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Survival is not the only valuable end point in melanoma screening

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Introduction

The impact and benefit of screening and early detection of melanoma in the general population is controversial. Discrepancies exist in recommendations across different organizations worldwide. In the US, a broad range of screening and surveillance strategies can be identified. The 2009 US Preventive Services Task Force (USPSTF) report stated that due to the limited evidence linking skin cancer screening to improved health outcomes, screening in the general primary care population could not be recommended (Wolff et al, 2009). This statement was predicated on the lack of evidence from randomized controlled studies addressing the survival benefit of screening for skin cancer based on whole body examination. Herein we will review the current data on alternative, non-survival outcomes and benefits, including: reduction of melanoma thickness at the time of diagnosis, reduced morbidity, enhanced primary and secondary prevention education, increased cost-effectiveness, and improved targeting of the highest-risk populations followed by methods to improve the effectiveness of screening. However, melanoma screening also comes with a price, which is not limited to financial implications. Some of the limitations challenging the effectiveness of screening efforts include potential “over diagnosis”, the difficulty of early identification of rapidly developing melanomas, and the challenge of reaching out to certain high-risk groups, such as older males.

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Why hasn't a survival benefit been demonstrated?

Physician detection of melanomas through routine physician exams or opportunistic screening is associated with thinner melanoma detection compared with patient-detection (Geller, Elwood et al 2009). However, whether this translates into improved melanoma survival remains unclear. The lack of a definitive survival advantage is believed to be due to the absence of randomized epidemiological studies with sufficient power and long-term follow-up. The challenge for these studies is the large number of cases required due to the relatively low incidence of melanoma, the extended time interval between diagnosis and disease recurrence, and the relatively low mortality for most early lesions. Therefore, randomized controlled studies for melanoma screening are costly (Geller, Johnson et al 2009). The Melanoma Screening Group (MSG) proposed a randomized Melanoma Early Detection (MED) Trial based on current melanoma incidence and mortality aiming for a 20% drecrease in mortality rate (Geller, 2009). The study will require a screened study population of 350,000 Americans (and 700,000 controls) aged 45 years and older, with a 4-year intervention period, and 8 years passive follow-up at an estimated cost of $30 to 40 million. With substantial data suggesting the usefulness of tumor thickness and stage of disease as a proxy for mortality, exploring the concept of melanoma severity as a primary endpoint in melanoma screening clincial trials should be entertained. In the current economic climate where the cost of medical care continues to escalate, especially in treatment related interventions, the potential savings from prevention and early detection programs need to be seriously considered, and are likely worth the research funding investment.

Research trials have shown supportive evidence on the value of screening

Attempts to carry out formal studies of melanoma screening have been undertaken, including a community-based trial in Queensland, a pilot study of general population screening in Germany, The Lawrence Livermore National Laboratory (LLNL) screening program, and a retrospective analysis of SEER data in the US, among others. The Australian clinical trial was designed to detect a 20% reduction in mortality from melanoma during the 15 year intervention period (Aitken et al, 2002). The proposed 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. Due to the associated cost the clinical trial could not be completed (From et al, 2007). However, important lessons have been 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 the control group (10.9%, $p < 0.001$)(Janda et al, 2006). In addition, the overall rate of skin cancer detected per 100 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, about 39% were in situ lesions, 55% were thin invasive lesions less than 1 mm thick, 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 melanomas; 48%, invasive melanomas less than 1 mm thick;

and 16%, invasive melanomas 1 mm thick or more, indicating that melanomas found through screening tend to be less advanced than those detected symptomatically. The specificity for detection of melanoma through whole-body skin examination by a primary care physician was comparable to that of other screening tests, including mammography (Aitken et al, 2006).

A screening program conducted by the LLNL between 1984–1996 involving melanoma education, self-examination, and opportunity for physician based skin screening resulted in a reduction in crude incidence of thicker melanomas (from 22 to 4.6/100,000 person-years). A reduction in mortality was estimated based on data from the California melanoma mortality data over the same time period. No eligible melanoma deaths occurred among LLNL employees during the screening period, whereas the expected number of deaths was calculated to be 3.39 deaths (P = .034) (Schneider et al, 2008). While the mortality analysis proposed in the study is subjected to some limitations, including demographic differences between the two populations, the reduction in crude incidence in melanomas thicker than 0.75 mm represents the most convincing outcome of this study and a significant contribution to the effectiveness of melanoma screening.

