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The consequences for human health of stratospheric ozone depletion in association with other environmental factors

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Due to the implementation of the Montreal Protocol, which has limited, and is now probably reversing, the depletion of the stratospheric ozone layer, only modest increases in solar UV-B radiation at the surface of the Earth have occurred. For many fair-skinned populations, changing behaviour with regard to exposure to the sun over the past half century – more time in the sun, less clothing cover (more skin exposed), and preference for a tan – has probably contributed more to greater levels of exposure to UV-B radiation than ozone depletion. Exposure to UV-B radiation has both adverse and beneficial effects on human health. This report focuses on an assessment of the evidence regarding these outcomes that has been published since our previous report in 2010. The skin and eyes are the organs exposed to solar UV radiation. Excessive solar irradiation causes skin cancer, including cutaneous malignant melanoma and the non-melanoma skin cancers, basal cell carcinoma and squamous cell carcinoma, and contributes to the development of other rare skin cancers such as Merkel cell carcinoma. Although the incidence of melanoma continues to increase in many countries, in some locations, primarily those with strong sun protection programmes, incidence has stabilised or decreased over the past 5 years, particularly in younger age-groups. However, the incidence of non-melanoma skin cancers is still increasing in most locations. Exposure of the skin to the sun also induces systemic immune suppression that may have adverse effects on health, such as through the reactivation of latent viral infections, but also beneficial effects through suppression of autoimmune reactivity. Solar UV-B radiation damages the eyes, causing cataracts and pterygium. UV-B irradiation of the skin is the main source of vitamin D in many geographic locations. Vitamin D plays a critical role in the maintenance of calcium homeostasis in the body; severe deficiency causes the bone diseases, rickets in children and osteomalacia in adults. Although many studies have implicated vitamin D deficiency in a wide range of diseases, such as cancer and cardio-vascular disease, more recent evidence is less compelling, with meta-analyses of supplementation trials failing to show a beneficial effect on the health outcomes that have been tested. It continues to be difficult to provide public health messages to guide safe exposure to the sun that are accurate, simple, and can be used by people with different skin types, in different locations, and for different times of the year or day. There is increasing interest in relating sun protection messages to the UV Index. Current sun protection strategies are outlined and assessed. Climatic factors affect the amount of UV radiation

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received by the skin and eyes, separately from the effect of ozone depletion. For example, cloud cover can decrease or increase the intensity of UV radiation at Earth's surface and warmer temperatures and changes in precipitation patterns may alter the amount of time people spend outdoors and their choice of clothing. The combination of changes in climate and UV radiation may affect the number of pathogenic microorganisms in surface waters, and could have an impact on food security through effects on plant and aquatic systems. It remains difficult to quantify these effects and their possible importance for human health.

Introduction

Stratospheric ozone limits the amount of biologically damaging UV radiation in the UV-B waveband (280–315 nm) that reaches the Earth's surface – a 1000-fold reduction in mutagenic UV radiation.[1] Depletion of the ozone layer results in greater potential exposure to UV-B radiation, while, for humans, actual exposure also depends on their behaviour, such as time spent outdoors, use of shade, and wearing of sun protective clothing. Global climate change is altering the recovery of the stratospheric ozone layer and, through effects on cloud cover, will modify the levels of UV radiation at Earth's surface (for detail, see Bais *et al.*[2]). Loss of snow cover will decrease albedo in mountain regions, possibly reducing UV radiation incident on body surfaces. Changing climate may also alter human behaviour with regard to exposure to the sun. Warmer temperatures may accelerate the genesis of skin cancer and vitamin D production. In the following sections, we assess the health risks associated with ozone depletion, focussing on effects related to UV radiation in the UV-B wavelengths. In addition, the risks and benefits of changing personal exposure to UV radiation under the combined effects of ozone depletion and global climate change are considered.

Effects of solar UV radiation on the skin

Human skin comprises an outer thin epidermis of about 10 cell layers and typically <100 μm deep and an inner layer, the dermis, that consists mainly of connective tissue and gives skin its mechanical properties. Epidermal cells are mostly keratinocytes, with melanocytes in the basal layer producing melanin that determines pigmentation of the skin. UV radiation is absorbed in the skin by specific molecules called chromophores, with the ensuing chemical changes initiating multiple biological processes. UV-A radiation (315–400 nm) penetrates the skin to a greater depth (into the dermis) than UV-B radiation. Exposure to solar UV radiation may cause skin cancer and photo-ageing, but also initiates the synthesis of vitamin D, which is critical for human health.

Skin cancer

Solar UV radiation is the major environmental risk factor for both melanoma and non-melanoma skin cancers (NMSCs).[3] Cutaneous malignant melanoma (CMM) is the least common of the skin cancers, but accounts for most deaths due to skin cancer. NMSCs include basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and other rarer skin cancers. BCC occurs approximately 3–4 times more frequently than SCC. It has the lowest mortality rate but can cause significant ill-health due to extensive local invasion, particularly when it arises on the face.

It is difficult to assess whether, or to what level, alterations in ozone or climate have contributed to the rising incidence of skin cancer globally. Over the 20th century, increasing travel to sunny locations and changed styles of clothing, at least in some populations, have led to higher personal exposure to the sun. This has probably been a more important driver of the increasing incidence of skin cancer than changes in ozone or climate.[4] Changes in the diagnostic criteria for skin cancers, including the use of dermoscopy or epiluminescent microscopy and molecular classification,[5] a lack of accurate recording of lesions, and a more general growing awareness of skin cancer and conservatism (erring on the safe side) in diagnoses,[6] may also have introduced temporal biases in some instances.

Cutaneous malignant melanoma

Geographic variation and temporal trends in incidence and mortality. World-wide, it is estimated that there were around 230 000 new cases of CMM and 55 000 deaths in 2012.[7] The incidence varies widely from country to country (Table 1), with the highest age-standardised annual incidence rates (~35 per 100 000 population in 2012) in Australia and New Zealand.[7] CMM is rare in darker skinned populations, such as in South Asia.[8]

The incidence of CMM in fair-skinned populations has approximately doubled every 10–20 years since the 1960s and this trend is projected to continue for at least 20 more years[9] (Table 1).

The rise in incidence of CMM has been attributed to changes in recreational behaviour leading to increased exposure to the sun.[12] The incidence rate has stabilised or is decreasing in younger age groups (<44 years) in some countries, such as Australia,[9] but continues to increase elsewhere.[13,14] Public health campaigns to encourage protection from the sun, beginning in the 1980s, have probably contributed to the decrease in incidence in younger age groups in Australia.[15]

Although CMM accounts for only 4% of all skin cancer cases, it is responsible for about 80% of deaths from skin cancer.[9] Mortality due to CMM is increasing in Southern and

Table 1 Illustrative examples of the change with time in the age-standardised (World Standard Population) incidence of CMM in men and women (per 100 000 population)

Country	Year	Incidence	Year	Incidence	Year	Incidence (projected)	Year	Incidence (projected)
Men								
Denmark[a]	1990	10.0	2007	16.0	2010	16.0	2015	18.0
England[a]	1990	4.6	2006	10.7	2010	12.2	2015	14.5
Spain[a]	1990	3.1	2004	8.1	2010	8.1	2015	9.3
Netherlands[a]	1989	7.4	2007	13.6	2010	15.1	2015	17.5
Australia[b]	1990	31.1	2000	38.3	2012	40.5	—	—
New Zealand[c,d]			1998–2002	34.8	2012	39.2	—	—
Canada[c,d]	1988–1992	7.7	1998–2002	10.9	2012	10.4	—	—
USA[c,d]			1998–2002	15.1	2012	16.8	—	—
Women								
Denmark[a]	1990	12.8	2007	19.5	2010	21.1	2015	24.4
England[a]	1990	6.0	2006	12.3	2010	14.2	2015	16.9
Spain[a]	1990	3.6	2004	9.5	2010	9.5	2015	10.7
Netherlands[a]	1989	10.7	2007	17.3	2010	19.0	2015	21.9
Australia[b]	1990	25.0	2000	28.8	2012	30.0	—	—
New Zealand[c,d]			1998–2002	31.4	2012	33.1	—	—
Canada[c,d]	1988–1992	6.9	1998–2002	9.3	2012	9.1	—	—
USA[c,d]			1998–2002	11.4	2012	12.6	—	—

[a] Data from ref. 10. [b] Data from www.aihw.gov.au. [c] Data from ref. 7. [d] Data from ref. 11.

Eastern Europe,[16,17] particularly in elderly men who tend to have thicker lesions that are more invasive and less likely than the thinner lesions to respond to treatment.[18] Here, the increase in deaths is probably due to the rising incidence of CMM. Mortality due to CMM is stable or decreasing in Australia,[19] some parts of the USA,[13] and Western Europe,[20] with this decrease likely due to earlier detection of the tumours, possibly as a result of more self-awareness of risks of skin cancer in subgroups of the population.

Anatomical location. In fair-skinned populations, melanomas in older people occur predominantly on the head and neck and are associated with chronic cumulative exposure to the sun. In younger people, the lesions most frequently occur on the trunk and extremities, thought to be the result of high overall exposure to the sun, episodes of sunburn in childhood, and the presence of multiple or atypical naevi (moles).[21] The trunk is the site where the greatest increase in the number of cases in both sexes over the past 30 years has occurred,[22,23] likely reflecting the increase in intermittent high dose exposure leading to sunburn as a result of wearing clothes with less coverage of the skin, and increased travel to sunny climates.[24]

Melanoma in deeply pigmented skin. There is a paucity of information about the incidence, or any change in incidence, in CMM in population groups with darker skin. The risk of CMM is estimated to be around 20-times lower in Black compared to White Americans.[25] A recent study in the North-East USA found no increase in the annual incidence of CMM in Hispanics and non-Hispanic Blacks since 1992, but a 4% increase in non-Hispanic Whites.[26] In contrast, there is evidence of increasing incidence of CMM in Hispanics from California between 1988 and 2001.[27] Darker-skinned people are more likely than those with fair skin to have advanced CMM at diagnosis in the USA[26] and in Brazil,[28] with a reduced chance of survival. The lower limb and/or hip is the commonest site for CMM in the dark-skinned populations of South Africa (around 70% of CMM) and Kenya (75%),[29] particularly the sole of the foot.[29,30] As these body sites are not normally UV-irradiated, direct exposure to the sun is unlikely to be a risk factor, although UV-induced systemic effects could be involved.[31]

Exposure to the sun as a causative factor in melanoma. Exposure to the sun is a key risk factor for CMM.[32,33] Incidence is greater at locations closer to the Equator (more UV radiation) in fair-skinned populations.[9] For example, in 2012, the age-standardised incidence (World Standard Population, per 100 000) was 35.8 in New Zealand and 34.9 in Australia, compared to 14.6 in the UK and 9.6 in Canada.[7] Epidemiological studies have shown an increased risk of CMM in people who self-report higher levels of sunburn, and in those with phenotypic characteristics associated with greater sensitivity to UV radiation, including fair skin, light hair and eye colour, poor ability to tan, freckling, and having multiple naevi (moles). Childhood exposure to the sun may be particularly important; for example, migration from a high to a low latitude location before age 10 years[34] or 20 years[35] confers a greater risk of melanoma than migration at an older age.

