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Solar Ultraviolet Radiation

Global burden of disease from solar ultraviolet radiation

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4.4 Chronic sun damage/solar keratoses

Disease incidence

Although we may not like the appearance of our ageing skin, there is no disability in health terms from the wrinkling, actinic lentigines and actinic (solar) keratoses that constitute photoageing. There is however, a disability related to removal of solar keratoses and there is a recognized progression of solar keratoses (SK) to SCC. It appears that SK, dysplasia, SCC-in-situ and invasive SCC are a continuum and it may be difficult to delineate these clinically. Current treatment options include local destruction with cryotherapy, curettage, electrodessication, or topical application of aminolevulinic acid and light.

It is clear that not only is there a latitudinal gradient in the prevalence of persons with solar keratoses, but at lower latitudes, it is more likely that there will be multiple solar keratoses. It is important in evaluating studies to be clear whether they are measuring prevalent lesions, or 'persons with lesions' as some people have a large number of lesions. In the Nambour study (*67*) 10% of the population had more than one lesion, while in South Wales there was a median of 2 solar keratoses in those aged over 60 years (*54*). In the later part of the Nambour study (*68*), 18% of the study population had 11 or more solar keratoses.

A few studies have examined the prevalence of solar keratoses and using these data we have extrapolated to achieve a theoretical distribution of prevalence of solar keratoses by latitude and age (*54, 68-72*). From this the incidence rates for removal of SK and for malignant transformation were estimated.

Population attributable fraction

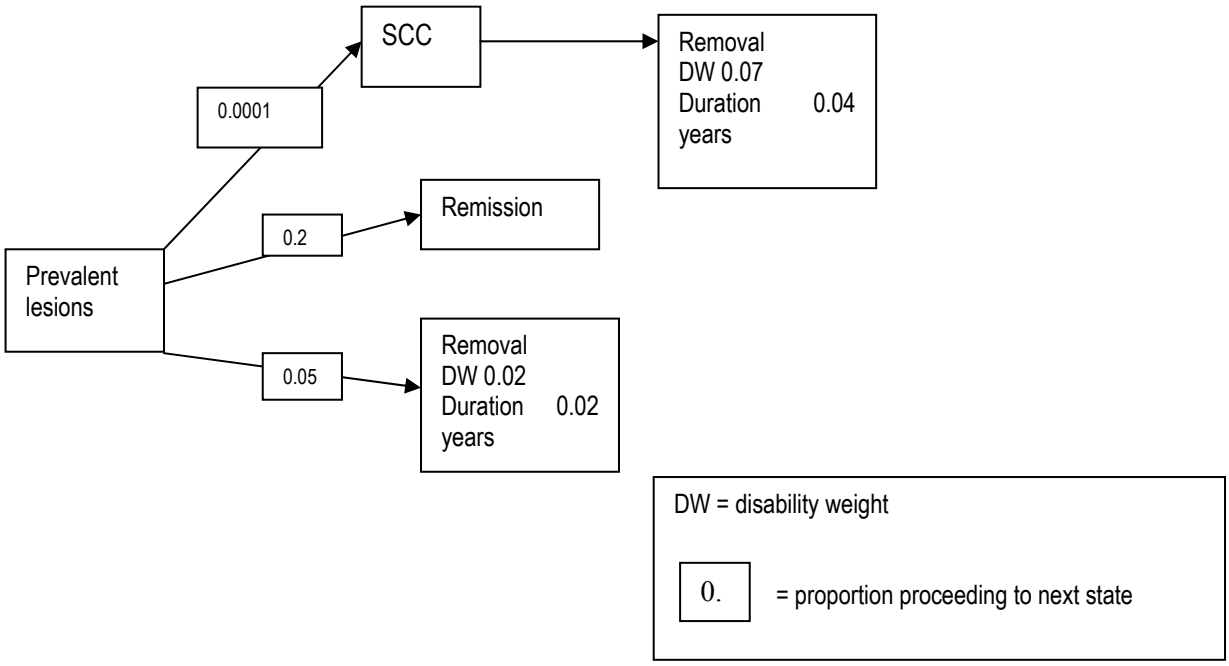
Chronic sun damage to the skin, or photoageing includes those sun-induced changes to the skin that, combined with the changes of intrinsic or chronologic ageing, represent the characteristic signs of ageing skin. Many of the changes in the skin that are evident with ageing are photo-induced (*73*).

Only solar keratoses are assessed in this report and they are considered to be entirely related to UVR exposure. (See appendix 3)

Disease model

From the epidemiological data we have assumed a removal rate of 5% (of those solar keratoses that do not remit) in developed countries, a zero removal rate in under-developed countries, a remission rate of 20% per year, (*54, 74*) and a progression to SCC of 0.01% per year (*75*). Figure 4.3 presents the disease model for solar keratoses.

