Progress and Prospects on Melanoma: The Way Forward for Early Detection and Reduced Mortality

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Abstract

The public health problem of melanoma is difficult. Recent decades have seen substantial efforts directed at primary prevention, yet the incidence of melanoma continues to increase. Substantial efforts have been devoted to improving treatment, yet melanoma retains a poor prognosis if simple surgical excision is not curative. Early detection has made remarkable progress, however. Five-year relative survival has increased from approximately 80% in 1975 to greater than 90% in 1996. Even so, almost 8,000 Americans are projected to succumb to melanoma in 2005. Because most of these fatal melanomas are visible on the skin surface at a curable phase in their evolution, more can and must be done. To improve the early detection practices of clinicians, we have developed an eight-step Basic Skin Cancer Triage algorithm, which forms the core of a curriculum that we have shown can result in improved skills, attitudes, and practices. We are now in the process of attempting to test a Web-based version of that curriculum in a randomized trial. Skin self-examination also has tremendous potential for contributing to early detection of melanoma. We have tested an intervention to encourage thorough skin self-examination in a randomized trial and found it effective in increasing the performance of this procedure, on increase that is sustained for at least a year, while resulting in only short-term increases in surgical procedures on the skin. Early detection has not yet reached its full potential effect on the public health problem of melanoma and is poised to further reduce melanoma mortality.

The public health problem of melanoma is a difficult one. We have one effective treatment: surgical excision of the primary lesion with a margin of surrounding skin. This treatment has remained essentially unchanged during the past several decades, except for narrowing of the margins removed. It remains effective for early disease but rather ineffective for more advanced melanoma. Other treatments, including adjuvant therapy for resected regional disease or chemotherapy for metastatic disease, provide at best modest improvement in prognosis. If melanoma is not cured by surgical therapy at the primary site, it is all too frequently fatal.

Confronted with this dismal picture, much effort in recent years and decades has focused on primary prevention of melanoma. The major, and for practical purposes the only, known avoidable cause of melanoma is UV radiation. This one ubiquitous exposure accounts for most melanoma cases in light-skinned populations worldwide (1). There are multiple available tools to reduce exposure to this carcinogen, including the current American Cancer Society mantra "Slip! Slop! Slap!," which was originally developed in Australia for this purpose.

Despite the coverage of this slogan, Australia continues to have the highest reported incidence of skin cancer of any large geographically based population. The slogan exhorts the populace to slip on a shirt, slop on the sunscreen, and slap on a hat to protect themselves from UV rays from the sun. Another slogan that has been used in the United States is "Avoid. Cover. Screen." for avoiding or limiting sun exposure, covering up with clothing when out in the sun, and applying sunscreen.

Some controversy has been associated with these recommendations in recent years because of the effect of sun exposure on cutaneous synthesis of vitamin D, the contention that a large portion of the population has inadequate stores of vitamin D, and the assertion by some that sun protection may be a significant contributor to this. Even apart from this, however, sun protection campaigns have been of limited effectiveness. Indeed, rather than a trend toward marked reduction in exposure to UV radiation, there has been a countervailing trend toward increased use of artificial tanning devices that may be having the effect of increasing exposure to UV radiation on a population basis. The evidence that links indoor tanning with melanoma risk is accumulating, with many case-control studies and one cohort study supporting this association (2, 3). The result is that melanoma incidence continues to increase (Fig. 1).

The one bright spot in this entire picture, however, is early detection of melanoma. We have seen a steady improvement in melanoma survival over decades. Five-year relative survival has increased from ~80% in 1975 to >90% in 1996 (Fig. 2), which seems to be related to increased awareness of melanoma and consequent surgical excision of primary lesions at an early stage, when surgery can be curative. Even
so, ~8,000 Americans are projected to succumb to melanoma in 2005 (4). One can make a compelling argument that we can do a better job of early detection. The central irony of melanoma is that most ultimately fatal lesions were visible on the surface of the skin at a curable phase in their evolution.

To improve our early detection activities, we must look (inspect) and see (recognize) the curable melanomas when they become visible on the skin (5). These early detection activities can be done by clinicians and by the general public, and efforts are under way to determine better ways to encourage this to happen.

For clinicians, a Basic Skin Cancer Triage algorithm has been published to assist in the recognition of potential melanomas (6). This eight-step algorithm allows the clinician to triage patients and skin lesions into one of three categories: Act (requires biopsy or referral), Reassure (patient can be confidently reassured), and Track (requires near-term surveillance to be sure it is stable; ref. 7). A curriculum was designed around this that includes related matters that a clinician can use to successfully manage the patient with skin lesions. This curriculum was used on a small sample of clinicians and found to result in improvement in their knowledge, skills, attitudes, and practices with regard to skin cancer (7, 8). It has now been implemented on the Web and is being tested in a randomized trial. If found to be effective, it can be readily disseminated in this form.

