Overview of Ultraviolet Radiation and Cancer: What Is the Link? How Are We Doing?

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Sun exposure has now been established as the most important avoidable cause of nonmelanoma skin cancer (NMSC) and melanoma. With specific reference to melanoma, there are several key issues that remain to be resolved. These include definition of the action spectrum, the importance of systemic effects of sun exposure, whether a tan is protective, the risk of tanning booth exposures, and the efficacy of sunscreens. Also the role, if any, of sun exposure in noncutaneous malignancies remains to be established. Melanoma incidence and mortality have increased dramatically over the past several decades, but these increases have now slowed, and for mortality among those 15 to 45 years of age, decreasing rates are now observed. Improving the coverage of the Surveillance, Epidemiology, and End Results (SEER) registries by requiring pathology laboratories in non-SEER areas to report cancers among SEER area residents will allow correct interpretation of these trends in the future at minimal cost. The available data on trends in NMSC incidence and mortality are suboptimal but suggest a pattern of declining mortality despite increasing incidence. Trends in NMSC morbidity have not been defined. Establishing NMSC registries in a few diverse sentinel areas would allow more reliable inference and monitoring. Techniques are being developed for reducing sun exposures and increasing early detection of skin cancers in the general population, but improved monitoring of incidence, mortality, and morbidity is required to monitor the effects of current and future ozone depletion and to evaluate prevention and early detection measures. — Environ Health Perspect 103(Suppl 8):251–254 (1995)

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Introduction

Ultraviolet radiation exposure has a variety of adverse health effects, including both malignancies and nonmalignant disorders of the skin and other organs. The most common ultraviolet-related malignancies are nonmelanoma skin cancers (NMSCs), which, in the United States, are approximately equal in incidence to all other malignancies combined (1). NMSC conventionally includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC); the former is more common, but the latter is more aggressive and more commonly leads to death (2).

Malignant melanoma is less common than either BCC or SCC, but is of greater public health concern. It is not uncommon; indeed, it is more common than any noncutaneous malignancy in the 25- to 29-year-old age group, and its incidence is increasing faster than any noncutaneous cancer site among men and, with the exception of lung cancer, among women (3). More significantly, it is responsible for approximately 7000 deaths per year, which is far greater than the mortality associated with NMSC (4).

There are nonneoplastic disorders and other cutaneous malignancies that have been linked to ultraviolet exposure, including atypical fibroxanthoma (5); other dermatoses (6,7); immune dysfunction (8); and ocular disease, particularly cataracts (9,10), but these will not be further discussed here.

The Link

A vast array of epidemiologic and other investigations allows us to conclude that sun exposure causes skin cancer of each of the three most common types: BCC, SCC, and melanoma. Melanoma has been more closely linked to intense, intermittent exposures to the sun, whereas NMSC is more closely linked to cumulative exposure. However, this distinction is far from absolute; in populations with high ultraviolet exposure, cumulative exposure may be closely linked to melanoma (11,12). Sun exposures early in life, especially in childhood and adolescence, are particularly associated with melanoma, although such exposures are likely to play an important role in BCC and SCC as well (13,14). Studies of special contexts (human models) have been informative (15). Even in the context of familial melanoma and of xeroderma pigmentosum, the very limited available evidence supports the link between sun exposure and cutaneous malignancy (16–20).

Unresolved Issues

Ultraviolet light is not a single entity but rather a spectrum of electromagnetic radiation that includes a broad band of wavelengths. Convention has defined ultraviolet A (UVA) to include those wavelengths longer than 320 nm, ultraviolet B (UVB) those in the range of 280 to 320 nm, and ultraviolet C (UVC) those below 280 nm. UVC does not penetrate the earth’s atmosphere, so human exposure is a result of exposures to artificial sources. UVB is responsible for sunburns and is the range most strongly blocked by common sunscreens. UVA, unlike UVB, varies relatively little with solar elevation, and hence with
the time of day or season of the year. The various recommendations for skin cancer prevention that have been offered to the general public differ in their relative effectiveness for different ultraviolet wavelengths. For example, clothing typically reduces ultraviolet exposure to the skin more uniformly across the spectrum than avoiding the midday sun, which will disproportionately reduce UVB exposure.

