Sun Exposure, Skin Cancers and Related Skin Conditions

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Skin cancer is the most commonly occurring cancer in humans. Solar keratoses are related benign tumours that are at least ten times commoner than skin cancers and photoageing of the skin is still more common. Descriptive studies show that incidence rates of the main types of skin cancer, basal cell carcinoma, squamous cell carcinoma and melanoma are maximal in populations in which ambient sun exposure is high and skin (epidermal) transmission of solar radiation is high, suggesting strong associations with sun exposure. Analytic epidemiological studies confirm that exposure to the UV component of sunlight is the major environmental determinant of skin cancers and associated skin conditions and evidence of a causal association between cumulative sun exposure and SCC, solar keratoses and photodamage is relatively straightforward. Results for BCC and melanoma are complicated by several factors including the existence of subgroups of these diseases which do not appear to be caused by sun exposure yet have been included in most aetiological studies to date. Complementary to epidemiological data is the molecular evidence of ultraviolet (UV) mechanisms of carcinogenesis such as UV-specific mutations in the DNA of tumour suppressor genes in skin tumours. With increased UV irradiation resulting from thinning of the ozone layer, skin cancer incidence rates have been predicted to increase in the future - unless, as is hoped, human behaviour to reduce sun exposure can offset these predicted rises. J Epidemiol, 1999; 9: S7-S13.

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Skin cancer is the most commonly occurring cancer in humans and the impact on human health is immense, especially in populations of European origin. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are epithelial skin cancers and are the dominant subtypes, while melanomas that arise from the skin's pigment-producing cells or melanocytes are less common though more likely to cause death. The exact magnitude of the epithelial skin cancer problem will always be unknown because many BCCs and SCCs are treated without histological diagnoses and few cancer registries record them. However annual estimates have been made of around one million new cases treated in the USA in 1994 ⁵ and in 1995 in a national survey in Australia, it was estimated that more than a quarter of a million people were treated for at least one BCC or SCC ².

Melanoma burden is more accurately known. Worldwide 92,000 new cases were estimated in 1985 (4% of the combined number of BCCs and SCCs ) ³. These figures are predicted to climb if the stratospheric ozone layer continues to be depleted. The US Environmental Protection Agency estimates that 12 million additional cases of skin cancer will occur in the US in the next 50 years from the current level of ozone depletion ⁴. Besides skin cancer, solar keratoses and premature skin ageing (photoageing) are the other major harmful conditions that result from exposure of unprotected human skin to sunlight. In fair-skinned sun-exposed populations, solar keratoses are about

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10 to 15 times more prevalent that skin cancers, while photoageing is almost universally present by the age of 50 years. Solar keratoses are non-malignant sun-related skin tumours that are an order of magnitude more common than skin cancer. Skin photodamage is even more common: of the estimated $US 14 billion per year spent each year in the United States on cosmetics, a material proportion is intended specifically to conceal the changes of photaged skin. The ultraviolet (UV) radiation spectral regions of sunlight—wavelengths between 280 and 320nm (UVB) and 320-400nm (UVA)—are those specifically implicated in actinic skin damage and carcinogenesis and this paper aims to review their epidemiology and highlight some of the public health issues involved.

**SUN EXPOSURE OF NORMAL SKIN**

A priori, a high UV irradiation of target cells in the skin can only occur when UV transmission through the skin is high. The chief defences of normal skin against UV transmission are thickening and protective pigmentation. Average skin thickness is between 1 and 2mm and it comprises the epidermis, a surface layer containing cells, sweat glands and hair follicles and the dermis, a deeper layer containing elastin fibres and collagen. The outermost layer of the epidermis is the stratum corneum of leathery, impermeable keratin that thickens in response to sun exposure. The keratinising epithelial cells arise in the basal layer of the epidermis alongside melanocytes whose function is to produce melanin pigment, a strong absorber of UV radiation. Variation in degree of melanisation is reflected in innate skin colour differences between ethnic groups as well as variations in tanning response to sun exposure within Caucasians.

