2. Studies of Cancer in Humans

2.1 Solar radiation

2.1.1 *Nonmelanocytic skin cancer*

Nonmelanocytic skin cancer is classified into two major histological types: basal-cell carcinoma and squamous-cell carcinoma. Basal-cell carcinoma is the commoner type in white populations. No information was available to the Working Group on other types of nonmelanocytic skin cancer.

(*a*) *Case reports*

In general, case reports were not considered, owing to the availability of more informative data.

(i) *Studies of xeroderma pigmentosum patients*

Xeroderma pigmentosum is a rare autosomal-recessive genetic disease in which there is an excision repair defect, as observed in cultured skin fibroblasts damaged by UVR (Cleaver, 1968). Patients display cellular and clinical hypersensitivity to UVR (Kraemer, 1980). The disease is present in about one in 250 000 people in the USA and Europe (Cleaver & Kraemer, 1989), and as many as 1 in 100 000 (Takebe *et al.*, 1987) or even 1 in 40 000 (Cleaver & Kraemer, 1989) people may be affected in Japan.

In a survey of 830 cases located through published case reports (Kraemer *et al.*, 1987), 45% had malignant skin neoplasms. Most of the patients were young, and the median age of development of the first skin cancer in the 186 patients for whom information was available was eight years; this observation presumably represents a substantial excess over the expected number. Only 259 neoplasms were specifically categorized as basal- or squamous-cell carcinoma in the published reports. Of these, 97% were on constantly exposed sites (face, head and neck) by comparison with 80% of similar tumours in the US general population. [The Working Group recognized that data collected from previously published case reports is not uniform and may not be typical of a true incidence or prevalence series.]

(ii) *Studies of transplant recipients*

Australian renal transplant recipients were reported to have an increased risk for nonmelanocytic skin cancer (Hardie *et al.*, 1980). Among 875 male and 669 female Australasian recipients, aged 35–64, 47 squamous-cell carcinomas and 27 basal-cell carcinomas were observed among males and 27 squamous-cell and 15 basal-cell carcinomas were observed among females (Kinlen *et al.*, 1979). The rates/10^5 person-years for squamous-cell carcinoma were 2680 in males and 1710 in females, or 3.0 and 5.9 times the rates observed among residents of the same age distribution surveyed in Geraldton, Western Australia (Kricker *et al.*, 1990). For basal-cell carcinoma, the rates for 1540 (males) and 940 (females) were 1.154 and 1.150 times the Geraldton rates, respectively.

By February 1980, a registry in Denver, Colorado (USA), had received data on 906 organ transplant recipients who had developed 959 types of cancer: 42% arose in the skin, of which 47% were squamous-cell carcinomas (Penn, 1980). While several studies from areas with lower solar radiation are available (Boyle *et al.*, 1984), neither singly nor collectively do they contain enough observations to permit a comparable calculation.

(*b*) *Descriptive studies*

Nonmelanocytic skin cancer is often not recorded in cancer registries (e.g., in the USA and in most parts of Australia), and when it is registered case ascertainment is likely to be incomplete since many patients are treated in consulting rooms, frequently without histological verification (Doll *et al.*, 1970). Thus, descriptive studies of the incidence of nonmelanocytic skin cancer can be difficult to perform because of the absence of routinely collected data or difficult to interpret because of incomplete registration. Studies in Australia and the USA have relied upon special surveys, while in the United Kingdom and the Nordic countries data from cancer registries have been used. Studies of mortality rates are also difficult to interpret because nonmelanocytic skin cancer is rarely fatal, and many deaths are incorrectly attributed to skin cancer (Muir *et al.*, 1987).

A number of features of the occurrence of nonmelanocytic skin cancer as revealed by descriptive studies have been taken as evidence that exposure to the sun is a major cause of the disease. These include features presumed to be related to sun exposure such as sex, anatomical site, latitude of residence (or annual dose of UVB radiation), migration from places of low insolation to places of high insolation, occupation and features related to sensitivity to the sun such as race (i.e., degree of skin pigmentation).

(i) *Host factors*

The occurrence of nonmelanocytic skin cancer according to host factors such as race provides indirect evidence that sunlight is a cause. In most white populations, nonmelanocytic skin cancer occurs more commonly in men than in women (Muir *et al.*, 1987). The highest incidence rates have been recorded among Australians, who are largely of British (Celtic) descent (Giles *et al.*, 1988). Populations with greater skin pigmentation have low rates of nonmelanocytic skin cancer, for instance, in South Africa (Oettlè, 1963) and Singapore (Shanmugaratnam *et al.*, 1983).

Albinism is an inherited disorder of melanin metabolism, with a decrease or complete absence of melanin. Large numbers of skin cancers (mostly squamous-cell carcinomas) have been reported in albinos (Luande *et al.*, 1985; Kromberg *et al.*, 1989).

(ii) *Anatomical distribution*

The majority of cases of skin cancer recorded in cancer registries (Haenszel, 1963 [USA]; Whitaker *et al.*, 1979 [United Kingdom]; Swerdlow, 1985 [United Kingdom]; Levi *et al.*, 1988 [Switzerland]; Østerlind *et al.*, 1988a [Denmark]; Moan *et al.*, 1989 [Norway]) and in special surveys in the USA (Haenszel, 1963; Scotto *et al.*, 1983) occurred on the head and neck. In contrast, in two studies in Australia—one of incidence (Giles *et al.*, 1988) and the other of prevalence (Kricker *et al.*, 1990)—the proportions of cancers on the head and neck were lower. [The Working Group noted that the contrasting results may be due to time differences.] In the incidence survey, 43% of squamous-cell carcinomas and 66% of

basal-cell carcinomas were on the head and neck. In the prevalence survey, about one-third of all basal-cell carcinomas were on the head and neck, whereas the trunk accounted for about half of these lesions. The density of tumours was five times greater in men and eight times greater in women on usually exposed sites than on sites which were sometimes exposed. Squamous-cell carcinomas occurred almost exclusively on exposed sites. The site distributions of both types of nonmelanocytic skin type are generally similar in the two sexes (Østerlind *et al.*, 1988a; Moan *et al.*, 1989; Kricker *et al.*, 1990).

A distinctive feature of the site distribution of basal-cell carcinoma is a virtual absence on the dorsa of the hands and infrequent occurrence on the forearms, compared with the distribution of squamous-cell carcinoma (Haenszel, 1963; Silverstone & Gordon, 1966; Levi *et al.*, 1988; Magnus, 1991). Basal-cell carcinoma also occurs frequently on parts of the face that receive comparatively little sun exposure (Urbach *et al.*, 1966).

[The Working Group noted that cancers on the head and neck may be more likely to be diagnosed than cancers at other sites.]

(iii) *Geographical variation*

Nonmelanocytic skin cancer incidence and mortality have long been known to increase with increasing proximity to the equator. Gordon and Silverstone (1976) demonstrated a negative correlation between incidence of nonmelanocytic skin cancer in various countries and latitudes by tabulating the incidence according to latitudinal zones. Much of the early evidence came from surveys conducted in the USA. In the first of these, Dorn (1944a,b,c) reported the results of the US First National Cancer Survey conducted in 10 urban areas in 1937–38. [Nonmelanocytic] skin cancer incidence was greater among whites living in the south than in the north of the country. Blum (1948) subsequently reanalysed these data, substituting latitude for place of residence, and showed a strong inverse relationship between incidence of mostly nonmelanocytic skin cancer and latitude. No other cancer, with the exception of the buccal cavity (including the lip), showed a similar latitude gradient.

Auerbach (1961), using data from the US Second National Cancer Survey conducted in 1947–48 in the same areas as the previous survey, calculated that the age-adjusted rates for skin cancer doubled for each 3 °48 ′ (approximately 265 miles) of latitude towards the equator; similar gradients were seen for men and women and in all age groups. Haenszel (1963) reanalysed data from this survey for four southern and four northern cities. The inverse gradient with latitude was present for both basal-cell and squamous-cell carcinoma. In addition, there was some evidence that the gradient was strongest for head, neck and upper limbs (sites which are usually exposed).

A similar latitude gradient was seen in the US Third National Cancer Survey (Scotto *et al.*, 1974). Inverse latitude gradients have also been reported in Australia (Silverstone & Gordon, 1966; Giles *et al.*, 1988) and in the Nordic countries (Teppo *et al.*, 1980; Moan *et al.*, 1989; Magnus, 1991).

Several authors have correlated nonmelanocytic skin cancer incidence (or mortality) with estimates of UVR. Green *et al.* (1976) reported a positive correlation between estimates of annual UV dose and of incidence rates in the USA, the United Kingdom, Canada and Australia. Estimates of UV dose were derived from models relating latitudinal and seasonal ozone distributions, adjusted for cloud cover. [The Working Group noted that no allowance

was made in the analysis for different methods of case ascertainment. It is not clear how well the predicted values were correlated with actual levels of UVR.]

A positive correlation, stated to be stronger than that for latitude, was seen between UVR, as measured by Robertson–Berger meters, and the incidence of nonmelanocytic skin cancer in four cities in the US Third National Cancer Survey (Scotto *et al.*, 1982). Scotto *et al.* (1983) examined incidence data collected in eight cities in 1977–78 and again showed an inverse relationship with latitude and a positive correlation with measurements of UVR. The gradient was steeper for squamous-cell than for basal-cell carcinoma.

Moan *et al.* (1989) examined nonmelanocytic skin cancer incidence in six regions of Norway from 1976 to 1985, excluding the area around Oslo to reduce bias due to possible differences in reporting and diagnosis. Two measures of UVR, one weighted according to the action spectrum for erythema and the other according to the action spectrum for mutagenesis in cells in the basal layer of the skin, were derived from atmospheric models. Similar, positive relationships between UVR and nonmelanocytic skin cancer incidence were obtained with each method.

Elwood *et al.* (1974) conducted a study of mortality from nonmelanocytic skin cancer in the contiguous states of the USA and in all of the provinces of Canada in 1950–67. The correlation between latitude and mortality was as strong as that between mortality and an index of UVR derived from a model relating erythemal dose according to latitude with adjustments for cloud cover.

(iv) *Migration*

Studies of migrants to Australia (and other countries with high exposure to the sun) offer the opportunity to examine, indirectly, the effect of exposure to the sun. Most migrants to Australia come from higher latitudes which have lower levels of exposure to the sun than Australia. The effect of exposure to the sun is most readily examined in migrants from the British Isles to Australia, from whom most Australians are descended.

Armstrong *et al.* (1983) found that the age-adjusted mortality rate among men born in England or Wales was 0.55 (95% confidence interval (CI), 0.43–0.71) times that in Australian-born men. There was little evidence that rates in migrants increased with duration of residence in Australia, although the numbers of deaths were small and the rates unstable.

Giles *et al.* (1988) found age-adjusted incidence rates of 402 per 100 000 person-years among immigrants from the British Isles and 936 in the Australian-born population.

(v) *Occupation*

Death certificates for 1911–44 in England and Wales were used in an analysis of cancer of the skin, excluding melanomas, in male agricultural workers, miners and quarriers and professionals (Atkin *et al.*, 1949). During part of the period (1911–16), cancers of the penis, scrotum and skin were classified together, and the numbers of cancers of the skin alone were estimated from the proportions occurring in the later period. The standardized mortality ratios (SMRs) were greater for those engaged in agriculture (142.4 [137.4–147.6]) than for those in mining (94.4 [88.8–100.3]), and lowest of all for professionals (47.5 [42.6–52.9]).

Whitaker *et al.* (1979) examined occupations among cases of squamous-cell carcinoma reported to the Manchester Regional Cancer Registry, United Kingdom, in 1967–69. The occupations of 23% of cases were not ascertained. In men, standardized registration ratios

(SRRs) were elevated for textile workers (238; $p < 0.001$) and farmers (243; $p < 0.001$). The SRR was also high for female farmers (690; $p < 0.001$). Male fishermen, chemical workers and paper/printing workers had high SRRs for squamous-cell carcinoma of the arm, and building workers for squamous-cell carcinoma of the ear.

The association between occupation and nonmelanocytic skin cancer was examined in England and Wales in 1970–75 in a 10% sample of all male incident cases for which occupation was recorded (Beral & Robinson, 1981). Individuals were assigned, on the basis of stated occupation, to one of three groups: outdoor workers, indoor office workers and other indoor workers, according to the classification of occupations of the Office of Population Censuses and Surveys. The SRRs for men aged 15–64 were 110 [95% CI, 109–116] for outdoor work, 97 [92–103] for office work and 92 [86–89] for other indoor work. Since place of work may be confounded with social class, the analyses were repeated for men aged 15–64 years in social class III; the SRRs were 112 [102–122] for outdoor work, 111 [100–123] for office work and 85 [78–92] for other indoor work.

Vågerö *et al.* (1986) linked cancer incidence data in Sweden from 1961 to 1979 with census data from 1960 to determine the occupations of cases of nonmelanocytic skin cancer. Occupations were classified into three main groups: office workers, other indoor workers and outdoor workers. SRRs standardized for age, county of residence and social class, were slightly higher for outdoor workers (106; 95% CI, 101–112) than for office workers (103; 96–110) and other indoor workers (95; 91–100). The authors noted that registration may have been more complete among high socioeconomic groups.

(*c*) *Cross-sectional studies*

Design features of cross-sectional studies of exposure to the sun are summarized in Table 9, and the results are shown in Table 10.

A population-based survey of the prevalence of nonmelanocytic skin cancer [types not separated] was conducted in County Galway, Ireland (O'Beirn *et al.*, 1970). Exposed areas of skin were examined for the presence of cancers. In the 26 cases found, there was no significant association with frequent severe sunburn for basal-cell or squamous-cell skin cancer; among males, there was a positive relationship between cumulative hours of exposure to sunlight and the prevalence of nonmelanocytic skin cancer.

Silverstone and Gordon (1966) and Silverstone and Searle (1970) reported the results of three surveys in Queensland, Australia. Exposed areas of the skin were examined, and subjects were asked to report previously treated nonmelanocytic skin cancer [types not separated]. Women performing home duties were classified as indoor workers. Outdoor occupation showed a weakly positive association with past and present incidence in men and a negative association in women.

Holman *et al.* (1984a) conducted a population-based survey of 1216 subjects in western Australia. After controlling for age, cutaneous sun damage (as assessed by microtopography) was strongly related to a past history of nonmelanocytic skin cancer.

Engel *et al.* (1988) analysed data on basal-cell epithelioma (carcinoma) from the First National Health and Nutrition Examination Survey in the USA (1971–74). Dermatologists diagnosed skin cancers and assessed actinic skin (solar) damage, but histological confirmation of the diagnosis was not obtained routinely. Strong associations between the

prevalence of basal-cell epithelioma and solar skin damage were seen in both men and women.

Green *et al.* (1988a) conducted a survey of the prevalence of nonmelanocytic skin cancer [types not separated for calculation of RR] in Queensland, Australia. Information about exposure to the sun was obtained from questionnaires; dermatologists diagnosed skin cancers and assessed signs of actinic damage (solar lentigines, telangiectasia of the face, solar elastosis of the neck and solar keratoses). After adjustment for age, sex, skin colour and ability to tan, outdoor occupation and number of sunburns were both weakly associated with increased prevalence. Stronger associations were seen for cutaneous indicators of sun exposure, particularly for solar lentigines on the hands and telangiectasia on the face. Recreational exposure was not associated independently with nonmelanocytic skin cancer.

In a later report (Green, 1991), the occurrence of nonmelanocytic skin cancer was positively correlated with grade of cutaneous microtopography.

In a subsequent study (Green & Battistutta, 1990), subjects were asked to report nonmelanocytic skin cancer treated between 1 December 1985 and 30 November 1987, around the survey in 1986. Medical records were searched to confirm the diagnoses. Subjects who had had a skin cancer diagnosed at the prevalence survey were excluded. Outdoor occupation, outdoor leisure activities and number of sunburns showed little association with basal-cell carcinoma in an analysis including past history of skin cancer. All three variables were related to incidence of squamous-cell carcinoma. [The Working Group noted that the exclusion of subjects found to have skin cancer during the prevalence survey makes interpretation of these results difficult. The inclusion of past history of skin cancer in the analysis would have weakened any association with exposure to the sun.]

Vitasa *et al.* (1990) conducted a survey of the occurrence of nonmelanocytic skin cancer among men engaged in traditional fishing practices ('watermen') in Maryland, USA. Subjects were examined by dermatologists and interviewed about their history of exposure to the sun. Estimates of individual annual and lifetime doses of UVB radiation were made by weighting the ambient UVR by a history of occupation and outdoor activities and by taking into account relative doses recorded by film dosimeters on the face. Patients with squamous-cell carcinoma aged 15–60 had had an 11% higher annual dose of UVB radiation and those with basal-cell carcinoma had had an 8% lower annual dose than that of age-matched watermen without cancers. The effect of cumulative UVB radiation was examined after adjustment for age, eye colour, childhood freckling and skin reaction to sunlight, all of which were positively associated with occurrence of both types of nonmelanocytic skin cancer. Cumulative UVB radiation dose was not associated with basal-cell carcinoma but was positively associated with squamous-cell carcinoma. The latter association was significant in a comparison of the top quarter of cumulative UVB *versus* the bottom three-quarters but not in a comparison of exposures above and below the median. [The Working Group noted that the results for the two types of cancer are not necessarily incompatible, both because of the small number of cases and the fact that the diagnosis was confirmed histopathologically in only 62%.]

