

The epidemiology of UV induced skin cancer

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Received 8 August 2001; accepted 13 August 2001

Abstract

There is persuasive evidence that each of the three main types of skin cancer, basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma, is caused by sun exposure. The incidence rate of each is higher in fairer skinned, sun-sensitive rather than darker skinned, less sun-sensitive people; risk increases with increasing ambient solar radiation; the highest densities are on the most sun exposed parts of the body and the lowest on the least exposed; and they are associated in individuals with total (mainly SCC), occupational (mainly SCC) and non-occupational or recreational sun exposure (mainly melanoma and BCC) and a history of sunburn and presence of benign sun damage in the skin. That UV radiation specifically causes these skin cancers depends on indirect inferences from the action spectrum of solar radiation for skin cancer from studies in animals and the action spectrum for dipyrimidine dimers and evidence that presumed causative mutations for skin cancer arise most commonly at dipyrimidine sites. Sun protection is essential if skin cancer incidence is to be reduced. The epidemiological data suggest that in implementing sun protection an increase in intermittency of exposure should be avoided, that sun protection will have the greatest impact if achieved as early as possible in life and that it will probably have an impact later in life, especially in those who had high childhood exposure to solar radiation. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Basal cell carcinoma; Squamous cell carcinoma; Cutaneous malignant melanoma; UVA; UVB

1. Introduction

By skin cancer we mean the three commonest types, basal cell (BCC) and squamous cell (SCC) carcinomas of the skin (also referred to, collectively, as nonmelanocytic skin cancer) and cutaneous malignant melanoma (melanoma).

That UV radiation per se causes these cancers is mainly an indirect inference from evidence that exposure to solar radiation, the main source of exposure to UV radiation, is their main cause and the fact that only UV radiation can damage DNA directly. That solar radiation causes these skin cancers is based on a substantial body of indirect and direct epidemiological studies. These studies are strongly supported by experimental evidence of the capacity of UV radiation to cause SCC and melanoma in animal models. There are no such models for BCC, although the presence of UV “signature mutations” in the TP53 gene in a high proportion of BCCs [1] provides biological evidence to support the epidemiological observations.

This paper summarises, the epidemiological evidence, as

it now stands, that sun exposure causes skin cancer and then briefly describes the basis on which a causal role for UV radiation can be inferred from a combination of experimental and epidemiological data. Finally, it describes the key implications of these data for prevention of skin cancer by control of sun exposure.

2. Epidemiological evidence that sun exposure causes skin cancer

2.1. Relationship to ambient solar radiation

2.1.1. Incidence by latitude or estimated ambient solar UV

The relationships between incidence rates of BCC and SCC in 1977–1978 and ambient solar UV across a latitude gradient are illustrated in Fig. 1 based on the data of Scotto et al. [2]. Rates increased with increasing estimated ambient solar UV (from Robertson-Berger meter observations of erythemal UV expressed as annual number of meter counts by 10^{-4}) in ten US metropolitan populations from 47.5° N (Seattle) to 30.0° N (New Orleans). The values of R^2 for the exponential relationships plotted in

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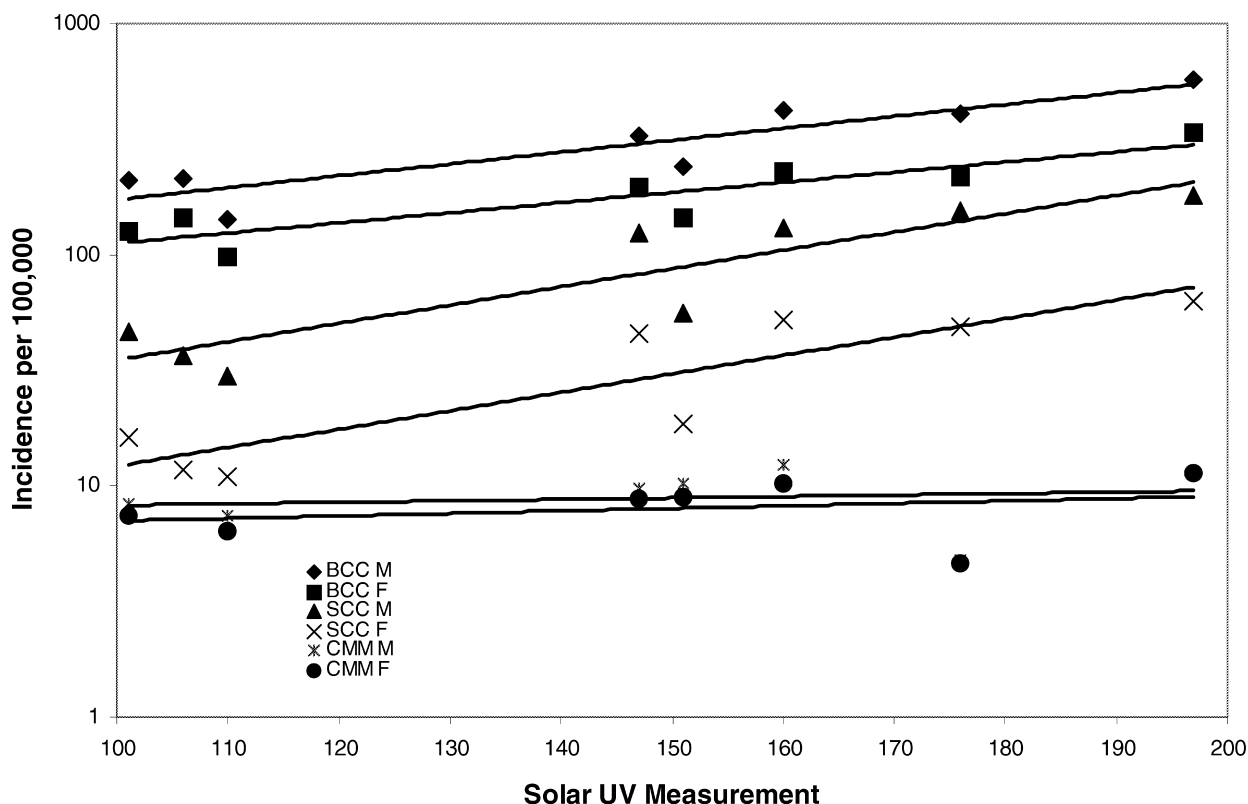


Fig. 1. Relationship of age-standardised incidence rates of BCC, SCC and melanoma (CMM) to estimated ambient erythemal UV radiation in ten US populations (Seattle, Minneapolis-St Paul, Detroit, Utah, San Francisco-Oakland, Atlanta, New Orleans, Albuquerque (New Mexico for melanoma)) in 1977–1978 (BCC and SCC) and 1978–1982 (melanoma) [2,3].