Even if UV transmissibility to target cells in the skin is high, target cells in normal skin will not be irradiated to any great extent unless the ambient solar UV radiation is high. Epidemiological studies confirm that white populations who live relatively close to the equator and are exposed to intense sunlight suffer far higher rates of skin cancer than other groups.

**CLINICOPATHOLOGICAL FEATURES OF SKIN CANCERS AND RELATED CONDITIONS**

**BCC**

The basal cell carcinoma, with its great diversity of appearance on the skin from a flesh-coloured lump to a diffuse crusting red lesion, is believed to arise from a stem cell in the basal layer of the epidermis or in adnexal structures. Despite having many mitotic figures microscopically, BCCs are slow to grow and rarely metastasise. While BCCs are most common on exposed areas of skin, the subsite distribution does not reflect sites of maximal UV exposure. An apparent predilection on the head for areas in the fold around and behind the ear, the fold of the inner canthus and around the nostril and occurrence on the trunk may be related to the lines of embryological closure or distribution of sebaceous glands. Several histological subtypes exist, nodular being the most common and superficial next most common, and each of these may have different relationships with sun exposure as described below.

**SCC**

These skin cancers arise from keratinocytes which show some degree of maturation toward keratin formation and thus appear as proliferative lesions which are often red and crusted. They may grow rapidly over several months and there is a risk of metastasis in a proportion of SCCs, especially large or poorly-differentiated lesions. Their site distribution on the body reflects sites of maximal sun exposure and they most commonly occur on the head and neck and forearms and hands.

**Melanoma**

These skin malignancies are usually brown-black in colour reflecting the pigment cell of origin and may be either flat, or raised if dermal invasion has occurred. Conventionally five histological subtypes are recognised, the commonest being superficial spreading melanoma (SSM) accounting for 60-70% of lesions. When surface area is accounted for, the highest incidence of invasive SSM is seen on the ears of men, followed by the shoulders, back and face in men and the face in women. Other notable subtypes are lentigo maligna melanoma, most often seen on the face and neck of the elderly and associated with severe sun damage of adjacent dermal collagen, and acral lentigious melanomas seen on the palms, soles and digits—most common in darkly-skinned populations and proportionately least common in Caucasians.

**Solar keratoses**

Solar keratoses are benign epidermal dysplasias which appear as discrete, variably inflamed, hyperkeratotic lesions. They are often multiple and arise on a background of sun-damaged skin, most frequently on habitually exposed sites such as the face and backs of the hands. It is believed that these lesions are precursors of SCCs because of their close epidemiological and histological similarities, though there is no conclusive evidence of malignant transformation or the rate at which it occurs.

**Photoageing**

Photodamaged skin results specifically from sun exposure, whereas photoageing is strictly defined as the superimposition of photodamage on the chronological ageing process. These terms are however mostly used interchangeably as in this review. Clinically photodamaged skin appears coarse, dry, lax and of a leathery texture due largely to the thickening of the epidermis that occurs on sun-exposed sites. Dermal elastosis
which results from UV-induced changes in dermal elastin is pathognomonic of skin photodamage 12.

**EPIDEMIOLOGICAL OVERVIEW**

Innate skin coloration is fundamentally important in protecting human skin against cancer as seen in its relative incidence within populations of ethnic diversity. Cancer registries in regions like Hawaii, New Zealand and San Francisco report incidence rates of melanoma in dark-skinned inhabitants which are approximately a tenth of the rates of their white-skinned counterparts 13. In Australia, extremes of skin cancer incidence are seen: exceedingly rare in the indigenous population and of epidemic proportions in white Australians. The effects of low versus high ambient UV are also well illustrated in the history and economy of Australia. For example, the comparatively low rates of skin cancer seen among inhabitants of Ireland and Scotland (latitudes of 51° to 59°N) increased dramatically when they migrated to low latitudes and settled in Australia (eg, Sydney at 34° or Brisbane at 27°S) and received around double the annual hours of sunshine. Now the highest skin cancer rates of all are reported in Australia where skin cancer is a major health problem. In the mid-1990s estimated national incidence rates were 788 per 100,000 for BCC and 321 per 100,000 for SCC 2 and 33.5 and 36.7 per 100,000 in men and women respectively for melanoma 14 totalling nearly 7,000 new cases of melanoma recorded annually. This was reflected in the prevailing health costs: of the 10 most expensive cancers in 1993-1994, BCC and SCC together were the most costly around a quarter of the costs of BCC and SCC 15.

