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Screening and Prevention Measures for Melanoma: Is There a Survival Advantage?

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Abstract

Controversy has emerged over the past decades regarding the value and impact of melanoma screening to detect early stage disease for improved prognosis. Those questioning the benefits of prevention efforts base their arguments on the absence of prospective, randomized studies demonstrating decreased melanoma mortality to justify the cost associated with screening and educational campaigns. For those in favor of melanoma screening, the lack of proven survival benefit is not a justification to abandon this approach, but rather a reflection of the lack of resources necessary to conduct a long-term trial. In 2009, the US Preventive Services Task Force (USPSTF) report did not recommend routine primary care screening for the general population given the absence of evidence. However, since the USPSTF report, a series of new studies are available, which support the potential benefit of screening and have the potential to significantly impact current policies regarding skin cancer screening, particularly for melanoma.

Keywords

Cutaneous melanoma; Surveillance; Survival; Prevention; Early detection

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Introduction

While marked therapeutic discoveries have been recently achieved for advanced melanoma, a significant proportion of patients continue to be diagnosed with thicker primary lesions, with increased risk of metastasis, and death. Although an increased melanoma incidence in young women (<40 years) in the US has been reported, suggesting a potential link to indoor tanning bed use [1–4, 5•], overall melanoma incidence has largely stabilized in recent years, mainly in the youngest age group (25–44 years) [6•]. This is in direct contrast to the steady increase in incidence in individuals born through the late 1940s, suggesting the potential effectiveness of primary prevention in younger age groups and highlighting older subpopulations at higher risk of developing melanoma. Similar trends have been observed in Australia, New Zealand, Canada, and Norway, although incidence rates continue to rise in Southern and Eastern Europe [6•].

With respect to mortality, whereas most early detectable cancers such as colorectal, breast, cervical, and prostate have demonstrated substantial declines over the past 3 decades, melanoma mortality rates have continued to rise and have only recently begun to stabilize [7, 8].

Identification of those individuals at risk of developing primary melanoma based on known predisposing risk factors and those at higher risk of dying from disease (eg, Caucasian men >50 year of age) presents an opportunity to target the right individuals for more effective melanoma screening [9–12]. The accessibility of the skin for both self- and physician examination coupled with the ability to readily identify those at greatest risk of developing and/or dying from disease should support the concept of targeted melanoma screening.

Although several recent studies suggest that prevention can halt and reverse the observed increasing burden of melanoma with an expected impact in mortality, there is still a significant need to effectively implement prevention strategies in countries that have not adopted guidelines inline with the most recent data.

Herein, we review the perceived barriers for implementation of melanoma screening and current direct and indirect data on the impact of primary and secondary prevention with respect to incidence, tumor thickness, and associated mortality rates using a worldwide approach, and with a particular focus on implementation in the United States. We also review some of the limitations regarding the effectiveness of screening efforts, including potential “over diagnosis” and the socio-economic cost of such, inconsistent melanoma reporting, difficulty of early identification, and effective surgical management of rapidly developing melanomas, and challenges of reaching out to certain high-risk groups.

Barriers and Proposed Solutions for Effective Implementation of Primary Prevention and Early Detection Interventions

Primary Prevention

Reducing rates of sunburn through sun avoidance during periods of peak UV radiation and the adoption of protective measures when exposed are methods that theoretically could reduce melanoma risk, thus promotion of these protective health behaviors is important. Reported estimates of sunscreen use vary considerably across studies, ranging from 7 % to 90 %. Adherence to sun protection recommendations is associated with several factors, including: female gender, sun-sensitive phenotype, greater perceived risk of skin cancer, greater perceived benefits of sun protection or screening, and physician recommendation for screening [13]. Sun-sensitivity is an important factor as those who burn easily are more likely to use sun protection [14, 15]. Individuals with lighter hair color (blond or red) are

more likely to participate in protective behaviors than people with dark hair. Persons who minimize the risk of sunbathing and who think it is worth becoming sunburned to obtain a tan tend to use less sunscreen [16, 17]. Common reasons not to use sunscreen include the perception that its application is time consuming and inconvenient and that sunscreen use reduces the likelihood of getting a desired tan [15, 18].