Table 9. Design features of cross-sectional studies of sun exposure and nonmelanocytic skin cancer

Reference	Place	Period of diagnosis	Population	Sample size	Response rate	Cases	Histological confirmation
O'Beirn *et al.* (1970)	County Galway, Ireland	1960s	Population-based	1338	Approx. 81%	13 BCC; 13 SCC on exposed sites only	Incomplete; 57% had biopsies
Silverstone & Gordon (1966); Silverstone & Searle (1970)	Queensland, Australia	1961–63	Population-based	About 2200	87%	221 BCC or SCC on exposed surfaces	Incomplete
Holman *et al.* (1984a)	Busselton, Western Australia	1981	Population-based	1216		102, type not stated	No
Engel *et al.* (1988)	USA	1971–74	Population-based	20 637	74%	BCC, number not stated	Incomplete [small proportion]
Green *et al.* (1988a)	Nambour, Australia	1986	Population-based	2095	70–78%	42 BCC or SCC [90% of subjects examined on head/neck/hands/ forearms only]	Yes
Green & Battistutta (1990)	Nambour, Australia	1985–87	Population-based	1770	84%	66 BCC; 21 SCC self-reported (confirmed from medical records)	Incomplete
Vitasa *et al.* (1990)	Maryland, USA	1985–86	Male fishermen >30 years old	838	70%	33 BCC; 35 SCC	Incomplete

BCC, basal-cell carcinoma; SCC, squamous-cell carcinoma

Table 10. Summary of results of cross-sectional studies of nonmelanocytic skin cancer

Reference	Index of exposure	Categories	Odds ratio (95% CI)	Comments
O'Beirn *et al.*, (1970)	Sunlight hours (lifetime)	< 30 000 h > 50 000 h	1.00 [8.10 (1.2–348.2)]	Mean aged > 60 years; calculated from raw data [p = 0.02]
Silverstone & Searle (1970)	Occupation	Indoors Outdoors	1.0 [1.29]	Men, chi-square = 1.4 [p > 0.1]; calculated from raw data, no adjustment
	Occupation	Indoors Outdoors	1.0 [0.6]	Women, chi-square = 0.3 [p > 0.1]; calculated from raw data, no adjustment
Holman *et al.* (1984a)	Cutaneous microtopography	Grades 1–3 Grade 4 Grade 5 Grade 6	1.0 3.9 3.6 9.2	p = 0.004, trend adjusted for age
Engel *et al.* (1988)	Solar skin damage	None Any None Any	1.0 [8.0] 1.0 [6.0]	BCC, men, age-adjusted prevalence ratio, p < 0.01 BCC, women, age-adjusted prevalence ratio, p < 0.01
Green *et al.* (1988a)	Occupational exposure	Indoors Indoors and outdoors Outdoors	1.00 1.01 (0.44–2.31) 1.76 (0.77–4.05)	Adjusted for age, sex, skin colour and propensity to sunburn
	Painful sunburns	None 1 2–5 ≥ 6	1.00 0.77 (0.22–2.61) 1.09 (0.41–2.95) 1.66 (0.59–4.64)	Adjusted for age, sex, skin colour and propensity to sunburn
	Solar lentigines on hands	None 1–10 11–20 ≥ 21	1.00 1.61 (0.78–3.35) 1.43 (0.43–4.77) 3.78 (1.06–13.41)	Adjusted for age, sex and other signs of actinic damage
	Telangiectasia on face	None Mild Moderate Severe	1.00 1.63 (0.58–4.57) 2.74 (0.89–8.40) 3.67 (0.79–17.11)	Adjusted for age, sex and other signs of actinic damage

Table 10 (contd)

Reference	Index of exposure	Categories	Odds ratio (95% CI)	Comments
Green *et al.* (1988a) (contd)	Actinic elastosis on neck	None	1.00	Adjusted for age, sex and other signs of actinic damage
		Mild to moderate	1.42 (0.53–3.80)	
		Severe	1.75 (0.56–5.45)	
	Solar keratoses on face	None	1.00	Adjusted for age, sex and other signs of actinic damage
		1–5	1.55 (0.67–3.59)	
		6–20	1.86 (0.69–5.04)	
		21–50	3.00 (0.54–16.69)	
		≥ 51	2.72 (0.73–10.15)	
Green & Battistutta (1990)	*BCC*			
	Occupational exposure	Mainly indoors	1.0	Adjusted for age, sex, skin colour and past history of skin cancer
		Indoors and outdoors	1.5 (0.8–2.9)	
		Mainly outdoors	1.3 (0.6–2.8)	
	Leisure exposure	Mainly indoors	1.0	Adjusted for age, sex, skin colour and past history of skin cancer
		Indoors and outdoors	1.0 (0.4–2.2)	
		Mainly outdoors	0.6 (0.3–1.3)	
	No. of painful sunburns	None	1.0	Adjusted for age, sex, skin colour and past history of skin cancer
		1	0.5 (0.2–1.4)	
		2–5	0.6 (0.3–1.5)	
		≥ 6	1.0 (0.4–2.5)	
	SCC			
	Occupational exposure	Mainly indoors	1.0	Adjusted for age, sex, skin colour and past history of skin cancer
		Indoors and outdoors	4.4 (0.9–20.9)	
		Mainly outdoors	5.5 (1.1–28.2)	
	Leisure exposure	Mainly indoors	1.0	Adjusted for age, sex, skin colour and past history of skin cancer
		Indoors and outdoors	2.0 (0.2–19.9)	
		Mainly outdoors	3.9 (0.5–30.9)	
	No. of painful sunburns	0–1	1.0	Adjusted for age, sex, skin colour and past history of skin cancer
		2–5	3.3 (0.9–12.3)	
		≥ 6	3.0 (0.7–12.2)	

Table 10 (contd)

Reference	Index of exposure	Categories	Odds ratio (95% CI)	Comments
Vitasa *et al.* (1990)	*SCC*			
	Cumulative UVB dose to face	Below median	1.0	Proportionate odds ratios; adjusted for age, eye colour, freckling and sunburn reaction
		Above median	2.05 (0.84–5.01)	
		Below 75 percentile	1.0	
		Above 75 percentile	2.53 (1.18–5.40)	
	BCC			
	Cumulative UVB dose to face	Below median	1.0	Proportionate odds ratios; adjusted for age, eye colour, freckling and sunburn reaction
		Above median	0.69 (0.31–1.53)	
		Below 75 percentile	1.0	
		Above 75 percentile	1.11 (0.50–2.44)	

BCC, basal-cell carcinoma; SCC, squamous-cell carcinoma; unless otherwise specified, all analyses are for the two types together

(d) Case–control studies

Design features of the case–control studies of exposure to the sun and the occurrence of nonmelanocytic skin cancer are summarized in Table 11. Most of the studies employed hospital- or clinic-based controls, which introduces potential for selection bias. The results are summarized in Table 12. The methods of analysis and of measurements of exposure to the sun, particularly in the earlier studies, were crude. Neither sensitivity to the sun, usually measured as the ability to tan or propensity to burn, nor pigmentary characteristics (such as skin colour and hair colour), which are likely to be confounding variables, were taken into account in most of the analyses.

The hospital-based study of Lancaster and Nelson (1957) in Sydney, Australia, was primarily a case–control study of melanoma (described in detail on p. 100). It can also be considered to be a case–control study of nonmelanocytic skin cancer, however, because it included two control groups—one of patients with basal-cell carcinoma, squamous-cell carcinoma or solar keratosis and the second of patients with leukaemia or cancer at a site other than the skin. All groups were matched by age and sex. Among males, long duration of occupational exposure to the sun was associated with an increased risk for nonmelanocytic skin cancer or solar keratosis. A summary of total exposure to the sun was devised by assigning scores to a number of factors considered to be related to exposure to the sun. Risk was highest among subjects judged to have excessive exposure to the sun. [The Working Group noted that the proportion of cases who had a solar keratosis is not stated, that no account was taken of matching in the analyses, and that the effect of exposure to the sun was not adjusted for sensitivity to the sun.]

Gellin *et al.* (1965) conducted a study in a single hospital in New York, USA, on 861 patients with basal-cell carcinoma and 1938 non-cancer dermatological patients attending the same clinic. Since 95% of cases and 43% of controls were 40 years old and over, the study was limited to these patients, resulting in 771 cases and 783 controls. The skin cancer patients spent more time outdoors per day than did control patients and were significantly more likely than controls to have light hair, fair complexion, blue eyes and an inability to tan. [The Working Group noted that the analyses were not adjusted for age, sex or sensitivity to the sun, and that confounding by age is likely because controls were younger than cases.]

Urbach *et al.* (1974) conducted a hospital-based study in Philadelphia, USA, and compared exposure to the sun of 392 patients with histologically confirmed basal-cell carcinoma, 59 patients with histologically confirmed squamous-cell carcinoma and 281 outpatients receiving treatment for a skin disease other than cancer. Controls were matched to cases by age and sex. Among male patients, those with basal-cell or squamous-cell carcinoma had more cumulative hours of exposure than did controls. Skin cancer patients also reported more sunburns. [The Working Group noted that the analyses were not adjusted for ability to tan, age or sex (apart from the sex-specific analysis).]

Vitaliano (1978) subsequently reanalysed the data of Urbach *et al.* (1974) and showed that, after adjustment for complexion (dark *versus* pale), ability to tan and age ($< 60, \geq 60$), the cumulative time spent outdoors was related to both types of nonmelanocytic skin cancer. For basal-cell carcinoma, the odds ratio for $\geq 30\,000$ h of exposure relative to $< 10\,000$ h was 3.19; for squamous-cell carcinoma it was 22.8. [The Working Group noted that confi-

dence intervals were not given. Part of the apparently stronger effect for squamous-cell carcinoma could be due to confounding by age: the controls were matched by age to the basal-cell carcinoma cases, who were younger than the squamous-cell carcinoma cases.]

A hospital-based case–control study was conducted in Montréal, Canada (Aubry & MacGibbon, 1985), in which patients with histologically confirmed squamous-cell carcinoma were identified in hospitals in 1977–78. Two patients with other conditions were matched as controls to each case by age, sex and hospital. Information on exposure to the sun was obtained from a postal questionnaire. Among 306 eligible cases, 94 (31%) replied, as did 186 (30%) of the eligible controls; 92 cases and 174 controls completed the questionnaire. Most of the controls who replied had been seen for seborrheic keratoses (61%) or intradermal naevi (16%). Scores for nonoccupational and occupational exposures were estimated, and the two scores were divided into thirds for analysis, which was based on logistic regression. The odds ratios, adjusted for each other and for host factors, were 1.08 and 1.64 for the middle and upper thirds of occupational exposure and 1.23 and 1.58 for the same levels of nonoccupational exposure, respectively. [The Working Group noted the low response rate and that the complexity of the recreational exposure to sun indices and the nature of the control group make the results difficult to interpret.]

O'Loughlin *et al.* (1985) conducted a case–control study in a hospital in Dublin, Ireland. Patients with histologically confirmed nonmelanocytic skin cancer [types not separated] were compared with age- and sex-matched patients who had cancers of other organs. There was no statistically significant difference between cases and controls in eight measures of exposure to the sun summarized in a single index of exposure and either type of nonmelanocytic skin cancer. [The Working Group noted that the measures of exposure to the sun were crude and likely to be subject to considerable misclassification. No adjustment was made for sensitivity to the sun.]

Herity *et al.* (1989) conducted a case–control study in the same hospital in Dublin of 396 histologically confirmed nonmelanocytic skin cancers in 1984–85. An equal number of age- and sex-matched patients with other cancers, attending the same hospital, were used as controls. More cases than controls lived in rural areas ($p = 0.007$), and cases reported more frequently spending more than 30 h outdoors per week, but the difference was not significant. For other indices of exposure to the sun, there was little difference between cases and controls. [The Working Group noted that results were not adjusted for reaction to sunlight.]

In a case–control study (reported as an abstract) conducted in 1983–84 in Alberta, Canada (Fincham & Hill, 1989), 225 men with basal-cell carcinoma and 181 men with squamous-cell carcinoma were compared with 406 age-matched male controls. Sunburn in adult life gave an odds ratio of 2.33 ($p < 0.05$) for all nonmelanocytic skin cancer; for basal-cell carcinoma, childhoood sunburn gave an odds ratio of 2.48 ($p < 0.05$) and peeling an odds ratio of 1.85 ($p < 0.05$).

A population-based case–control study was conducted in Saskatchewan, Canada (Hogan *et al.*, 1989), which included all patients diagnosed with basal-cell carcinoma in the Province in 1983. Two controls, matched by year of birth, sex and municipality of residence, were selected for each case from a universal Provincial health insurance plan. Replies to mailed questionnaires were received from 55.5% of the cases and 43.7% of the controls. A number of measures of exposure to the sun were associated with incidence of basal-cell

carcinoma. In a stepwise logistic regression analysis, occupation as a farmer, history of severe sunburn and working outdoors for more than 3 h per day in winter were independently associated with basal-cell carcinoma, after adjustment for freckles in childhood, family history of skin cancer, 'Celtic' mother, skin colour and hair colour. [The Working Group noted that the measures of exposure were crude and that the estimates do not appear to have been adjusted for the matching variables. The low response rate makes interpretation of the results difficult.]

On the basis of a population-based survey in Western Australia in 1987 of skin cancer among residents aged 40–64 years of age (Kricker *et al.*, 1990), Kricker *et al.* (1991a) conducted a case–control study of 226 confirmed cases of basal-cell carcinoma and 45 of squamous-cell carcinoma; two sets of 1015 controls with no lesions, who had completed an interview, were available for each type of cancer. The response rate among those eligible to participate was identical for cases and controls: 89%. Separate analyses were undertaken for basal-cell carcinoma and squamous-cell carcinoma using unconditional logistic regression analysis. Risks for both cancers were higher in native-born Australians than in migrants, and the risk for basal-cell carcinoma decreased with increasing age at arrival in Australia. Only four of the subjects with squamous-cell carcinoma had been born outside Australia—an insufficient number to examine the effects of age at arrival. Indicators of sun damage to the skin (facial telangiectasia, solar elastosis of the neck, facial solar lentigines and number of solar keratoses), assessed by dermatologists during the prevalence survey, were examined in models adjusted for age, sex, ethnicity and migrant status and including all other sun damage indicators except solar keratoses, which were considered to be preneoplastic lesions and thus inappropriate for inclusion in models concerned with etiology. Cutaneous microtopography, an objective measure of actinic skin damage, graded without knowledge of the person's skin cancer status, and solar elastosis of the neck had significant residual effects for basal-cell carcinoma, while solar elastosis and facial telangiectasia had significant residual effects for squamous-cell carcinoma. The independently significant indicators of sun damage were analysed in models which included adjustment for age, sex, ethnicity and migrant status as well as measures of sun sensitivity. Solar elastosis of the neck remained an independent predictor of risk of basal-cell carcinoma (odds ratios, $> 1.50; p = 0.003$) and squamous-cell carcinoma (odds ratios, $> 2.00; p = 0.04$).

A subsequent analysis of individual sun exposure was published as an abstract (Kricker *et al.*, 1991b). A positive association was found between nonmelanocytic skin cancer and life-time potential for exposure to the sun, but no evidence of increasing risk for either basal-cell carcinoma or squamous-cell carcinoma with increasing total hours of actual exposure to the sun as recalled by subjects. Risk for basal-cell carcinoma on the trunk was increased substantially in association with maximal exposure of the trunk to the sun, but there was no consistent pattern of association of site-specific basal-cell or squamous-cell carcinoma with exposure of the head and neck or limbs. Neither basal-cell nor squamous-cell carcinoma showed evidence of an association with sun exposure on working days; however, there was persuasive evidence of increased risk for both types of skin cancer with intermediate and high levels of accumulated exposure to the sun on non-working days. Moreover, there was evidence of an association, stronger for basal-cell carcinoma than for squamous-cell carcinoma, with a measure of intermittent exposure to the sun.

Gafá *et al.* (1991) conducted a case–control study of nonmelanocytic skin cancer in Sicily, Italy, in which 133 cases identified from a population-based registry (response rate, 94%) were compared with 266 sex- and age-matched controls. For each case, one control was selected randomly from among patients with non-neoplastic diseases at the same hospital as the case, and a second control was selected randomly from among friends or relatives of the case. After adjustment for family history of skin cancer, 'cancer-related cutaneous disease', skin colour and skin reaction to sunlight, sun exposure for at least 6 h per day and residence for at least 10 years at more than 400 m above sea level were significantly related to risk for nonmelanocytic skin cancer. In crude analyses in which the two types of cancer were separated, sun exposure for at least 6 h per day without a hat was strongly associated with risk for squamous-cell carcinoma [site unspecified] (odds ratio, 6.4; 95% CI, 1.9–21.1) but not for basal-cell carcinoma (1.4, 0.7–2.6). [The Working Group noted that the nature of the control group, the assessment of exposure and the failure to account for age in the analysis make the results difficult to interpret. The crude analysis of the type-specific results, the lack of data on the site of the tumours and the small numbers may explain the different results for the two types.]

(*e*) *Cohort studies* (Tables 13 and 14)

In a study in Chicago, IL (USA), Robinson (1987) investigated the incidence of second nonmelanocytic skin cancer among a group of 1000 patients who had had basal-cell carcinoma. Among 978 who were followed for five years after the initial diagnosis, 22% developed a second basal-cell carcinoma at the end of the first year and 36% within five years. There was no significant correlation between developing a second cancer and frequent exposure through sunbathing or outdoor leisure activities, work or currently living in an area with heavy exposure to the sun, or according to estimated number of hours of daily exposure to the sun. Among those with skin types I and II (always burn easily and never or minimally tan) who reported frequent sun exposure, there was an increased risk of second cancer ($p < 0.03$). [The Working Group noted that the methods of assessing exposure and the methods of analysis were not described, and that no numbers were reported. Risk factors for second cancers might not be the same as for the first.]

Marks *et al.* (1989) conducted a longitudinal series of examinations of the head, neck, forearms and hands of a population in Maryborough, north-central Victoria, Australia, for one week annually between 1982 and 1986. The incidence rates of squamous-cell and basal-cell carcinoma were higher in outdoor workers than in indoor workers. In an analysis of the two types combined, occupation was not significantly associated after adjustment for age, sex and reaction to sunlight ($p = 0.09$). [The Working Group noted that no account was taken of lesions that might have been removed between surveys.]

Hunter *et al.* (1990) conducted a study of basal-cell carcinoma in a cohort of female nurses in the USA. A total of 771 cases were identified from responses to follow-up questionnaires sent to the women two and four years after the initial exposure questionnaire was given. In a sample of 29 women, the diagnosis was confirmed for 28; confirmation of the diagnosis was not obtained routinely. Residents of California and Florida had the highest incidence rates. There was a trend of increasing incidence with increasing number of sunburns. With respect to time spent outdoors during the summer, nurses who spent more than

Table 11. Design features of case–control studies of sun exposure and nonmelanocytic skin cancer

Reference	Place	Period of diagnosis	Cases		Controls	
			No.	Source	No.	Source
Lancaster & Nelson (1957)	Sydney, Australia	Unknown	173 BCC, SCC or solar keratosis	Major hospitals	173	Other cancers, same hospitals
Gellin *et al.* (1965)	New York, USA	1955–59	771 BCC ≥ 40 years old	One skin hospital	783 ≥ 40	Other diagnoses, same skin clinic
Urbach *et al.* (1974)	Philadelphia, USA	1967–69	392 BCC 59 SCC	One skin and cancer clinic	281	Other diagnoses, same clinic
Aubry & MacGibbon (1985)	Montréal, Canada	1977–78	92 SCC	12 hospitals	174	Skin conditions, same hospitals
O'Loughlin *et al.* (1985)	Dublin, Ireland	Unknown	63 SCC 58 BCC	One hospital	121	Other cancers, same hospital
Herity *et al.* (1989)	Dublin, Ireland	1984–85	396 BCC and SCC	One hospital	396	Other cancers, same hospital
Hogan *et al.* (1989)	Saskatchewan, Canada	1983	538 BCC	Population	738	Population
Kricker *et al.* (1991a)	Geraldton, Australia	1987	226 BCC 45 SCC	Population	1015 1015	Population
Gafá *et al.* (1991)	Ragusa, Sicily, Italy	1987–88	133 BCC and SCC	Cancer registry	133 133	Non-neoplastic diseases, same hospital; friends or relatives

BCC, basal-cell carcinoma; SCC, squamous-cell carcinoma

Table 12. Summary of results of case–control studies of nonmelanocytic skin cancer

Reference	Exposure	Categories	Odds ratio (95% CI)	Comments
Lancaster & Nelson (1957)	Years of occupational exposure	< 5	1.0	[p < 0.001, trend; p and odds ratio calculated from raw data]
		5–10	[1.9]	
		> 10	[4.2]	
	Total sun exposure	Minimal	1.0	[p = 0.13; p and odds ratio calculated from raw data]
		Moderate	[1.8]	
		Excessive	[2.4]	
Gellin *et al.* (1965)	Hours per day outdoors	0–2	1.0	BCC [p < 0.001]
		3–5	[4.9 (3.8–6.3)]	
		≥ 6	[7.7 (5.6–10.6)]	
Urbach *et al.* (1974)	Cumulative hours (× 1000)	< 30	1.0	BCC
		30–50	[3.5 (2.0–6.6)]	
		> 50	[9.3 (3.2–37.4)]	
		< 30	1.0	SCC
		30–50	[4.0 (1.7–9.6)]	
		> 50	[11.1 (2.8–53.6)]	
Aubry & MacGibbon (1985)	Non-occupational exposure score	Low	1.0	SCC [p = 0.07] for continuous variable, adjusted for occupation and host factors
		Medium	1.23	
		High	1.58	
	Occupational score	Low	1.0	SCC [p = 0.02] for continuous variable, adjusted for non-occupational score and host factors
		Medium	1.08	
		High	1.64	
	Use of sunlamps	Never	1.0	SCC [p = 0.008], adjusted for sun exposure and host factors
		Ever	13.4 (1.38–130.48)	
O'Loughlin *et al.* (1985)	Outdoor occupation	No	1.0	Not significant (McNemar's test) [odds ratio calculated from raw data ignoring matching]
		Yes	[1.5]	
	Hours per week outdoors	< 10	1.0	Not significant
		≥ 10	[1.4]	
	Sunbathing > 4 h per day on vacations	No	1.0	Not significant
		Yes	[1.0]	
Herity *et al.* (1989)	Living in rural area		[1.4]	p = 0.007
	> 30 h outdoors/week		[1.1]	p = 0.7

Table 12 (contd)

Reference	Exposure	Categories	Odds ratio (95% CI)	Comments
Hogan *et al.* (1989)	Farmer	No	1.0	BCC, adjusted for each other, plus freckles, family history of skin cancer, Celtic mother, skin colour, hair colour
		Yes	1.29 [1.12–1.46]	
	Severe sunburn	No	1.0	
		Yes	1.19 [1.04–1.35]	BCC
	Working outdoors > 3 h per day in winter	No	1.0	
		Yes	1.13 [1.01–1.27]	BCC
Kricker *et al.* (1991a)	*BCC*			
	Age at migration (years)	Australian born	1.0	$p < 0.001$, adjusted for other variables below and for ethnicity, ability to tan, freckling as a child and number of moles on back
		< 10	1.37 (0.55–3.42)	
		> 10	0.32 (0.18–0.59)	
	Solar elastosis of the neck	None	1.00	$p = 0.03$, comments as above
		Mild	1.85 (0.80–4.26)	
		Moderate	2.75 (1.16–6.50)	
		Severe	3.96 (1.58–9.93)	
	Cutaneous microtopography	Grades 1–3	1.0	$p = 0.10$, comments as above
		Grade 4	2.01 (1.00–4.07)	
		Grade 5	2.42 (1.17–5.01)	
		Grade 6	2.15 (0.99–4.70)	
	SCC			
	Migrant to Australia	No	1.0	$p = 0.13$, adjusted for variables below plus ability to tan, skin colour, freckling as a child
		Yes	0.46 (0.15–1.38)	
	Permanent colour difference between neck and adjacent skin	No	1.0	$p = 0.03$, comments as above
		Yes	2.58 (1.03–6.47)	
	Telangiectasia of face	None/mild	1.0	$p = 0.10$, comments as above
		Moderate	2.22 (1.06–4.67)	
		Severe	1.88 (0.72–4.90)	
	Solar elastosis of the neck	None/mild	1.00	$p = 0.04$, comments as above
		Moderate	2.31 (1.00–5.34)	
		Severe	3.33 (1.23–9.04)	

Table 12 (contd)

Reference	Exposure	Categories	Odds ratio (95% CI)	Comments[a]
Gafá *et al.* (1981)	Residence > 400 m above sea level	No Yes	1.0 2.0 (1.2–3.2)	Adjusted for family history of skin cancer, cutaneous-related conditions, skin colour, skin reaction to sunlight and sun exposure
	Sun exposure ≥ 6 h/day	No Yes	1.0 1.9 (1.2–3.1)	Adjusted for family history of skin cancer, cutaneous-related conditions, skin colour, skin reaction to sunlight and residence > 400 m above sea level

BCC, basal-cell carcinoma; SCC, squamous-cell carcinoma; unless otherwise specified, analyses are for the two types together

8 h per week outside and who used sunscreens had the highest incidence rates. The rates in women who spent the least time outdoors were similar to those who spent more time outdoors and did not use sunscreens. [The Working Group noted that the high incidence rate in nurses using sunscreens, despite control for reaction to sunlight, might be due partly to confounding.]

