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REVIEW

Sun exposure and non-melanocytic skin cancer

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Non-melanocytic skin cancer has long been regarded as one of the harmful effects of solar ultraviolet (UV) radiation on human health. In this review, we examine epidemiologic evidence linking sun exposure and skin cancer coming from both descriptive studies in populations and analytical studies involving estimates of exposure in individuals. Particular attention is given to the quality of the published data. The epidemiologic evidence that sun exposure causes skin cancer is mainly indirect. Incidence or mortality is inversely related to latitude in populations of mainly European origin (*e.g.*, the United States, Australia), and is higher in people born in Australia (high ambient solar radiation) than in migrants to Australia from the United Kingdom (lower ambient radiation). Skin cancer occurs mainly at sun-exposed body sites and in people who are sensitive to the sun; a reduced capacity to repair UV-induced DNA damage appears to increase the risk. The direct evidence linking sun exposure and skin cancer is weaker with few well-conducted studies of sun exposure in individuals. Mostly, studies of total sun exposure have not found statistically significant positive associations; those that did, had not adjusted for potential confounding by age and gender and thus their interpretation is limited. Studies of occupational sun exposure had relative risks not greater than 2.0; recreational exposure has been little studied. Other measurements, less direct but potentially less prone to measurement error, are sunburn (not evidently associated with skin cancer risk) and indicators of benign cutaneous sun-damage (strongly associated but lacking empirical evidence that sun exposure is their main cause). Many questions remain about the relationship between sun exposure and skin cancer. *Cancer Causes and Control* 1994, **5**, 367 - 392

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Introduction

The non-melanocytic cancers of the skin (hereafter referred to as skin cancer), basal cell carcinoma (BCC), and squamous cell carcinoma (SCC), are among the most common cancers in White populations,[1-5] accounting for 13 percent of cancer registrations in Denmark in 1983-87[6] and perhaps one-third of all cancers in the United States.[7] Australia, which has the highest rate of skin cancer in the world,[2] had an estimated incidence in 1985 that was twice that for all other cancers combined.[8,9]

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Histopathologically, SCC has been described as a malignant proliferation of epidermal cells that retain characteristics of the normal suprabasal epidermis, and BCC as a low-grade, indolent, epidermal neoplasm recapitulating the normal basal layer of the epidermis.[10] Of the two types, SCC is the rarer but still comparatively frequent: in 1983-87 it was the twelfth most common cancer in Sweden and the sixteenth in Norway,[3] approximately two percent of patients with an SCC will develop a metastasis.[11] BCC rarely metastasizes.[12,13]

Mortality from non-melanocytic skin cancers is low—no more than 0.85 percent of all cancer deaths in Australia in 1990,[14] and is mostly due to SCC.[6,7] That some, at least, of these cancers are difficult to treat, with important human and financial consequences, is emphasized by indicators of cost to the health system: in 1981 in western Australia, non-melanocytic skin cancer ranked third in terms of hospital-bed use after lung and breast cancer.[15]

Solar radiation has been regarded as a major risk factor for non-melanocytic skin cancer in humans since 1896, when Unna described the skin changes which ended in skin cancer among sailors exposed to the sun.[16,17] From a comprehensive review linking clinical, experimental, and epidemiologic evidence, Blum[16] concluded in 1948, "we now have a number of lines of evidence, all of which converge to indict sunlight as the major cause of cancer of the skin in man." Later reviewers have repeated and elaborated this conclusion.[17-20]

Most of the data relating to the causal association between ultraviolet radiation (UVR) and skin cancer comes from investigations of the process of ultraviolet (UV) carcinogenesis in experimental animals.[21] These data relate mainly to SCC; BCC have not been reported in UV-exposed mice and rarely in other UV-exposed animals.[21] The number and quality of the studies leaves no room for doubt as to the causal association between experimental exposure to UVR and skin cancers.[21]

Epidemiologic evidence relevant to the effects of UVR on risk of skin cancer has been largely indirect, concerned with the anatomic distribution of skin cancer, place or latitude of residence as related indirectly or directly to presumed ambient solar irradiance, changes in incidence with migration, the apparent protective effect of racial pigmentation, and evidence that skin cancer is increased by occupational exposure to the sun. Well-designed epidemiologic studies linking sun exposure and skin cancer directly in individuals have rarely been attempted. The importance of such studies has increased recently because of the near certainty that depletion of stratospheric ozone will lead to an increase in solar UV irradiance at ground level.[22]

Evidence from descriptive epidemiology

The epidemiology of skin cancer is difficult to describe accurately. First, mortality rates are poor surrogates for incidence rates because the disease is rarely fatal. In addition, substantial proportions of deaths registered to skin cancer have been found to have been due to cancers of other sites.[6,7] Second, routine recording of skin cancer is often not attempted by cancer registries because of the large numbers of cases and difficulties involved. If attempted, such recording is invariably incomplete due to the rarity with which primary skin cancers require hospital treatment and the frequency with which probable skin cancers are not sent for histopathologic verification of the diagnosis.[23,24] Thus, many skin lesions that are provisionally diagnosed and treated as skin cancer do not come to the attention of the usual sources of cancer registrations; in addition, an unknown proportion of skin cancers is not diagnosed within the lifetime of those affected. Routine incidence estimates, therefore, are not always available and are unlikely to be accurate. Special surveys have been attempted in particular populations (see, for example,[1,8,25]) but even they have probably not ascertained all clinically diagnosed skin cancers, nor have they dealt with the issue of skin cancers that do not come to clinical attention.

The inaccuracy of estimates of skin cancer incidence limits the inferences that can be drawn from descriptive epidemiology on the relationship between sun exposure and skin cancer. This will be particularly true if the extent of error in incidence estimates is correlated with the sun exposure of populations. While no directly relevant empirical data exist, it is reasonable to speculate that the emphasis on the detection and accurate diagnosis of skin cancer is greater in populations at high sun exposure, or known high incidence-rates of skin cancer, than in populations with low exposure or presumed low rates. Similarly, presentation for diagnosis of skin lesions and care in diagnosis have probably increased with time, especially in response to concern about the effects of sun exposure and the effects of environmental change on ambient UV irradiance, and perhaps more strongly in people of higher socioeconomic status. These issues should be kept in mind when considering the data which follow.

Geographic variation in the incidence of skin cancer

Evidence on the relationship between sun exposure and skin cancer may be obtained from consideration of geographic variation in skin cancer incidence in relation to ambient solar irradiance and ethnic characteristics.[26,27]

Annual incidence rates of skin cancer in 29 popu-

Table 1. Estimated age-standardized incidence of non-melanocytic skin cancer (per 100,000 person-years) in 1982-87 in 29 populations of mainly western European origin (from Parkin *et al*[3]) by latitude and gender

Population	Incidence		
	Latitude	Male	Female
North America			
Canada			
Maritime provinces	45°N	117.7	73.4
Quebec	46°N	21.6	12.7
Newfoundland	49°N	73.6	43.7
British Columbia	50°N	134.1	91.2
Manitoba	50°N	95.2	60.2
Alberta	52°N	109.9	77.1
Saskatchewan	52°N	94.4	61.6
Europe			
Spain			
Granada	37°N	39.9	20.0
Murcia	38°N	34.0	17.5
Tarragona	41°N	56.2	33.0
Zaragoza	42°N	26.0	12.6
Navarra	42°N	42.0	21.8
Italy			
Florence	44°N	27.6	12.8
Genoa	44°N	20.9	9.8
Torino	45°N	38.6	23.0
Varese	45°N	42.0	24.8
Switzerland, 5 registries[a]	46°N	78.7	50.2
France			
Doubs	47°N	45.5	37.6
Calvados	49°N	21.0	9.2
Somme	50°N	23.2	12.9
Germany, Saarland	49°N	34.8	20.8
Ireland (south)	52°N	71.5	48.0
England			
Birmingham	52°N	42.1	27.6
Northwest	53°N	37.1	26.1
Southwest	51°N	45.5	28.6
Denmark	56°N	44.2	32.8
Scotland	56°N	42.9	27.9
Finland	62°N	47.6	41.8
Oceania			
Australia, Tasmania	43°S	213.2	113.1

[a] Population weighted average rates were calculated for the five Swiss registries of Basel, Geneva, Neuchatel, St Gall, and Vaud because each covered a population of < 500,000 and had a latitude of 46°N or 47°N.

lations detailed in *Cancer Incidence in Five Continents, Volume 6*[3] are listed in Table 1. These were all the populations of mainly western European origin which, if not a whole country or the only population representing a whole country, had a total of more than 500,000 people. The highest incidence rates were in the populations of Tasmania, Australia (213.2 per 100,000 in men, and 113.1 per 100,000 in women) and, British Columbia, Canada (134.1 in men and 91.2 in women), with high rates in all the other Canadian populations except Quebec. Incidence was also comparatively high in Switzerland (78.7 in men and 50.2 in women) and southern Ireland (71.5 in men and 48.0 in women).

There is little evidence in Table 1 of any consistent relationship between skin cancer incidence and latitude. If anything, the rates tended to be higher in the more northerly parts of Canada and Europe than in the more southerly and there is no evidence of the U-shaped pattern (minimum at about 50° north) that has been described for melanoma incidence in Europe.[28] When the latitude band occupied by the Canadian populations (45° to 52° north) is superimposed on the corresponding band in Europe (Torino, Italy, to Birmingham, England) the Canadian rates (except those for Quebec) are seen to be of the order of double the corresponding European rates. Similarly, the rates in Tasmania, Australia, are some four times higher than those in populations at corresponding latitudes in northern Spain and Italy.

In contrast to these international patterns, incidence rates of skin cancer within countries do appear to increase with proximity to the equator as indicated by broad place of residence, latitude, or measures of solar irradiance. Geographic variation in skin cancer incidence in the United States has been described in three National Cancer Surveys[16,29-34] and several related studies.[1,35,36] Incidence of all types increased with increasing proximity to the equator, with similar gradients for men and women and for all ages. Latitude and skin cancer incidence or prevalence were inversely related in Norway,[37] Finland,[38] and Australia,[2,8,39] and latitude was inversely related to skin cancer mortality in Canada and the 48 contiguous states of the US.[40]

Migration

The skin cancer experience of light-skinned migrants from areas of low, to areas of high, ambient solar irradiance, in comparison with ethnically similar populations born in the high-irradiance areas, has generally been consistent with an effect of sun exposure on skin cancer incidence.

In Australia, mortality from skin cancer is lower in migrants, most of whom had come from the UK, an area of lower sun exposure, than in native-born Australians. The age-adjusted mortality rate among men born in England or Wales was 0.55 (95 percent confidence interval [CI] = 0.43-0.71) times than in Australian-born men.[41] Similarly, in the Australian household surveys of skin cancer,[2,8] the age-adjusted incidence rates in migrants from the UK were ≤ 50 percent of those in the Australian-born.

Higher rates of skin cancer in an ethnic group living closer to the equator than in their country of origin has also been observed in Chinese migrants. Incidence

rates of skin cancer in Chinese migrants to Singapore in 1968-77, 5.4 per 100,000 person-years for men and 3.7 for women, were similar to those of Chinese born in Singapore, 5.5 for men and 3.0 for women.[42] In contrast, rates reported by cancer registries in China itself[3] were some four to five times lower, a difference which may have arisen from the greater sun exposure near the equator in Singapore compared with China, where even the southern regions are situated at around 16°N. Another possible contribution to these rates, however, may be greater detection due to the higher socio-economic status of Chinese in Singapore.

Age and gender

Skin cancer is rarely observed in persons younger than 20 years of age; the incidence has generally been reported to increase progressively with age and to be higher in men than women.[1,2,8,36,43-46] These observations have been seen as consistent with the effects of more or less continuous exposure to the sun throughout life and a greater prevalence of outdoor work in men than in women.