For early detection of melanoma, patients themselves or family members must look (inspect) and see (recognize) when a skin lesion may be suggestive of melanoma. Although looking at one’s own skin is simple in theory, in practice thorough skin self-examination is not commonly done, although it might be life saving. The one case-control study on the topic associated skin self-examination with a 63% reduction in melanoma mortality (9). Looking at one’s skin is a common activity, but doing so thoroughly is not, with only ~9% to 18% of individuals looking at all areas, including the high-risk areas for melanoma, such as the calves in women and the back in both men and women (10, 11).

The Check-It-Out Project evaluated an intervention to increase thorough skin self-examination in a randomized trial. At baseline, the main predictors of thorough skin self-examination performance were (a) having been advised to do so by a physician, (b) availability of a partner (generally a spouse) to help, and (c) availability of a wall mirror (11). The intervention included cues, aids, a video designed to assist viewers in all stages of adoption of this practice (available from the American Cancer Society), and brief in-person counseling by a health educator. The result was a sustained increase in performance of thorough skin self-examination in the intervention group. This effect was accompanied by a temporary increase in surgical procedures on the skin. However, at the final (12 months after intervention) evaluation, there was little difference in surgical procedures, but the substantial difference in performance of skin self-examination persisted. This shows that increasing the practice of this type of examination is possible, thereby potentially facilitating early detection of melanoma.

This must be accompanied by an improvement in recognition of potential warning signs. We need guidance that is simpler than the eight-step Basic Skin Cancer Triage algorithm developed for clinicians. For the past 20 years, the early detection guidance for the public has focused on ABCD: A for asymmetry, B for irregular border, C for multiple colors, and D for diameter >6 mm (12). This tool has been useful, but it has certain major limitations. It is useful because many melanomas show some or all of the ABCD features, and undoubtedly this approach has led to cure of many of these lesions. However, ambiguity exists regarding the threshold for action (presumably the presence of just one of these features should precipitate a visit to the physician, but some may think that a lesion does not require action until two or more of these features are present). More importantly (and regrettably), melanomas do not necessarily manifest any of these signs.

Nodular melanomas are of particular concern, because they account for a large proportion of the ultimately fatal lesions (13, 14). They are often thick, and hence have a poor prognosis, by the time they achieve a 6-mm diameter, and they are typically symmetric, regularly bordered, and of just one color. These ABCDs do not work for nodular melanoma (15). ABCD also may fail to detect an amelanotic melanoma. Finally, as we have been getting better at early detection of melanoma, we are increasingly diagnosing lesions when they are <6 mm in...
diameter, which now represent a considerable and growing minority of melanomas (16). Various modifications of the ABCD rule have been suggested, including Cs for change, contour, and color; Es for elevation, enlargement, and evolution; and other letters.

In fact, expert dermatologists may be unable to recognize melanomas early in their evolution, before they develop distinctive physical signs. In high-risk patients followed up with photographs of the skin, many melanomas were discovered only by virtue of change from a prior image (17). It is optimal to recognize them at this point, because surgical excision would be more likely to be curative than if the surgery were delayed until distinctive signs developed. Hence, the primary message needs to emphasize evaluation of any “new or changing skin lesion.” In addition, nodular melanomas more than other types of melanoma tend to present as new and/or rapidly growing lesions, and because this type is disproportionately represented among the ultimately fatal lesions, the new or changing skin lesion message has great potential to enhance recognition of the early nodular melanoma. The ABCD signs and the “ugly duckling sign” (one skin lesion looks different from the others) may still be useful but cannot be relied on for adequate sensitivity to substantially advance early detection on melanoma among the general population.

“Look and see” is the essence of reducing melanoma mortality. Clinicians need the skills, confidence, and incentive to inspect the skin and recognize skin lesions that require action. The general population can be motivated to look with monthly thorough skin self-examinations and trained with simple guidelines (new or changing skin lesions) to see skin lesions that may need a clinician’s attention. Early detection has not yet reached its full potential to have an effect on the public health problem of melanoma and is poised to further reduce melanoma mortality.

Open Discussion

Dr. Atkins: A lot of patients who have melanoma are most concerned about avoiding and reducing their sun exposure and potentially preventing their second melanoma. Efforts of the melanoma advocacy groups are focused on reducing sun exposure: wearing hats, wearing sun-protective clothing, building dug-outs at little league games, etc. You don’t hear as much about early detection or skin self-exams. What is your experience?