Recent experimental studies indicate that both UV-A and UV-B radiation are involved in the development of CMM.[36] Initiation of melanoma following UV-A irradiation involves oxidative damage to DNA and requires the presence of melanin, whereas UV-B-induced melanoma is independent of melanin and involves direct UV-B-induced damage to DNA.[36] A two-hit model proposes that initiation of the tumour follows DNA damage induced by UV radiation, and then progression to melanoma depends on the host's genetic make-up

(particularly for melanoma of the trunk) and/or tumour promotion by ongoing exposure to both UV-A and UV-B radiation.[37]

There is growing interest in the effects of exposures in early life on the risks of diseases that develop later in life. One indication that exposure early in life is important for melanoma comes from observations that, in predominantly fair-skinned populations, people with the disease are more likely to have been born in particular months of the year, compared with the general population. In two studies, young women (aged 15–24 years) with CMM from northern England[38] and Sweden[39] were significantly more likely to have been born in March (early Spring). The data are consistent with the two-hit model suggested in animal studies[37] – early exposure to UV radiation during the months soon after birth initiates the first event, then later exposure causes progression to CMM. It is interesting to note that, in the past, exposure of infants to sunlight was encouraged in some countries, a practice that has not continued in more recent years.[40–43]

The higher incidence of small (<2 mm) melanomas during summer compared to winter in Northern Ireland (1984–2006) is consistent with exposure to UV radiation having a short-term promotional effect on melanocytes.[44]

Genetics of cutaneous melanoma. Susceptibility to CMM is partially determined by genetic factors (reviewed in Eggermont *et al.*[5] and Nikolaou & Stratigos[12]). A family history of CMM confers a two-fold increase in risk.[45] Alternatively, in approximately 10% of people with CMM, there is a strong family history,[46] associated with specific mutations in genes involved in control of the cell cycle (*e.g.*, *CDKN2A*, *CDK4*). Increased risk in association with polymorphisms in other genes, including those associated with fair-skin phenotype (*MC1R*)[46] and characteristic UV-induced cytosine to thymine (C → T) mutations in the tumour-control pathways,[47] provide strong evidence of a causal role for UV radiation in the development of CMM. Very recently, further experimental corroboration for the involvement of UV radiation in accelerated development of melanocytes has been obtained.[48] Most strikingly, recent studies show that melanomas (and cell lines thereof) have more mutations in their genomes than most other tumour types, *e.g.*, more than 30 000 point mutations per cell, and hundreds of mutations in protein-coding genes. Tumours from sun-exposed skin have the greatest number of mutations, most of which are characteristic of those induced by exposure to UV radiation.[49,50] It is difficult to distinguish causative from incidental mutations, but special intron–exon comparative analyses provide evidence of likely causative mutations that are related to UV radiation.[47]

Non-melanoma skin cancer

Geographic variation and temporal trends in incidence. BCC and SCC are the most frequently occurring cancers in fair-skinned populations. However, establishing accurate incidence data, and comparing incidence rates between countries or regions, or over time, is challenging for several reasons. First, these cancers may be treated using destructive therapies without prior biopsy, and such clinically-diagnosed lesions, particularly BCC, are often not included in estimates of incidence.[51] Differences in therapeutic approaches between countries or changes over time can therefore have a considerable influence on comparisons and trends. Secondly, there are very few regions that require mandatory reporting of NMSCs to cancer registries and population-based studies are rare. Thirdly, most reports are person-based rather than lesion-based so they do not account for the multiple lesions often observed in people living at lower latitudes; and lastly, variability in the population used to age-standardise incidence rates makes reported results difficult to compare.

Despite these difficulties, there is a strong association between intensity of ambient UV radiation and incidence of both BCC and SCC.[52] In a recent review, the highest annual incidence rates were in Australia (>1000 per 100 000 population for BCC) and the lowest in Africa (<1 per 100 000 population).[53] Data for the latter are sparse and the low incidence masks relatively high incidence in some sub-populations, for example among people with oculocutaneous albinism (OCA) [see section below], and in Caucasians in South Africa, where BCC and SCC are typically among the top 5 or 10 cancers reported (depending on year).[54]

There have been substantial increases in the incidence of NMSC over the past several decades. Across Europe, the annual incidence of BCC was estimated to be around 50 per 100 000 persons in 1980.[53] It has more than doubled since then in many parts of this region, and has quadrupled in the Netherlands.[55] The incidence of SCC was approximately 10 per 100 000 persons in Europe in 1980[53] with an increase to about 25 per 100 000 by 2000.[53] There are no estimates of SCC and BCC separately for the United States, but a study of a study of data from national Medicare claims suggests that the age-adjusted rate of procedures for skin cancer increased by 77% between 1992 and 2006.[56]

A recent quantitative review of data published between 1979 and 2012 showed that, in fair-skinned populations worldwide, after adjustment for age, sex, and the levels of ambient UV radiation, the average annual increases in SCC and BCC incidence were 4% and 1%, respectively.[52] The incidence of SCC increased over time in both the older (≥60 years) and younger (<60 years) age groups, but only in the older age group for BCC.

Exposure to the sun as a risk factor for non-melanoma skin cancer. As the studies showing latitudinal variation suggest, exposure to solar UV radiation is the primary cause of BCC and SCC; almost 40% of the variability in incidence in SCC and BCC in populations of predominantly European ancestry could be explained by differences in the average daily levels of ambient UV radiation alone.[52] Nevertheless, evidence suggests that the timing and patterns of exposure to the sun that give rise to the two tumour types are different. SCC appears to be strongly associated with cumulative exposure to the sun. In fair-skinned people, SCC is rare on parts of the body that are not routinely exposed to the sun[57–59] and the presence of actinic keratoses, which are a marker of cumulative exposure

to the sun, confers a 30–40-fold increase in the risk of SCC.[60] In contrast, BCC appears to be caused by intermittent exposure to the sun;[61,62] up to 25% of BCCs occur on the trunk or lower limbs[59] and the association with actinic keratosis is considerably weaker than for SCC.[63] However, some studies have found no difference in the pattern of exposure in relation to the risk of BCC and SCC,[64] possibly because the risk factors for BCC vary according to the site and/or subtype of BCC. For example, chronic exposure to the sun may be more important for nodular BCC commonly found on the head and neck, and intermittent exposure to the sun more important for superficial BCCs that have a tendency to occur on the trunk.[65] It is of interest to note that there is a 3-fold increased risk of developing CMM after either SCC or BCC, even after adjustment for the self-reported reaction of the skin to chronic exposure to the sun.[66] This may indicate risk factors in common between the NMSCs and CMM, *e.g.*, susceptibility of specific skin phototypes, and excessive (intermittent) exposure to the sun.

Non-melanoma skin cancer in more deeply pigmented skin. There have been few studies of incidence of NMSCs in dark-skinned populations.[53] Data collected by the National Cancer Registry of South Africa in the early 2000s indicated that the annual age-standardised incidence (per 100 000) of reported SCC was 4.6, 7.0, 41.5 and 101.3, and of reported BCC was 4.7, 13.0, 85.7 and 311.1 in the Black, Asian, Coloured and White population groups respectively.[30]

The epidemiology, clinical presentation, and prognosis of NMSC differ between people with fair skin and those with darker skin. For example, in several studies, SCC was more common than BCC in those with deeply pigmented skin[29,67] and these tumours typically arose in sites of chronic inflammation or scarring, so that solar UV radiation may not be the major risk factor.[31] In contrast, the site-distribution of BCCs is similar in fair- and dark-skinned populations, occurring predominantly on the head or neck, suggesting that exposure to UV radiation is an important risk factor.

Over time, there has been little increase in the incidence of NMSC in Asian populations and almost none in dark-skinned populations (reviewed in Agbai *et al.*[31] and Gloster & Neal,[68]). However, mortality and morbidity from NMSC is disproportionately high in dark-skinned populations in comparison with incidence, due to diagnosis occurring at a more advanced stage, atypical presentation, lack of screening, and socio-economic factors.[31] Public health education regarding protection against the sun and self-awareness, tailored appropriately for each population group, should be expanded to include people of all skin types.[69]

Genetics of non-melanoma skin cancer. Common variants in several genes influence the risk of BCC, including those in known pigmentation genes.[70,71] In addition, there are rare genetic disorders in which NMSCs arise at a young age and incidence is dramatically increased. For example, incidence of skin cancer in people under the age of 20 years is increased 10 000-fold in patients with xeroderma pigmentosum, a disorder where the repair of UV-induced DNA damage is severely impaired.[72]

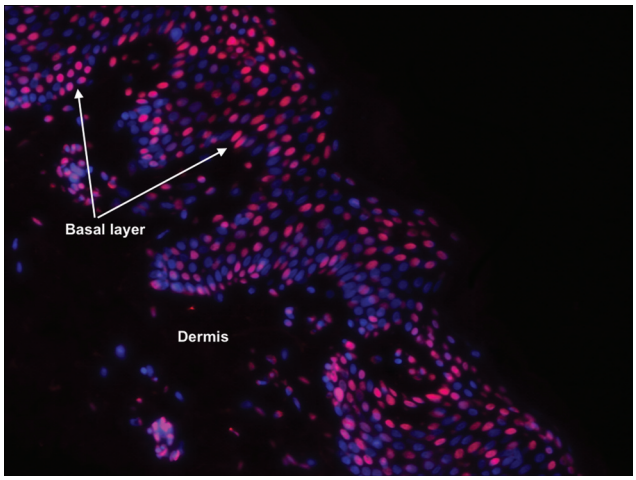

Fig. 1 Human skin shows cyclobutane pyrimidine dimers (CPD, red nuclei) when a biopsy is taken immediately after 4 standard erythema doses of simulated solar radiation. Note the presence of CPD in the epidermal basal layer that contains stem cells and that CPD are also present in the dermis. Photograph provided by Professor Antony Young, Faculty of Life Sciences and Medicine, Kings College London, UK.

SCCs and BCCs are the cancers with the highest mutational loads (33 and 76 mutations per million DNA-bases, respectively), especially those from skin regularly exposed to the sun.[73,74] The majority of these mutations bear the "UV signature" (cytosine to tyrosine transitions at cyclobutane pyrimidine dimers, CPD, Fig. 1). Both BCC and SCC show UV-signature mutations in tumour suppressor genes (*PTCH1* and *p53* respectively),[74–76] suggesting these are key abnormalities driving the development of these tumours.[77] These genetic studies clearly indicate the causal role of exposure to UV radiation in the development of NMSC.