In contrast, individuals with better knowledge, higher skin cancer awareness, and those who perceive themselves as being at risk of developing skin cancer are more inclined to report greater use of sun protection measures [15]. Even if the desire and intent to engage in sun protective practices are present, public health implementation remains a significant challenge, and a large proportion of the general population practices suboptimal sun protection, although there is substantial variability in findings [13]. For example, at least 1 severe sunburn has been reported in over 27 % of individuals in the preceding year from diagnosis [19]. Although participants in this study reported the adoption of sun protection measures, the frequency or thoroughness of protection was evidently insufficient to avoid severe sunburn.

Recent work by Linos et al suggests that the general population who report using sunscreen are not doing so effectively, as evidenced by their higher serum vitamin D levels compared with those who use barrier methods and sun avoidance [20]. These studies emphasize the importance of seeking shade and using sun protective clothing in addition to sunscreen, when disseminating a sun protection message.

Secondary Prevention (Early Detection)

The importance of early diagnosis of melanoma cannot be overemphasized, as epitomized in the current TNM staging system and corresponding survival rates for the different stages of disease [21]. Moreover, there is now increasing evidence that a visual inspection of the skin by individuals or health care provider may result in reduced thickness of melanoma at diagnosis and leading to improved survival [22–25]

The critical elements responsible for effective self-identification of lesions suspicious for skin cancer by the general population include increased public awareness and knowledge of the skin self-examination (SSE) practices, physician teaching of the SSE, and consistent performance by patients. Between 23 % and 61 % of individuals self report engaging in SSE at least once per year [26–32], and the documented prevalence of annual clinical skin examination by a health care provider is inconsistent across countries and provider types, ranging from only 8 % to 21 % [33–37]. The American Cancer Society recommends thorough SSE of all body areas, including the back, back of the legs, and scalp [38], areas that are difficult to inspect. However, the prevalence of such behavior is low in the general population. In a population based telephone survey in Queensland, Australia, [26] 26 % of participants self-examined the skin of their whole body at least once in the past year, but only 20 % of men 50 years or older did so. For at-risk populations, a number of small trials have successfully increased SSE [26, 39–41]. Other studies have demonstrated that intervention with tailored information, using videos and telephone reminders may increase the prevalence of SSE [42].

The complementary approach to SSE, which entails skin examination by a health provider, has also demonstrated a series of challenges. Both dermatologists and primary care physicians (PCPs) must align efforts to meet these demands since the dermatology workforce shortage precludes dermatologists from achieving this goal on their own [43•]. PCPs often see patients with skin complaints, and they can serve as an important point of skin cancer diagnosis and triage for Americans, who make an average of 1.7 visits to PCPs each year. PCPs are thus well positioned to detect early melanoma and, not surprisingly, the

initial presentation of melanoma is often to PCPs, who perform initial biopsy of 1.4 %–13 % of all melanomas.

However, published data suggest that PCPs in the US may not be prepared or sufficiently trained to identify early skin cancer [44, 45]. Most physicians have minimal exposure to skin cancer exam practices during medical school and residency, resulting in lack of confidence in skin cancer diagnosis and effective patient assessment which ultimately translate into barriers to routine skin exams by PCPs [43•]. An effective training program is therefore essential to increase the efficacy of clinician skin examination and its impact on melanoma mortality reduction. A number of web-based educational programs have been designed for this purpose, including an interactive case-based program called INFORMED (INternet-based program FOR Melanoma Early Detection), available at www.skinsight.com/info/for_professionals/skin-cancer-detection-informed/skin-cancer-education. In addition, lower socioeconomic status and reduced access to medical evaluation in individuals who lack health insurance poses additional challenges to physician-based melanoma detection [46].

Barriers and facilitating factors to skin cancer screening practices via whole body skin examinations (WBSE) among US PCPs and dermatologists have been evaluated through surveys delivered to randomly-selected physicians [47]. With an overall response rate of 59.2 % (1669/2999), more dermatologists (81.3 %) reported performing WBSE on patients than did family practitioners (59.6 %) ($P<.05$) or internists (56.4 %) ($P<.05$). Among all physicians, time constraints, competing comorbidities, and patient embarrassment were reported as the top 3 barriers to performing WBSE. Facilitating factors among all physicians included having patients at high risk for skin cancer, patient demand for complete examination/mole check, and the influence of medical training.

Based on the above-reported studies the implementation of consistent SSE and comprehensive skin examinations by healthcare providers in at-risk populations can be properly implemented through effective educational and training programs [48].

However, the implementation of methods for early melanoma detection in the general population must account for the variability in racial distribution and genetic melanoma susceptibility among and across different countries. In the US, which encompasses a broad range of skin phenotypes, early detection strategies will be considered more cost-effective if implemented in a defined at-risk population.