Figure 4.3 Disease model for solar keratoses



Tables 4.16 to 4.17 summarize the prevalence and burden of disease due to solar keratoses (as part of the photoageing process).

4.6 Cortical cataract

Disease incidence

Early studies on cataract used a number of different definitions to define presence of cataract, making comparison of cataract rates in different locations very difficult. However, in later studies there is consistency in the definition of the various types of cataracts, which has led to reliable estimates from a number of parts of the world as to percentage of all cataracts that are cortical cataract, and cataract incidence, prevalence and progression.

While there does seem to be a latitudinal gradient in the proportion of all cataracts that are cortical, with higher proportions of cortical cataract at lower latitudes (*91-95*) the prevalence of cataract does not vary with latitude and, if there is any latitudinal variation, prevalence of cortical cataract increases with increasing latitude.

Population attributable fraction

Population attributable fractions were calculated from case-control studies for cortical cataract, and graphed against latitude (see cortical cataract workbook, Appendix 3). There was a non-significant latitudinal gradient ($p = 0.62$) with an intercept of 0.26, mean = 0.19. A PAF for UVR exposure causing cortical cataract of 0.2 was used in this assessment. This may be low due to recall inaccuracy as already noted, but reflects the efforts made in some cataract studies to accurately quantify the ocular UVR dose.

Disease model

Cataract per se attracts no disability weight – the disability results from loss of vision, from cataract surgery and from the increased mortality associated with visual impairment.

Few studies that have measured cortical cataract have also measured visual loss in those with cortical cataract. It does however, appear likely that cortical cataract is less likely to be associated with visual impairment than other forms of cataract, particularly mixed and nuclear cataract (*91, 96*). In addition, cortical cataract has a weaker relationship with mortality than other forms of cataract and is less likely to result in cataract surgery (*97, 98*).

The Barbados Eye Study (*91*) looking at visual impairment of greater than 20/40 due to cataract, found a prevalence of cortical cataract of 20.4%, over all age groups. In the Tibet Eye Study, also looking at visual impairment of greater than 20/40, a much higher proportion of cataracts were cortical, with little variation in different age groups – around 60% (*92*). In the POLA study, the proportion of those with cortical cataract who were visually impaired due to cataracts was 13-17% with little variation due to age (*94*).

For the purposes of this burden of disease study, the proportion of all cataracts causing visual loss that is due to cortical cataract is taken as 30% (average of above is 31%, range 13% to 60%). Cortical cataracts are likely to cause mild rather than moderate or severe visual loss and thus contribute less to the global burden of disease, based on disease severity, than other forms of cataract. However, mild visual loss is likely to be more prevalent than moderate or severe visual loss, and despite its lower severity, may thus contribute strongly to the total burden of disease due to cataract. We have therefore assumed that 25% of the total burden of disease due to cataract calculated by WHO for 2000 (*99*) is due to cortical cataract. The calculated PAF was applied to the resultant estimated burden of disease due to cortical cataract. Clearly this is only a rough approximation, and further work is needed in this area.

Table 4.20 summarizes the incidence of cataract globally; Table 4.21 summarizes the burden of disease due to all cataracts; Tables 4.22 and 4.23 summarize the burden of disease due to cortical cataract and the burden of disease due to cortical cataract that is attributable to UVR exposure.

4.7 Pterygium

Disease incidence

There are moderately good descriptive data on incidence and prevalence of pterygium worldwide (*100, 101*). However, there is a large discrepancy in the prevalence of pterygium within a small area, depending on whether one looks at urban or rural populations. Thus, in the Melbourne Visual Impairment project (*102*) the prevalence of pterygium in males, 80-89 years who lived in an urban area was 1.79%, while in those in a rural area it was 31.3%.

Despite Cameron's work on the distribution of pterygium worldwide, initial inspection of prevalence rates by latitude shows a wide range of rates at similar latitudes, with no clear latitudinal gradient and no clear racial differences. However, closer review of the prevalence rates reveals that some of the rates are for total population prevalence, while some are prevalence rates only in older age groups. For example, Wong et al (*103*) cite a prevalence of 6.9% in the Chinese population of Singapore aged 40 or older, Panchapakesan et al (*104*) a rate of 7.3% in the Blue Mountains, NSW population over the age of 49 years and Taylor et al (*105*) a rate of 44% in Aborigines over the age of 30 years in Northwestern Australia.