Skin cancer in oculocutaneous albinism. Oculocutaneous albinism (OCA) refers to a group of congenital developmental disorders in which there is either partial or complete lack of melanin in the skin, hair and eyes.[78] The number of melanocytes is not reduced, but there is decreased or absent production of melanin due to mutations in genes in the melanin biosynthetic pathway.[78] The four major types (OCA1, 2, 3 and 4) are present at different frequencies in various populations throughout the world; for example OCA2 is the most common type in sub-Saharan Africa.[78] Globally, about 1 in every 17 000 people have OCA (with about 1 in 70 people carrying the OCA gene),[79,80] but this figure can be considerably higher, such as 1 in 3900 in South Africa.[81]

People with OCA experience visual impairment including photophobia (discomfort from exposure to light, leading to avoidance).[82] They are also highly susceptible to skin damage induced by solar UV radiation and it has been estimated that the risk of NMSC in people with OCA in Africa is one thousand times greater than that of the general population.[83] In most instances, the skin cancer occurs at 20–30 years of age, which is considerably younger than in those without OCA.[84] Cutaneous tumours in Africans with OCA are predominantly

SCCs, with BCCs less frequent, and CMMs only occasionally seen,[85,86] although the last may be under-reported as they are normally amelanotic (non-pigmented).[87] Most commonly, the skin cancers in Africans with OCA occur on the head and neck and tend to progress rapidly with metastasis to the cartilage, bone, and muscle, resulting in high mortality.[84,88] The key role of exposure to the sun in the oncogenic process is emphasised by finding an increased frequency of skin tumours and lower life expectancy in people with OCA living in equatorial regions of sub-Saharan Africa than in parts further from the Equator.[84]

Viruses and skin cancer

There are two instances (see following sections) where an association between certain viruses and skin cancer has been demonstrated. In both cases, the tumours occur predominantly on body sites most exposed to the sun, suggesting that exposure to solar UV radiation is likely to play a crucial role in the carcinogenic process.

Merkel cell carcinoma and polyomavirus. Merkel cell carcinoma (MCC) is a rare, aggressive, neuroendocrine skin cancer with high rates of recurrence, metastasis, and mortality.[89] It mainly affects fair-skinned, elderly people (peak age around 75 years) or those who are immunosuppressed, particularly if they live in a sunny location.[89] The tumours occur most frequently on sun-damaged skin on the head and neck.[90] There is a positive correlation between ambient levels of UV radiation and age-adjusted incidence of MCC across the USA.[91] The incidence has risen in recent years, for example, from 0.15 cases to 0.44 cases per 100 000 between 1986 and 2001 in the USA.[92] This could be explained by increasing life expectancy, greater exposure to the sun and the rising number of immunosuppressed people in the general population as a result of an increasing number and range of organ transplants[93] and infection with HIV.[89]

Merkel cell polyomavirus is present in around 80% of MCCs. The viral DNA is integrated into the host DNA and is thought to cause cancer after genomic mutations that eliminate its ability to replicate but maintain its oncogenic function (reviewed in Arora *et al.*[94]). Exposure to UV radiation may play a role in the integration or mutagenic processes (for example, Demetriou *et al.*[95] and Mogha *et al.*[95,96]) or in suppression of the immune response to the virus.[97]

Squamous cell carcinoma and papillomaviruses. Human papilloma viruses (HPVs) can infect the squamous epithelium of the skin and may play a causative role in the development of cutaneous SCC. There are many types of HPVs; phylogenetic analysis describes 120 different types across 5 genera.[98] Several studies have found that the presence in serum of antibodies to the beta or gamma HPV types is associated with an increased risk of SCC.[99–101] Furthermore, people with SCC have higher levels of beta HPV DNA in hair follicles of the eyebrow (used as a marker of infection) than controls without SCC.[102] The beta and gamma HPV types code for proteins that affect the normal controls of the cell cycle and may also subvert the normal immune response. The mechanism by which various types of HPV might influence the risk of cutaneous SCC is unclear, but is most likely through potentiating the effects of exposure to UV radiation.[103]

Photoageing

Chronic exposure to solar UV radiation results in photoaged skin, which is wrinkled, leathery, shows loss of elasticity, and is often associated with the development of SCC. Photoageing results from the UV-induced degradation of proteins such as collagen and elastin in the extracellular matrix of the dermis. UV-A radiation may be primarily responsible for chronic photoageing, given its greater depth of penetration.[104] In addition, a role for UV-B radiation is indicated. First, UV-B radiation can directly degrade some proteins, such as fibrillin and fibronectin, involved in maintaining the structure of the dermis.[105] Second, the action spectrum for the induction of matrix metalloproteinase (an enzyme that degrades collagen) in human skin is similar to that for erythema (reddening of the skin, inflammation), suggesting that this is primarily an effect of exposure to UV-B radiation.[106] While not a risk to health *per se*, photoageing of the skin incurs considerable costs through the use of cosmetic and hydrating agents to improve the appearance and feel of the skin.

Melasma

Melasma appears as dark, macular, pigmented patches on the brow, cheek, upper lip and jaw, and is due to a localised increase in melanin production.[107] It can result in profound emotional and psychological stress, significantly reducing quality of life.[108] Melasma is particularly common in adult women living in tropical areas of the world and occurs more frequently in individuals with skin types of intermediate pigmentation (*i.e.*, types III–V) than in those with fair (skin types I and II) or very dark skin (skin type VI).[107,109] Its prevalence has been estimated as 3.4% in the general population in Beirut, Lebanon, 10.1% in Cuzco, Peru,[107] 34% in adult women in Botucatu, Brazil,[110] and 40% in adult women and 20% in adult men in South-East Asia.[111]

The precise pathophysiology of melasma is unclear, but is known to be complex. There is a genetic predisposition and several environmental triggers, one of which is exposure to sunlight. For example, a report from Tunisia indicated that 51% of patients recognised exposure to the sun as a triggering factor and 84% as an aggravating factor, with high lifetime exposure to the sun increasing the risk of severe melasma three-fold.[112] A case-control study in Brazil found that patients with melasma had a greater number of years of seaside or rural residence and greater exposure to the sun at work or during leisure than the controls; there was a lack of association with sunburn, implying that cumulative exposure to the sun may be more important than acute exposure.[109] Solar UV radiation can induce proliferation and migration of melanocytes[113] and the production of several cytokines that increase the production of melanin. In addition, inflammatory cells, especially mast cells, which produce a variety of potent pro-inflammatory substances, are likely to play key roles.[114]

Effects of solar UV radiation on the eye

The eye is partly protected from direct UV radiation by the brow ridges. This means that reflected radiation is likely to contribute more to the total UV radiation received than occurs for the skin. Higher intensity UV radiation induces the most damage, although less intense exposure over a long period also increases the risk of disease. Transmission of UV radiation through the eye (Fig. 2) generally decreases with increasing age, but there is wide inter-individual variability.[115] The cornea filters out wavelengths less than about 280 nm, although this is relevant for artificial sources only, as sunlight at the Earth's surface is confined to wavelengths >290 nm. There is further absorption in the aqueous humour (Fig. 2). The lens of a young child (*e.g.*, <5 years) transmits close to 100% of the visible light spectrum (wavelength >400 nm), but absorbs UV radiation, except for a small window at 320 nm.[116] The lens of an older person (*e.g.*, 60+ years) commonly filters out even some of the short blue visible light (400–500 nm) so that this, and UV radiation of shorter wavelengths, do not reach the retina.

Exposure to UV radiation increases the risk of a number of ocular conditions, with the strongest evidence of a specific effect of UV-B radiation for photokeratitis, pterygium, and cataract.

Photokeratitis and photoconjunctivitis

Exposure of the eye to high-dose UV radiation from the sun can result in inflammation of the cornea (photokeratitis) and/or conjunctiva (photoconjunctivitis) (Fig. 2). The maximum sensitivity is to the UV-B wavelengths.[117] The damage is probably caused by oxidative stress,[118–120] with the squamous cells of the epithelium of the cornea, the keratocytes of the stromal layer of the cornea, and the endothelial cells lining the back of the cornea, being affected.

Transmission of UV radiation decreases across the cornea from the centre to the periphery, due to scattering and absorption.[121] The centrally located endothelial cells receive a higher dose of UV radiation, and show evidence of higher oxidative stress than cells in the periphery. It is the damage to these central corneal endothelial cells that particularly causes corneal swelling and temporary loss of vision in UV-induced photokeratitis.[121]

Pterygium

Pterygium, a wing-shaped invasive growth of the conjunctiva (Fig. 3), is common in adults living in environments with high UV radiation. For example, it affects at least one eye in approximately 10% of: adults (≥15 years) on Norfolk Island, Australia;[122] south Indians (≥40 years) in Chennai, India;[123] and indigenous people (≥40 years) in Central Australia.[124] Some recent studies show that the prevalence of pterygium increases with increasing age and is more common in men than women,[123] but the increase with age is not consistently found.[125] Key risk factors for pterygium are greater time outdoors (including sports with high ocular exposure to UV radiation, such as surfing[126]), rural residence, having a skin type that tans[122] and non-use of spectacles.[123] Of note, the only study that has examined the risk of pterygium in association with wavelengths of solar radiation other than those in the UV range (using retrospectively reconstructed exposure behaviour during working hours) found a stronger association with visible light, and a weaker but still significant association with UV-B radiation.[127] Recent evidence suggests that a pterygium

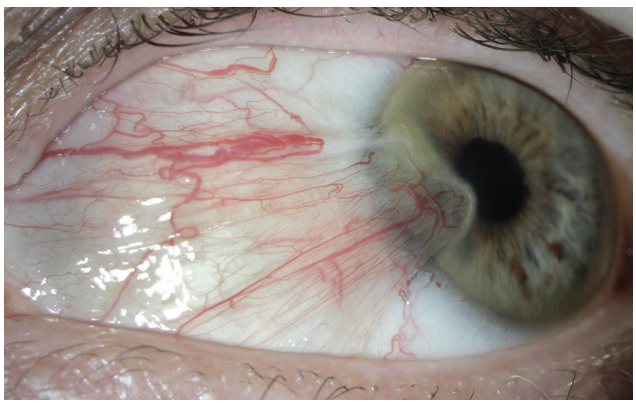

Fig. 3 Pterygium of the eye; photograph provided by Dr David Mackey, University of Western Australia, Perth, Australia.

