Malignant Melanoma in the Year 2000

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Much progress in the prevention, early detection, and treatment of malignant melanoma has been made in the 20th century. However, this progress, well documented in the review by Rigel and Carucci1 in this issue of CA, has not always been straightforward, and in some respects, two steps forward have been followed by one step back.

Australia—A Unique Case

Australia is unique in the world in that direct health care expenditures for skin cancer—about $16 per person per year—exceed those spent for any other cancer.2 About 1.5% of the Australian population undergoes excision of at least one skin cancer each year, and about 10,000 of these are in-situ or invasive melanomas.3 Invasive melanoma (melanoma) incidence rates in Australia are the highest in the world, with a marked latitudinal gradient: In Queensland (latitudes 12–28S), melanoma incidence is 53.5 per 100,000 person years compared with that observed in Victoria (latitudes 36–38S) where the rate is only 30.3 per 100,000 person (1992–1996).4 The lifetime risk for development of a melanoma in an Australian male is now 1 in 25 and for a female, 1 in 34.4

Sun Exposure vs. Blistering Sunburn?

It has been estimated that 65% of melanomas occurring in white populations worldwide is attributable to sun exposure;5 however, the precise role of sun exposure in the causation of melanoma is still unclear. For example, outdoor workers generally have a lower risk of melanoma as compared to indoor workers.6 Blistering sunburn in childhood and adolescence is, however, an almost universal risk factor for melanoma in white populations.6 The fact that epidemiological studies indicate that cumulative lifetime sun exposure is not necessarily a risk factor for melanoma suggests that sunburn is not merely an index of total exposure.6 Therefore, ultraviolet dose per episode of exposure in childhood and adolescence may be important in initiating the disease.

The overall age-standardized mortality from melanoma, the incidence of melanoma in Australian females born after 1950, and the incidence of non-melanocytic skin cancer in Australians younger than 50 years, have all been falling for about a decade.7-9 These trends have been attributed to public health programs like “Slip (T-shirt)–Slop (sunscreen)–Slap (hat)” and Sun-Smart,7,9 that began in the late 1960s and

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1970s and that stressed avoiding the sun in the middle of the day, seeking shade while outdoors, wearing sun-protective clothing while outdoors, and use of sunscreens.

**Sunscreen vs. Sun Protection?**

In Australia, the use of sunscreens is understood as a default option. The public health message is that sunscreens are only to be used when other measures do not provide sufficient protection. This hierarchy of sun protection messages was stressed in the Clinical Practice Guidelines for the Management of Cutaneous Melanoma, published in 1999 by the National Health & Medical Research Council of Australia (Australia’s counterpart of the National Institutes of Health in the US).

The notion that one should not rely on a sunscreen as the frontline protective measure against melanoma is particularly important in light of eight epidemiological studies published in the period from 1979 to 2000, which reported that sunscreen use was a statistically significant risk factor for melanoma. While this finding may be artifactual—resulting from excessive sun exposure in those who are protected against sunburn through sunscreen use and/or from inappropriate application or use of low SPF (sun protection factor) sunscreens—it should give health care professionals pause. Recommendations regarding sunscreens should be offered as part of an overall sun protection strategy.

Australian-based population surveys in the State of Victoria (population 4.7 million) have shown that for almost a decade (1991 to 1998), the proportion of the adult population avoiding sun exposure in the middle of the day on weekends has increased from 52% to 65%; the wearing of hats outdoors has increased from about 40% to 50%; and the wearing of clothes that cover most exposed skin has remained steady at about 45%. During this same time period, between 40% and 50% of the population reported regular sunscreen use. Summertime random population surveys in Melbourne (population 3.4 million), the capital city of Victoria, conducted between 1988 and 1998 (Professor David Hill, personal communication), have shown that the proportion of Melbournians reporting being sunburned on weekends was halved during this period.

Therefore, while it is clear that Australians engage in a variety of sun protection behaviors that have significantly reduced their sunburn rate, it is far from certain which sun protection behavior or combinations of behaviors has been effective in reducing sunburn rates, as well as decreasing age-specific melanoma and non-melanocytic skin cancer incidence rates.

**Older Men at Higher Risk**

Earlier detection of melanoma, with its attendant improvements in melanoma survival and mortality rates, has been one of the triumphs of public and professional awareness campaigns in the US, the United Kingdom, and Australia. In Australia today, 75% of all fatal melanoma is diagnosed in adults 50 years of age or older, and two thirds of these cases are in men. Therefore, while it is certainly important to identify high-risk individuals on the basis of family history, phenotype (hair color, propensity to sunburn, freckles), and presence of actinic keratoses and/or non-melanocytic skin cancers, in Australia, the population most in need of both regular self examination and professional screening is older adults, particularly men.

A randomized controlled trial has begun looking at about 560,000 residents of Queensland, Australia in 44 rural communities. Participants, who must be at least 30 years of age, have been random-
ized by community to a program of self skin examination and screening by a health care professional or to observation only (Dr. J. Aitken, personal communication). This very large randomized controlled screening trial has the power to detect a 20% difference in mortality between the two experimental groups within a 13-year time period.