Is Therapeutic Prevention an Alternative to Decrease the Risk of Developing Melanoma in High-Risk Patients?

A relatively unexplored strategy to reduce cutaneous melanoma (CM) risk is therapeutic prevention or chemoprevention, defined as “the use of natural or synthetic agents to delay, reverse, suppress, or prevent premalignant molecular or histological lesions from progressing to invasive cancer”, especially in high-risk groups, including those with prior personal or significant family history of melanoma, or/and those with atypical nevi, which may serve as nonobligate biologic intermediates in melanoma tumorigenesis [49]. Long-term use of chemopreventive agents is likely to be required for successful cancer prevention, and effectiveness is often limited to the period of use. Commonly used drugs with a safety profile that is acceptable and other potential health benefits represent the most attractive candidates for therapeutic prevention. Some of these agents include non-steroidal anti-inflammatory drugs (NSAIDs), in particular acetylsalicylic acid (ASA), epigallocatechin (in green tea), resveratrol, curcumin, and vitamin D [50–54]. A series of recent case control and cohort studies using a variety of epidemiological methods indicate a potential protective effect of NSAIDs in the setting of cutaneous melanomas [54, 55•, 56•]. In addition, a

randomized placebo controlled trial of sulindac in atypical nevi patients documented the effective delivery of sulindac metabolites to the study nevi, suggesting that an oral administration route could provide an effective means for melanoma chemoprevention [57•]. In the case of lipid lowering agents (LLAs), in particular statins, the majority of the epidemiological studies to date have failed to demonstrate a protective effect in the setting of CM. Future intervention studies to explore the effect of NSAIDs and other agents on intermediate end-points including melanoma biomarkers will be of value to determine the value of this type of approach in melanoma prevention.

What Indications Do We Have That Primary Prevention and Screening of Melanoma Can Ultimately Decrease Mortality/Increase Survival?

Research Trials Have Shown Some Evidence on the Value of Primary Prevention

Melanoma control measures were instituted in Australia decades ago, with early detection programs beginning in the 1960s and primary prevention in the 1980s. An analysis of incidence trends for in situ and invasive melanoma from the Queensland Cancer Registry between 1982–2002 by Coory et al demonstrated proportionately more in situ melanomas over time (10.4 % increase per year in men, 8.4 % in women). Thickness data from 1991–2002 showed a faster increase in thin invasive melanoma incidence compared with thick invasive lesions, although mortality rates were stable across all ages. The authors concluded that after a substantial period of sustained primary prevention efforts in Queensland, there is “suggestive, but not definitive, evidence that progress is being made” and noted that potential decreases in melanoma incidences will likely not be forthcoming for at least 20 years [58•].

A more recent analysis of melanoma thickness distribution based on time trends and latitudinal differences in Australia was conducted by Baade et al from 1990–2006 and demonstrated marked increases in thin (<1 mm) melanoma in both men and women during the early 1990s, which then stabilized between 1996 and 2006 [55•]. Reductions in thin melanoma incidence were observed in younger (<age 50) but not older men and women, suggesting an impact of early detection and skin awareness campaigns rather than primary prevention. In addition, rates of thick melanomas continued to increase over the entire period in both men and women, making the results difficult to interpret in terms of a potential primary prevention benefit on melanoma mortality [59].

Research Studies Have Shown Supportive Evidence on the Value of Early Detection Through SSE and Screening

Self Skin Examination—The effectiveness of SSE practices in early melanoma detection includes a case-control study by Berwick et al [22] demonstrating a potential reduction in melanoma mortality by as much as 63 %, with mean thickness of melanomas significantly reduced in the patients who performed SSE compared with those who did not. Pollitt et al [24] showed that the thoroughness of SSE, as measured by the number of body sites examined and use of a picture aid illustrating a melanoma, was the best predictor of reduced melanoma thickness, and was associated with thinner tumors in patients who frequently examined at least some of their skin in the year prior to melanoma diagnosis (OR 2.66:95 % CI, 1.48–4.80). The effect of SSE was even greater in men and in older patients (>60 years) [60••].

While the United States Preventive Services Task Force (USPSTF) mentions insufficient evidence to recommend SSE for the general population, it recognizes the potential benefit in high-risk groups such as older men [61].

