Cancer Causes and Control, 1997, 8, pp. 271-283

REVIEW PAPERS

Sunlight and cancer

Dallas R English, Bruce K Armstrong, Anne Kricker, and Claire Fleming

(Received 3 June 1996; accepted in revised form 19 August 1996)

Epidemiologic evidence on the relation between sunlight and cancer is reviewed. Strong evidence implicates sunlight as a cause of skin cancer, although, for melanoma and basal cell carcinoma, the relationship is complex. Both types of cancer are associated more strongly with nonoccupational exposure than with occupational exposure, and the pattern and amount of exposure each appear to be important. Squamous cell carcinoma appears to be related more strongly to total (*i.e.*, both occupational and nonoccupational) exposure to the sun. The evidence that sunlight causes melanoma of the eye is weak. It shows no latitude gradient and the results of case-control studies are conflicting. There is inadequate evidence to suggest that sunlight does or does not cause any other type of cancer. *Cancer Causes and Control* 1997, 8, 271-283

Key words: Melanoma, skin neoplasms, sunlight.

Introduction

Strictly speaking, sunlight is *visible* light from the sun. We are using the term loosely here to refer to the ultraviolet (UV) radiation (wavelengths from about 295 to 400 nm) and visible light (400 to 780 nm) that reach the surface of the earth. UV radiation of less than about 295 nm does not reach the earth's surface because it is absorbed by the atmosphere.

UV radiation is probably responsible for all the carcinogenic effects of sunlight. UVB (280 to 315 nm) is much more effective at producing cancer in animals, erythema (sunburn) in humans, and DNA damage, than is UVA (315 to 400 nm) – wavelengths of about 340 nm or more are less than 1/1,000 times as potent in causing cancer in experimental animals as wavelengths of about 295 nm.[1] It is difficult to separate the effects of UVB, UVA, and visible light in epidemiologic studies; thus, epidemiologic studies generally deal with sunlight as a whole rather than with any of its components.

Six categories of epidemiologic evidence are relevant to the proposition that sunlight causes skin cancer. They are that these cancers are: (i) more frequent in residents of areas of high ambient solar irradiance; (ii) more frequent in sun-sensitive people; (iii) occur mainly on sun-exposed body sites; (iv) more frequent in people with high sun exposure; (v) more frequent in people with benign sun-related skin conditions; and (vi) reduced by protection of the skin against the sun. Evidence can be gained within each of these categories by both descriptive and analytical studies.

We review here the epidemiology of cancers of the skin – melanoma, and the nonmelanocytic skin cancers squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) – and melanoma of the eye. We also briefly discuss other neoplasms for which relationships with sunlight have been postulated. Our aim is to produce a synthesis of the evidence relating sunlight to cancer and to identify areas for further research.

Dr English is with the Department of Public Health, The University of Western Australia. Dr Armstrong and Ms Fleming are with the NSW Cancer Council, Woolloomooloo, NSW, Australia. Dr Kricker is with the National Breast Cancer Center, Woolloomooloo, NSW, Australia. Address correspondence to Dr English, Department of Public Health, University of Western Australia, Perth, WA 6907, Australia. *Financial support was provided, in part, by the Cancer Foundation of Western Australia, the Health Promotion Foundation of WA, and the Australian Rotary Health Research Fund.*

Melanoma of the skin

Descriptive studies

Ethnic origin. Melanoma is predominantly a disease of people of European origin. In the United States, its incidence is some 20-fold higher in Whites than Blacks.[2] Rates of melanoma are also very low in Asians in the US and very low in Asia.[2]

Place of residence. The incidence of melanoma is greatest in the White population of Australia, a sun-sensitive population in an area of high ambient sunlight[2] and increases with proximity to the equator in many populations.[3,4] In Europe, however, incidence of melanoma is higher in Norway and Sweden in the north than in France, Italy, and Spain in the south.[2] This apparent anomaly may be due to the tendency for skin color in Europe to increase in darkness with increasing proximity to the equator.[3]

Migration. When people of European origin migrate from areas of low incidence of melanoma and generally low ambient sunlight to areas of high incidence and higher ambient sunlight, their subsequent rates of melanoma are generally higher than those in their home country and less than those in the host country.[5,6] Age at arrival of these migrants in the host country is a powerful predictor of subsequent risk of melanoma – the older the age at arrival, the lower the incidence.[5,7] However, it is not possible to distinguish age at arrival from duration of residence in these studies.

Occupation. Incidence and mortality rates of melanoma are generally higher among indoor workers than outdoor workers,[8-10] which is not consistent with a simple relationship between sun exposure and melanoma. They are also higher in people of high socioeconomic status than of low socioeconomic status. In the absence of any plausible alternative explanation, this relationship with socioeconomic status is presumed to be due to complex effects of sun exposure.

Anatomic site. In a recent Australian survey,[11] melanoma had its highest density on the usually exposed parts of the head and neck and its lowest density on rarely exposed sites (buttocks and abdomen in both genders and scalp in women). Its density was low on the forearms, backs of hands, upper arms and lower limbs, and intermediate on the sometimes exposed shoulders and back in both genders and the chest in males (Table 1).

Table 1. Surface density of occurrence of cutaneous melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC) by body site, relative to a density of 1.0 for the whole body in whole population series[a]

	Melanoma		BCC	SCC
	Level 1	Level 2+		
Men				
Usually exposed				
Scalp, face, neck, ears	4.9	2.0	3.9	6.5
Forearms, backs of hands	0.8	0.5	1.4	2.0
Occasionally exposed				
Shoulders, back, chest	1.7	2.5	1.8	0.3
Upper arms, lower limbs	0.3	0.5	0.4	0.3
Rarely exposed				
Abdomen, buttocks	0.2	0.2	0.0	0.0
Women				
Usually exposed				
Face, neck	7.6	2.5	6.7	8.9
Forearms, backs of hands	0.8	0.6	1.3	3.3
Occasionally exposed				
Shoulders, back	0.9	1.8	1.8	0.2
Upper arms, lower limbs	0.8	1.1	0.5	0.4
Rarely exposed				
Scalp, ears, chest, abdomen, buttocks	0.3	0.3	0.2	0.4

[a] Data on melanoma are from Green *et al*;[11] data on BCC and SCC are unpublished observations based on incident cases from Geraldton, Western Australia.

Analytic studies

Sensitivity of skin to sunlight. People who sunburn easily and tan poorly are at increased risk of melanoma.[12] In two recent case-control studies from the western US,[13,14] risk relative to that in those who developed a deep tan following chronic sun exposure increased steadily to 9.0 (95 percent confidence interval [CI] = 3.8-21.1) in those who developed no tan or only freckles and to 2.6 (CI = 1.6-4.1) in those who burnt without tanning following acute exposure.

Ambient sunlight at places of residence. Associations between melanoma and measures of ambient sunlight at places of residence and measures of personal exposure to sunlight in case-control or cohort studies published since about 1980 are summarized in Table 2. This table is based on recent reviews[12,15] and recently published studies.[14,16-23]

Eight out of 10 studies showed significant associations between risk of melanoma and measures of ambient sunlight at places of residence (*e.g.*, daily hours of bright sunlight at places of residence and history of residence closer to or farther from the equator than the study area). The relative risks (RR) for the highest exposure categories varied between 1.7 and 8.0. The remaining two studies showed weakly positive associations. The strongest association (RR = 8.0, CI = 2.0-34.7) was in US veterans of World War II who served in the tropics compared with other men of draft age who did not serve or did not serve in the tropics.[24]

Exposure of skin to sunlight.