A key issue for each of the three common types of skin cancers is, therefore, documentation of the action spectrum (i.e., the relation between carcinogenesis and wavelength). Epidemiologic research has not been able to document an action spectrum for any of these malignancies. Fortunately, there are well-established animal models for SCC, which have been used to estimate the action spectrum. These studies have documented maximal carcinogenicity in the UVB region (21, 22).

Animal models have been proposed for melanoma; some action spectrum data have been derived from a fish model, which suggests substantial carcinogenic potential for UVA, but the relevance of these experiments to the disorder in human remains to be clarified (23–26).

A second key unresolved issue is the relative importance of local versus systemic effects of sun exposure. The majority of BCCs and of SCCs occur on the chronically sun-exposed skin of the face, although most melanomas occur elsewhere on the body, and the evidence from case–control studies regarding melanomas that occur at common locations has not demonstrated associations between location of sun exposure and location of the melanoma (27–29).

Among patients with xeroderma pigmentosum, NMSCs are more concentrated on the face than melanomas (30). On the other hand, the most sun-protected areas of the body do have the lowest incidence per unit surface area of melanoma (12). It is also clear from the laboratory that both local and systemic effects of ultraviolet exposure exist (8, 31). For anogenital or vaginal melanoma, where direct sun exposure is not involved, populations with greater presumed cutaneous sun exposure because they live nearer to equatorial latitudes do not have a higher incidence (32, 33). Hence, epidemiologic evidence has not been able to completely resolve the relative importance of a systemic effect, if any, of sun exposure on the genesis of melanoma, although direct exposure appears to be important.

A third key unresolved issue is whether a tan (facultative pigmentation) protects against melanoma for some groups. It is clear that individuals with darker untanned skin color (constitutive pigmentation) are at substantially lower risk of melanoma. Suntans also protect against sunburn, which is associated with melanoma risk (34). There have been several studies published that suggest that frequent sun exposure may be associated with lower relative risks among those who tan readily (presumably as a result of their developing a photoprotective tan) compared to the relative risks of similar exposures among those who are more sun sensitive and less capable of tanning; however, this hypothesis remains controversial (28, 35–38).

The risk of melanoma associated with exposure to artificial sources of ultraviolet is also uncertain. Several, but not all, studies of this question have noted an association between these exposures and melanoma risk (39, 40).

The fourth issue is the efficacy of sunscreens for melanoma prevention. We know from trials among human populations that conventional sunscreens are efficacious for preventing sunburns and for reducing the multiplicity of actinic keratoses (41). However, we have no direct evidence, from either animal models or human studies, about their efficacy for melanoma prevention. Indeed, one publication has even suggested that sunscreen use causes melanoma and was responsible for the sharp rise in melanoma incidence observed over the last several decades (42), although this suggestion is not supported by any substantial evidence and does not fit with our current understanding of the genesis of melanoma. Hence, although we presume that sunscreens are effective, we do not have proof and cannot presently quantify their effectiveness.

Finally, the role of sun exposure, if any, in noncutaneous malignancies has not been established. A number of cancer sites exhibit a latitude gradient that is presently unexplained. However, there is no strong evidence to support a role for the sun in the etiology of any noncutaneous malignancy, except perhaps as a cause of ocular malignancy due to direct exposure.

These half dozen issues represent key areas of uncertainty in our understanding of the link between the ultraviolet radiation and cutaneous malignancy. The list is not comprehensive, and it focuses on those issues that pertain to melanoma. The uncertainties stand out against a background of general acceptance of sun exposure as the major avoidable cause of melanoma, accounting for over 90% of the melanomas in the United States and about two-thirds of the melanomas worldwide (43).