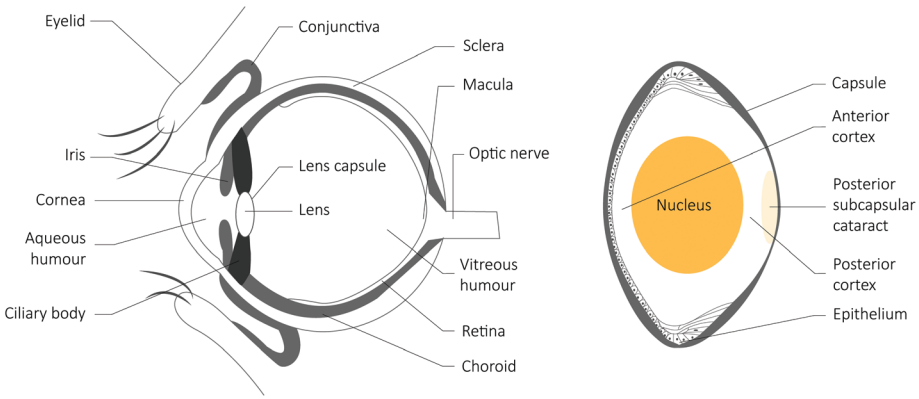

Fig. 2 A schematic drawing of a section through the human eye, with an enlarged schematic of the lens to the right.

is not always benign: there is histological evidence of inflammatory and dysplastic changes in the epithelium and underlying connective tissue,[128] and of neoplasia in 2–10% of excised pterygia.[129,130]

Squamous cell carcinoma of the cornea and conjunctiva

Squamous cell carcinoma of the cornea and conjunctiva (SCCC) is rare; the annual incidence in the USA is estimated to be 0.84 per 100 000 population.[131] The incidence is higher in men, and in association with older age, residence at lower latitude, infection with HIV, and high exposure to UV radiation.[131] Infection with HPV and exposure to UV radiation may be common risk factors for pterygium and SCCC.[132]

Cataract

In 2010, cataract was the leading cause of blindness worldwide.[133] Of the three main types of age-related cataract – cortical, nuclear, and posterior subcapsular (Fig. 2) – UV radiation is primarily linked to an increased risk of cortical cataract.[134]

The action spectrum for acute/short term cataract development is relatively consistent across animal models, with UV-B radiation of shorter wavelengths being most damaging.[135] However, these models have limited relevance for cataract formation in humans because of wide inter-species variation in the dose of UV irradiation required,[136] and the typical use of a single very high dose, rather than repeated lower doses. Melanin in pigmented irises may absorb UV radiation, leading to fewer cataracts in those with more pigmented, than less pigmented, irises.[137] Lenses in older individuals may be more susceptible to UV-induced cataracts due to poorer defence against oxidative damage and decreased repair mechanisms.[138–140]

In the large Salisbury Eye Evaluation Study with participants aged 65–84 years, the incidence and progression of cortical cataract (but not nuclear cataract) were associated with higher levels of estimated exposure to UV-B radiation (calculated based on an empirical model incorporating self-reported time outdoors and use of protection from the sun).[141] In contrast, in the 15 year follow-up of participants in the Beaver Dam Eye Study,[142] there was no association between exposure to the sun (as measured by residential history) and cumulative incidence of any type of age-related cataract, after controlling for age and sex. However, the combined use of sun-sensitising medications and high exposure to the sun led to a significantly increased risk of cortical cataract.[142]

Ocular malignancies

There is strong evidence to support exposure to UV radiation as a risk factor for tumours of the eyelid and weaker evidence for ocular melanomas (reviewed in Yam and Kwok[143]). Over 90% of the malignancies of the eyelid are BCCs, particularly affecting the lower lid (50–65%), but also the medial canthus (inner corner of the eye, 25–30%), upper eyelid (15%) and lateral canthus (outer corner of the eye, 5%).[143] SCC accounts for most of the remainder of the periocular cutaneous tumours.[143]

Melanomas of the eye can involve the surface (*i.e.*, the eyelid or conjunctiva), or occur at an intra-ocular location, affecting the elements of the uvea (*i.e.*, the iris, ciliary body, and choroid; Fig. 2). Uveal melanoma is the most common primary intraocular malignancy (>90%) and the leading cause of death from intraocular cancer.[144,145] The reported annual incidence varies from 0.53 to 1.09 cases per 100 000 population, and is stable or decreasing.[144,145] Uveal melanoma is primarily a disease of white populations; light-coloured irises, blond hair, and fair skin are risk factors.[146] There is mixed evidence implicating UV radiation as a risk factor for uveal melanoma: latitudinal variation in incidence is not consistently found;[145] occupational exposure to UV radiation may have a protective effect, but intermittent exposure may increase risk (reviewed in Mallet *et al.*[146]). People with the disease xeroderma pigmentosum, in which there is impaired ability to repair UV-induced DNA damage (see discussion above), have a 58-fold increased risk of uveal melanoma.[146,147] Genetic studies show that the mutation patterns of the most frequently mutated genes in CMM and uveal melanoma (*i.e.*, *BRAF vs. GNAQ*, *GNA11*) are similar,[146] and a mutation recently identified in CMM (*RAC1*) is also found in 20% of uveal melanoma cell lines.[146] Given the strong evidence supporting a role for UV radiation as a cause of CMM, these studies also provide some evidence that exposure to UV radiation is a risk factor for uveal melanoma.

Age-related macular degeneration

Age-related macular degeneration (AMD) was the cause of 7% of blindness worldwide in 2010,[133] and was the most frequent cause of blindness in older (50–75 years) white populations in Europe.[148] UV radiation had been discounted previously as a risk factor in AMD as it does not reach the retina. However, recognition of the considerable individual variability in the transmission of longer UV-B/shorter UV-A wavelengths (<320 nm) in older adults (60+ years) has led to reconsideration of a potential role of UV radiation. Possible mechanisms include: UV-induced oxidative damage to mitochondrial DNA, particularly in the macular region of the neural retina and the retinal pigment epithelium;[149] and/or upregulation of inflammatory cytokines (*e.g.*, IL-6) and transcription factors (*e.g.*, STAT3). Higher vitamin D status is associated with lower risk of AMD in women <75 years, but a higher risk in women ≥75.[150]

In a systematic review and meta-analysis of case-control and cross-sectional studies, higher exposure to the sun was associated with a 38% increase in the odds of having AMD.[151] However, blue light (400–500 nm) may be more important than UV radiation as a risk factor for AMD.[143,152,153]

Other possible effects on the eye

There is a well-established association between spending less time outdoors and an increased risk of developing myopia in childhood.[154–157] While early hypotheses focused on the importance of variation in focal length with a mix of indoor and outdoor activities, more recent work suggests the importance

of exposure to light, possibly through increased secretion of dopamine in the retina, with effects on the growth of the eye.[158] The wavelength dependence of this effect, and whether the pathways are mediated by vitamin D[159] or not,[157] are currently unknown.

Evidence from animal studies suggests that UV irradiation of the eye can cause systemic immunosuppression,[160,161] but the relevance of these findings for human health is unclear at present.

Effects of solar UV radiation on immune function and consequences for disease

Mechanisms

UV photons penetrate the epidermis and upper dermis[162] and are absorbed by chromophores (Table 2), which then initiate a cascade leading to changes in immune responses.

While much of this information has been gathered from studies *in vitro* or in rodent models, less is known about humans. However, an action spectrum for the UV-induced suppression of the human immune response to a previously-encountered antigen (termed memory or recall immune responses) has been constructed: it has two peaks, one within the UV-B waveband at 300 nm and one at 370 nm in the UV-A waveband.[164,165] There is also evidence from studies in both humans and mice that interactive and additive effects between wavebands can occur.[166–168]

Briefly, exposure to UV radiation causes up-regulation of some innate immune responses, and down-regulation of some acquired primary and memory immune responses, mainly through effects on T cell activity (reviewed in Gibbs & Norval,[163] Schwarz & Schwarz,[169] and Ullrich & Byrne[170]). The up-regulation includes the production of several antimicrobial peptides (AMPs) in the epidermis,[171,172] possibly through a vitamin D pathway (see below). The AMPs provide immediate protection against a variety of pathogens (bacteria, fungi, and viruses having a viral envelope) and they are also involved in the promotion of cell growth, healing, and angiogenesis. In contrast to these stimulatory functions, exposure to UV radiation induces T regulatory cells (T_{regs}) and other cell types which contribute to immunosuppression and help to restore cutaneous homeostasis.[172,173] Mediators such as platelet-activating factor, prostaglandin E_2, histamine, and tumour necrosis factor-α are produced locally at the irradiated site. These alter the migration patterns and functions of various populations of immune cells. The end result is the generation of cell subsets with suppressive activity which are thought to remain for the life-time of the individual.[174,175]

The UV-induced alterations in the normal immune response can be beneficial for some human diseases and detrimental for others. Vitamin D, synthesised following exposure of the skin to UV-B radiation, also has positive and negative effects on immune-related diseases. Indeed, it is difficult to distinguish between immunoregulation by vitamin D and other mediators induced by UV radiation,[176–180] since the downstream effects on immune parameters are similar. For clarity, the effects of UV radiation and those of vitamin D have been assessed separately in the sections below. We first focus on the effects of UV radiation on immunity, and address vitamin D-related effects on immune function in the section specifically on vitamin D.

Polymorphic light eruption

Polymorphic light eruption (PLE) is the commonest of the photodermatoses, with a prevalence of up to 20%.[181] PLE manifests as an intermittent itchy red skin eruption which resolves without scarring after a few days to weeks. It occurs 2–3 times more frequently in women than in men, with onset typically in the first three decades of life,[181] and is found predominantly in those with fair skin, although all skin types can be affected.[181] A recent study of Indian patients with dark skin phototypes (IV and V) who suffered from various photodermatoses revealed that PLE was the commonest of these, affecting 60% of the group.[182] The lesions occur most often in the spring and early summer or during a sunny holiday, following the first exposure to a large dose of sunlight. After repeated exposures, the lesions are less likely to occur. This process, called photohardening, is used therapeutically with good results. Recent investigations indicate that key events in photo-

Table 2 Cutaneous chromophores involved in the initiation of UV-induced changes in immune function (reviewed in ref. 163)

Chromophore	Change in structure following irradiation	Effect on immune function
DNA	Cyclobutane pyrimidine dimers and reactive oxygen species-induced base oxidation after exposure to radiation in both the UV-A and UV-B wavelengths	Oxidative stress; up-regulation of several immunosuppressive mediators and down-regulation of some immunostimulatory mediators
trans-Urocanic acid	*cis*-Urocanic acid (peak effectiveness of isomerisation about 300 nm)	Oxidative damage; up-regulation of several immunosuppressive mediators; stimulation of neuropeptides; mast cell degranulation; cell growth arrest
Membrane phospholipids	Oxidative stress and lipid peroxidation	Clustering of receptors; activation of transcription factors; release of immune mediators
7-Dehydrocholesterol	Previtamin D after UV-B irradiation, leading to vitamin D, then 25-hydroxyvitamin D and finally the active form, 1,25-dihydroxyvitamin D	Up-regulation of some antimicrobial responses and DNA repair; down-regulation of most acquired immune responses
Tryptophan	Activation of the arylhydrocarbon receptor following exposure to UV-B radiation	Clustering and internalisation of growth factor receptors

hardening include a decrease in the number of Langerhans cells in the epidermis and recruitment of mast cells into the dermis,[183] together with changes in systemic cytokine levels.[184]

PLE is immunologically-mediated as a result of a failure to establish the normal suppression of immune responses following exposure to UV radiation. The antigen involved has not been identified but is likely to be novel, induced by the DNA damaging properties of UV radiation. Various abnormalities in the cutaneous immune response following UV radiation have been demonstrated in people with PLE compared with controls.[185,186] This disease therefore illustrates the positive evolutionary advantage of UV-induced immunosuppression in individuals who are not susceptible to PLE and what can happen if it is absent.

Asthma

Asthma comprises a group of diseases that evidence as wheeze, chest tightness, or shortness of breath, occurring as a result of obstruction of the airways and restriction of airflow that is usually reversible. The level of severity, frequency of symptoms, age of onset, main inflammatory phenotypes, and triggers and pathways are variable. This heterogeneity may explain the current lack of consistency in results from studies examining the relationship between UV radiation and the risk of asthma.