Recent cancer registry data show skin cancer incidence rates to be higher in men than women in most countries.[3] This also has been found in special surveys carried out in the US and Australia, with about a two-fold or greater difference between the genders.[1,18,24,25] Only 11 of the 120 registries reporting skin cancer incidence rates in *Cancer Incidence in Five Continents Volume 6*[3] had higher incidence rates in women than in men; they included some South American and Asian populations, Kuwaitis in Kuwait, and the population of Mali. In other data, women in Nagpur, India, had higher rates than men (4.6 compared with 2.2 per 100,000 person years[23]) as did Bantu women in Johannesburg (1.7 per 100,000 compared with 1.0 per 100,000[47]). These are all darker-skinned populations.

The incidence rates in men and women have generally been observed to diverge with increasing age.[1,2,8,23,25,48] In the US incidence survey of 1977-78,[1] this divergence began at a younger age (30 years) in the south than in northern and central areas (45 years).

The patterns of incidence with age and gender for BCC and SCC separately[1,2,36,43-46] are similar to those observed for skin cancer as a whole.

Race

The rarity of skin cancer in populations with dark skins is generally cited as evidence that it is caused by exposure to the sun.[49-52]

In data from cancer registries in which direct comparisons of skin cancer incidence in different ethnic groups can be made within a single geographic area, incidence rates in the light-skinned populations were consistently the highest.[3,23,53-55] This applied when the comparison was between Black Africans (rates between 0.8 and 4.2 per 100,000 person-years) and White Europeans (rates between 72.0 and 133.0) in South Africa where the differential was of the order of 100-fold (although greater underascertainment was likely in Blacks), and where it was between those of Spanish- or Mexican-American origin (*i.e.*, a Spanish surname in the El Paso, Texas (US) registry, and persons identified as having Spanish and/or Mexican heritage in the New Mexico (US) registry: rates between 9.9 and 30.9 per 100,000 person-years[54]) and those of other White European origins (rates between 42.4 and 144.9) where the differential was much less at three- to fourfold. Similar differentials were observed between ethnic groups in the 1977-78 US survey of skin cancer:[1] rates were higher in Whites (232.6 per 100,000 person-years) than Blacks (3.4 per 100,000) and higher among other Whites in New Mexico (333.9 per 100,000 for women and 638.8 per 100,000 for men) than among Hispanics (less than 100 per 100,000 in both genders).[1]

It may be of interest to note that the incidence in those of Chinese origin (8.9 per 100,000 person-years in men and 7.4 per 100,000 in women) was about double that in those of Malay or Indian origin (between 2.1 and 4.3 per 100,000) in Singapore in 1983-87.[3] While this difference is small, it has been present in the Singapore data from 1968 to 1987 in the four volumes of *Cancer Incidence in Five Continents* in which this registry has reported.[3,23,54,55] It is consistent with the observation that the Chinese generally have lighter skins than do the Malays and Indians in Singapore. Additional detail on incidence rates in Singapore is provided by Shanmugaratnam *et al*[42] for the period 1968 to 1977. Here the group of 'others,' including those of European ethnic origin, had skin cancer incidence rates nearly four times those of the Chinese.

Available evidence suggests that BCC occurs less frequently than SCC among darker-skinned populations. BCC was the most common skin cancer reported in South African Whites in 1949-75 but was rare among Black Africans, occurring mainly in albinos.[47,56-58] SCC, principally on the lower limb and associated with previous trauma, was more common than BCC in Blacks.[47,56-59] In a case series from New Orleans, Louisiana (US), slightly more cases of SCC (147) than BCC (124) were observed in Black patients between 1948 and 1975.[60] Melanesians[61] and Polynesians[62] had less BCC than SCC, while no BCCs were reported in the Melanesians of North Samoa, a particularly heavily-pigmented people.[61]

Occupation

Early reports associated skin cancer with outdoor

occupation.[16,17,63] The descriptive evidence for this association, however, is weak.

Standardized mortality ratios (SMR) for all skin cancers (including melanoma) in the UK in 1911-44 were greater for those engaged in agriculture than in mining, and lowest of all for professional workers.[64] The proportion of skin cancers in this series that was non-melanocytic was not reported and, during part of the period (1911-16), cancers of the penis and scrotum were included with the skin cancers. Later, standardized registration ratios (SRR) for SCC were reported to be high for male textile workers and farmers of both genders in the northwest of England.[65] Male fishermen, chemical workers and paper and printing workers had high SRRs for SCC of the arm, and building workers had high SRRs for SCC of the ear.

The relationship between occupation and skin cancer was examined in a 10 percent sample of all registered cases for whom occupation was recorded in England and Wales in 1970-75.[66] Cases were assigned on the basis of stated occupation to one of three groups, outdoor workers, indoor office workers, and other indoor workers. The SRRs for men aged 15-64 were 110 for outdoor work, 97 for office work, and 92 for other indoor work. Because 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 for outdoor work, 111 for office work, and 85 for other indoor work.

A negative association between incidence of skin cancer and employment in farming and fishing was observed in an ecologic study of cancer registry data from Finland.[38] This association was discounted by the authors, however, because of possible underascertainment of cases in rural municipalities. In Sweden in 1961-79, registration ratios of skin cancer, standardized for county of residence and social class, were slightly higher for outdoor workers (106, 95 percent confidence interval [CI] = 101-112) than for office workers (103, CI = 96-110) and other indoor workers (95, CI = 91-100).[67]

Table 2. Average annual changes (%) in age-standardized incidence of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) in different populations, by gender

Population and reference	Calendar period	BCC		SCC		Source of data
		M	F	M	F	
British Columbia[4]	1978-82 to 1983-87	3	2	3	3	Cancer registry
	1973-77 to 1978-82	5	5	4	5	
Two areas of the USA[a,73]	1971-72 to 1977-78	3	3	1	2	Survey
Portland, Oregon, USA[70]	1970-79 to 1980-86	—	—	7	8	Health plan
	1960-69 to 1970-79	—	—	3	4	
SE Netherlands[71]	1978-81 to 1985-88	4	4	4	3	Cancer registry
Norway[3,23,55]	1980 to 1985	—	—	−1	−3	Cancer registry
	1975 to 1980	—	—	5	6	
Sweden[3,23,55]	1980 to 1985	—	—	5	6	Cancer registry
	1975 to 1980	—	—	1	1	
Vaud, Switzerland[44]	1974-78 to 1976-85	4	8	5	11	Cancer registry
Tasmania[74]	1978 to 1987	9	8	7	6	Cancer registry

[a] Minneapolis and San Francisco.

Trends in incidence with time

The incidence of skin cancer in White populations has been reported to be increasing, and several authors have suggested that changes in sun exposure have contributed to these trends.[4,35,68-71]

The average, annual, percentage increases in incidence of skin cancer in 19 populations of European origin between succeeding volumes of *Cancer Incidence in Five Continents* have been summarized in Kricker *et al.*[72] The trends fluctuated substantially from period to period, sometimes rising and sometimes falling. Overall, the trend was upwards between 1970 and 1985 in eight out of 13 populations for which data over this period were available.

There have been several reports of trends in incidence of BCC and SCC separately. These data, summarized in Table 2, show more consistent trends than those reported from cancer registries for skin cancer as a whole, with average increases in incidence of each histopathologic type of three to six percent per year in most populations. The rates of increase were similar for BCC and SCC. The increases in non-melanocytic skin cancer cannot be explained by improved differentiation from melanoma in cancer registration, since increases in incidence and mortality of melanoma also have been observed worldwide.[72]

Percentage increases in incidence of BCC and SCC at different body sites, calculated wherever possible from published papers, are shown in Table 3. These increases were least for BCC on the head and neck, and consistently large, except in women in the USA, on the trunk. Indeed, while BCC was once regarded as a disease of sun-exposed sites such as the head, face, and

Table 3. Average annual changes (%) in age-standardized incidence of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) at different body sites, by gender

Body site and population	Calendar period	BCC		SCC	
		M	F	M	F
Head and neck					
Two areas of the USA[a,73]	1971-72 to 1977-78	1	3	1	2
Portland, Oregon[70]	1970-79 to 1980-86	—	—	3	3
	1960-69 to 1970-79	—	—	8	8
British Columbia[4]	1979-81 to 1985-87	4	3	3	5
	1973-75 to 1979-81	4	3	6	3
Trunk					
Two areas of the USA[a,73]	1971-72 to 1977-78	9	1	13	−3
Portland, Oregon[70]	1970-79 to 1980-86	—	—	5	5
	1960-69 to 1970-79	—	—	9	1
British Columbia[4]	1979-81 to 1985-87	10	7	0	0
	1973-75 to 1979-81	8	12	0	0
SE Netherlands[71]	1978-81 to 1985-88	8	5	0	0
Upper limbs					
Two areas of the USA[a,73]	1971-72 to 1977-78	11	4	−1	11
British Columbia[4]	1979-81 to 1985-87	15	9	6	6
	1973-75 to 1979-81	3	14	4	7
SE Netherlands[71]	1978-81 to 1985-88	5	10	7	29
Lower limbs					
Two areas of the USA[a,73]	1971-72 to 1977-78	7	7	2	2
British Columbia[4]	1979-81 to 1985-87	3	6	7	11
	1973-75 to 1979-81	12	16	12	10
SE Netherlands[71]	1978-81 to 1985-88	−6	17	0	0
Upper and lower limbs combined					
Portland, Oregon[70]	1970-79 to 1980-86	—	—	2	2
	1960-69 to 1970-79	—	—	4	12
Site unspecified					
British Columbia[4]	1979-81 to 1985-87	−6	−4	−4	−8
	1973-75 to 1979-81	12	8	5	10

[a] Minneapolis and San Francisco.

neck,[51] it has been observed in sizeable proportions on the trunk in a number of recent surveys.[4,8,36,43,44] Trends in BCC on the upper and lower limbs (Table 3) were rather erratic, although they also tended to be larger than those on the head and neck. SCC did not show any very consistent pattern of trends by body site; if anything the trends were less on the trunk than at other sites.

Anatomic site distribution

That skin cancer occurs predominantly on sun-exposed sites has generally been taken as strong evidence that it is caused by sun exposure.[51,52,75,76] To examine this issue more closely, we have summarized the body-site distributions of BCC and SCC reported from incidence studies in whole populations (Table 4).

Most of the SCCs occurred on the head and neck and the upper limbs (Table 4). The proportions of SCCs on the limbs were consistently higher in women than men and, correspondingly, the proportions on the head and neck were lower.

The predominant site of BCC was also the head and neck, with more than 60 percent on these sites in all studies (Table 4). Around 10-20 percent of BCCs were on the trunk. The limbs were rare sites for these cancers, with less than five percent on the upper or lower limbs. There was a fairly consistent difference in the distributions of BCCs between the genders the proportions on the head and neck and lower limbs were slightly higher in women than men and the proportions on the upper limbs and trunk were slightly higher in men than women.

In each report listed in Table 4, the site distribution of SCC differed from that of BCC. The most consistent differences were a greater proportion of SCCs on the upper limbs and a greater proportion of BCCs on the trunk. At the sub-site level, BCCs have been reported to be almost completely absent on the backs of the hands and infrequent on the forearms compared with the upper arms, whereas SCCs occur relatively frequently on these sub-sites.[1,25,33,39,78-80]

Several investigators have attempted to establish a more direct correlation between the amount of exposure to the sun at particular body sites and the relative incidence of skin cancer at those sites. These studies have concentrated on patterns of BCC distribution which are apparently discrepant with the distribution of sun exposure.