**Current Trends—Melanoma**

Age-adjusted mortality rates for malignant melanoma in the United States have been increasing consistently over many decades and continued to increase throughout the 1980s. This increase occurred among whites but not blacks. In 1990 the rate among whites was 2.5 per 100,000 individuals per year, and among blacks 0.4 per 100,000 individuals per year. Age-adjusted melanoma incidence has also been increasing among whites since at least the 1930s, and is now over 10 times more common than it was. In recent years, the incidence has been more than 12 times higher among whites (12.0 per 100,000 individuals per year) than among blacks (0.9 per 100,000 individuals per year) (3).

Some stratospheric ozone depletion has occurred since the 1930s, but that appears to have contributed little to the present increase in melanoma because the magnitude of the depletion has been quite modest. Rather, the observed increases in both incidence and mortality appear to be most closely linked to behavioral and lifestyle factors, including the popularity of tanning and the corresponding unpopularity of pale skin among whites, the changing styles of dress in general and recreational (particularly beach) attire in particular, the increase in leisure time during these decades, and the increased accessibility of recreation in areas of intense sunlight because of the widespread availability of automobiles and air travel.

Past trends will not necessarily continue, however, and recent data provide evidence that these trends may indeed change. Age-specific mortality data were evaluated for the years 1969 through 1990 for whites in the United States. Despite an overall increase in mortality during this period, the youngest age groups (ages 15–29 years and 30–44 years) experienced declines in mortality for both genders (44). These data have been used to project an actual decline in age-adjusted melanoma mortality in the second decade of the 21st century (45, 46). Without understanding the cause of the current trends, however, predictions regarding future trends must be viewed cautiously.

It is clear that case fatality from melanoma has declined substantially despite the
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absence of major therapeutic advances. This decline undoubtedly played an important role in the observed changes in mortality. However, the role of changes in incidence remains unclear.

The primary source of melanoma incidence data in the United States is the SEER Program of the National Cancer Institute. Despite the general excellence of the SEER program, it has encountered difficulties in recent years in attaining complete registration of melanoma (47-50). As a result, the observed pattern in the SEER data of relatively stable incidence rates must be interpreted with care.

Among these issues, out-of-area diagnosis may be the most difficult problem for a disorder such as melanoma, which is cured in the majority of patients and frequently diagnosed and cured in an outpatient setting. Dermatologists frequently biopsy a skin lesion to diagnose melanoma. They typically excise the melanoma in their offices, and then mail the specimen to a pathology laboratory. If the pathology laboratory is in the cancer registry area and the registry is functioning properly, these cases will be registered. However, the pathology laboratory sometimes is located outside the registry area, in which case the cancer registry may miss the case entirely. This trend toward outpatient and out-of-area diagnosis threatens the usefulness of the existing system of cancer registries in guiding policy, practice, and research for cancers that are commonly diagnosed among outpatients.

Were a national cancer registry to be developed, this problem would largely disappear. However, much less expensive alternatives are available. It would be sufficient to require that pathology laboratories in non-SEER areas record their patients' zip codes and report the cancers that occur among SEER area residents. Effort and expense involved in this approach would be minimal, yet would be essential to guarantee the integrity of the SEER registry data in the current changing health care climate.

Current Trends—NMSC

NMSCs as a group have a case fatality rate of less than 1%; however, this low percentage still results in over a thousand deaths annually because of the frequency with which these malignancies occur. Unfortunately, NMSC mortality is poorly tracked by our vital statistics in the United States. We recently investigated over 100 deaths among residents of Rhode Island that were attributed to NMSC by vital statistics data. Over half of these deaths were misclassified, and the majority of misclassified cases were instances of squamous carcinoma of the mucosal surfaces in the head and neck. These cases were described on death certificates as dying from squamous or epidermoid carcinoma of the head and neck and the coding rules assigned them the code 173.4, which incorrectly classified the cause of death as NMSCs. Therefore, to obtain accurate mortality estimates for NMSC, it is recommended that the International Classification of Diseases (ICD) coding system be modified to exclude squamous cell carcinoma of the head and neck and other similar terms from code 173.4 (the NMSCs of the scalp and neck).

