Screening for Skin Cancer: A Summary of the Evidence

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Epidemiology

In 1999, approximately 1 million new cases of basal cell and squamous cell carcinoma, and about 44,000 new cases of malignant melanoma, were diagnosed in the United States.[1] Melanoma mortality is the sixth leading cause of cancer mortality, and incidence of melanoma and other skin cancers is increasing.[1]

Malignant Melanoma

In the United States, the lifetime risk of being diagnosed with melanoma is 1.74% in white men and 1.28% in white women.[2] The lifetime risk of dying of melanoma is 0.36% in white men and 0.21% in white women.[2] According to data from the California Cancer Registry, from 1988 to 1993, average, annual, age-adjusted incidence rates per 100,000 people were 17.2 for men and 11.3 for women for non-Hispanic whites; 2.8 for men and 3.0 for women for Hispanics; 0.9 for men and 0.8 for women for Asians; and 1.0 for men and 0.7 for women for non-Hispanic blacks.[3]

Between 1973 and 1995, the incidence of melanoma in the United States increased about 4% per year, from 5.7 per 100,000 in 1973 to 13.3 per 100,000 in 1995, according to data from the Surveillance, Epidemiology, and End Results program (SEER) of the National Cancer Institute.[2] The elderly and, in particular, elderly men, bear a disproportionate burden of morbidity and mortality from melanoma. In 1995, the age-adjusted incidence rate was 68.7 per 100,000 in white men aged over 65 years and 30.6 per 100,000 in white women aged over 65 years. Men aged over 65 years, who constitute 5.2% of the U.S. population, have 22% of newly diagnosed malignant melanomas each year; women aged over 65 years, who constitute 7.4% of the population, have 14%. In the United States, about 50% of deaths from melanoma are in men aged 50 years or older.[2] Some experts argue that the elderly, particularly elderly men, may have lower "skin awareness" and lower rates of skin self-examination, resulting in higher rates of advanced melanoma.[4]

Overall mortality from melanoma has increased. Between 1973 and 1995, overall mortality rates for

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The U.S. Preventive Services Task Force recommendations based on this evidence review can be found in Screening for Skin Cancer: Recommendations and Rationale (which precedes this chapter), available on the AHRQ Web site and through the AHRQ Publications Clearinghouse.

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melanoma increased by 1.3% per year, from 1.6 per 100,000 in 1973 to 2.2 per 100,000 in 1995.[2] Nearly all of the increase was in white men (2.2% to 3.6%), especially older white men. Five-year survival for melanoma has improved to 88% currently, from 80% 20 years ago. During this time, the rate of diagnosis of "early" or thin melanoma increased sharply, but so did the incidence of thicker (>3 mm) melanomas.[5] According to data from the California Cancer Registry, among men, melanoma is diagnosed after it has metastasized to a remote site for 15% of Hispanics, 13% of Asians, and 12% of blacks, compared with 6% of non-Hispanic whites. Among women, diagnosis is late stage in 7% of Hispanics, 21% of Asians, and 19% of blacks, compared with 4% of non-Hispanic whites.[3]

The thickness of the primary tumor is the strongest predictor of prognosis.[6] In general, melanomas less than 1 mm in depth have a very small chance of metastasizing. Five-year survival for those with melanomas between 1.5 mm and 4 mm is approximately 70%, and for those with melanomas thicker than 4 mm it is about 45%. Thickness of the melanoma also guides the choice of therapy.

Changes over time in ascertainment, diagnostic criteria, self-examination, and registry procedures make it difficult to draw reliable inferences about the effectiveness of early detection from epidemiologic data.[5,7,8] In an analysis of trends in Australia and New Zealand, Burton and Armstrong[9] noted that, although there has been a huge increase in the incidence of very thin melanomas, the incidence of thick melanomas has increased as well. Some experts interpret this to mean that increased surveillance in the population may detect a relatively unaggressive, unimportant type of thin melanoma.[8-11] According to this view, increased detection of these very thin, nonmetastasizing melanomas would increase the incidence and five-year survival rates of melanoma, but would have little impact on mortality. However, in contrast to prostate and thyroid cancers, in which a large reservoir of unaggressive cancers are known to exist, longitudinal studies of melanoma have not established the frequency or existence of histologically malignant, but behaviorally benign, melanoma in the general population.

Nonmelanoma Skin Cancer

Basal cell carcinoma and squamous cell carcinoma are the most common forms of skin cancer. In the United States, age-standardized basal cell cancer rates range from 175 to 1,073 per 100,000 in non-Hispanic white men and from 124 to 415 per 100,000 in non-Hispanic white women. Squamous cell cancer rates range from 63 to 214 and from 22 to 50 per 100,000 for non-Hispanic white men and women, respectively.[12-14] Squamous cell cancer accounts for the majority of skin cancer deaths in very eldery men and blacks.[15-17]

Squamous cell cancers usually occur in chronically sun-exposed areas of the skin, especially on the face, ears, or backs of the hands. Squamous cell cancer has the potential to metastasize and may account for up to 20% of deaths from skin cancer.[15,16] A large primary tumor (>2 cm) is associated with an increased risk of metastasis. While there is strong suspicion on clinical grounds that advanced locally invasive or metastatic nonmelanoma skin cancers result from medical neglect, careful studies of the rate of progress of nonmelanoma skin cancers in the elderly are lacking.