There are anecdotal accounts that sunny holidays or living at high altitude decrease asthma symptoms. The prevalence of asthma was inversely associated with the intensity of UV radiation,[187] or past personal exposure to solar UV radiation.[188] However, in a study where different sub-types of asthma were considered, residence at latitudes closer to the equator (and with greater intensity of UV-B radiation) was associated with an increased risk of having asthma in atopic participants (with a history of allergic responses to specific antigens) but a decreased risk in those without atopy.[189] These findings highlight the importance of differentiating between subtypes of asthma in examining associations with exposure to UV radiation. Nevertheless, individual-level exposure to UV radiation was not measured (only latitude and ambient UV radiation), so the results could reflect exposure to other latitude-associated factors such as temperature and indoor heating.

Infection and vaccination

Studies over the past 20 years have shown that exposure to solar UV radiation suppresses microbe-specific acquired immune responses in animal models of infection. This modulation can lead to an increased microbial load, reactivation from latency, and more severe symptoms, including death (reviewed in Norval *et al.*[190]). A recent study showed that spending 8 or more hours outdoors per week when the UV Index was $\geq$4 was associated with an increased risk of ocular recurrence of herpes simplex virus (HSV) infection resulting in eruptive lesions.[191] UV radiation prior to vaccination causes a less effective immune response in several mouse models (reviewed in Norval & Woods[192]), but whether exposure to UV radiation adversely affects the course of infections and the efficacy of vaccination in humans remains an open question.

Despite the paucity of new information, there remains the possibility that UV-induced immunosuppression could convert an asymptomatic infection into a symptomatic one, reactivate a range of persistent infections, increase the oncogenic potential of microbes, and reduce the memory immune response, for example after vaccination, so that it is no longer protective.

Autoimmune diseases

Many autoimmune diseases are considered to have both environmental and genetic risk factors. Evidence to support the importance of environmental exposures comes from geographical variation (changing incidence with changing latitude), temporal patterns (such as variations in incidence with season or season-of-birth) and results from observational epidemiological studies. Several studies show an inverse association between exposure to UV radiation and immune-mediated diseases, suggesting that the UV may be protective. In many cases, the assumed pathway has been through enhanced synthesis of vitamin D (see section on Vitamin D below). However, this evidence is now being re-evaluated in light of possible alternative pathways, including UV-induced immune modulation and altered susceptibility to relevant viral infections, and non-UV pathways such as changes in the secretion of melatonin (reviewed in Hart *et al.*[193]). While there have been suggestions that exposure to UV radiation may be important for conditions such as inflammatory bowel disease (for example, Nerich *et al.*[194]), type 1 diabetes,[195] and rheumatic diseases (including rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, and others),[196] the strongest evidence is for multiple sclerosis.

Multiple sclerosis. Many studies (but not all) have shown that the prevalence, incidence, or mortality from multiple sclerosis (MS) increases with increasing latitude and decreasing altitude or intensity of ambient UV radiation, in predominantly fair-skinned populations (reviewed in Hewer *et al.*[197]). In the US Nurses Health Studies, a latitudinal gradient present in a cohort of female nurses born before 1946 was not apparent in a similar cohort born after 1946.[198] The findings reflected an increase in incidence in the south in the later cohort (rather than a decrease in the north). One explanation given to explain this change was that increasing sun-protective behaviours in the south had reduced the difference in personal dose of UV between the north and south.[199] Studies from the northern[200] and southern[201] hemispheres show that, compared to the general population, people with MS were more likely to have been born in late spring and less likely to have been born in late autumn. This timing would be consistent with a hypothesis that exposure of the mother to more UV radiation during the late first trimester, when the foetal nervous system is developing and maturing, is protective for the development of MS in later life.[201] Alternatively, it is also possible that exposures early in infancy, rather than in pregnancy, influence risk, or other factors that vary seasonally could be important. Animal studies suggest that UV-B irradiation can prevent the onset of experimental autoimmune

encephalomyelitis, used as a model for MS,[202] and there is supportive evidence from recent studies in humans.[203,204]

The role of UV-induced immune suppression in skin cancer

Cutaneous malignant melanoma. Evidence that the immune response is important for the development of CMM is clearly shown by the increase in incidence following organ transplantation that requires ongoing treatment with immunosuppressive medications.[205] UV radiation, particularly UV-B, can cause suppression of many aspects of cell-mediated immunity but, until recently, how it influenced the initiation of CMM was unknown. In a transgenic mouse model, the recruitment of macrophages to the skin following UV-B irradiation and their subsequent proliferation were shown to be critical in the survival of melanocytes, including those with UV-induced DNA damage.[206–208] In addition, inflammation induced by UV radiation increased metastasis of melanoma, with neutrophils being the main drivers of the inflammatory process.[209] Consistent with these reports from animal models, in patients with metastatic melanoma there was a shorter survival time if metastases contained a high proportion of macrophages.[210]

Non-melanoma skin cancer. Tumours induced by UV radiation are highly antigenic. UV-induced immune suppression plays a critical role in the development of NMSC as evidenced by the dramatically increased incidence in immunosuppressed people, for example, following organ transplantation.[211] This is especially shown for SCCs in organ transplant recipients receiving immunosuppressive drugs that suppress T cell activity, suggesting that effector T cells are of particular importance in the control of SCC.[212] Furthermore, T_{regs} induced by UV irradiation infiltrate SCCs and surround BCCs. Pharmacologically blocking steps in the pathway of UV-induced immunosuppression may be effective in preventing the development of skin cancers and actinic keratoses.[212–214]

UV-induced vitamin D and its effect on health

Metabolism of vitamin D

Vitamin D can be synthesised in the skin or ingested in the diet or as a supplement. The pathway by which vitamin D is produced in the skin and metabolised to its active form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) is shown in Fig. 4. Synthesis is initiated by absorption of UV-B radiation by 7-dehydrocholesterol. The enzymatic steps converting vitamin D to $1,25(OH)_2D$ occur predominantly in the liver and the kidney but also in other tissues, including the skin.

Both pre-vitamin D_3 and vitamin D_3 can be converted to inactive photoproducts by continued UV-A or UV-B irradiation (discussed in Galkin & Terenetskaya[215] and Norval *et al.*[216]). Once pre-vitamin D has formed and isomerization to vitamin D has occurred, there is preferential degradation of vitamin D compared with synthesis of pre-vitamin D at wavelengths of UV radiation between 300–330 nm.[217] This may explain why vitamin D toxicity from exposure to solar UV radiation does not occur and may be of importance to public health messages about safe exposure to the sun – recurrent shorter periods of

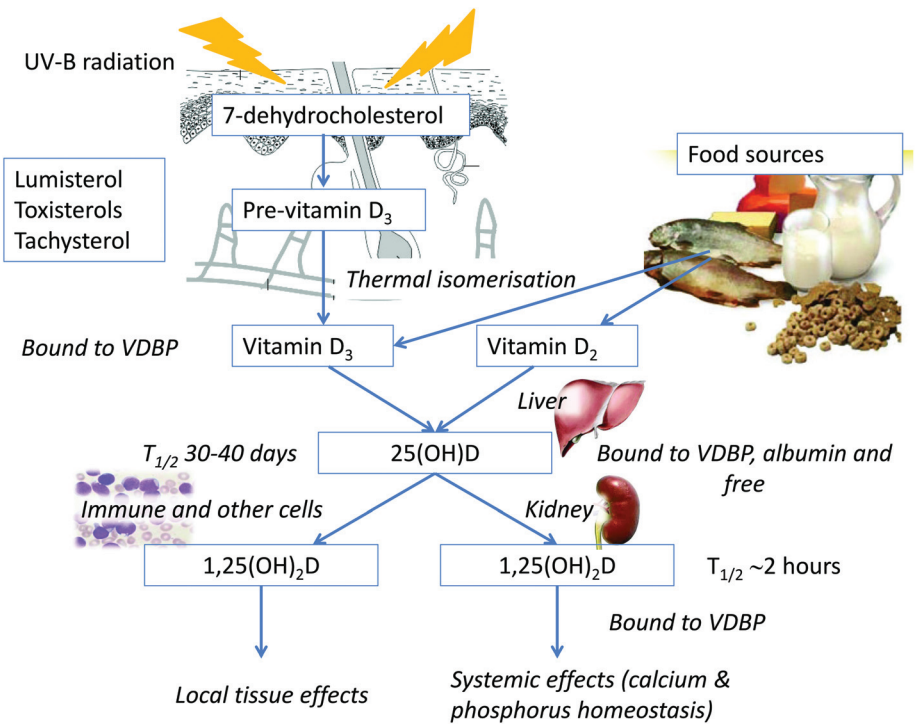

Fig. 4 Synthesis of vitamin D and the vitamin D metabolic pathway. VDBP: vitamin D binding protein; 25(OH)D: 25-hydroxyvitamin D; $1,25(OH)_2D$: 1,25-dihydroxyvitamin D; $T_{1/2}$: half-life.

Table 3 Commonly used cut-off points for vitamin D status based on serum concentrations of 25(OH)D in nmol L^{-1}

		Concentration of 25(OH)D in nmol L^{-1}			
Author	Year	Deficiency	Insufficiency	Sufficiency	Optimal
Hollis[221]	2005			>80	
U.S. Institute of Medicine[222]	2010	<30	30–50	≥50	
Pearce and Cheetham[223]	2010	<25	25–50	50–75	>75
US Endocrine Society[224]	2011	<50	52.5–72.5	≥75	

exposure to the sun are preferable to prolonged exposure to achieve vitamin D production while minimizing UV-induced damage of DNA.[218]

Vitamin D status – assessment and geographic variability

Vitamin D status is assessed by measuring the concentration of the intermediate metabolite, 25-hydroxyvitamin D (25(OH)D) (Fig. 4) in serum. Vitamin D deficiency is reportedly widespread globally, but it is important to note that there are considerable problems with the accuracy and reproducibility of vitamin D assays[219] as well as a lack of consensus on the concentration of 25(OH)D that denotes deficient, insufficient, sufficient, or optimal vitamin D status.[220] Common cut-off points are provided in Table 3.