A US retrospective study by Pennie (Pennie et al, 2007) showed that tumor detection by a dermatologist vs. non-dermatologist was associated with earlier stage and thinner tumors with potential implication of a significant survival benefit. Specifically, their analysis of SEER data from 1991–1996 showed that non-cancer-related mortality was similar for the melanoma patients diagnosed by dermatologists vs. non-dermatologists, but the patients whose tumors were detected by dermatologists had lower cancer-related mortality (13% vs. 21%; P<.01) and overall mortality (29% vs. 37%; P<.01). Multivariate analysis showed that age, sex, stage at diagnosis, and melanoma detection by a dermatologist were all significantly predictive of survival.

In Schleswig-Holstein, a pilot study 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 (Katalinic et al, 2003). 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 services provided by the Health Insurance Funds. The Federal Joint Committee will evaluate the success of skin cancer screening and will introduce any necessary changes to the program (Geller et al, 2010). 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. While this massive endeavor is not a randomized clinical trial, it can be anticipated that the resulting voluminous data on incidence, morbidity, mortality, and burden of disease will be highly 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. (Geller et al, 2010)

Taken together, these studies demonstrate the utility of tumor depth as a target measure of successful screening intervention. Furthermore, the LLNL and US retrospective study by Pennie suggest a beneficial effect on mortality despite the lack of direct survival endpoints.

Additional benefits to melanoma screening

Surveillance offers a number of benefits beyond a potential survival advantage that may also improve patient care. These include the opportunity to decrease morbidity by diagnosing patients with early stage disease, increased education/prevention, reduced costs, and the identification of family members at increased risk to develop melanoma.

Surveillance decreases morbidity in patients diagnosed with early stage disease

The identification of thinner melanomas has the potential to minimize the morbidity associated with surgical procedures. Specifically, the NCCN recommends a 5mm margin and extension into the subcutaneous fat for the re-excision of melanoma in situ, while 1–2 cm and deep margins extending to the muscular fascia are recommended for thicker tumors (Coit et al, 2009)). The difference in surgical margins can have significant consequences for the patient depending on the location of the melanoma and associated co-morbidities. An additional level of morbidity associated with thicker lesions includes the sentinel lymph node biopsy (SLNB) for pathologic staging of the regional lymph nodes. Patients with a positive SLNB result are often also subjected to the significant morbidity of a complete lymph node dissection (CLND), which highlights the relevance of identifying thin melanomas. Early melanoma detection will also lead to decreased risk for distant metastasis and therefore, decreased morbidity associated with further surgical and medical interventions.

Screening allows for increased education/prevention

Perhaps one of the most powerful and least quantifiable benefits associated with melanoma screening relates to the opportunity to educate patients with respect to skin cancer risk factors and primary and secondary prevention methods. These encounters with patients at risk of melanoma provide an important opportunity for patient education and dissemination of effective information.

Surveillance also allows for anxiety management, a benefit that has been primarily evaluated in the setting of patients diagnosed with melanoma (Kasparian et al, 2009).

The capacity of achieving an early stage of diagnosis through education and simple visual inspection either by the patient or a healthcare provider is a unique aspect of melanoma and other skin cancers. This is in comparison to other cancers such as colon, prostate or lung where more invasive screening methods are necessary to achieve effective secondary prevention interventions.

Several reports have demonstrated a sub-optimal level of skin cancer screening behavior even in patients at high-risk of developing melanoma (Kasparian et al, 2010; Robinson et al, 2007;Geller et al, 2003; Bränström et al, 2010). Factors such as doctor recommendation, self-efficacy/confidence in the ability to effectively perform skin self-examination (SSE),

positive beliefs about melanoma treatment and intention to perform SSE in the future, comfort with having a partner help with SSE, perceived melanoma/skin cancer risk, concern about developing skin cancer/skin damage, and melanoma/skin cancer knowledge have demonstrated to be relevant variables driving the effectiveness of implementing SSE.