Table 13. Design features of cohort studies of sun exposure and nonmelanocytic skin cancer

Reference	Place	Period of diagnosis	Population	Sample size	Response rate	Cases	Histological confirmation
Robinson (1987)	Chicago, IL, USA	Not stated	Patients with previous BCC	1 000	98%	BCC, approx. 350	Not stated
Mark *et al.* (1989)	Maryborough, Australia	1982–86	Population-based	1 981	74%	35 SCC; 113 BCC on light-exposed surfaces only	Yes
Hunter *et al.* (1990)	USA	1980–84	Female nurses	73 366	74%	771 BCC (self-reported)	Not routinely [records of 28 out of sample of 29 confirmed]

BCC, no. of people with basal-cell carcinoma; SCC, no. of people with squamous-cell carcinoma

(f) Collation of results

The results discussed in this section come from cross-sectional studies by Holman *et al.* (1984a), Engel *et al.* (1988), Green *et al.* (1988a) and Vitasa *et al.* (1990), a case–control study by Kricker *et al.* (1991a) and cohort studies by Marks *et al.* (1989) and Hunter *et al.* (1990), all of which included information pertinent to the association between nonmelanocytic skin cancer and different aspects of sun exposure. Other studies described individually were not considered to provide useful information because of various methodological deficiencies. No data were available on short periods of residence and intermittent exposure, issues which are addressed for melanoma of the skin.

(i) *Total sun exposure: potential exposure by place of residence*

Consistent with descriptive data in a case–control study, migrants to Australia had a lower risk for squamous-cell carcinoma than did native-born Australians, after adjustment for host factors related to risk for nonmelanocytic skin tumours. Late age at arrival in Australia was associated with a lower risk for basal-cell carcinoma (Kricker *et al.*, 1991a).

(ii) *Biological responses to total sun exposure*

Cross-sectional studies and a case–control study are consistent in showing a strong relationship between cutaneous indicators of sun damage and both types of nonmelanocytic skin cancer. In most studies, the indicators of damage and diagnoses of skin cancer were made by the same examiner, but cutaneous microtopography, graded without knowledge of outcome, also showed strong associations.

Table 14. Summary of results of cohort studies of nonmelanocytic skin cancer

Reference	Exposure	Categories	RR (95% CI)	Comments
Marks *et al.* (1989)	Occupation	*BCC*		
		Indoors	1.0	Adjusted for age, $p = 0.03$
		Outdoors	1.6	
		SCC		
		Indoors	1.0	Adjusted for age, $p = 0.109$
		Outdoors	1.7	
Hunter *et al.* (1990)	Severe sunburns on face or arms			BCC
		None	1.0	Adjusted for age; p (trend) = 0.001
		1–2	1.40 (1.13–1.75)	
		3–5	1.78 (1.42–2.25)	
		≥ 6	2.91 (2.37–3.58)	
	Severe sunburns on face or arms	None	1.0	Adjusted for age, time period, region, time spent outdoors, sunscreen habit, hair colour, childhood tendency to sunburn; p (trend) < 0.001
		1–2	1.18 (0.94–1.48)	
		3–5	1.34 (1.05–1.71)	
		≥ 6	1.90 (1.50–2.40)	
	Time spent outdoors during summer (h/week)	≥ 8 (sunscreen)	1.0	Adjusted for age
		≥ 8 (no sunscreen)	0.59 (0.50–0.69)	
		< 8	0.71 (0.58–0.88)	
	Time spent outdoors during summer (h/week)	≥ 8 (sunscreen)	1.0	Adjusted for age, time period, region, number of sunburns, hair colour, childhood tendency to sunburn
		≥ 8 (no sunscreen)	0.70 (0.60–0.82)	
		< 8	0.73 (0.59–0.90)	

[a]BCC, basal-cell carcinoma; SCC, squamous-cell carcinoma

(iii) *Total sun exposure assessed by questionnaire*

No effect of time spent outdoors during summer was seen in a cohort study of basal-cell carcinoma (Hunter *et al.*, 1990). In a cross-sectional study of fishermen, cumulative exposure to UVB radiation was positively associated with the occurrence of squamous-cell carcinoma but not of basal-cell carcinoma (Vitasa *et al.*, 1990). The different results may be attributable in part to small numbers and incomplete histopathological confirmation of diagnoses.

(iv) *Occupational exposure*

In two studies from Australia, outdoor occupation was not significantly associated with the prevalence of the two types of carcinoma combined (Green *et al.*, 1988a) or with the incidence of squamous-cell carcinomas (Marks *et al.*, 1989).

(v) *Sunburn*

A cohort study of basal-cell carcinoma in the USA showed a trend of increasing risk with increasing number of sunburns after adjustment for various factors, including tendency to sunburn (Hunter *et al.*, 1990). Number of sunburns showed a nonsignificant positive association with risks for basal-cell and squamous-cell carcinoma of the skin after adjustment for various constitutional variables, including propensity to burn (Green *et al.*, 1988a).

2.1.2 *Cancer of the lip*

Assessment of the carcinogenicity of solar radiation for the lip is complicated by the fact that carcinoma at this site is actually diagnosed as a mixture of cancers of the external lip and cancers of the buccal membranes (oral cavity). Use of alcohol and tobacco are known causes of the latter tumours (IARC, 1985, 1986b, 1988).

While there are wide variations in the apparent incidence of cancer of the lip with latitude, evaluation of the association is difficult because of inconsistency in the definitions of the boundaries of the lip. 'Cancer of the lip' is defined as cancer of the vermilion border and adjacent mucous membranes and thus excludes cancers of the skin of the lip (WHO, 1977). Most are squamous-cell carcinomas and are located on the lower lip (Keller, 1970; Lindqvist, 1979), which is more heavily exposed to sunlight than is the upper lip (Urbach *et al.*, 1966).

In general, case reports were not considered, because of the availability of more informative data. One case report from Nigeria described the occurrence of two lip tumours in albinos (Onuigbo, 1978).

(*a*) *Descriptive studies*

The incidence of lip cancer is 4–10 times higher in men than in women in most white populations, and higher in whites than in populations of darker skin complexions living in the same geographical areas (Muir *et al.*, 1987).

(i) *Geographical variation*

The incidence of lip cancer is higher in rural than in urban areas, in particular among men (Doll, 1991).

Mortality from and incidence of lip cancer are substantially lower in migrants to Australia than in native-born Australians (Armstrong *et al.*, 1983; McCredie & Coates,

1989). Groups of migrants to Israel all show lower risks for lip cancer than the locally born population (Steinitz *et al.*, 1989).

(ii) *Occupation*

As reviewed by Clemmesen (1965), several observations during the nineteenth century pointed to an increased risk of lip cancer among people in outdoor occupations, in particular farmers and farm labourers. In England and Wales, increased risks for lip cancer were reported among agricultural labourers, fishermen, other dock workers and railwaymen employed outdoors (Young & Russell, 1926). Atkin *et al.* (1949) studied the occupations of 1537 men in England and Wales who died from lip cancer between 1911 and 1944. They reported that mortality from cancer of the lip was 13 times higher among men employed in agriculture than in men with professional jobs. Excess risks for lip cancer have also been observed in farmers in western Canada (Gallagher *et al.*, 1984) and in Denmark (Olsen & Jensen, 1987; Lynge & Thygesen, 1990).

(*b*) *Case–control studies*

Keller (1970) compared 301 men with lip cancer admitted to veterans' hospitals in the USA between 1958 and 1962 with two groups of white age-matched controls admitted to the same hospitals, comprising 301 oral cancer controls and 265 general controls. Altogether, 59.9% of the lip cancer cases, 37.1% of the cancer controls and 40.6% of the general controls had been born in the south of the USA. Farming was recorded as the occupation of 27% of the lip cancer cases but of only 8% of cancer controls and 4% of the general controls [crude odds ratios, 4.0 and 8.4, respectively]. Any type of outdoor work was recorded for 39% of cases of lip cancer, for 20% of cancer controls and for 12% of the general controls [crude odds ratios, 2.6 and 4.8, respectively]. Risk estimates were not adjusted for smoking, another risk factor identified in the study.

Spitzer *et al.* (1975) obtained information by personal interview on 339 men with squamous-cell carcinoma of the lip registered with the Newfoundland (Canada) Cancer Registry between 1961 and 1971 and 199 male controls chosen from the electoral register, matched for age and geographical location in nine census divisions; the overall response rate was 93%. An association was found between lip cancer and outdoor work (odds ratio, 1.52; $p < 0.05$); an odds ratio of 1.50 ($p < 0.05$) was found for occupation as a fisherman for at least eight full seasons, after adjustment for outdoor work, pipe smoking and age. No positive association was found for specific fishing activities, such as use of mouth as a third hand or of cast nets.

Lindqvist (1979) obtained information by mailed questionnaires from 171 cases (149 men, 22 women; 74% response rate) of epidermoid carcinoma of the lip registered with the Finnish Cancer Registry in 1972–73 and from a control group of 124 patients (56 men, 68 women; 77% response rate) registered with squamous-cell carcinoma of the skin of the head and neck. Risk estimates were adjusted for age. Odds ratios for men working outdoors ranged from 2.2 to 3.2 according to the calendar period during which the subjects had worked outdoors. The odds ratio was significantly increased only for those who both worked outdoors and smoked. [The Working Group noted that the choice of head and neck skin cancer patients as controls would lead to an underestimate of the odds ratio for outdoor work.]

Dardanoni *et al.* (1984) obtained information by personal interviews from 53 men with lip cancer registered in the Ragusa Cancer Registry in Italy and from 106 male controls matched for age and municipality of residence and admitted to the same hospitals for non-neoplastic diseases. An association was found between lip cancer and working or spending at least 6 h each day outdoors (odds ratio, 4.9; $p < 0.001$). After control for socio-economic level, the odds ratio was 1.7 ($p < 0.001$). [The Working Group noted that the latter p value is inconsistent with the number of subjects.]

2.1.3 *Malignant melanoma of the skin*

Melanoma of the skin is divided into three major histological types. The majority of melanomas in white-skinned populations (of European origin) are superficial spreading and nodular melanomas. Lentigo maligna melanoma—also known as Hutchinson's melanotic freckle—occurs later in life than the other types, and more specifically on exposed sites; however, the body site and evidence of sun damage in surrounding skin may influence its pathological classification (McGovern *et al.*, 1980). Acral lentiginous melanoma has not been studied epidemiologically; it is rare in white-skinned populations, although it comprises a substantial proportion of melanomas in Japan (Elwood, 1989a).

(*a*) *Case reports*

In general, case reports were not considered, owing to the availability of more informative data.

In a survey of 830 cases of xeroderma pigmentosum located through published case reports (Kraemer *et al.*, 1987), melanomas were reported in 37 patients (5%). As the median age at last follow-up of these cases was only 19 years, this observation is likely to represent a substantial excess over the number expected, although the exact nature of the study population precludes an accurate comparison. Site was specified for 29 of the 37 cases; 65% of these were on the face, head and neck (normally constantly UVR-exposed sites) as compared with 19.4% on this site among affected members of the US general population. [The Working Group recognized that data collected from previously published case reports are not uniform and may be atypical of a true incidence or prevalence series. Furthermore, no information is available on the relationship between solar exposure and the occurrence of malignant cutaneous melanoma in these patients.]

(*b*) *Descriptive studies*

(i) *Sex distribution*

The sex distribution of melanoma, adjusted for age, varies widely between populations. In many, it occurs as often as or more commonly in women than in men (Lee & Storer, 1980; Lee, 1982), in contrast to other types of skin cancer which are uniformly commoner in men (Muir *et al.*, 1987).

(ii) *Age distribution*

Age distributions of melanoma in human populations vary with sex (Lee, 1982). They cannot easily be interpreted because they represent a variable combination of the different patterns of melanomas at different sites as well as a combination of time trends and trends in the experience of birth cohorts.

(iii) *Anatomical distribution*

Melanoma is proportionately commonest on the back and face in men and on the legs in women (Crombie, 1981); however, the incidence of melanoma per unit of body area is similar on fully exposed sites, such as the face, and on partially exposed sites, such as the lower limbs in women and the back in men. The frequency on body sites that are usually covered, such as the buttocks, is much lower (Elwood & Gallagher, 1983).

(iv) *Ethnic origin*

Melanoma is predominantly a disease of white-skinned populations. Rates in dark-skinned populations are much lower, the age-standardized incidence rate in India being 0.2 per 100 000 compared to around 30 in Queensland, Australia. In Los Angeles, USA, rates were less than 1 per 100 000 in Japanese and Chinese subjects and 11–12 in white subjects (Muir *et al.*, 1987; Whelan *et al.*, 1990). The site and histological distribution of melanoma are different in non-white populations and have been little studied epidemiologically. The remainder of this section deals only with melanoma in white populations.

The incidence of melanoma is substantially lower among Hispanics than among other whites in the USA. For example, the incidence among Hispanics in New Mexico is less than 2 per 100 000 person years, but in other whites it is about 11 per 100 000 (Muir *et al.*, 1987). In several case–control studies (described in detail below), subjects with a southern or eastern European background had lower risks than those with northern European or British origins (Elwood *et al.*, 1984; Holman & Armstrong, 1984a).

In a Canadian study (Elwood *et al.*, 1984), people with an eastern or southern European background had a crude odds ratio of 0.5 relative to those with an English background. This effect was not changed appreciably after adjustment for constitutional factors of hair, eye and skin colour and the skin's reaction to sun exposure. In contrast, the effect of ethnic origin observed in Western Australia was substantially reduced after adjustment for pigmentation characteristics (Holman & Armstrong, 1984a).

(v) *Geographical variation*

Armstrong (1984) showed that the relationship between melanoma incidence in Caucasians and latitude of residence decreases from around 35 ° to a minimum around 55 ° and then rises with latitude due to high rates in Scandinavian and Scottish populations. This pattern is likely to be due to both latitudinal and pigmentation factors. Within countries, inverse relationships of incidence or mortality with latitude have been seen in England and Wales (Swerdlow, 1979), Norway (Magnus, 1973), Sweden (Eklund & Malec, 1978) and Finland (Teppo *et al.*, 1978).

In the first comprehensive analysis of the geography of melanoma in whites, Lancaster (1956) noted that mortality from the disease was higher in Australia and South Africa than in the parts of Europe from which their populations originated; that mortality in Australia, New Zealand and the USA increased with proximity to the equator; but that within Europe it was higher in Norway and Sweden in the north than in France and Italy in the south. These patterns are also evident in more recent data (Armstrong, 1984).

Geographical variation in relationship to ambient UV irradiation levels: Several studies have compared melanoma incidence and mortality rates in different areas of North America to estimated or measured levels of ambient UVR, and Elwood (1989b) estimated the change

in rate for a 10% change in UVR level (Table 15). [The Working Group noted that these studies did not assess any other component of the solar spectrum.]

Elwood *et al.* (1974) showed, using mortality data for US states and Canadian provinces, that the correlation coefficients with latitude were 0.79 for men and 0.72 for women. A variation in latitude of 2 °, which is equivalent to 138 miles, was associated with a change in death rates from melanoma of about 10%. Annual UV flux at erythema-producing wavelengths was calculated from information on latitude and meteorological data on cloud cover. This calculated index of exposure was very strongly correlated with latitude (correlation coefficient, 0.89), so melanoma mortality rates were strongly related to this index; a 10% increase in received UVR dosage would be expected to give an increase of 3.7–4.5% in the death rate from melanoma at latitude 50 °, and 6.8–10.3% at latitude 30 ° (Table 15). These values were somewhat higher for men than for women; for example, 4.4% in men compared with 3.0% in women at latitude 50 ° using the exponential model.

Fears *et al.* (1976) related melanoma incidence to latitude and to a calculated measure of UVR. Their data cover a slightly narrower range of latitude, and they calculated that a 10% increase in UVR would cause an increase in melanoma mortality of 7–12%, the higher figure applying to more southerly latitudes, which already have higher rates. Incidence rates vary more rapidly with latitude than do mortality rates, and therefore they predicted that a 10% increase in UVR would be likely to give a 14–24% increase in the incidence of melanoma (see Table 15).

Estimates using calculated UVR levels: Fears *et al.* (1977) used measurements from Robertson–Berger meters for four areas and a power model, in which the calculated percentage changes are not dependent upon the initial latitude. These calculations showed considerably stronger effects, with an estimated 25% increase in incidence for a 10% increase in solar UVR (see Table 15).

Scotto and Fears (1987) used annual UVR counts from Robertson–Berger meters in seven areas of the USA (Detroit, Seattle, Iowa, Utah, San Francisco, Atlanta and New Mexico) and data on melanoma from incidence registries (the Surveillance Epidemiology and End Results system). They fitted a power model and presented analyses by sex and by body site of the melanoma divided into trunk and lower limb *versus* head, neck and upper limb. They obtained data on covariates, including ethnic origin, pigmentation characteristics, hours spent outdoors during weekdays and during weekends and use of suncreens, suntan lotion and protective clothing, from telephone interviews with at least 500 households in each area. Data on the melanoma patients were not available, however. The results predict greater increases for females than for males, unlike the earlier work. The overall effects of a 10% increase in UVR are a 5.5% increase for trunk and lower limb tumours and a 9% increase for head, neck and upper limb tumours, averaged over the two sexes. Adjustment for the various covariates reduces the predicted increases to a 3.5% increase for trunk and lower limb tumours, and 5.5% for head, neck and upper limb tumours (see Table 15).