There is a striking lack of data on the vitamin D status of infants, children, and adolescents and an almost complete lack of data from Africa and South America.[225–227]

Variation in vitamin D status according to latitude is apparent when results arise from a single assay with good agreement across batches of samples,[228] and is stronger where blood is taken in winter compared to summer.[229] Comparisons across studies may not show a latitudinal gradient due to the analytical challenges and lack of standardisation of the season of blood collection.[225–227] In addition, contributions to vitamin D status from dietary intake and sunny holidays may obscure latitudinal gradients that would otherwise occur. For example, a lower latitude holiday in the previous year with the purpose of sun-bathing was associated with higher 25(OH)D levels by 20–30 nmol L^{-1} in the following winter months in residents of Uppsala, Sweden.[230]

Skin pigmentation and vitamin D status

Within a given location, people with darker skin commonly have lower concentrations of 25(OH)D than those with fairer skin[231,232] and this is usually attributed to the photoprotective properties of melanin. However, recent work highlights the importance of cultural practices, or personal preferences, leading to avoidance of the sun.[233] In a recent study, however, black Americans (n = 2085) had lower concentrations of 25 (OH)D, but also lower concentrations of vitamin D binding protein, than white Americans.[231] The consequence of this was similar (calculated) levels of "free" (not bound to vitamin D binding protein) or loosely bound (to albumin), *i.e.*, bioavailable, 25(OH)D. This observation may explain why black people with low total 25(OH)D have higher bone mineral density than white people with similar 25(OH)D concentrations. Furthermore, it may mean that vitamin D status should be defined by the concentration of bioavailable, rather than total, 25(OH)D.[234,235]

Several recent experimental studies have examined the impact of pigmentation of the skin on synthesis of vitamin D. Most of these,[236,237] although not all,[238] show that for a specific dose of simulated solar UV irradiation there is a greater increase in the concentration of 25(OH)D in fairer-skinned than in darker-skinned participants. The lack of effect in the latter study has been attributed to the short wavelength UV-B output from the source lamp, resulting in penetration only into the superficial layers of the epidermis above the main concentration of melanin.[239]

Exposure to the sun and vitamin D status

In general, laboratory studies show an initial linear dose–response between exposure to UV radiation and change in concentration of 25(OH)D,[240] but a plateau with continuing exposures over a longer period of time.[218,241–243] Results suggest that the shape of the dose–response curve depends on the baseline concentration of 25(OH)D, with a greater response to UV irradiation[238] and no plateau effect in those with a lower starting concentration (<50 nmol L^{-1}),[244] although conflicting results have also been obtained.[245]

Understanding the relationship between the dose of UV radiation, the surface area of skin exposed and the production of vitamin D is important for the development of public health messages. Results from population-based epidemiological studies and experimental studies using artificial irradiation demonstrate that exposing a larger area of skin to UV radiation results in a greater increase in the concentration of 25(OH)D.[246,247] Field studies have shown that increases in the concentrations of 25(OH)D are positively associated with DNA damage (assessed by concentration of CPDs in urine), suggesting that improved vitamin D status is always associated with some potentially mutagenic damage to DNA.[248] However, production of vitamin D may be optimised, and skin DNA damage minimised, by increasing the body surface area exposed, and decreasing the UV-B-dose per unit area.

The World Health Organization's INTERSUN programme recommends sun protection when the UV Index is ≥3 and there have been concerns that there may be little or no vitamin D production when the UV Index is <3. However, recent computational work suggests that vitamin D could be synthesised at these lower levels of UV radiation, albeit more slowly.[249] Webb and colleagues have shown that for the white-skinned

population of Manchester, UK, a normal lifestyle with relatively short, regular exposures to summer sunlight in northern mid-latitudes could increase vitamin D enough at the end of summer to maintain sufficiency levels (>50 nmol L^{-1} or 20 ng ml^{-1}) throughout the winter.[218,250]

Evidence of associations between vitamin D and human disease

The vital role of $1,25(OH)_2D$ in maintaining the concentration of calcium in the blood within a narrow range is well-established; vitamin D deficiency causes rickets in children and osteomalacia in adults. In recent years, many protective functions have been attributed to vitamin D. However, two recent systematic reviews of observational and intervention studies cast doubt on the importance of vitamin D in decreasing the risk of many of these diseases.[251,252]

Immune function, infections, autoimmune diseases and cancer

Many of the cell types involved in immune function are able to convert 25(OH)D to the active form, $1,25(OH)_2D$.[253] The actions of $1,25(OH)_2D$ are mediated through ligation with a nuclear vitamin D receptor (VDR) that regulates gene transcription, or *via* rapid-response membrane receptors. The VDR is expressed in many human cells, including those with immune functions. Polymorphisms in the VDR can affect the effectiveness of gene transcription, altering the action of the active hormone. Immunostimulatory and immunosuppressive pathways are induced by $1,25(OH)_2D$ (reviewed in Hewison[254,255] and Christakos *et al.*[255]). Immunostimulatory effects include the production of AMPs such as cathelicidin by macrophages, neutrophils, and epithelial cells, and the maturation of macrophages. Immunosuppressive effects include the inhibition of proinflammatory cytokines and the differentiation and maturation of dendritic cells and their ability to present antigens. Furthermore, $1,25(OH)_2D$ can inhibit the differentiation and proliferation of B cells and their production of antibodies, and activate T_{reg} cells that have suppressor activity. These multiple effects make it difficult to determine what role, if any, vitamin D has in protection against disorders of immunity. Studies of infectious diseases (using tuberculosis and respiratory viral infections as examples), autoimmune diseases (using multiple sclerosis as an example), and the risk of cancer incidence and progression are discussed below.

Vitamin D and tuberculosis. Tuberculosis (TB), a disease caused by infection with the bacterium *Mycobacterium tuberculosis*, is a massive global health burden, with an estimated 9 million new cases and 1.7 million deaths each year. Infection can lead to symptomatic active disease or, more commonly, to a latent infection which can reactivate later in a small proportion of cases. Recent studies suggest an association between low vitamin D status (or lower ambient UV radiation as a presumed proxy) and the prevalence of TB (reviewed in Ralph *et al.*[256]), but it is not clear whether low vitamin D status increases the risk of symptomatic TB or *vice versa*. A beneficial effect of vitamin D is plausible through its immune properties, such as the macrophage-induced death of the *M. tuberculosis*.[256] However, vitamin D supplementation as an adjuvant to standard antimicrobial therapy has shown no clinical benefit in most studies.[257–259] In a trial in Mongolian children, supplementation with vitamin D stimulated innate immunity against *M. tuberculosis*, which could be sufficient to prevent the infectious process.[260] Further research using optimal doses of vitamin D supplementation and with exploration of the effect of host determinants, such as VDR genotype, are required to establish whether improving vitamin D status could aid in the prevention or treatment of TB.

Vitamin D and respiratory infections. Viruses infecting the respiratory tract and causing disease, such as bronchiolitis and pneumonia, are a leading cause of hospitalisations and death in young children, and of serious illness and death in those over 65 years. Examples include influenza virus, respiratory syncytial virus, and rhinovirus. Viral respiratory infections are most common in winter and least common in summer. This seasonal pattern is diminished in the tropics where there is also relatively little seasonal variation in solar UV-B radiation, although there are two peaks of infection in some countries, perhaps reflecting the rainy seasons.[261] It is hypothesised that vitamin D-dependent immunoregulation mediates these seasonal patterns.[262]

Recent observational studies typically show that lower concentrations of 25(OH)D are associated with greater risk of having a respiratory tract infection (for example[263–266]). However, in most cases, study participants had disease symptoms when they were first assessed, so that low vitamin D status could be either a cause or a consequence of the infection. The results from supplementation trials with vitamin D are inconsistent, as indicated by the following studies. Separate trials in Japanese[267] and Mongolian[268] children showed reduced incidence of respiratory infection in the supplemented groups, and there is some evidence of benefit in postmenopausal women,[269] young Finnish men[270] and older Australian adults (using antibiotic use as a surrogate for infection).[271] In contrast, trials of supplementation in adults from the United States[272,273] and New Zealand[274] failed to show any beneficial effect of vitamin D.

Reducing the risk of infectious diseases would have significant impacts on personal morbidity and global economies; however, the role of vitamin D in promoting this is unclear at this time.

Vitamin D and multiple sclerosis. Observational studies consistently show that higher concentrations of 25(OH)D are associated with lower risk of MS (reviewed in Hewer *et al.*[197]), and that vitamin D deficiency is associated with decreased responsiveness to MS treatment, and may be a risk factor for higher MS disease activity and more rapid progression (for example, Ascherio *et al.*[275]).

Most studies, however, cannot distinguish between cause and effect; that is, does low vitamin D status cause the disease or does the disease cause the low vitamin D status? Indeed,

there is evidence that concentrations of 25(OH)D are reduced by inflammation.[276] Further, a review of randomised controlled trials of supplementation with vitamin D in people with MS found no evidence of improvement in clinical endpoints.[251] Overall, the authors hypothesised that either uncontrolled confounding or reverse causality provided an explanation for the strong and consistent associations in observational studies and the lack of effect of supplementation.

It is also important to consider possible heterogeneity in MS, coupled with a lack of understanding of the timing of the onset of disease pathology and thus the most appropriate time to test vitamin D status or to give vitamin D supplementation. In addition, the risk factors for disease onset may differ from those of progression.[277]

Vitamin D and cancer risk. Vitamin D deficiency may increase the risk of developing cancer as $1,25(OH)_2D$ has regulatory effects on cellular growth, apoptosis and formation of new blood vessels. Observational studies consistently show associations between low circulating 25(OH)D and increased risk of colorectal cancer (reviewed in Autier *et al.*[251]) but, for other cancers, there have either been too few studies or the results are inconsistent.[251,252] Trials do not show evidence of beneficial effects with vitamin D supplementation.[278] In addition to the reasons discussed above for similar discrepant findings in relation to MS, the null findings from trials with supplementation of vitamin D may be due to too low a supplement dose, poor compliance, too short a follow-up, inadequate statistical power of the study, or, parsimoniously, suggest that vitamin D has no effect.[251]

It is particularly difficult to assess the effects of vitamin D on the risk of skin cancer, as UV radiation induces both. Production of $1,25(OH)_2D$ in the skin enhances the repair of UV-induced DNA damage.[279,280] Cohort studies have shown protective[281,282] and adverse[283] associations between concentrations of 25(OH)D and risk of NMSC and similar inconsistencies for the risk of CMM.[283,284] Post-hoc analyses of the Women's Health Initiative trial did not show a protective effect of supplementation with vitamin D on the risk of NMSC or CMM, but in people with a history of NMSC, the incidence of CMM was reduced in those randomised to 400 IU of vitamin D per day.[285]

In summary, the evidence that higher vitamin D status is protective for cancer is weak and inconsistent, except possibly for colorectal cancer risk. If vitamin D deficiency is truly a risk factor, it is low concentrations of 25(OH)D (*i.e.*, <30 nmol L^{-1}) that are associated with increased risk with little additional benefit for concentrations >50 nmol L^{-1}.[286]

Vitamin D and cancer-survival. Higher vitamin D status has been positively associated with survival from a number of different cancers,[251,287] but there is a paucity of trial data, and confounding by severity of disease or co-morbidities is highly likely. At this time there is insufficient evidence to draw any conclusions.

Effects of vitamin D on other health conditions. Several studies suggest that maternal vitamin D deficiency is associated with adverse outcomes in the offspring across multiple domains: bone mineral content,[288] cognitive function,[289] depression and risk of eating disorders,[290] and autism.[289] Furthermore, vitamin D deficiency in early life has been linked to increased risk of schizophrenia in later life.[291] These results may indicate that vitamin D status during pregnancy is important for foetal development, but further research will be required to confirm whether these are causal associations or due to a related factor(s).