Fig. 1 are 0.81 for BCC in males, 0.80 for BCC in females, 0.82 for SCC in males and 0.78 for SCC in females (R is the coefficient of correlation between incidence and estimated ambient solar UV and takes values from -1 to $+1$, where -1 indicates a perfect negative correlation, $+1$ indicates a perfect positive correlation and 0 indicates an absence of any correlation, and R^2 is an estimate, in this case, of the proportion of variation in each incidence rate that is explained by its association with ambient UV). While the incidence rates in the two sexes were quite different, the slopes of the trends in incidence with ambient solar UV were similar.

By comparison, melanoma incidence rates showed a much shallower trend with ambient solar UV, when rates in 1978–1982 were added to Fig. 1 from Cancer Incidence in Five Continents (Vol. 5) [3] for nine of the ten populations. The R^2 -values were also very low: 0.02 in males and 0.07 in females. However, a much more persuasive relationship was shown in data relating melanoma mortality in 1950–1967 to estimates of annual erythemal solar UV dose across the ten provinces of Canada and the 48 continental states of the USA [4]. The R^2 -values were 0.44 for males and 0.31 for females. In addition, Moan et al. [5] have shown that the slope of the relationship across 30 populations of European origin in ten countries was much steeper if a measure of ambient solar UVA instead of erythemal UV (mainly UVB) was related to melanoma incidence.

Inconsistencies have been observed in these patterns depending on the populations studied, particularly for melanoma. They could be seen as arguing against a relationship of melanoma and solar UV at the geographical level. Alternatively, they may be explained by geographic gradients in ethnic mix of the population or the balance of recreational to occupational sun exposure [6].

2.1.2. Personal residence history and effect of migration

The effect of length of residence in an area of high ambient solar radiation on risks of BCC, SCC and melanoma is shown in Table 1. Here, length of residence is indicated by age at the beginning of residence in Australia, a high ambient solar radiation area. The three studies on which this and several other tables are based were chosen because they were all conducted in the same general area (Western Australia), used similar methods and recorded similar measurements. Risk of each type of skin cancer was less in people who migrated to Australia after birth than in those who were born there, though risk was little if at all less in those who migrated there in the first 10 years of life than in those born in Australia, while it was some three-fold less in those who migrated after the first 10 years of life. These results could suggest, simply, that risk of skin cancer increases with increasing length of residence in an environment with high ambient solar radiation, but they have also been taken to suggest that exposure to solar

Table 1

Relationship of age at arrival in Australia, an area of higher ambient solar radiation than most of the areas from which the migrants came, with risks of BCC, SCC and melanoma [11,12,41]

| Age at arrival in Australia (years) | BCC ^a | SCC ^a | Melanoma |
|-------------------------------------|------------------|------------------|------------------------------|
| Birth | 1.00 | 1.00 | 1.00 |
| 0–9 | 1.05(0.38–2.54) | 0.66(0.07–2.8) | 0.89(0.44–1.80) ^b |
| 10–19 | 0.14(0.02–0.53) | 0.40(0.05–1.6) | |
| 20+ | 0.22(0.11–0.42) | 0.36(0.16–0.72) | |
| 10–29 | | | 0.34(0.16–0.72) |
| 30+ | | | 0.30(0.08–1.13) |

^a The relative risks of BCC and SCC are for migrants other than those of Southern European origin.

^b Relative risk estimates with 95% confidence intervals in brackets.

radiation early in life may be particularly important in increasing the risk of skin cancer [7].

Risk also increased with increasing average annual hours of bright sunlight at all places of residence regardless of migration, but the gradients were generally not as steep as those seen with migration (Table 2). The gradient for SCC appeared to be steeper than that for either BCC or melanoma, which is consistent with the way rates vary across geographic regions in relation to ambient solar radiation (Fig. 1). The rather weaker gradient for BCC, though, is not consistent, but nor is it precise. Lack of a strong correlation between bright sunlight hours and ambient UV radiation could be a cause of inconsistency in these patterns. However, the use of global solar radiation instead of bright sunlight hours in studies of BCC and SCC did not appear to produce any greater consistency [8,9].

2.2. Relationship to cutaneous sun sensitivity

2.2.1. Ethnic origin

The best current comparisons of risk of skin cancer by ethnic origin comes from population-based cancer incidence estimation or registration in multi-ethnic populations in single environments. Rates of BCC, SCC and melanoma are compared between hispanic and non-hispanic whites in New Mexico in Fig. 2. For each cancer in each sex, rates in non-hispanic whites were 5–10 times higher than those

in the darker skinned hispanic whites. More detail is given for melanoma in Los Angeles County in Fig. 3. Again the differential in rates is 5–10-fold between non-hispanic and hispanic whites, and the rates in hispanic whites are twice or more those in blacks and in people originating in China, The Philippines and Japan. The very low rates in the Chinese population are notable and consistent with similarly low rates reported from China itself (0.3–0.4 in males and 0.3 in females) and are not greatly less than those in the Chinese in Singapore (0.6 in both males and females), who live on the equator. Chinese people generally have substantially lighter skin than do US blacks, thus, it appears that their very low incidence of melanoma is not solely related to density of skin pigmentation.

2.2.2. Color of unexposed skin

Recent and comparable estimates of the association between skin colour and risk of BCC, SCC and melanoma are shown in Table 3. The weakest evidence for an increase in risk with increasing fairness of the skin is seen for BCC and the strongest for melanoma. The apparent strength of such associations, however, is influenced by the accuracy of measurement of the “exposure” characteristic, in this case the colour of unexposed skin. Taking the difference between light absorption at 420 and 400 nm is now thought to be preferable to reflectance at 650 nm as an objective measure [10]. Thus measurement error may have contributed to the weaker association of skin colour with BCC.