Numerous descriptive epidemiological studies of all three types of skin cancer 16 have been highly consistent in confirming that when sun exposure of skin cells is low or absent then cancers, solar keratosis and photoageing rarely develop. Thus skin cancers are rare in innately darkly pigmented Asian or Black populations as seen above, and skin sites that are virtually never sun-exposed like the buttocks are not affected. On the other hand, the converse situations are predictive of risk, eg, BCC incidence rate per unit surface area is some 40 times higher on the face than on the trunk 17. Permanent residents of high latitude regions are protected from skin cancers while populations who migrate from high to low latitudes take on a higher risk 18 19.

Analytic epidemiological studies also show that skin cancer patients share several risk factors pointing to solar aetiology, in particular white skin which tans poorly and sunburns easily because it is unprotected by melanin 16. Moreover different skin cancers tend to occur in the same patients. Those with a history of BCC/SCC are at significantly raised risk of melanoma and vice versa 20 22. More direct evidence of the causal role of solar UV radiation in skin cancer is the extremely high rate at which xeroderma pigmentosum (XP) patients suffer all three types. XP patients inherit a mutation which makes them unable to repair UV-induced DNA damage in their skin cells 23. Their body site distributions of melanoma, BCC and SCC are the same as in the general population.

In addition to this weight of evidence of the sun exposure-skin cancer nexus, recent analytic studies have permitted more detailed appraisal of the association. Meanwhile the results of molecular studies have revealed insights into possible mechanisms of carcinogenesis.

**EPIDEMIOLOGY OF SPECIFIC SKIN CANCER TYPES**

**BCC**

In a large study of population-based study of skin cancer that has been conducted for over a decade in the sub-tropical Queensland township of Nambour (latitude 26°S), the age-adjusted annual incidence rates of BCC in men and women aged 18-69 years in 1986 were 2,074 and 1,579 per 100,000 respectively 24. People with fair skin colour, blond or red hair and a history of multiple sunburns were at significantly raised risk of skin cancer compared with those with dark complexions and no sunburns. Heavy occupational sun exposure was not linked to increase in risk in Queensland however 24, and neither was a high level of overall sun exposure during life based on recall linked to high risk of BCC in a Western Australian study 25. Thus when subjective assessment (recall) of outdoor exposure is used as the measure of sun exposure, the simple relation of BCC with chronic sun exposure appears to waver. Various theories of UV dose-rate dependence have been proposed to explain this apparent lack of association with high outdoor sun exposure such as the intermittent versus continuous UV exposure theory 26. The intermittent exposure theory of BCC may explain some exceptional observations but it is inconsistent with other objective observations of BCC's cumulative UV dose-dependence eg, the strong and highly significant positive association between signs of chronically sun damaged skin (diagnosed by dermatologists) and risk of BCC, controlling for age 26 28.

There are several plausible explanations for some departure from a simple dose-response effect in epidemiological studies of sun exposure and BCC. The first is that not all BCCs appear to be caused by chronic sun exposure. Other risk factors are exposure to ionizing radiation therapy 27 and arsenic 28 29 and possibly some dietary factors 30. It appears to be the superficial histological subtype that has the different aetiology, though only a few studies have examined risk according to subtype and found this 30. Recent work in Australia 30 and the Netherlands 31 showed that superficial BCCs were seen more often in females and in younger patients (the mean age of
superficial BCC patients was 57 years, compared with patients with other types who were almost a decade older on average. Superficial BCCs also differed markedly in their site distribution (23% on the head and neck; 49% on the trunk) from the other types (65% on the head and neck; 20% on the trunk in Australian series [33]). Indeed the superficial subtype appears to have an almost identical site distribution to that of certain types of melanoma 30.

