See related article on pg 1666

Melanoma Is Up: Are We Up to This Challenge?

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Linos and colleagues provide important evidence that the increasing incidence of melanoma is not solely from increases in thin melanomas discovered by more intensive screening. This underscores the inadequacy of primary prevention to date, and the importance of early detection for reducing mortality in the near future. The US Preventive Services Task Force finds insufficient evidence to recommend for or against skin self-examination and clinician skin examination. Neither is commonly practiced now, but both are required for effective early detection. Evidence regarding benefits, harms, and costs of melanoma screening will help in securing widespread endorsement of these activities.

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Melanoma incidence has been increasing in the United States since population-based measures became available more than 70 years ago. As long as the mortality from melanoma also continued to rise, there was relatively little controversy about whether this neoplasm was really increasing in frequency. However, for the past decade or two, melanoma mortality has leveled off, giving rise to a debate about whether the continuing increase in incidence is due to a real increase in the frequency of the disease or whether it is an artifact of increasing public and medical attention to skin cancer, with associated increased rates of skin biopsies leading to increased diagnosis of thin, relatively indolent lesions or lesions that are diagnosed as melanoma but are not actually malignant (Edman and Klaus, 2000; Welch *et al.*, 2005).

Linos and colleagues (2009, this issue) step into the fray with their analysis of the population-based Surveillance, Epidemiology, and End Results (SEER) data, which reveal an increase in incidence of all major histologic subtypes and thickness groups of melanoma, including the thickest melanomas, which have the worst prognosis. The increases are reported to occur across the spectrum of socioeconomic status, including individuals with the poorest melanoma prognosis (Eide *et al.*, 2009) and the poorest access to screening. With this analysis. Linos *et al*. have advanced the debate, but they have not ended it.

No longer can it be credibly claimed that the increase in melanoma incidence can be attributed solely to increases in the detection of thin melanomas. Although the number of melanomas with unknown tumor thickness in the SEER database was higher than desired, the authors conducted reasonable sensitivity analyses to suggest it is not responsible for the persistent increase in the disease across thickness groups. Fluctuations in the completeness of melanoma registration are always a concern in database studies. However, perhaps the most serious concern is the apparent discrepancy between the increasing incidence of thick as well as thin melanomas and stable mortality rates. Marginal therapeutic advances have been made in recent decades, but it remains undocumented whether they are of sufficient magnitude to account for this observed discrepancy. Alternatively, misdiagnosis of benign lesions as melanoma may be more common, as may the detection of relatively indolent thick melanomas. We must consider the possibility of a shift in the distribution of melanoma types (we do not refer here to classic histologic types) to melanomas that are less aggressive at a given thickness than those occurring a decade ago. Perhaps the lag between diagnosis of a thick melanoma and death from that melanoma is relevant.

Although the debate about trends in melanoma is not over, the evidence is now substantially stronger that the increase in incidence is not merely an artifact of better detection practices but is due at least in part to an actual rise in the frequency of real disease. Recent research has also provided more insight into the impact of early detection practices on incidence and mortality, with the publication of the experience of employees at the Lawrence Livermore National Laboratories (Schneider *et al.*, 2008). The group was subjected to increased awareness programs and ultimately intensive screening, consisting of education about skin self-examination as well as clinical melanoma screening examinations. Among the participants there were progressively more diagnoses of *in situ* melanoma during this period but progressively fewer thick invasive melanomas were detected (see Figure 1). This adds to earlier evidence that intervention to promote thorough skin self-examination (TSSE) is associated with more skin surgery as an apparently transient consequence of regular TSSE performance (Weinstock *et al.*, 2007), but that lower melanoma mortality may be a result (Berwick *et al.*, 1996).

> The increase in incidence of melanoma is not merely an artifact of better detection.