2.2.3. Propensity to sunburn and ability to tan

Table 3 shows representative and comparable estimates of trends in skin cancer risk with increasing sun sensitivity, as measured by decreasing ability to tan following repeated exposure to the sun in summer. There was a substantial gradient to increasing risk with increasing sensitivity for each of BCC, SCC and melanoma. The steepest gradient was for SCC with a relative risk of 6.9 in people in the most sensitive group. All of these gradients were steeper than the corresponding gradients in risk with decreasing skin colour.

Confounding with sun sensitivity, or whatever the complex of inherited characteristics is that mediates it, is

Table 2

Relationships of average annual daily hours of bright sunlight averaged or accumulated over all places of residence in people born in Australia with risks of BCC, SCC and melanoma [41,8,9]

| Hours of bright sunlight ^a | BCC | SCC | Melanoma ^b |
|---------------------------------------|-----------------|--------------|------------------------------|
| First quarter | 1.00 | 1.00 | 1.00 |
| Second quarter | 0.90(0.50–1.65) | 1.8(0.7–4.5) | 1.34(0.96–1.86) ^c |
| Third quarter | 1.45(0.65–3.24) | 5.2(1.6–16) | 1.92(1.16–3.18) |
| Fourth quarter | 1.47(0.58–3.71) | 3.5(0.97–12) | |

^a For melanoma, the measure was average annual hours of bright sunlight at all places of residence, for BCC and SCC it was accumulated hours of bright sunlight at all places of residence.

^b Accumulated hours of bright sunlight was categorised into thirds for the analysis of melanoma.

^c Relative risk estimates with 95% confidence intervals in brackets.

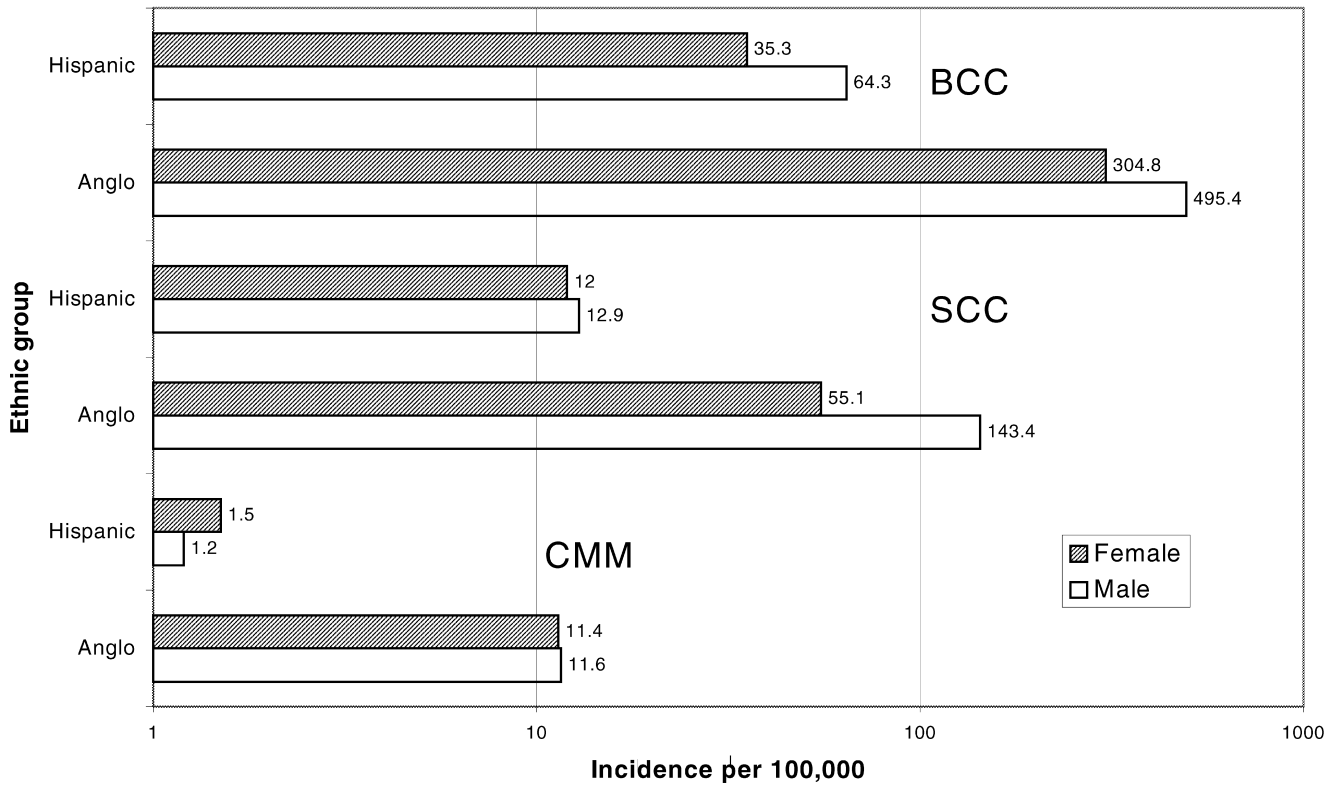


Fig. 2. Relationship of age-standardised incidence rates of BCC, SCC and melanoma (CMM) to ethnic origin in New Mexico, USA, in 1977–1978 (BCC and SCC) and 1978–1982 (melanoma) [2,3].

