Environmental Factors in Nonmelanoma and Melanoma Skin Cancer

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We discuss the role of sunlight, mostly ultraviolet light (UV), in the induction of nonmelanoma and melanoma skin cancer. Whilst the former seems to be correlated with accumulated exposure, the causation of melanoma is more complex, and may also involve the pattern of, and age at, exposure. The efficacy of sunscreens is debatable; while they protect against UVB wavelengths (290-320 nm), and so extend the time that may be spent in the sun before becoming sunburnt, their use may subject wearers to excessive exposure to UVA (320-400 nm) and visible light. Both epidemiological surveys and experiments with animal models suggest that UVA, and perhaps the visible, may induce melanomas.

Although Japanese have a much lower incidence of skin cancer than Caucasians, the dramatic rise in skin cancer in Japanese-Americans in Hawaii exposed to high-intensity irradiation raises concerns. If the Japanese people adopt sun-seeking behavior, or should the levels of UV irradiation rise significantly through depletion of the ozone layer, then this could become an important health problem in future.

ultraviolet radiation; skin cancer; UVB; UVA; animal models

Observations, epidemiological studies, and experimental studies starting over two centuries ago, showed that excessive exposure to sunlight (ultraviolet radiation, UV) can lead to nonmelanoma and melanoma skin cancer and other degenerative changes, particularly in light-skinned individuals, and also that chemical agents may modify the carcinogenic effects of light (see Urbach, 1997a for historical review). The implications of these researches to public health went largely unheeded until the period between the early 1960s and the end of the 1980s when the incidence of skin cancer rose dramatically, at a rate of 3-7% a year, among many Caucasian populations throughout the world; in tropical areas, such as Australia, South Africa, and Hawaii, rates were even higher, over 8% (Armstrong and Kricker, 1990; Saxe et al., 1998). The increase in malignant melanoma was particularly alarming; presently, at 11% of all skin cancers, cutaneous malignant melanoma is the fourth commonest cancer in Australia and New Zealand, the tenth in the United States, Canada, and Scandinavia, and the eighteenth in England (Serraino et al., 1998). In cloudy Scotland, for example, incidence rates rose by 80% from the early 1980s to the early 1990s (MacKie, 1993). Concerns rocketed with the depletion of the UV-protective stratospheric layer, and the predicted probable rise in skin cancer (particularly nonmelanoma) as more UVB reached the earth's surface; Urbach (1997b) predicted an increase in skin cancer of 4-9%, depending upon the location and season. Between mid-August and early October, 1998, the Antarctic ozone hole was bigger than ever, about three times the size of the United States. Its record size was due to El Nino that strengthened the vortex of cold air that sits over the Pole each year. At -86°C its core was 4°C colder than usual, and the situation was ideal for the formation of polar stratospheric clouds within which anthropogenic chlorine and bromine destroy ozone (NASA News, October 6, 1998). A disquiet is that as the hole breaks up, the ozone-depleted air will diffuse over mid-latitudes of the southern hemisphere.

To some small extent, these concerns have been mitigated, as it has become apparent that behavior (increased sun exposure) might account for much of the increase in skin cancer, rather than the rise in UV radiation (Urbach, 1997b) - and behavior possibly might be changed. Due to active national programs in several countries promoting sensible behavior to
reduce sun exposure, people have become more aware of the
danger, and, together with earlier diagnosis of the disease, inci-
dence rates and mortality rates have stabilized (Liu and Soong,
1996). Although all forms of skin cancer, especially melanoma, are rarer in Japan, it was one of the few countries
where this leveling-off had not occurred by the late 1980s
(Elwood, 1989; Armstrong and Kricker, 1990; Ichihashi et al.,
1995). In 1996, Suzuki and his colleagues reported a five-times
higher rate of nonmelanoma skin cancer in the southern part of
Japan compared with northern regions; the average daily dose
of solar ultraviolet light was about 1.8 times higher in the
south. The predicted increases in UVB radiation at ground
level appear to have been cancelled out since the late 1970s by
an increase in tropospheric pollution, at least in non-urban pol-
luted regions (Ma and Guicherit, 1997), and probably else-
where. Nevertheless, there still is considerable cause for con-
cern as habits die hard, and to many people, sunbathing and
acquiring a tan remain seductive. Therefore, continued
research is needed into the disease. Extensive epidemiological
studies seeking to establish the relation between the pattern
of lifetime sun exposure and the incidence of skin cancer have not
provided unambiguous answers, nor have those exploring the role
of chemical exposures in the disease. The findings from experi-
mental studies are often unclear and conflicting, part of which
may be due to the lack of a suitable animal model. Ley and his
colleagues have used the American opossum, Monodelphis
domestica, in looking at the induction of melanoma (Ley,
1987; Ley et al., 1989), and hairless albino mice in looking at
the efficacy of sunscreens (Ley and Fourtanier, 1997). Kato et
al. (1998) are developing a promising transgenic mouse line in
which skin melanosis advances, stepwise, to a benign
melanocytic tumor, and finally to a metastasizing malignant
melanoma; the transformation appears akin to that of the
human giant congenital melanocytic nevus present in new-
borns. However, for these mammalian models there are draw-
backs, including the difficulties of experimental manipulation
and the long period of repeated exposures.