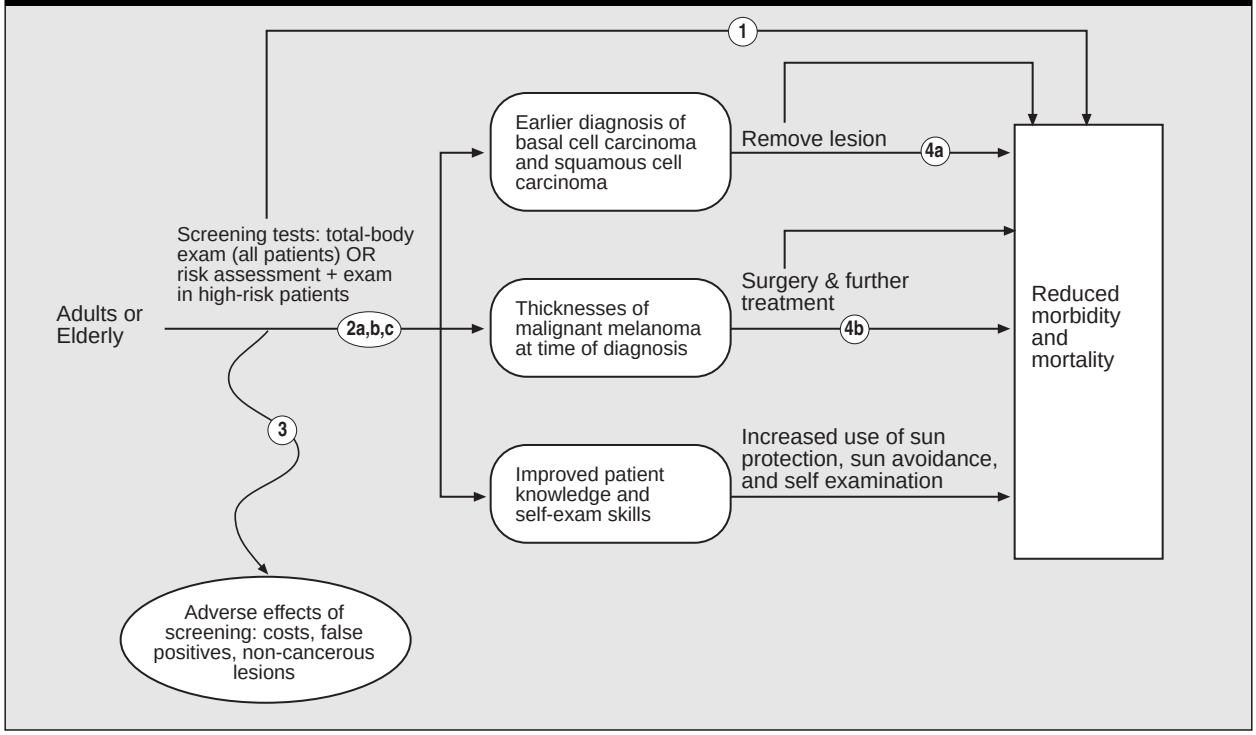
Early detection is commonly promoted as a way to reduce mortality from skin cancer. The purpose of this review is to update the evidence on the effectiveness of screening for skin cancer by primary care clinicians using periodic total-body skin examination or risk assessment tools since the U.S. Preventive Services Task Force's recommendation in 1996.

Methods

Available Interventions

We sought studies of the accuracy of 2 methods of screening for skin cancer: (1) routinely performing a total-body skin examination in all patients seen in the primary care setting, and (2) assessing the risk for skin cancer in all patients,

Figure 1. Screening for skin cancer: analytic framework



followed by a total-body skin examination in those found to be high risk. The primary aim of these strategies is earlier detection of melanoma, for which an examination confined to areas not covered by clothing is likely to miss a high proportion of potentially lethal cancers. To assess the accuracy of these methods, both for melanoma and for nonmelanoma skin cancer, we sought studies that used these initial tests to screen in the general population or in the elderly and then confirmed positive screening test results with skin biopsy results.

Analytic Framework

Figure 1 shows the populations, interventions, and outcome measures we examined. We did not find direct evidence from controlled studies of the effect of screening on health outcomes (Arrow 1) such as mortality and quality of life. We examined the consequences of screening on detection of squamous cell carcinoma and basal cell carcinoma (Arrow 2a), and on malignant melanoma (Arrow 2b). Specifically, we examined how often patients are found to have skin cancer, how often suspected skin cancer is confirmed by biopsy, and at what stage cancer is found. We also sought evidence about the effect of screening on patients' health beliefs and practices regarding skin cancer prevention, such as increased use of sun protection, sun avoidance, and self examination (Arrow 2c), and about the adverse effects of screening (Arrow 3).