Decreasing mortality is a key goal of prevention programs. Melanoma is projected to have killed 8,420 Americans in 2008, and a similar number of deaths are expected in 2009. Primary prevention through reduced UVR exposure may ultimately reduce the number, but the lag time between exposure and death

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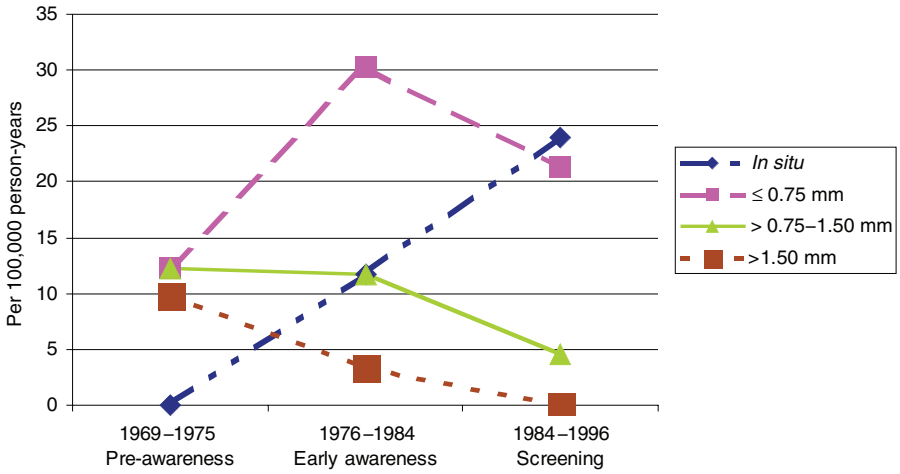

Figure 1. Crude incidence of melanoma at the Lawrence Livermore National Laboratory (LLNL). The pre-awareness period (1969–1975) is the interval before widespread awareness of the high incidence rates of melanoma at LLNL. The early awareness period (1976–1984) involved increased awareness of the high incidence rates prior to the institution of a formal screening program. During the screening period (1984–1996), a screening and education program was in place (Schneider *et al.*, 2008).

from disease is typically long, and public health efforts have not proven effective at markedly reducing the population's exposure. Indeed, sunburns are on the increase (Centers for Disease Control and Prevention, 2007), as well as incidence of melanoma of all thicknesses. If the goal is to cut melanoma deaths at least by half in the next decade despite the trends noted by Linos *et al.* (2009), primary prevention by reducing individuals' exposure to UVR will not accomplish this. Improved early detection might.

Early, curable melanoma is almost always asymptomatic but visible on the surface of the skin. To detect it, someone needs to look at the skin and see the lesion (Weinstock, 2000). Unfortunately, early detection practices for melanoma are not widely established. In a national survey of primary care providers (PCPs), only 32% reported routinely performing full-body skin examinations (FBSEs) on average-risk patients, and only 59% of physicians conducted FBSEs on patients at high risk for melanoma (Geller *et al.*, 2004). National patient population surveys have reported much lower screening rates, ranging from 16 to 21% (Oliveria *et al.*, 2001; Santmyire *et al.*, 2001). TSSE is reported by less than 20% of the population, although some individuals may examine focused portions of their body (Weinstock *et al.*, 1999, 2007). Thus, most Americans undergo no systematic skin surveillance.

Skin is not thoroughly scrutinized by patients or their physicians for several reasons. Many patients lack the knowledge, skills, and confidence to examine the skin for cancer or to distinguish suspicious from benign lesions; others are simply not motivated to do so, perhaps in part because of a lack of interest on the part of their health-care providers. Patients without partners or TSSE aids such as handheld or wall mirrors are also less likely to conduct TSSE, as are those whose physicians have not recommended this practice (Martin *et al.*, 2007). On the physician side, PCPs often cite lack of time as the most significant barrier to performing FBSE. Poor reimbursement and competing patient comorbidities may pose additional hindrances, as may a lack of sufficient knowledge and skills. Physicians who doubt the effectiveness of FBSE and who lack confidence in their ability to detect lesions of concern are less likely to examine a patient's skin (Geller *et al.*, 2004).