We have used a nonmammalian model, fish of the genus
Xiphophorus, which has allowed us to determine the sensitivity
to melanoma induction at a number of UV wavelengths, that
is, to generate an action spectrum. As far as we know, this is
the only model with which such studies can be made. We are
now exploring the genetic control of tumor development
(Kazianis et al., 1998). The eventual applicability of this
model to human pathology is based upon our belief that the
basic mechanisms of physiology are similar throughout a
broad spectrum of phyla (see Kleinkeller, 1989; Bitensky,
1989, for discussions of nonmammalian models in research).

In this paper, we briefly review the present consensus on the
relation of sun exposure to skin cancer, especially melanoma,
noting areas where opinions differ. We suggest that a clearer
picture of the disease could become available, sooner, from
studies with animal models.

**PATTERNS OF SUN EXPOSURE
AND SKIN CANCER**

Although epidemiological and experimental data have
strongly implicated sunlight as the primary cause of all skin
cancers, including melanoma for which exposure accounts for
90-95% among Caucasians in Australia and the United States
(Armstrong and Kricker, 1993), the exact patterns of exposure
are unclear. It is questionable whether the duration of expo-
sure, intensity, frequency, or age at exposure carries the most
risk; similarly, the offending wavelengths are uncertain.

Squamous cell carcinoma appears to be related to the total
exposure to the sun, both occupational and nonoccupational;
it shows a clear latitudinal gradient among people of the same skin color, and it predominantly occurs on areas of
the body exposed to the sunlight.

The relationship of UV radiation to melanoma and basal cell
carcinoma is more complex. While the incidence of malignant
melanoma generally increases towards the equator and seems
to be related to the total accumulated exposure, it also increases
above 50° latitude in Europe (rates are higher in northern
Europe than in southern regions), and seems related to intense
intermittent exposure. Moreover, the effect of latitude on
melanoma mortality rates seems to be declining in the United
States and they are expected not to be affected by latitude by
this apparent anomaly by suggesting that short-term intense
exposures, such as might occur for indoor workers on week-
ends and vacations, are associated with an increase in risk;
long-term continuous exposure, characteristic of outdoor work-
ners, may show no effect. (Interestingly, British women have
the same rates as their husbands suggesting a social and not
occupational cause). Although melanoma occurs with greatest
frequency on exposed areas of the body, the increased age-
standardized rate of occurrence of melanoma on areas of the
body infrequently exposed (Elwood and Gallagher, 1998) also
supports the idea that intermittent exposures may be riskier
than continuous exposure. An extreme example of this differ-
ence is shown in data from Scotland where the incidence of
melanoma on the feet is five times that at the hands (MacKie
et al., 1992). Kricker et al. (1995a,b) associated the risks of
basal cell carcinoma with lifetime exposure on vacations, as
infrequent but intense increments of sun exposure.

A hypothesis that the epidemiological data on melanoma is
explicable by increases in the temperature of exposed skin with
decreasing latitude (Christophers, 1998) is readily rejected by
the existence of high incidences of melanoma in the Nordic
countries (Magnus, 1991; Moan and Dahlback, 1993), and by
the fact that populations deficient in repairing UV damage
(individuals with xeroderma pigmentosum) have 1000-fold
higher incidence of melanoma (Kraemer et al., 1984; Kraemer, 1997).