Literature Search and Synthesis

We searched the MEDLINE® database for papers published from 1994 to June 1999, using search terms for screening, physical examination, morbidity, and skin neoplasms. For information on accuracy of screening tests, we used the search terms "sensitivity" and "specificity." We also used reference lists and expert recommendations to locate additional articles published after 1994. We identified the most important pre-1994 studies from the G*uide to Clinical Preventive Services*, second edition, and from high-quality reviews published in 1994 and in 1996; from reference lists of recent studies; and from experts. Two reviewers independently reviewed a subset of 500 abstracts. Once consistency was established, the remainder were reviewed by 1 reviewer.

We included studies if they contained data on yield of screening, screening tests, risk factors, risk assessment, effectiveness of early detection, or cost-effectiveness. We excluded studies of surveillance by skin examination in patients known to have familial atypical mole and melanoma syndrome.[18-20] Of 54 included studies, 5 contained data on accuracy of screening tests, 24 contained data on yield of screening, 8 contained data on stage or thickness of lesions found through screening, 11 addressed risk assessment, and 7 addressed the effectiveness of early detection (some studies addressed more than 1 topic). From each study we abstracted descriptive information and the number of referrals made, biopsies performed, and cancers diagnosed, and, when available, the type, stage, or thickness of cancers. For studies that reported test performance, we also recorded the definition of a suspicious lesion, the "gold standard" determination of disease, and the number of true-positive, false-positive, true-negative, and false-negative test results.

The positive predictive value (PV+) was computed in 2 ways to account for noncompliance in studies. The lower bound (Low PV+) of the predictive value was computed by dividing the number of patients with confirmed skin cancer by the number of patients who were diagnosed with a suspicious lesion. The upper bound (High PV+) was computed by dividing the number of patients with confirmed skin cancer by the number of patients who had biopsies. If the study provided sufficient detail, we calculated the PV+ of examination for each type of skin cancer. Most studies, however, did not report results in sufficient detail; for these, we combined the results for different types of skin cancer. We also calculated likelihood ratios (LR) using the formula:

LR={High PV/(1-High PV)}/{p(cancer)/(1-p(cancer))}

where p(cancer) is the observed prevalence of disease, estimated as

p(cancer)=(number of true positives + number of false negatives)/(number of patients screened).

Results

Accuracy of Tests

Examination of a biopsy specimen under a microscope is the "gold standard" for the diagnosis of melanoma. The pathologic diagnosis of suspicious pigmented lesions can be difficult, especially for borderline and in situ neoplasms. In 1 recent study, 4 histopathologists evaluated 140 slides and classified each lesion as "melanoma" or "other pigmented lesion"; they were in agreement on diagnoses for 74% (kappa=0.61) of the slides.[21] Similarly, when 8 expert pathologists (recruited based on publications and reputations) classified 37 slides as "benign," "malignant," or "indeterminate," they had unanimous agreement, or only 1 discordant, on 62% (kappa=0.50) of the cases.[22]

How Accurate are Risk-Assessment Tools as a Screening Test for Skin Cancer?

Established risk factors for melanoma include a high count of common moles >2 mm[23] and the presence of atypical moles.[24] The risk of malignant melanoma rises with the number of common moles, with relative risks of 1.7 to 1.9 for 11 to 50 moles, 3.2 to 3.7 for 51 to 100 moles, and 7.6 to 7.7 for more than 100 moles.[24,25] Similarly, the likelihood of melanoma increases several times the odds ratio (OR) range, 1.6 to 7.3 for patients with 1 to 4 atypical moles, compared to patients with no atypical moles.[24,25] A well-instructed patient can count the number of moles on the trunk or total body with sensitivity ranging from 0.57 to 0.79, and specificity of 0.88 to 0.97.[26,27] However, untrained patients cannot accurately distinguish atypical moles from others.[28]

Other risk factors for melanoma are red or light hair (OR range, 1.4-3.5); a few (OR, 1.9) or many (OR, 3.5) actinic lentigines; very heavy sun exposure (OR, 2.63); reported growth of a mole (OR, 2.3); skin that does not tan easily (OR, 1.98); a family history of melanoma (OR, 1.81); light eye color (OR range, 1.55-1.60); and light skin color (OR

range, 1.40-1.42).[24,25,29-31] The validity of some risk factors, such as hair color and sun exposure, is lower in the elderly.[25,32]

No longitudinal studies to predict melanoma using a risk assessment tool have been done in a primary care setting. A large, prospective study validated the use of an initial count of atypical moles in predicting the incidence of melanoma over 5 years.[33] In that study, 3,889 employees at the Lawrence Livermore National Laboratory had total-body skin examinations performed by a dermatology fellow specializing in melanoma. Atypical moles were diagnosed clinically using previously defined criteria: "ill-defined border; irregular border; irregularly distributed pigmentation; a diameter more than 5 mm; erythema (blanchable in lesion or at edge); and accentuated skin markings."[34] Seven percent of the subjects were in the highest-risk category, that is, they clearly had atypical nevi. This highest-risk group accounted for 56% (5/9) of the subjects who developed melanoma over 5 years. By contrast, 64% of the patients were in the lowest-risk category, that is, they had no atypical moles. This lowest-risk group accounted for 11% (1/9) of the patients who developed melanoma.