Urbach[19] exposed plastic manikin heads, coated with a chemical dosimeter, to the sun at different times of the day and used shading mechanisms to simulate the effects of direct, scattered, and reflected UV radiation. The resulting estimates of relative sun exposure were

Table 4. Percentage distribution of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) by body site in different populations

Population and period	Gender	No. of cases	Body site				
			Head and neck	Upper limbs	Lower limbs	Trunk	Site unspecified[a]
SCC							
USA, 1977-78[1]	M	3,539	74.8	17.6	1.3	4.5	1.8
	F	1,756	60.1	25.2	5.7	5.3	3.7
New Hampshire and Vermont, 1979-80[36]	M	202	76.3	14.0	2.4	5.8	—
	F	75	62.8	16.7	6.4	9.0	—
Portland, Oregon, 1960-86[70]	M	1,380	78.4	16.9[b]		4.6	—
	F	496	70.5	24.2[b]		5.0	—
British Columbia, 1973-87[4]	M	1,683	65.5	15.3	1.9	5.0	12.3
	F	936	58.8	19.4	9.5	3.8	8.4
Finland, 1967-81[77]	M	1,481	75.7	13.3[b]		7.8	2.0
	F	1,446	75.8	15.6[b]		6.8	1.3
Switzerland, 1976-85[44]	M	685	80.7	10.4	2.6	4.5	1.8
	F	491	69.0	16.7	7.7	5.7	0.8
Denmark, 1978-82[43]	M	1,354	76.3	15.4	3.8	4.5	5.8
	F	651	66.7	17.1	7.5	8.7	4.6
Norway, 1976-85[46]	M	2,204	71.8	11.3	3.6	8.0	5.3
	F	1,518	69.8	10.3	6.0	9.8	4.1
South Wales, 1988[5]	M & F	56	66.0	9.0	16.0	9.0	—
Australia, 1985[8]	M & F	51	43.0	22.0	22.0	14.0	—
Australia, 1990[2]	M	113	48.0	33.0	10.0	6.0	4.0
	F	53	24.0	49.0	17.0	4.0	6.0
BCC							
USA, 1977-78[1]	M	13,770	81.2	4.8	1.3	12.0	0.7
	F	10,692	84.1	3.3	2.9	8.9	1.4
New Hampshire and Vermont, 1979-80[36]	M	1,022	78.2	4.2	2.3	14.0	—
	F	739	82.6	3.1	3.0	10.3	—
British Columbia, 1973-87[4]	M	6,282	63.6	5.6	1.4	12.2	17.2
	F	5,235	67.9	4.9	4.0	9.4	13.9
Finland, 1967-81[77]	M	9,899	77.5	3.3[b]		12.2	4.5
	F	14,076	81.4	2.9[b]		9.1	4.8
Switzerland, 1976-85[44]	M	1,970	72.8	4.2	2.0	18.0	3.1
	F	1,841	76.8	2.5	3.9	15.3	1.5
Denmark, 1978-82[43]	M	5,587	80.2	2.4	2.3	15.1	8.9
	F	5,259	77.5	2.5	3.6	16.4	8.3
Norway, 1976-85[46]	M	8,085	61.5	1.7	2.1	27.6	7.1
	F	8,400	64.1	1.5	3.1	25.2	6.1
South Wales, 1988[5]	M & F	201	81.0	0.5	4.0	14.5	—
Australia, 1985[8]	M & F	202	66.0	8.0	8.0	18.0	—
Australia, 1990[2]	M	272	66.0	8.0	4.0	21.0	1.0
	F	186	69.0	9.0	6.0	14.0	2.0

[a] The high proportions of unspecified sites reported in some of these studies generally represent multiple skin cancers. When more than one skin cancer of the same histology was registered with the same diagnosis date in Denmark, they were coded to 'site unspecified.'[43] In British Columbia, a second primary cancer of the same histology and at the same anatomic site was coded to 'site unspecified.'[4]

[b] Percentage for upper and lower limbs are combined since these were not separately specified.

compared with the distribution of BCC and SCC of the head and neck in clinic patients in Sweden, and in Philadelphia, Pennsylvania (US) in 1957-62. He concluded that approximately 38 percent of all BCC on the head and neck in these patients occurred in areas receiving less than 20 percent of the maximum UV radiation, whereas SCC occurred rarely on these more sheltered areas. A similar analysis of BCC on the face was conducted with results from exposure of a manikin on nine autumn days in Canterbury, UK (51° north)[49] and the sub-site distribution of BCC in clinic patients from New York City, NY (US) (latitude 41° north) in 1955-58.[78] A 100-fold range of UV exposure was found over the face and the correlation between the number of BCCs per unit area and the relative UV dose was 0.58. How well these patterns of exposure correlate with sun exposure to the human face has not been established.

Table 5. General characteristics of eight non-population based and fifteen population based studies of non-melanocytic skin cancer

Author (reference)	Place	Period of diagnosis of cases	No. of cases and source population	No. of controls and source population
Non-population-based studies				
Lancaster and Nelson, 1957[82]	Sydney, Australia	Uncertain	173 with BCC, SCC or solar keratoses from major hospitals	173 patients with other cancers from major hospitals
Gellin *et al*, 1965[83]	New York, NY, USA	1955-59	771 with BCC from skin clinic	783 other patients from same skin clinic 1958-60
Lane-Brown *et al*, 1971[84]	Sydney, Australia	1962-66	650 with BCC and 233 with SCC from a major public hospital	300 with no skin cancer from two major hospitals
Urbach *et al*, 1972[85]	Philadelphia, PA, USA	1967-69	392 with BCC and 59 with SCC from a skin and cancer clinic	281 without cancer from the same clinic
Aubry and MacGibbon, 1985[86]	Montreal, Canada	1977-78	92 with SCC from 14 hospitals	174 with skin condition other than cancer from same hospitals
O'Loughlin *et al*, 1985[87]	Ireland	Not stated	63 with BCC and 58 with SCC from one hospital	121 with other cancers from the same hospital
Herity *et al*, 1989[88]	Ireland	1984-85	396 with BCC or SCC (approximately equal numbers) from one hospital	396 with other cancers from the same hospital
Gafá *et al*, 1991[89]	Italy	1987-88	108 with BCC and 25 with SCC from hospital-based Cancer Registry	133 with non-neoplastic disease from same hospital and 133 friends or relatives
Population-based studies				
Silverstone and Gordon, 1966[39] Silverstone and Searle, 1970[90]	Queensland, Australia	1961-63	221 with histories of skin cancer in 3 population surveys	1,979 with no history of skin cancer in these population surveys
O'Beirn *et al*, 1970[91]	Ireland	1960s	13 with BCC and 13 with SCC in a population survey	1,000 without skin cancer from the same survey[a]
Holman *et al*, 1984[92]	Western Australia	1981	102 with past history of BCC or SCC	Approximately 1,114 subjects with no past history of BCC or SCC
Robinson, 1987[93]	USA	NR	Approximately 350 patients who developed a BCC subsequent to a previous BCC	Approximately 650 patients without a subsequent BCC
Giles *et al*, 1988[8]	Australia	1985	202 with BCC and 51 with SCC in medical records of past 12 months	30,400[b] approximately with no history of skin cancer in past 12 months
Engel *et al*, 1988[94]	USA	1971-74	Not stated[c]	20,637 persons in cohort
Green *et al*, 1988[95]	Queensland, Australia	1986	34 with BCC and 9 with SCC in population survey	>2,000[b] without skin cancer from the same population
Marks *et al*, 1989[80]	Victoria, Australia	1982-86	113 with BCC, 35 with SCC in a population survey	1,828 without skin cancer from same population
Hogan *et al*, 1989[96]	Canada	1983	538 with BCC from Cancer Foundation records	738 controls from the Provincial Medicare Plan
Hogan *et al*, 1990[97]	Canada	1982-83	178 with SCC from Cancer Foundation records	284 controls from the Provincial Medicare Plan
Vitasa *et al*, 1990[98]	Maryland, USA	1985-86	33 with BCC and 35 with SCC in a population survey of watermen	588 watermen without BCC, SCC or solar keratosis
Hunter *et al*, 1990[99]	USA	1981-84	771 with BCC in a cohort of women nurses	72,595 nurses with no reported BCC

Continued...

Table 5. Continued

Author (reference)	Place	Period of diagnosis of cases	No. of cases and source population	No. of controls and source population
Green and Battistutta, 1990[45]	Queensland, Australia	1985-87	66 with BCC and 21 with SCC in a population survey[d]	>1,600[b] with no skin cancer in the same survey
Kricker *et al*, 1991[100]	Western Australia	1986-87	226 with incident or prevalent BCC and 45 with incident or prevalent SCC	1,021 for BCC and 1,064 for SCC analyses without incident or prevalent cancer of the same pathologic type
Marks *et al*, 1993[2]	Australia	1990	458 with BCC and 166 with SCC in medical records of past 12 months	60,250[b] approximately with no history of skin cancer in past 12 months

[a] There were only 152 controls for the analysis of sun exposure in men.
[b] Exact number not given in the publication.
[c] Actual numbers not given, only gender-specific rates of BCC associated with different grades of skin damage.
[d] The prevalent cases reported in Green *et al*[95] were excluded from this report.

Table 6. Conduct of 23 studies of nonmelanocytic skin cancer

Author (reference)	Type of skin cancer	Confirmation of diagnosis by histopathology	Participation rate of subjects	Method of collection of data	Adjustment of analyses for age and gender	Adjustment of sun exposure for cutaneous sun sensitivity
Non-population-based studies						
Lancaster and Nelson, 1957[82]	Combined[a]	Uncertain	NR[b]	Interview	No	No
Gellin *et al*, 1965[83]	BCC	Yes	NR	NR	No	No
Lane-Brown *et al*, 1971[84]	BCC; SCC	Uncertain	NR	NR	No	NA[c]
Urbach *et al*, 1972[85]	BCC; SCC	Yes	NR	Interview	No[d]	No
Aubry and MacGibbon, 1985[86]	SCC	Yes	30%	Mail	Yes	Yes
O'Loughlin *et al*, 1985[87]	Combined	Yes	NR	Interview	No	No
Herity *et al*, 1989[88]	Combined	Yes	NR	Interview	No	No
Gafá *et al*, 1991[89]	Combined & BCC; SCC	Uncertain	94% of cases	Uncertain	Uncertain	Yes
Population-based studies						
Silverstone and Gordon, 1966[39]						
Silverstone and Searle, 1970[90]	Combined	Incomplete	87%	Interview	No[e]	No
O'Beirn *et al*, 1970[91]	BCC; SCC	Incomplete	NR	Interview	Yes	No
Holman *et al*, 1984[92]	Combined	No	NR	Interview	Age only	NA
Robinson, 1987[93]	BCC	NR	98%	Interview	Uncertain[f]	Yes[f]
Giles *et al*, 1988[8]	Combined	Incomplete	99%	Interview	Yes	NA
Engel *et al*, 1988[94]	BCC	Uncertain	74%	Interview	Yes	NA
Green *et al*, 1988[95]	Combined	Yes	70%	Interview	Yes	Yes[g]
Marks *et al*, 1989[80]	BCC; SCC	Yes	60%[h]	Interview	Yes	No[g,i]
Hogan *et al*, 1989[96]	BCC	Uncertain	50%	Mail	Uncertain	No[g]
Hogan *et al*, 1990[97]	SCC	Uncertain	46%	Mail	Uncertain	No[g]
Vitasa *et al*, 1990[98]	BCC; SCC	Incomplete	70%	Interview	Yes	Yes
Hunter *et al*, 1990[99]	BCC	No	74%	Mail	Yes	Yes[i]
Green and Battistutta, 1990[45]	BCC; SCC	Incomplete	84%	Interview	Yes	Yes[i]
Kricker *et al*, 1991[100]	BCC; SCC	Yes	89%	Interview	Yes	NA
Marks *et al*, 1993[2]	BCC; SCC	Incomplete	NR	Interview	Yes	NA

[a] The two types together.
[b] NR = not reported.
[c] NA = not applicable. Lane-Brown *et al*[84] studied 'Celticity' only using surname, others did not measure sun exposure directly.
[d] A logistic regression of these data with adjustment for age but not gender was reported by Vitiliano.
[e] Gordon *et al*[20] reported RRs for this study but no details of method of analysis or numbers of subjects.
[f] The report included neither methods of analysis nor numbers of subjects.
[g] Occupational sun exposure only.
[h] 74% responded among those who attended for an initial examination; this represented 60% of the total eligible population.
[i] Adjusted for skin color but not sun-sensitivity itself.

Sun exposure recordings on a whole-body manikin in Canterbury for 1 h either side of solar noon showed that the hands and upper arms received higher doses than some parts of the face.[81] The rarity of BCC on the hands and forearms, therefore, appeared not to be due simply to lack of exposure of these sites.