Therefore there should be a continued attempt to directly or indirectly evaluate the effect of education in ongoing and future melanoma prevention studies.

Is surveillance cost effective?

Cost-effectiveness analysis is a useful indicator of the value of screening methods when decisions are being made in the absence of randomized trials with mortality end points, and when the best available data can be combined from numerous sources to inform policy. Such analyses have been used to guide clinical decision making in colon cancer screening, breast cancer screening, and human immunodeficiency virus disease management (Losina et al, 2007; Mandelblatt et al, 2003; Weinstein et al, 2001). As mentioned above, this approach will also be valid in melanoma where there is every reason to believe that decreased mortality can be achieved through early detection, despite the absence of randomized controlled studies. The quality-adjusted life year (QALY) is a measure of disease burden, including both the quality and the quantity of life lived. Using this methodology, interventions in the United States are generally considered cost-effective at less than $50,000/QALY gained or less than $100,000/QALY gained (Goldman, 2005; Ubel et al, 2003). The cost-effectiveness of melanoma surveillance has been evaluated from multiple perspectives including the impact of melanoma screening with respect to years of life saved, the financial implications of early detection, and the role of long-term surveillance and testing of patients diagnosed with early stage melanoma.

Several studies have estimated the cost-effectiveness of melanoma screening (Youl et al, 2007; Girgis et al,1996). Freedberg estimated a cost-effectiveness ratio of $39,600/years life saved (YLS) for 1-time screening in a population at high risk (Freedberg et al,1999). This study was limited to 1-time screening, was applied in a younger population, and did not account for increased progression and recurrence of melanoma. Benningfield estimated a cost-effectiveness ratio of $220,700/YLS for 1-time screening of a white population of all ages at average risk (Beddingfield, 2003). However, the cost-effectiveness for older patients was much lower, at $28,700/YLS. The study by Losina used a computer simulation to evaluate 4 alternative melanoma screening strategies: background screening only, and screening 1 time, every 2 years, and annually, all beginning at age 50 years. Their study demonstrated a1.6 QALYs per 1,000 persons for one-time melanoma screening of the general population older than 50 years and a cost-effectiveness ratio of US dollars 10,100/QALY; a very cost-effective value compared with other cancer screening programs in the United States. 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. (Losina et al 2007), The discrepancies in the cost-effectiveness observed in older patients between the Beddingfield and the Losina studies were explained by

differences in defining the higher risk population and screening cost. However, the policy recommendations were similar.

An additional perspective with respect to cost-effectiveness of melanoma relates to the impact on stage of disease at diagnosis and its consequences with respect to morbidity and financial cost. Specifically, Alexandrescu demonstrated a dramatic incremental total cost associated with progressively higher initial stages of the disease, ranging from a total of $4,648.48 for in situ tumors to $159,808.17 for Stage IV melanoma (Alexandrescu, 2009).

An additional cost associated with the diagnosis of thicker primary tumors includes the indication for sentinel lymph node biopsy (SLNB). Patient charges for SLNB have been reported to range from $10,096 to $15,223 US dollars, compared with $1,000 to $1,740 US dollars for outpatient wide local excision (WLE) alone (Agnese et al,2003). In a study evaluating the cost-effectiveness of SLNB in Australia, a Markov model was populated with probabilities of disease progression and survival (Morton et al, 2009). The results suggested that, over a 20-year timeframe, the mean total cost per patient receiving WLE only was AU $23,182 with 10.45 life years (LY) and 9.90 QALYs. The mean cost per patient for WLE + SLNB was AU $24,045 with 10.77 LY and 10.34 QALYs. The incremental cost effectiveness ratio for WLE + SLNB was AU $2,770 per LY and AU $1,983 per QALY.

Surveillance allows for identification of family members at increased risk to develop melanoma

Screening of patients at risk of developing the disease based on nevi/skin phenotype or family history fosters promotion of effective primary and secondary prevention strategies (Brady et al, 2000; Albert et al, 1990). Ultimately, information dissemination and adoption of effective and consistent skin surveillance techniques has the potential to result in early detection of melanomas and decrease the morbidity associated with later stages of diagnosis.