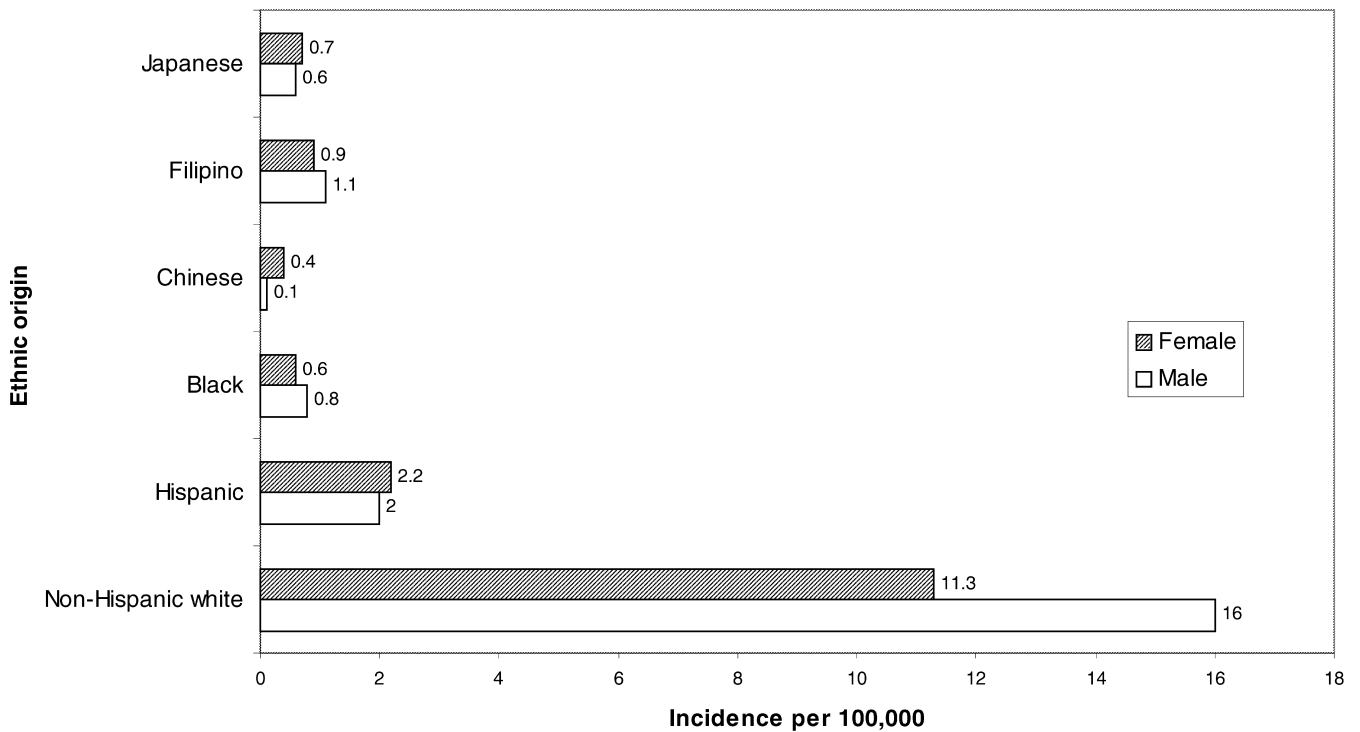


Fig. 3. Relationship of age-standardised incidence rates of melanoma to ethnic origin in Los Angeles County, USA, in 1988–1992 [38]. (The San Francisco Bay Area rates were used for the Chinese population because the Chinese population of that area was appreciably larger and gave non-zero rates).

Table 3

Relationships of colour of unexposed skin and ability to tan with risks of BCC, SCC and melanoma [13,11,12]

| | BCC ^a | SCC ^a | Melanoma |
|---|----------------------------|------------------|---------------|
| <i>Colour of unexposed skin^b</i> | | | |
| Darkest quarter | 1.0 | 1.0 | 1.00 |
| Second quarter | 1.3(0.83–2.0) ^c | 1.6(0.93–2.9) | 1.0(0.7–1.6) |
| Third quarter | 1.0(0.68–1.6) | 1.6(0.93–2.9) | 1.6(0.95–2.7) |
| Lightest quarter | 1.5(0.99–2.4) | 2.3(1.3–4.0) | 3.1(1.5–6.4) |
| <i>Ability to tan</i> | | | |
| Deep tan | 1.0 | 1.0 | 1.0 |
| Moderate tan | 1.9(1.3–2.8) | 2.3(1.3–4.0) | 1.4(1.1–1.9) |
| Light tan | 3.2(2.0–4.9) | 4.6(2.5–8.3) | 2.3(1.6–3.3) |
| No tan | 3.7(1.9–7.3) | 6.9(3.2–15) | 3.5(1.8–6.8) |

^a Estimate for BCC adjusted for age, sex, age at arrival in Australia and Southern European ethnicity, estimate for SCC based on subjects not of Southern European origin and adjusted for age, sex and year at interview.

^b Relative risk estimates with 95% confidence intervals in brackets.

^c Skin colour of melanoma cases and controls was measured by comparison with a grey scale viewed through monochromatic filters; for BCC and SCC it was measured by reflectometry at 650 nm.

usually regarded as explaining the relationship of pigmented variables with skin cancers. When sun sensitivity and skin colour were analysed in a single logistic regression model with hair colour and eye colour, only the ability to tan remained a significant predictor of risk for BCC [11], and ability to tan and tendency to sunburn for SCC [12]. Skin reaction to sun exposure was a strong independent predictor of risk for melanoma in Western Australia [13] and appeared to explain the effect of skin colour and eye colour but not hair colour.

2.3. Distribution on the body

Recent data on the relative density of incident BCC, SCC and melanoma in Queensland, Australia, are shown separately for males and females in Fig. 4. Broadly speaking, relative body density of all three cancers was high on the face and neck, which are more-or-less continually exposed when outdoors, and very low on the scalp in women and the buttocks in both sexes, which are rarely exposed. It was also low on the chest, abdomen and thighs, which are generally little exposed. Outside this broad generalisation, there are some interesting differences in the patterns. SCC stands out with a substantially higher density on the backs of the hands than either BCC or melanoma. These two, however, had similar and quite high densities on the shoulders and back, whereas SCC had a low density on these sites.

Comparing males and females there are also some notable differences. Density of all three cancers was greater on the scalp in men than women, which might reasonably be attributed to loss of hair in men giving rise to increased exposure of the scalp to solar radiation. The same is true when the density on the ears is estimated separately from that on the face (data not shown). Density of SCC and, to a lesser extent, melanoma was higher on the arms and lower legs in women than it was in men,

which may reflect a higher exposure of these sites to the sun in women than men.

These data are then consistent with an effect of sun exposure on risk of all three cancers given the high densities on the usually exposed face and ears and the low densities on the rarely exposed sites. That this effect is not the same for all three cancers, however, is suggested by the differences in density on the frequently but intermittently exposed shoulders and back where the density of SCC is low and the densities of BCC and melanoma are moderate and similar. As noted above, the site distribution of melanoma has been taken to suggest an effect of pattern of sun exposure on its incidence, and the somewhat similar distribution of BCC may indicate a similar effect. Equally, however, it may be a simple dose effect for BCC given its extreme density on the face. The near absence of BCC and melanoma from the backs of the hands has generally been assumed to be due to the nature of the skin rather than to complex effects of sun exposure.