Analytic epidemiologic studies

Studies reviewed

The major epidemiologic features relevant to the effects of sun exposure on skin cancer risk have been drawn from a limited number of studies of uneven quality.

All case-control, cross-sectional, and cohort studies that examine either sun exposure variables or potential confounders of their relationship with skin cancer have been reviewed. In Table 5, the characteristics of studies with cases and controls from potentially different populations are summarized as 'non-population-based studies,' and those of studies based more certainly on one population are summarized as 'population-based studies.' The eight studies with cases and controls from potentially different populations (Table 5) were based only on hospital or clinic populations. Cases comprised patients presenting to the hospital or clinic for diagnosis or treatment of skin cancer; other clinical patients (including, in some, others with skin disease) served as controls. Twelve of the 15 population-based studies (Table 5) were case-control or cross-sectional in type, including, variously, incident cases, prevalent cases or both, with subjects from the same population as controls and exposure measured at or after diagnosis of disease. Three studies[80,93,99] were cohort studies which measured exposure before identification of disease. Of these, the study of US nurses[99] achieved reasonably complete follow-up of subjects over a specified time period while the Australian study,[80] which relied on voluntary presentation of subjects for examination over a number of years, did not. Insufficient detail was reported for assessment of the methodological adequacy of the third,[93] a follow-up study of patients with BCC for development of a subsequent BCC.

Low case numbers would be expected to produce imprecise estimates of risk. The numbers of BCC were about 100 or less in eight of 14 studies. Among the 10 studies of SCC, only four had 50 or more cases,[84,85,97,100] only two of which included any direct[85] or indirect[97] measurement of sun exposure.

Aspects of the conduct of the 23 studies listed in Table 5 are summarized in Table 6. Generally, BCC and SCC were distinguished as separate case-groups (16 studies), although seven studies reported results only for the two types of skin cancer combined. Histopathologic confirmation of cases was reported in eight studies, including five studies of hospital or clinic patients. Other groups of cases included clinical as well as histopathologic diagnoses (labeled 'incomplete' in Table 6), self-reported cases in what was regarded as a 'medically sophisticated population' of female nurses,[99] or cases with no details of confirmation of the diagnosis (labeled as 'uncertain'). The proportion of eligible subjects who participated was not adequately reported in nine studies.

Methods for measuring pigmentary and cutaneous characteristics and sun exposure were inadequately described in most studies and few gave any indication that objective or quantitative methods had been used. Further details of methods of measurement will be provided, where relevant, with the results for the individual variables. Methods of analysis were generally weak. Only one of the eight non-population-based studies[86] reported effect measures, *P* values, and adjustment for the potential confounding effects of age and gender, although not of cutaneous sensitivity to the sun (propensity to burn or ability to tan) which is a fundamental confounder of the relationship between sun exposure and skin cancer. The population-based studies were generally better analyzed, although few of these provided *P* values or 95 percent confidence intervals about effect measures. These studies, however, were not comprehensive in their coverage of pigmentary and cutaneous characteristics (Tables 7-9) and sun exposure (Tables 10 and 11), and when examining sun exposure, only two included a measure of cutaneous sun sensitivity in an appropriate statistical model.[95,98]

To summarize and compare studies in the tables that follow, relative risk estimates, CIs, and *P* values for relevant variables have been listed wherever possible. Where odds ratios or other relative risk estimates have been published, those adjusted most appropriately for potential confounding variables have been given. For studies which did not estimate effect measures, we have calculated odds ratios, CIs, and *P* values by the exact method in EGRET[101] from raw data given in the relevant papers. In these analyses, adjustment of fundamental confounding variables such as age and gender has generally not been possible, and in matched studies unmatched analyses have been necessary. The odds ratios so calculated, therefore, are given as an indication of the direction and, perhaps less certainly, of the size of the effects observed. Little reliance, however, will be placed on these studies which include those reported by Lancaster and Nelson,[82] Gellin *et al*,[83] Silverstone and Gordon,[39] Silverstone and Searle,[90]

Table 7. Associations of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) with pigmentary characteristics

Author (reference)	Method of measurement	Comparison	OR[a]	(CI)[a]	*P* value for trend[a]
Non-population-based studies (BCC)					
Hair color					
Gellin *et al*, 1965[83]	Uncertain	Light *cf* black or brown	*3.0*	*(2.2-4.1)*	*< 0.001*
Urbach *et al*, 1972[85]	Uncertain	Blond or red *cf* black or brown	*2.0*	*(1.2-3.2)*	*0.002*
Eye color					
Gellin *et al*, 1965[83]	Uncertain	Blue, green, or grey *cf* brown	*2.2*	*(1.8-2.7)*	*< 0.001*
Urbach *et al*, 1972[85]	Uncertain	Blue, green, or grey *cf* brown	*2.7*	*(1.9-3.9)*	—
		Other *cf* brown	*1.5*	*(0.9-2.4)*	*< 0.001*[b]
Skin color					
Gellin *et al*, 1965[83]	Uncertain	Fair *cf* dark or medium	*1.7*	*(1.4-2.2)*	*< 0.001*
Urbach *et al*, 1972[85]	Uncertain	Fair *cf* dark or medium	*2.0*	*(1.5-2.8)*	*< 0.001*
Gafá *et al*, 1991[89]	Uncertain	Intermediate *cf* dark	*2.3*	*(0.9-7.2)*	—
		Fair *cf* dark	*6.4*	*(2.6-19.1)*	*< 0.001*
Population-based studies (BCC)					
Hair color					
Hogan *et al*, 1989[96]	Self-report	Red or blond *cf* other	1.2	(NR[c])	< 0.05
Hunter *et al*, 1990[99] (women only)	Self-report	Black *cf* dark brown	0.7	(0.5-1.2)[d]	—
		Light brown *cf* dark brown	1.1	(1.0-1.3)	—
		Blond *cf* dark brown	1.1	(0.9-1.4)	—
		Red *cf* dark brown	1.5	(1.1-2.0)	0.002
Green and Battistutta, 1990[45]	Dermatologist	Blond or light brown *cf* dark brown or black	2.1	(1.1-4.0)[e]	—
		Red or auburn *cf* dark brown or black	2.9	(1.1-7.6)	NR
Kricker *et al*, 1991[100]	Trained observer	Light brown *cf* dark brown	1.2	(0.8-1.6)[f]	—
		Blond or fair *cf* dark brown	1.5	(0.9-2.5)	—
		Red *cf* dark brown	1.8	(1.2-6.7)	0.02
Eye color					
Hogan *et al*, 1989[96]	Self-report	Blue or grey *cf* other	*1.2*	*(1.0-1.5)*	*0.13*
Vitasa *et al*, 1990[98] (Men only)	Dermatologist	Blue *cf* hazel or brown	3.4	(1.2-10.2)[g]	NR
Kricker *et al*, 199[100]	Trained observer	Blue *cf* dark brown or hazel	1.2	(0.7-1.4)[f]	—
		Green *cf* dark brown or hazel	1.1	(0.8-1.8)	0.79[b]
Skin color					
Hogan *et al*, 1989[96]	Self-report	Light *cf* other	1.2	(NR)	< 0.01
Green and Battistutta, 1990[45]	Dermatologist	Medium *cf* olive	1.3	(0.3-6.1)[e]	—
		Fair *cf* olive	2.9	(0.7-12.9)	NR
Kricker *et al*, 1991[100]	Trained observer	78-80% reflectance *cf* 51-77% (dark)	1.3	(0.8-2.0)[f]	—
		81-83% *cf* 51-77% (dark)	1.0	(0.7-1.6)	—
		84-95% (light) *cf* 51-77% (dark)	1.5	(1.0-2.4)	0.13
Non-population-based studies (SCC)					
Hair color					
Urbach *et al*, 1972[85]	Uncertain	Blond or red *cf* black or brown	*2.7*	*(1.3-5.5)*	*0.003*
Aubry and MacGibbon, 1985[86]	Self-report	Blond or red *cf* other	*2.1*	*(1.2-4.0)*	*0.01*
Eye color					
Urbach *et al*, 1972[85]	Uncertain	Blue, green or grey *cf* brown	*3.9*	*(1.9-8.2)*	—
		Other *cf* brown	*0.2*	*(0.0-1.3)*	*< 0.001*[b]
Aubry and MacGibbon, 1985[86]	Self-report	Blue, green, or grey *cf* brown	*1.4*	*(0.8-2.4)*	*0.20*
Skin color					
Urbach *et al*, 1972[85]	Uncertain	Fair *cf* dark or medium	*2.0*	*(1.1-3.7)*	*0.02*
Aubry and MacGibbon, 1985[86]	Self-report	Fair *cf* dark or medium	*2.5*	*(1.5-4.4)*	< 0.001

Continued . . .

Table 7. Continued

Author (reference)	Method of measurement	Comparison	OR[a]	(CI)[a]	*P* value for trend[a]
Population-based studies (SCC)					
Hair color					
Hogan *et al*, 1990[97]	Self-report	Blond or red *cf* other	*1.8*	*(1.2-2.6)*	*0.004*
Green and Battistutta, 1990[45]	Dermatologist	Blond or light brown *cf* dark brown or black	1.8	(0.6-5.3)[e]	—
		Red or auburn *cf* dark brown or black	3.3	(0.7-14.4)	NR
Kricker *et al*, 1991[100]	Trained observer	Light brown *cf* dark brown	1.7	(0.9-3.4)[h]	—
		Blond, fair or red *cf* dark brown	2.4	(1.0-6.1)	0.03
Eye color					
Vitasa *et al*, 1990[98] (Men only)	Dermatologist	Blue *cf* hazel or brown	3.4	(1.1-9.9)[g]	NR
Kricker *et al*, 1991[100]	Trained observer	Blue *cf* dark brown or hazel	1.4	(0.6-3.0)[h]	—
		Green *cf* dark brown or hazel	1.0	(0.5-2.1)	0.67[b]
Hogan *et al*, 1990[97]	Uncertain	Light *cf* other	*1.7*	*(1.1-2.5)*	*0.01*
Green and Battistutta, 1990[45]	Dermatologist	Fair *cf* olive or medium	2.3	(0.9-6.2)[e]	NR
Kricker *et al*, 1991[100]	Trained observer	78-80% reflectance *cf* 51-77% (dark)	1.9	(0.7-5.0)[h]	—
		81-83% *cf* 51-77% (dark)	2.6	(1.0-6.6)	—
		84-95% (light) *cf* 51-77% (dark)	3.3	(1.3-8.7)	0.01

[a] OR = odds ratio; (CI) = 95% confidence interval. OR, (CI), and *P* values in italics have been calculated from raw data given in the publications.
[b] Overall *P* value for difference of ORs from 1.0.
[c] NR = not reported.
[d] RRs from a model including age, childhood tendency to sunburn, time period, region, time spent outdoors in summer and sunscreen habit, and lifetime number of severe and painful sunburns.
[e] RRs adjusted for age and gender.
[f] ORs from a model including age, gender, age at arrival in Australia and southern European ethnicity.
[g] ORs from a model which included age, ease of sunburning, cumulative UVB exposure, childhood freckling, light hair, main job, and any episode of drug-induced photosensitivity.
[h] ORs from a model including age, gender, ethnic origin, and migrant status.

