

British Society for Dermatological Surgery

Undergraduate Essay Prize 2008

Discuss the impact of climate change on skin cancer.

...Daedalus warned Icarus to fly at medium altitude. If he flew too high, the sun could melt the wax of his wings, and the sea could dampen the feathers if he flew too low. Once they escaped Crete Icarus became exhilarated with flight. Ignoring his father's warning, he flew higher and higher. The sun melted the wax holding his wings together, and the boy fell into the water and drowned...

Human beings have worshipped the sun for millennia, yet our relationship with it has always been an ambivalent one. There is no doubt that without UV radiation the beginnings and continued existence of life on earth would be impossible, and like any drug UV light has its own therapeutic window: beneficial in a wide range of conditions, not least in the production of essential vitamin D3, but an overdose may prove fatal. In the UK someone dies of skin cancer every four hours (British Association of Dermatologists) and malignant melanoma is increasing faster than any other human cancer. It is responsible for an estimated 1800 deaths per year in UK ,and 7500 in the US, more than double the figures of 20 years ago. {{169 Agnew, K.L 2005;}} and it is estimated 1 in 35 Australians will be diagnosed with melanoma by the age of 75. In Scotland the incidence reportedly trebled between 1979 and 2003 {{161 MacKie,R.M. 2007;}}. The combined incidence of non-melanoma skin cancers (NMSCs), namely squamous cell carcinoma (SCC) and basal cell carcinoma (BCC),is 18-20 fold greater than that of melanoma incidence is also increasing. In

1994 squamous cell carcinomas (SCC) alone accounted for 2500 deaths in the US, and although not fatal and difficult to quantify BCC is the most common malignant neoplasm in white populations, affecting 2% of Australian males. Unfortunately epidemiological data on NMSCs in the UK is difficult to estimate accurately due to exclusion of NMSC from most skin cancer registries, and few if any cancer registries record subsequent lesions once the first BCC has been registered. Yet, it is more than likely the workload generated by these lesions is consistently underestimated, relevant when it comes to allocating resources and training dermatologists!

The sun's ambiguous role in health has also long been recognised. The Hippocratic doctors regarded heliotherapy as a panacea against a pantheon of human ailments, not only correctly recognising its particular value in healing fractures of the bone but also for a cure for complaints from asthma to elephantiasis {{178 Muller, I 1997;}}. Yet they also warned of excess that might provoke a blockade by thickening of the phlegma.

Evidently our understanding of molecular events has increased greatly in recent years, but arguably we are still struggling to strike the right balance in our relationship with the sun. Fashion of the middle ages held pallor in much higher esteem, perhaps due to its association with persons of rank, as opposed to those who would work outside. The medical benefit of sunbathing returned in the 19th century but the current cosmetic preference of a tan probably became fashionable in the mid 20th century, perhaps as it represented wealth but via the implication of increased leisure time and

foreign holidays. Some have even suggested it was the fashion diva Coco Chanel's accidental acquiring of a tan on the French Riviera that led to the tan's new identity from 1960s on. It may have also represented a newfound liberation for women who could embrace their freedom to take part in outdoor pursuits. Whatever the case, the cosmetic and behavioural trends of today seem to be still pushing towards increased sun exposure in pale-skinned Caucasians. Despite the recent promotion and uptake of fake tans among women, there has not been a backlash against the desirability of a tan itself. This trend, as opposed to climate change itself, coupled with the colossal increase in overseas holidays taken by the British that in the future poses the greatest impact on trends in skin cancer in the UK. Whether there will be a reversal of the trend is to be seen. However if trends continue they will only be compounded by the predicted changes in climate, which is expected to lead to an increased frequency of extreme temperature events and high summer temperatures will become more frequent in the UK. This in turn is presumed to influence human exposure by encouraging people to spend more time in the sun in this country, and thus be exposed to more UV light and more skin cancers, in a pattern reminiscent of Australia and to a lesser extent New Zealand where ozone degradation has led to increased penetration of harmful UVB.