2.4. Relationship to personal exposure to the sun

Because of the evidence that melanoma and possibly also BCC are related to pattern as well as amount of sun exposure, personal sun exposure is now usually represented in three ways: total exposure, occupational exposure (the archetypal example of a more continuous pattern of exposure) and non-occupational or recreational exposure (“intermittent” exposure). In addition, history of sunburn is usually recorded in studies of skin cancer; sunburn is generally thought to be an indicator of high levels of intermittent sun exposure. Each of these may be estimated over the whole or a part of life. When sun exposure occurs in life may also be important [7], but only estimates of lifetime exposure will be considered here.

Our present, best understanding of the relationship between the different types of personal sun exposure and

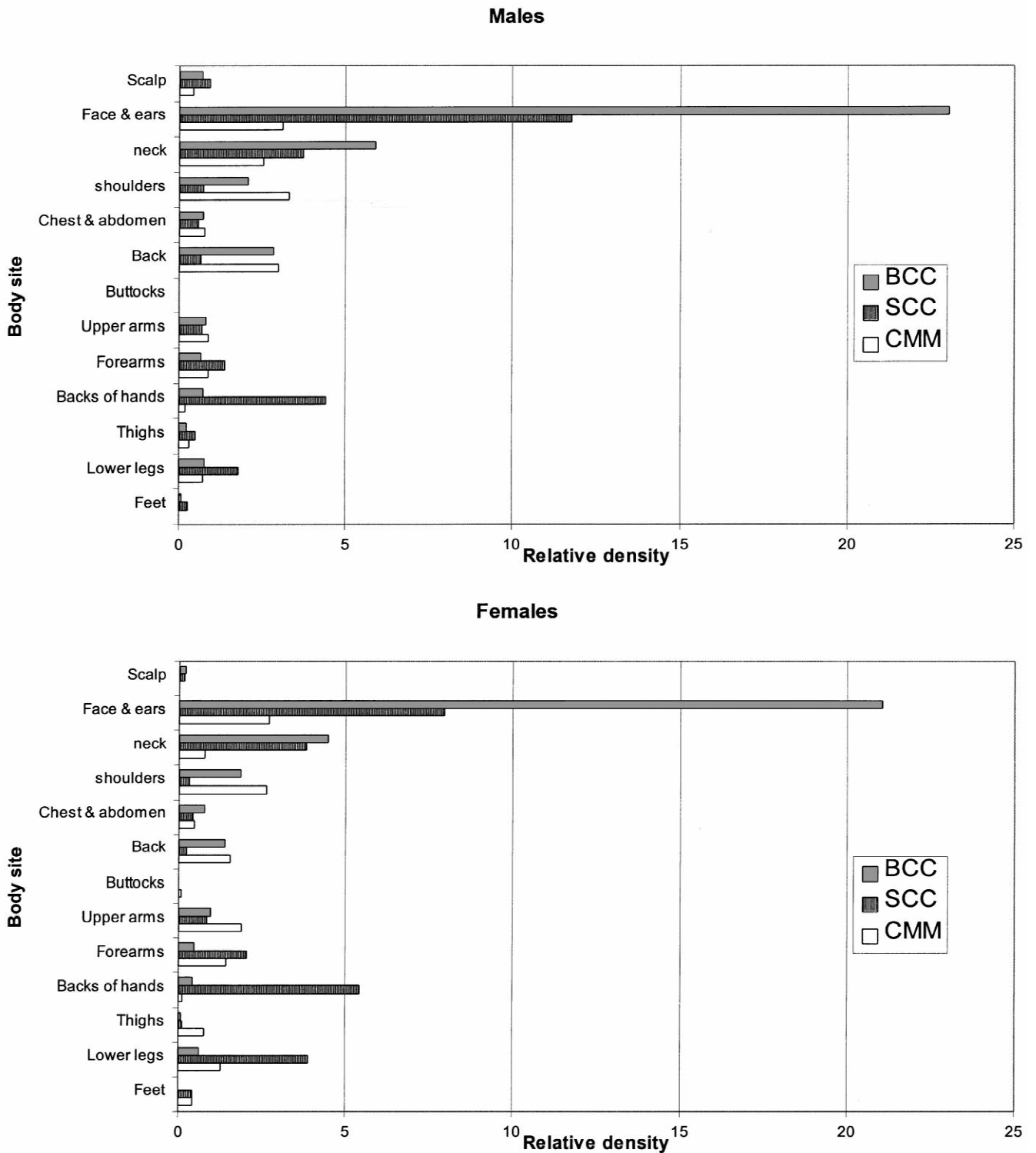


Fig. 4. Relative density (the density on a particular site relative to the density on the body as a whole) of BCC, SCC and melanoma (CMM) on different body sites in Queensland, Australia (prepared from data of Green et al. [39] and Buettner and Raasch [40]).

risk of BCC, SCC and melanoma is summarised in Table 4. This table is based on an overview (metanalysis) of published studies of melanoma prepared by Elwood and Jopson [14] and a similar overview, which we have prepared, of published studies of BCC and SCC. In each

case, the result used in the overview analysis was the published relative risk (odds ratio) for the highest category of exposure documented compared to the reference group chosen by the authors, which was the lowest exposure category in all cases. Where there was a choice of variable

Table 4
Relationships of personal sun exposure with risks of BCC, SCC and melanoma [14]

| Type of exposure | BCC ^a | SCC ^a | Melanoma |
|------------------------------------|------------------------------|------------------|-----------------|
| Total | 0.98(0.68–1.41) ^b | 1.53(1.02–2.27) | 1.20(1.00–1.44) |
| Occupational | 1.19(1.07–1.32) | 1.64(1.26–2.13) | 0.86(0.77–0.96) |
| Non-occupational or “intermittent” | 1.38(1.24–1.54) | 0.91(0.68–1.22) | 1.71(1.54–1.90) |
| Sunburn at any age | 1.40(1.29–1.51) | 1.23(0.90–1.69) | 1.91(1.69–2.17) |

^a Values for BCC and SCC are from an unpublished overview of published studies (see text).