Lifetime total exposure. By 'total exposure' we mean occupational and nonoccupational exposure together. Six case-control studies of melanoma have attempted to estimate lifetime total exposure to sunlight (Table 2). In three,[23,25,26] statistically significant positive associations were observed, and a statistically significant negative association was observed in one. The three positive associations were from studies in France and Spain.

Recent total exposure. The measures of recent or usual total exposure to sunlight are a heterogeneous and often crude group mainly concentrated on sun exposure in the 10 to 20 years before diagnosis of melanoma. Studies using them have found no consistent pattern of association with melanoma (Table 2).

Occupational exposure. Twenty case-control studies and one cohort study have examined the relationship between estimated occupational exposure to sunlight and melanoma; they have shown negative associations as often as positive ones (Table 2). Two of the studies showing positive associations were based on an analysis of occupational titles, not on specific estimation of occupational exposure. The remaining three studies were all from Europe and included two of the southern European studies[23,26] in which positive associations with lifetime total sun-exposure were observed.

Some understanding of these seemingly contradictory results is offered by studies which suggest that melanoma on body sites that usually are covered is highest in office workers, whereas the incidence on sites that usually are exposed is as high or higher in outdoor workers.[27,28] Thus, contradictory results well may arise as a result of differences in the distributions of indoor and outdoor workers in the population, and resulting differences in distributions of melanoma by body site.

Nonoccupational exposure. A majority of studies of nonoccupational exposure to sunlight and melanoma has observed statistically significant, positive associations (Table 2). These results have come from a variety of different measures of exposure such as time spent sunbathing, time spent in sunny vacations, estimated

Table 2. Summary of results of case-control or cohort studies of sunlight exposure and melanoma reported from 1980 to 1996[a]

Measure of sun exposure	Number of studies	Associations between sunlight and melanoma		
		Number positive	Number null	Number negative
Ambient sunlight at places of residence	10	8	2	0
Personal exposure to sunlight				
Lifetime total exposure	6	3	2	1
Recent or usual total exposure	6	1	4	1
Occupational exposure	20	5	10	5
Nonoccupational exposure	21	12	8	1
History of sunburn	24	21	3	0
Other sunlight-related skin damage	8	7	1	0

[a] Table includes results of studies summarized in reviews by the International Agency for Research on Cancer,[15] Armstrong and English,[12] and those of other recently published studies.

hours of nonoccupational sun exposure in summer, time spent in particular outdoor recreations (fishing, boating). Only one study found a significant, negative association, and all but two of the remaining studies found RRs for the highest exposure categories that were greater than 1.0. Some RRs were very high – eight or greater.

Despite the difficulty presented by disparate measures of exposure among different studies, one group of investigators[29] has attempted a pooled analysis of published results with respect to nonoccupational ('intermittent') and occupational ('chronic') exposure to sunlight. In seven population-based studies, which showed less heterogeneity in RR estimates than hospital-based studies, the pooled estimates of RR for melanoma were 1.6 (CI = 1.3-1.9) for the highest category of nonoccupational exposure and 0.7 (CI = 0.6-0.9) for the highest category of occupational exposure.

History of sunburn. Almost all studies that have investigated it have found a positive association between past history of sunburn and risk of melanoma with RRs typically above two and up to 12 (Table 2).

Other sunlight-related skin damage. Exposure to sunlight is believed to cause nonmelanocytic skin cancers, as reviewed here, and a range of benign skin conditions (*e.g.*, solar elastosis, solar lentigines, solar keratoses).[30] Presence or history of these conditions often has been documented in case-control studies of melanoma; positive associations have almost always been found (Table 2).

Exposure-response relationship. What few data exist on the exposure-response relationship for sunlight and melanoma suggest that risk increases sharply at low exposures, reaches a plateau and, if anything, falls at higher exposures.[31,32] The matter is complicated by possible contributions of both amount and pattern of exposure to causing the disease and confounding between these two. As Elwood and Gallagher[32] have pointed out: "It may therefore be inappropriate to produce a unified dose response curve for the whole relationship. Intermittent and constant exposure (amount and pattern) may be intrinsically different, with conflicting effects, so that the risk for an individual depends on the balance between these two exposures."

Is total amount of exposure important? The relationship between ambient sunlight and melanoma suggests that, given a particular pattern of exposure, as amount increases risk increases. That melanoma is most dense on some more-or-less continuously exposed sites and that melanoma on exposed sites appears to increase with increasing occupational exposure also suggests that risk increases with increasing total amount of exposure. On the other hand, melanoma is associated strongly with nonoccupational exposure to the sun and sunburn, both of which probably reflect an intermittent pattern of exposure, and risk overall generally does not rise and even may fall as occupational exposure increases and increasing amount of exposure is traded off against falling intermittency of exposure. Thus, pattern of exposure also appears to be important.

We now postulate that, given a particular pattern of exposure to sunlight, risk of melanoma increases with increasing amount of exposure and, given a particular amount of exposure, risk increases as exposure becomes more intermittent. The independence of effects of amount and pattern of exposure and the shapes of their relationships with melanoma have not yet been shown empirically.

Protection against sunlight. Most case-control and cohort studies have found positive rather than negative associations between sunscreen use and cutaneous melanoma[30,33] which have not been eliminated by control for sun sensitivity and sun exposure. Two recent case-control studies, however, have observed protective effects. In a study from the south of Spain,[23] the RR, adjusted for sun exposure and sun sensitivity, fell from 1.0 in those who never used sunscreens to 0.6 (CI = 0.3-1.4) in occasional users and 0.2 (CI = 0.0-0.8) in those who always used them when in the sun. Similarly, among women in the San Francisco Bay area (California, US) in the 1980s,[14] those who never used sunscreens had an RR for melanoma of 2.3 (P = 0.001) when compared with those who always used them, adjusted for sun exposure, sunburn, and host factors. Lack of information on the sun protection factors of sunscreens used in these various studies makes it difficult to explain the inconsistencies.

Basal cell carcinoma of the skin

Basal cell carcinoma (BCC) is more common than squamous cell carcinoma (SCC) of the skin. These two types of nonmelanocytic skin cancer have often been grouped in epidemiologic studies, although recent evidence suggests that they may differ in their relationship to sunlight. Their epidemiology has been reviewed in detail by Kricker *et al.*[34]

Descriptive studies

Ethnic origin. Nonmelanocytic skin cancer is rare in non-White populations. In a US survey conducted in 1977-78, the incidence rate of SCC and BCC combined was 232.6 per 100,000 person-years in Whites but only 3.4 among Blacks.[35] In populations of mainly European origin, inci-

dence rates are lower in people with ethnically darker skins.[35,36]

Place of residence. In Australia and the US, incidence is greatest in regions closest to the equator.[35,37] The incidence of BCC in Australia in 1990 increased three-fold from latitudes south of 37°S to latitudes north of 29°S.[37]

Occupation. Early reports associated nonmelanocytic skin cancer with outdoor occupation.[38-40] More recent and more rigorous studies have shown much less evidence of such an association.[27,28] None of these studies has distinguished between BCC and SCC.

Migration. In 1990, the incidence of BCC in migrants to Australia was half that in those born in Australia.[37] Most migration to Australia is from areas of lower ambient sunlight.

Anatomic site. Table 1 shows the relative density on the skin of incident cases of BCC in a recent whole-population study in Western Australia. The highest density of BCC was on the usually exposed sites and the lowest on the rarely exposed sites. Intermediate densities occurred on sometimes exposed sites, including the trunk.