The role of sunburns in melanoma is also problematic. Several studies have claimed a relationship between the incidence of the disease and the number of episodes of sunburn, although not with age at sunburn (Elwood and Jopson, 1997); this seems a reasonable assumption if sunburns reflect intermittent exposures. Others see no such relationship, suggesting that peoples' memories are faulty. It is difficult to assess what may be encompassed by the imprecise term "intermittent exposure", which presumably includes sunbathing, boating, swimming, skiing and so on; also ill-defined is "sunburn" which generally is given as pain and blistering over two days. Berwick (1998) considers that sunburn, per se, may not be a risk factor, but rather, a marker for susceptible skin types together with excessive sun exposure.

The time of life at which excessive sun exposure is the most detrimental also is debatable. Autier and Dore (1998) believe that melanoma risk associated with a given level of exposure in adulthood is increased with higher childhood exposure, and the increase is greater than additive. In turn, high exposure as a child constitutes a significant risk only if there is significant exposure as an adult. They conclude that the avoidance of the sun during childhood has a greater impact on reducing risk than does avoidance as an adult. This is borne out by the observation that white immigrants to Australia who were born and spent their early years in places where the mean annual hours of bright sunlight were low have a lesser risk of melanoma than people who were born in Australia (Armstrong et al., 1986).

Genetic factors, including the number of atypical nevi (dysplastic nevi), are strong indicators of melanoma risk (Goldstein and Tucker, 1993; Whiteman et al., 1997); further, data from England and Australia also showed that the number of common nevi, as well as atypical ones, was an important risk factor (Bataille et al., 1998). In Japanese people with multiple dysplastic nevi, skin color and sun sensitivity were closely linked (Hara et al., 1992). Further, undue exposure to the sun in early life may increase the production of dysplastic nevi (Heenan, 1985; Armstrong et al., 1986). In contrast to these findings, Crijns et al. (1997), comparing people of Dutch extraction living in the tropical island of Curacao with people in The Netherlands, found the association between number of nevi and sun exposure was valid only at low exposures; after a critical threshold, the association no longer held. They reported that very high exposures contribute to the development of atypical nevi. Not only are fair coloration, red hair, the inability to tan, and a family history of melanoma independent risk factors (Whiteman et al., 1997) but ancestry itself may be an independent factor, as it seems to be for Celts (Long et al., 1998).

**SUNSCREENS**

Most sunscreens are demonstratively effective in filtering out UVB wavelengths (290-320 nm) and preventing sunburn provided that they are applied adequately and properly. The sun protection factor (SPF) is measured as the ratio of exposures to the sun that can be tolerated without sunburn (minimal erythema) with a sunscreen and without one. Erythema (redness and burning) is a good spectral surrogate for DNA damage caused by UVB exposure (Young et al., 1998); depending upon their composition, to varying extents sunscreens reduce the rate of induction of UV-induced pyrimidine dimers in the DNA of human skin (Freeman et al., 1988; Ley and Fourtanier, 1997) and prevent the development of pigmentation. UVB sunscreens also suppress the development of solar (actinic) keratoses, the precursor lesions of squamous cell carcinoma (Thompson et al., 1993), and a risk factor for basal cell carcinoma and melanoma (Mark et al., 1988). In mice, sunscreens significantly lower the incidence of mutations in the tumor-suppressor gene, p53, by 88-92% (Anathaswany et al., 1998).

Even though sunscreens prevent acute inflammation of the skin, they appear to vary markedly in their ability to prevent local and systemic immunosuppression, an important risk factor in skin cancer. De Luca et al. (1997) showed that UVB radiation directly interferes with the functioning of immunocompetent cells. Furthermore, shortwave UV-A2 (320-340 nm) and longwave UV-A1 (340-400 nm) increased the frequency of tolerance induction to contact allergens applied through irradiated skin. UVA also caused the appearance of a novel population of skin-infiltrating antigen-presenting cells. Immunosuppression caused by exposure to UVB, but not UVA, is reported to have a four-fold lower dose threshold than erythema (Hurks et al., 1997; Kelly et al., 1998). An action spectrum for immune suppression would be invaluable for our understanding of skin cancer. Interestingly, Mukhar (1998) suggested adding a polyphenolic extract of green tea, which contains four known antioxidants, to sunscreens; topical and oral administration of the extract inhibited radiation effects in mice, and when applied to the backs of humans who were exposed to twice the minimum erythemal dose (MED), it reduced erythema.