Prospective studies have reported moderate to strong inverse correlations between concentrations of 25(OH)D and cardiovascular diseases, concentrations of serum lipids, inflammation, disorders of glucose metabolism, weight gain, mood disorders, declining cognitive function, dementia, Alzheimer's disease, impaired physical functioning, and mortality. In contrast, intervention trials show no effect of vitamin D supplementation on these outcomes.[251]

Table 4 Health outcomes for which a U-shaped association with serum 25(OH)D levels has been described, and the 25(OH)D level of lowest risk

Disease/condition	Concentration (nmol L^{-1}) of lowest risk, *i.e.* the turning point of the U-shaped dose response
All-cause mortality[292–294]	80–100
Cardiovascular events[295,296]	50–100
Cancer mortality[297,298]	100 (men only)
Prostate cancer[299,[300]]	50 [≤55 (highest risk, 91–106)]
Pancreatic cancer[301]	<100
Allergen-specific IgE during childhood[302]	50–74.9
Tuberculosis[303]	76–140
Schizophrenia (neonatal vitamin D status)[291]	47
Small-for-gestational-age births among white women[304]	60–70
Physical frailty in older women[305]	50–74.9

U-shaped associations between vitamin D metabolites and disease

Recent research shows that both high and low concentrations of 25(OH)D are associated with increased disease risk – a so-called U-shaped association. Table 4 provides a summary of studies showing this effect.

An additional U-shaped association has been shown between concentration of $1,25(OH)_2D$ and viral load in patients with HIV.[306]

There is a trend to advocate ever higher cut-offs to denote the concentration of 25(OH)D concentrations that is optimal to prevent disease.[307] It is therefore important to continue to investigate possible disease risks at higher concentrations of 25(OH)D, especially if the aim is to maintain such levels over the long-term.

Other effects of solar UV radiation on human health

Chronic exposure to UV radiation has been weakly linked to a range of other adverse health outcomes, including: decreased

epidermal[308] and subcutaneous[309] lipid synthesis resulting in weakening of the barrier function of the skin; hearing impairment, through oxidative stress pathways;[310,311] lactase non-persistence;[312] increased risk of prostate cancer;[313] and acquired bilateral nevus-of-Ota-like macule, a common pigmentation disorder in Asian females.[314]

In contrast, there is evidence of a protective effect of higher UV radiation on development of restless legs syndrome[315] and keloid formation in scars.[316] There are a growing number of studies examining the apparently beneficial effects of exposure to the sun. A recent study has shown that UV-A irradiation is effective in lowering blood pressure, possibly through UV-A-induced nitric oxide bioactivity.[317] A reduced risk of cancer and particularly breast cancer has been reported in association with greater exposure to the sun in early life,[318] as well as a decreased risk of myocardial infarction, and all-cause mortality, and hip fracture in those below age 90, where history of skin cancer was the measure of past exposure to the sun.[319] In Chile the most frequent cases of food-related anaphylaxis (severe allergic reaction) occur at higher latitudes where there is lower solar radiation.[320]

Personal protection from solar UV radiation

The threat of increasing levels of UV-B radiation due to stratospheric ozone depletion, and rising skin cancer incidence rates, led to the development of sun protection programs and strategies. Despite the partial recovery of the ozone layer (reviewed in Bais *et al.*[2]), such strategies remain important because changes in climate are likely to alter both ambient UV radiation and behaviour that affects exposure to the sun.

A sustained effort is required to change attitudes and behaviours in relation to exposure to the sun, especially in young people.[321] Several recent surveys indicate that adults,[322,323] adolescents,[324] and children,[325,326] still commonly report having been sunburned in the previous year, and this applies to both fair- and dark-skinned populations.[327]

While in some locations a majority of children use some form of photoprotection, particularly shade,[325,326,328] this is not true of adults.[323] Good knowledge of protection from the sun may not translate into attitudes and practices for reducing exposure.[326,328,329] Further, more education about the specific needs for photoprotection in different situations may be required. In a sample of young German children, parental knowledge of appropriate use of shade, clothing, a sunhat, and sunscreen was considered to be adequate for summer holidays at the beach, but not for everyday outdoor activities.[330] In a Danish study, travel to a sunny destination was common (almost 50% of those aged 15–59 years took such a holiday each year), with a high likelihood of sunburn and intentional tanning.[331] There are limited data on strategies for photoprotection in tropical countries but one survey in adolescents living in Bangkok, Thailand, found that sunscreens, sun-protective clothing, and shade were seldom used, particularly in males, compared with Western countries.[332] In a study in Philadelphia, USA, Hispanic adolescents and young adults who showed evidence of greater adoption of US culture were less likely to use sunscreen and more likely to deliberately expose themselves to the sun than those who retained their traditional culture.[333] Barriers to personal protection from the sun in young Australians include peer pressure, lifestyle, fashion and social norms.[334]

The ultraviolet index (UVI) is routinely published in the media in some countries, available online,[335] on a mobile phone,[336] on mobile phone apps,[337] or can be approximated using a compact disk as a sundial.[338] However, its use to guide behaviour in relation to exposure to the sun remains limited.[339] Furthermore, the specific guidance in relation to the UVI varies across different countries. For example, in Australia, photoprotection is recommended when the UV Index is ≥ 3.[335] In New Zealand, a "UV Sun protection Alert Period" is provided daily, rather than the UVI, and is defined as the period of the day where the forecast clear-sky UVI is >3.[340] The United States Environmental Protection Agency provides a UV Alert when the forecast UVI is ≥ 6, with advice to minimise time in the sun and use protection.[341] As noted, exposure to the sun when the UVI is <3 is relatively ineffective for vitamin D production, whereas, for some fair-skinned individuals, even short exposures at a UVI of 6 may result in erythema. It is difficult to provide blanket recommendations, even according to the UVI and skin type, as there is wide variation in the minimal erythema dose (MED, the dose of UV radiation required to cause a slight reddening of the skin) even within a specific skin type, and different messages may be required for different regions.[69]

It is not generally realised that measures for protection against the sun may be required on cloudy days, in addition to clear days, due to diffuse solar UV radiation,[342,343] and that some shade devices, such as umbrellas, provide incomplete protection from UV-B radiation.[344]

Sunscreens

Public health bodies have long advocated the use of sunscreens as a means of photoprotection. A long-term prospective study in Queensland, Australia, showed that daily use of sunscreen reduced the incidence of SCC[345] with some evidence of reduction in the incidence of CMM.[346] In addition, such use also reduced photoageing of the skin.[347] However, a recent meta-analysis of the effectiveness of interventions promoting use of sunscreen in adults and children in recreational settings showed no reduction of sunburn in adults and only a modest effect in children.[348]

Sunscreens are formulated and tested for their ability to prevent erythema *in vivo* and their index of efficacy is the sun protection factor (SPF).[349] The labelled SPF is equal to: $[\mathrm{MED}_{\text{protected skin}}]/[\mathrm{MED}_{\text{unprotected skin}}]$, when tested under laboratory conditions with simulated solar radiation. The erythema action spectrum dictates that this is primarily an index of protection from UV-B radiation, although sunscreens are also required to have a measure of protection against UV-A

Table 5 Newer active sunscreens and evidence of their effectiveness

Class	Route and Effectiveness
α-Melanocyte stimulating hormone analogues – stimulate melanogenesis (tanning), *e.g.*, afamelanotide	Sub-cutaneous; effective in some photosensitive patients[362,363]
Natural anti-oxidants, *e.g.*, vitamin A (retinol), vitamin C (ascorbic acid), vitamin E (tocopherol), pycnogenol (pine bark extract), carotenoids	Oral; not as effective as topical sunscreens[361,364]
Nicotinamide (an amide form of vitamin B3)	Topical; enhances DNA repair, prevents UV-induced immunosuppression, reduces incidence of NMSC[365]
Resveratrate, found in red wine, grapes, plums and peanuts	Topical; application immediately after exposure to the sun protected against erythema and sunburn cell formation[366]
Flavonoids, *e.g.*, luteolin (a)	Protects skin by a combination of UV-absorbing, DNA-protective, antioxidant and anti-inflammatory effects.[367]
Lycopene, found in tomato paste	Oral; ingestion over a 12 week period reduced acute & chronic effects of photodamage[368]
Green tea polyphenols	Oral; some evidence of modest effect[369,370]
Diet rich in omega-3 fatty acids	Oral; may reduce risk of skin cancer[371,372]
Liposomes containing natural endonucleases or photolyases	Topical; enhance nucleotide excision repair of UV-induced DNA damage; shown to reduce the incidence of solar keratoses and the severity of polymorphic light eruption.[373–375]

radiation.[350] Sunscreens with uniform absorption across the whole UV spectrum (broad-spectrum) provide photoprotection that is similar to shade or some types of clothing fabric[351] (for more detail, see Andrady *et al.*[352]). Some UV radiation filters may also have anti-inflammatory properties,[353] in which case the SPF may be more than a measure of optical filtering.[354]

One requirement of the SPF test is that sunscreen is applied at a coverage of 2 mg cm^{-2}, but several studies have shown that people apply much less (for example, Petersen *et al.*[355]). The thickness of the application is also dependent on the formulation, with coverage of only 0.22 mg cm^{-2} achieved by children applying sunscreen with a roll-on.[356] Use of a higher SPF sunscreen or two applications of sunscreen can achieve a greater level of protection.[357,358] In addition to inadequate thickness of application, failure to apply sunscreen to all areas of exposed skin also limits the amount of photoprotection achieved. There are concerns that using sunscreen will decrease synthesis of vitamin D. Current evidence suggests that, if sunscreen is correctly applied, there may be no increase in concentrations of 25(OH)D following exposure to the sun.[359] However, with usual applications, there is minimal impairment of the synthesis of vitamin D.[282,360]

Traditional topical sunscreens depend on the filtering or scattering of UV radiation, *i.e.*, "passive" photoprotection. Table 5 summarises some recent developments in compounds providing "active" photoprotection at a topical and systemic level.[361]

Overall, people are probably getting much less protection from the harmful effects of UV radiation than they believe when they use sunscreens, especially if their intention is to prolong their time in the sun. This is a public health issue that has to be addressed either by encouraging people not to go outdoors when the UVI is high, or to use appropriate clothing (see also Andrady *et al.*[352]) for sun protection.[335] Alternatively, people need to apply sunscreen more thickly, or use sunscreen of a higher SPF to compensate for inadequate application.

Clothing and shade

Clothing modifies the skin surface area exposed to solar UV radiation. It offers good protection against sunburn, although this is dependent on the properties of the fabric such as colour, structure (*e.g.*, woven *vs.* knit and tightness of the weave for woven fabrics), and wetness (see Andrady *et al.*[352]). Clothing typically strongly attenuates transmission of erythemally-effective UV radiation (*i.e.*, weighted with the erythema action spectrum) to the skin. However, this blocking of UV-B radiation commonly leads to low vitamin D status in people who wear full body clothing,[376] for example for religious or cultural reasons.[377,378] It may be possible to design and manufacture clothing from fabrics that allows synthesis of vitamin D while preventing a visible erythema.[379] However, it is likely that this will not protect from suberythemal damage, such as to the DNA of the epidermal cells.