Extrapolation from our observations to the existing nationwide statistics regarding NMSC mortality suggested that the mortality rate from this cause has indeed been declining over the past two decades. The age-adjusted rates for whites and blacks for 1987 to 1988, which is the most recent published data, were 0.5 and 0.3 per 100,000 individuals per year, and the rate among men was substantially higher than that among women (51).

Data regarding the incidence of NMSC is also quite limited compared with corresponding data on melanoma. The only available data from diverse areas of the United States are from a 17-year-old study of the National Cancer Institute. Since sun exposure accounts for the vast majority of NMSCs as well as melanomas, one would expect NMSC incidence to be increasing substantially in recent decades. This expectation was confirmed by data from the British Columbia Cancer Registry and from Kaiser-Permanente data from Oregon. Extrapolation of these trends to the entire U.S. population suggested that 900,000 to 1,200,000 persons would be diagnosed with NMSC nationwide in 1994 (1). Approximately this many people are diagnosed with all other types of cancer combined. This projection may be subject to considerable error, but it is presently the best available estimate because NMSC is not included in standard U.S. cancer registries. Registration of NMSC in a few diverse sentinel areas, therefore, would be crucial for understanding future trends in the incidence of NMSC, particularly in view of ozone depletion and public health campaigns for prevention and early detection of cancer.

Since NMSC is so common, morbidity becomes a key component of its public health impact. In individual cases, morbidity ranges from quite minor to severe, which can include the loss or impairment of vital facial structures such as eyes, ears, or the nose. There is at present no published method for assessing NMSC morbidity among the general population, although one is under development in our unit. Use of morbidity data will become increasingly important in the assessment of the public health impact of this disorder.

Conclusions

Actual ultraviolet exposure received by the general population is affected both by the flux in the environment—which in turn is a function of stratospheric ozone depletion, cloud cover, artificial cover, surface albedo, altitude and latitude—and by behaviors of the populations exposed. Significant progress is being made in understanding how to affect behaviors of high risk populations, but more accurate monitoring of incidence, morbidity, and mortality will be required to assess the effects of these factors on the public health burden from skin cancers.