Table 8. Associations of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) with tendency to sunburn and ability to tan

Author (reference)	Method of measurement	Comparison	OR[a]	(CI)[a]	*P* value for trend[a]
Non-population-based studies					
BCC					
Gellin *et al*, 1965[83]	Uncertain	Tans moderately *cf* tans easily	*1.7*	*(1.3-2.3)*	—
		Sunburns easily *cf* tans easily	*2.3*	*(1.7-3.0)*	*< 0.001*
Urbach *et al*, 1972[85]	Uncertain	Tans slowly *cf* tans easily	*1.8*	*(1.3-2.7)*	—
		Tans not at all *cf* tans easily	*2.7*	*(1.6-4.5)*	*< 0.001*
Gafá *et al*, 1991[89]	Uncertain	Tans easily: no *cf* yes	*2.6*	*(1.6-4.3)*	*< 0.001*
SCC					
Urbach *et al*, 1972[85]	Uncertain	Tans slowly *cf* tans easily	*3.7*	*(1.6-9.6)*	—
		Tans not at all *cf* tans easily	*4.0*	*(1.3-12.4)*	*0.002*
Aubry and MacGibbon, 1985[86]	Self-report	Difficulty in tanning: yes *cf* no	*1.5*	*(0.8-2.6)*	*0.18*
Gafá *et al*, 1991[89]	Uncertain	Tans easily: no *cf* yes	*1.0*	*(0.3-2.4)*	*0.91*
Population-based studies					
BCC					
Hogan *et al*, 1989[96]	Self-report	Skin type I or II *cf* other	*1.9*	*(1.5-2.4)*	*< 0.001*
Marks *et al*, 1989[80]	Self-report	Burn only *cf* tan only	2.1[b]	(NR[c])	0.006

Continued . . .

Table 8. Continued

Author (reference)	Method of measurement	Comparison	OR[a]	(CI)[a]	*P* value for trend[a]
Vitasa *et al*, 1990[98] (Men only)	Interview	Sunburns *cf* tans	2.7	(1.1-6.6)[d]	NR
Hunter *et al*, 1990[99] (Women only)	Self-report	Type of tan after repeated exposure as a child or adolescent:			
		Average tan } *cf* deep tan	1.3[e]	(NR)	
		Light tan } *cf* deep tan	*1.6*	(NR)	
		No tan } *cf* deep tan	*2.5*	(NR)	*< 0.001*
Hunter *et al*, 1990[99] (Women only)	Self-report	Skin reaction to 2 or more hours of sunlight as a child or adolescent			
		Some redness only } *cf* practically none	1.6	(1.2-2.0)[e]	
		Burn } *cf* practically none	2.5	(2.0-3.2)	
		Painful burn } *cf* practically none	2.6	(2.0-3.5)	
		Painful burn with blisters } *cf* practically none	4.0	(3.0-5.3)	< 0.001
Kricker *et al*, 1991[100]	Interview	Moderate tan } *cf* deeply tanned	1.7	(1.1-2.5)[f]	
		Mild tan } *cf* deeply tanned	2.2	(1.4-3.6)	
		Freckle or no tan } *cf* deeply tanned	2.1	(1.0-4.6)	0.002
Marks *et al*, 1993[2]	Interview	Burn then tan } *cf* always tan	3.9[b]	(NR)	
		Always burn } *cf* always tan	6.1	(NR)	NR
SCC					
Marks *et al*, 1989[80]	Self-report	Burn only *cf* tan only	3.3[b]	(NR)	0.009
Hogan *et al*, 1990[97]	Self-report	Skin types I or II *cf* other	*1.8*	*(1.2-2.7)*	*0.002*
Vitasa *et al*, 1990[98] (Men only)	Interview	Sunburns *cf* tans	1.8	(0.8-3.9)[d]	NR
Kricker *et al*, 1991[100]	Interview	Moderate tan } *cf* deeply tanned	1.6	(0.6-4.0)[g]	
		Mild tan } *cf* deeply tanned	2.0	(0.7-6.1)	
		Freckle or no tan } *cf* deeply tanned	4.3	(1.0-17.6)	0.05
Marks *et al*, 1993[2]	Interview	Burn then tan } *cf* always tan	3.3[b]	(NR)	
		Always burn } *cf* always tan	4.5	(NR)	NR

[a] OR = odds ratio; (CI) = 95% confidence interval. OR, (CI) and *P* values in italics have been calculated from raw data given in the publications.

[b] Rate ratios were calculated from the age-standardized incidence rates provided.

[c] NR = not reported.

[d] ORs from a model which included age, cumulative UVB exposure, childhood freckling, hair and eye color, main job, and any episode of drug-induced photosensitivity.

[e] RRs from a model including age, time period, region, time spent outdoors in summer and sunscreen habit, hair color, childhood tendency to sunburn, and lifetime number of severe and painful sunburns on the face and arms. Estimates were reported with 'no tan' as the baseline; in this table 'deep tan' has been used as the baseline.

[f] ORs from a model including age, gender, age at arrival in Australia and southern European ethnicity, freckling on the arms in childhood, number of moles ≥ 5 mm on the back, solar elastosis of the neck, and cutaneous microtopography.

[g] ORs from a model including age, gender, migrant status, freckling on the arms in childhood, skin reflectance on the forearm, solar elastosis of the neck, facial telangiectasia, and having a permanent color difference between the neck and adjacent protected areas.

O'Beirn *et al*,[91] Urbach *et al*,[85] Aubry and MacGibbon,[86] O'Loughlin *et al*,[87] Herity *et al*,[88] Hogan *et al*,[96,97] and Gafá *et al*.[89]

The descriptive evidence strongly suggested that BCC and SCC may differ in their etiology: compared with SCC, BCC was infrequent in heavily-pigmented races, less consistently distributed on exposed body sites, and occurred less frequently among patients with *xeroderma pigmentosum* (XP) and albinism (inherited syndromes of cutaneous sensitivity to the sun, reviewed briefly below). Thus, studies of BCC and SCC combined would be expected *a priori* to add little if anything to the understanding of the relationship between these cancers and pigmentary characteristics or sun exposure. Results of studies of the two cancer types together, therefore, will be excluded from the detailed review which follows (Tables 7-12) and referred to only if especially pertinent.

Pigmentary and other characteristics indicating cutaneous sensitivity to the sun

"There is a certain type of skin which is more fertile soil for the development of epithelioma, namely, that of the person with blond, sandy or ruddy complexion which freckles readily but does not tan, usually associated with light hair and eyes."[102] Such pigmentary characteristics are generally accepted as risk factors for skin can-

cer.[17,26,52,99] They implicate sun exposure as a cause of skin cancer indirectly insofar as they are markers of cutaneous sun sensitivity.

A high correlation would be expected between hair, eye, and skin color,[103] and, in addition, between these pigmentary characteristics and other constitutional characteristics, such as ethnic origin, sun-sensitivity, and freckling, which may underlie the individual's capacity to protect against the effects of sun exposure. Few of the analytical studies reporting on the relationship between pigmentary characteristics and skin cancer (Table 7) have been conducted and reported in accordance with appropriate methodologic standards, and their analyses have failed, in particular, to take adequate account of potential confounding among these highly intercorrelated variables. An orderly approach to data analysis has been suggested as essential to the identification of independently predictive measures of the constitutional determinants of skin cancer risk (*e.g.*, see Holman *et al*[104]). Among the studies to be reviewed, however, only one described the use of any objective or quantitative measurements of pigmentary and cutaneous characteristics and attempted to apply a method of analysis with a sound theoretical basis.[100]

Pigmentary characteristics. The non-population-based studies which examined pigmentary characteristics had reported that light hair, eye, and skin color were individual risk factors for BCC and SCC;[83,85,86] the ORs were elevated in crude analyses of their data (Table 7). In the population-based studies (Table 7), the pigmentary characteristic with the strongest evidence of increased risk for BCC and SCC was a light hair color (red, blond, or light brown), although the risk increase was small when appropriate account was taken of potential confounding with ethnic origin.[100] In the study which took account of confounding with ethnic origin, eye color had no appreciable effect on risk of either skin cancer.[100] Although there was no consistent evidence of an association between skin color and BCC, a 'light' or 'fair' complexion increased the risk for SCC in three studies.[45,97,100]

Tendency to sunburn and ability to tan. Cutaneous sun sensitivity, or 'skin type' is thought to be a fundamental determinant of skin cancer risk.[104-106] It is also highly correlated with hair, eye, and skin color and may be determined by skin color.

A skin that burns easily or tans poorly was identified as a risk factor for BCC in all studies in which it was investigated (Table 8). Relative risk estimates in the population based studies were between 2.1 and 4.0 for the comparison of the most sensitive with the least sensitive categories, in analyses which included adjustment for age, gender, pigmentary characteristics, and indicators of sun exposure.[98-100]

While SCC was apparently positively associated with sun-sensitivity, the evidence for the association was weaker (Table 8). An increased risk persisted in two studies after adjustment for pigmentary and sun exposure variables (ORs of 1.8 for a skin that sunburns,[98] and 4.3 for a skin that freckles and does not tan[100]) although confidence intervals were wide and included 1.0. The number of cases in these studies were small (45 and 35; Table 6). Two studies of BCC and SCC combined in Australian populations reported positive associations with sun sensitivity[8,95] but did not adjust for potential confounding with pigmentary characteristics or sun exposure.

When Kricker *et al*[100] included sun-sensitivity (as measured separately by propensity to burn and ability to tan) together with hair, eye, and skin color in separate models of risk of BCC, and of SCC, the effects of the pigmentary variables were no longer statistically significant. Hair color however, remained appreciably associated with risk of BCC and SCC, and skin color with SCC, with ORs ranging up to about 2.0.

Freckles and moles. The status of freckles and moles as potential indicators of risk of skin cancer is unclear. Both are probably in part genetically determined,[107,108] bear a relationship to cutaneous sun-sensitivity,[109] and are probably caused by exposure to the sun.[107,110]

Childhood or adolescent freckling was associated with increased risks of both BCC and SCC in population-based studies. In the watermen's (fishermen) study in the US, Vitasa *et al*[98] reported relative risks of 3.7 (CI = 1.5-8.8) and 2.4 (CI = 1.1-5.3) for these cancers respectively after adjustment for, among other things, age, sun-sensitivity, hair color, and sun exposure. Moderate or heavy childhood freckling had elevated ORs for both skin cancers in Australian subjects (ORs 1.7 and 2.6 for BCC and 1.1 and 4.2 for SCC) although only the relationship with BCC remained statistically significant after adjustment for ethnic origin, pigmentary characteristics, sun-sensitivity, and other indicators of cutaneous sun damage.[100]

Risk of BCC increased with increasing number of moles $\geqslant 5$ mm on the back in an Australian study (OR = 2.0, CI = 1.0-3.9 for 10-48 *cf* no moles) but the presence of moles was not positively associated with risk of SCC.[100] A history of having had a mole excised also increased the risk of BCC (OR = 1.9, CI = 1.3-2.7). The association of number of moles with BCC was independent of ethnic origin, pigmentary characteristics, sun-sensitivity and indicators of cutaneous sun damage.

Ethnic origin. Among Caucasians, Celtic ancestry was thought to increase the risk of skin cancer.[5,51,111] Various indices, however, derived mainly from patient surnames have not convincingly demonstrated such a role for 'Celticity.'[20,63,84-86,112] In Australia, Kricker *et al*[100] reported that there was no evidence for an effect of Celtic ancestry on BCC or SCC and no significant trend with increasing numbers of grandparents born in Ireland, Scotland, or Wales relative to no grandparents born in these Celtic countries. In this study, no subject with confirmed skin cancer was born in a southern European country, and a protective effect of having any grandparents born in southern Europe was observed for BCC (OR = 0.4, CI = 0.2-0.9). No case of SCC had even one grandparent of southern European ethnic origin.

Ethnic origin is likely to be correlated with both pigmentary characteristics[103] and sun-sensitivity and could also be correlated with other genetic determinants of skin cancer risk. The protective effect of southern European ancestry was not explained by differences in ability to tan since it remained after adjustment for all significant independent predictors of risk among the pigmentary and cutaneous variables.[100]

Inherited syndromes of sun sensitivity. Xeroderma pigmentosum (XP) is a rare autosomal-recessive disorder characterized by clinical and cellular hypersensitivity to solar radiation and deficiency in the capacity for excision repair of DNA damage; this capacity is important in the repair of damage caused by UVR.[18,113] Evidence of cutaneous sun damage may appear as early as one to two years of age in the absence of specific protection from the sun, and skin cancers are very frequent. The median age of diagnosis of the first skin cancer in 485 published case reports was eight years.[113] In a review of reports of histopathologic findings in 220 XP patients with skin cancer,[113] 36 percent (79 patients) had BCC, 51 percent (112 patients) SCC, and 17 percent (37 patients) melanoma. Ninety-seven percent of the BCCs and SCCs occurred on the head and neck, compared with 80 percent on these sites in a general population.[113]

Some patients with trichothiodystrophy, another genetic disorder, are sun-sensitive and many have a defect in excision repair of DNA said to be indistinguishable from that of XP patients. These patients, however, are said not to have an increased risk of skin cancer.[114] Lehmann and Bridges[114] have argued, from experimental evidence about differences in the activity of natural killer cells between patients with XP and trichothiodystrophy, that the cause of skin cancer in XP patients is a failure of the immune system to restrict the growth of mutated cells. Thus, it may be that skin cancers in XP patients result from a defect in immunity rather than defective repair of UVR-caused DNA damage.[115] Recent reports, however, show a correlation between the capacity for excision repair of UVR-induced DNA damage and risk of skin cancer in humans without known genetic disorder.[116,117] These reports, together with the evidence from XP, provide indirect support for a role for UV in causing skin cancer by way of its capacity to cause damage to DNA.