Screening—Numerous worldwide studies have demonstrated that physician detection of melanoma is associated with thinner tumors at diagnosis compared with patient detection (Table 1) [62]. The strongest evidence for improved melanoma outcome with physician skin screening was reported in a population based case control study by Aitken et al of all Queensland residents aged 20–75 years with histologically-confirmed first primary invasive melanoma, diagnosed between January 2000 and December 2003. This study [63•] demonstrated a 14 % lower risk of being diagnosed as having a thick melanoma following a clinician skin exam within 3 years of diagnosis, resulting in an estimated 26 % fewer melanoma deaths in screened cases vs unscreened cases within 5 years. Specifically, WBSE by a physician within 3 years of diagnosis was inversely associated with thickness (χ^2 test for trend=44.37, $P<0.001$), ranging from a 14 % lower risk of being diagnosed with a melanoma >0.75 mm (OR 0.86, 95 % CI, 0.75–0.98) to a 40 % lower risk for melanomas ≥ 3 mm (OR=0.60, 95% CI, 0.43–0.83). Skin screening was associated with a 38% increased risk of thin melanoma (defined as ≤ 0.75 mm) at diagnosis and a 32 % higher risk of T1 tumors (≤ 1 mm) as defined by the current AJCC staging system (OR 0.82, 95 % CI, 0.69–0.99).

A complementary survey study of 566 recently diagnosed adults with cutaneous melanoma assessed the role of physician skin examination in the year prior to diagnosis and found that men over age 60 appeared to benefit the most from this practice [60••]. Thinner tumors (≤ 1 mm) were significantly associated with physician discovery ($P=.0001$), which was reported by only 19 % of patients. However, patients who had a WBSE by a physician in the year prior to diagnosis were more than twice as likely to have a thinner tumor (OR 2.51; 95 % CI, 1.62–3.87), largely due to the effect of physician skin exam in men >60 years, who had over 4 times the odds of a thinner tumor (OR, 4.09, 95 % CI, 1.88–8.89). These 2 studies suggest a strong effect of physician screening on successful early detection of melanoma and should serve as a basis for larger trials that could utilize the endpoint of thinner tumor detection as a proxy for lower mortality.

Attempts to perform formal studies of melanoma screening have been undertaken, including a community-based trial in Queensland, The Lawrence Livermore National Laboratory (LLNL) screening program, and a pilot study of general population screening in Germany (Table 1).

The Queensland based clinical trial was designed to detect a 20 % reduction in mortality from melanoma during the 15 year intervention period [64]. The estimated sample included 44 eligible Queensland communities (aggregate population of 560,000 adults aged 30 or more) randomized into intervention or control groups to receive a community-based melanoma screening program for 3 years vs usual medical care. Because of the financial constraints, the clinical trial could not be completed [65]. However, important lessons were learned from the 18 towns enrolled and randomized in the study.

Within intervention communities, the prevalence of clinical skin examinations in 2 of the intervention groups reported significantly higher prevalence of clinical examinations (16.5 % and 27.1 %) than in the control group (10.9 %, $P<0.001$) [62]. In addition, the overall rate of skin cancer detected per patients screened was increased, and men and attendees older than 50 years more frequently received a referral and diagnosis of melanoma. Of those melanomas found through the screening program, 39 % were in situ lesions, 55 % were thin (<1 mm) invasive lesions, and 6 % were 1 mm thick or greater. Within the population of Queensland during the period from 1999 through 2002, the corresponding percentages were: 36 % in situ, 48 % invasive thin melanomas, and 16 % invasive melanomas 1 mm thick or more, indicating that melanomas found through screening tend to be less advanced than those detected when symptomatic. The specificity for detection of melanoma through

WBSE by a PCP was comparable to that of other screening tests, including mammography for breast cancer [66, 67].

A screening program initiated at the Lawrence Livermore National Laboratory and conducted between 1984 and 1996 demonstrated that increased melanoma education, self-examination, and opportunity for physician skin screening resulted in a reduction in crude incidence of thicker melanomas (>0.75 mm) during 3 phases of increasing melanoma surveillance: pre-awareness (1969–1975), early awareness of increased melanoma risk (1976–1984), and the active screening program. A 69 % reduction in thick melanoma diagnosis was reported in the screening program period compared with the early awareness period, with a reduction in mortality in the study workforce during this timeframe compared with California mortality data (no deaths compared with expected number of 3.39 deaths [$P=0.34$] based on observed mortality in 5 San Francisco-Oakland Bay area counties as reported to the SEER program from 1984–1996) [9]. While criticisms have arisen regarding the mortality analysis proposed in the study, including demographic differences between the 2 populations, the reduction in crude incidence in melanomas thicker than 0.75 mm represents the most substantial outcome of this study and a significant contribution to the effectiveness of melanoma screening.