^b Relative risk estimates with 95% confidence intervals in brackets.

for any exposure type, priority for selection was given to variables that represented the nearest to lifetime exposure of that type. For non-occupational or intermittent exposure, the variable likely to represent the most clearly intermittent type of exposure was also sought. Only results that were adjusted for age and sex were used (a number of the early studies of BCC and SCC did not make this adjustment) and results that were also adjusted for some measure of sun sensitivity were chosen where there was a choice.

While none of the associations illustrated in Table 4 are very strong, possibly because of the difficulty people have in recalling past sun exposure accurately and a lack of specificity of measurements for the site of the skin cancer in most studies, they do show a coherent pattern that is consistent with present thinking on differences in the ways in which BCC, SCC and melanoma are related to sun exposure.

First, only SCC is at all strongly related to estimated total sun exposure (RR=1.53, 95%; CI=0.02–2.27). The limited data indicate a weak relationship of total sun exposure with melanoma. While there is little evidence for such a relationship with BCC, the wide confidence interval indicates that it could be at least as strong as that with melanoma.

Second, only SCC shows a strong relationship with occupational sun exposure (RR=1.64, 95%; CI=1.26–2.13). There is a weak, but significant association of BCC with occupational exposure (RR=1.19) but, if anything, the association of melanoma with it is inverse (RR=0.86, 95%; CI=0.77–0.96). While the latter observation might be taken to suggest that risk of melanoma is reduced by occupational sun exposure, to do so would be wrong given the data on which it is based. The reference, low-occupational exposure groups with which the high exposure groups have been compared have probably contained, in most if not all cases, some people with higher levels of recreational sun exposure. Thus, the lower than baseline risk of melanoma in people with high occupational exposure probably reflects simply the association of melanoma with high levels of recreational or intermittent exposure.

Third, both BCC (RR=1.38) and melanoma (RR=1.71) show significant associations with non-occupational (intermittent) sun exposure, while SCC shows no such association (RR=0.91). There is, however, no overlap between the 95% confidence intervals about the relative risks for BCC and melanoma, thus, suggesting that melanoma is

more strongly related to intermittent exposure than is BCC. A similar pattern is seen for sunburn except that SCC shows a weak positive, but not statistically significant, association with sunburn. The patterns for BCC and melanoma can reasonably be taken to support previous inferences that a history of sunburn generally reflects an intermittent pattern of sun exposure. A weak association, such as that seen for SCC, could be due to residual confounding between sun sensitivity and sunburn.

2.5. Association with benign sun-related conditions

Associations of benign sun-related conditions with BCC, SCC and melanoma are compared in Table 5.

Cutaneous microtopography was used in the Western Australian studies as a semi-objective measure of sun damage to the skin of the backs of the hands. In principle, it is a reasonably accurate measure of total sun exposure to these body sites, but it is not highly correlated with histopathological assessment of grade of solar elastosis [15]. Risk of each type of skin cancer was higher in higher-graded categories of microtopography. While SCC appeared less strongly related to microtopography grade than BCC and melanoma, the baseline category used for this assessment was grades 1–4 instead of 1–3 as used for

Table 5
Relationships of benign sun-related conditions with risks of BCC, SCC and melanoma^a

| | BCC | SCC | Melanoma |
|---|---------------------------|-------------------|--------------|
| <i>Grade of cutaneous microtopography</i> | | | |
| 1–3 | 1.00 | 1.00 ^b | 1.00 |
| 4 | 2.6(1.3–4.9) ^c | | 1.6(1.0–2.8) |
| 5 | 3.2(1.6–6.4) | 1.7(0.8–3.5) | 1.8(1.0–3.2) |
| 6 | 3.1(1.5–6.4) | 1.8(0.8–4.2) | 2.7(1.4–5.0) |
| <i>Freckling as a child</i> | | | |
| Yes cf. no | 1.8(1.2–1.5) | 1.6(1.0–2.4) | 1.5(1.2–1.9) |
| <i>Solar keratoses</i> | | | |
| Some cf. none | 3.9(3.0–5.1) | 15.4(8.3–28.8) | 1.9(1.4–2.5) |
| <i>Melanocytic naevi</i> | | | |
| Some cf. none | 1.0(0.8–1.4) | 0.8(0.4–1.4) | 2.7(2.1–3.5) |

^a Sources of results: cutaneous microtopography [41]; freckling [16,17]; solar keratoses [11,18]; melanocytic naevi [11].

^b First category for SCC is grades 1–4, no, mild or moderate damage.

^c Relative risk estimates with 95% confidence intervals in brackets.

BCC and melanoma; thus, the evidence for a difference is weak.

BCC, SCC and melanoma were equally strongly associated with a history of freckling on the face as a child, based on the results of studies conducted by use of common methods and near simultaneously in Western Canada [16,17]. Freckling is almost certainly determined by genetic factors as well as sun exposure and these results could indicate that either or both of these factors are related to all three types of skin cancer.

Presence of solar keratoses, as assessed by dermatologists, on most of the body [11] or just on the left forearm and the face [18], were also associated with all three types of cancer; thus, suggesting that all are related to total accumulated sun exposure. SCC was much more strongly associated with solar keratoses than were BCC and melanoma. In addition to sun exposure being a cause of both solar keratoses and SCC, this may be because a solar keratosis directly precedes some 60% of SCCs [19]. The weaker association of melanoma with solar keratoses than BCC should not be over-interpreted because of the difference between the body sites on which the solar keratoses were measured in the two studies compared; 45% of subjects were in the reference “none” category in the study of BCC and 64% in the study of melanoma.

A similar pattern is seen for the associations with melanocytic naevi (moles) as for solar keratoses except that the strong association was with melanoma, for which melanocytic naevi are precursors, and there was no evidence of an association of melanocytic naevi with BCC or SCC. While there is substantial evidence that melanocytic naevi are caused by sun exposure [20], as well as being strongly genetically determined [21], they probably only reflect sun exposure in childhood. This, together with their strong genetic determination, may make their presence insufficiently predictive of the sun exposure needed to produce BCC and SCC to be a surrogate measure of it.

2.6. Effect of reduction in sun exposure

2.6.1. Population sun exposure

There are no data available on long-term trends in sun exposure in any population. It is difficult, therefore, to draw any certain conclusions about effects of changes in sun exposure from analysis of trends in incidence of skin cancer. There are, however, a few suggestions that recent but poorly documented down trends in sun exposure may have reduced risk of melanoma and BCC, but not SCC.