Another reason for inconsistent evidence is the presence of selection bias that distorts any assessment of the effect of outdoor sun exposure. Significant self-selection can be seen among outdoor workers, whereby people with fair complexions and a tendency to sunburn are systematically underrepresented among those in long-term outdoor occupations 36. For instance although they accounted for over 80 percent of the community study sample in the Nambour study fair, sunburn-prone people accounted for only 20% of the persons who had worked in outdoor occupations. That is, in sunny environments people who are at low risk of skin cancer are systematically more likely to gravitate to outdoor work and indeed tend to be affected by skin cancer less than fair-skinned persons without outdoor jobs 36. A further severe limitation is the inability to accurately measure long-term sun exposure in individuals. Recall of the amount of sun exposure experienced through one's life can only be viewed as indicative at best and the scope for misclassification of poorly-defined proxy measures eg. "average number of days spent at the beach annually" is great 36.

At the molecular level, sunlight-induced gene mutations in BCC patients have been found in studies of the mechanisms of their photocarcinogenesis. Since UV radiation causes distinctive mutations in DNA especially CC to TT tandem base mutations 36, these can be tracked in tumour suppressor genes such as p53. Around half of BCCs have been shown to have UV-specific mutations in the p53 tumour suppressor gene 36. As well BCC case subjects have been reported as three times more likely to have a p53 mutation in normal skin taken from the mirror-image site to the cancer site (excluding face and ears) than normal skin taken from a random site in control subjects 36. Frequency of CC to TT mutations (involving codons 247 and 248) did not reflect recalled total UV-radiation exposure however.

SCC

SCC has a far more straightforward relation with chronic sun exposure than the other skin cancers. In the Nambour study there was again no strong or significant association of SCC with outdoor work though the associations with clinical signs of chronic skin damage were clearly seen 36. On the other hand in a recent case-control study of SCC in Western Australia, total site-specific sun exposure based on recall was strongly related to risk of SCC 27. Molecular studies have found UV-mutations in the p53 gene in over 90% of SCCs 36 pointing to a causal link of UV damage to cell-cycle control in squamous cell carcinogenesis. In addition the role of solar-induced deficiency in immune function in the development of skin cancer is probably most prominent for SCC, adding to greater overall dependence of SCC on cumulative UV dose. In transplant recipients SCCs rather than BCCs predominate, a reversal of the usual situation 36.

Melanoma

Ambient sun exposure, when averaged over participants' lifetimes based on residential history, has been positively associated with risk of melanoma in case-control studies 36. Recalled total sun exposure by an individual, taking ambient exposure into account, has a complex relationship to melanoma similar to BCC. Similar explanations pertain, including self-selection bias among outdoor workers and the perennial difficulty in exposure measurement. Sun exposure during childhood rather than over a lifetime has been reported by many to be critically important, though few researchers have examined the association between melanoma and sun exposure in more than one life period at a time. Results of a European study 46 have recently shown that, for a given level of sun exposure in adulthood, the risk of melanoma increased as the level of sun exposure experienced in childhood increased. Although the highest melanoma risk was found among adults who had intense sun exposure as children, only those who experienced high levels of sun as adults as well as in childhood were at significantly increased risk of melanoma.

Also as seen for BCC, there seem to be at least two different aetiological subgroups of melanoma. Recent evidence from two case-control studies conducted in Australia supports the existence of two paths to melanoma, one of which is caused predominantly by sun-exposure and the other linked to people's proneness to develop naevi on their skin. In a case-control study of melanoma in Queensland men over 50 years, the melanomas of cases were classified as p53 positive (based on overexpression of the p53 tumor-suppressor gene) or p53 negative. P53 positive melanomas were twice as likely as p53 negative melanomas to have occurred on the head and neck and legs as on the back or arms. Compared with men having a p53 negative melanoma or men without melanoma, men who had had a past BCC or SCC or whose skins were sun-sensitive were more likely to have a p53 positive lesion 41. In contrast p53 negative melanomas were strongly associated with having a large number of naevi on the skin of the arm, back and shoulders, and with having many freckles as a child. As a follow-up to these results, Bataille et al 46 confirmed an inverse relationship between the number of solar keratoses and the number of naevi among cases of melanoma.