Analytic studies

Earlier cross-sectional and case-control studies of BCC generally were not population-based and had a number of methodologic difficulties, including few subjects, crude measurement of exposure to sunlight, and inadequate control of confounding.[34] The following review, therefore, is based on the more recent, population-based studies.

Sensitivity of skin to sunlight. RRs of 2.0 or more have been found for BCC with a skin that burns rather than tans.[36,41-43] Light skin color was associated significantly with BCC in one study only.[44]

Consistent with the descriptive observations referred to above, case-control studies have shown that people of southern-European ethnic origin born in Australia or Canada have half or less the risk of BCC of people of other (generally lighter skinned) ethnic origins born in the same country.[36,44]

Ambient sunlight at places of residence. In Western Australia, risk of BCC increased with increasing intensity of ambient solar radiation at all places of residence.[45] In a cohort study of US nurses,[43] those who had lived in California or Florida (US) had increased rates of BCC compared with those who had lived in northeastern states.

Exposure of skin to the sun.

Total exposure. The evidence linking reported total (occupational and nonoccupational) sun exposure to BCC is weak: of five studies,[42-47] none showed a statistically significant, positive association. Earlier reports of strong associations came from studies in which confounding of the association by age and gender was likely.[34]

Only the Western Australian study[48] has examined sun exposure to the site of the skin cancer. While risk of BCC did not correlate well with total site-specific exposure to the sun, the patterns of RRs differed by body-site. Relative risk of BCC of the head and neck and the limbs fell with increasing lifetime total exposure, but, on the trunk, it increased with increasing total exposure; the RR for the highest category of total exposure to the trunk was 2.4 (CI = 1.2-4.8). Amounts of exposure differed across body sites and the entire range of exposure of the trunk fitted into the first quarter of exposure to the head and neck.

Occupational exposure. Exposure to the sun at work is not associated strongly with BCC. Two[41,49] of five studies showed statistically significant positive associations with occupational exposure, but with only small increases in risk (RRs of 1.3 and 1.4) for what were quite crude summary variables. Two[44,45] of three studies not supportive of occupational exposure as a risk factor for BCC were based on well-defined quantitative measurements.

Nonoccupational exposure. All studies of nonoccupational exposure, measured as summer holiday or weekend exposure, which have used quantitative measurements of sun exposure have shown statistically significant positive associations with BCC. These results were obtained in Western Australia,[48] Canada,[44] and southern Europe (*i.e.*, the Helios study[46]). In addition, a specific measure of intermittent exposure, constructed by Kricker *et al*[48] from estimates of exposure on working days and nonworking days in each week, showed strongly increasing risks of BCC with increasing intermittency of sun exposure at 15 to 19 years of age, with a high RR (3.9, CI = 1.9-7.8) for the most intermittent pattern of exposure.

Sunburn. Risk of BCC increased significantly with lifetime measures of sunburn in two[43,46] of six population-based studies. RRs ranged from 2.9 for six or more sunburns in one study[43] to 1.7 in two studies[46,48] and around 1.0 in three.[44,49,50]

Other sun-related skin damage. Strong positive relationships have been observed between BCC and solar keratoses[36,50] and more moderate associations between BCC and telangiectasia and solar elastosis.[36]

Exposure-response relationship. The quantitative relationship between sunlight exposure and BCC has been modeled in three studies: a survey of skin cancer in Chesapeake Bay (Maryland, US) watermen,[51] the Western Australian case-control study,[45] and the Helios study.[46] The three studies are reasonably consistent in suggesting that risk of BCC first rises with increasing exposure but then reaches a plateau.

In the Western Australian study,[45] risk of BCC increased with increasing sun exposure in those who tanned well, but the risk was initially flat and then fell with increasing exposure in those who tanned poorly. This pattern is consistent with the reported exposure-response relationships because, for any given incident exposure, actual exposure of the basal layer of the skin would be less in those who tan well than in those who tan poorly.

Protection against sunlight. In Western Australia, use of sunscreens and the wearing of a hat were associated with an increased risk of BCC rather than a decreased risk.[48] This association was strongest in the 10 years before diagnosis of the cancer, thus suggesting that it may have been due to recent adoption of protection against the sun in those already at high risk of skin cancer. An apparently paradoxical association was also found in US nurses;[43] risk of BCC was 40 percent higher in those who regularly spent time outdoors and used sunscreen than in those who regularly spent time outdoors and did not use sunscreen.

Squamous cell carcinoma of the skin

Descriptive studies

Ethnic origin. Nonmelanocytic skin cancer, including SCC, is rare among populations not of European origin. Among populations of mainly European origin, the incidence rate of SCC is lower in ethnic groups with darker skin pigmentation.[35,36]

Place of residence. Within Australia, the US, and Norway, the incidence rate of SCC increases with increasing proximity to the equator.[35,37,52] The pattern is less clear among countries, but is likely to be confounded by ethnic origin and by varying degrees of completeness of ascertainment.[34] SCC is related more strongly to latitude[37] or measured UVB radiation[35] than is BCC.

Migration. Migrants to Australia from the United Kingdom, an area of lower sun exposure, have incidence rates of SCC about half those of the Australian-born population.[37]

Occupation. No separate descriptive studies of SCC have been reported. Analytic studies of occupation are discussed below.

Anatomic site. SCC has its highest density on usually exposed sites. Unlike melanoma and BCC it has low density on sometimes exposed sites (Table 1). Urbach[53] examined SCC occurring on the head and neck and found that, in contrast to BCC, they rarely occurred on the more sheltered parts.

Analytic studies

The following review is based mainly on the more recent, population-based studies.

Sensitivity of skin to sunlight. Estimates of RR have been between 1.5 and 4.5 for comparisons of the most sensitive skin with the least sensitive skin.[34]

Ambient sunlight at places of residence. Grodstein *et al* [54] observed an association between risk of SCC and place of residence in a cohort of US nurses. Compared with women living in northeastern states, women living in California or Florida had increased rates. US veterans of World War II who served in the Pacific were more likely than their counterparts who served in Europe to have an SCC.[55]

Exposure of skin to the sun.

Total lifetime exposure. Total lifetime exposure to the sun, measured in hours, showed a strong dose-response relationship with SCC in an early hospital-based case-control study.[56] However, because age was not controlled, substantial confounding is likely. Much weaker positive associations have been observed in more adequate studies,[34] although a strong association was seen in the Helios study.[46] No increased risk was seen in the cohort study of US nurses (although the data were based on a single question, "Do you regularly spend time outdoors in the summer?"),[54] nor in a case-control study from Canada[57] that had extensive data on exposure.

Occupational exposure. Crude measures of occupational exposure were considered in four studies;[34] all RRs were greater than 1.0. More recently, Gallagher *et al*[57] estimated the number of hours of exposure at work. Although little effect was seen for total lifetime exposure at work, odds ratios (OR) increased with increasing exposure at work in the last 10 years – the OR in the highest category was 4.0 (CI = 1.2-13.1). Rosso *et al*[46] found increasing risks with increasing hours of exposure at work.

Nonoccupational exposure. Gallagher *et al*[57] estimated hours outdoors during recreation over the lifetime, in the first 20 years of life and in the last 10 years. Only for exposure in the first 20 years were ORs greater than unity and even then, the highest OR was only 1.6. Similarly, Rosso *et al*[46] found little or no association with a number of measures of nonoccupational exposure.