The need to incorporate UVA (320-400 nm) filters in sunscreens for better protection was highlighted by several experimental studies over the last decade showing that UVA causes considerable damage to the skin at morphological, biochemical, and molecular levels (reviewed by Gasparro et al., 1998). Ley and Fourtanier (1997) showed that in hairless mice, UVA was responsible for the induction of about a quarter of the pyrimidine dimers per equivalent edematous response compared to solar-simulated irradiation. At about the same time, several epidemiological studies suggested that prolonged expo-
sure to UVA as a result of using sunscreens might be important in causing melanoma. Thus, Garland et al. (1993) hypothesized that because people wearing sunscreen would not experience sunburn, they might remain in the sun for longer than if they were unprotected; consequently, they would be exposed to greater doses of UVA. Diffey (1992) calculated that 6 J/cm² of UVA would be absorbed by unprotected skin in 20 min, at which time the person would have received 1 MED, and then, presumably, have gone indoors. With an SPF-8 sunscreen, that person could remain 2.5 to 3 hr in sunlight before receiving 1 MED, but meanwhile would be exposed to 15 J/cm² UVA. Miller et al. (1998a) evaluated four sunscreens with sun protection factors of 8, 15, 30, and 45; they calculated that if wearers remained in the sun until they had accumulated 1 MED, then UVA exposure would have increased by 300-600% compared with the unprotected skin.

The importance of UVA in inducing melanoma is uncertain, and there is little experimental evidence that it has detrimental effects, other than that of Ley and his colleagues, and our work with Xiphophorus; epidemiological studies have yielded conflicting answers. As pointed out by Gasparro et al. (1998), the idea that sunscreen promotes prolonged sun exposure is appealing and logical, but it has not been substantiated. Although Urbach (1997b) emphasizes that the photocarcinogenic action spectrum parallels the erythema action spectrum in human skin in the UVB and short UVA regions, but that they are not parallel in the long UVA wavelengths, the two spectra have somewhat similar values at the long wavelengths (McKinley and Diffey, 1987; deGruijl et al., 1993). Berwick (1998) evaluated ten epidemiological studies on the relation between melanoma and sunscreen use, and found a positive association in five of them, a protective association in two studies, and no association in the other three; she discussed the problems in interpreting epidemiological data. Autier et al. (1997) have a different view. They consider that experiments do not necessarily reproduce typical human behavior, and that the marketing of sunscreens fosters undue exposure to sunlight by associating their use with the acquisition of a safe suntan. Indeed, Autier (1998) states that "... nearly all epidemiological studies done so far have found sunscreen use to be associated with a higher risk of melanoma or nonmelanoma skin cancer."

Wolf et al. (1998) concluded from an Austrian case-control study that the use of sunscreens does not help prevent melanoma.

Faced with a possible causal association, countries that are vigorously promoting a campaign of sun protection advocate the choice of sunscreens containing UVA filters, along with other measures to reduce exposure to sunlight. Still more public education is needed; those most likely to benefit are people under 25, elderly people, people living alone, and poor people. Data from a survey of 10,048 white Americans in 1992 showed only 32% were likely to use sunscreen if they were outside on a sunny day for more than one hour (Hall et al., 1997). Further, not only may people fail to use sunscreen, or fail to use it properly (liberal application every two hours), the products themselves may undergo rapid photodecomposition, affording less protection than claimed; Dowdy and Sayre (1998) showed that the efficacy of a UVA sun filter was destroyed with less than 0.2 MED UVA1 exposure. However, it may not be valuable for everyone to use sunscreen year-round in temperate countries, such England and Japan, because exposure to sunlight is critical for some groups of people in increasing vitamin D levels (Ohnaka, 1993).

Exposure to UV radiation from sunlamps has become a health concern since several epidemiological studies have found a significant association between melanomas of the trunk with > 10 exposures per year. Conversely, some studies found no relationship; the problem is exacerbated by the small numbers in the samples. In exploring this association, Miller et al. (1998b) used our action spectrum determined in Xiphophorus fishes, which they called the XFM spectrum, to track the UVA exposures from six different commercial sunlamps and one older model (the UVB-emitting FS lamp) and compared the results to solar exposure. When combined with UV exposure received from the sun, typical usage of a fluorescent sunlamp increased the annual effective XFM dose by six times, and by twelve times for the newer high-pressure lamps. The authors caution that for people living in areas of low solar exposure, bathing under sunlamps could be a greater relative risk than for people living in areas of high sunshine. This scenario might be applicable to Japanese people should a suntan become as popular as it is in other parts of the world. Miller et al. stressed the need for a comprehensive action spectrum and dose response relationship to evaluate the comparative risks from exposure different types of sunlamp.