Albinism is an inherited disorder of melanin metabolism with a decrease in or complete absence of melanin; as a result, the skin of albinos is highly sensitive to the sun. The most common type of albinism occurs in one in 15,000 American Blacks, one in 40,000 European or American Caucasians, and has estimated frequencies as high as one in 3,900 in Soweto, South Africa,[118] and one in 1,000 in Nigeria.[119] Albinos have been reported to be substantially over-represented in series of ethnic Africans with skin cancer. Among albinos, SCCs were eight times more frequent than BCCs and melanomas apparently rare.[119-121] Death from skin cancer at quite young ages has been reported in albinos.[119-121] Ecologic evidence for sun exposure as a cause of these skin cancers is provided by a latitude gradient: African albinos who lived far from the equator in South Africa were reported to have less skin cancer and a longer life span than those who lived close to the equator in Tanzania[120] or Nigeria.[119]

Exposure of skin to the sun

Direct measurement of exposure of the skin to the sun, over periods probably relevant to the cause of skin cancer, presents substantial difficulties. To do this prospectively would require frequent documentation of exposure from early childhood to the time of development of cancer; to do this on a sufficiently large sample of subjects would be practically impossible. Case-control studies could be regarded as having a limited capacity for investigation of the effects of sun exposure because of their dependence on recall measures over 40 years or more of life. Nonetheless, this has been the most common approach adopted.

Methods of measurement of sun exposure in the studies reviewed were generally poor. In most studies (eight of 10 with sun exposure measurements shown in Tables 9 and 10), measurement of sun exposure, if it has been described at all adequately, has been based on very simple questions. Only three studies attempted a quantitative estimate of lifetime exposure to the sun.[85,86,98] Many studies reported results for broad summary variables such as 'working outdoors six hours per day,'[96] or 'estimated average daily outdoor exposure,'[83] usually without indication of exactly how the data were obtained or the time period over which the

Table 9. Associations of BCC and SCC with total sun exposure

Author (reference)	Method of measurement	Measure of sun exposure	OR[a]	(CI)[a]	*P* value[a] for trend
Non-population-based studies					
BCC					
Gellin *et al*, 1965[83]	Crude	Average daily outdoor exposure:			
		3-5 h } *cf* 0-2 h	*4.9*	*(3.8-6.3)*	—
		⩾6 h }	*7.7*	*(5.6-10.6)*	*< 0.001*
Urbach *et al*, 1972[85] (Men only)	Quantitative	Cumulative 'outdoor' exposure hours × 1000:			
		30-50 h } *cf* < 30 h	*3.5*	*(2.0-6.6)*	—
		⩾50 h }	*9.3*	*(3.2-37.4)*	*< 0.001*
Gafá *et al*, 1991[89]	Crude	Solar exposure 6 h/day:			
		Yes *cf* no	*1.2*	*(0.8-2.1)*	*0.38*
SCC					
Urbach *et al*, 1972[85] (Men only)	Quantitative	Cumulative 'outdoor' exposure hours × 1000:			
		30-50 h } *cf* < 30 h	*4.0*	*(1.7-9.6)*	—
		⩾50 h }	*11.1*	*(2.8-53.6)*	*< 0.001*
Gafá *et al*, 1991[89]	Crude	Solar exposure 6 h/day:			
		Yes *cf* no	*3.0*	*(1.0-12.3)*	*0.04*
Population-based studies					
BCC					
Hunter *et al*, 1990[99] (Women only)	Crude	At least 8 h/week outdoors in summer[b]:			
		Yes, with little or no protection } *cf* no	1.0	(NR[c])	—
		Yes, with sunscreen }	1.4	(NR)	NR
Vitasa *et al*, 1990[98] (Men only)	Quantitative	Cumulative UVB exposure[d]			
		Above *cf* below median	0.7	(0.3-1.5)[e]	NR
SCC					
Vitasa *et al*, 1990[98] (Men only)	Quantitative	Cumulative UVB exposure[d]			
		Above *cf* below median	2.1	(0.8-5.0)[e]	NR

[a] OR = odds ratio; (CI) = 95% confidence interval. OR, (CI), and *P* values in italics have been calculated from raw data given in the publications.

[b] The RRs in this table have been converted to make 'no regular sun exposure' the reference category. The model included adjustment for age, childhood tendency to sunburn, hair color, time period, region, and lifetime number of severe and painful sunburns.

[c] NR = not reported.

[d] 'The personal exposure to ultraviolet-B of each participant was determined by combining field-derived and laboratory-derived and published ambient ultraviolet-B data with personal exposure histories[98].'

[e] ORs from a model which included age, ease of sunburning, hair and eye color, childhood freckling, main job, and any episode of drug-induced photosensitivity.

reported exposure occurred. Because of these difficulties, some more indirect, surrogate measures of sun exposure have also been used. They include potential for sun exposure based on ambient solar irradiance at places of residence, clinical evidence of benign sun damage to the skin, recall of episodes of sunburn, and use of protective measures against the sun. The contribution of all the various measures of sun exposure to understanding the relationship between sun exposure and skin cancer is reviewed mainly from material in the population-based studies (Tables 9 and 10).

Total sun exposure. Various general approaches have been adopted to the measurement of total sun exposure (Table 9). The one substantial cohort study[99] asked a very simple question: 'Do you regularly spend time outdoors in the summer?'. In only one study,[98,122] that of Chesapeake Bay watermen, did the exposure index (cumulative exposure to UVB radiation) have a strong theoretical and empirical basis, although its validity may be limited by incomplete evaluation of exposure on non-working days and absence of documentation of exposure in childhood. Few studies have attempted to take account of the modifying effects of clothing habits on exposure of the skin. A further difficulty is presented by the fact that people who have sun-sensitive skin and are at higher risk of skin cancer will tend to expose themselves less to the sun. To obtain an accurate measure of the effects of personal sun exposure, this confounding with sun sensitivity should be con-

Table 10. Associations of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) with sun exposure at work and in non-working hours

Author (reference)	Method of measurement	Measure of sun exposure	OR[a]	(CI)[a]	*P* value for trend[a]
Sun exposure at work—non-population-based studies					
BCC					
Gafá *et al*, 1991[89]	Crude	Working in agriculture ⩾ 10 years:			
		Yes *cf* no	*1.6*	*(1.0-2.6)*	*0.04*
SCC					
Aubry and MacGibbon, 1985[86]	Composite score	Low work exposure *cf* none	1.0[b]	(NR[c])	—
		Medium exposure *cf* none	1.1[b]	(NR)	—
		High exposure *cf* none	1.6	(NR)	0.02
Gafá *et al*, 1991[89]	Crude	Working in agriculture ⩾ 10 years:			
		Yes *cf* no	*2.4*	*(0.9-6.3)*	*0.04*
Sun exposure at work—population-based studies					
BCC					
Hogan *et al*, 1989[96]	Crude	Farmer *cf* not farmer	1.3	(NR)[d]	< 0.001
		Working outdoors 6 h/day:			
		Yes *cf* no	*1.4*	*(1.1-1.8)*	*0.003*
Marks *et al*, 1989[80]	Crude	Outdoors *cf* indoors work	1.6	(NR)[e]	0.03
Green and Battistutta, 1990[45]	Crude	Indoors and outdoors *cf* indoors work	1.5	(0.8-2.9)[f]	—
		Outdoors *cf* indoors work	1.3	(0.6-2.8)	NR
SCC					
Marks *et al*, 1989[80]	Crude	Outdoors *cf* indoors work	1.7	(NR)[e]	0.11
Hogan *et al*, 1990[97]	Crude	Farmer *cf* not farmer	1.5	(1.2-1.8)[g]	NR
Green and Battistutta, 1990[45]	Crude	Indoors and outdoors *cf* indoors work	4.4	(0.9-20.9)[f]	—
		Outdoors *cf* indoors work	5.5	(1.1-28.2)	NR
Sun exposure in non-working hours—population-based studies					
BCC					
Green and Battistutta, 1990[45]	Crude	Indoors and outdoors *cf* indoors leisure	1.0	(0.4-2.2)[f]	—
		Outdoors *cf* indoors leisure	0.6	(0.3-1.3)	NR
SCC					
Green and Battistutta, 1990[45]	Crude	Indoors and outdoors *cf* indoors leisure	2.0	(0.2-19.9)[f]	—
		Outdoors *cf* indoors leisure	3.9	(0.5-30.9)	NR
Sun exposure in non-working hours—non-population-based studies					
SCC					
Aubry and MacGibbon, 1985[86]	Composite score	Non-occupational exposure score:			
		Medium *cf* low	1.2[h]	(NR)	—
		High *cf* low	1.6	(NR)	NR

[a] OR = odds ratio; (CI) = 95% confidence interval. ORs, 95% CIs, and *P* values in italics have been calculated from raw data given in the publications.

[b] ORs for continuous variable, adjusted for age, gender, eye, and hair color, complexion, ethnic characteristics, and non-occupational exposure.

[c] NR = not reported.

[d] The analysis included childhood freckles, family history of skin cancer, Celtic mother, skin and hair color, severe sunburn, and working outdoors > 3 h/day in winter.

[e] Adjusted for age.

[f] Relative risk estimates adjusted for age, gender, skin color, and past history of skin cancer reported.

[g] From a 'multivariate analysis' of family history of skin cancer, childhood freckles, skin and hair color, skin type, history of severe sunburn, use of the herbicide 2,4-D.

[h] ORs for continuous variable, adjusted for occupational sunlight exposure and host factors.

trolled. This, however, has not always been done (see Table 6).

In short, measurements of total sun exposure, even in the population-based studies, are likely to be subject to substantial error. Indeed, at a very basic level of quality control, only one of the studies reviewed[100] made any statement regarding attempts to ensure that interviewers were blind to the case or control status of subjects and to ensure that subjects were not alerted to the nature of the hypotheses being tested.

The limited picture for BCC in Table 9 is not at all clear. The crude ORs of two of the non-population-based studies were high, with evidence of a dose-response relationship.[83,85] In neither of these studies, however, was confounding with age controlled. In addition, the reasons for restricting the comparison of outdoor exposure to men only were not stated by Urbach *et al.*[85] The more recent US studies[98,99] found no evidence of a positive association between BCC and measures of total sun exposure after adjustment for cutaneous sun-sensitivity, in selected occupational groups of men (fishermen[98]) and women (nurses[99]). The 'negative' result of Hunter *et al*[99] could have been contributed to by the inclusion of lifetime number of sunburns (another measure of total sun exposure for which there was a positive association with BCC) in the statistical model with total sun exposure. The study of Vitasa *et al*[98] lacked statistical power with its low number of cases (33).