Sunburn. Kricker *et al*[34] reviewed three studies of sunburn. Two found strong associations (ORs = 3 or greater)[50,56] and the other found a weak association (OR of 1.5).[58] Three studies have been completed subsequently: rate ratios increased with lifetime number of burns in the cohort study of US nurses[54] and most, but not all, measures of sunburn were related to risk of SCC in the Canadian case-control study.[57] However, no association was seen in the Helios study.[46]

Other sun-related skin damage. Strong associations have been seen with biological markers of long-term sun exposure.[34] These markers include solar lentigines, facial telangiectasia, elastosis of the neck and dorsum of the hands, and presence of solar keratoses. The association with solar keratoses is particularly strong.

Exposure-response relationship. Two reports[46,51] provide quantitative data on the exposure-response relationship. The first, of Chesapeake Bay watermen,[51] included only 35 men with SCC. The prevalence of SCC was modeled as a power function of average, annual estimated UVB-exposure and age (*i.e.*, Prevalence = Exposure^{a} × Age^{b}). When four cases with the lowest exposure levels were excluded, a strong relationship was seen with annual exposure (the exponent was 1.7). Although these data suggest that the prevalence of SCC, and presumably also the incidence, increases with increasing exposure, the effect would have been much weaker had the arbitrary exclusion of cases not been made. Data from the Helios study[46] are more convincing – the RR increased exponentially with increasing total hours of exposure.

Protection against sunlight. The effect of sunscreens on risk of SCC has been considered in only one study, the Nurses' Health Study.[54] The OR for regular time outdoors with use of sunscreens, compared with no regular time outdoors, was 0.9 (CI = 0.6-1.2). The OR for time outdoors without use of sunscreens was 0.7 (CI = 0.4-1.1). Persuasive evidence that sunscreens protect against solar keratoses (probable precursors to SCC) is provided by the results of two randomized trials.[59,60]

Melanoma of the eye

Most UV radiation incident on the eye is absorbed by the cornea and the lens. Approximately four percent of it reaches the retina in early childhood and this proportion falls with increasing age to less than one percent of radiation below 340 nm and two percent of radiation between 340 and 360 nm.[61] Thus, while exposure of the retina is low, induction of choroidal melanoma by solar UV radiation is still possible.

Descriptive studies

Ocular melanoma is classified and often reported under the same rubric as all other cancers of the eye. However, since ocular melanoma comprises some 80 percent of cancers of the eye, the descriptive patterns of all cancers of the eye probably give a reasonable reflection of its patterns, particularly in adults.

Ethnic origin. Ocular melanoma is primarily a disease of populations of European origin. Among mixed populations residing at the same latitude, its incidence is higher in Whites than Blacks and Asians.[62-64]

Place of residence. No evidence has been found of a latitude gradient for ocular melanoma or cancers of the eye as a whole.[65-67] Incidence rates for cancers of the eye as a whole in nine countries showed a rural excess in males.[68]

Migration. Whereas rates of cutaneous melanoma are higher in Jews born in Israel than in Jews born in Europe and America,[6] there is little difference in rates of ocular melanoma between these two groups.[69]

Occupation. Ocular melanoma has been associated inconsistently with farming in descriptive studies. Two studies found a positive association,[70,71] but three did not.[72-74]

Anatomic site. Ocular melanomas are located most frequently in the central posterior choroid and the inferior and temporal iris.[75] The central posterior choroid corresponds to the region of maximal light focusing by the refractive components of the eye. Studies using model eyes have shown that the inferior and temporal regions of the iris are relatively unprotected from incident light by surrounding anatomic structures.[76,77]

Analytic studies

Sensitivity of skin to sunlight. People who burn easily and tan poorly had moderately increased risk of ocular melanoma (RR = 2 or less) in two[78,79] of four relevant

case-control studies. No association was seen with hair and eye color when ethnicity was taken into account,[78-82] but in one of these studies,[82] an increased risk with light skin color persisted after adjustment for ethnicity.

Ambient sunlight at places of residence. Two case-control studies from the US[81,82] showed an association between ocular melanoma and birth or residence in the southern US; but in two other studies,[79,80] no associations were observed with place of residence.

Exposure of eye to the sun. There is little evidence for an association between personal sun exposure and ocular melanoma. Total cumulative sunlight exposure was not associated with ocular melanoma in two case-control studies.[80,82] Four case-control studies[80,82-84] found no significant association with farming, but one[84] found an increased risk in sailors, ships' officers, and fishermen. Three studies[78,80,82] found no association with personal leisure time or vacation exposure to the sun. One other study,[81] however, found weak associations with gardening and frequent sunny vacations but not with high leisure time outdoors.

Protection against sunlight. In one case-control study,[81] those who occasionally, rarely, or never used sunglasses, hats, or sun visors when in the sun had increased risks of ocular melanoma (up to RR = 1.9 with rare use) relative to those who almost always used them. However, another study[82] found no evidence of a protective effect with use of sunglasses or a sun visor.

Other cancers

Conjunctival cancer

Squamous cell carcinoma of the conjunctiva usually presents in the exposed area of the eye between the lids.[85] It has been shown in a study of incidence rates in 47 populations[86] to decrease in incidence by 49 percent per 10-degree increase in latitude and by 29 percent for a one minimal erythemal-dose-fall in estimated ambient UV irradiance. Additionally, a recent study[87] of conjunctival and limbal epithelial dysplasia (carcinoma *in situ* and squamous cell carcinoma) reported increased risks for fair skin, being outdoors at < 30° latitude for greater than 50 percent of the time before age 12 years, estimated cumulative UV exposure and a history of skin cancer.

Non-Hodgkin's lymphoma

Studies in Europe[88-93] have shown an increased risk of non-Hodgkin's lymphoma subsequent to non-melanocytic skin cancer and malignant melanoma. The parallel dramatic increase in incidence rates in Europe and the US over recent decades and the generally similar geographic variation for non-Hodgkin's lymphoma and skin cancer also suggest that these malignancies may have a common risk factor, possibly sunlight exposure.[94] However, in the US, the mortality rates from non-Hodgkin's lymphoma are highest in the north, not the south.[95]

Breast and colon cancer

It has been hypothesized that sunlight might prevent breast cancer and colon cancer[96,97] on the grounds that vitamin D might protect against these cancers. Mortality rates for both breast and colon cancer and incidence rates for colorectal cancer were found to be highest in parts of the US with the lowest ambient sunlight.[96-98] The incidence of breast cancer in the former Union of Soviet Socialist Republics (USSR) also was inversely related to ambient sunlight levels,[99] but the correlation between breast cancer and socioeconomic status was stronger than that between sunlight and breast cancer. No studies in individuals have been reported.