**ANIMAL STUDIES**

A number of animal models have been used to explore light-induced melanoma (Kusewitt and Ley, 1996; Setlow, 1996). However, only a fish model, the Xiphophorus model, has been used to determine the sensitivity of melanoma induction for different wavelengths (Setlow, 1999). This nonmammalian model has several advantages, and has been used for more than six decades to study melanoma formation. The fish are easy to handle, and single exposures at seven days of age induce melanomas that are readily observable at four months; the melanomas are histologically similar to those in humans. As in humans, the fish possess photoreactivating enzyme that, in the presence of long UV or visible light, removes UV-induced pyrimidine dimers from DNA; these dimers, mostly induced by UVB (Freeman et al, 1989) are in part responsible for tumor induction (Hart et al., 1977; Ley et al., 1991). The development of melanomas in these fishes after UVB irradiation is
reversed by exposure to white light (Setlow et al., 1989; Setlow, 1999).

We used highly sensitive backcross hybrids of X. maculatus and X. couchianus; their sensitivity appears to reflect the presence of a single tumor suppressor gene in the melanocytes. We obtained a dose-response curve for melanoma induction at six wavelengths: 320, 313, 365, 405, 436, and 547 nm. Data for these wavelengths are shown in Figure 1 (Setlow et al., 1993). The data for the four longer wavelengths show that the relative melanoma sensitivity is much higher than is the erythema sensitivity. To obtain the relative effects that would be observed in natural daylight, Setlow and Woodhead (1994) and Setlow (1999) multiplied the action spectrum points by the relative intensity of sunlight at each wavelength (Figures 2). They concluded that if the action spectrum for human melanoma were similar to the fish spectrum then, since > 90% of the effective sunlight dose is in the UVA and longer wavelengths, ozone depletion affecting mostly UVB would be inconsequential. Added to this, the existence of photoreactivation acting in the presence of the long wavelengths in sunlight would further ameliorate the effects of UVB. They cautioned that the use of sunscreens to minimize erythema could enhance melanoma if people extended exposure until they reached the minimal erythemal dose. In a recent genetic mapping with our collaborators, a strong candidate for the tumor suppressor gene was identified that may be the same as that in humans (Kazianis et al. 1998).

The effects of UVB in melanoma induction are supported by the work of Ley et al. (1989). They found that chronic exposure of the American opossum to ultraviolet radiation for many weeks results in nonmelanoma skin cancer and a few melanocytic hyperplasic lesions that sometimes developed into melanoma. Chronic exposure to UVA, on the other hand, gave equal numbers of nonmelanomas and melanocytic hyperplasias (Ley, 1997, 1998). Setlow (1999) suggested that these findings demonstrated that the action spectrum for melanocytic hyperplasia differed considerably from that for nonmelanomas, but that UVA alone may not be a complete carcinogen.

**ETHNIC DIFFERENCES IN SUSCEPTIBILITY TO MELANOMA**

Although fair-complexioned individuals of skin-type I and II are more likely to develop nonmelanoma and melanoma skin cancer with excessive sun exposure than do people with darker skins with the same lifestyle, the latter group are not without risk. Cress and Holly (1997) analyzed the California cancer registry for malignant melanoma by racial background from 1988 to 1993 and showed that the average, annual, age-adjusted incidence rates per 100,000 people were 17.2 and 11.3 for non-Hispanic white males and females, respectively, and 0.9 and 0.8 for Asian men and women, respectively. They also noted that the site distribution, stage of diagnosis, and histological types differed in the racial groups, with Asian people being more likely to have acral lentiginous melanoma. Epidemiological studies mostly focus on whites with superficial spreading and nodular melanomas: there is a need for more work on the pattern of sun exposure and other factors in the etiology of the disease in different ethnic peoples. Surveys have