Clinical Detection of Melanoma

Recent Australian data from a controlled trial have shown that General Practitioners (GPs, primary health care professionals) can achieve a sensitivity for the diagnosis of melanoma equivalent to that of skin cancer specialists (dermatologists and plastic surgeons); GPs, however, excise many more benign pigmented lesions to achieve this sensitivity than do skin cancer specialists.22

As sensitivity is generally more important than specificity in a cancer screening program, comparisons of diagnostic ability between GPs and dermatologists may not yield accurate estimates of how GPs would perform in screening for melanoma. Computer modeling was used in this same Australian study to test the cost-effectiveness of screening for melanoma by GPs, using sensitivity and specificity data from the study. This analysis revealed that biennial screening of men between 50 and 70 years of age by GPs would result in a cost per life-year saved of $26,078—within the range of acceptability in Australia.

It is worth noting that while there was a sharp overall increase in the incidence of melanoma in Australia during the mid- to late 1980s, mortality leveled off in men and declined in women.23 A similar phenomenon was reported in Scotland and New Zealand during the same period, and an analysis of these data concluded that a proportion of the melanomas that contributed to the sharp increase in incidence were probably non-metastatic early indolent melanomas with no clinical potential for mortality.21,23 Early detection alone should have resulted in a subsequent decrease in melanoma incidence, as lesions that might have been diagnosed in subsequent years were diagnosed earlier and thinner. This did not occur.24 It is not surprising that formal or informal screening programs will reveal in-situ and very early invasive cancers that may have a different biology than symptomatic clinical disease.21,23,24

Surgical Margins and Lymph Node Dissection

Rigel and Carucci1 rightly stress the importance of adequate surgical excision of a primary melanoma if early diagnosis is to result in cure. The Australian melanoma clinical practice guidelines10 also emphasize the importance of excisional biopsy wherever possible, with definitive excision margins for surgical treatment of a primary melanoma similar to those recommended by Rigel and Carucci. There is, however, no evidence from randomized controlled trials that an excision margin greater than 1 cm for melanomas of any thickness offers additional benefits for the patient in terms of survival; greater excisional margins may, however, decrease local recurrence.10

In the surgical treatment of primary melanoma, the respective roles of elective lymph node dissection and sentinel node biopsy have not yet been settled. In Australia, elective lymph node dissection is no longer routinely practiced for melanomas of any thickness, and major melanoma units are participating in randomized controlled trials of sentinel lymph node biopsy to determine its appropriate use in staging and treatment of primary melanoma. In the interim, based on the Intergroup randomized controlled trial,25 the Australian guidelines recommend that elective lymph node dissection be considered only for patients younger than 60 years
of age with 1-to-4 mm thick primary melanomas on the trunk.\textsuperscript{10}

**Radiotherapy**

Rigel and Carucci\textsuperscript{1} briefly describe the use of cytotoxic chemotherapy, biological agents, and vaccines, both as adjuvant treatments and as treatments for advanced melanoma, but do not consider the place of radiotherapy in certain types of melanoma. The Australian clinical practice guidelines recommend considering radiotherapy for unresectable lentigo-malignant melanoma; postoperative radiotherapy after resection of mucosal melanoma; or radiotherapy for cutaneous melanoma where local recurrence is likely (i.e., when lesions are more than 4 mm thick; when there are satellite nodules or there has been neurotropic spread).\textsuperscript{10} Likewise, postoperative radiotherapy after therapeutic lymph node resection is recommended where multiple nodes are involved and/or where there has been extracapsular spread.\textsuperscript{10} These guidelines also remind us that radiotherapy has a definite place in the treatment of metastatic melanoma, where palliation of symptoms and/or temporary local control is needed.\textsuperscript{10}

**Biologic Therapies and Vaccines**

Because results with chemotherapy for melanoma have not improved over a quarter of a century of randomized controlled trials, Rigel and Carucci rightly stress the promise of biological agents and vaccines. Nevertheless, although there is good evidence that human melanoma is immunogenic and that the immune system can respond to it, biological therapies and vaccines have, as yet, no established place in the management of the disease.

The Australian clinical practice guidelines recommend referring patients with primary melanomas that are more than 4 mm thick and/or with involved lymph nodes, and patients with advanced disease to melanoma centers for inclusion in trials of immunotherapy, chemotherapy, or gene therapy.\textsuperscript{10} In this context, it should be noted that six randomized controlled trials of adjuvant interferon \(\alpha\) (IFN-\(\alpha2b\)) have been completed and an additional six are in progress or will commence in the year 2000.

Of the six that have been reported, only one has shown a significant effect on absolute survival, and that trial employed the highest dose of IFN-\(\alpha2b\) administered intravenously.\textsuperscript{26} Apart from a small, but significant, effect on disease-free survival in two subsequent trials\textsuperscript{27,28} none of the other completed trials have shown any beneficial effect of adjuvant IFN-\(\alpha2b\).\textsuperscript{29-31} The Australian clinical practice guidelines state that “there is no conclusive evidence that adjuvant therapy is beneficial for anyone with melanoma.”\textsuperscript{10}

Melanoma has always been one of the most promising cancers for trials of immunotherapy. However, we would do well to recall that attempts to treat cancer in humans by immunotherapy began in the 1890s,\textsuperscript{32} and 110 years later we have only a small and select group of indications for the use of this treatment modality in any cancer. Nonetheless, advances in basic science have provided a range of new antigenic targets on melanoma cells. Moreover, better understanding of the immune response has resulted in the use of dendritic cells and the development of better adjuvants for use with cancer vaccines. Therefore, it is not surprising that early results from clinical trials of a number of these new approaches have been promising, and it is likely that biological and immunological treatments for melanoma will win an established place in the management of this disease in the near future.
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