Molecular effects of ultraviolet radiation

UV radiation produces a number of photoproducts in DNA. The most common are cyclobutane-type pyrimidine dimers and pyrimidine-pyrimidone (6-4) photoproducts formed between adjacent pyrimidines (cytosine [C] and thymine [T]).[100] The action spectrum for formation of photoproducts in DNA in human skin closely approximates that for the induction of squamous cell carcinoma in mice.[1,101] UV photoproducts are mutagenic if they are not repaired before cell division occurs. The most common UV-induced mutations are C→T transitions, which occur at dypyrimidine sites.[102] Tandem transitions CC→TT also occur – these mutations are almost specific to UV.[103]

Patients with xeroderma pigmentosum (XP), an inherited disorder characterized by increased sensitivity to acute exposure to the sun and defective repair of DNA photoproducts, have histories of high numbers of BCC, SCC, cutaneous melanoma at young ages on body sites commonly exposed to sunlight, and of cancers of the anterior eye.[104] These observations strongly implicate unrepaired photoproducts in DNA in the genesis of these cancers, although two other syndromes of inherited deficiency in excision repair of DNA are not associated with increased incidence rates of skin cancer.[105,106]

In 1991, Brash and co-workers[107] reported mutations in the p53 tumor suppressor gene in 14 (58 percent) of 24 SCCs. Three mutations were CC→TT transitions, five were C→T transitions and all mutations occurred at dipyrimidine sites. Other investigators have also reported p53 mutations at dipyrimidine sites in SCC, BCC, and

solar keratoses.[108-114] Mutations of the p53 gene occur in up to 90 percent of SCC and about 50 percent of BCC.[115] They also have been observed in normal skin. Transitions from CC to TT were observed in normal skin on sun exposed sites in 17 of 23 (74 percent) samples from Australian skin cancer patients compared with one of 20 (five percent) samples of skin from sites not exposed to the sun,[116] suggesting that p53 mutations occur frequently in response to sunlight. However, p53 mutations are rare in melanomas.[117] Mutations possibly due to UV radiation have been observed[118] in another putative tumor suppressor gene, the CDKN2 gene, in melanoma cell lines, and infrequently in tumors.

Conclusions

The strength of evidence that sunlight causes melanoma of the skin, BCC, SCC, and melanoma of the eye is summarized in Table 3 for each epidemiologic feature discussed in the text. For all three skin cancers, the distributions by anatomic site, ethnic origin, and place of residence, and the effects of migration implicate sunlight as a cause. Of all the descriptive characteristics considered, only occupation provides little evidence that sunlight causes skin cancer. The increased risk of melanoma in indoor workers once was considered to be persuasive evidence against sunlight causing the disease.

Melanoma of the skin and BCC appear to share many epidemiologic features, while SCC stands apart. Evidence that melanoma of the skin and BCC are related to total and occupational exposure to the sun is largely absent (Table 3). Strong evidence, particularly for melanoma, exists for a relationship with nonoccupational exposure. In contrast, there is evidence that SCC is related to total and occupational exposure, but almost no evidence that it is related to nonoccupational exposure. All three skin cancers are related to sunburn (particularly melanoma) and all are related also to other indicators of sunlight-induced skin damage. Finally, studies of mutations in BCCs and SCCs provide evidence that they were caused by sunlight. There is much less evidence of this kind for melanoma.

The risk of melanoma of the skin and BCC appears to increase with increasing exposure to sunlight at low levels of exposure, before leveling off and perhaps falling at high levels. This pattern may be due to confounded effects of amount and pattern of sunlight exposure in causing melanoma and BCC. It might be argued reasonably that, as amount of exposure increases, pattern of exposure becomes more continuous and thus ameliorates the effect of the increased amount. There are at present, however, no adequate empirical data which would enable these complex interacting and confounded effects to be disentangled.

Table 3. Summary of strength of evidence that sunlight causes cancer based on epidemiologic features discussed in text[a]

Epidemiologic feature	Skin			Eye melanoma
	Melanoma	BCC	SCC	
Descriptive studies				
Ethnic origin	+	+	+	+
Place of residence	+	+	+	0
Migration	+	+	+	0
Occupation	0	0	0	0
Anatomic site	+	+	+	+
Analytic studies				
Sensitivity of skin to sunlight	+	+	+	0
Ambient sunlight at places of residence	+	+	+	0
Exposure of the skin to sunlight				
Total exposure	0	0	+	0
Occupational exposure	0	0	+	0
Non-occupational exposure	+	+	0	0
Sunburn	+	+	+	0
Other sun-related skin damage	+	+	+	0
Protection against sunlight	0	0	0	0
Molecular effects				
Effects of DNA repair deficiency	+	+	+	0
Mutations in tumors characteristic of UV radiation	+	+	+	0

[a] ++ indicates strong evidence; + indicates weak evidence; 0 indicates conflicting evidence, lack of evidence or lack of effect.

Data on the quantitative nature of the exposure-response relationship for SCC indicate a monotonic increase in risk with increasing exposure. These observations are supported by the anatomic site distribution and the strong latitude gradient.

No consistent evidence that sunlight causes melanoma of the eye emerges from descriptive studies or analytic studies in which individual exposure to the sun was measured. Only differences by ethnic origin, the anatomic site of melanoma within the eye, and some conflicting results showing decreased risk associated with protection against sunlight are supportive.

In 1992, the International Agency for Research on Cancer (IARC) concluded that there is sufficient evidence that solar radiation causes melanoma of the skin and nonmelanocytic skin cancer.[15] What, then, are the outstanding issues? Identifying the exposure-response relationships, with particular emphasis on distinguishing between pattern and amount of exposure is the most important outstanding issue. This is not merely of academic interest, because if pattern of exposure is important, a reduction in amount of exposure might not result in a reduction of risk of melanoma (and possibly also of BCC) if pattern of exposure changes at the same time. Another unresolved, but not unrelated, issue is the relationship between exposure to a particular anatomic site and risk of skin cancer on that site. A number of the inconsistencies seen in current literature may be due to failure to measure exposure to the anatomic site where the cancer occurred. The lack of protective effects of sunscreen and hat use is also notable, and there is limited other direct evidence that protection from sun exposure reduces risk of any skin cancer in the general population. The possibility that sun exposure causes ocular melanoma remains tantalizing and should not be discarded without some further study although, given that sun exposure in early life could be of dominant importance, it will not be easy.

How might we address the outstanding issues? Because of the low salience of sun exposure, measuring lifetime exposure to particular anatomic sites, including pattern and amount, is an error-prone task. The problem may not be so great in young adults who may be able to remember relevant exposures in childhood, adolescence, and early adulthood, and whose parents may be available to corroborate their memories. International, collaborative case-control studies, involving centers with widely varying ambient exposures may prove useful. Cohort studies are of limited value unless large numbers of young subjects can be recruited and resurveyed frequently to update their sun exposure. This would be a formidable task.

What is the role of 'molecular' epidemiology? We need a range of short-term and long-term biomarkers that can be used to distinguish the effects of pattern and amount of exposure. We know little about the relationship of most current biomarkers (*e.g.*, UV-induced mutations in the p53 gene, formation of DNA photoproducts) to pattern and amount of exposure. It would not be difficult to design short-term experimental studies in humans to elucidate some of these issues. It is doubtful that continued analysis of UV-induced mutations in the p53 gene or other genes in tumors will be of value if used in the absence of appropriate measures of exposure. Lack of association between some genetic changes in BCC and sun exposure,[119] for example, may be due to failure to measure pattern of exposure.