We have observed down trends in melanoma incidence in New South Wales, Australia, in women 15–49 years of age and men 15–34 years of age over the period 1983–1996, which are consistent with a falling incidence in people born since about 1950, particularly women [22]. Similar trends have been reported from some other populations, mainly in North America and New Zealand. There has been substantial public education in Australia over the

past 20 years regarding the need to reduce sun exposure to protect against skin cancer, and a number of surveys suggest that falls in exposure have followed this education. The falls in incidence of melanoma in younger people in New South Wales are consistent with greater benefit or earlier effects from exposure reduction earlier than later in life and the greater fall in women than men is consistent with greater efficacy of sun protection education in women.

A near identical pattern of trends in incidence of BCC in Australia as a whole has been observed between surveys done in 1985 and 1995 [23] with a fall in rate of BCC in people under 50 years of age, which was greater in the younger than the older age groups in this range and appears to have been greater in women than in men. There was no similar trend in incidence of SCC, which could be a consequence of the differences in the relationship of sun exposure to SCC and BCC and melanoma summarised in Table 5.

2.6.2. Personal sun protection

A number of case-control studies have examined the relationship between sun protection measures, including use of hats, clothing and sunscreen, and risk of BCC, SCC and melanoma. These results, however, are unreliable because of the great difficulty of controlling negative confounding between sun protection and sun sensitivity and sun exposure.

One observational study only, of BCC, might be taken as indicative of a probable effect of sun protection measures in reducing risk. Robinson and Rademaker [24] randomised 61 patients with a past history of two or more biopsy proven BCCs to receive either 10 mg a day of isotretinoin or placebo. All patients were also given written recommendations on sun protection. They had follow-up skin examinations at 6, 12, 18 and 36 months and all clinically suspicious lesions were surgically removed. At the end of the study, all patients completed a questionnaire regarding their sun exposure. Thirty-five patients were classified into a high exposure group and 26 into a low exposure group — people who had changed their sunscreen use since developing a cancer tended to use an SPF 15+ sunscreen and limited their outdoor activities. Those with low sun exposure had, on average, one less BCC before entry to the study than those with high sun exposure (2.5 cf. 3.5). In the first 18 months of the study they had an average of 0.2 BCCs compared with 3.0 in the high exposure group and 1.4 compared with 5.5 in the second 18 months. The level of sun exposure significantly predicted the number of new BCCs ($P=0.02$) independently of number of previous BCCs. While these results suggest a short-latency effect of sun exposure reduction on risk of BCC, a randomised controlled trial of daily sunscreen use in a general population sample in Queensland, Australia, showed no effect on risk of BCC over 4–5 years of intervention and follow-up [25] (see below).

There are two lines of evidence suggesting that reduction in sun exposure by daily use of a sunscreen may reduce risk of SCC. First, two randomised controlled trials have shown that daily use over 6 months (one summer) to 2 years (SPF 17 and 29, respectively) can reduce the rate of appearance of new solar keratoses and, in one of the studies, increase the rate at which existing ones regress [26,27]. Second, and more importantly, a randomised controlled trial of SPF 15+ sunscreen applied daily to skin of the head, neck, hands and arms reduced the numbers of new SCCs that were diagnosed in 812 people randomised to sunscreen over 4–5 years from entry into the study by 39% (RR=0.61, 95%; CI=0.46–0.81) [23].

There is no direct evidence that personal sun protection can reduce risk of melanoma. One randomised controlled trial of SPF 30+ sunscreen use in Vancouver school children, however, has shown that it might reduce the incidence of new melanocytic naevi [20]. A median of 24 new naevi developed over nearly 3 years in 222 children randomised to sunscreen use whenever they were expected to be in the sun for 30 min or more compared with 24 new naevi in 236 children who were not given or directly encouraged to use sunscreen ($P=0.048$). These results suggest that sunscreen use by children could reduce their later risk of melanoma. They say nothing about any effects that sunscreen use by adults might have on risk of melanoma.

3. Evidence that UV radiation per se causes skin cancer in humans

There is no practical way that the action spectrum for skin cancer can be measured directly in humans. Inferences, however, can be made about it in a number of ways.

First, the action spectrum for SCC has been rigorously determined experimentally in albino hairless mice [28]. This action spectrum shows an initial peak at 293 nm in the UVB range, falls to a trough at 354 nm of between 10^{-4} and 10^{-5} of the effect at the peak, rises to another small peak at 380 nm in the UVA range (still nearly 10^{-4} of the UVB peak) and then falls again. The action spectrum for melanoma has been estimated experimentally in a hybrid of two species of tiny fish, which is prone to melanoma [29], and suggests a peak in the UVA in the vicinity of 365 nm that is about a third of the effect at 302 nm in the UVB. A study of the effect of UVA (320–400 nm with peak at about 370 nm) on induction of melanoma in the South American opossum [30] found it to be effective but much less so than would be predicted from the action spectrum in the fish model.

Second, the high proportions of SCCs and BCCs in humans found to have C to T or CC to TT mutations at dipyrimidine sites, the UVB “signature” mutations, in the TP53 gene [1] suggest that the action spectrum for the formation of pyrimidine dimers in humans may apply to these cancers. This action spectrum shows a peak at around

300 nm and effectiveness at 366 nm that is about 10^{-4} of the peak, which is similar to the action spectrum for SCC in albino hairless mice [31]. The evidence that UVB “signature” mutations are also more frequent than expected in the INK4A gene in melanoma suggests a role for UVB in melanoma. These observations in no way exclude a role for UVA in these cancers.

Third, the latitude gradient of incidence of SCC is substantially greater than that of melanoma and, correspondingly, the latitude gradient of UVB is substantially greater than that of UVA [20]. This suggests that melanoma may be less influenced by ambient UVB than is SCC and more influenced by ambient UVA. The latitude gradient for BCC is between the two, but closer to that for SCC than that for melanoma.

Fourth, there is accumulating evidence that use of sunbeds and related devices that produce a tan through controlled exposure to UV increases risk of melanoma [32]. UVA has constituted a much higher proportion of total UV released by these devices relative to that in solar radiation since the early 1980s. Before that, the relative proportion of UVB in the radiation was higher. It will be difficult, though, to interpret these data in terms of the action spectrum for melanoma in the absence of good data that relate relative risk of melanoma quite accurately to the period of use of artificial tanning devices.