![Figure 1](image-url)  
**Figure 1.** Action spectra, relative sensitivity normalized to 1.00 at 302 nm, for melanoma induction in fish (Setlow et al., 1993; Setlow, 1999) and human erythema (McKinlay and Diffey, 1987). The right-side ordinate gives the midsummer sunlight spectrum at 41° N.
been made in Israel of the incidence and behavior of melanoma in immigrants from different backgrounds. Gutman et al. (1993) found that among 380 people with melanoma, only 68 were Sephardic Jews (dark-skinned), the majority being fair-skinned Ashkenazic Jews; disturbingly, the disease seemed more virulent in the former group. A later survey by Iscovitch et al. (1995) showed that Jews born in Europe, America, and Israel had a higher incidence of melanoma than those born in Asia or Africa. A steep increase in incidence in all racial groups until the mid 1970s was attributed to cumulative sun exposure over 40-50 years; a later leveling-off of the rate was thought to reflect increasing awareness of the dangers, and earlier diagnosis of the disease. Malignant melanoma and other skin diseases also increased in Spanish people in the late 1960s to the early 1980s and was related to a progressive rise in exposure to UV radiation (Morales Suarez-Valera et al., 1990; Pollan and Lopez, 1993).

These limited data show that although risks are less for people with more skin pigment, nevertheless they are real, and under conditions of high solar exposure, the rates of skin disease can rise dramatically. Thus, in Puerto Rico, age-adjusted melanoma incidence increased 528% for males, and 200% for females from 1975 to 1991 (Matta et al., 1998). These risks are unequivocally demonstrated by the data from Japanese ethnic peoples in Hawaii. Leong et al. (1987) found that the crude rates of nonmelanoma skin cancer in Japanese residents of Kauai, Hawaii were 88 times higher than in Japan. Moreover, they believe that this difference in rates between the two countries cannot be solely explained by the difference in latitude, but must also reflect the outdoor-oriented lifestyle in Kauai, often as agricultural workers. They also implicated arsenic, which was common in pesticides and paints, as a co-carcinogen. The rate was higher in women than in men; they suggested that this was because women were employed on the plantations, and men in the mills. This difference is not seen in Japan. More recently, Chuang et al. (1995) found that the incidence rates for basal cell carcinoma and squamous cell carcinoma were 45 times higher for these Japanese-Americans than they are for Japanese in Japan: again, they found a comparable difference between females and males. Figure 3 compares melanoma incidence in three ethnic groups in Hawaii, Japanese, whites, and Filipinos, 1984 to 1997; although the incidence in Japanese is about an order of magnitude less than that in Caucasians in Hawaii, signifying that the Japanese skin type is more protective, the number of cases is increasing similarly in both groups. Most of the occurrences of all skin cancers were in older Japanese, suggesting that they resulted from long exposure to the intense sunlight radiation in Hawaii, possibly with a lifestyle emphasizing outdoor activities; there is a longer latent period before the tumor develops that in whites. This population also has a much higher incidences of keratoacanthoma (benign squamous cell carcinoma) than people living in Japan (Reizner et al., 1995). Hawaii has the thinnest ozone layer outside the Antarctic Circle (Bergmanson and Sheldon, 1997). In 1984, Lee reported a higher Standardized Relative Proportional risk for nonmelanoma skin cancers among farmers in Singapore; now, this is the seventh most common cancer in the people of Singapore (Tan et al., 1996).

The statistics on skin cancer in Japanese-American people in Hawaii, and other non-Caucasian people, together with the information on the role of intermittent recreational exposure on melanoma, and probably basal cell carcinoma, sound a strong warning. Added to this are the real problems with assuring the efficacy of sunscreens against all UV wavelengths. Outdoor recreation has become very popular in Japan in recent years, and there is no end in sight according to the Japanese
Figure 3. Melanoma incidence versus time, not age-adjusted, shown as the average per year obtained from 2-year intervals for different ethnic groups of males plus females in Hawaii. We are indebted to the Hawaii Tumor Registry Director, M.C Hurst, and the Data Collection Coordinator, M. Green, for these data.