Finally, insufficient evidence is cited as a critical impediment to conducting FBSE and even to recommending TSSE. The US Preventive Services Task Force (USPSTF) acts as an authoritative body in providing evidence-based recommendations to clinicians regarding the effectiveness of various prevention-related strategies and procedures, particularly in primary care. Earlier this year, the agency reevaluated their recommendations on screening for skin cancer and concluded, "There is insufficient evidence to assess the balance of benefits and harms of whole-body skin examination by a clinician or patient skin self-examination for the early detection of skin cancer" (US Preventive Services Task Force, 2009). But in the same document, the USPSTF noted that "clinicians should remain alert for skin lesions with malignant features." This apparent inconsistency illustrates a difficulty in adhering to their own criteria when evaluating clinical practices such as skin cancer screening (Weinstock, 2000). However, recent developments may address this difficulty.

As a response to the perceived insufficient guidance for clinicians regarding many practices, even in the absence of evidence-based guidance, the USPSTF has identified a series of domains that it will take into account to provide guidance to clinicians when the relevant evidence is insufficient to meet its criteria for endorsing a recommendation (Petitti *et al.*, 2009). These include (i) the potential preventable burden, (ii) the potential harms, (iii) costs, and (iv) current practice. In setting forth these domains, the USPSTF recognizes that the level of evidence that may be appropriate to persuade a clinician to recommend an invasive procedure, perhaps with some risk of death or severe morbidity, must be more stringent than the level of evidence appropriate for a procedure such as skin self-examination. Indeed, the USPSTF recognizes that some procedures, perhaps including skin cancer screening, may never have sufficiently rigorous evidence to support a recommendation by their criteria, so clinically informed reasoning based on available evidence of potential benefits and harms, as well as costs, will be key.

Because of the high costs of conducting a randomized controlled trial, no such study has been conducted to document the relationship between screening and mortality. The Queensland, Australia, Melanoma Screening Trial came close to this goal; the investigators randomized 9 of 18 communities to receive a melanoma screening intervention. Physicians in the intervention communities received training and support; residents of these communities received educational materials, as well as free screenings

by physicians. The prevalence of FBSE increased by approximately 20% over baseline, with self-screening by elderly men and women comprising the largest increase (Aitken *et al.*, 2006b). The specificity of an FBSE was 86%, comparable to that of other routine screening procedures, for example, mammography (Aitken *et al.*, 2006a). Unfortunately, the Queensland study could not be extended to the remainder of the 44 communities required for adequate power because of a lack of governmental funding, and the investigators could not adequately measure the effect of their intervention on melanoma mortality.

While the medical community optimistically waits for a large-scale randomized study on screening to provide the strongest evidence, a key research focus must be to augment available evidence in the domains identified by the USPSTF, including potential harms and costs. Melanoma is generally visible on the skin at a curable phase in its evolution, when cure consists of a simple office procedure. Yet for most people, periodic, systematic skin surveillance is not practiced—not by a clinician, the patient, or the patient's family. The absence of physician recommendation to perform skin exams is an important factor. The recent broadening of the USPSTF's view of relevant evidence for issues such as this offers a challenge to the research community and an opportunity to improve public health: are we up to the challenge of cutting melanoma mortality in half by providing adequate scientific support for broad implementation of effective early detection?

CONFLICT OF INTEREST
The authors state no conflict of interest.

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See related article on pg 1710

Perp and Pemphigus: A Disease of Desmosome Destabilization

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In this issue, Nguyen *et al.* demonstrate a role for Perp in desmosome assembly and trafficking and pemphigus IgG–mediated acantholysis, providing further insights into the complexity of desmosome structure and regulation.

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Desmosomes are multiprotein, polymeric cell–cell adhesion complexes

The desmosome intercellular adhesive interface is formed by the extracellular domains of desmogleins and desmocollins, single-pass transmembrane proteins belonging to the cadherin family of cell adhesion proteins. Other known desmosome components include plakophilins, desmoplakins, and the catenin plakoglobin. The cytoplasmic tail of desmoglein binds to plakoglobin, which in turn binds to desmoplakin. Plakophilins bind to desmoplakins, plakoglobin, desmogleins, and desmocollins, and

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