References

1. de Gruijl FR. Photobiology of photocarcinogenesis. *Photochem Photobiol* 1996; 63: 372-5.
2. Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J, eds. *Cancer Incidence in Five Continents.* Lyon, France: International Agency for Research on Cancer, 1992; IARC Sci. Pub. No. 120.
3. Armstrong BK. Melanoma of the skin. *Br Med Bull* 1984; 40: 346-50.
4. Bulliard JL, Cox B, Elwood JM. Latitude gradients in melanoma incidence and mortality in the non-Maori population of New Zealand. *Cancer Causes Control* 1994; 5: 234-40.
5. Khlat M, Vail A, Parkin DM, Green A. Mortality from melanoma in migrants to Australia: variation by age at arrival and duration of stay. *Am J Epidemiol* 1992; 135: 1103-13.
6. Iscovich J, Andreev H, Steinitz R. Incidence of cutaneous malignant melanoma in Israel, 1960-1989. *Public Health Rev* 1995; 23: 1-23.
7. Mack TM, Floderus B. Malignant melanoma risk by nativity, place of residence at diagnosis, and age at migration. *Cancer Causes Control* 1991; 2: 401-11.
8. Holman CD, Mulroney CD, Armstrong BK. Epidemiology of pre-invasive and invasive malignant melanoma in Western Australia. *Int J Cancer* 1980; 25: 317-23.
9. Lee JA, Strickland D. Malignant melanoma: social status and outdoor work. *Br J Cancer* 1980; 41: 757-63.
10. Cooke KR, Skegg DC, Fraser J. Socio-economic status, indoor and outdoor work, and malignant melanoma. *Int J Cancer* 1984; 34: 57-62.
11. Green A, Maclennan R, Youl P, Martin N. Site distribution of cutaneous melanoma in Queensland. *Int J Cancer* 1993; 53: 232-6.
12. Armstrong BK, English DR. Cutaneous malignant melanoma. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention. Second Edition.* New York, NY (USA): Oxford University Press, 1996.
13. White E, Kirkpatrick CS, Lee JA. Case-control study of malignant melanoma in Washington State. I. Constitutional factors and sun exposure. *Am J Epidemiol* 1994; 139: 857-68.
14. Holly EA, Aston DA, Cress RD, Ahn DK, Kristiansen JJ. Cutaneous melanoma in women. I. Exposure to sunlight, ability to tan, and other risk factors related to ultraviolet light. *Am J Epidemiol* 1995; 141: 923-33.
15. International Agency for Research on Cancer. *Solar and Ultraviolet Radiation*. Lyon, France: IARC, 1992: *IARC Monogr Eval Carcinog Risks Humans:* 1-316.

16. Pion IA, Rigel DS, Garfinkel L, Silverman MK, Kopf AW. Occupation and the risk of malignant melanoma. *Cancer* 1995; 75: 637-44.
17. Autier P, Dore JF, Lejeune F, *et al.* Recreational exposure to sunlight and lack of information as risk factors for cutaneous malignant melanoma. Results of an European Organization for Research and Treatment of Cancer (EORTC) case-control study in Belgium, France and Germany. The EORTC Malignant Melanoma Cooperative Group. *Melanoma Res* 1994; 4: 79-85.
18. Autier P, Dore JF, Schifflers E, *et al.* Melanoma and use of sunscreens: an EORTC case-control study in Germany, Belgium and France. The EORTC Melanoma Cooperative Group. *Int J Cancer* 1995; 61: 749-55.
19. Westerdahl J, Olsson H, Ingvar C, Brandt L, Jonsson PE, Moller T. Southern travelling habits with special reference to tumour site in Swedish melanoma patients. *Anticancer Res* 1992; 12: 1539-42.
20. Westerdahl J, Olsson H, Ingvar C. At what age do sunburn episodes play a crucial role for the development of malignant melanoma? *Eur J Cancer* 1994; 30A: 1647-54.
21. Marghoob AA, Slade J, Salopek TG, Kopf AW, Bart RS, Rigel DS. Basal cell and squamous cell carcinomas are important risk factors for cutaneous malignant melanoma. Screening implications. *Cancer* 1995; 75: 707-14.
22. Goodman KJ, Bible ML, London S, Mack TM. Proportional melanoma incidence and occupation among White males in Los Angeles County (California, United States). *Cancer Causes Control* 1995; 6: 451-9.
23. Rodenas JM, Delgado-Rodriguez M, Herranz MT, Tercedor J, Serrano S. Sun exposure, pigmentary traits, and risk of cutaneous malignant melanoma – a case-control study in a Mediterranean population. *Cancer Causes Control* 1996; 7: 275-83.
24. Brown J, Kopf AW, Rigel DS, Friedman RJ. Malignant melanoma in World War II veterans. *Int J Dermatol* 1984; 23: 661-3.
25. Lê MG, Cabanes PA, Desvignes V, Chanteau MF, Mlika N, Avril MF. Oral contraceptive use and risk of cutaneous malignant melanoma in a case-control study of French women. *Cancer Causes Control* 1992; 3: 199-205.
26. Grob JJ, Gouvernet J, Aymar D, *et al.* Count of benign melanocytic nevi as a major indicator of risk for nonfamilial nodular and superficial spreading melanoma. *Cancer* 1990; 66: 387-95.
27. Vågerö D, Ringbäck G, Kiviranta H. Melanoma and other tumours of the skin among office, other indoor and outdoor workers in Sweden 1961-1979. *Br J Cancer* 1986; 53: 507-12.
28. Beral V, Robinson N. The relationship of malignant melanoma, basal and squamous skin cancers to indoor and outdoor work. *Br J Cancer* 1981; 44: 886-91.
29. Nelemans PJ, Rampen FH, Ruiter DJ, Verbeek AL. An addition to the controversy on sunlight exposure and melanoma risk: a meta-analytical approach. *J Clin Epidemiol* 1995; 48: 1331-42.
30. World Health Organization. *Ultraviolet Radiation (Environmental Health Criteria 160).* Geneva, Switzerland: WHO, 1994.
31. Elwood JM, Gallagher RP, Hill GB, Pearson JC. Cutaneous melanoma in relation to intermittent and constant sun exposure—the Western Canada Melanoma Study. *Int J Cancer* 1985; 35: 427-33.
32. Elwood JM, Gallagher RP. Sun exposure and the epidemiology of melanoma. In: Gallagher RP, Elwood ME, eds. *Epidemiological Aspects of Cutaneous Malignant Melanoma.* Boston, MA (USA): Kluwer Academic Publishers, 1994: 15-66.
33. Westerdahl J, Olsson H, Masback A, Ingvar C, Jonsson N. Is the use of sunscreens a risk factor for malignant melanoma? *Melanoma Res* 1995; 5: 59-65.
34. Kricker A, Armstrong BK, English DR. Sun exposure and non-melanocytic skin cancer. *Cancer Causes Control* 1994; 5: 367-92.
35. Scotto J, Fears TR, Fraumeni JF Jr. *Incidence of Non-melanoma Skin Cancer in the United States.* Bethesda, MD (USA): US Department of Health and Human Services, 1983; NIH Pub. No. 82-2433.
36. Kricker A, Armstrong BK, English DR, Heenan PJ. Pigmentary and cutaneous risk factors for non-melanocytic skin cancer—a case-control study. *Int J Cancer* 1991; 48: 650-62.
37. Marks R, Staples M, Giles GG. Trends in non-melanocytic skin cancer treated in Australia: the second national survey. *Int J Cancer* 1993; 53: 585-90.
38. Molesworth EH. Rodent ulcer. *Med J Aust* 1927; 1: 878-99.
39. Blum H. Sunlight as a causal factor in cancer of the skin in man. *JNCI* 1948; 9: 247-58.
40. Emmett EA. Ultraviolet radiation as a cause of skin tumors. *CRC Critical Reviews in Toxicology* 1973; 2: 211-55.
41. Marks R, Jolley D, Dorevitch AP, Selwood TS. The incidence of non-melanocytic skin cancers in an Australian population: results of a five-year prospective study. *Med J Aust* 1989; 150: 475-8.
42. Vitasa BC, Taylor HR, Strickland PT, *et al.* Association of nonmelanoma skin cancer and actinic keratosis with cumulative solar ultraviolet exposure in Maryland watermen. *Cancer* 1990; 65: 2811-7.
43. Hunter DJ, Colditz GA, Stampfer MJ, Rosner B, Willett WC, Speizer FE. Risk factors for basal cell carcinoma in a prospective cohort of women. *Ann Epidemiol* 1990; 1: 13-23.
44. Gallagher RP, Hill GB, Bajdik CD, *et al.* Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer. I. Basal cell carcinoma. *Arch Dermatol* 1995; 131: 157-63.
45. Kricker A, Armstrong BK, English DR, Heenan PJ. A dose-response curve for sun exposure and basal cell carcinoma. *Int J Cancer* 1995; 60: 482-8.
46. Rosso S, Zanetti R, Martinez C, *et al.* The multicentre South European Study, 'Helios.' 2. Different sun exposure patterns in the aetiology of basal cell and squamous cell carcinomas of the skin. *Br J Cancer* 1996; 73: 1447-54.
47. Zanetti R, Rosso S, Martinez C, *et al.* The multicentre South European Study, 'Helios.' 1. Skin characteristics and sunburns in basal cell and squamous cell carcinomas of the skin. *Br J Cancer* 1996; 73: 1440-6.
48. Kricker A, Armstrong BK, English DR, Heenan PJ. Does intermittent sun exposure cause basal cell carcinoma? A case-control study in Western Australia. *Int J Cancer* 1995; 60: 489-94.
49. Hogan DJ, To T, Gran L, Wong D, Lane PR. Risk factors for basal cell carcinoma. *Int J Dermatol* 1989; 28: 591-4.
50. Green A, Battistutta D. Incidence and determinants of skin cancer in a high-risk Australian population. *Int J Cancer* 1990; 46: 356-61.
51. Strickland PT, Vitasa BC, West SK, *et al.* Quantitative carcinogenesis in man: solar ultraviolet B dose dependence of skin cancer in Maryland watermen. *JNCI* 1989; 81: 1910-3.
52. Magnus K. The Nordic profile of skin cancer incidence. A comparative epidemiological study of the three main types of skin cancer. *Int J Cancer* 1991; 47: 12-9.