The data of Urbach *et al*[85] for both genders were reanalyzed by Vitaliano[123] with adjustment for complexion, ability to tan, and age, but not for gender. The adjusted ORs for BCC, relative to less than 10,000 h outdoors, were 1.8 for 10,000 to 19,999 h, 2.9 for 20,000 to 29,999 h, and 3.2 for $\geq$ 30,000 h outdoors ($P < 0.001$, the 95 percent CIs were not reported). While this may appear to be a more adequate representation of the results of this study, there are some problems. First, there are unexplained differences in the numbers of subjects and their distribution over exposure levels in the two reports. For example, there were 100 male patients with BCC, 28 with SCC, and 24 controls who had $\geq$ 30,000 h outdoors in the report of Urbach *et al*,[85] whereas there were only 23, 14 and 10 subjects, respectively, in total in these subject-exposure categories in Vitaliano's report.[123] Second, there may be residual confounding by age and gender; gender was not controlled at all by Vitaliano[123] and it appears that age may have simply been dichotomized in the logistic regression model as 0-59 and $\geq$ 60 years. The distributions by gender and age of the BCC cases and the controls, however, were similar. These difficulties cast doubt on the magnitude of the reported estimates, although there is an apparent positive association between risk of BCC and increasing sun exposure in these data.

There is somewhat more evidence for an association between total sun exposure and SCC (Table 9). A strongly positive association was seen in crude ORs for men calculated from the data of Urbach *et al*[85] with a dose-response relationship to the highest OR of 11.1 (2.8-53.6; $P < 0.001$). Confounding by age, however, was not controlled in this study. The relationship observed by Vitasa *et al*[98] in the fishermen of Chesapeake Bay was weak, although adjusted for sun-sensitivity. When the upper quartile of sun exposure was compared with the lower three quartiles, the relative risk was higher (OR = 2.5, CI = 1.2-5.4).[98] This is an unusual comparison to make, however, and raises some questions about the shape of the exposure-response relationship. These results were, in addition, based on 35 cases of which only half were confirmed histopathologically.

Vitaliano[123] also reanalyzed the results of Urbach *et al*[85] for SCC, taking confounding by age, complexion, and ability to tan into account. A single result for sun exposure was not reported because of a significant interaction between complexion and sun exposure. For those with a 'pale' complexion, the adjusted ORs were 5.7 for 10,000-19,999 h outdoors and 22.6 for $\geq$ 20,000 h; the corresponding ORs for those with a 'moderate-dark' complexion were 2.3 and 3.7. The reservations given above in the description of BCC apply here also. In particular, the problem of confounding with age and gender may be much greater; Urbach *et al*[85] reported that 13.6 percent of the cases of SCC were female compared with 50.3 percent of controls and that 70.9 percent of the cases, compared with 35.6 percent of controls, were $\geq$ 70 years of age.

In a study of risk factors for a further skin cancer in those who had already had a BCC, risk was reported to be significantly increased in those whose skin burnt easily and had frequent sun exposure.[93] It was not significantly increased by sunbathing, residence in a sunny area, or in relation to estimated daily hours of sun exposure. The subjects, assessment of sun exposure, and method of analysis were not well described in this study.

Sun exposure at work. A number of case-control and cross-sectional studies have evaluated the relationship between sun exposure at work and BCC and SCC (Table 10). The comments made above regarding measurement of total exposure to the sun apply with equal force to measurement of sun exposure at work and in non-working hours (see below). Occupational exposure, even in the population-based studies, was measured in very broad terms such as 'indoors' or 'outdoors,' 'farmer' or 'not farmer,' without validation of the assignment to these categories in terms of actual sun exposure.[45,80,86,96,97]

The results of population-based studies in Australia[45,80] and Canada[96,97] showed a generally consistent, but not strong, association between BCC and SCC and various rather crude measures of working in outdoor occupations (Table 10). For BCC, the highest relative risk estimate was 1.6 and for SCC it was as high as 5.5, although with very wide confidence intervals. In an

additional study of BCC and SCC combined, Green *et al*[95] reported an OR for 'outdoors' occupational exposure, adjusted for skin reaction to the sun, of about the same order, although not apparently significant (OR = 1.8, CI = 0.8-4.1). The results of studies of Green *et al*[95] and Green and Battistutta[45] may have been weakened somewhat by the inclusion of an unknown percentage of unconfirmed cases (see Table 6) or by possible overadjustment of the analyses by inclusion of a past history of skin cancer (a likely correlate of sun exposure) in the statistical model. The positive associations obtained by Aubry and MacGibbon[86] and Hogan *et al*[96] add little weight to the other observations because of low participation rates (50 percent or less) and uncertainty as to whether potential confounding by age and gender was appropriately dealt with (Table 6).

Sun exposure in non-working hours. The study of exposure to sunlight in non-working hours (largely recreational sun exposure) and skin cancer has been neglected (Table 10). Of the two studies available, that by Green and Battistutta[45] used a rather crude measure of leisure time exposure, *i.e.*, 'mainly indoors,' 'indoors and outdoors,' and 'mainly outdoors,' and the other, reported by Aubry and MacGibbon,[86] used a composite exposure index constructed from a variety of different indicators (sunburns and sunbathing, use of sunscreen, place of residence in childhood during summer, sports, time outdoors, and holidays) with neither theoretical justification nor empirical validation.

Leisure time exposure to the sun was not significantly associated with either BCC or SCC in the study of Green and Battistutta.[45] The OR was 3.9 for SCC but had a wide 95 percent confidence interval. The trend to increasing risk of SCC with increasing exposure was described as significant in the study of Aubry and MacGibbon[86] in an analysis which included adjustment for host factors and occupational sunlight exposure. A low response rate in this study (30 percent), however, provides substantial scope for bias.

Potential for exposure to the sun. Potential for exposure to the sun, based on various indicators of ambient solar irradiance at places of residence, has been shown to be associated with risk of melanoma in case-control studies.[106] This kind of variable has been little used as a separate indicator of sun exposure in studies of non-melanocytic skin cancer.

Hunter *et al*[99] observed an association between risk of BCC and residence in southern parts of the US (California: relative risk [RR] = 1.57, CI = 1.30-1.89; Florida: RR = 2.12, CI = 1.54-2.92).

One study in individuals (as distinct from the descriptive studies of populations examined above) has examined the effect of migration on risk of skin cancer. Kricker *et al*[100] studied the relationship between BCC and SCC and migration to Australia; in the main, migrants to Australia have had less potential for sun exposure during the period of their life outside Australia than have those born in Australia. Migrants (excluding those from southern Europe who may be at lower constitutional risk for skin cancer) had a lower risk of both BCC and SCC (OR = 0.29, CI = 0.07-0.81) than did those born in Australia. Interestingly, the RR of BCC was not reduced in migrants who arrived in Australia within the first 10 years of life (OR = 1.05, CI = 0.4-2.5, adjusted for age and gender with those of southern European ethnic origin excluded); those who arrived at 10-19 years of age and $\geq$ 20 years of age had ORs for BCC of 0.14 (CI = 0.0-0.5) and 0.22 (CI = 0.1-0.4). While the effects of the variables age at diagnosis, age at arrival in Australia and duration of residence in Australia cannot be modeled together, age- and gender-adjusted ORs for BCC did not increase consistently with increasing duration of residence suggesting that age at arrival was the more important variable. This may suggest that the effect of sun exposure early in life is particularly important in determining the risk of BCC. As there were only four subjects with SCC in this study who were born outside Australia, similar detailed analyses could not be made for SCC.

Benign sun damage to the skin. Two analytical studies have examined the relationship between skin cancer and various clinical indicators of benign sun damage to the skin in Australian subjects (Table 11). These were population-based case-control studies with adequate (>70 percent) participation, appropriate analyses including adjustment for age and gender, confirmation of all diagnoses,[95,100] and adjustment for other relevant variables, *i.e.*, ethnicity and migrant status, in one.[100] The indicators used have included cutaneous microtopography (a reasonably objective measure of the loss of fine skin markings on the backs of the hands),[95] solar elastosis of the neck (diagnosed when the skin of the neck was thickened and leathery with deep furrows and wrinkles), facial solar lentigines (defined as brown to black macules with well defined edges which may be irregular), and solar keratoses.

The interpretation of relationships between skin cancer and these variables in terms of sun exposure assumes that they provide some measure of total exposure of the skin to the sun. While this may be true, the relationship of these benign conditions to sun exposure has generally not been studied at all rigorously. It is interesting to note, however, that a recent randomized controlled trial of sunscreen use has

Table 11. Associations of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) with indicators of cutaneous sun damage diagnosed by a dermatologist in two population based studies in Australia

Author (reference)	Measure of cutaneous sun damage	OR	(CI)[b]	*P* value for trend
Population-based studies—BCC				
Green & Battistutta, 1990[45]				
Solar lentigines on hands	1-10 *cf* none	1.5[a]	(0.8-2.8)	—
	11-20 *cf* none	2.9	(1.2-7.0)	—
	>20 *cf* none	3.7	(1.2-11.7)	NR[c]
Telangiectasia of face	Mild *cf* none	2.3[a]	(1.1-4.7)	—
	Moderate *cf* none	2.9	(1.2-7.1)	—
	Severe *cf* none	7.3	(2.1-26.0)	NR[c]
Elastosis of the neck	Mild-moderate *cf* none	3.7[a]	(1.6-8.3)	—
	Severe *cf* none	3.6	(1.3-9.8)	NR[c]
Solar keratoses on face	1-5 *cf* none	3.9[a]	(1.9-8.0)	—
	6-20 *cf* none	5.6	(2.3-13.3)	—
	>20 *cf* none	10.0	(3.5-28.2)	NR[c]
Kricker *et al*, 1991[100]				
Facial solar lentigines	1-10 *cf* none	0.7[d]	(0.5-1.0)	—
	11-20 *cf* none	1.0	(0.5-2.0)	—
	≥21 *cf* none	1.2	(0.5-2.6)	0.56
Facial telangiectasia	Mild *cf* none	1.4[d]	(0.9-2.2)	—
	Moderate *cf* none	1.6	(1.0-2.6)	—
	Severe *cf* none	2.3	(1.3-4.1)	0.003
Elastosis of the neck	Mild *cf* none	2.2[d]	(1.0-5.0)	—
	Moderate *cf* none	3.8	(1.6-8.8)	—
	Severe *cf* none	6.0	(2.5-14.7)	<0.001
Cutaneous microtopography	Grade 4 *cf* grades 1-3	2.6[d]	(1.3-4.9)	—
	Grade 5 *cf* grades 1-3	3.3	(1.7-6.4)	—
	Grade 6 *cf* grades 1-3	3.1	(1.5-6.4)	0.007
Solar keratoses	1-5 *cf* none	2.1[d]	(1.3-3.4)	—
	6-14 *cf* none	2.8	(1.6-4.6)	—
	15-39 *cf* none	5.3	(3.3-8.6)	—
	40+ *cf* none	10.4	(5.8-18.8)	<0.001
Population-based studies—SCC				
Green and Battistutta, 1990[45]				
Solar lentigines on hands	1-10 *cf* none	0.8[a]	(0.3-2.1)	—
	11-20 *cf* none	0.6	(0.1-4.5)	—
	>20 *cf* none	1.2	(0.1-9.6)	NR
Telangiectasia of face	Mild *cf* none	1.5[a]	(0.4-5.8)	—
	Moderate *cf* none	3.9	(1.0-16.1)	—
	Severe *cf* none	3.3	(0.3-36.0)	NR
Elastosis of the neck	Mild-moderate *cf* none	5.4[a]	(0.7-43.7)	—
	Severe *cf* none	8.3	(1.0-72.7)	NR
Solar keratoses on face	1-5 *cf* none	1.7[a]	(0.4-6.5)	—
	6-20 *cf* none	4.2	(1.1-16.1)	—
	>20 *cf* none	11.0	(2.6-46.6)	NR
Kricker *et al*, 1991[100]				
Facial solar lentigines	1-10 *cf* none	0.8[d]	(0.4-1.6)	—
	≥11 *cf* none	1.0	(0.3-2.8)	0.7
Facial telangiectasia	Moderate *cf* none or mild	2.9[d]	(1.5-5.9)	—
	Severe *cf* none or mild	6.5	(2.6-16.1)	<0.001
Elastosis of the neck	Moderate *cf* none or mild	2.8[d]	(1.3-6.4)	—
	Severe *cf* none or mild	6.5	(2.6-16.1)	<0.001
Cutaneous microtopography	Grade 5 *cf* grades 1-4	1.7[d]	(0.8-3.5)	—
	Grade 6 *cf* grades 1-4	1.8	(0.8-4.2)	0.12
Solar keratoses	15-39 *cf* 0-14	7.2[d]	(3.0-17.3)	—
	≥40 *cf* 0-14	34.3	(14.0-84.0)	<0.001

[a] OR = odds ratios adjusted for age and gender.
[b] (CI) = 95% confidence interval.
[c] NR = not reported.
[d] ORs adjusted for age, gender, migrant status and ethnicity.