No prospective evidence is available linking risk assessment by limited physical examination with incidence of melanoma, but 1 well-done prospective study demonstrated that this strategy could identify a relatively small (<10%) group of primary care patients for more thorough evaluation.[35] Most of the high-risk patients were not aware of their high-risk status.

How Accurate is Total-Body Skin Examination in the Detection of Skin Cancer?

Table 1 summarizes 5 recent prospective studies of the accuracy of skin examination in screening programs. In all studies the participants were self-selected individuals who responded to an advertisement that may have emphasized skin cancer risk factors. In some studies, total-body skin examinations were performed on all participants; in others, the examination focused on specific lesions identified by the patient. One study examined the accuracy of skin examination by a primary care physician;[36] in the others, examinations were conducted by dermatologists.

Only 1 of the studies in Table 1 followed up with patients to determine the false-negative rate of a screening skin examination. Overall sensitivity of the initial examination was 94%, and specificity was 98%. For a patient with a negative initial skin examination, the probability of having no skin cancer on follow-up was 0.998.[37]

The last study shown in Table 1 focuses on detection of melanoma in self-selected individuals.[38] The study demonstrated that dermatologists found lesions suspicious for melanoma in a very small proportion of individuals. In this study, 282,555 members of the general public were recruited to free examinations without regard to risk factors for skin cancer. Clinical suspicion was classified as "suspected melanoma" or "rule-out melanoma." Only 0.3% (n=763) of the participants had a clinical diagnosis of suspected melanoma; of these, 679 patients had a biopsy and 130 had melanoma (positive predictive value=0.19). The use of a lower cut-off, "rule-out melanoma," identified an additional 234 patients with melanoma, but an additional 2,316 patients without melanoma were biopsied (positive predictive value=0.09). Interestingly, compliance with biopsy was significantly lower for participants given a diagnosis of "rule-out melanoma," 0.69 compared to 0.89 for patients with a diagnosis of "suspected melanoma."

Several studies have examined the accuracy of primary care physicians' assessments of photographs of skin lesions or of preselected patients with lesions, using the histologic diagnosis as the reference standard. A recent review summarized studies that used color slides (rather than actual patients) to test physicians' accuracy in predicting the histologic diagnosis (mostly nonmelanoma skin cancer).[39] When these studies were combined, dermatologists performed better (93% correct) than family medicine attending physicians (70% correct) and internal medicine attending physicians (52% correct). Another recent review found that, in studies that used photographs or selected patients with known lesions, use of the ABCD(E) system

Table 1. Skin cancer screening accuracy

Author	Study sample and setting	Recruitment focus	Patients n	Index test	PCP or d	Defn. of susp. lesion
Screening for all skin cancer						
de Rooij et al[45] Rampen et al[37]	Volunteers for skin cancer screening in the Netherlands	Patients with skin cancer risks	1,961	Lesion-specific exam or TSE	d	Skin cancer
Limpert[36]	Free skin cancer clinic at family physician's office	NR	247	TSE	PCP	Skin cancer
de Rooij et al[46]	Volunteer melanoma screenings in the Netherlands following a public campaign on melanoma and risk factors	Patients with melanoma risk	4,146	Lesion-specific exam or TSE	d	Skin cancer
Jonna et al[43]	Free skin cancer screening in San Diego for self-selected high risk	Patients with skin cancer risk	464	TSE	d	Skin cancer
Screening for melanoma						
Koh et al[38]	Volunteer skin cancer education and screenings by the American Academy of Dermotology	Not targeted	282,555	NR	d	Suspected melanoma
Koh et al[38]	Volunteer skin cancer education and screenings by the American Academy of Dermotology	Not targeted	282,555	NR	d	Rule out

continued

[a]The overall probability of cancer was calculated as the total number of cancers diagnosed divided by the number of patients screened.

[b]Methods for calculating the high and low estimates of predictive value and likelihood ratios are described in the text.

[c]Proportion of patients referred for biopsy who actually had one.

[d]Method for estimating likelihood ratio of a positive test is described in the text.