While the epidemiological evidence is weak, taken with the experimental evidence it seems probable that UVB is the main cause of SCC. The epidemiological evidence for melanoma, on the other hand, could indicate a greater role for UVA, but the supporting experimental evidence makes this little more than a possibility. It is not possible, on present evidence to draw any conclusion regarding the relative contributions of UVB and UVA to the production of human BCC.

4. Comment

In 1992, an expert working group of the International Agency for Research on Cancer reviewed all the evidence for carcinogenicity of solar and ultraviolet radiation [33]. It concluded that: “*There is sufficient evidence in humans for the carcinogenicity of solar radiation. Solar radiation causes cutaneous malignant melanoma and non-melanocytic skin cancer*”. All the epidemiological evidence that has accumulated since 1992 has strengthened this qualitative conclusion.

While we, like the International Agency, have focused on the qualitative question “Does exposure to solar radiation increase risk of skin cancer?” There are now more quantitative data than in 1992 on the way in which risk of skin cancer increases with increasing exposure to solar radiation. These data have served to strengthen the evidence that BCC and SCC have different exposure–response relationships with sun exposure [8,9,34], as first suggested in limited results published by Strickland et al.

in 1989 [35]. In addition, very limited data on the exposure response relationship for melanoma suggests that it is more like that for BCC than for SCC [36].

Without attempting to argue them in any detail, we believe that the data we have reviewed here, together with these additional quantitative data, permit the formulation of two important hypotheses relevant to sun protection strategy.

The first is that pattern of sun exposure and amount of sun exposure operate as independent determinants of risk of skin cancer. This hypothesis is represented graphically in Fig. 5 and suggests for melanoma, for example, that if pattern is held constant risk increases monotonically with increasing amount of exposure to solar radiation and that if amount is held constant risk increases monotonically with increasing intermittency of exposure. It also suggests that the slope of increase with amount of exposure is greater for SCC than it is for BCC and melanoma, and that the slope of increase with increasing intermittency is greatest for melanoma, less for BCC and zero for SCC. Straight lines have been used for convenience in representing these trends, while the available evidence favours monotonic trends there is no certain basis for believing that they would be arithmetically linear. The possibility of paradoxi-

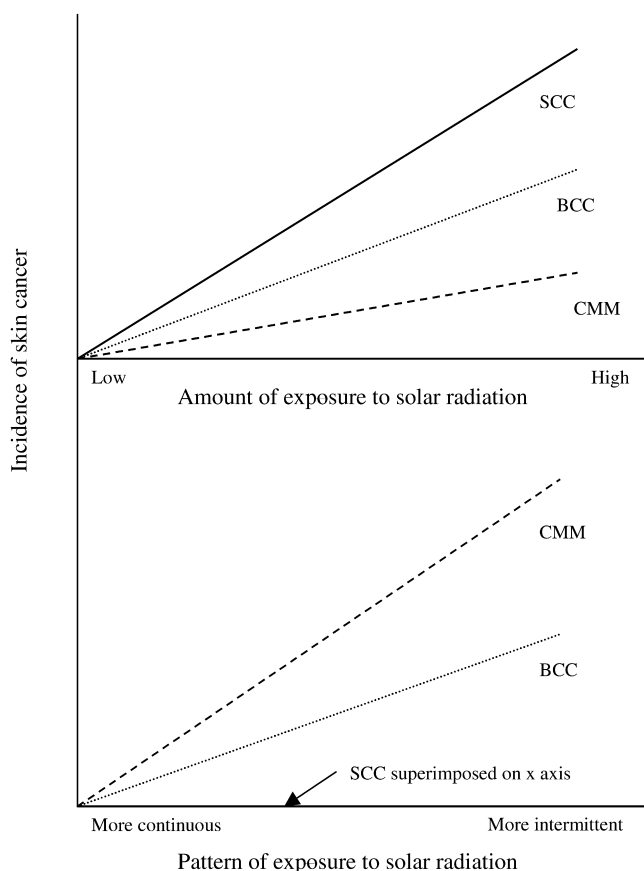


Fig. 5. Illustration of hypothesis regarding independence of amount and pattern of exposure to solar radiation and determining risk of BCC, SCC and melanoma (CMM). In the top panel, amount of exposure varies while pattern is held constant and in the bottom, pattern varies while amount is held constant.

cal increases in risk of melanoma and BCC, but not SCC, with reduction in sun exposure if intermittency of exposure is allowed to increase as exposure falls (e.g., through introduction of sun protection practices at work but their non-adoption in leisure exposure) is the main practical consequence for sun protection of this hypothesis. Indeed, available empirical exposure response relationships for melanoma and BCC, which do not separate amount and pattern of exposure, suggest that a rise in risk would be a consequence of moderate reductions in exposure from a high level [36,8].

The second hypothesis is that the lifetime potential for skin cancer is determined to a substantial degree by sun exposure in the first 10 years of life and the extent to which this potential is realised is determined by sun exposure in later life. The first proposition is based mainly on the migration data summarised in Table 1, which suggest that people who migrate to Australia after childhood, who have historically been ethnically similar to the majority Australian population, have a half or less of the risk of skin cancer as people who migrate earlier in life or are born in Australia. Melanocytic naevi are a potential mediator of this high risk in melanoma, since they develop mainly during childhood, reach their maximum density on the skin at about 10 years of age, are caused by sun exposure, and correlate with a high risk of melanoma [37]. The second proposition is based on the results of observational studies of melanocytic naevi and melanoma, which show short-latency responses to sun exposure that suggest promotion of carcinogenesis [7], and the intervention studies against solar keratoses and SCC, which have shown short-latency responses to reduction in sun exposure [26,25]. If this hypothesis were true, it would suggest that a very high priority should be placed on sun protection in children and that sun protection in later life is also valuable in preventing skin cancer, especially in people who have had heavy exposure to solar radiation in childhood.

While these two hypotheses are useful working hypotheses for sun protection, they are far from being rigorously established, and they probably do not apply equally to all three forms of skin cancer. To establish them rigorously is a major challenge for epidemiology.

Acknowledgements

We thank Chris Goumas for doing the summary analysis of results of studies of sun exposure and nonmelanocytic skin cancer.

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