Pitcher and Longstreth (1991) used data on melanoma mortality over a 30-year period and calculated UV flux on the basis of satellite data from the US National Aeronautics and Space Administration, including measurements of ozone concentrations at high atmospheric conditions. The models fitted are complex, as they are fitted for the two sexes, for three different places covering a range of latitudes, and separately for changes in the annual UV

Table 15. Estimates by Elwood (1989b) of percentage increase in frequency of melanoma among whites with a 10% increase in solar ultraviolet radiation, based on differences with latitude in Canada and the USA

Ultraviolet radiation level derived from[a]	Model	50 ° latitude		30 ° latitude		References on which estimates based
		Incidence	Mortality	Incidence	Mortality	
Calculation of erythema-weighted index	Linear		4.5		6.8	Elwood *et al.* (1974)[b]
	Exponential		3.7		10.3	
Calculation of erythema-weighted index	Exponential	14.0	7.0	23.5	12.0	Fears *et al.* (1976)[c]
RB meter (1974)	Power	25.0		25.0		Fears *et al.* (1977)[d]
RB meter (1978–81)	Power					Scotto & Fears (1987)[e]
	Trunk and lower limb					
	Crude	5.5		5.5		
	Adjusted	3.5		3.5		
	Head, neck and upper limb					
	Crude	9.0		9.0		
	Adjusted	5.5		5.5		
	Total					
	Crude	6.7		6.7		
	Adjusted	4.2		4.2		
Calculation of erythema-weighted estimate from NASA including satellite ozone column measurements	Power					Pitcher & Longstreth (1991)[f]
	Annual		3.2		3.2	
	Peak		7.0		7.0	
	Exponential					
	Annual		2.1		4.5	
	Peak		5.8		8.2	

Both sexes (simple average of sex-specific results)

[a]RB, Robertson–Berger; NASA, National Aeronautics and Space Administration

[b]Mortality data, USA and Canada 1950–67 by state/province; 58 areas

[c]Incidence data. Third National Cancer Survey (1969–71) for nine areas; US mortality by state. Calculation based on latitude equivalent to change in ultraviolet radiation

[d]Incidence data, Third National Cancer Survey (1969–71) for four areas

[e]Incidence data, Surveillance Epidemiology and End Results Program for seven areas. Crude results take account only of age; adjusted results are controlled for ethnic origin, hair or skin colour, suntan lotion use and hours spent outdoors; total, for comparison, is based on 67% trunk and lower limb and 33% head, neck and upper limb tumours

[f]Mortality data by US county 1950–79; estimates of changes in mean annual dose and in peak doses (clear day in June); estimates using DNA action spectrum were also made and were 1–8% higher than those shown.

flux and changes in the peak levels in clear summer conditions. Larger effects were again found for males than for females, and a larger effect when using the peak measurements than when using the annual measurements. The overall estimates of the percentage increase in melanoma mortality associated with a 5% decrease in ozone level, on the assumption that this is roughly equivalent to a 10% increase in solar UVR, ranged from 2.1 to 7.0 at 50 °N and from 3.2 to 8.2 at 30 °N (see Table 15).

[The Working Group noted that, despite the sophistication of some of the mathematical models, these results are derived from population-based descriptive data and not from individual measurements and are restricted to North America.]

(vi) *Migration*

The most informative data on risk in migrants come from Australia, New Zealand, Israel and the USA. Native residents of Australia (McCredie & Coates, 1989; Khlat *et al.*, 1992) and New Zealand (Cooke & Fraser, 1985), mostly of British origin, experienced incidence and mortality rates of melanoma roughly twice those of British immigrants. Native Israelis had a risk at least twice that of immigrants to Israel from Europe for at least 30 years after immigration (Steinitz *et al.*, 1989).

The higher incidence in white immigrants to Hawaii from the US mainland compared with white natives has been attributed to a difference in skin colour (Hinds & Kolonel, 1980). Non-Hispanic migrants to Los Angeles County (California, USA) from higher latitudes in the USA are still substantially protected against melanoma of all histological types decades after migration. Similar relative protection is enjoyed by native residents of more northerly US communities in comparison with co-resident migrants from the south-western USA (Mack & Floderus, 1991).

(vii) *Socioeconomic status and occupation*

Melanomas are much commoner in higher socioeconomic groups, as shown in data from the United Kingdom since 1949–51. In the United Kingdom, the distribution of melanoma in married women by social class (categorized by their husbands' social class) is similar to that of men, indicating that this is a social rather than a specific occupational factor (Lee, 1982). In the USA, the risk increases with income for men aged 30–69; at age 70 and above, the trend is reversed, suggesting a role for long-term exposure to the sun (Kirkpatrick *et al.*, 1990). In case–control studies, the effect of socioeconomic status is weakened after adjustment for measures of exposure to the sun (Gallagher *et al.*, 1987; Østerlind *et al.*, 1988b).

Assessment of outdoor exposure on the basis of routine data on job descriptions showed that melanoma is commoner in indoor than in outdoor workers, even within the same socioeconomic group (Lee & Strickland, 1980; Lee, 1982). Cutaneous melanoma incidence rates during 1972–76 in New Zealand showed no pattern according to outdoor workplace (Cooke *et al.*, 1984). An analysis of 3991 cases of cutaneous melanoma registered during 1971–78 in England and Wales and of 5003 cases registered during 1961–79 in Sweden suggested an elevated incidence in professional occupations. The incidence among farmers was close to that expected (Vågerö *et al.*, 1990).

Garland *et al.* (1990) reported 176 incident cases of melanoma among US Navy personnel. The rate for indoor occupation was higher than that for outdoor workers.

(*c*) *Case–control studies*

Elements of each case–control study described below are given in Table 16.

(i) *Australia*

Lancaster and Nelson (1957) carried out a case–control study on 173 patients aged over 14 years treated for malignant melanoma in hospitals in Adelaide, Melbourne and Brisbane, and 173 hospital controls with cancers other than of the skin, matched for sex and age. Information was obtained by interviews [response rate not given], and analysis was done by single factor cross-tabulations only. Unmatched crude odds ratios were calculated by the Working Group. Skin [odds ratio, 1.95 for fair *versus* olive and medium], hair colour [odds ratio, 1.7 for fair and red *versus* black and brown], eye colour [odds ratio, 1.75 for blue and green-grey *versus* brown and hazel] and skin reaction to sunlight [2.9; 95% CI, 1.9–4.5 for red *versus* brown reaction] were significantly associated with risk for malignant melanoma. Among the other factors studied were birth outside Australia [0.8; 0.4–1.6], 10 years' or more occupational exposure to sunlight in males [1.4; 0.7–2.7], sunbathing [1.5; 0.9–2.4] and moderate [1.2; 0.5–3.1] and excessive [2.3; 0.8–6.3] total exposure to the sun compared to minimal exposure. There were only eight cases and 11 controls in the latter category of sun exposure.

Beardmore (1972) studied 468 cases of histologically confirmed malignant melanoma and 468 sex- and age-matched hospital controls (including patients with skin cancer) at one hospital in Brisbane. Information was obtained by interview [response rate and method of evaluation of hair, skin and eye colour not given]. Hair, skin and eye colour and skin reaction to sunlight were not associated with risk for malignant melanoma. Comparison of exposure to sunlight from mainly outdoor occupations to that from mainly indoor occupations resulted in a crude odds ratio of [1.42; 95% CI, 1.03–1.97]; a similar comparison for recreational activities gave a crude odds ratio of [1.03; 0.75–1.42]. Fewer cases than controls had a history of treatment for keratosis and/or skin cancer or currently had keratosis and/or skin cancer [crude odds ratios, 0.51, 0.38–0.69; and 0.16, 0.12–0.22, respectively].

In the Western Australia Melanoma study (Holman & Armstrong, 1984a,b), 511 cases aged 10–79 years and 511 population controls matched for sex, age and area of residence were interviewed at home using a questionnaire based on that of the Western Canada study, which included objective measurements and naevi counts. The study also included a review of pathology slides. Analyses were presented for superficial spreading, nodular and lentigo maligna melanomas and for a fourth, unclassifiable group. Response rates were 76% for cases and 62% for controls, and adjustment was made for chronic and acute skin reaction to sunlight, hair colour, ethnic origin and age at arrival in Australia using a multiple logistic regression model. Hair colour, acute and chronic reaction to sunlight, number of naevi and family history of melanoma were significantly associated with risk; skin and eye colour were significantly associated in a crude analysis only. Duration of residence in Australia was strongly, positively associated with risk for all melanomas and for all sub-types except for unclassifiable melanoma. After control for ethnic origin, the odds ratios for superficial spreading melanoma were 1.2 (95% CI, 0.25–5.5) for people arriving in Australia at age 0–4, 1.7 (0.34–8.0) for those arriving at age 5–9, 0.74 (0.17–3.3) for those arriving at age 10–14, 0.25 (0.05–1.4) for those arriving at age 15–19 years or older (< 30 years) and 0.38

(0.19–0.78) for those arriving at age $\geq$ 30 years (p for trend, $<$ 0.0001) compared to those born in Australia. A lifetime residential history was used to calculate the mean annual hours of bright sunlight based on place of residence as a measure of potential exposure to the sun. An analysis restricted to native-born Australians showed positive associations for all melanomas and for each subtype except nodular melanoma. An analysis dichotomizing exposure at an annual mean of $>$ 2800 h sunlight at different ages showed that the highest risk ratio for all melanomas and for the superficial spreading subtype were for high exposure at ages 10–24. Cutaneous microtopography was used to measure skin damage; a positive association was found with all melanomas, being strongest for lentigo maligna melanoma.

In a further analysis by individual habits of exposure to the sun (Holman *et al.*, 1986a), no significant association was seen for total outdoor exposure. Analysis by recreational outdoor exposure, expressed as a proportion of total exposure, at ages 10–24 years showed no significant association. For superficial spreading melanoma, analysis by specific activity showed positive associations with boating (p = 0.04) and fishing (p = 0.07) and weaker, nonsignificant associations with swimming and sunbathing at ages 15–24 or 0–9 years before diagnosis. For other types of melanoma, no clear positive association was found; regular swimmers had a lower risk of lentigo maligna melanoma (trend test significant). Occupational exposure was analysed on the basis of whether the site of the melanoma was usually covered by clothing and compared to that of a referent group for whom the site was usually covered: subjects for whom the site was exposed showed a significant positive association. In comparison with the same referent group, patients who had never worked outdoors had significantly increased risks for all melanomas. The type of bathing suit usually worn by females in summer was assessed, and a positive association was found for wearing bikinis or for nude bathing, which was significant for all trunk melanomas and for superficial spreading melanoma on the trunk. When previous sunburns were classified by severity, no significant trend was observed for all melanomas; but there was a positive trend for lentigo maligna melanoma (p = 0.06) and a significant negative association for nodular melanoma.

In the smaller Queensland Melanoma study (Green, 1984; Green *et al.*, 1985a), 183 patients with histologically confirmed melanoma, other than lentigo maligna melanoma or acral lentiginous melanoma, and 183 population controls matched for sex, age and area of residence were interviewed at home using a standardized questionnaire, which included objective measurements and naevi counts. The response rates were 97% and 92%, respectively. Adjustment was made using a multiple logistic regression model. Hair colour, acute sun reactions and naevi were significantly associated with risk. Skin colour, eye colour, chronic sun reaction, freckling and family history of melanoma were significant in a crude analysis only. Hours of occupational and recreational exposure to the sun from 10 years of age across three categories gave risks of 1, 3.2 (95% CI, 0.9–12.4) and 5.3 (0.9–30.8) after adjustment for naevi, hair colour and propensity to sunburn. Average levels of exposure to UVB radiation were also allocated by residential history but showed no association with risk for melanoma. People born in Queensland had moderately higher risks than those who arrived there later in life or who had lived somewhere else at any time. Melanoma patients had more kerotoses or skin cancers on their faces (odds ratio, 2.8; 1.1–7.2). Sunburn (Green *et al.*, 1985a) was defined as pain persisting longer than 48 h, with or without blistering, and was recorded as the number of episodes in each decade. Risk increased with the number of

severe sunburns and was 1.9 and 5.0 in the two higher categories on matched analysis, decreasing to 1.5 (0.7–3.2) and 2.4 (1.0–6.1), respectively, when adjusted for naevi and exact age. An additional analysis of 49 cases of lentigo maligna melanoma and 49 controls showed no association with sunburn (Green & O'Rourke, 1985; Green *et al.*, 1986).

In a more detailed review of these data (Green *et al.*, 1986), no association was observed with occupational exposure to the sun. Analyses of recreational hours spent on the beach in the sun were made for lifetime exposures, exposures at 10–19 years of age and exposures in the five years prior to diagnosis; no strong or consistent association was seen in either crude or adjusted analyses. Associations with total accumulated hours of exposure to the sun (calculated by adding occupational and total recreational exposures) showed a positive trend for lifetime exposure and exposure at ages 10–19 (odds ratio, 4.4; 95% CI, 1.8–184.5), but no association was seen for exposure during the previous five years. Analysis of levels of UVR by lifetime residential history showed no major association and no site-specific association.

(ii) *Europe*

In a case–control study of residents of Oslo, Norway (Klepp & Magnus, 1979), 78 malignant melanoma patients over 20 years of age were compared with 131 unmatched hospital controls with other cancers. Both cases and controls with advanced disease were excluded. Information was obtained by questionnaire [response rate not given]. Hair and eye colour were recorded independently by the interviewer and subject but were not associated with risk for the disease, whereas skin reaction to sunlight and freckling were. A nonsignificant odds ratio of [1.5] was found for men working outdoors for more than 3–4 h/day; the odds ratio for taking sunbathing holidays in southern Europe was 2.4 ($p = 0.05$). No significant association was seen with degree of exposure of different body sites, classified from 'as often as possible' to 'hardly ever'.

Adam *et al.* (1981) conducted a population-based case–control study in the United Kingdom of 111 female cases of malignant melanoma aged 15–49 traced from registries and 342 female controls randomly selected from general practitioners' lists and matched for age and marital status. Information was obtained by postal questionnaire; response rates were 66% for cases and 68% for controls. Hair colour and skin reaction to sunlight, but not skin colour, were significantly associated with risk for malignant melanoma. Slightly more cases than controls reported deliberately tanning their legs or trunk, either at home or abroad. No difference was reported in the amount of work, leisure or total time spent outdoors. [The Working Group noted that the study concentrated on oral contraceptive use and that information on exposure to the sun was very limited.]

MacKie and Aitchison (1982) conducted a case–control study in western Scotland of 113 malignant melanoma patients aged 18–76 years and 113 sex- and age-matched hospital controls with conditions not related to the skin. Cases of lentigo maligna melanoma were excluded. Information about exposure to the sun within the previous five years was obtained by questionnaire [response rate not given] and included occupational and recreational exposure ($\geq$ 16 h *versus* $<$ 16 h outdoor exposure per week) and history of severe sunburn, defined as either 'blistering sunburn' or 'erythema persisting for a week or longer'. Other factors included in the multivariate analysis were social class and skin type. A significant negative association was observed for recreational exposure and for occupational exposure

to the sun in males. A significant positive association was observed for severe sunburn. No significant difference was observed for the number of continental holidays taken or total number of days spent in sunnier climates.

Sorahan and Grimley (1985) studied 58 patients aged 20–70 years with cutaneous malignant melanoma (other than lentigo maligna melanoma) in two hospitals in the United Kingdom and 182 hospital controls with diseases other than of the skin and 151 unmatched controls from electoral rolls. The response rates were 64% for cases and 60% for each control group. Information was obtained by postal questionnaire, and analyses were adjusted using a multiple logistic regression model. A significant positive association was observed for number of bouts of painful sunburn ever experienced, with an odds ratio reaching 7.0 for five or more bouts compared to none. A significant positive association was also seen with the number of holidays ever spent abroad in a hot climate, reaching 6.5 for 21 holidays or more, compared to none. Both associations were weakened, and the latter became nonsignificant, after adjustment for propensity to sunburn, number of moles and history of sunburn.

In another study in the United Kingdom (Elwood *et al.*, 1986), 83 histologically confirmed cases over 18 years of age and 83 hospital controls (in- and out-patients), matched for sex, age and area of residence, were interviewed at home using a questionnaire which included objective measurements and naevi counts. The responses were validated by replies to a postal questionnaire. The response rates were 74% for cases and 92% for controls. Adjustment was made using a multiple logistic regression model. Skin reaction to sunlight, freckling and naevi were significantly associated with risk. A history of sunburn causing pain for two days or more gave a significant odds ratio of 3.2 (95% CI, 1.7–5.9). Past outdoor occupational exposure showed a significantly reduced odds ratio of 0.2 (0.1–0.9) for the second highest category but a nonsignificant odds ratio of 1.7 (0.3–8.6) for the highest category and no overall trend.

In northern Italy, Cristofolini *et al.* (1987) compared 103 patients aged 21–79 under treatment for cutaneous malignant melanoma at one hospital with 205 hospital controls with diseases other than skin tumours. Subjects were interviewed [response rate not given] and assessed by a dermatologist. Adjustment was made using a multiple logistic regression model. Hair and skin colour and family history were significantly associated with risk, but eye colour, freckling and number of naevi were not. A history of frequent sunburn as an adult gave an odds ratio of 1.2 (95% CI, 0.7–2.1) and that of severe sunburn in early life an odds ratio of 0.7 (0.4–1.2). Heavy or frequent exposure to sunlight during the previous 20 years, categorized as yes or no, gave a significantly reduced odds ratio of 0.6 (0.4–0.95). Outdoor compared to indoor occupation gave a nonsignificant odds ratio of 0.9 (0.5–1.7), and a history of carcinoma of the skin gave a risk ratio of 0.4 (0.02–2.9), based on small numbers. Melanoma at exposed sites showed positive associations with heavy sun exposure (1.44; 0.8–2.8) and outdoor occupation (1.8; 0.9–3.7), while melanoma at normally unexposed sites showed a significant negative association with heavy exposure to the sun (odds ratio, 0.25; 95% CI, 0.13–0.47).

In a study of melanoma in eastern Denmark (Østerlind *et al.*, 1988b,c; Østerlind, 1990), 474 cases of melanoma, excluding lentigo maligna melanoma patients, aged 20–79 were compared with 926 population controls and matched for sex and age. Subjects were interviewed at home using a questionnaire which included objective measurements and naevi

counts, and adjustment was made using a multiple logistic regression model. Response rates were 92% for cases and 82% for controls. The number of sunburns (defined as those causing pain for two days or longer) before age 15, from age 15 to 24 and over the previous 10 years were all significantly associated with risk: crude odds ratios for the maximal categories, 3.7 (95% CI, 2.3–6.1), 2.4 (1.6–3.6) and 3.0 (1.6–5.4), respectively. Adjustment for sex and host factors, including naevi, freckles and hair colour, reduced the risk ratios, but they remained significant. Adjustment for sunburns before age 15 rendered the associations with later sunburn weak and nonsignificant. Joint analysis of sunburns and naevi suggested independent, additive risks. Significantly increased risks were seen with residence near the coast before age 15 or for more than 30 years. Specific recreational activities were investigated and categorized by the number of years of regular participation, adjusted for sex and host factors, including number of naevi, and for other activities. Significant positive associations were observed with sunbathing, boating, winter skiing and swimming, the latter becoming nonsignificant after adjustment. Regular participation in gardening, ball games, golf, horseback riding or hiking was not associated with risk for melanoma. A positive trend was seen with vacations spent in beach resorts in southern Europe (odds ratio, 1.7; 95% CI, 1.2–2.4), which was weakened after adjustment for sunbathing and sunburn (1.4; 1.0–2.1). Socioeconomic status showed a strongly positive association in men, which became nonsignificant when adjusted for sunburn and recreational exposure to the sun. Occupational exposure outdoors for at least six months was associated with a significantly reduced odds ratio of 0.7 (0.5–0.9) in men; the protective effect was most pronounced in men who started working outside at an early age and continued for at least 10 years. No association was seen with skin grading categories defined by microtopography.

In a study in northern Italy (Zanetti *et al.*, 1988), 208 cases of histologically confirmed malignant melanoma were identified from the regional tumour registry and were compared with 416 controls chosen from the National Social Service Registry. Response rates were 87% for cases and 68% for controls. An increased risk was observed with light hair colour, tendency to burn and a history of sunburn in childhood. No significant effect of region of origin was observed. Exposure to the sun was assessed by activity: for outdoor work, a nonsignificant increased risk was seen with the maximal duration of exposure ($\geq$ 33 years) in men, but the overall trend was nonsignificant. Outdoor sports, assessed by years of participation, showed an increased risk at the maximal level in men and women (significant for men). A significantly increased risk was found for men participating in sports categorized as involving the greatest exposure to the sun. A nonsignificantly increasing trend in men was observed for total number of weeks' holiday, but little effect was seen in women; a significant positive trend was observed in men, but not for women, for the number of weeks spent at the seaside in childhood. Similar exposure in adult years resulted in a nonsignificant positive trend.

Garbe *et al.* (1989) studied 200 malignant melanoma patients at a dermatological follow-up clinic in Berlin, Germany, in 1987 and 200 controls from the same clinic who had any other skin disease (response rate, 90%). Subjects of non-German origin were excluded, as were those seeking consultation for pigmented naevi or who had been treated previously by UVR (10%). Occupational exposure to the sun, assessed as none, sometimes or nearly all the time, showed a strongly increased risk up to an odds ratio of 5.5 (1.2–25.3). No significant

relationship was found with duration of leisure-time exposure to the sun or number of sunburns. [The Working Group noted that little detail was given about exposure and that the control group consisted of patients with other skin disease.]