Note: BCC indicates basal cell carcinoma; d, dermatologist; Defn. of susp. lesion, definition of suspicious lesion; MM, malignant melanoma; NR, not reported; PCP, primary care provider; SCC, squamous cell carcinoma; TSE, total skin examination

(asymmetric [A], irregular border [B], varied color [C], diameter (6 mm [D], elevation or enlargement [E]); or the seven-point checklist (change in mole size, shape, and color; crusting or bleeding; sensory change; diameter >7 mm) had a sensitivity of 50% to 97% and a specificity of 96% to 99% for the histologic diagnosis of skin cancer.[40] Nondermatologists' examinations were less sensitive than examinations performed by dermatologists. Many of these studies were small and used convenience samples of attending physicians at academic medical centers. More importantly, these studies did not examine the accuracy of a total-body skin examination or the ability of physicians to efficiently identify suspicious lesions in the setting of a screening program.

One well-designed British prospective study of the accuracy of total-body skin examination found that skin cancer specialists' decisions about biopsy were more sensitive and much more specific than those of general practitioners.[41] Four skin cancer specialists and 63 randomly selected general practitioners (GPs) in part of Australia performed total-body skin examinations on 109 selected

Table 1. Skin cancer screening accuracy (continued)

Suspicious lesions n	Suspicious lesions %	Probability of cancer[a]	BCC/skin cancer %	MM/skin cancer %	SCC/skin cancer %	Positive predictive value[b] Low	Positive predictive value[b] High	Biopsy rate[c]	Likelihood ratio[b,d]
93	4.7	0.031	85.1	12.8	2.1	0.51	0.54	0.935	37.32
51	20.6	0.057	92.9	7.1	0.0	0.27	0.42	0.647	12.26
173	4.2	0.011	73.5	26.5	0.0	0.28	0.30	0.912	37.95
132	28.4	0.060	85.2	11.1	3.7	0.21	0.58	0.364	21.80
763	0.3	0.001	NR	NR		0.17	0.19	0.890	183.57
3,695	1.3	0.001	NR	NR		0.06	0.09	0.690	78.33

patients, 43 of whom had suspicious pigmented lesions diagnosed previously by a skin specialist. The sensitivity of total-body skin examination for detecting suspicious lesions was 0.72 for the GPs versus 0.97 for 4 skin specialists. The positive predictive value for the GPs was 0.[39] Twelve (28%) of the 43 patients with suspicious lesions had melanomas. While the general practitioners' diagnoses were highly sensitive for melanomas (0.97), they classified about 11 benign lesions as suspicious for each melanoma. For the 4 dermatologists, the ratio was 2.1 benign lesions to 1 melanoma.

Because the proportion of patients who had suspicious lesions (and melanoma) was much higher in this study than would occur in actual practice, the positive predictive value of primary care physicians' examinations would be lower in an actual screening program.

Results of Screening Programs

We examined the consequences of screening reported in 26 recent reports of screening programs.[33,36-38,42-63] In these studies, rates of suspected melanoma in mass screening, casefinding, and population-based screening range from 0 to 9 per 100 people screened, with the most common findings between 1 and 3 per 100. Most studies have found from 2 to 10 suspected nonmelanoma skin cancers per 100 screened.

Rates of confirmed melanoma and melanoma in situ were consistently in the range of 1 to 4 per 1,000 people screened, with 2 exceptions. An Australian study that targeted high-risk people[48] had a rate of 8 confirmed melanomas per 100 people screened. The other, a population-based study in Sweden,[55] had no confirmed melanomas of 152 suspected melanomas in 1,654 people screened. In

the largest screening study,[38] 213 confirmed melanomas were diagnosed in 282,555 people, of whom 4,458 had lesions suspicious for melanoma.

Eight studies reported the number of histologically confirmed nonmelanoma skin cancers. The prevalence varied widely, from 0.05 of people screened to 0.0004, with most reporting between 0.01 and 0.05.

In the 24 screening studies, rates of referral for follow-up care of suspicious lesions ranged from 2 to 34 per 100 people screened. From 4 to 31 biopsies per 100 people screened were performed. Among patients with suspected melanoma, from 0% to 17% had a final diagnosis of melanoma. Among all patients who underwent a biopsy, about 3% proved to have a melanoma (range 0% to 4%).

The use of total-body skin examination, as opposed to a partial examination or an examination that focused on a lesion the patient identified, did not appear to increase the rate of confirmed melanomas. In 1 study,[64] 2,910 of 4,146 (70%) people screened complained of at least 1 skin lesion. When these lesions were examined, 13 melanomas and 44 nonmelanoma skin cancers were diagnosed on biopsy. For these patients who originally came in with specific lesions, an additional total-body skin examination was offered. For the 1,356 patients who went on for a total-body skin examination, no malignant melanomas and 3 basal cell carcinomas were identified.

Effectiveness of Early Detection

Screening in a population is justified if there is evidence that early detection and treatment reduce mortality and improve quality of life. Other issues to be considered include consequences of false-negative and false-positive tests, acceptability of the test, and the risks of screening and of treatment.

Compared to Usual Care, How Much Earlier Does Screening Detect Skin Cancers and Precancerous Lesions?