The largest systematic population-based skin cancer screening program in the world (SCREEN) was initiated in the northern Germany state of Schleswig-Holstein, in which statewide screening of citizens 20 years was conducted from July 2003 to June 2004. Screening physicians (both dermatologists and non-dermatologists) were trained and performed dual screens (initial general practitioner WBSE followed by dermatologist referral for suspicious skin findings). In the feasibility and preliminary analyses, increased incidence of melanoma and non-melanoma skin cancers were detected, and 5 years after SCREEN, mortality rates in both men and women were nearly 50 percent lower than expected (47 % decline in men and 49 % in women) compared with prior Schleswig-Holstein mortality data and in comparison to non-screened areas in Germany. This pilot study also demonstrated that the percentage of early Stage I disease increased from 52 % in the pre-screening period (7/2001–6/2003) to 64 % in the actual screening period (7/2003–6/2004) following a large-scale multimedia campaigns [68, 69•, 70].

Based on the identification of an increased number of thinner tumors associated with this pilot study, the German Federal Joint Committee established the inclusion of skin cancer screenings as part of the nationwide services provided by the Health Insurance Funds. Since July 1, 2008, complete whole-body screenings are being offered free of charge once every 2 years for all 45 million German residents ages 35 years and above, with the same dual screening process as in the pilot study in Schleswig-Holstein [71•]. While this extensive effort is not a randomized clinical trial, it can be anticipated that the ample data on incidence, morbidity, mortality, and burden of disease will be greatly informative. To date, more than 10 million examinations have taken place, and the goal of training the nation's 45,000 physicians with an 8-hour training program has been nearly reached. It remains to be seen what the economic impact of this ambitious nationwide skin cancer screening endeavor will be and how the German health care system will handle the various screening related outcomes [71•].

While these large population-based studies indicate thinner melanomas at detection with intense screening, it is quite unlikely that such an ambitious nationwide screening program will be needed or is feasible in the US. With the latest US census data demonstrating a significant increase among darker-complexioned ethnicities with lower inherent skin cancer risk [72], a targeted approach toward highest risk populations (eg, fair-skinned, older

individuals, those with atypical moles and/or strong family history of melanoma) would be considered a more cost-effective approach.

What are the Collateral Consequences of Establishing a Wide Prevention/ Screening Effort vs a Targeted Approach Towards a High-Risk Population?

Several studies support the concept that identification of individuals at increased risk of melanoma is important since targeted surveillance has demonstrated an increased sensitivity and specificity in diagnosis [73–77]. While general agreement exists regarding the value of targeted screening there is significant variability in the implementation of this approach among dermatology-based practices [78]. To facilitate the identification of high-risk populations and implementation of more comprehensive and longitudinal surveillance strategies, a series of population-specific risk assessment tools have been designed to increase the objectivity of the selection process [79–81].

The majority of these instruments share a similar structure with respect to the type of risk factors included in the model (eg, personal and family history of melanoma, hair color, etc). However, the consistent adoption and application of risk assessment strategies into daily practice requires further improvement. A challenge to the implementation of targeted screening includes the need for optimal education of health providers to effectively identify those individuals in need of a WBSE and/or referral to a specialist for comprehensive surveillance with or without the use of diagnostic aids (dermoscopy, body photography, automated individual lesion assessment, etc).

When evaluating the cost-effectiveness of melanoma screening, a variety of studies have been published which differ significantly in the design and selection of risk cohorts and models. For example, in 1 analysis, the cost-effectiveness ratio ranged from \$220,700/years of life saved (YLS) for 1-time screening of a white population of all ages at average risk to \$28,700/YLS when older patients were considered [82]. In the case of a computer simulated study published by Losina et al, a 1.6 quality-adjusted life year (QALYs) per 1,000 persons was observed for a one-time melanoma screening of the general population older than 50 years and a cost-effectiveness ratio of US dollars 10,100/QALY, which is considered a very cost-effective value compared with other cancer screening programs in the United States [83]. In addition, screening every 2 years in siblings of patients with melanoma (relative risk, 2.24 compared with the general population) was also cost-effective with a 9.8 QALY per 1000 people screened and associated cost-effectiveness ratio of US dollars 35,500/QALY. It should be noted that these health economic studies are performed under many assumptions within the clinical parameters of the model, including a perceived mortality benefit from screening.