Targeted and comprehensive surveillance is an opportunity to improve the effectiveness of melanoma screening

A number of studies support the notion that identification of individuals at increased risk of melanoma is important since targeted surveillance has demonstrated an increased sensitivity and specificity in diagnosis (Wang et al, 2004; Rademaker et al, 2010; Feit et al, 2004; Banky et al, 2005). However, a significant variability with respect to skin cancer screening practices targeting high-risk patients has been described in dermatology based practices (Federman, 2002). To facilitate the identification of high-risk populations to intervene with 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 (Mar et al, 2011;Fortes et al, 2010;Cho et al, 2005). The vast majority of these tools share a similar configuration with respect to the type of risk factors included in the model (e.g. personal and family history of melanoma, number of common and atypical nevi, history of sunburns, hair color, and freckling). However, the consistent adoption and implementation of these tools into daily practice requires further improvement.

When evaluating methods to improve the value of screening, the implementation of imaging techniques such as dermoscopy and photographic documentation at the single lesion, regional, and total body level (TBDP) should be given particular consideration. The added value of this comprehensive approach in the evaluation of high-risk melanoma patients has been documented in both the community dermatology setting (Wang et al, 2004; Rademaker et al, 2010) and particularly in the case of specialized Pigmented Lesion Clinics (PLCs) (Feit et al, 2004; Banky et al, 2005).

Melanoma detection remains the most important indication of dermoscopy and in melanoma screening the aim of dermoscopy is to maximize early detection while minimizing the unnecessary excision of benign skin tumors. Specifically, the implementation of dermoscopy in the evaluation of pigmented skin lesion evaluation has demonstrated a benign/malignant (B/M) ratio improvement from 18:1 to 4.3:1 ($P = 0.037$) (Carli et al, 2004). In the last few years, 3 meta-analyses and 2 randomized studies have definitely proven that dermoscopy improves the sensitivity for melanoma diagnosis as compared to the naked eye examination alone.

In the case of TBDP, the study by Feit, a follow-up of 576 patients with TBDP were found to have had a total of 93 lesions biopsied. Twenty-seven (35%) of 77 melanocytic lesions were histologically diagnosed as melanoma (Feit et al, 2004). In a study by Banky using TBDP, the benign to malignant ratio was also approximately 3:1 (Banky et al, 2005). These ratios compare very favorably with the ratios of 12:1 or 30:1 reported for dermatologists not implementing the use of TBDP and general physicians respectively (Banky et al,2005). While B/M ratio of biopsies is a useful indicator of diagnostic accuracy, the patient mix seen by each individual physician can modify the outcome of this parameter. In addition to improvement on B/M ratio of biopsies, the melanomas detected using photographic aid tend to be thinner. In the Banky study, 44% of melanomas were in situ and the median thickness of the invasive tumors was 0.39mm. In comparison, 35% of melanomas in the region were in situ and the median thickness of the invasive tumors was 0.60 mm.

While the above studies were primarily conducted in settings enriched for patients at high risk of developing melanoma in community dermatology practices and PLCs, their comprehensive approach can help disseminate diagnostic methodologies that are more effective in identifying early melanomas. Ultimately, the most efficient approach for melanoma detection may involve a tiered system which the patients at highest risk receiving the most intensive surveillance.

What are the limitations of the current evidence supporting the implementation of melanoma screening?

Important considerations when evaluating the outcome of the clinical studies evaluating the effect of melanoma surveillance include the difference in the study design, demographic variability the bias introduce by “over diagnosis” of thin melanomas, and the importance of identifying a decrease in the population-based incidence of deeply invasive disease as a target measure of successful intervention. In the case of cost-effectiveness studies major limitations for these analyses include the fact that they are based upon models that

incorporate assumptions believed to be relevant by a certain group of investigators conducting the studies. In addition, the studies evaluating the cost-effectiveness of screening intervention do not account for the potential effect of "overdiagnosis" in their models. Despite this limitation and irrespective of the difference in healthcare systems and financial cost associated with the surgical management of melanoma, a significant savings could be generated from minimizing the number of cases undergoing SLNB for staging purposes.