In order to develop a global distribution of prevalence for pterygium, prevalence rates using only parts of the population were adjusted to the total population using the World Standard Population (*106*) to derive the approximate age-standardised summary prevalence. Prevalence data from within each latitude band were then averaged to provide the representative age-standardised prevalence for each latitude band. Using this as a summary prevalence for the latitude band, and the age and sex distribution outlined in the literature (*102-104, 107*), a theoretical distribution of global pterygium prevalence was developed by back-calculating from the summary prevalence to give age and sex-specific prevalence data for each latitude band.

Population attributable fraction

Case-control studies were examined to calculate the population attributable fraction due to UVR exposure. Unfortunately, a number of these studies failed to measure confounding factors, particularly exposure to particulate matter. Also, Threlfall et al (*108*) showed that there is a difference in the PAF if different methods of sun exposure are used. There is little latitudinal gradient in the PAF for pterygium ($p = 0.35$) with an intercept of 0.33 and mean of 0.42 in studies using averaged annular ocular dose. Using daily ocular dose as the exposure measure (*108*), the PAF is 0.74. These two PAFs were used as the upper (0.74) and lower (0.42) estimates of PAF and were applied to the calculated disease burden due to pterygium. (See Appendix 3)

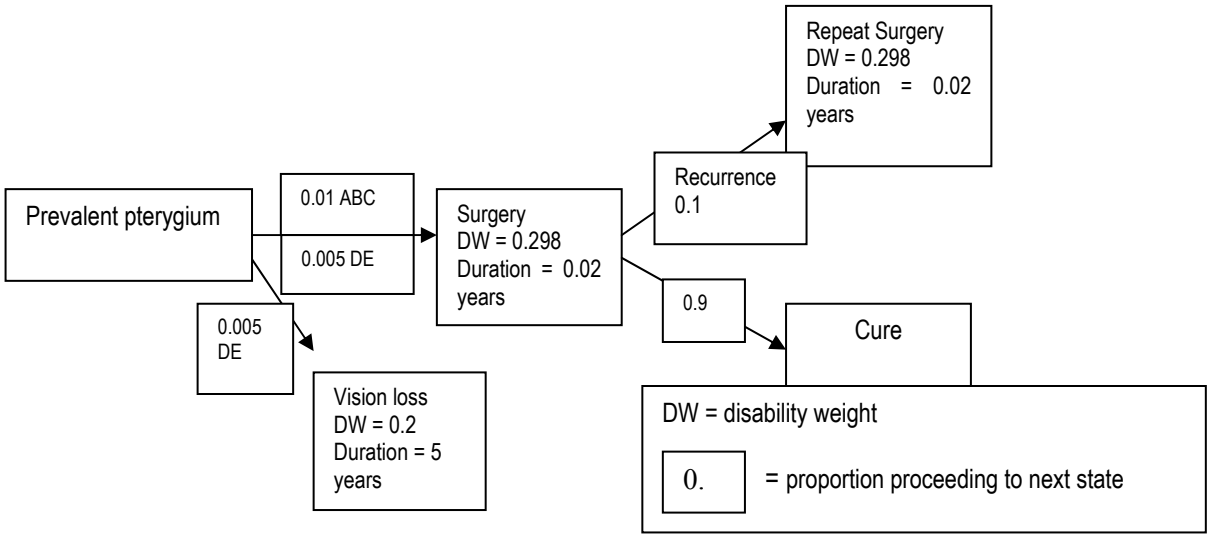
Disease model

Pterygium per se attracts no disability weight, as there is usually no associated vision loss. Only a small proportion of all pterygia are operated on in developed countries and this is likely to be less in under-developed countries. However, the incidence of operations for pterygia may have less to do with the prevalence of pterygia than with the level of ophthalmological service to the area. For example, Wlodarczyk et al have examined the cost of pterygia in Australia (*109*). The lowest rate of pterygium removal is in the Northern Territory and the highest in Queensland – yet these states have similar latitude. This could be explained if the two states had a greatly different age structure (since prevalence of pterygium increases with age) or some other risk factor for pterygium. A more likely explanation is that the Northern Territory has lower access to specialist ophthalmological services.

We have assumed a 1% surgical removal rate for ABC regions (see disease model, Figure 4.5), based on published rates of surgery (*100, 104, 109*). Pterygium surgery is performed in developing countries, probably less for cosmetic reasons and more to avoid loss of vision. In

Nigeria, Ashaye cites pterygium surgery as making up 20% of all ocular surgery (*110*). We have therefore assigned a removal rate of 0.5% of all pterygia, for DE countries (less commonly performed than in ABC countries). However, it is likely that there is a higher prevalence of visual loss due to pterygium in these countries, so that the remaining 0.5% (who are not operated on compared to ABC countries) have a disability related to visual loss.