Weiss *et al.* (1990) studied 1079 cases of malignant melanoma reported to the German Dermatological Society Registries in 1984–87 and 778 hospital controls from the same clinics. Positive associations were seen with occupational exposure to the sun, which increased with the number of years of exposure. No association was seen with exposure to the sun during leisure time or with sunbathing. [The Working Group noted that this study appears to overlap with that of Garbe *et al.* (1989) and that the data were presented with relative risks but with no test of significance.]

Beitner *et al.* (1990) studied 523 incident cases of malignant melanoma seen at a hospital in Stockholm, Sweden (representing 64% of all cases registered in Stockholm County), and 505 controls selected from the population register for Stockholm County. Cases completed a questionnaire while waiting at the clinic, and controls received the questionnaire by mail (response rates, 99.6% and 96.2%, respectively). A significant positive effect was seen for the number of sunbathing sessions each summer, with a history of erythema after sunbathing and with sunbathing vacations abroad. Residence in countries around the Mediterranean or in a sub-tropical or tropical climates for more than one year during the previous 10 years gave a significant odds ratio of 1.9 [95% CI, 1.0–3.6]. There was no increase in risk with sunbathing during winter vacations at high altitudes. Outdoor workers had a significantly reduced risk of 0.6 (0.4–1.0) after adjustment for age, sex and hair colour.

Elwood *et al.* (1990) studied 195 cases of superficial spreading or nodular melanoma in people aged 20–79 from five pathology laboratories in the United Kingdom and 195 controls chosen from among all in- and out-patients in the region. Cases and controls underwent an interview and a limited examination by an interviewer in their homes (participation rate—cases and controls, 73%; voluntary response rate—cases, 91%; controls, 78%). Risk was significantly increased with sunburn at age 8–12 (odds ratio, 3.6; 1.4–11.2), but no significant increase was observed with sunburn at age 18–22 or with sunburn received 18–20 or five years prior to diagnosis. No other sun exposure variable was reported.

Grob *et al.* (1990) compared 207 consecutive white patients, 18–81 years old, with histologically confirmed invasive melanoma (at least level 2; lentigo melanoma and acral lentiginous melanoma excluded) seen in one dermatology clinic in Marseilles, France, with 295 controls. Controls under 65 years of age were chosen from among subjects interviewed after reportedly random selection and examined at a public health centre; those over 65 were chosen from among out-patients with non-cancer and non-dermatological conditions. Patients and controls were examined and interviewed by the same dermatologist. Multiple logistic model analysis was used. The risk for melanoma was increased significantly in association with annual outdoor leisure exposure during the previous two years (odds ratio, 8.4; 95% CI, 3.6–19.7), outdoor occupation (6.0; 2.1–17.4) and total lifetime sun exposure (odds ratio for maximum category, 3.4; 1.6–7.1). There was a nonsignificant association with sunburns in recent years (1.7; 0.63–4.6) after adjustment for number of naevi, maximal depth of suntan, hair colour, social level, complexion and age. [The Working Group found the study

difficult to interpret because of the nature of the control group and the relative recency of measurements of exposure to the sun.]

In a report designed to produce a risk prediction model, MacKie *et al.* (1989) studied 280 cases of invasive cutaneous malignant melanoma (level 2 or deeper) from Scottish melanoma registries. Controls were 280 hospital patients with non-dermatological diseases. Response rates were 76% for cases and unknown for controls. An increased risk was observed for history of severe sunburn (adjusted odds ratio, 7.6 (95% CI, 1.8–32.0) for men and 2.3 (0.9–5.6) for women). A significant positive association for tropical residence was noted for men, which became nonsignificant after adjustment. [The Working Group noted that, apart from tropical residence, no data were presented on exposure to the sun.]

(iii) *North America*

Gellin *et al.* (1969) studied 79 patients, aged 30–79, with histologically confirmed malignant melanoma at one hospital in New York, USA, and compared them with 1037 hospital controls with skin conditions other than cancer. Information was obtained by interview and examination [response rate not given]. The odds ratios for duration of daily outdoor activity were [2.8 (95% CI, 1.3–5.8)] for 6 h or more and [4.1 (2.5–6.8)] for 3–5 h, compared to 0–2 h. [The Working Group noted that the controls had skin diseases.]

Paffenbarger *et al.* (1978) reported on cases found by follow-up of subjects first examined when entering Harvard University in 1916–50 and the University of Pennsylvania in 1931–40. Out of a total of 50 000 male subjects and 1.71 million person-years of observation, 45 deaths from melanoma were observed and each compared to four controls born in the same year, who were classmates and who had survived as long as the case subjects. Of the many factors investigated, only outside remunerative work was associated with a significant risk for melanoma (odds ratio, 3.9; $p = 0.01$). Within the cohort, students from New England had a 50% lower risk for melanoma than other students, presumably owing to more northerly residence.

Lew *et al.* (1983) carried out a study in Massachusetts on 111 cases of cutaneous malignant melanoma, aged 23–81, followed at one hospital and 107 controls who were friends of cases, matched by age and sex. Information was obtained by interview at the clinic; response rates were 99% for cases and 90% for controls, and analysis was made using a logistic regression model. Cases showed poorer tanning ability, and a significant association was observed with blistering sunburn during adolescence (odds ratio, 2.1; 95% CI, 1.2–3.6) and with 30 days or more vacation in sunny, warm places during childhood (2.5; 1.1–5.8). The association with history of sunburn persisted after controlling for tanning ability. [The Working Group noted that the nature of the controls and the simplicity of the analyses presented make interpretation of the results difficult.]

Rigel *et al.* (1983) analysed data on 114 melanoma patients (out of a total of 328) seen in a referral centre in New York between 1978 and 1981, and on 228 controls who were staff and patients at the centre. Significantly increased risks were seen with > 2 h per day sun exposure 11–20 years previously (odds ratio, 2.5; $p = 0.005$) and outdoor *versus* indoor recreation (2.4; $p = 0.01$). [The Working Group noted that the selection of subjects and the nature of the control group make these results difficult to interpret.]

In the Western Canada Melanoma case-control study (Elwood *et al.*, 1984, 1985a,b), carried out in four Canadian provinces, 595 cases of malignant melanoma, aged 20–79, and 595 population controls, matched for sex, age and province of residence, were questioned by trained interviewers at their homes (response rates: cases, 83%; controls, 48–59%). Cases of lentigo maligna melanoma and acral lentiginous melanoma were excluded. Analyses were made using a multiple logistic regression model. Significant positive associations were found after adjustment for host factors and ethnic origin for frequent recreational (odds ratio, 1.7; 95% CI, 1.1–2.7) and holiday exposure (1.5; 1.0–2.3) and with the number of sunny vacations per decade (1.7; 1.2–2.3). No overall trend was observed for occupational exposure, but a significantly increased risk was associated with moderate occupational exposure, defined as seasonal or short-term occupational exposure. Maximal occupational exposure was associated with a significantly reduced odds ratio in men (0.5 [CI not given]) but not in women (1.5 [CI not given]). Analysis of total annual exposure to the sun from all sources showed no overall trend (odds ratio, 1.0–1.6 in various categories above the minimal exposure referent group). Severe or frequent sunburn in childhood resulted in a nonsignificant odds ratio of 1.3, after adjustment for host factors and sun sensitivity. From variables relating to sunburn on vacation and the usual degree of suntan in winter and summer, positive associations were observed for increasing sunburn and with decreasing usual tan. Cross-tabulation of sunburn with tendency to sunburn (skin type) did not change the significant positive effect of tendency to burn, but the odds ratio for sunburn fell from 1.8 in the maximal category to 1.4 ($p > 0.2$) after adjustment for sun reaction. Similarly, cross-tabulation of usual degree of suntan against skin type gave little difference in the positive association with reaction to the sun, but a weakening of the association with usual degree of suntan was seen which became nonsignificant. A multivariate analysis including history of sunburn, usual degree of suntan, skin type and host factors showed significance for the two latter factors, nonsignificant positive effects of holiday sunburn and a significant negative effect of usual degree of suntan. These results are interpreted as showing a primary association with tendency to burn easily or to tan poorly rather than with history of either sunburn or suntan. For men, a significant negative association was seen with outdoor occupation, but this weakened and became nonsignificant when adjusted for recorded exposure to the sun. Similarly, the crude odds ratio for upper compared to lower socioeconomic groups was 3.8 (2.0–7.4) but was reduced to 2.3 (1.0–5.1) after adjustment for host factors and for occupational, recreational and holiday sun exposure (Gallagher *et al.*, 1987).

Elwood *et al.* (1987) made an analysis separating superficial spreading melanoma, nodular melanoma and lentigo maligna melanoma in the western Canada study, based on 415, 128 and 56 cases, respectively. Recreational exposure, holiday exposure and the number of sunny vacations per decade were positively and significantly (trends) associated with superficial spreading melanoma (odds ratios, 1.4, 2.0 and 2.2; 95% CI, 1.0–2.0, 1.4–2.9 and 1.5–3.3, respectively); recreational exposure was also positively associated with nodular melanoma (2.4; 1.3–4.5), but neither holiday exposure nor the number of sunny vacations showed an association. None of these measures of intermittent exposure was significantly associated with lentigo maligna melanoma. Occupational exposure showed no significant association with any of the three types. History of sunburn showed positive but nonsignificant

associations with superficial spreading and lentigo maligna melanomas but not with nodular melanoma.

Brown *et al.* (1984) identified 120 men who had been aged 18–31 during the Second World War from among 1067 patients seen at a melanoma clinic in New York City in 1972–80 and sent them questionnaires (response rate, 74%). Controls were 65 age-matched subjects attending the same dermatology department with skin diseases other than melanoma [response rate unknown]. Within the total of 74 cases and 49 controls who had been in the armed services, the odds ratio for service in the tropics as compared to service in the USA or Europe was [7.7; 95% CI, 2.5–23.6].

In a hospital-based study in Buffalo, NY, USA (Graham *et al.*, 1985), 404 cases of cutaneous malignant melanoma referred to the Roswell Park Memorial Institute, aged from under 30 to over 65, were compared with 521 controls with other neoplasms at the same institute, using questionnaires completed on admission. There was a weak negative trend with total number of hours of exposure to the sun, which was significant in men; a similar trend was observed for average annual exposure to the sun. Occupational exposure to the sun gave a nonsignificant reduction in risk in men in the highest exposure group after adjustment for tendency to burn. Multivariate analysis showed a negative association with cumulative exposure to the sun, which was significant in men when adjusted for tendency to burn, freckling and light complexion. Results specific to recreational or holiday exposure to the sun were not presented.

Dubin *et al.* (1986) compared 1103 cases of melanoma seen at the New York University Medical Center from 1972 to 1982 (mostly in 1977–79) to 585 controls interviewed in 1979–82 at the skin clinic for conditions excluding cancer. Both cases and controls were interviewed by physicians; response rates were 98% for cases and 78% for controls. In order to complete the data on risk factors, a postal questionnaire was sent requesting information on exposures to fluorescent lights and to the sun and on skin colour (response rates, 45% of cases and 30% of controls). Mostly outdoor compared to mostly indoor work gave an odds ratio of 2.5 (95% CI, 1.4–4.4) and mostly outdoor compared with mostly indoor recreation gave an odds ratio of 1.7 (1.2–2.3), although mixed indoor and outdoor recreation gave a significantly reduced risk of 0.6 (0.5–0.8). Overall exposure to the sun (three categories) showed no trend. A history of the presence of solar keratosis gave a significant risk ratio of 5.0 (2.3–10.5). Quantitative total sun exposure was assessed for 623 cases and all 585 controls: there was no significant trend with total hours of exposure to the sun per day 0–5, 6–10 or 11–20 years before diagnosis. [The Working Group noted that the cases and controls were not interviewed over the same period.]

In a study based on a subset of the above (Dubin *et al.*, 1989), 289 cases and 527 controls were interviewed using the same method (response rates, 100% of eligible cases; 70% of controls [19% of potential controls were excluded because of diagnosis of a lesion known to be caused by exposure to the sun]). Mostly outdoor occupation gave a nonsignificant elevated risk. Mostly outdoor recreation was associated with a significantly elevated risk in light tanners but a nonsignificant elevated risk in dark tanners (interaction nonsignificant). Overall exposure to the sun was associated with significantly increased risks in all groups. A history of sunburn was associated with a significantly increased risk in light tanners and in all subjects but had a nonsignificant protective effect in dark tanners (interaction significant).

When analysed by age group, a history of sunburn gave a positive association at age 20–39, a weak association at 40–59 and a negative association at 60 or over (interaction significant). Prior skin cancer or solar keratosis had a significant effect, which was stronger in men than in women (interaction nonsignificant).

In a study in San Francisco, Holly *et al.* (1987) compared 121 patients with nodular or superficial spreading melanoma at a university melanoma clinic with 139 controls from a medical screening clinic or from an orthopaedic clinic at the same centre. Response rates were 'over 95%'. Sunburn score, based on the number of blistering sunburns during school and young adult years, showed a significant odds ratio of 3.8 (95% CI, 1.4–10.4) after controlling for naevi, hair colour and previous skin cancers. A positive association was seen with previous skin cancer (3.8; 1.2–12.4).

Weinstock *et al.* (1989) reported a case–control study within a cohort of US nurses (see Hunter *et al.*, 1990, p. 86). Data on 130 cases and 300 controls (response rates to post-diagnosis questionnaire, 85% and 81%, respectively) were analysed using multivariate models. Following adjustment for skin sensitivity, significant positive effects were seen for sunburn at ages 15–20 (odds ratio, 2.2; 95% CI, 1.2–3.8), but not at age ≥ 30 (1.3; 0.7–2.3), and for residence at a southern latitude at age 15–20 (2.2; 1.1–4.2), but not at age ≥ 30 (1.6; 0.9–2.8). No direct recording of exposure to the sun was reported.

A further analysis (Weinstock *et al.*, 1991a) assessed the use of swimsuits in these subjects. There was a significant positive association of melanoma risk with the frequency of use of swimsuits of any type in sun-sensitive women (odds ratio, 6.4; 95% CI, 1.7–23.8) but not in sun-resistant women (0.3; 0.1–1.0). After controlling for type of swimsuit and sensitivity factors, melanoma risk was increased with increasing hours per day of outdoor swimsuit use (any type) after age 30, but no association was seen with intensity of exposure or with the number of winter vacations in warm and sunny locations. The use at age 15–20 of a bikini compared to high backline, one-piece swimsuits, gave an odds ratio for all melanomas of 1.9 (1.0–3.7) and for trunk melanoma specifically of 0.8 (0.3–2.6); the risks were 3.5 [CI not given] among sun-sensitive women and 1.3 [CI not given] among less sun-sensitive women, but the interaction was not significant.

In a case–control study of patients attending a pigmented lesion clinic in Boston, USA (Weinstock *et al.*, 1991b), 186 had cutaneous melanoma; the 239 controls had other dermatological diagnoses, the most frequent of which were common naevus and solar keratosis. Data were obtained from medical records and from a self-administered questionnaire completed before clinical examination and were analysed by a multivariate method. Significantly increased risks for melanoma were associated with lack of tan after repeated exposures as a teenager (odds ratio, 2.3; 95% CI, 1.0–4.9). A nonsignificant trend towards increased risk was observed for residence in southerly areas. [The Working Group noted that the paper dealt primarily with dysplastic naevi and the results on melanoma are not given in detail, and that the controls also had dermatological conditions.]

Table 16. Case–control studies of melanoma in which exposure to the sun and/or artificial ultraviolet radiation was assessed

Place	Period of diagnosis	No. of cases	Source of cases	Melanoma type	No. of controls	Type of control	Reference
Australia							
East Australia	NS	173	3 hospitals	All types	173	Other cancers	Lancaster & Nelson (1957)
Queensland, Australia	1963–69	468	1 hospital	All types	468	Hospital patients, including skin cancers	Beardmore (1972)
Western Australia	1980–81	511	Population	All types	511	Population	Holman & Armstrong (1984a,b)
Queensland, Australia	1979–80	183	Population	No LMM	183	Population	Green (1984); Green *et al.* (1985a)
Europe							
Oslo, Norway	1974–75	78	1 hospital	All types	131	Other cancers, same hospital	Klepp & Magnus (1979)
United Kingdom	1971–76	111	Population	All types	342	General practice lists	Adam *et al.* (1981)
Western Scotland	1978–80	113	Hospital	No LMM	113	Hospital, non-skin	MacKie & Aitchison (1982)
Birmingham, UK	1980–82	58	2 hospitals	No LMM	333	Hospital and population	Sorahan & Grimley (1985)
Nottingham, UK	1981–84	83	Population (2 hospitals)	All types	83	Matched hospital	Elwood *et al.* (1986)
Trento, Italy	1983–85	103	1 hospital	All types	205	Hospital	Cristofolini *et al.* (1987)
East Denmark	1982–85	474	Population	No LMM	926	Matched population	Østerlind *et al.* (1988a,b); Østerlind (1990)
Turin, Italy	1984–86	208	Population	All types	416	Population	Zanetti *et al.* (1988)
Berlin, Germany	1987	200	1 hospital	All types	200	Skin clinic patients	Garbe *et al.* (1989)

Table 16 (contd)

Place	Period of diagnosis	No. of cases	Source of cases	Melanoma type	No. of controls	Type of control	Reference
Scotland	1987	280	Population	Invasive MM at least type 2	280	Hospital, excluding skin	MacKie *et al.* (1989)
Germany	1984–87	1079	6 dermatology clinics	All types	778	Skin clinic patients	Weiss *et al.* (1990)
Stockholm, Sweden	1978–83	523	1 hospital	All types	505	Matched population	Beitner *et al.* (1990)
Midlands, UK	1984–86	195	Population	SSM and NM	195	Hospital in-/out-patients	Elwood *et al.* (1990)
Southeast France	1986–88	207	Hospital	Invasive, all types	295	Health centre	Grob *et al.* (1990)
North America							
New York, USA	1955–67	79	1 hospital	All types	1037	Other skin diseases, non-cancer	Gellin *et al.* (1969)
Boston, MA, USA Philadelphia, PA, USA	NS	45	Cohort of university alumni	All types	180	Classmates	Paffenbarger *et al.* (1978)
Boston, MA, USA	1978–79	111	1 hospital	All types	107	Friends of cases	Lew *et al.* (1983)
New York, USA	1978–81	114	1 hospital	All types	228	Patients and staff	Rigel *et al.* (1983)
New York, USA	1972–80	74	1 melanoma clinic	All types	49	Skin clinic patients	Brown *et al.* (1984)
Western Canada	1979–81	595	Population	SSM, NM or UCM	595	Population	Elwood *et al.* (1984, 1985a,b)
Buffalo, NY, USA	1974–80	404	Hospital patients	All types	521	Cancer patients	Graham *et al.* (1985)
New York, USA	1972–82	1103	3 hospitals	All types	585	Skin clinic patients	Dubin *et al.* (1986)
Western Canada	1979–81	415 128 56	Population	SSM NM LMM	415 128 56	Population	Elwood *et al.* (1987)
San Francisco, CA, USA	1984–85	121	1 melanoma clinic	NM and SSM	139	Clinic patients	Holly *et al.* (1987)

Table 16 (contd)

Place	Period of diagnosis	No. of cases	Source of cases	Melanoma type	No. of controls	Type of control	Reference
New York, USA	1979–82	289	3 hospitals	All types	527	Non-cancer skin patients	Dubin *et al.* (1989)
USA	1976–84	130	Nurses cohort	AM excluded	300	Nurses cohort	Weinstock *et al.* (1989)
Boston, MA, USA	1982–85	186	1 hospital	All types	239	Skin clinic patients	Weinstock *et al.* (1991b)

NS, not specified; SMM, superficial spreading melanoma; NM, nodular melanoma; UCM, unclassifiable melanoma; LMM, lentigo maligna melanoma (or Hutchinson's melanotic freckle); AM, acral lentiginous melanoma

(d) Collation of results

The studies summarized above show that a range of host characteristics are related to melanoma risk, including ethnic origin, skin, hair and eye pigmentation, and, importantly, a tendency to sunburn or suntan, often expressed clinically as skin type. These factors can be assumed to reflect genetic sensitivity to cutaneous effects of sun exposure and, in addition to the indirect evidence of a role of exposure to the sun in melanoma that they provide, should be considered as confounders in a relationship between sun exposure and melanoma. The numbers of acquired benign naevi and of dysplastic naevi have been shown to be very strong risk factors for melanoma in several studies; the density of freckling on the skin has also been shown to be a risk factor. Because there is evidence that these outcomes are themselves related to sun exposure, and in the case of naevi may be intermediate steps in the genesis of melanoma, they should not be considered confounding factors (Armstrong, 1988). Most of the studies relied on a wide range of questions to assess different aspects of sun exposure. Armstrong (1988) developed a useful classification of such questions, dividing them into those that assess potential exposure, such as place of residence and time of migration, those that record actual exposure and those that record response to exposure, such as questions on sunburn and suntanning.