No study of screening directly followed an unscreened population to compare the distribution of thickness or stage of melanomas detected. Nonetheless, the proportion of thin melanomas is clearly higher in screening programs than in usual care. In an analysis of SEER data from 1992 to 1994,[a] 57% of melanomas were thinner than 0.76 mm, 23% were 0.76 to 1.5 mm, 15% were 1.51 to 3.99 mm, and 5% were 4.0 mm or thicker.[38] In population-based studies, moreover, the incidence of melanoma detected by screening is higher than base rates, and the increase is almost entirely attributable to thin melanomas.

Is There Direct Evidence That Screening for Skin Cancers Leads to Reduced Morbidity and Mortality?

No randomized trials or case-control studies of screening for skin cancer have been completed. The absence of randomized trials is not surprising because melanoma is relatively rare in the general population. A recent review by Elwood[65] examined the options for conducting a randomized trial of screening in detail. Elwood calculated that to have a 90% chance of detecting a one-third reduction in mortality, a trial of screening with total-body skin examination in the general population aged 45 to 69 would require 400,000 subjects in each group. Put differently, about 21,000 people would need to be screened to prevent 1 death. An alternative would be to conduct a trial in patients classified as high risk by a risk assessment questionnaire. Using this approach, Elwood assumed that 7% of the population would be classified as high risk; 35% of all melanomas occur in this high-risk group; 60% of patients complete the questionnaire; and 80% of the high-risk patients would comply with total-body skin examination. He calculated that to have a 90% chance of detecting a one-third reduction in mortality, 6 million questionnaires would need to be administered to enroll 100,000 high-risk subjects in each group. In fact, a trial involving 600,000 subjects has begun in Australia and is expected to require 9 more years to complete.

[a]The SEER registry routinely reports the tumor, node, metastases (TNM) stage, but not the thickness, of melanomas at the time of diagnosis. From 1989 to 1994, 81% of melanomas detected through usual care were localized, 9% regional, 4% distant, and 6% unstaged.

There are no case-control studies of screening for skin cancer. One case-control study has examined the effect of skin self-examination on mortality from melanoma.[29] In this study, 650 incident cases of melanoma in 1987-1989 were identified through the Connecticut Tumor Registry and compared with randomly selected, age- and gender-matched controls. After 5 years of follow-up, cases were classified as "lethal" if the individual died or had distant metastases. A structured questionnaire was used to assess skin self-examination attitudes and behavior. The definition of skin self-examination used in this study was "[D]id you ever (in your life) carefully examine your own skin? By this I mean actually check surfaces of your skin deliberately and purposely?" Based on their responses to this and related questions, 13% of the cases and 17.5% of control subjects were classified as careful or rigorous examiners, and an additional 57.4% of cases and 66.7% of controls were classified as casual examiners.

The investigators performed 2 multivariate analyses: 1 for primary prevention and 1 for secondary prevention. In the first analysis, after adjustment for sun exposure, skin color, the number of nevi, and other risk factors, skin self-examination was negatively associated with incidence of melanoma (OR, 0.66; 95% CI, 0.44-0.99).[29]

In the second analysis, after adjustment for confounding risk factors, skin self-examination was associated with a reduced risk of lethal melanoma (OR, 0.37; 95% CI, 0.16-0.84). Survival analysis comparing patients who practiced skin self-examination with those who did not suggested that, after an average of 5.4 years, self-examination was associated with a lower probability of lethal melanoma. The authors noted that the shape of the survival curves—the curve for the self-examination group plateaus after 3 years, while survival continues to decrease up to 5 years in the patients who did not practice self-examination—offers some reassurance that the observed benefit is due to actual improvement in survival rather than to lead-time bias.[29]

As noted by the authors, this case-control study provides suggestive, rather than definitive, evidence for the effectiveness of skin self-examination. While the study indicates that patients who practiced self-examination had undergone more biopsies than those who had not, it does not report the frequency of these intermediate steps, or whether their frequency was different enough from that of other patients to explain the observed differences in outcome.[29]

Apart from concerns about the strength of the study design, how relevant is a study of skin self-examination to screening by primary care providers? If skin self-examination prevents death from melanoma, it may be more likely that examination by a physician could also prevent deaths, especially if examination by a physician promotes more accurate self-examination. In fact, case finding by a physician might be expected to be more effective because it reaches patients, especially elderly men, who are at high risk and are the least likely to practice self-examination effectively[66] or respond to an invitation or health promotion campaign. However, self-examination occurs much more frequently (monthly, on average, in the case-control study) than screening by a physician and can note findings—in particular, changes in size, border, or color of lesions—that cannot be recognized easily by infrequent examinations.Well-done, frequently cited observational studies of the relationship between early detection and mortality have been done,[67] but in such studies the effect of promoting primary prevention and self-examination cannot be distinguished from that of routine screening in patients seeing the physician for unrelated reasons.[68]

Does Treatment of Melanoma Found by Screening Reduce Morbidity and Mortality?