REFERENCES

1. Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. J Am Acad Dermatol 30:774–778 (1994).
2. Weinstock MA, Boguara HA, Ashley M, Litle V, Bilodeau E, Kimmel S. Nonmelanoma skin cancer mortality: a population-based study. Arch Dermatol 127:1194–1197 (1991).
3. Miller BA, Ries LAG, Hankey BF, Kosary CL, Harras A, Devesa SS, Edwards BK, eds. SEER Cancer Statistics Review, 1973-1990. NIH Publ No 93-2789. Bethesda, MD:National Institutes of Health, 1993.
4. Boring CC, Squires TS, Tong T, Montgomery S. Cancer statistics, 1994. CA Cancer J Clin 44:7–26 (1994).
5. Di Tomaso A, Maestro R, Dogliani C, Gasparotto D, Boiocchi M, Laurino L, Fletcher CD. Ultraviolet-induced p53 mutations in atypical fibroxanthoma. Am J Pathol 145:11–17 (1994).
6. Council on Scientific Affairs. Harmful effects of ultraviolet radiation. JAMA 262:380–384 (1989).
7. Taylor CR, Stern RS, Leyden JJ, Gilchrest BA. Photocoagulation/photodynamic therapy. J Am Acad Dermatol 22:1–15 (1990).
8. Baadsgaard O. In vivo ultraviolet radiation of human skin results in profound perturbation of the immune system: relevance to ultraviolet-induced skin cancer. Arch Dermatol 127:99–109 (1991).
9. Quigley-McGown J, Klein R, Klein BEK. Sunlight and age-related macular degeneration: the Beaver Dam Eye Study. Arch Ophthalmol 111:514–518 (1993).
10. Taylor HR. The biological effects of UVB on the eye. Photochem Photobiol 50:489–492 (1989).
11. Elwood JM. Melanoma and sun exposure: contrasts between intermittent and chronic exposure. World J Surg 16:157–166 (1992).
12. Green A, MacLennan R, Youl P, Martin N. Site distribution of cutaneous melanoma in Queensland. Int J Cancer 53:232–236 (1993).
13. Weinstock MA. Ultraviolet radiation and skin cancer: epidemiologic data from the United States and Canada. In: Environmental UV Photobiology (Young AR, Bjørn LO, Moan J, Nultsch W, eds). New York: Plenum Press, 1993:295–344.
14. Armstrong BK, Kricker A. Skin cancer. Dermatol Clin 13:583–594 (1995).
15. Weinstock MA. Human models of melanoma. Clin Dermatol 10:83–89 (1992).
16. Kraemer KH, Greene MH. Dysplastic nevus syndrome: familial and sporadic precursors of cutaneous melanoma. Dermatol Clin 3:225–237 (1985).
17. Lynch HT, Frichot BC, Lynch JF. Cancer control in xeroderma pigmentosum. Arch Dermatol 113:193–195 (1977).
18. Davis BE, Koh HK, Rohrer TE, Gonzalez E, Cleaver JE. Sunlight avoidance and cancer prevention in xeroderma pigmentosum. Arch Dermatol 130:806–808 (1994).
19. Cox SE, Roberts LJ, Bergstresser PR. Prevention of skin cancer in xeroderma pigmentosum: the physician as advocate. J Am Acad Dermatol 29:1045–1046 (1993).
20. Bech-Thomsen N, Wulf HC, Ullman S. Xeroderma pigmentosum lesions related to ultraviolet transmittance by clothes. J Am Acad Dermatol 24:365–368 (1991).
21. de Grujil FR, Sterenborg HJ, Forbes PD, Davies RE, Cole C, Kelkens G, van Weelden H, Slaper M, van der Leun JC. Wavelength dependence of skin cancer induction by ultraviolet irradiation of albino hairless mice. Cancer Res 53:53–60 (1993).
22. Cole CA, Forbes D, Davies RE. An action spectrum for UV photocarcinogenesis. Photochem Photobiol 43:275–284 (1986).
23. Setlow RB, Grist E, Thompson K, Woodhead AD. Wavelengths effective in induction of malignant melanoma. Proc Natl Acad Sci USA 90:6666–6670 (1993).
24. Klein-Stanto AJP, Silvers WK, Minrz B. Ultraviolet radiation-induced malignant skin melanoma in melanoma-susceptible transgenic mice. Cancer Res 54:4569–4572 (1994).
25. Epstein JH. Experimental models for primary melanoma. Photodermatol Photoimmunol Photomed 9:91–98 (1992).
26. Green A, Bain C, McLaren R, Siskind V. Risk factors for cutaneous melanoma in Queensland. Recent Results Cancer Res 120:76–97 (1986).