(i) *Total sun exposure: potential exposure by place of residence* (Table 17)

Consistent with the descriptive studies, Holman and Armstrong (1984b) showed that the risk in migrants arriving in Australia before age 10 (odds ratio, 0.89; 95% CI, 0.44–1.80) is as high as that of the Australian born (1.00), and the risk in those arriving at age 10 or above is much less (0.34; 0.16–0.72 for age 10–29; 0.30; 0.08–1.13 for age ≥ 30). These data are an improvement on descriptive data as they allow control for ethnic background and pigmentation. In the same study, an association was seen with annual hours of bright sunlight averaged over all places of residence.

In the USA, two case–control studies (Graham *et al.*, 1985; Weinstock *et al.*, 1989) showed increased risks for people who had lived at southerly latitudes.

Increased risks in people who have lived near the coast were seen in Denmark (Østerlind *et al.*, 1988b) and in Queensland, Australia (Green & Siskind, 1983). It was assumed in the Danish study that coastal residence would involve more exposure to the sun. In Queensland, living near the coast is not related to annual ambient UVR, which varies with latitude, so that peak summer UV irradiance is higher in the interior than on the coast (Green & Siskind, 1983). The observations are thus due either to different behavioural patterns with geographical location or to differences in exposure to UVR.

(ii) *Biological response to total sun exposure*

It has been assumed that a history of nonmelanocytic skin cancer, solar keratoses, actinic tumours or changes on cutaneous microtopography are all indicators of cumulative sun damage. Positive associations are seen with these measures in studies in Australia and in the USA, although Østerlind *et al.* (1988b) in Denmark saw no relationship with microtopographical change (Table 17).

Table 17. Results of case–control studies on melanoma: place of residence, biological markers

Place	Direction of association	OR[a]	95% CI	*p* value	Measurement of exposure	Reference
Potential exposure by place of residence						
Australia	Up	5			Residence near coast; mortality rate/100 000 (incidence rate/ 100 000, 37)	Green & Siskind (1983)
Australia	Down	0.3	(0.1–1.1)	< 0.001	Age at arrival in Australia; OR given for age ≥ 30 years; *p* value for trend	Holman & Armstrong (1984b)
Australia	Up	2.8	(1.8–4.8)	< 0.001	Mean annual hours of bright sunlight at places of residence; *p* for trend	Holman & Armstrong (1984b)
USA	Up	1.4	(0.9–2.0)	> 0.05	Ever resided below 40 °N latitude	Graham *et al.* (1985)[b]
Australia	Down	0.3	(0.1–1.4)	> 0.05	Length of residence in Australia; risk associated with migration to Australia	Green *et al.* (1986)
Denmark	Up	1.7	(1.1–2.7)	0.006	Residence near coast; crude OR	Østerlind *et al.* (1988b)
USA	Up	2.2	(1.1–4.2)	0.02	Residence in southerly latitude at age 15–20, OR for 12.6 °	Weinstock *et al.* (1989)
Biological markers of cumulative sun exposure						
Australia	Up	2.7	(1.4–5.0)	0.003	Cutaneous microtopography; *p* for trend	Holman & Armstrong (1984b)
Australia	Up	3.7	(2.1–6.6)	< 0.001	History of nonmelanocytic skin cancer	Holman & Armstrong (1984b)
Australia	Up	3.6	(1.8–7.3)	< 0.001	Actinic tumours on face	Dubin *et al.* (1986)
USA	Up	5.0	(2.3–10.5)	< 0.01	History of solar keratosis	Green & O'Rourke (1985)
USA	Up	3.8	(1.2–12.4)	0.03	History of nonmelanocytic skin cancer, adjusted	Holly *et al.* (1987)
Denmark	Flat	1.1	(0.7–1.8)	> 0.05	Cutaneous microtopography; crude OR	Østerlind *et al.* (1988b)

[a]Odds ratio for maximal category

[b]Results calculated by Armstrong (1988)

(iii) *Total sun exposure assessed by questionnaire*

The results of studies in which total sun exposure was assessed using questionnaires, either over lifetime or at different periods of life, have been mixed (Table 18). Positive associations were seen by Green (1984) in Queensland, Australia; no consistent overall association was seen in western Canada, and in Western Australia the association was negative. The results of the other studies are similarly mixed. This inconsistency, in contrast to the results noted above by place of residence and by biological response, could be due either to the difficulty of assessing total sun exposure by questionnaires (Armstrong, 1988) or to different effects of differing patterns of exposure to the sun.

(iv) *Short periods of residence implying high potential exposure*

Several case–control studies have reported, usually as incidental findings, that subjects who have had a short period of residence in tropical or sub-tropical environments have an increased risk for melanoma (Table 19).

(v) *Occupational exposure*

Regular outdoor occupational exposure is probably the most convenient measure of relatively constant sun exposure and has been assessed with differing degrees of detail, from simple questions on ever/never or a basic amount of outdoor exposure, to detailed assessments involving assessments of clothing habits, geographical location of work and so on. The results appear to be inconsistent (Table 20). The more detailed studies, however, show more consistency, with a significant negative association, particularly in men, who constitute most of the highly exposed subjects (Table 21).

An overall irregular pattern was seen in western Canada, probably because individuals with relatively little occupational exposure are those who perform outdoor work seasonally or for short periods, often in early life, so that this exposure may be an indication of intermittent rather than constant exposure (Elwood *et al.*, 1985b). Such results are consistent with the effects of a short period of residence in a sunny place, as reviewed earlier. Paffenbarger *et al.* (1978) also showed that students who recorded outdoor work before college [presumably summer employment] had a significantly increased risk of melanoma in later life.

(vi) *Intermittent exposure*

To assess the effects of intermittent exposure, investigators have asked questions about specific activities that would be likely to represent relatively severe intermittent exposure, such as sunbathing, or asked particularly about holidays in sunny places, or used more complex questionnaires to attempt to assess total intermittent exposure through recreational or holiday activities. Most of these studies show positive associations, but few show large effects (Table 22).

In general, the more detailed studies show reasonably consistent positive results. For example, in western Canada, significant positive associations were seen with recreational and holiday sun exposures in activities involving reasonably intense sun exposure, such as beach activities (Elwood *et al.*, 1985b). In Denmark, rather similar relative risks of 1.5–1.9 were seen with regular participation in activities such as sunbathing, boating, skiing, swimming and vacations in sunny places (Østerlind *et al.*, 1988b). Significant positive associations with sunbathing were seen in the Swedish study of Beitner *et al.* (1990). In the study of Zanetti *et al.*

Table 18. Results of case–control studies on melanoma: total sun exposure assessed by questionnaire

Place	Direction of association	OR[a]	95% CI	*p* value	Measurement of exposure	Reference
USA	Up	2.5	NA	< 0.001	Sun exposure 2 h/day, 11–20 years previously	Rigel *et al.* (1983)
Australia	Up	5.3	0.9–30.8	NA	Total sun exposure throughout life > 50 000 h, adjusted	Green (1984)
Canada	Weakly up	1.2	0.7–2.0	> 0.1	Hours of sun exposure per year, *p* for trend	Elwood *et al.* (1985b)
USA	Down	0.6	0.4–0.9	< 0.05	Total sun exposure throughout life	Graham *et al.* (1985)[b]
USA	Weakly up	1.1	0.6–2.1	> 0.05	Hours of sun exposure 0–5 years previously, > 5 h/day	Dubin *et al.* (1986)
USA	Down	0.85	0.5–1.4	> 0.05	Hours of sun exposure 11–20 years previously, > 5 h/day	Dubin *et al.* (1986)
USA	Weakly up	1.1	0.8–1.6	> 0.05	Lifetime sun exposure	Dubin *et al.* (1986)
Australia	Down	0.7	0.4–1.1	0.13	Mean total outdoor hours/week in summer, > 23 h/week; *p* for trend	Holman *et al.* (1986a)
Italy	Down	0.7	0.4–1.1	> 0.05	Heavy or frequent exposure in previous 20 years	Cristofolini *et al.* (1987)
France	Up	3.4	1.6–7.1	< 0.05	Total lifetime outdoor sun exposure, adjusted	Grob *et al.* (1990)

[a]Odds ratio for maximal category

[b]Results calculated by Armstrong (1988)

Table 19. Evidence of melanoma risk with short periods of residence implying high potential exposure

Place	Direction of association	Odds ratio	95% CI	*p* value	Measurement of exposure	Reference
USA	Up	[7.7	2.5–23.6]	0.0002	US service: tropics *versus* USA/Europe	Brown *et al.* (1984)
UK	Up	1.8	0.6–5.1	> 0.05	≥ 1 year living in tropics, subtropics	Elwood (1986)
Scotland	Up	2.6 (males) 1.8 (females)	1.3–5.4 0.8–4.0	< 0.05 > 0.05	> 5 years living in tropics, subtropics; crude OR	MacKie *et al.* (1989)
Sweden	Up	1.9	1.0–3.6	< 0.05	Living in Mediterranean, tropics, subtropics > 1 year in last 10 years	Beitner *et al.* (1990)

Table 20. Results of case–control studies on melanoma: occupational exposure

Place	Direction of association	OR[a]	95% CI	*p* value	Measurement of exposure	Reference
USA	Up	3.9	NR	0.01	Outdoor work recorded at college medical examination; prospective	Paffenbarger *et al.* (1978)
Norway	Up	1.4	0.6–3.5	0.37	At least 3–4 h of outdoor work a day	Klepp & Magnus (1979)[b]
Scotland	Down	0.5	0.2–1.2	> 0.05	Hours of outdoor occupation a week	MacKie & Aitchison (1982)[b]
USA	Up	1.2	NR	> 0.05	Outdoor occupation *versus* indoor	Rigel *et al.* (1983)
Canada	Irregular	0.9	0.6–1.5	< 0.01	Hours of outdoor occupation a week in summer	Elwood *et al.* (1985b)
USA	Down	0.7	0.3–1.3	> 0.05	Lifetime hours of outdoor occupation	Graham *et al.* (1985)
USA	Up	2.5	1.4–4.4	< 0.05	Mostly outdoors; multiple logistic OR = 2.4, $p < 0.05$	Dubin *et al.* (1986)
UK	Irregular	1.7	0.3–8.6	0.5	Lifetime hours of outdoor occupation	Elwood *et al.* (1986)
Australia	Down	0.5	NR	0.04	Mean hours of outdoor occupation a week in summer	Holman *et al.* (1986a)
Denmark	Down	0.7	0.5–0.9	< 0.05	Outdoor occupation *versus* indoor	Østerlind *et al.* (1988b)
Italy	Irregular	2.1	0.6–6.8	0.32	Outdoor occupation	Zanetti *et al.* (1988)
Germany	Up	5.5	1.2–25.3	< 0.05	Outdoor occupation; adjusted OR = 11.6 (2.1–63.3)	Garbe *et al.* (1989)
Sweden	Down	0.6	0.4–1.0	NR	Outdoor occupation, yes/no	Beitner *et al.* (1990)
France	Up	6.0	2.1–17.4	< 0.05	Outdoor occupation *versus* indoor	Grob *et al.* (1990)

NR, not reported

[a]Odds ratio for maximal category

[b]Calculated by Armstrong (1988)

Table 21. Results of case–control studies on different types of melanoma and occupational exposure

Place	Type of melanoma	Odds ratio	95% CI	*p* value	Measurement of exposure	Reference
Canada	Excluding LMM and ALM	0.5	[0.3–1.0]	NR	> 32 h outdoor occupation a week in summer (men)	Elwood *et al.* (1985b)
Queensland, Australia	Excluding LMM and ALM	No association			Outdoor occupation	Green *et al.* (1986)
Western Australia	SSM	0.5	NR	0.04 for trend	Top quartile, hours of outdoor occupation a week in summer	Holman *et al.* (1986a)
Denmark	Excluding LMM and ALM	0.7	0.5–0.9	< 0.05	Outdoor occupation (men)	Østerlind *et al.* (1988b)

LMM, lentigo maligna melanoma; ALM, acral lentiginous melanoma; SSM, superficial spreading melanoma; NR, not reported

Table 22. Results of case–control studies on melanoma: intermittent exposure

Place	Direction of association	OR[a]	95% CI	*p* value	Measurement of exposure	Reference
Norway	Up	2.4	1.0–5.8	0.06	Sunbathing holidays in southern Europe in previous 5 years	Klepp & Magnus (1979)[b]
UK	Up	1.5	0.9–2.5	0.16	Spent some time deliberately tanning their legs	Adam *et al.* (1981)[b]
	Up	1.6	1.0–2.5	0.05	Spent some time deliberately tanning their trunk	
Scotland	Down	0.4	0.2–0.9	< 0.05	Hours a week in outdoor recreation	Mackie & Aitchison (1982)[b]
USA	Up	2.5	1.1–5.8	< 0.05	Days of vacation in a sunny warm place in childhood	Lew *et al.* (1983)
USA	Up	2.4	NR	0.01	Outdoor *versus* indoor recreation	Rigel *et al.* (1983)
Canada	Up	1.7	1.1–2.7	< 0.01	Hours of high exposure in recreational activities per week in summer	Elwood *et al.* (1985b)
	Up	1.5	1.0–2.3	< 0.01	Hours of high and moderate exposure in recreational activities per day in summer vacations	
	Up	1.7	1.2–2.3	< 0.001	Number of sunny vacations per decade	
UK	Up	5	NR	> 0.05	Number of holidays abroad in hot climate; adjusted	Sorahan & Grimley (1985)
USA	Irregular	1.7	1.2–2.2	< 0.01	Recreation type; multiple logistic OR, 1.0	Dubin *et al.* (1986)
Australia	Irregular	1.9	0.5–7.4	0.62	Recreational hours spent in sun on beach over whole life; crude RR	Green *et al.* (1986)
Australia	Up	1.3	0.9–1.9	0.25	Proportion of recreational outdoor exposure in summer at 10–24 years of age; *p* for trend	Holman *et al.* (1986a)
	Up	2.4	1.1–5.4	0.04	Boating in summer; *p* for trend	
	Up	2.7	1.2–6.4	0.07	Fishing in summer; *p* for trend	
	Irregular	1.1	0.7–1.8	0.66	Swimming in summer; *p* for trend	
	Up	1.3	0.8–2.2	0.26	Sunbathing in summer at 15–24 years of age; *p* for trend	
Denmark	Up	1.9	1.3–2.9	0.004	Sunbathing; crude RR; *p* for trend	Østerlind *et al.* (1988b)
	Up	1.7	1.1–2.8	0.012	Boating; crude RR; *p* for trend	
	Up	1.5	0.9–2.4	0.006	Skiing; crude RR; *p* for trend	
	Up	1.5	1.2–2.0	0.004	Swimming (outdoors); crude RR; *p* for trend	
	Up	1.7	1.2–2.4	< 0.01	Vacations in sunny resorts; crude RR; *p* for trend	

Table 22 (contd)

Place	Direction of association	OR	95% CI	*p* value	Measurement of exposure	Reference
Italy	Irregular	2.6	1.0–6.9	0.003	Years of outdoor sport (men); *p* for trend	Zanetti *et al.* (1988)
	Up	3.8	1.1–13.0	NR	High-exposure sports (men)	
	Irregular	1.9	0.6–5.8	0.27	Total weeks' vacation (men); *p* for trend	
	Up	3.7	1.4–9.7	0.001	Weeks' vacation near sea; early life (men); *p* for trend	
	Up	1.6	0.7–3.6	0.77	Weeks' vacation near sea; adult life (men); *p* for trend	
	Irregular	2.1	0.6–7.9	0.37	Years of outdoor sport (women); *p* for trend	
	Up	2.3	0.6–9.1	NR	High-exposure sports (women)	
	Irregular	1.1	0.5–2.4	0.56	Total weeks' vacation (women); *p* for trend	
	Up	1.2	0.6–2.5	0.56	Weeks' vacation near sea; early life (women); *p* for trend	
	Up	1.5	0.9–2.7	0.16	Weeks' vacation near sea; adult life (women); *p* for trend	
Germany	No association	NR	NR	NR	Free-time sun exposure	Garbe *et al.* (1989)
Sweden	Up	1.8	1.2–2.6	< 0.05	Number of sunbaths per summer	Beitner *et al.* (1990)
	Up	2.4	1.5–3.8	< 0.05	Sunbathing vacations abroad	
France	Up	8.4	3.6–19.7	< 0.05	Outdoor leisure exposure	Grob *et al.* (1990)

NR, not reported
[a]Odds ratio for maximal category
[b]Calculated by Armstrong (1988)

(1988) in Turin, Italy, positive associations were seen with doing an outdoor sport for many years and with number of weeks of holidays spent near the sea. These consistently positive associations contrast with the less consistent pattern seen in Australia. In Western Australia, stronger associations are seen with boating and fishing than with swimming and sunbathing, which would be expected to involve more intense exposure to the sun, and only a weak association was seen with the proportion of outdoor time spent on recreational activities in teenage and early adult years (Holman *et al.*, 1986a). In Queensland, Green *et al.* (1986) found only irregular associations with recreational hours spent at the beach or in other activities with intense exposure to the sun. This finding might be consistent with the concept that, in a sunny environment, recreational activities may involve sufficient frequency or intensity of sun exposure to result in a constant rather than an intermittent dose pattern.

(vii) *Sunburn*

Most of the studies show positive associations between risk for melanoma and a history of sunburn (Table 23). The questionnaires usually defined very severe sunburn as a burn that causes pain lasting for at least two days or blistering. The greater consistency of this relationship compared to that with intermittent exposure may indicate a specific association with sunburn *per se* or that sunburn is simply a more easily remembered measure of intermittent and/or intense exposure to the sun.

A history of sunburn indicates both unusually intense exposure and skin sensitivity, and therefore studies which assess sunburn while controlling for sensitivity through a separate question on tendency to burn are important. Both the western Canada and Western Australia studies when analysed in this way show that the association is primarily with tendency to burn rather than with a history of sunburn (Elwood *et al.*, 1985a; Holman *et al.*, 1986a). The studies in Queensland, Denmark and Scotland, however, show strong associations with sunburn history even after controlling for tendency to burn and other measures of skin sensitivity.

Because sensitivity to the sun and sunburn are likely to be highly correlated and both are likely to be measured with a degree of error, it is difficult to distinguish their effects. Similarly, sunburn is likely to be confounded with intermittent exposure of a less intense nature, from which it cannot readily be distinguished because of measurement error (Armstrong, 1988).

The study in England by Elwood *et al.* (1990) assessed sunburn at different ages and showed the strongest association with sunburn at ages 8–12; a stronger association with sunburns at young age was also seen by Weinstock *et al.* (1989) and by Østerlind *et al.* (1988b).

2.1.4 *Malignant melanoma of the eye*

(*a*) *Case reports*

In general, case reports were not considered, owing to the availability of more informative data.