Less common but more easily-identified aetiological sub-
groups of melanoma are lentigo maligna melanoma (LMM) and acral lentigious melanoma. LMM is strongly associated with chronic sun exposure by definition (the pathology includes the presence of solar elastosis in the surrounding dermis) while acral lentigious melanoma occurs on the non-sun exposed skin of soles, palms and digits including subungually. Only two case-control studies have been conducted to investigate the aetiology of the latter group, one in Paraguayans and one in Caucasians. While both studies implicate local trauma and the presence of acral naevi, the study in Caucasians also found significant associations with chemical exposure and unexpectedly with sun-sensitive skin and cumulative sun exposure. The latter suggests the action of systemic mediators of UV-exposure effects in the evolution of acral melanomas.

Solar keratoses

In the Nambour skin cancer study, individual sun exposure was quantified for the first time in relation to the occurrence of solar keratoses (SKs). Individuals with fair skin were at 14 times the risk of SK development than the olive-skinned, and high levels of occupational exposure were strongly and significantly associated with SK prevalence, especially in those people with multiple SKs. There was no consistent pattern of association between recreational sun exposure at any age and SK prevalence, but sunburns were strongly associated with SKs. This suggests that sunburn is a marker, not only of episodic sun exposure, but also of high UV dose at the basal epidermal level (contributing materially to overall cumulative UV dose to the target cells for skin tumours). People who reported even one painful sunburn were six times more likely to have a prevalent SK than people reporting no sunburns.

Photoageing

Cross-sectional studies of photoageing have been undertaken in Queensland and Western Australian study populations using ordinal grading of microscopic evaluation of silicone impressions of the back of the hand and these demonstrated significant associations with skin cancer as noted above. Extensive longitudinal studies have also been conducted in Queensland, to examine among other things, the details of sun exposure in relation to rate of progression of photoageing (Battistutta, unpublished data). A strong log-linear association between degree of photoageing and lifetime sun exposure was confirmed, with the UVA component of sun exposure implicated far more than the UVB component. Lightly pigmented persons photoaged faster than more darkly-pigmented persons over a five year period after adjusting for daily sun exposure hours (Battistutta, unpublished data). A strong log-linear association was also found between degree of photoageing and lifetime sun exposure in relation to rate of progression of photoageing.

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PREVENTION THROUGH SUNLIGHT REDUCTION

Numerous cumulative sun exposure models exist for the incidence of skin cancer and for examining the future consequences of thinning of the ozone layer. For example a model based on the optical amplification factor to assess the increase in cumulative UVB over time, indicates that the incidence of BCCs in Queensland is expected to increase by 9% in males and 7% in females over a 20 year period. SCCs would be expected to rise by 15% in the same period.

Such predictive models are based on the assumption that human behaviour with respect to sun exposure remains constant over time. This is a remarkable assumption because human behaviour is an overriding determinant of skin cancer risk, influencing duration of sun exposure and extent of sun protection practices. Studies among residents of the city of Melbourne, Australia, have shown that knowledge about skin cancer is now generally high and that a favourable attitude to suntans is widespread but is decreasing. People with sun-sensitive skins who are more likely to suffer skin cancers and related actinic skin damage are not surprisingly also the people who take more precautions in the sun. Thus significant changes have already occurred in knowledge, attitude and behaviour towards preventing sunburn. Results from randomised trials of sunscreen are available that suggest that numbers of solar keratoses can be reduced by regular sunscreen application, although evidence from trials of BCC, SCC and melanoma is lacking. Thus there are grounds to hope that through shifts towards sun-reduction and sun-protection behaviour especially among high-risk populations, harmful health effects of sun exposure, especially skin tumours and photoageing, may ultimately be controlled.

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