53. Urbach F. Geographic pathology of skin cancer. In: Urbach F, ed. *Biologic Effects of UVR with Emphasis on the Skin*. Oxford, UK: Pergamon Press, 1969: 635-50.
54. Grodstein F, Speizer FE, Hunter DJ. A prospective study of incident squamous cell carcinoma of the skin in the Nurses' Health Study. *JNCI* 1995; 87: 1061-6.
55. Ramani ML, Bennett RG. High prevalence of skin cancer in World War II servicemen stationed in the Pacific theater. *J Am Acad Dermatol* 1993; 28: 733-7.
56. Urbach F, Rose DB, Bonnem M. Genetic and environmental interactions in skin carcinogenesis. *Environmental Cancer*. Baltimore, MD (USA): Williams & Wilkins, 1972: 355-71.
57. Gallagher RP, Hill GB, Bajdik CD, *et al.* Sunlight exposure, pigmentation factors, and risk of nonmelanocytic skin cancer. II. Squamous cell carcinoma. *Arch Dermatol* 1995; 131: 164-9.
58. Hogan DJ, Lane PR, Gran L, Wong D. Risk factors for squamous cell carcinoma of the skin in Saskatchewan, Canada. *J Dermatol Sci* 1990; 1: 97-101.
59. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. *N Engl J Med* 1993; 329: 1147-51.
60. Naylor MF, Boyd A, Smith DW, Cameron GS, Hubbard D, Neldner KH. High sun protection factor sunscreens in the suppression of actinic neoplasia. *Arch Dermatol* 1995; 131: 170-5.
61. Lerman S. Light induced changes in ocular tissues. In: Miller D, ed. *Clinical Light Damage to the Eye*. New York, NY (USA): Springer-Verlag, 1987: 183-215.
62. Neugut AI, Kizelnik-Freilich S, Ackerman C. Black-white differences in risk for cutaneous, ocular, and visceral melanomas. *Am J Public Health* 1994; 84: 1828-9.
63. Polednak AP, Flannery JT. Brain, other central nervous system, and eye cancer. *Cancer* 1995; 75: 330-7.
64. Raivio I. Uveal melanoma in Finland. An epidemiological, clinical, histological and prognostic study. *Acta Ophthalmol* 1977; Suppl: 1-64.
65. Scotto J, Fraumeni JF Jr, Lee JA. Melanomas of the eye and other noncutaneous sites: epidemiologic aspects. *JNCI* 1976; 56: 489-91.
66. Gislason I, Magnusson B, Tulinius H. Malignant melanoma of the uvea in Iceland 1955-1979. *Acta Ophthalmol (Copenh)* 1985; 63: 389-94.
67. Schwartz SM, Weiss NS. Place of birth and incidence of ocular melanoma in the United States. *Int J Cancer* 1988; 41: 174-7.
68. Doll R. Urban and rural factors in the aetiology of cancer. *Int J Cancer* 1991; 47: 803-10.
69. Iscovich J, Ackerman C, Andreev H, Pe'er J, Steinitz R. An epidemiological study of posterior uveal melanoma in Israel, 1961-1989. *Int J Cancer* 1995; 61: 291-5.
70. Saftlas AF, Blair A, Cantor KP, Hanrahan L, Anderson HA. Cancer and other causes of death among Wisconsin farmers. *Am J Ind Med* 1987; 11: 119-29.
71. Gallagher RP, Elwood JM, Rootman J. Epidemiologic aspects of intraocular malignant melanoma. *Cancer Treat Res* 1988; 43: 73-84.
72. Milham SJ. *Occupational Mortality in Washington State 1950-1979*. Cincinnati, OH (USA): National Institute for Occupational Safety and Health. 1983; DHSS (NIOSH) Pub. No. 83-116.
73. Office of the Population Censuses and Surveys. *Occupational Mortality: the Registrar General's Decennial Supplement for Great Britain 1979-80, 1982-83*. London, UK: Her Majesty's Stationery Office, 1986; Series DS No. 6.
74. Vågerö D, Swerdlow AJ, Beral V. Occupation and malignant melanoma: a study based on cancer registration data in England and Wales and in Sweden. *Br J Ind Med* 1990; 47: 317-24.
75. Horn EP, Hartge P, Shields JA, Tucker MA. Sunlight and risk of uveal melanoma. *JNCI* 1994; 86: 1476-8.
76. Coroneo MT, Muller-Stolzenburg NW, Ho A. Peripheral light focusing by the anterior eye and the ophthalmohelioses. *Ophthalmic Surg* 1991; 22: 705-11.
77. Narayanan P, Merriam JC, Vazquez ME, Dillon J. Experimental model of light focusing of the peripheral cornea. *Invest Ophthalmol Vis Sci* 1996; 37: 37-41.
78. Holly EA, Aston DA, Char DH, Kristiansen JJ, Ahn DK. Uveal melanoma in relation to ultraviolet light exposure and host factors. *Cancer Res* 1990; 50: 5773-7.
79. Van Hees CL, De Boer A, Jager MJ, *et al.* Are atypical nevi a risk factor for uveal melanoma? A case-control study. *J Invest Dermatol* 1994; 103: 202-5.
80. Gallagher RP, Elwood JM, Rootman J, *et al.* Risk factors for ocular melanoma: Western Canada Melanoma Study. *JNCI* 1985; 74: 775-8.
81. Tucker MA, Shields JA, Hartge P, *et al.* Sunlight exposure as risk factor for intraocular malignant melanoma. *N Engl J Med* 1985; 313: 789-92.
82. Seddon JM, Gragoudas ES, Glynn RJ, Egan KM, Albert DM, Blitzer PH. Host factors, UV radiation, and risk of uveal melanoma. A case-control study. *Arch Ophthalmol* 1990; 108: 1274-80.
83. Ajani UA, Seddon JM, Hsieh C-c, Egan KM, Albert DM, Gragoudas ES. Occupation and risk of uveal melanoma. An exploratory study. *Cancer* 1992; 70: 2891-900.
84. Holly EA, Aston DA, Ahn DK, *et al.* Intraocular melanoma linked to occupations and chemical exposures. *Epidemiology* 1996; 7: 55-61.
85. Ni C, Searl SS, Kriegstein HJ, Wu BF. Epibulbar carcinoma. *Int Ophthalmol Clin* 1982; 22: 1-33.
86. Newton R, Ferlay J, Reeves G, Beral V, Parkin DM. Effect of ambient solar ultraviolet radiation on incidence of squamous-cell carcinoma of the eye. *Lancet* 1996; 347: 1450-1.
87. Lee GA, Williams G, Hirst LW, Green AC. Risk factors in the development of ocular surface epithelial dysplasia. *Ophthalmology* 1994; 101: 360-4.
88. Hall P, Rosendahl I, Mattsson A, Einhorn S. Non-Hodgkin's lymphoma and skin malignancies—shared etiology? *Int J Cancer* 1995; 62: 519-22.
89. Adami J, Frisch M, Yuen J, Glimelius B, Melbye M. Evidence of an association between non-Hodgkin's lymphoma and skin cancer. *Br Med J* 1995; 310: 1491-5.
90. Frisch M, Melbye M. New primary cancers after squamous cell skin cancer. *Am J Epidemiol* 1995; 141: 916-22.
91. Levi F, Randimbison L, Te VC, La Vecchia C. Non-Hodgkin's lymphomas, chronic lymphocytic leukaemias and skin cancers. *Br J Cancer* 1996; 74: 1847-50.
92. Frisch M, Hjalgrim H, Olsen JH, Melbye M. Risk for subsequent cancer after diagnosis of basal-cell carcinoma. A population-based, epidemiologic study. *Ann Int Med* 1996; 125: 815-21.
93. Wassberg C, Thorn M, Yuen J, Ringborg U, Hakulinen T. Second primary cancers in patients with cutaneous malignant melanoma: a population-based study in Sweden. *Br J Cancer* 1996; 73: 255-9.
94. McMichael AJ, Giles GG. Have increases in solar ultraviolet exposure contributed to the rise in incidence of non-Hodgkin's lymphoma? *Br J Cancer* 1996; 73: 945-50.