Kraemer *et al.* (1987) reported on 830 cases of xeroderma pigmentosum, with a median age of 12 years at last observation, located through a survey of published case reports. Ocular abnormalities were found in 328 of 337 patients on whom information was available. Of these, 88 were reported to have some form of ocular neoplasm, mostly in the limbus, cornea and conjunctiva. Five of these patients were reported as having ocular melanoma; only one

Table 23. Results of case–control studies on melanoma: history of sunburn

Place	Direction of association	OR[a]	95% CI	*p* value	Measurement of exposure	Reference
Scotland	Up	2.8	1.1–7.4	< 0.05	Blistering sunburn or erythema persisting > 1 week	MacKie & Aitchison (1982)
USA	Up	2.1	1.2–3.6	< 0.05	Blistering sunburn during adolescence (yes/no)	Lew *et al.* (1983)
Canada	Up	1.8	1.1–3.0	< 0.01	Vacation sunburn score	Elwood *et al.* (1985a)[b]
Australia	Up	2.4	1.0–6.1	< 0.05	Number of severe sunburns throughout life	Green *et al.* (1985a)
UK	Up	4.2	NR	< 0.01	Bouts of painful sunburn; adjusted	Sorahan & Grimley (1985)
Canada	Up	3.2	1.7–5.9	< 0.001	Sunburn causing pain for ≥ 2 days	Elwood *et al.* (1986)[c]
Australia	Irregular	0.9	0.5–1.5	0.43	Sunburn causing pain for ≥ 2 days, during last 10 years	Holman *et al.* (1986a)[b]
	Up	1.2	0.6–2.3	0.1	Sunburn causing pain for ≥ 2 days, < 10 years of age	
	Up	1.7	1.0–2.9	0.003	Blistering sunburn	
Italy	Down	0.7	0.4–1.2	> 0.05	Severe sunburn in adolescence or early adult life (yes/no)	Cristofolini *et al.* (1987)
	Up	1.2	0.7–2.1	> 0.05	Sunburn as an adult (yes/no)	
USA	Up	3.8	1.4–10.4	NA	Number of blistering sunburns up to adult age, adjusted	Holly *et al.* (1987)
Denmark	Up	3.7	2.3–6.1	< 0.001	Sunburn causing pain for ≥ 2 days, < 15 years of age	Østerlind *et al.* (1988)
	Up	3.0	1.6–5.4	< 0.001	Sunburn causing pain for ≥ 2 days, during previous 10 years	
Italy	Up (men)	4.1	1.8–9.2	< 0.05	Sunburn in childhood (yes/no)	Zanetti *et al.* (1988)
	Up (women)	2.7	1.3–5.6	< 0.05		
Germany	No association	NR	NR	NR	Number of sunburns	Garbe *et al.* (1989)
Scotland	Up (men)	7.6	1.8–3.2	NR	Number of episodes of severe sunburn, any age, adjusted	MacKie *et al.* (1989)
	Up (women)	2.3	0.9–5.6	NR	Number of episodes of severe sunburn, any age, adjusted	

Table 23 (contd)

Place	Direction of association	OR[a]	95% CI	*p* value	Measurement of exposure	Reference
USA	Up	2.2	1.2–3.8	0.01	Number of blistering sunburns at ages 15–20	Weinstock *et al.* (1989)
Sweden	Up	1.7	1.0–2.9	NR	Erythema after sunbathing	Beitner *et al.* (1990)
UK	Up	3.6	1.4–11.2	< 0.05	Moderate sunburn at ages 8–12 (yes/no)	Elwood *et al.* (1990)
	No association	1.0	0.6–2.0	> 0.05	Moderate/maximum sunburn at ages 18–20 (yes/no)	
	Up	1.8	0.9–3.7	> 0.05	Moderate/maximum sunburn 18–20 yrs before diagnosis (yes/no)	
	Up	1.2	0.6–2.3	> 0.05	Moderate/maximum sunburn 5 years before diagnosis (yes/no)	

NR, not reported
[a]Odds ratio for maximal category
[b]Data calculated by Armstrong (1988)
[c]Exposure to fluorescent and other lighting sources

was specified as being of uveal origin. [The Working Group recognized that data collected from previously published case reports is not uniform and may not be typical of a true incidence or prevalence series. Furthermore, no information is available on the relationship between solar exposure and the occurrence of ocular melanoma in these patients.]

(b) Descriptive studies

As there is no separate ICD code for intra-ocular melanoma, descriptive data for cancer of the eye (ICD-9 190) as a whole have been used as a surrogate. Intra-ocular melanoma comprises some 80% of tumours of the orbit of the eye (Østerlind, 1987), and cancer of the eye has been used as a surrogate for adult ocular melanoma in previous studies (Swerdlow, 1983a,b).

(i) *Ethnic origin*

Examination of incidence figures from many parts of the world reveals higher rates of ocular tumours in whites than in blacks or Asians residing at the same latitude and under similar conditions (Waterhouse *et al.*, 1976; Muir *et al.*, 1987).

(ii) *Place of birth and residence*

When rates for whites are evaluated separately, no variation in incidence rates for ocular tumours is seen with decreasing latitude in the northern hemisphere (Table 24). Similarly, no incidence grading was seen among whites in the USA (Table 25). The more northerly states of Australia do not show higher incidence rates for ocular tumours than the southern states (Table 25).

Table 24. Trends in cancer of the eye for whites by latitude and by time period (rates per 100 000 age standardized to UICC 'world population')

Latitude	Area	~ 1968–72[a]		~ 1972–77[b]		~ 1977–82[c]	
		Men	Women	Men	Women	Men	Women
56 °–61 ° N	Denmark	1.4	1.2	0.8	0.7	1.0	0.7
	Finland	0.9	1.0	0.9	0.7	1.0	0.7
	Sweden	1.3	1.2	0.9	0.8	0.9	0.6
47 °–55° N	Canada						
	British Columbia	1.0	0.8	0.9	0.6	0.7	0.4
	Alberta	0.8	0.6	0.8	0.9	0.7	0.7
	Saskatchewan	1.3	0.8	1.1	1.0	1.0	0.7
	Manitoba	1.7	0.9	1.2	1.0	0.8	0.8
46 °N	Geneva, Switzerland	0.4	0.2	0.8	1.1	0.6	1.1
38 °N	San Francisco, CA, USA	0.9	0.9	0.9	0.5	0.9	0.8
35 °N	New Mexico, USA	1.0	0.7	1.3	0.7	0.9	0.9
32 °–38 °S	Australia						
	New South Wales	NR	NR	0.8	0.8	0.9	0.5
	South Australia	NR	NR	0.9	1.0	0.7	0.6

Table 24 (contd)

Latitude	Area	~ 1968–72[a]		~ 1972–77[b]		~ 1977–82[c]	
		Men	Women	Men	Women	Men	Women
22 °S	Hawaii, USA	0.4	0.2	1.2	0.2	1.0	0.0
3 °S	Cali, Colombia	0.6	0.2	0.4	0.5	0.5	0.5

NR, not reported
[a]From Waterhouse *et al.* (1976)
[b]From Waterhouse *et al.* (1982)
[c]From Muir *et al.* (1987)

Table 25. Incidence of cancer of the eye (ICD-9 190) in US and Australian whites 1978–82 in various locations by latitude

Latitude	Location	Male rate/ 100 000	Female rate/ 100 000
USA			
47 °N	Seattle	0.9	0.8
42 °N	Detroit	0.7	0.6
42 °N	Iowa	1.0	0.7
41 °N	Connecticut	0.6	0.3
41 °N	New York City	0.5	0.4
41 °N	Utah	1.4	1.1
38 °N	San Francisco Bay Area	0.9	0.8
35 °N	New Mexico	0.9	0.9
34 °N	Los Angeles	0.7	0.6
33 °N	Atlanta	0.7	0.8
22 °N	Hawaii	1.0	0.0
Australia			
43 °S	Tasmania	1.2	0.8
38 °S	Victoria[a]	1.1	0.4
34 °S	South Australia	0.7	0.6
33 °S	New South Wales	0.9	0.5
32 °S	Western Australia	1.6	0.5
28 °S	Queensland[a]	0.6	0.7

From Muir *et al.* (1987); rates standardized to UICC 'world population'
[a]Data available only for 1982

Schwartz and Weiss (1988) compared the state of birth of 763 white (not of Spanish origin) US patients with uveal melanoma diagnosed between 1973 and 1984 and identified in nine cancer registries with those of the whites covered by the registries as recorded in the 1980 census. Patients with unknown or foreign birthplace or non-uveal ocular melanomas were excluded. Risk estimates were adjusted for age, sex and residence. The odds ratio for subjects born in the southern USA (south of 40 °N) was 1.1 (95% CI, 0.8–1.5). When states

were classified according to average daily global solar radiation, a nonsignificant gradient was observed, only among women (odds ratio for > 15 500 kJ/m^2 *versus* ≤ 12 300 kJ/m^2, 1.6; 95% CI, 0.7–3.6).

Mack and Floderus (1991) examined birthplace and residence of patients diagnosed with intra-ocular melanoma among non-latino whites in 1972–82 in Los Angeles County. The proportional incidence ratio was not higher for cases born in California and Arizona than for those born in more northerly areas.

Doll (1991) observed a small rural excess in the incidence of cancer of the eye compared with urban residence, in a number of countries.

(iii) *Occupation*

Four studies of occupational mortality and one of incidence gave inconsistent results with regard to ocular cancer. Two investigations using proportional mortality ratios demonstrated more deaths from ocular cancer than expected among male farmers (Saftlas *et al.*, 1987; Gallagher, 1988), a group likely to have substantial exposure to solar UVR. These findings were not confirmed, however, in two other studies using similar methods (Milham, 1983; Office of Population Censuses and Surveys, 1986).

An investigation of ocular melanoma carried out on data from the cancer registry of England and Wales did not show an elevated incidence in farmers, but an increased risk was seen for professionals (relative risk, 124; 95% CI, 99–153), which was significant for teachers (177; 120–248) (Vågerö *et al.*, 1990).

(iv) *History of skin cancer*

Cancer registry-based studies (Østerlind *et al.*, 1985; Tucker *et al.*, 1985a; Holly *et al.*, 1991) found no or a nonsignificant (Lischko *et al.*, 1989) association between the occurrence of cancer of the eye and cutaneous melanoma or nonmelanocytic skin cancer. A single investigation of 400 sequential cases of uveal melanoma (Turner *et al.*, 1989) suggested that intra-ocular melanoma patients have an elevated frequency of prior cutaneous melanoma. Thus, although one study indicated a possible association, the overall evidence does not support an association between ocular melanoma and either melanoma or nonmelanocytic skin cancer.

(*c*) *Case–control studies*

Four case–control studies were evaluated. The first study (Gallagher *et al.*, 1985) evaluated all ocular melanomas, while the other three (Tucker *et al.*, 1985b; Holly *et al.*, 1990; Seddon *et al.*, 1990) studied uveal melanomas (excluding conjunctival melanomas).

Gallagher *et al.* (1985) conducted a study of ocular melanoma in patients diagnosed in the four western provinces in Canada between 1 April 1979 and 31 March 1981. Of the 90 ascertained cases, 87 were eligible by age for interview (20–79 years); of these, 65 cases (75%) were actually interviewed. For each case, a single control was randomly selected from the general population, matched by age (± 2 years), sex and province of residence. Response rates for controls were 59% for Alberta, Saskatchewan and Manitoba and 48% for British Columbia. Personal interviews were conducted in subjects' homes, and conditional logistic regression was used to control for matching variables and eye, hair and skin colour. No significant association was seen between ocular melanoma and either intermittent (occupational,

recreational and holiday) or cumulative exposure to solar UVR. A strong association was detected between ocular melanoma and blue or grey iris colour (crude odds ratio, 3.0; $p = 0.04$) and blond or red hair colour (crude odds ratio, 7.7; $p = 0.03$). (In a multivariate analysis, these odds ratios became nonsignificant.) A nonsignificantly elevated risk (crude odds ratio, 2.8; $p = 0.08$) for ocular melanoma was also seen for subjects with light skin colour by comparison with subjects with darker skin.

A case–control study conducted by Tucker *et al.* (1985b) evaluated risk factors in 444 white patients with intra-ocular (uveal) melanoma treated at the Wills Eye Hospital in Philadelphia, USA, and 424 controls with detached retinas seen at the same centre. [The Working Group noted that use of a single disease category for the controls could introduce spurious associations with risk factors for that condition.] Response rates were 89% for cases and 85% for controls. Interviews were conducted by telephone; interviews were with next-of-kin for 17% of the cases and 14% of the controls. Logistic regression models were fitted which included sun-exposure variables, age, sex, eye colour and presence of cataracts, which was included to reduce bias in view of the association between cataracts and detached retina. Sunbathing appeared to increase the risk of intra-ocular melanoma, although no gradient of risk was noted with frequency of exposure (frequent *versus* never, odds ratio, 1.5; 95% CI, 0.9–2.3). A significantly elevated risk was detected for those who engaged in gardening (1.6; 1.0–2.4), but similar associations were not seen for other recreational outdoor activities, such as fishing, camping and hunting. Cases of intra-ocular melanoma also reported increased exposure to the sun during vacations in comparison with controls, with an odds ratio of 1.5 (95% CI, 0.97–2.3) for subjects 'frequently' experiencing increased exposure *versus* subjects never exposed (test for linear trend over four strata, $p = 0.01$). Cases reported less frequent use of eye protection (sunglasses, headgear, visors) when outdoors as compared with controls, but there was no dose–response relationship with frequency of use of these protective devices. A gradient of risk was seen with use of any eye shading when iris melanomas were examined separately, suggesting that eye shading may have been specifically important for lesions at the front of the eye (never *versus* occasional use of eye protection, odds ratio, 4.9; 95% CI, 1.4–13.7). [Numbers of iris melanomas were not given.] Subjects who were born in the southern USA (lower than 40 °N latitude) were found to have a significantly elevated risk of intra-ocular melanoma (2.7; 1.3–5.9) after adjustment for number of years spent in the south and for the presence of cataracts; with adjustment for all other sun-related variables, the odds ratio was 3.2 (95% CI, 1.8–5.7). The association persisted after excluding subjects not living close to Philadelphia. There was no relation between the number of years spent in the south and the risk of intraocular malignant melanoma, after adjustment for having been born in the south. Blue-eyed subjects had the highest risk of intra-ocular melanoma, with grey-green and hazel-eyed subjects at intermediate risk, and brown-eyed subjects at lowest risk (unadjusted odds ratio for brown- *versus* blue-eyed subjects, 0.6; 95% CI, 0.4–0.8). Cases were more likely than controls to have fair skin and blond or brown hair, although no odds ratios are given and the differences disappeared when eye colour was taken into account. Cases were also more likely to have 25 or more freckles (used as an indirect measure of sun exposure and sensitivity) than controls (odds ratio, 1.4; 95% CI, 1.0–2.0).

A case–control study by Holly *et al.* (1990) involved 407 white cases of uveal melanoma and 870 controls. The cases were diagnosed between January 1978 and February 1987 at the

Ocular Oncology Unit of the University of California, San Francisco, USA, were aged 20–74 at diagnosis and lived in 11 western states. Controls were selected by random digit dialling and were matched to cases on age and area of residence. Telephone interviews were conducted by interviewers unaware of the study hypotheses, most cases being interviewed within four years of their diagnosis. The response rate was 93% of cases and 77% of eligible controls. No clear association was seen between uveal melanoma and vacation time spent in sunny climates or high proportion of leisure time spent outdoors. Individuals who spent 50% of their leisure time indoors and 50% outdoors had a reduced risk for uveal melanoma (odds ratio, 0.6; 95% CI, 0.4–0.9) when compared to subjects who stayed mainly indoors. Significantly elevated risks were seen in subjects with grey, green, hazel or blue eyes, compared to those with brown eyes, with increasing frequency of large naevi (≥ 7 mm) ($p = 0.04$ for trend) and with a propensity to burn rather than tan in the sun.

Seddon *et al.* (1990) compared 197 white patients with uveal melanoma diagnosed in 1984–87, who were resident in the six New England states close to the Massachusetts Eye and Ear Infirmary, with 385 controls obtained through random digit dialling and matched to cases by age (± 8 years), sex and area of residence. All subjects were interviewed by telephone using a standard questionnaire. The response rate was 92% among cases, and 85% of the eligible controls contacted agreed to participate in the study. Matched logistic regression techniques were employed to evaluate potential associations between exposure to UVR and risk of uveal melanoma, adjusting for age, sex, constitutional factors and socioeconomic variables. An inverse association with southern birthplace (south of 40 °N latitude) was detected (odds ratio, 0.2; 95% CI, 0.0–0.7) after adjustment for constitutional and other factors. When cumulative lifetime residence in the south was examined, subjects who had lived for more than five years south of 40 °N had an odds ratio of 2.8 (95% CI, 1.1–6.9) after adjustment for birthplace. Several indices of sun exposure were computed for each subject. The first combined duration of residence in the north or south with self-reported severity of sun exposure (low, medium, high). Subjects in the highest exposure group appeared to have a higher risk of uveal melanoma by comparison with those in the lowest exposure category (1.7; 0.9–3.0) although no dose–response relationship was seen over the three categories of exposure. A further index was obtained by taking average values of solar radiation for each state in which the subject has resided and multiplying this value by the duration of residence within the state and the reported amount of time spent in the sun. No association was seen between this index and risk of uveal melanoma. Individuals who reported having spent a great deal of time working outdoors 15 years prior to diagnosis showed a somewhat lower risk of uveal melanoma than those who worked minimally outdoors or were retired (odds ratio, 0.6; 95% CI, 0.3–1.4) after control for age, skin, eye colour and southern residence. No association was seen with sunbathing, use of sunglasses or visors, or outdoor hobbies all conducted 15 years prior to diagnosis. Use of eye glasses was not related to uveal melanoma risk. Cases reported more cutaneous naevi and lighter skin colour than controls and were more likely to be of northern European or British ancestry than controls. An expanded analysis comparing 387 cases of uveal melanoma with 800 sibling controls was also conducted. There was a gradient of risk with cumulative years of intense sun exposure; the odds ratio for the highest exposure was 2.1 (1.4–3.2).

2.1.5 *Other cancers*

No adequate data were available to the Working Group.

2.2 Artificial sources of ultraviolet radiation

Epidemiological investigations that have attempted to assess exposure to artificial sources of UVR have neither measured actual UVR nor considered the emission spectra. It is presumed that in the studies described below, subjects were exposed to sources that varied in intensity and emission spectra.

2.2.1 *Nonmelanocytic skin cancer*

Three case–control studies, described in detail on p. 84, addressed this issue. In the study in Montréal, Canada, of Aubry and MacGibbon (1985), any use of a sunlamp gave an odds ratio of 13.4 [95% CI, 1.4–130.5] after adjustment for sun exposure and constitutional factors. O'Loughlin *et al.* (1985) in Ireland found that fewer cases than controls reported frequent exposure to 'artificial sunlight' (nonsignificant). In the study of Herity *et al.* (1989) in Ireland, a smaller proportion of cases than of controls reported ever having used sunlamps or sunbeds ($p = 0.2$).

2.2.2 *Malignant melanoma of the skin*[1]

The results of case–control studies of exposure to fluorescent light and melanoma are summarized in Table 26.

Beral *et al.* (1982) conducted a case–control study in Sydney, Australia, of 274 female cases aged 18–54 identified at a melanoma clinic between 1978 and 1980 and 549 hospital and population controls matched by age and, for population controls, residence. The response rate for cases was 71% [response rates for controls not given]. Each job lasting 12 months or longer was recorded, together with information about whether the work had been carried out predominantly indoors or outdoors, whether fluorescent lighting was present, and whether the fluorescent lights were switched on most of the time or less frequently. Among women who always worked indoors, the odds ratio increased with duration of working with fluorescent lights most of the time to a maximum of 2.6 (95% CI, 1.2–5.9) for 20 or more years' exposure. The effect was greater for office workers (odds ratio, 4.3) than for other indoor workers (2.0). Stratification by amount of time spent outdoors, main outdoor activity and amount of clothing worn, history of sunburn, place of birth, hair colour and skin colour did not diminish the association. Among cases exposed to fluorescent lights, there was a relative excess of melanomas on the trunk (a site likely to be covered at work); 24% in exposed cases *versus* 4% in unexposed cases. [The Working Group noted that crude estimates of sun exposure were used.]

Rigel *et al.* (1983) conducted a case–control study in New York, USA, described on p. 106. Cases had had shorter average daily exposure to fluorescent lights (4.9 h) than had

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[1]After the meeting, the Secretariat became aware of a study by Walker *et al.* (1992) on the risk of cutaneous malignant melanoma associated with exposure to fluorescent light.

controls (5.4 h). Among office workers, average daily exposures were similar for cases and controls. The crude odds ratio for any exposure was 0.7 among all subjects and 0.6 among office workers.