This hypothesis assumes climate change will create a hotter environment, yet not so hot it encourages people to seek shade; evidence collected by Hill and Boulter in Australia showed that although likelihood of sunburn doubled when ambient temperatures were 19-27°C, as opposed to 18°C or lower (the typical average summer temperatures in UK) temperatures above 27°C saw a fall in sunburn as people sought

shade for comfort. An alternative climate change hypothesis, such as that postulated by Al Gore in his film *An Inconvenient Truth*, predicts that global warming may lead to melting of the polar ice caps and so the cooling of the Gulf stream and a subsequent descent into the next Ice Age for Northern Europe. However, this theory will be also conveniently overlooked for the purposes of an essay on skin cancer.

Climate change and increased exposure to ultraviolet radiation

Climate change may increase exposure to UV in 3 ways: through (1) increased UV radiation reaching the earth due to stratospheric ozone depletion, in particular UVB and UVA, (2) due to the increase in temperatures accompanying global warming having a synergistic effect with UVB light and (3) increase in ambient temperature leading to increased exposure via greater sun-seeking behaviour and/or time spent outdoors. Ozone (O₃) itself is noxious and its existence in the troposphere (the air which we breathe) is deleterious to health, contributes to global warming, and may even stunt plant photosynthesis and growth. However 10-50km above the Earth's surface in the stratosphere ozone absorbs parts of the UV spectrum less than 320nm, comprising the all the UVC and most UVB part of the spectrum. From the 1970s the ozone layer began to be depleted, particularly over the poles, via chlorine and bromine particles. The source of these halogen atoms has been mainly from the photo-dissociation of chlorofluorocarbons (CFCs), used as refrigerants, propellants and cleaning solvents and other haloalkane compounds. Since the Montreal Protocol (1987) on Substances That Deplete the Ozone Layer hailed by Kofi Annan as "perhaps the single most international agreement to date, the atmospheric concentration of CFCs has levelled off and it is estimated that the ozone layer will

recover to its 1980 status by 2050. However, this recovery may also be slowed by climate change itself, indeed a 2001 report by NASA reported the ozone hole as being the same size as ever{{173 Anonymous ;}}.

Nevertheless, evidence continues to appear showing the rate at which ozone is being destroyed in the stratosphere is slowing{{155 Diffey,B. 2004;}} . Predictions from the United Nations Environment Programme (1998) however do not seem to reflect UV monitoring on the ground and it has been suggested that solely relying on the Montreal Protocol and not the subsequent stricter Copenhagen Amendments would see a runaway increase in skin cancer incidence, up to a quadrupling and doubling, respectively, by the year 2100. {{175 Slaper,H. 1996;}} By contrast, the Copenhagen Amendments scenario would lead to an ozone minimum around the year 2000, and a peak relative increase in incidence of skin cancer of almost 10% occurring 60 years later. These results demonstrate the importance of the international measures agreed upon under the Vienna Convention. Thus, assuming compliance with these protocols *and* no interactions between ozone depletion and global warming, there will be only small changes in ambient U.V. as caused by ozone depletion in the future.

This stability is questioned by an interesting analysis of animal studies by van der Leun and de Gruijl who suggest that an increase in temperature may actually increase the carcinogenic effectiveness of solar UV by 10%. Given that it is estimated skin cancer increases in a quadratic manner with UV, the synergistic interaction could lead to an increase in skin cancer in the UK from an estimate 5000 to 6000 cases per year by 2050 {{155 Diffey,B. 2004;}}.

UV's role in carcinogenesis

The role of UV radiation in photocarcinogenesis is two-fold. It causes damage to DNA, and hence mutations in genes that regulate cell growth, including proto-oncogenes (*RAS* family) and tumours suppressor genes (e.g. p53, p16, PTCH gene). Secondly it has an immunosuppressive effect on the skin which may favour tumour survival. UVB is more photocarcinogenic than UVA, photon for photon, but UVA is more abundant in sunlight.