27. Weinstock MA, Colditz GA, Willett WC, Stampfer MJ, Bronstein BR, Mihm MC Jr, Speizer FE. Melanoma and the sun: the effect of swim suits and a "healthy" tan on the risk of nonfamilial malignant melanoma in women. Am J Epidemiol 134:462–470 (1991).
28. Lee JAH, Metcalf JM, Sunlight and the etiology of malignant melanoma: a synthesis. Med J Aust 2:846–851 (1970).
29. Kraemer KH, Lee MM, Andrews AD, Lambert WC. The role of sunlight and DNA repair in melanoma and nonmelanoma skin cancer: the xeroderma pigmentosum paradigm. Arch Dermatol 130:1018–1021 (1994).
30. Stierer U, Rosdahl I, Augustsson A, Kagedal B. UVB irradiation induces melanocyte increase in both exposed and shielded human skin. J Invest Dermatol 92:561–564 (1989).
31. Weinstock MA. Epidemiology and prognosis of anorectal melanoma. Gastroenterology 104:174–178 (1993).
32. Weinstock MA. Malignant melanoma of the vulva and vagina in the United States: patterns of incidence and population-based estimates of survival. Am J Obstet Gynecol 171:1225–1230 (1994).
33. Weinstock MA, Colditz GA, Willett WC, Stampfer MJ, Bronstein BR, Mihm MC Jr, Speizer FE. Nonfamilial cutaneous melanoma incidence in women associated with sun exposure before 20 years of age. Pediatrics 84:199–204 (1989).
34. Dubin N, Mosseson M, Pasternack BS. Sun exposure and malignant melanoma among susceptible individuals. Environ Health Perspect 81:139–151 (1989).
35. White E, Kirkpatrick CS, Lee JAH. Case-control study of malignant melanoma in Washington State. 1: constitutional factors and sun exposure. Am J Epidemiol 139:857–868 (1994).
36. Nelemans PJ, Groenhed H, Kemeny L, Rampen F. Effect of intermittent exposure to sunlight on melanoma risk among outdoor workers and sun-sensitive individuals. Environ Health Perspect 101:252–255 (1993).
37. Herzfeld PM, Fitzgerald EF, Hwang SA, Stark A. A case-control study of malignant melanoma of the trunk among white males in upstate New York. Cancer Detect Prev 17:601–608 (1993).
38. Walter SD, Marrett LD, From L, Hertzman C, Shannon HS, Roy P. The association of cutaneous malignant melanoma with the use of sunbeds and sunlamps. Am J Epidemiol 131:232–243 (1990).
39. Westerdahl J, Olsson H, Mämbäck A, Ingvart C, Jonsson N, Brandt L, Jonsson PE, Muller T. Use of sunbeds or sunlamps and malignant melanoma in southern Sweden. Am J Epidemiol 140:691–699 (1994).
40. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. N Engl J Med 329:1147–1151 (1993).
41. Garland CF, Garland FC, Gorham ED. Rising trends in melanoma: a hypothesis concerning sunscreen effectiveness. Annu Epidemiol 3:103–110 (1993).
42. Armstrong BK, Kricker A. How much melanoma is caused by sun exposure? Melanoma Res 3:395–401 (1993).
43. Weinstock MA. Epidemiology of melanoma. In: Current Research and Clinical Management of Melanoma (Nathanson L, ed). Boston:Kluwer Academic Publishers, 1993:29–56.
44. Kotloff KL, Narod SA, Breast cancer screening and melanoma incidence: the effect of screening and sun exposure among white women in southwestern Ontario. Cancer Causes Control 3:167–172 (1992).
45. Karagas MR, Thomas DB, Roth GJ, Johnson LK, Weiss NS. The effects of changes in health care delivery on the reported incidence of cutaneous melanoma in western Washington State. Am J Epidemiol 133:58–62 (1991).
46. Wright M. Underreporting of melanoma gives false sense of security. Dermatology Times. August 1991:45.
47. Koh HK, Geller A, Miller DR, Clapp RW, Lew RA. Underreporting of cutaneous melanoma in cancer registries nationwide. J Am Acad Dermatol 27:1035–1036 (1993).
48. Bolognia JL, Headley A, Fine J, Berwick M. Histologic evaluation of pigmented lesions in Connecticut and its influence on the reporting of melanoma. J Am Acad Dermatol 26:198–202 (1992).
49. Weinstock MA. Nonmelanoma skin cancer mortality in the United States, 1969 through 1988. Arch Dermatol 129:1286–1290 (1993).