Melanoma "Over diagnosis" and "Diagnostic drift"

An important consideration when assessing the effectiveness of screening methods and reported incidence of melanoma relates to the controversial topics of (Welch and Black, 2010): (a) "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, and (b) "diagnostic drift" as a consequence of increased sensitivity for the pathologic diagnosis of melanoma when evaluating atypical melanocytic lesions; particularly in the case of melanomas in situ.

Several studies have raised the concern of an error amplification effect generated by the above-mentioned phenomena through melanoma screening (Shuster, 2009; Welch and Black, 2010; Torres-Cabala et al, 2010, Welch et al, 2005). Through this process the histopathological reclassification of benign disease as malignant results in a situation where overdiagnosis of malignancy could outweigh underdiagnosis. The error would then be amplified through patient screening. Some of the factors that makes melanoma screening particularly susceptible to a "diagnostic drift" include the limited rate of histological agreement between pathologists when evaluating borderline melanocytic lesions (Shoo et al, 2010; Farmer et al, 1996), and the potential effect of medical liability associated with misdiagnosis (High et al, 2008). An additional consideration when assessing a drift in diagnosis include the contribution of molecular diagnostic tools to determine wheather an atypical melanocytic lesion represnts melanoma or not (Braun-Falco et al, 2009). To what extent the increased in melanoma incidence rate "truly" reflects a larger exposure to associated risk factors, as UV exposure, and not just as a result of "overdiagnosis" or "diagnostic drift" still needs to be properly investigated (Linos et al, 2009). Overall, the continued rise in melanoma mortality rates suggest that the increased incidence in melanoma is a real phenomenon and not just an artifact due to "over diagnosis" (ACS Cancer Facts & Figures 2011)

Melanomas not as amenable to early detection

The accurate diagnosis of melanoma is challenged by a group of melanomas subtypes that significantly contribute to melanoma mortality and are likely to be missed since they are not as amenable to early detection strategies. This group of lesions includes nodular melanomas (accounting for approximately 40% of newly diagnosed thick (>2mm) tumors (Geller et al, 2009) and 46% of ultimately fatal melanoma (Shaikh 2011), desmoplastic melanomas (Feng et al, 2011), and amelanotic melanomas (2–8% of all melanomas, (Menzies et al, 2008)). In addition, it is unclear what percentage of cases presenting as metastatic melanoma of unknown primary (3.2% of melanomas) represent cases of primary lesions that would have been amenable for early detection (Kamposioras et al, 2010). Melanomas arising in mucosal

sites and other less favorable sites for early detection also contribute to the mortality rates (McLaughlin et al,2005). Even though these types of melanoma represent a small proportion of melanomas overall, the survival benefit of melanoma screening might be inherently limited by the incidence of these types of tumors.

Older males

Another challenge to the effective testing and implementation of melanoma screening is the documented resistance to screening evaluations and self skin exams by men 50 years of age and older (Geller et al, 2006; Swetter et al, 2004; Geller et al, 2009; Geller et al, 2009). Despite recent trends showing improved survival, and stabilization of incidence rates in younger Americans, melanoma incidence and mortality continue to rise steadily in older individuals, particularly in men over age 65 (Geller et al, 2003). A similar trend in this demographic group has been observed in Australia (Chamberlain et al, 2002) and Germany (Buettner et al, 2005).

Conclusion

While it is likely that melanoma surveillance will ultimately prove a survival benefit, the value of medical care is not simply based on reduction of mortality. There are numerous potential benefits to be considered when making policy regarding the value of melanoma screening. On the other hand, the expense and morbidity associated with over-biopsy, misdiagnosis, over diagnosis, and those patients destined to succumb to melanoma despite intervention must be factored into the equation. Therefore, recommendations for melanoma surveillance in the general population must carefully weigh these costs and benefits. Ultimately, a rational approach to melanoma surveillance through educational efforts to the public, effective education of health care providers to increase diagnostic accuracy, and screening and referral patterns according to risk factor stratification will lead to a more balanced intervention while reducing the mortality associated with the disease.

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Abbreviations

SEER	Surveillance, Epidemiology and End Results

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