Information Network (Ministry of Foreign Affairs). Some 7.5 million went car-camping in 1995, four times the number that did so in 1985. Whilst the amount of time Japanese people spend outdoors is less than of many Americans and Europeans, this is not a trifling matter. Further, many schools and companies which formerly had a six-day week have changed to a five-day schedule, and the average number of vacation days per year rose from 92.4 in 1984 to 111.0 in 1996. Japanese Travel Agencies advertise that the beaches swarm with sun-worshipers in mid-July, and suggest that the appropriate summer attire is light clothing, short sleeves, and swim-wear. Traveling abroad is also popular among people between 20 and 34, particularly women - 20% of whom took sightseeing trips; thereafter, the numbers fell below half. About 10% of men in this age group went abroad sightseeing, but their numbers remained steady throughout their thirties until age 64.

INDUSTRIAL EXPOSURES AND MALIGNANT MELANOMA

Other environmental factors have been sought to explain the complexities in the causation of malignant melanoma, including exposures to industrial chemicals. In the 2nd edition of Occupational Skin Disease (1990), Epstein et al. gave an overview of the evidence that chemicals may be responsible for some skin cancers, or may act together with UV, either as initiators or as promoters. They listed the occupations in which workers have prolonged exposure to natural light, such as outdoor maintenance workers, and also those in which people are exposed to artificial sources of UV, some of which may emit UVC (arc welding, plasma torch operations, germicidal lamps, laser rays, and drying and curing processes). Beral and Robinson (1981) implicated fluorescent lighting in causing melanoma, particularly when the source is close to the skin, but Righer et al. (1983) could not confirm this finding. Epstein et al. (1990) discussed the role of polycyclic aromatic hydrocarbons (PAHs) in skin cancer, particularly shale-oil products, a few of which seem to have additive effects with UV. Another chemical they discussed in detail was arsenic, pointing to the strong link between chronic exposure to inorganic arsenic and the development of pronounced hyperpigmentation, keratoses, and skin cancer, along with other cancers. This was dramatically illustrated recently by the arsenic crisis in Bangladesh in which 70 million people have been potentially poisoned from long-term exposure to arsenic in their drinking water drawn from wells installed 10 to 20 years ago (Lepkowski, 1998). Measured arsenic concentrations reach up to twenty times the allowable limit in that country of $50 \mu g/l$ (Nickson et al., 1998). There have been other smaller incidences. Thus, Tseng et al. (1968) reported a dramatic increase in such conditions among a population of Taiwanese after years of exposure to arsenic in their drinking water. In comparable unexposed populations skin cancer is relatively low, about 2.5%, and appears on exposed parts of the body; after
long-term ingestion of arsenic, it exceeded 10%, and many people had multiple occurrences. However, about 75% of these cancers were on parts of the body not exposed to sunlight. Further, there was a clear-cut increase in incidence related to an increase in the concentration of the metal. Miki et al. (1982) also reported the occurrence of Bowen's disease (intraepidermal squamous cell carcinoma) along with primary skin cancers in a small population of thirty-one Japanese who supposedly were exposed to arsenic for a short period. In discussing the role of physical agents, such as heat and trauma, Epstein et al. (1990) suggested that the practice of kairo was responsible for the development of nonmelanoma skin cancer on the abdomen of some older Japanese women.

In the same volume, Emmett (1990) considered chemicals in the workplace that may cause phototoxic dermatitis and chronic skin changes that eventually could lead to melanoma. Interestingly, he cited evidence that UVA as well as UVB might be responsible. Thus, Gardiner et al. (1972) found that workers handling the dye Disperse blue 35 noted transient erythema on leaving the factory on sunny days, and also from sunlight shining through a window. Glass allows the passage of UV radiation, especially UVA (Urbach, 1998). Furthermore, experimental irradiation with wavelengths from 400-700 nm elicited the same response. Emmett et al. (1977) showed that amyl ortho-dimethyl aminobenzoic acid caused phototoxicity in workers making cured inks. These individuals experienced a sharp burning sensation on exposed areas of the body, followed by erythema and swelling; sunscreens effective against UVB and UVA blocked the reaction, but not those containing UVB filters alone. Emmett considers that narrow-band sunscreens effective only against UVB are of little or no use in preventing phototoxicity.

More recent epidemiological studies implicate the same chemicals, some of which we discuss below. However, the evidence for causation between exposure to chemicals and melanoma is weak, despite many surveys having been made of its incidence and mortality rate among a wide range of occupations (Elwood, 1993). The registries upon which most of these surveys were based are comprehensive, particularly those from Australia, Canada, the Netherlands, Scandinavia, the United Kingdom, and the United States, and they have collectively involved many thousands of men and a few hundreds of women. Most often, authors proffer the correlations cautiously. We found only two studies where there was an apparently clear dose relationship between exposure and incidence of the disease; two other studies indicated that chemical exposures might act synergistically with UV radiation.