In the absence of randomized trials and case-control studies of screening or of early treatment, the inference that earlier treatment as a result of screening improves health outcomes must rely on (1) comparison of the stages of cancers and mortality found in screening to those found in usual practice,

and (2) evidence from studies of the consequences of delay in diagnosis. These are summarized below.

Stages of cancers and mortality found in screening versus usual practice. Advocates cite the results of public information campaigns in Australia and the United Kingdom as evidence of the potential benefits of early detection.[67,69] However, these programs emphasized primary prevention and self-examination, so is not possible to determine what role, if any, screening by physicians has played. In the West of Scotland study,[67] melanoma thickness and mortality decreased after implemention of a public information campaign and rapid referral system in 1985. A subsequent implementation of a similar program in 7 British districts failed to replicate these results.[60,70,71] The incidence rates of both thin and thick melanomas increased during the public information campaign (1987–1989) and have remained higher than before the program began.

Retrospective studies of the consequences of delay in diagnosis. Nine case series examined the causes and consequences of apparent delay in the diagnosis of melanoma. The validity of these studies is questionable because all of them assessed delay retrospectively. The 2 largest studies, 1 from Scotland and the other from Australia, found no relation between delay in diagnosis and tumor thickness.[60,72] The Australian study found that male sex, nodular melanoma, and location on the head and neck (but not delay) were associated with thick melanoma. Five studies, which were performed in specialty clinics, observed patients with melanoma of the hand, foot, eye, penis, or nailbeds.[73-77] In these studies, misdiagnosis was a common cause of delay in treatment. Effects of delay on tumor thickness or survival were reported in 3 of the studies, and the results were inconsistent.[73,77,78]

Two recent case series from specialized clinics in major referral centers reported that lesions detected by physicians were thinner than those detected by patients.[79,80] In 1 of these,[79] 24 of 102 consecutive patients had physician-detected melanomas; the median thickness was 0.23 mm versus 0.9 in self-detected melanomas. Eleven of the 24 physician-detected melanomas were in situ. In the other study,[80] 172 of 590 consecutive patients had physician-detected melanomas; these were significantly thinner, but the difference was not as striking (0.9 mm vs 1.3 mm). The latter study[80] concluded that poor prognosis was due to rapidly growing tumors rather than delays.

Does Treatment of Nonmelanoma Skin Cancer Found by Screening Reduce Morbidity and Mortality?

Early treatment of basal and squamous cell carcinoma might reduce morbidity and disfigurement, but no studies have evaluated whether screening improves the outcomes of these cancers.

Aside From Cancer Detection, are There Other Potential Benefits of Screening?

Advocates of screening note that having a total-body skin examination might increase skin awareness and sun protection measures. In a follow-up study to the American Academy of Dermatology's melanoma/skin cancer screening programs (see reference to Koh et al[38] in Table 1), 1,049 self-selected screening participants who had skin lesions were surveyed 2 months after undergoing a total-body skin examination. Among the 643 respondents, the proportion of individuals who regularly checked their skin increased from 60% to 84% after screening.[81] Patient satisfaction with screening was high (81%), and only a small proportion of patients reported embarrassment or discomfort as a result of screening (4.8%).[81]

Harms of Screening

In skin cancer screening programs, most lesions referred for biopsy are found to be false positive for skin cancer. There are no studies by which to judge the extent of harm, if any, related to these tests.

Misdiagnosis is another potential adverse effect of screening. The diagnosis of melanoma has a serious emotional and financial impact, and even when the melanoma is very thin and has an excellent prognosis, obtaining insurance can be very difficult.[8] Critics worry that, if screening becomes widespread, pathologists may set the threshold low for

diagnosing borderline lesions as melanoma, since the risk to the patient and the potential legal cost to the pathologists for missing melanoma are overwhelming.[10] However, there are no data about the frequency with which misdiagnosis occurs in community practice settings.

Screening detects large numbers of benign skin conditions, especially seborrheic keratoses, which are very common in the elderly. Detection of these lesions could be considered an "adverse effect" of screening if it leads to additional biopsies and unnecessary or expensive procedures. While this has been shown to occur in usual care,[82] none of the studies of screening examined the rate at which this occurred.

Cost-Effectiveness

A cost-effectiveness analysis of screening for malignant melanoma[83] found that the average projected discounted life expectancy without screening was 15.0963 versus 15.0975 with screening. This difference is equivalent to an increase of about 9 hours per person screened or 337 days for each person with melanoma.

Assuming that a screening examination by a dermatologist costs $30, the incremental cost-effectiveness (CE) ratio was $29,170 per year of life saved. The CE ratio was unexpectedly low because, in the model, savings from prevention of late-stage melanomas offset most of the costs of screening. Thus, the key assumptions in the model, affecting the calculation of both effectiveness and cost, were that the proportion of late stage melanomas would decrease from 6.1% without screening to 1.1% with screening. Similarly, the model assumed invasive cancers would decrease from 70.3% to 58.1%, and melanomas thicker than 1.5 mm would decrease from 20.1% to 12.6% of invasive melanomas. These assumptions are based on comparison of cross-sectional data on the stages of melanoma in individuals who attended the American Academy of Dermatology's mass screening programs to data on usual care from the SEER registry.