Dr. Weinstock: Primary prevention has been the major focus of most of the public health campaigns and this has not reduced the incidence of melanoma. If primary prevention were effective, it probably would have an effect on melanoma. Primary prevention can be effective during childhood because according to the epidemiologic evidence, sun exposure in childhood is an important factor for later melanoma.

Dr. Sosman: It seems virtually impossible to design a trial with the bottom-line question of reducing the mortality by detecting melanoma early. This would be analogous to what has been done for mammograms and breast cancer.

Dr. Weinstock: That is very difficult because melanoma mortality is low. With ~8,000 people in a population of 300 million dying per year of melanoma, how many people would you have to enroll in a trial to get a statistically significant difference? In addition, actually conducting that trial would be difficult. There has been an attempt, in Queensland, which has the highest incidence of any large population in the world. This group attempted to randomize communities to get either intensive screening or usual care. Funding issues intervened, so the trial ended up not being conducted as designed. It was conducted on a much smaller scale, which is less likely to be definitive. The results have yet to be reported. That was the closest we’ve come.

Dr. Elder: Are you applying intervention to a high-risk population?

Dr. Weinstock: No, this was an average-risk population.

Dr. Elder: How do the logistics of that translate in terms of not only biopsies but also doctor’s office time? Is that supportable at a national level?

Dr. Weinstock: In the Basic Skin Cancer Triage trial, we will assess as best we can some of these other factors, although we probably won’t be able to get as good a measure as we did with the Check-It-Out trial. In the Check-It-Out trial, we found that in the first 6 months it had a substantial effect on health care utilization and then it returned to the baseline level.

Dr. Keilholz: Are you concluding that in the long run more frequent skin examinations do not produce any other unnecessary procedures?

Dr. Weinstock: Our data included 12 months after randomization. Based on my clinical experience, which is consistent with these data, when people look thoroughly at their skin they start noticing things and they become concerned; they then go to the doctor, and doctors these days don’t want to miss a melanoma, so they cut the lesion out. However, this seems to be a relatively short-term effect of intensive surveillance.

Dr. Hwu: Are there any efforts to try to go beyond visual evaluation to determine whether a lesion needs to be resected or not?

Dr. Weinstock: There is a lot of visual inspection of these lesions in terms of epiluminescence microscopy, computer imaging analysis, and so on. There are also other types of efforts that are experimental.

Dr. Essner: What is the role of sunscreen for patients who already had melanoma? Should we tell them to use sunscreen or is it too late?

Dr. Weinstock: On a population basis, the main effect of sun exposure seems to be in childhood in terms of later melanoma risk. However, now there is increasing epidemiologic evidence that there may be different types of melanoma. Although for the most common types of melanoma the effects of sun exposure are primarily in childhood, for some of the other types of melanoma, particularly melanomas on the face and neck, later exposure may be particularly important.

Dr. Ross: Does vitamin D have an effect on prognosis?

Dr. Weinstock: Vitamin D is an essential vitamin whose primary known importance for human health is musculoskeletal. There’s no question that at least among the elderly, vitamin D levels are often suboptimal. Several other factors feed into this equation. First is the whole effect of vitamin D on cancer risk. A large amount of observational evidence indicates that vitamin D levels are related to colon cancer risk. The data on breast cancer, prostate cancer, and a variety of other conditions are fairly weak at the moment. The colon cancer data are stronger, but none of the data are based on
randomized trials. The randomized trials support the musculoskeletal effect very strongly, but not these others.

**Dr. Ross:** Another topic worth addressing is how avidly we should recommend sun protection for patients who are diagnosed as having melanoma. Obviously, for young patients with thin melanomas this is an important issue, because their second melanoma is important. But for a middle-aged person with a bad melanoma, this is probably not as important an issue.

**Dr. Sosman:** Do you think intervention/prevention trials are feasible?

**Dr. Weinstock:** Chemoprevention would be great. We just need enough preliminary data with some particular agent to justify such a trial, as it would have to be large. There were a number of randomized trials of statins for cardiovascular end points, and they noticed in two of them that there were fewer melanomas, but the numbers were very small. There was interest in doing a statin chemoprevention trial for melanoma, but the numbers would have been huge and then further analysis of other statin trials didn’t seem to confirm that initial trend.

**Dr. Atkins:** It seems that maybe we’ve done a disservice by communicating the message that melanoma is a bad disease. Maybe we should be talking about melanoma being a curable disease and place a lot of the effort on early detection. That, of course, assumes that if you find the melanoma early, you actually can cure it.

### References

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