English *et al.* (1985) conducted a study in 1980–81 of the exposure to fluorescent light of 337 cases and 349 age-matched controls who had already participated in a population-based case–control study in Western Australia (see Holman and Armstrong (1984a), p. 100). The response rate was 68% for cases and 91% for controls. Detailed information was obtained from telephone interviews about lifetime hours of residential and occupational exposure, the distance to the nearest light fixture and the presence of diffusers. Neither the duration of occupational exposure, the rate of total exposure (hours/year) nor cumulative total exposure was associated with risk for melanoma. Analyses by body site showed no consistent association with exposure to lights without diffusers. Adjustment for measures of total and intermittent exposure to the sun did not alter the results. Subjects were also asked about exposure to plan printers, laboratory equipment emitting UVR, insect tubes, black lights and photocopiers. No association was seen with any of these sources, although the number of exposed subjects was small. The odds ratio for any use of sunlamps was 1.1 (95% CI, 0.6–1.8), although few subjects had used sunlamps (Holman *et al.*, 1986b).

Sorahan and Grimley (1985) examined fluorescent light exposure in 1980–82 in a case–control study in the United Kingdom, described in detail on p. 103. Information on exposure was confined to whether lights were 'mainly on' or 'sometimes on' at work. After adjustment for age and sex, no consistent association was seen for duration of exposure when cases were compared with electoral register controls.

Dubin *et al.* (1986) examined fluorescent light exposure in a subset of subjects in a case–control study in New York, USA, described on p. 108. Subjects were interviewed and/or sent postal questionnaires. In data obtained from interview, but not in data obtained from postal questionnaires, the odds ratios increased with average daily exposure in the five years before interview, after adjustment for age and sex (p value for linear trend, < 0.05). A similar pattern was seen for exposure 6–11 years and 11–20 years previously.

Elwood *et al.* (1986) examined fluorescent light exposure in their case–control study in the United Kingdom in 1981–84, described in detail on p. 103. Subjects were interviewed and later sent postal questionnaires to validate the responses. From the interview data, exposure to undiffused lights at work was associated with an odds ratio of 4.0 (95% CI, 0.8–19.2) for those maximally exposed (p value for trend = 0.2). Control for constitutional factors did not change the results. From the questionnaire data, the odds ratio for maximal exposure (undiffused lights) was 1.9 (95% CI, 0.4–8.4). No association was seen with exposure at home, and no association was seen for use of sunlamps. Subjects were also asked about exposure to particular or unusual light sources, such as vacuum or discharge lamps, insecticidal or germicidal lamps or welding equipment. The odds ratio for exposure to any such source was 2.2 (95% CI, 1.0–4.9). [The Working Group noted that the use of open-ended questions about lighting sources may have introduced recall bias.]

In the Western Canada case–control study in 1979–81 (see Elwood *et al.*, 1984, 1985a,b, p. 107), no association was seen with use of sunlamps ($\chi^2 = 6.1$, 5 df) (Gallagher *et al.*, 1986).

Østerlind *et al.* (1988b) examined exposure to fluorescent lighting at work and use of sunlamps and sunbeds in their case–control study in Denmark in 1982–85, described on pp. 103–104. The same proportions of cases and controls reported having been exposed to fluorescent lights at work, and no association was seen with age at first exposure, duration of exposure or type of work place. Past use of sunlamps was also not associated with melanoma, and a smaller proportion of cases than controls had ever used sunbeds (odds ratio, 0.7; 95% CI, 0.5–1.0).

In a case–control study in Scotland (Swerdlow *et al.*, 1988), 180 cases aged 15–84 from three clinics during 1979–84 were compared with 197 age- and hospital-matched patients with various non-malignant diseases. Subjects were interviewed about exposure to fluorescent lights and UV lamps, use of sunbeds, sun exposure and constitutional factors. Controls with skin conditions were excluded from the analysis of UV lamps and sunbeds. No consistent association was seen with exposure to fluorescent lights at home or at work, with or without adjustment for constitutional factors and sun exposure. Significant, positive associations were seen for duration of use of UV lamps and sunbeds (p value for trend, < 0.05). The odds ratio for use for more than one year was 3.4 (95% CI, 0.6–20.3) after adjustment for constitutional factors and sun exposure. Amount of use within five years (1.9; 0.6–5.6) of the interview and more than five years (9.1; 2.0–40.6) before the interview were both positively associated with the risk for melanoma.

MacKie *et al.* (1989) examined use of sunbeds and sunlamps in their case–control study in Scotland described on p. 106. Use was associated with melanoma in men (odds ratio, 2.6; 95% CI, 0.9–7.3) but showed little association in women (1.5; 0.8–2.9). The effect on men largely disappeared after adjustment for sun exposure and constitutional factors.

In the study of Zanetti *et al.* (1988) from Turin, Italy, described in detail on p. 104, an odds ratio of 0.9 (0.4–2.0) was found for use of UVA lamps, although few subjects reported exposure.

A large population-based case–control study on occupational exposures was conducted during 1979–85 in Montréal, Canada (Siemiatycki, 1991). Overall, there were 3730 male cases of cancer aged 35–70, including 124 cutaneous melanoma cases; the participation rate was 82%. Each cancer site was compared with the other cancer sites. Exposure to 293 agents, including arc welding fumes and UVR, was assessed by a team of chemists and industrial hygienists on the basis of each individual's occupational history. Neither arc welding fumes nor exposures to UVR was associated with the risk for cutaneous melanoma (odds ratios, 0.5; 90% CI, 0.3–1.1 and 0.3; 0.1–1.5, respectively).

In a population-based study in southern Ontario, Canada (Walter *et al.*, 1990), 583 cases identified from pathology laboratories and from the cancer registry between 1984 and 1986 were compared with 608 controls randomly sampled from property tax rolls. Participation rates were 90% for cases and 80% for controls. Odds ratios for any use of sunbeds or sunlamps were 1.9 (95% CI, 1.2–3.0) in men and 1.5 (0.99–2.1) in women. Adjustment for constitutional factors did not affect the results. The odds ratios increased with duration of use; for more than 12 months' use, the odds ratios were 2.1 (0.9–5.3) in men and 3.0 (1.1–9.6) in women.

Table 26. Case–control studies of melanoma of the skin and exposure to fluorescent lights

Country	Cases/controls	Odds ratio	95% CI	Definition of exposure	Reference
Australia	274/549	2.6[a,b]	1.2–5.9	Indoor workers, ≥ 20 years' occupational exposure	Beral *et al.* (1982)
		4.3[a,b]	NR	Office workers, ≥ 20 years' occupational exposure	
USA	114/228	0.7	NS	Any exposure	Rigel *et al.* (1983)
		0.6	NS	Any exposure, office workers	
Australia	337/349	1.2[a,b]	0.8–1.9	≥ 35 000 h exposure	English *et al.* (1985)
		1.2[a,b]	0.7–1.9	≥ 1600 h per year	
		1.3[a,b]	0.8–1.9	≥ 22 500 h undiffused lights	
		1.2[a,b]	0.8–1.9	≥ 1300 h per year undiffused lights	
		1.2[a,b]	0.6–2.6	≥ 22 500 h head, neck, upper limbs, undiffused lights	
United Kingdom	58/333	0.6[a]	NR	≥ 20 years, occupational exposure (mainly on)	Sorahan & Grimley (1985)
		0.5[a]	NR	≥ 20 years, indoor workers only (mainly on)	
USA	1103/585	2.3[a]	1.0–5.8	≥ 9 h per day, 0–5 years previously (interview)	Dubin *et al.* (1986)
	508/222	0.6[a]	0.3–1.3	≥ 9 h per day, 0–5 years previously (postal questionnaire)	
United Kingdom	83/83	1.4[a,b]	0.4–5.1	≥ 50 000 h occupational exposure (total fluorescent light, interview)	Elwood *et al.* (1986)
		4.0[a,b]	0.8–19.2	≥ 50 000 h occupational exposure (undiffused lights, interview)	
	67/66	1.2[a,b]	0.3–5.7	≥ 50 000 h occupational exposure (total fluorescent light, postal questionnaire)	
		1.9[a,b]	0.4–8.4	≥ 50 000 h occupational exposure (undiffused lights, postal questionnaire)	
Denmark	474/926	No association		Duration of exposure, age at first exposure, type of workplace	Østerlind *et al.* (1988b)
Scotland, United Kingdom	180/197	1.2[b]	0.7–1.9	Any occupational exposure < 5 years previously	Swerdlow *et al.* (1988)
		0.8[b]	0.4–1.4	Any exposure at home < 5 years previously	
		1.6[b]	0.9–2.6	≥ 5 h per day < 5 years previously at work and at home	
		1.4[b]	0.9–2.3		
		0.8[b]	0.4–1.4	Any occupational exposure > 5 years previously	
				Any residential exposure > 5 years previously	

NR, not reported; NS, not significant

[a]Odds ratio for category with highest level of exposure

[b]Adjusted for sun exposure

2.2.3 *Malignant melanoma of the eye*

In the case–control study carried out in Philadelphia, USA, which is described in detail on p. 128, cases of uveal melanoma were more likely to report use of sunlamps than controls. After adjustment for age, eye colour and a history of cataracts, there was a trend to increasing risk with frequency of use (odds ratio for frequent *versus* never, 2.1; 95% CI, 0.3–17.9; test for linear trend over four levels: $p = 0.10$). The odds ratios for those who had ever worked as welders was 10.9 (2.1–56.5) (Tucker *et al.*, 1985b).

In the case–control study from San Francisco, USA, described on pp. 128–129, exposure to artificial UV light or 'black light' [details not given] conferred over three-fold risks for intra-ocular melanoma after adjustment for other significant factors (odds ratio, 3.7; 95% CI, 1.6–8.7). The odds ratios were 2.9 for 1–5 years of exposure and 3.8 for 6 or more years (Holly *et al.*, 1990).

In the case–control study from Boston, USA (Seddon *et al.*, 1990), described on p. 129, exposure to fluorescent lighting was associated with an elevated risk of uveal melanoma (odds ratio, 1.7; 95% CI, 1.1–2.5 for 40 h or more per week as compared to no exposure) in the larger data set, based on case–sibling comparison. In the population-based comparison, the corresponding odds ratio was 1.2 (95% CI, 0.6–2.1). A history of working with welding arcs was reported with similar frequency among cases and controls in both comparisons. Cases reported more frequent use of sunlamps in comparison with both sets of controls. After adjustment for constitutional factors and exposure to the sun, the odds ratios for frequent/occasional use *versus* never were 3.4 (1.1–10.3) in the population comparison and 2.3 (1.2–4.3) in the sibling comparison.

In the large Canadian study on occupational exposure, described on p. 132, 23 cases of ocular melanoma were included. Analysis only of French Canadians revealed four cases of eye melanoma with exposure to arc welding fumes (odds ratio, 8.3; 90% CI, 2.5–27.10) (Siemiatycki, 1991). No increase was found for substantial exposure; no increase in risk was reported for exposure to UVR.

2.3 Premalignant conditions

2.3.1 *Basal-cell naevus syndrome*

Basal-cell naevus syndrome is a hereditary condition (Gorlin, 1987) in which affected family members may show, among other major manifestations, an apparent excess of basal-cell carcinomas. These seem to occur more commonly in sun-exposed parts of the body or in unusual patterns. There is no other evidence that solar radiation plays a role in their development.

2.3.2 *Dysplastic naevus syndrome*

Dysplastic naevus syndrome is a hereditary condition in which affected family members have multiple dysplastic naevi and a greatly increased risk of malignant melanoma (Green *et al.*, 1985b). The distribution of tumours conforms to the usual distribution, and there is anecdotal evidence that solar radiation plays a role in their development (Kraemer & Greene, 1985).

2.4 Molecular genetics of human skin cancers

Analysis of mutations in DNA isolated from tumours and believed to be relevant to carcinogenesis can potentially help in making a causal link with exposures to carcinogens. Two important qualifications must, however, be borne in mind. Firstly, the changes detected may have arisen late in tumour development (whether or not the tumour is the result of exposure to UVR) and may not be involved in initiation or other early steps. Secondly, the spectrum of mutations that is seen may be constrained to those changes that can lead to a functional gene product. This qualification applies, for example, to mutations that activate *ras* genes but to only a lesser extent to tumour suppressor gene mutations in which inactivation of gene function is involved.

Experimental studies indicate that UV-induced mutations have a distinctive pattern of base-substitution mutations (see section 4.5):

- Virtually all mutations occur at dipyrimidine sites, especially 5′TC and 5′CC sequences.
- The majority of the base substitution mutations involve cytosine with the C→T transition predominating.
- Tandem 5′CC→5′TT mutations occur.

2.4.1 ras *Gene mutations*

Primary melanomas, metastases and cell lines derived from melanomas which developed at body sites characterized as exposed 'rarely', 'intermittently' or 'continuously' to the sun were analysed for the presence of N-*ras* mutations. Of 37 cutaneous melanomas, seven had N-*ras* mutations; all were from 'continuously' exposed sites. All mutations in the N-*ras* gene were at TT or CC sites, which are potential locations for mutagenic UV photoproducts, suggesting a role of sun exposure in N-*ras* mutation (van't Veer *et al.*, 1989).

In several investigations, base-substitution mutations were found in Ha-, Ki- and N-*ras* genes in human skin melanomas (Table 27) and in squamous-cell and basal-cell carcinomas (Table 28) from xeroderma pigmentosum and normal patients. In single studies, Ha- and N-*ras* gene amplification was found in squamous-cell carcinomas of the skin (Ananthaswamy & Pierceall, 1990), and loss of the Ha-*ras* allele was seen in basal-cell and squamous-cell carcinomas (Ananthaswamy *et al.*, 1988). Whether exposure to the sun was involved in tumour induction in these studies is, however, less clear.

2.4.2 *p53 Gene mutations*

Brash *et al.* (1991) found p53 mutations at various codons in 14 out of 24 (58%) invasive squamous-cell carcinomas from sun-exposed skin (Table 29). The mutations found were predominantly C→T (5 of 14 total mutants, 36%) and CC→TT (3 of 14, 21%) transitions, exclusively at tandem pyrimidine stretches. This finding is consistent with the hypothesis that these mutations are induced by UV irradiation. CC→TT double-base changes in the p53 gene have not yet been found in tumours in any internal organ. These results strongly suggest that solar radiation plays a role in the induction of p53 gene mutations.

Pierceall *et al.* (1991) found p53 mutations in exon 7 in 2 out of 10 squamous-cell carcinomas from sun-exposed body sites; one was a C→T transition and the other a C→A transversion.

Table 27. *ras* Gene mutations detected in human naevi and primary and secondary melanomas that developed at sites subject to sun exposure

Oncogene codon	Base change	Base-substitution mutation	Site of original tumour	Reference
N-*ras*-61	*GGA* C*AA* G*AA*			
	AAA	C to A	Neck	van't Veer *et al.* (1989)
	AAA	C to A	Lower leg	van't Veer *et al.* (1989)
	AAA	C to A	Nose	van't Veer *et al.* (1989)
	AAA	C to A	Cheek	van't Veer *et al.* (1989)
	CGA	[T to C]	Lower leg	van't Veer *et al.* (1989)
	CAT	[T to A/G]	Xeroderma pigmentosum patient[a]	Keijzer *et al.* (1989)
	CAT	[T to A]	Site unspecified, probably metastasis	Sekiya *et al.* (1984)
N-*ras*-13	*GGT* *GGT* G*TT*			
	GAT	[C to T]	Finger	van't Veer *et al.* (1989)
	GTT	[C to A]	Finger	van't Veer *et al.* (1989)
	GTT	[C to A]	Lower leg	van't Veer *et al.* (1989)
N-*ras*-12	GAT	[C to T]	Leg	van't Veer *et al.* (1989)
N-*ras*-61	CAT/C	[T to A/G]	Back	Shukla *et al.* (1989)
Ki-*ras*-61	*GGA* C*AA* G*AA*			
	AAA	C to A	Lower leg	Shukla *et al.* (1989)
Ki-*ras*-12	G*CT* *GGT* *GGC*			
	TGT	[C to A]	Abdomen	Shukla *et al.* (1989)
	TGT	[C to A]	Knee	Shukla *et al.* (1989)
	TGT	[C to A]	Site unspecified, probably metastasis	Shukla *et al.* (1989)
	TGT	[C to A]	Site unspecified, probably metastasis	Shukla *et al.* (1989)
	TGT	[C to A]	Site unspecified, probably metastasis	Shukla *et al.* (1989)
	TGT	[C to A]	Site unspecified, probably metastasis	Shukla *et al.* (1989)
		[C to T]	Buttock	Shukla *et al.* (1989)
		[C to T]	Site unspecified, probably metastasis	Shukla *et al.* (1989)
		[C to T]	Forearm (naevus)	Shukla *et al.* (1989)
		[C to T]	Abdomen (naevus)	Shukla *et al.* (1989)
Ha-*ras*-12	G*CC* *GGC* *GGT*			
	TGC	[C to A]	Abdomen	Shukla *et al.* (1989)

Italics indicate potential pyrimidine dimer site including neighbouring codon; [ ], base changes occurring in anti-sense strand

[a]Malignant melanoma probably resulting from metastasis of a primary skin tumour

Table 28. *ras* Gene mutations detected in human keratoacanthomas (KA), basal-cell carcinomas (BCC) and squamous-cell carcinomas (SCC) that developed at sites subject to sun exposure

Oncogene codon	Base change	Base-substitution mutation	Tumour	Site	Reference
Ki-*ras* 12	GCT *GGT GGC*				
	TGT	[C to A]	SCC	Lip	van der Schroeff *et al.* (1990)
			BCC	Shoulder	van der Schroeff *et al.* (1990)
			BCC	Neck	van der Schroeff *et al.* (1990)
	GAT	[C to T]	BCC	Face	van der Schroeff *et al.* (1990)
Ha-*ras* 61	*GGC* CA*G GAG*				
	CTG	[T to A]	SCC	Not specified	Corominas *et al.* (1989)
	CTG	[T to A]	KA	Not specified	Corominas *et al.* (1989)
	CAT	[C to A]	BCC	Face	van der Schroeff *et al.* (1990)
	AAG	C to A	KA	Not specified	Corominas *et al.* (1989)
Ha-*ras* 12	G*CC GGC GGT*				
	AGC	[C to T]	SCC	Not specified	Corominas *et al.* (1989)
	AGC	[C to T]	KA	Not specified	Corominas *et al.* (1989)
	AGC	[C to T]	KA	Not specified	Corominas *et al.* (1989)
	TGC	[C to A]	SCC	Not specified	Corominas *et al.* (1989)
	TGC	[C to A]	SCC	Not specified	Corominas *et al.* (1989)

Italics indicate potential pyrimidine dimer site including neighbouring codon; [ ], base changes occurring in anti-sense strand

Table 29. p53 Tumour suppressor gene mutations in human squamous-cell carcinomas that developed at sites subject to sun exposure

Codon	Nucleotide sequence	Base-substitution mutation	Incidence[a]	Site of tumour origin	Reference
7	TCT	TGT; C→G	1/14/24	Preauricular	Brash *et al.* (1991)
56	*T* *TCA*	TAA; C→A	1/14/24	Chest	Brash *et al.* (1991)
104/105	*CG* *CCT*	deletion of a C	2/14/24	Preauricular/temple	Brash *et al.* (1991)
151	*CCC CC*	CAC; C→A	1/14/24	Scalp	Brash *et al.* (1991)
152	*CC* *CCC*	CAC; C→T	1/14/24	Hand	Brash *et al.* (1991)
179	A *CCA*	CAA; C→A	1/14/24	Scalp	Brash *et al.* (1991)
244	*CCG* G	TCG; C→T	1/2/10	Face	Pierceall *et al.* (1991)
245	G *CCG*	CAG; C→A	1/14/24	Cheek	Brash *et al.* (1991)
245	G *CCG*	T T; CC→TT	1/14/24	Chest	Brash *et al.* (1991)
247/248	*AC* *CG*	T T; CC→TT	1/14/24	Nose	Brash *et al.* (1991)
248	G*CC*	GAC; C→A	1/2/10	Face	Pierceall *et al.* (1991)
258	*T* *TCC*	TTC; C→T	1/14/24	Face	Brash *et al.* (1991)
278	T *CCT*	TCT; C→T	1/14/24	Cheek	Brash *et al.* (1991)
285/286	TC *CT*	T T; CC→TT	1/14/24	Face	Brash *et al.* (1991)
286	TC *CT*	CTT; C→T	1/14/24	Forehead	Brash *et al.* (1991)
317	*CC* *CCA*	TCA; C→T	1/14/24	Postauricular	Brash *et al.* (1991)

Italics indicate potential pyrimidine dimer site

[a]No. of specific mutations/no. of total mutations found/Total number of samples tested only from sites continuously exposed to the sun