As previously mentioned, the implementation of a nationwide screening campaign is cost-prohibitive in the United States, and as supported by published cost-effectiveness studies, there is a need to define risk stratification with specific recommendations for targeted melanoma screening which can be effectively and sustainably funded by the healthcare system.

Additional considerations when evaluating the impact and effectiveness of screening relates to the controversial topics of [84•] “over diagnosis” resulting from detection pressure leading to the identification of early melanomas that biologically are not destined to progress into invasive and/or metastatic disease. On the other hand, it has been demonstrated that significant melanoma underreporting to SEER registries occurs in multiple states, which may underestimate the rates of thinner melanomas in particular [85, 86]. This is particularly relevant since 27 % of fatal melanomas are diagnosed at 1 mm depth [86–88].

Conclusions

A significant benefit of melanoma screening with respect to detection of thinner tumors and subsequent impact on melanoma-associated mortality has now been demonstrated by several well-designed and conducted observational and interventional studies. In the case of primary prevention, the current results are encouraging but as expected, the contribution of this type of intervention will not be quantifiable for several decades in those communities carrying out a consistent primary prevention effort.

With the data described herein, although there is no absolute proof of mortality reduction from a randomized controlled trial, the evidence is compelling enough to support the efficacy of targeted screening programs for detecting thinner melanomas, as a proxy measure for reduced mortality. Considering our current understanding and identification of high-risk patients, as well as barriers and solutions for adoption of SSE and effective PSE, absolute proof is not necessary in the public health domain to implement a targeted screening program that has the immediate potential to save lives.

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Table 1

Screening and behavioral studies evaluating the impact of early melanoma detection in tumor thickness and mortality rates

Study	Study population: type/size	End-points	Findings	Support secondary prevention
Aitken JF, et al 2006, 2002 (59–60).	Community-based: Queensland, Australia. 44 eligible Queensland communities (aggregate population of 560,000 adults aged 30 or more) randomized into intervention or control groups to receive, a community-based melanoma screening program for 3 years vs. usual medical care.	Designed to detect a 20 % reduction in mortality from melanoma during the proposed 15 year intervention period	Due to the associated cost the clinical trial could not be completed. However, on the communities where the program was implemented overall thinner melanomas were identified in comparison with neighboring communities without screening intervention.	Yes
Schneider et al 2008 [9].	Community-based: Lawrence Livermore National Laboratory (LLNL). California, USA. Population ranged between 8,056–9,217 over 12.5 years (1984–1996) Screening program involving melanoma education, self-examination, and opportunity for physician based skin screening particularly targeting high-risk individuals. The study was divided in the early awareness period (1/1976–6/1984) and the education and screening program phase (starting 7/1984–12/1996).	Impact in thickness of diagnosed melanomas and mortality rates (1984–1996)	Resulted in a reduction in crude incidence of thicker melanomas (from 22 to 4.6/100,000 person-years) No eligible melanoma deaths occurred among LLNL employees during the screening period, whereas the expected number of deaths was 3.39.	Yes
Swetter S et al 2011 [56•]	Community-based survey study: California and Michigan, USA. 566 adults with invasive melanoma completed questionnaires within 3 months of diagnosis on demographics, health care access, skin self-examination (SSE), and physician skin examination (PSE) practices in the year before diagnosis	To identify differences in pre-diagnosis behavioral and medical care factors associated with thinner versus thicker melanoma	Patients who used a melanoma picture aid and performed routine SSE were more likely to have thinner tumors than those who did not (OR 2.66). Full-body PSE was associated with thinner tumors (OR, 2.51), largely driven by the effect of PSE in men aged >60 years (OR 4.09).	Yes
Katalinic A et al 2012. (65)	Population-based: Schleswig- Holstein, Germany. 360,288 individuals aged >20 years were screened by means of a whole-body examination. Between 7/2003–6/2004 Control: Reported melanomas in adjacent regions without screening program.	Impact in mortality rates through 2009	Melanoma mortality declined by 47 % per 100,000 men and by 49% per 100,000 women by 2008/2009. The annual percentage change in the most recent 10-year period (2000–2009) was 7.5 % for men and 7.1 % for women.	Yes