Discussion

Table 2 summarizes the literature review by describing the evidence for each link in the analytic framework. The quality of the evidence at each link ranged from poor to fair. The effectiveness of early detection in reducing melanoma mortality and other clinical outcomes is uncertain. Studies of early detection have not focused on screening and have not adequately linked it with reduced incidence of invasive disease.

Community trials of screening are underway in Australia, but will take many years to complete. In the meantime, observational studies should address the potential harms of screening, including mislabeling, unnecessary biopsies, and the direct and indirect costs of screening programs. Gaps in our knowledge of the progression to thick melanoma in the elderly should also be addressed. Better information is needed about the natural history of thick nodular melanoma, the type typically found in the elderly, since there is little evidence that lethal tumors in this group could be detected while still in a curable stage.

Future research is also needed to help the clinician identify primary care patients at high risk for melanoma. Skin cancer screening using a risk assessment technique to identify high-risk patients is the most promising strategy for addressing the excess burden of disease in the elderly. Observational studies should assess the validity, reliability, and feasibility of standardized, brief risk assessments used to identify these patients. These assessments should incorporate age, mole counts, and a count of atypical moles, the best established risk factors for the later development of melanoma. Trials of validated risk assessment programs in the primary care setting, as well as more data regarding the accuracy of skin examination conducted by specialists and primary care clinicians in routine clinical practice, are needed.

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Table 2. Summary of evidence for screening for skin cancer

Linkage in analytic framework	Evidence code	Quality of evidence
1a. Accuracy of total-body skin examination: evidence that total-body skin examination can detect skin cancer.	II-2	Fair: The accuracy of a total-body skin examination by primary care physicians in unselected patients may be low. Reliability of pathologic diagnosis in community practice in the United States is not known.
1b. Accuracy of risk-assessment: evidence that a questionnaire or interview, followed by examination in selected patients, can detect skin cancer.	II-2	Fair: Mole counts and other factors predict elevated risk over time, but no study has determined the accuracy of risk stratification followed by total-body skin examination in selected patients as a screening method.
1c. Effect of screening on patients' skin knowledge and self-care behavior (use of sun protection, sun avoidance, and self-examination).	II-2	Poor: Patients with skin lesions who attended skin cancer screenings increased their rate of performing skin self-examination. However, there is no evidence about the effect of screening or skin knowledge on sun protection behaviors.
2. Adverse effects of screening: evidence that screening causes significant harms.	III	Poor: most postulated adverse effects have not been evaluated in studies.
3. Effectiveness of early detection: evidence that persons detected through screening have better outcome than those who are not screened.	II-3	Poor: There are no studies that directly link screening to lower mortality and morbidity. Most well-done, population-studies concern promotion of self-care based behaviors such as self-examination rather than universal screening.
4a. Effectiveness of treatment of nonmelanoma skin cancer found by screening.	III	Poor: The hypothesis that early detection by screening could reduce mortality and morbidity is plausible but has not been examined in studies.
4b. Effectiveness of treatment of melanoma found by screening.	II-1, III	Fair: There are no controlled studies of treatment in patients found by screening to have thin melanomas, but epidemiologic studies, studies of skin health behaviors, and studies of factors associated with advanced melanoma suggest that elderly men are at high risk and are unlikely to benefit from health promotion efforts. Studies of delay in diagnosis have conflicting results, and the ability of screening to reach individuals at high risk and to find aggressive tumors while they are still curable have not been established.

Note: I: Randomized controlled trial; II-1: Controlled trial without randomization; II-2: Cohort or case-control analytic studies; II-3: Multiple time series, dramatic uncontrolled experiments; III: Opinions of respected authorities, descriptive epidemiology

This article is based on a more comprehensive Systematic Evidence Review, which is available on the AHRQ Web site. (www.ahrq.gov/clinic/uspstfix.htm). That document was reviewed by content experts, including Marianne Berwick, PhD, MPH, Memorial Sloan-Kettering Cancer Center; Allan C. Halpern, MD, Memorial Sloan-Kettering Cancer Center; R.A. Swerlick, MD, Emory University School of Medicine; and professional organizations, including the American Academy of Family Physicians, the American College of Obstetricians and Gynecologists, the American College of Preventive Medicine, and the American College of Physicians/American Society of Internal Medicine; and public health organizations, including the Canadian Task Force on Preventive Health Care, the Indian Health Service, the National Cancer Institute, the National Institutes of Health, and the Centers for Disease Control and Prevention. Review by these individuals and groups does not necessarily

imply endorsement of this article or of the accompanying recommendations of the U.S. Preventive Services Task Force.

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