When UV photons are absorbed by DNA distorted linkages form, most commonly between two adjacent pyrimidine bases. The photoproduct that accounts for 85% of DNA lesions after UV radiation is the cyclobutane pyrimidine dimer. If not repaired, this may lead to a point mutation in DNA because DNA polymerase is unable to interpret the altered bases and inserts the wrong “partner” in the new complementary strand. A defect in the repair mechanism of thymidine dimers, as seen in young adults with xeroderma pigmentosum, increases the incidence of melanoma by 1000 times, but with the same anatomical distribution{{176 Menzies,S.W. 2008;}}. Nucleotide-excision-repair enzymes avert tumor formation by repairing these, but there is evidence that this repair mechanism declines with age – in part explaining the exponential rise of all skin cancers with age. The mechanism of UV-induced immunosuppression is poorly understood despite extensive study. It may be that sunlight causes cells to release cytokines that alter the antigen presenting function of Langerhan's cells. It may also generate potent suppressor or regulatory T lymphocytes preferentially to T helper cells.

Non-melanoma skin cancers (NMSCs) and melanoma have very distinct pathologies. The former are malignancies of the epidermal keratinocyte, whereas melanoma is a cancer of the melanocyte, and although UV exposure plays a major role in each, and fair skinned, freckled, red haired people are most at risk for all types, the patterns of exposure are also quite different. The link between sunlight and NMSCs is generally more compelling than that for myeloma; in part due to the fact that BCC and SCC occur on areas regularly exposed to the sun (hands, face, neck) whereas melanoma tends to affect the trunk (men) and legs and back (women) Whereas NMSCs are associated with chronic exposure, melanoma seems to be associated with intermittent burning and childhood exposure. Reasons for these differences might be found in how the different cells respond to exposure: melanocytes produce melanin and distribute it to surround keratinocytes where it can absorb photons that might damage DNA or cell membranes. When skin is irradiated with UV melanin production increases and so does the capacity for DNA repair so it is thought that skin cells are most vulnerable after periods of sun avoidance where the melanin content and DNA repair capacity are low. Add this to the increased resistance to UV induced apoptosis in melanocytes and it is easy to see why they are more likely to survive damaging exposures – rather than undergo apoptosis which occurs in suprabasilar keratinocytes from which SCC develop. It is thought basal cells have a resistance to apoptosis between melanocytes and suprabasilar keratinocytes and so BCC is caused by both by chronic and intermittent exposure.

It is speculated there may be that there are at least 2 divergent pathways to melanoma: those induced by chronic exposure which have a preferential head and neck site, association with a history of NMSC and no mutation in the BRAF gene (which controls the proliferation of melanocytes) and fewer naevus counts, and those by intermittent exposure, which are related to naevus density, BRAF mutation, and preferential trunk site. UV is needed to induce BRAF mutations found in melanoma and naevi but other factors may also be necessary {{176 Menzies,S.W. 2008;}}. Of the melanoma subtypes, sun exposure is implicated in at least two thirds. An important caveat is the case of acral lentiginous melanoma, which accounts for 2% of melanomas in white populations but is the most common in black populations, and people from S.E. Asia and the Indian subcontinent. It occurs on palms and soles or the feet or beneath the nail plate and is unlikely this is related to sun exposure.

Other Risk Factors

BCC is associated with albinism, xeroderma pigmentosum, nevoid BCC syndrome (Gorlin's syndrome) and HIV, exposure to arsenic, and previous radiotherapy. SCC risk factors include history of severe sunburn, sunbed use, 200+ treatments with psoralen and UVA phototherapy (PUVA, e.g. for psoriasis), and especially chronic immunosuppression, e.g. from alcoholism, HIV, chronic lymphatic leukaemia and organ transplantation – indeed much of the research between immunosuppression and SCC has been performed in the organ transplant population. The ratio of BCC to SCC (usually 4:1) is reversed in this population. One might speculate on the impact of increased organ donation through adopting an opt out scheme, such as that seen in Spain or Norway, might have on the incidence of SCC. Exposure to human papilloma virus, arsenic, and polycyclic hydrocarbons, and any genetic risk factors with the

“guardian of the genome” p53 will also predispose to this cancer. Invasive SCC is recognised to develop from actinic keratosis as well as at sites of chronic injury such as ulceration, infection, and scars. The role of HLA phenotypes, in particularly HLA-DR4 found in increased frequency among Celts, could provide an independent risk factor for skin cancer in addition to skin type and might provide interesting avenues for further research. {{35 Low,Russell N. 2007;}}

