (40,000-80,000 patients)	Population-based nonrandomized trial	Skin cancer screening training for family physicians and dermatologists	Diagnostic accuracy, harms, skin cancer incidence	September 2019	Active, not recruiting
NCT04534868	Patient Acceptance And Satisfaction of Teledermoscopy In General Practice In a Belgian Rural Area	Belgium	Cliniques universitaires Saint-Luc-Université Catholique de Louvain, Belgium	100 patients	Interventional clinical trial, single group assignment	Taking macroscopic and dermoscopic pictures of suspicious skin lesions	Patient acceptability of and satisfaction with teledermoscopy	March 2021	Not yet recruiting
NCT05148455	Pregnancy-related Changes in Melanocytic Nevi	Switzerland	University Hospital, Basel, Switzerland	50 females (pregnant and non-pregnant)	Observational cohort	Standard-of-care clinical skin examination	Change in psychological impact of skin cancer screening	February 2022	Active, not recruiting
NCT05246163	ARTIficial Intelligence-based Smartphone Application for Skin Cancer Detection (ARTIS)	Belgium	University Hospital, Ghent, Belgium	1500 patients	Observational cross-sectional	Skin cancer screening smartphone application (Skinvision App)	Diagnostic performance of skin cancer screening smartphone application	October 2023	Recruiting

Appendix References

Identifier	Study Name	Location	Sponsor	Planned N	Study design	Intervention	Relevant Outcomes	Estimated completion	2022 Status
NCT04358276	Technology-Enabled Activation of Skin Cancer Screening for Stem Cell Transplant Survivors and Their Primary Care Providers	United States	City of Hope Medical Center, National Cancer Institute (NCI)	720 patients	Randomized clinical trial	Educational intervention and text messages (for patients), dermatoscope and training (for physicians)	Receipt of physician skin exam, time to diagnosis of suspicious lesions	October 2024	Recruiting

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