Table 12. Associations of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) with sunburn

Author (reference)	Sunburn measure	OR[a]	(CI)[a]	*P* value for trend[a]
Non-population-based studies				
BCC				
Urbach *et al*, 1972[85]	History of severe sunburn:			
	Once *cf* never	*1.1*	*(0.8-1.6)*	—
	Occasional *cf* never	*5.0*	*(2.4-11.5)*	—
	Many times *cf* never	*8.6*	*(3.0-34.1)*	*< 0.001*
SCC				
Urbach *et al*, 1972[85]	History of severe sunburn:			
	Once *cf* never	*0.9*	*(0.4-1.7)*	—
	Occasional *cf* never	*7.0*	*(2.5-20.3)*	—
	Many times *cf* never	*7.3*	*(1.5-39.3)*	*< 0.001*
Population-based studies				
BCC				
Hogan *et al*, 1989[96]	History of severe sunburn:			
	Yes *cf* no	1.2	(NR[b])	< 0.01
Hunter *et al*, 1990[99]	Number of painful sunburns:			
(Women only)	1-2 times *cf* never	1.4[c]	(1.1-1.8)	—
	3-5 times *cf* never	1.8	(1.4-2.3)	—
	6 or more times *cf* never	2.9	(2.4-3.6)	< 0.001
Green and Battistutta, 1990[45]	Number of painful sunburns:			
	1 *cf* none	0.5[d]	(0.2-1.4)	—
	2-5 *cf* none	0.6	(0.3-1.5)	—
	6+ *cf* none	1.0	(0.4-2.5)	NR
SCC				
Hogan *et al*, 1990[97]	History of severe sunburn: Yes *cf* no	1.5	(1.2-1.8)	NR
Green and Battistutta, 1990[45]	Number of painful sunburns			
	2-5 *cf* 0-1	3.3[d]	(0.9-12.3)	—
	⩾6 *cf* 0-1	3.0	(0.7-12.2)	NR

[a] OR = odds ratio; (CI), = 95% confidence interval. OR, (CI), and *P* values in italics have been calculated from raw data given in the publications.
[b] NR = not reported.
[c] Age-adjusted ORs.
[d] ORs adjusted for age, gender, skin color, and past history of skin cancer.

shown that a presumed reduction in UV exposure over a period of one year can reduce the rate of formation and increase the rate of regression of solar keratoses.[124]

All indicators of benign sun damage to the skin except solar lentigines on the face and hands were related, generally strongly, to risk of both BCC and SCC (Table 11), including when adjusted for cutaneous sun-sensitivity.[100] In analyses including adjustment for age, gender, ethnicity, and migrant status, Kricker *et al*[100] observed that solar elastosis of the neck was the strongest predictor of risk of both BCC and SCC when other variables of this type were included with it in a logistic regression analysis. Number of solar keratoses was not included in this analysis because these lesions were considered to be as much indicators of early neoplasia as indicators of sun exposure.

In the National Health and Nutrition Examination Survey of 1971-74 in the US,[94] prevalence of clinically-suspected BCC was significantly higher in those with sun damaged skin (0.8 percent in men and 1.2 percent in women), as indicated by 'actinic keratoses, fine telangiectasia and senile elastosis,' than in those without (0.1 percent in men and 0.2 percent in women; $P < 0.01$).

A high prevalence of elastosis has been observed histologically in and around BCCs and SCCs.[125,126] However, no data were given in these reports on the prevalence of elastosis in those without skin cancer.

Sunburn. A history of sunburn can be taken to indicate one or more episodes of sun exposure sufficient to exceed the protective capacities of the skin. It has generally been thought to be more indicative of intermittent intense exposure to the sun, as perhaps in occasional sun-related recreation,[106] than total exposure, although there are no empirical data to support this position. It has been argued that in modeling the relationship of sunburn with skin cancer, pigmentary characteristics and sun-sensitivity should not be included as potentially confounding variables since

sunburn indicates exposure of the target cells for skin cancer after the protective capacity of the superficial layers of the epidermis has been taken into account.[127]

While Urbach *et al*[85] found strong associations between BCC and SCC and sunburn (Table 12), these results are of uncertain validity because of the use of skin clinic patients as controls and because of lack of adjustment for age and gender. In the three other studies of BCC, all of which were population-based, risk was increased with a history of sunburn only in the study of Hunter *et al*.[99] This study depended on self-reports of BCCs and histopathologic confirmation was not documented. Risk of SCC was increased with sunburn in the study of Green and Battitstutta[45] but did not increase consistently with increasing frequency of burning. Risk of SCC was also associated with sunburn in the study of Hogan *et al*[97] but this study may be biased by its low response rate.

The lack of convincing associations between BCC or BCC and SCC combined and sunburn in the studies of Green and Battistutta[45] and Green *et al*[95] could have been contributed to by their inclusion of sun-sensitivity, skin color, and past history of skin cancer (a likely correlate of sun exposure) in their statistical models. Little detail was given in any of the studies about how history of sunburn was documented.

Protection against the sun. If behavioral measures designed to protect the skin from the sun were to be associated with a reduced risk of skin cancer, this would provide indirect evidence of a causal association between sun exposure and skin cancer. In their cohort study of US nurses, Hunter *et al*[99] found a higher risk of BCC in those who regularly spent time outdoors and used sunscreen (OR = 1.0) than in those who regularly spent time outdoors and did not use sunscreen (OR = 0.6, CI = 0.5-0.7, age-adjusted). Addition of other sun exposure and sun-sensitivity variables (hair color, childhood tendency to sunburn, and lifetime number of severe and painful sunburns on the face and arms) to the statistical model did not eliminate the increased risk of BCC associated with sunscreen use: the OR in those who regularly spent time outdoors and did not use sunscreen, relative to those who did use sunscreen, increased only to 0.7 with CI = 0.6-0.8.

Conclusion

The indirect epidemiologic evidence that sun exposure causes skin cancer is strong.

First, within countries covering an appreciable span of latitude, an inverse relationship between skin cancer incidence and latitude, and therefore solar irradiance, has consistently been observed. A similar pattern has not been observed internationally. However, this is not surprising given the difficulties in measuring skin cancer incidence accurately (and therefore reproducibly from one country to another) and the negative confounding that may exist between ethnically determined sensitivity of the skin to the sun and ambient UV irradiance in some regions.

Second, the incidence of skin cancer is substantially lower in migrants from the UK (an area of low solar irradiance) to Australia (an area of high solar irradiance) than it is in persons of similar ethnic origin born in Australia. This difference is not observed in those who migrate to Australia within the first 10 years of life which may suggest that sun exposure in childhood is particularly important in determining subsequent risk of skin cancer.

Third, the anatomic site distribution of skin cancer favors sites that are more or less continuously exposed to the sun when outdoors. In almost all population-based studies, a majority of skin cancers occurred on the head and neck, the most exposed area of the body's surface. Outside of the head and neck, the correlation with exposure is reasonably clear for SCC with the upper limbs the next most frequent site, but less so for BCC which favors the trunk.

Fourth, skin cancer incidence is observed to be less in darker-skinned ethnic groups than it is in those with lighter skins residing in the same geographic area, thus suggesting that pigment that protects the skin from the sun reduces the risk of skin cancer. This suggestion is reinforced by studies of individuals which show that, within populations that are reasonably homogeneous ethnically, risk of skin cancer increases with decreasing pigmentation of the skin and reduced ability to produce a protective tan. In addition, albinos, who lack cutaneous pigmentation, appear to have an increased risk of skin cancer.

Fifth, there is evidence both from the recessively-inherited syndrome, *xeroderma pigmentosum*, and from direct measurement of DNA repair capacity in subjects with and without skin cancer, that a reduced capacity to repair UV-induced DNA damage is associated with an increased risk of skin cancer.

The direct epidemiologic evidence linking sun exposure and skin cancer is much less strong. Contrary to popular belief, the evidence that occupational exposure to the sun causes skin cancer is weak. At the population level, the best-conducted studies which attempted to classify occupational sun exposure on the basis of occupational title found only small differences in skin cancer incidence between outdoor and indoor workers. There have been few well-conducted studies at the individual level and, while most have shown a positive association between some measure of outdoor

work and skin cancer, the relative risks have generally been under 2.0.

The evidence linking measured total sun exposure of individuals to skin cancer is also weak. A majority of studies have not shown a statistically significant positive association of total sun exposure with skin cancer. Those that found the strongest associations did not adjust adequately for potential confounding of these associations by age and gender and are, in consequence, difficult to interpret.

That this direct evidence is weak is not at all surprising. Measurement of lifetime exposure to the sun is very difficult and only two questionnaires[85,98,122] have attempted to measure sun exposure in any detail. Crude measurements of sun exposure are even less likely to be accurate and bias of the relative risk estimates towards unity is probable. In addition, the period of life (childhood, adolescence, adulthood) when sun exposure is most relevant to skin cancer risk is unknown. As a consequence, any measurement is potentially subject to error in the sense that it may not cover the relevant exposure period.

Two additional categories of measurement of sun exposure have been implemented in epidemiologic studies which, while less direct, may be less subject to measurement error. The first, history of sunburn, may be recalled more accurately because it is more salient to the individual but with the possibility of differential recall bias between cases and controls. The second, indicators of benign cutaneous sun damage, do not depend on recall but are made by expert observers or semi-objectively.

The evidence that sunburn is associated with risk of skin cancer is little, if at all, stronger than the evidence for total sun exposure. On the other hand, there is strong evidence linking indicators of cutaneous sun damage with skin cancer. The associations were generally strong and showed a graded relationship between amount of damage and degree of increase in risk of skin cancer. However, while the clinical impression is strong that these indicators of sun damage correlate with sun exposure there is no sound empirical evidence that they can be taken to be surrogate measures of total or any other component of sun exposure.

Taking the indirect and direct evidence together, it is reasonable to conclude that sun exposure causes nonmelanocytic skin cancer. This was the conclusion of an expert working group of the International Agency for Research on Cancer:[21] "There is sufficient evidence in humans for the carcinogenicity of solar radiation. Solar radiation causes cutaneous malignant melanoma and nonmelanocytic skin cancer."

There remain, however, many questions about this relationship, including: Are the relationships between sun exposure and BCC and SCC the same? What is the shape of the exposure-response relationship? What is the quantitative relationship between radiant exposure and incidence of skin cancer? How is the effect of sun exposure modified by, for example, age at exposure, time since last exposure and pattern of exposure (whether, for example, a particular dose is received intermittently or more-or-less continuously)? Does sun exposure contribute to skin cancer etiology in dark-skinned populations and how, in general, does cutaneous sensitivity modify both quantitatively and qualitatively the relationship between sun exposure and skin cancer? Are the associations of red hair and freckling with skin cancer explained by effects of skin pigmentation or sensitivity to the sun or are they mediated by other susceptibility mechanisms? Do pigmentary characteristics or cutaneous sun-sensitivity explain most of the ethnic variation in skin cancer incidence or are there other ethnically related susceptibility characteristics?

Partial answers can be given to some of these questions on the basis of data reviewed here but to none of them can substantial answers be given with any certainty. Such answers will be necessary if the possible consequences of increasing UV irradiance due to stratospheric ozone depletion are to be adequately evaluated and well-formulated advice given to different communities about how to prevent sun-induced skin cancer.

The overwhelming impression given by this review is that the necessary knowledge will not be obtained unless better quality epidemiologic studies are undertaken. There is a need for studies that meet acceptable standards for the design, conduct and analysis of epidemiologic studies. In addition, specific work is required to improve the measurement of key variables such as cutaneous sensitivity to the sun and sun exposure.

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