95. Hartge P, Devesa SS, Grauman D, Fears TR, Fraumeni JF Jr. Non-Hodgkin's lymphoma and sunlight. *JNCI* 1996; 88: 298-300.
96. Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol* 1980; 9: 227-31.
97. Garland FC, Garland CF, Gorham ED, Young JF. Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. *Prev Med* 1990; 19: 614-22.
98. Emerson JC, Weiss NS. Colorectal cancer and solar radiation. *Cancer Causes Control* 1992; 3: 95-9.
99. Gorham ED, Garland FC, Garland CF. Sunlight and breast cancer incidence in the USSR. *Int J Epidemiol* 1990; 19: 820-4.
100. Brash DE. UV mutagenic photoproducts in Escherichia coli and human cells: a molecular genetics perspective on human skin cancer. *Photochem Photobiol* 1988; 48: 59-66.
101. Freeman SE, Hacham H, Gange RW, Maytum DJ, Sutherland JC, Sutherland BM. Wavelength dependence of pyrimidine dimer formation in DNA of human skin irradiated in situ with ultraviolet light. *Proc Natl Acad Sci USA* 1989; 86: 5605-9.
102. Sage E. Distribution and repair of photolesions in DNA: genetic consequences and the role of sequence context. *Photochem Photobiol* 1993; 57: 163-74.
103. Hutchinson F. Induction of tandem-base change mutations. *Mutat Res* 1994; 309: 11-5.
104. 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* 1994; 130: 1018-21.
105. Bridges B. Sunlight, DNA damage and skin cancer: a new perspective. *Jpn J Cancer Res* 1990; 81: 105-7.
106. Barrett SF, Robbins JH, Tarone RE, Kraemer KH. Evidence for defective repair of cyclobutane pyrimidine dimers with normal repair of other DNA photoproducts in a transcriptionally active gene transfected into Cockayne syndrome cells. *Mutat Res* 1991; 255: 281-91.
107. Brash DE, Rudolph JA, Simon JA, *et al.* A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. *Proc Natl Acad Sci USA* 1991; 88: 10124-8.
108. Pierceall WE, Mukhopadhyay T, Goldberg LH, Ananthaswamy HN. Mutations in the p53 tumor suppressor gene in human cutaneous squamous cell carcinomas. *Mol Carcinog* 1991; 4: 445-9.
109. Ziegler A, Leffell DJ, Kunala S, *et al.* Mutation hotspots due to sunlight in the p53 gene of nonmelanoma skin cancers. *Proc Natl Acad Sci USA* 1993; 90: 4216-20.
110. Rady P, Scinicariello F, Wagner RF Jr, Tyring SK. p53 mutations in basal cell carcinomas. *Cancer Res* 1992; 52: 3804-6.
111. Molès JP, Moyret C, Guillot B, *et al.* p53 gene mutations in human epithelial skin cancers. *Oncogene* 1993; 8: 583-8.
112. Burns JE, Baird MC, Clark LJ, *et al.* Gene mutations and increased levels of p53 protein in human squamous cell carcinomas and their cell lines. *Br J Cancer* 1993; 67: 1274-84.
113. van der Riet P, Karp D, Farmer E, *et al.* Progression of basal cell carcinoma through loss of chromosome 9q and inactivation of a single p53 allele. *Cancer Res* 1994; 54: 25-7.
114. Ziegler A, Jonason AS, Leffell DJ, *et al.* Sunburn and p53 in the onset of skin cancer. *Nature* 1994; 372: 773-6.
115. Ziegler A, Jonason AS, Simon J, Leffell DJ, Brash DE. Tumor suppressor gene mutations and photocarcinogenesis. *Photochem Photobiol* 1996; 63: 432-5.
116. Nakazawa H, English D, Randell PL, *et al.* UV and skin cancer: specific p53 gene mutation in normal skin as a biologically relevant exposure measurement. *Proc Natl Acad Sci USA* 1994; 91: 360-4.
117. Daya-Grosjean L, Dumaz N, Sarasin A. The specificity of p53 mutation spectra in sunlight induced human cancers. *J Photochem Photobiol B* 1995; 28: 115-24.
118. Pollock PM, Pearson JV, Hayward NK. Compilation of somatic mutations of the CDKN2 gene in human cancers – non-random distribution of base substitutions. *Genes Chromosom Cancer* 1996; 15: 77-88.
119. Gailani MR, Leffell DJ, Ziegler A, Gross EG, Brash DE, Bale AE. Relationship between sunlight exposure and a key genetic alteration in basal cell carcinoma. *JNCI* 1996; 88: 349-54.