Shade-seeking is a well-recognised and effective way of reducing exposure to solar UV radiation, as evidenced by a lower level of sunburn[380] and lower vitamin D status in adults from the USA who reported frequent use of shade on a sunny day, compared to those who used shade rarely.[360] Provision of shade over playgrounds, particularly in sunny locations, is a relatively inexpensive method of mass protection from the sun. Nevertheless, a systematic review of 23 publications found no evidence that health promotion interventions had any effect in increasing shade-seeking in adults or children.[348] Shade may be less effective at reducing exposure to diffuse UV radiation and this may account for about 80% of people's cumulative annual erythemal exposure.[343] A recent study has used a manikin head (in a fixed position) to measure exposure to UV radiation under different conditions of shade, cloud cover and solar angle.[381] This approach can be used to quantify the protective benefits of shade that are currently not well documented.

Preventing skin cancer *versus* ensuring adequate vitamin D status

There is no simple message to guide optimal levels of exposure to the sun. There is considerable variation between individuals

in the doses of UV radiation that cause damage to DNA and induce synthesis of vitamin D. However, some broad recommendations can be made. Repeated short exposures to the sun are more efficient at vitamin D production than a single prolonged exposure.[218] Levels of UV-B radiation are greatest at midday and vitamin D synthesis is thus most efficient at this time,[382] although it is also the time when sunburn occurs most quickly.[383] The amount of time in the sun that is needed for the synthesis of vitamin D varies according to location, time of day, and time of year. After controlling for the level of exposure to UV radiation, having more skin not covered by clothing is associated with higher concentrations of 25(OH)D in serum.[246,247] As noted above, there are conflicting results on the effect of darker pigmentation of skin on the UV-induced production of vitamin D. In high latitude locations where UV-B levels are too low for vitamin D synthesis and a cooler climate may mean that little skin is exposed to the sun even during summer, greater intake of vitamin D may be required to avoid vitamin D deficiency.

Protection of the eye

One of the cheapest and most practical methods of protecting the eye from exposure to UV-B radiation is wearing a hat with a brim of at least 6–7 cm.[335,384] Sunglasses provide variable protection, and standards are more rigorous for UV-B than for UV-A radiation. For UV-B radiation the upper transmission limits range from 1.0% to 12.5% depending on the international jurisdiction and the type of use. For UV-A radiation, the limit is either a maximum of 50% of visible transmittance or is unspecified. The size of the frame and design can influence eye protection and some standards for sunglasses incorporate a minimum size limit.[385] Wrap-around designs are most protective and are especially important when in highly reflective conditions, for example when skiing.[385] Many ordinary eye-glass lenses have UV filters in them.

The American National Standards Institute (ANSI) requires that contact lenses absorb at least 95% of UV-B radiation and 70% of UV-A radiation for a "UV blocking" claim. A recent survey on a selection of lenses showed compliance with claims for photoprotection.[386]

Studies using manikin heads[387,388] have shown that, although the ambient UV radiation is greatest at solar noon, the highest dose of UV radiation was received by the eye at 4 hours before and after noon, when the solar elevation angle was lower. Thus, photoprotection of the eyes during outdoor activities is important not only at noon, but also at other times, and during winter.[389] In some occupations, *e.g.*, working on a building site, the reflectivity of the building materials may influence the amount of UV radiation received by the eye[390] and should be considered when wearing eye-protection.

Protection of the eyes from the sun should reduce the risk of pterygium; UV absorbing contact lenses that cover most of the cornea can protect against UV-induced damage.[385,391] Eye drops for the prevention of pterygium and photokeratitis/photoconjunctivitis through anti-oxidant and anti-inflammatory pathways have been effective in animal models, but are not commonly used in humans.[119,392]

Effects of interactions between solar UV radiation and the environment

Environmental contaminants may interact synergistically with UV radiation to harm human health. For example, in the presence of UV-B radiation, chrysene,[393] a common environmental contaminant produced by incomplete burning of fossil fuels, and some pesticides[394] have adverse effects on human health, including through damage to DNA.[395] Topical corticosteroids are unstable under UV-B irradiation, possibly causing skin damage as well as loss of therapeutic effect.[396] Engineered nanoparticles (NPs) are increasingly incorporated into sporting equipment, sunscreens, clothing and cosmetics (see also Andrady *et al.*[352]). Concerns have been raised about possible health risks of NPs.[397,398] A recent review of the evidence on NPs in sunscreens concluded that "on current evidence, neither TiO_2 nor ZnO NPs are likely to cause harm when used as ingredients in sunscreens".[399] Nevertheless, exposure of skin to UV radiation may enhance the penetration of engineered NPs,[400] and the formulations using these particles are often used around the time of irradiation when skin damage may occur. Further, UV-induced immunosuppression could potentially impair an immune protective response induced by engineered NPs applied to the skin.[400]

On the positive side, UV radiation is a potent environmental disinfectant able to inactivate viruses in clear water (for further discussion see Häder *et al.*[401]). This property is used in the SODIS (solar disinfection) technique, where exposure of surface water within a transparent bottle to sunlight effectively disinfects the water, decreasing the incidence of diarrhoeal diseases (reviewed in McGuigan *et al.*[402]).

Health implications of interactions between ozone depletion and climate change

Past studies have estimated the health gains in terms of skin cancers avoided through the implementation of the Montreal Protocol and its amendments.[403] A recent update of this work that also integrated coupled climate-chemistry models has estimated that the world-wide incidence of skin cancer would have been 14% greater (2 million people) by 2030 without implementation of the Montreal Protocol and its amendments,[404] with the largest effects in the South West USA and in Australia (see Bais *et al.*[2] for further details).

Model estimates[405] suggest that by 2050, any increases in erythemal UV radiation above present levels will be small and confined to the tropical region (reviewed in Bais *et al.*[2]). These should have only a small effect on the incidence of skin

cancer[406] but may impair immune responses to some vaccinations. However, outside the tropical region, erythemal UV radiation is projected to be lower, especially in winter (reviewed Bais *et al.*[2]), which could be detrimental for the vitamin D status of populations in these regions, as well as for diseases that may be modulated by exposure to UV radiation, such as some of the autoimmune diseases discussed above. Estimates of exposure times for erythema and vitamin D synthesis in Europe, taking account of ozone recovery and interactions with different concentrations of greenhouse gases (GHG),[406] suggest that there will be very little change in the exposure time for both endpoints for Southern Europe. However, an increased exposure time of about 30% for vitamin D production would be required in a worst case scenario in Stockholm in spring with high levels of GHGs.[406]

A major determinant of the received dose of UV radiation is behaviour in relation to exposure to the sun.[407] Ambient temperature is likely to influence time spent outdoors. In temperate parts of Australia, the increase in temperature is likely to increase skin cancer incidence because people will spend more time outside with less clothing.[408,409] However, with temperature increases in already warm climates, people will be more likely to stay indoors or to seek shade.[229] Warmer ambient temperatures may have direct physiological effects to accelerate both skin cancer development[410] and vitamin D production.[411]

In addition to these direct effects of interactions between climate change and ozone depletion and/or UV radiation for human health, there are potential indirect effects that may become important, but at this stage remain ill-defined.[412] Concurrent changes in climate and levels of ambient UV radiation will influence aquatic and terrestrial ecosystems (see also Häder *et al.*[401] and Bornman *et al.*[413]), which may have consequences for food safety, quality and supply (reviewed in[412]).

Migration of populations, often with dark skin pigmentation, from low-lying tropical regions because of rising sea levels, to higher latitude regions may increase the diseases associated with vitamin D deficiency.

Higher temperatures should foster microbial growth in surface waters, and this will be more pronounced in the presence of lower levels of disinfecting UV-B radiation, or where increases in colour due to dissolved organic matter limit penetration of UV-B radiation (for more detail, see Häder *et al.*,[401] Bornman *et al.*,[413] and Erickson *et al.*[414]). However, there has been little research to date that allows prediction or quantification of the risks to human health that might arise from these interactions.

Gaps in our knowledge

Considerable evidence from animal models suggests that UV-induced immunosuppression may increase the risk of some infections and decrease the protection offered by vaccination (reviewed in Norval & Halliday[212]). Studies in humans are required to determine whether any increased risk is clinically relevant, for example, requiring changes in vaccination protocols. Although some animal studies similarly suggest that vitamin D status affects the outcomes of vaccination or immune responses to infection, results from clinical trials mostly show no effect.[415,416]

There is currently considerable controversy about which health conditions are influenced by vitamin D. Large-scale vitamin D supplementation trials that are in progress will provide some answers (see Table 1 in Byrne[417]). While there is consensus that vitamin D is important for bone health, there is lack of agreement about the concentration of 25(OH)D required. In addition, there is substantial individual variability in the change in concentration in 25(OH)D in response to UV irradiation and vitamin D supplementation, and in the clinical effects associated with different concentrations of 25(OH)D. The reasons for this are poorly understood, but are likely to depend on variation in the genes encoding the vitamin D binding protein and/or the vitamin D receptor.

Production of vitamin D occurs readily at sub-erythemal doses, but repeated sub-erythemal exposures can also cause accumulation of CPDs that repair only slowly (over 24–36 hours) and thus may increase the risk of skin cancer.[418] Until there is a better understanding of the numbers of CPDs that accrue during brief sun exposures, and their importance in determining the risk of subsequent skin cancer, it is difficult to recommend safe exposures that would result in sufficient production of vitamin D.

There is a lack of data on the vitamin D status of infants, children, and adolescents and for populations in Africa and South America. Further, the lack, until recently, of accurate and precise assays has limited our ability to examine variability in vitamin D status across countries (for example those with and without fortification of food) and over time. The advent of the standardised vitamin D assays[419] means that this is now possible. Development of a less invasive sampling method, for example using saliva, would allow more widespread assessment of the vitamin D status of infants and children.

Protection from the sun is currently recommended by the World Health Organization when the UVI is ≥ 3. The corollary of this message is that photoprotection is not required when the UVI is <3. At these low UVI values, there is little UV-B radiation (and thus little vitamin D synthesis), but, with prolonged exposure, there may be a relatively high dose of UV-A radiation. With recognition that UV-A radiation can induce immune suppression[164] and is involved in the initiation of CMM, but may also have beneficial effects on blood pressure, the doses received and potential health effects need to be better defined.

The action spectra for a number of health outcomes have not been determined. These include cataract from protracted exposure, myopia, carcinoma in deeply pigmented skin, melanoma and production of pre-vitamin D from a polychromatic source (the sun) and in both dark and fair skin types. However, the relevance of the currently available animal models is uncertain, so obtaining these action spectra with definite relevance to humans is very difficult.

There is emerging evidence that exposure to the sun may have beneficial effects independently of vitamin D. The lack of a strong evidence-base challenges our ability to provide accurate guidance to the public regarding exposure to the sun.

As noted above, there is much uncertainty about the effect of the potential indirect interactions of climate change and ozone depletion on human health. Effects on disinfection of surface water and on supply and security of food could become important sources of risks to health, particularly in some regions of the world. Modelling now may be able to identify those areas at greatest risk, and allow forward planning to mitigate the risks.

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