Use of Sunscreen

Paradoxically, the preventative measure of using sunscreen has been associated with an increase risk of melanoma in several case-control studies although the conclusions of the International Agency for Research on Cancer to evaluate data concluded sunscreens probably prevent SCC when used during unintentional sun exposure, but no conclusion can be drawn about the preventive activity against BCC and cutaneous melanoma {{155 Diffey,B. 2004;}} . The reasons for these observations is not completely understood and may well be the victim of both negative and positive confounding i.e. vigilant sunscreen users may also stay in the shade and wear protective clothing or conversely those most at risk of burning are most likely to use sunscreens. Other likely possibilities are that it encourages people to stay in the sun longer, and insufficiency amounts may be applied, and areas may be missed. {{156 Autier,P. 2007;171 Diffey,B. 2001;172 Lautenschlager,Stephan ;}} What remains however is the impact of this research on public health campaigns such as SunSmart which would be advised to place greater emphasis on suitable clothing and seeking shade and application of sunscreen, rather than its use exclusively.

Surprisingly, there is still some controversy over the causation of melanoma, with some dermatologists arguing that the reported increase in melanoma is an erroneous reclassification of benign naevi {{177 Shuster,S. 2008;}}. To give this argument much credence would be exceptionally dangerous and threatening to current public health messages. It has also been suggested that a shift in public health messages in sun exposure is needed because of vitamin D deficiency from not enough sun, and that increased exposure might reduce incidence of prostate, colon, and breast cancer; this argument is undermined when it is pointed out that Australians should have a lower incidence of these cancers, which they categorically do not. {{174 Diffey,B. 2006;}}. Diffey does concede however that a more relaxed approach to adventitious sun exposure, say at lunchtimes only, could be adopted by dermatologists given that harmful effects are largely the result of high dose-rates during recreation.

Impact of human behaviours

Despite the changes in UV exposure that will probably be seen with climate change, the greatest impact on skin cancer has been and will continue to come sun seeking behaviour. Although the UK itself does not have UV levels comparable to Australia as yet, the increasing ease and availability of overseas holiday has led to a 7-fold increase in the number taken by British residents between 1971-98, with the most rapid increases to long haul destinations at low latitudes where UV levels are high already and it is expected that this level recreation, longevity and hedonism is set to continue. Furthermore, sunbeds in current use in the U.K. carry a cancer risk comparable to Mediterranean sunlight. This is due to the use of new high power lamps, and it has been revealed new British and European standards are being largely

ignored with more than four out of five sunbeds exceeding the limit specified in the standard. {{154 Oliver,H. 2007;}} This makes for a strong case for greater regulation of sunbed operators coupled to improved public education. Regarding education about the dangerous of exposure to UV, a 1999 survey from the office of national statistics revealed 64% of respondents had heard of the global solar UV index, mainly through weather forecasts. Although only 7 % could interpret the meaning (it is the estimate of the average maximum solar UV at the earth's surface, its intensity varies throughout the day and with cloud cover but reaches a maximum at midday) it nevertheless encouraged greater sun protective measures.

In Australia primary prevention programmes have been aimed at reducing the desire for a tan and subsequent overexposure to sunlight. Although implicit messages in women's magazines seem to undermine health messages, argues Helen Dixon, with most models portrayed outdoors were not in shade and the proportion wearing hats declined between 1987 and 2005. {{168 Dixon,Helen 2007;}} Secondary prevention (early detection) programmes have encouraged people in the community to seek early attention if they notice a new or changing pigmented lesion. {{165 Marks,R. 2002;}} In the younger cohorts--groups that it has been possible to influence by public health campaigns in recent decades--both incidence and mortality rates are dropping. {{157 van der Leun,J.C. 2008;}}, and this suggests that the deleterious effects of increased UV exposure can be overcome via public health campaigns . Trends in fashion remain to be seen and it is conceivable that there may be a retreat from the fashion for a "healthy tan" as awareness is increased via public campaigns such as Sunsmart, or simply if there is a trend in concepts of beauty towards paler skin in Caucasians again.

If, as both a cause and effect of climate change, air travel becomes too expensive and inaccessible getaways to sunnier climes may become less attractive. Whether or not UV exposure in the UK reaches the levels of Australia with the threat of global warming is yet to be seen, but the main impact on skin cancer for the foreseeable future will be trends in human behaviour and whether as those at threat heed the warning not to fly too close to the sun.

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