The printing industry is suspect. Linet et al. (1995) evaluated the incidence of malignant melanoma in a 19-year follow-up of 3,850 Swedish workers, and found excess risk. Dubrow (1986) reported an elevated age-standardized proportionate mortality rate in white males in this industry in Rhode Island, USA; however, he acknowledged that the affected men may also have been exposed to UV. An unconfirmed excess risk among workers in the printing industry in Denmark was reported by Lyng (1990-1991). Neilson et al. (1996) surveyed 837 lithographers and reported 5 cases of melanoma where 1.5 were expected; they suggested that the tumor might be related to hydroquinone used in photographic development which causes depigmentation and morphological changes in melanocytes. McLaughlin et al. (1988) also found that employees in this industry had almost twice the expected incidence of melanoma; surprisingly, the elevated rates occurred among journalists, editors, and executives as well as among typographers and machine repairers.

Some epidemiological studies have shown links between exposure to polychlorinated biphenyls (PCBs) and melanoma. Sink et al. (1992) recorded eight deaths versus the expected two in 3,588 U.S. workers making electrical capacitors who had known exposure to PCBs; in a retrospective cohort mortality study, Mazzucchelli and Schulte (1993) found that the data did not allow them to construct a dose/response curve. However, Loomis et al. (1997) obtained a significant relationship between exposure to PCB-containing fluids and melanoma in their survey of mortality in 138,905 men employed at any one of five electrical power companies for at least six months. Without considering latency, the following were the rate ratios, and the 95% Confidence Intervals, CI, compared with controls: 1.23 (CI 0.56-2.52) for < 2,000 hours; 1.71 (0.68-4.28) for > 2,000 but < 10,000 hours; and, 1.93 (0.52-7.14) for > 10,000 hours. When a latency of 20 years was factored in, these numbers rose to 1.29 (CI 0.76-2.18), 2.56 (1.09-5.97), and 4.81 (1.49-15.50), respectively.

A small cluster of deaths from melanoma was recorded in oil-refinery workers (Magnani et al., 1987) although an earlier study of men in this industry was only suggestive of excess risk (Savitz and Moure, 1984). More recently, a large retrospective assessment of mortality in 34,597 oil-industry workers in Canada revealed a significant excess that was related to the duration of exposure (Schnatter et al., 1992); the authors suspected that there might be synergism between exposure to hydrocarbons and to sunlight. Rushton (1993) also noted increased mortality from melanoma in workers in several jobs in British oil refineries. There were indications of heightened risk in a small minority of surveys of workers in the rubber industry (reviewed by Kogevinas et al., 1998). Because of the excess risk for other cancers, this industry undertook strong preventive measures whose effects are still unknown. Coal miners do not appear to face an increased likelihood of developing melanoma according to Alexson (1995) and Brown et al. (1997); the increase among open-cut miners demonstrated in the latter study was probably related to their prolonged exposure to sunlight. Workers in the telecommunications industry in Montreal, Canada had an increased incidence of melanoma,
Although melanoma and nonmelanoma skin cancer are much rarer in Japanese than in Caucasians, there is no room for complacency. The dramatic rise in rates among Japanese-Americans in Hawaii might be reproduced in Japan should there be a change in peoples' behavior or an increase in UVB radiation; a worrying aspect is that already there appears to be a rise in age-adjusted mortality rates from the disease, along with the beginning of a trend to a pattern of acute exposures. If there is no vigorous intervention to inform people of the dangers, then skin cancer could become a very important public health problem in future decades (an aggressive information program is vital because people commonly ignore health warnings, New Scientist, 28 November 1998 "Avoiding Action"). Epidemiological studies have shown the complexity of the problem of sun exposure, but it still is not certain what particular pattern is the most harmful. The role of chemicals is suspect, but not established; they may act as promoters. This contrasts with the ease of inducing melanotic nevi and melanoma in rodents with chemical carcinogens, but the difficulty of induction with UV exposures, although, here, they may act as promoters. In view of the uncertainties, and the dearth of precise data from animal models on the wavelength effects, the message must be to avoid sunburn and reduce total exposure.

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