Figure 4.5 Disease model for pterygium



The results of the burden of disease assessment are presented in Tables 4.24 – 4.26.

4.8 Carcinoma of the cornea and conjunctiva

Disease incidence

Age-standardized incidence rates for eye cancers are available for a number of countries (*30*). In addition, the proportion of eye cancers that are histologically proven SCCC is given. Using this information it is possible to obtain approximate age-standardized incidence rates for SCCC globally. Using the literature to establish an age breakdown of the disease (*111, 112*), and using the Segi World Standard Population (*106*), age-specific incidence rates were back calculated (using an Excel spreadsheet and repeated iterations of possible values, to achieve age-specific incidence rates that were compatible with both the final age-standardized rate and the population distribution of the disease in that region).

It is clear that this is predominantly a rare disease of the elderly, except in sub-Saharan Africa, where the mean age at presentation is 35 years (compared to 60.4 years in Mexico City) (*112, 113*). For this reason, the same male to female ratios and age distribution of disease were applied to all regions, except AFR E for which a younger age distribution was applied.

Population attributable fraction

Squamous cell carcinomas of the cornea and conjunctiva (SCCC) are rare tumours, particularly in white populations. There appears to be a continuum from simple dysplasia to carcinoma in situ to invasive squamous cell carcinoma involving the conjunctiva as well as the cornea (*114*).

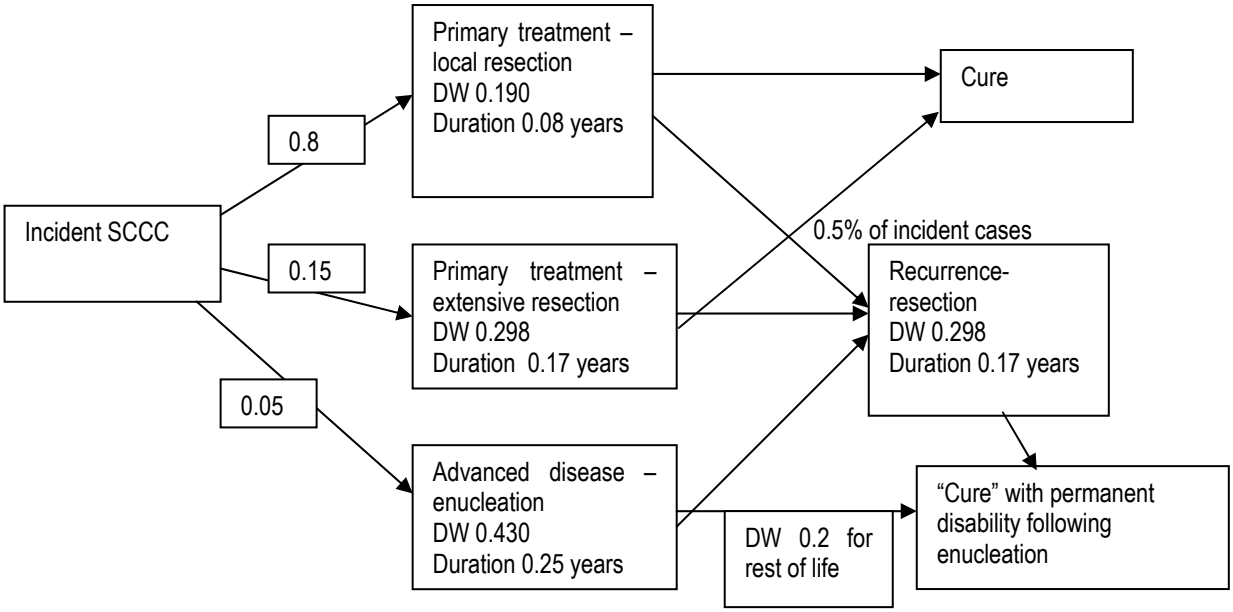
The incidence of this tumour has greatly increased in recent years associated with HIV infection. The proportion of SCCC that is attributable to AIDS (PAF for AIDS for SCCC) has been calculated to be 0.66 (*112*). Sun (*115*) found links between SCCC and ultraviolet radiation exposure of a similar magnitude to SCC of the eyelid. The PAF calculated from the single relevant study by Lee et al (using as a UV exposure measure cumulative exposure at ≤ 30° latitude for ≥ 50 years), was 0.62, based on an odds ratio of 3.9 (1.0-14.8) (*114*). We have used the same PAF as for SCC in lightly pigmented populations (lower estimate 0.5, upper estimate 0.7), and applied this to all pigment groups. This assumes that the protective effect of pigmentation present for SCC of the skin is not present when considering disease of the cornea and conjunctiva.

Disease model

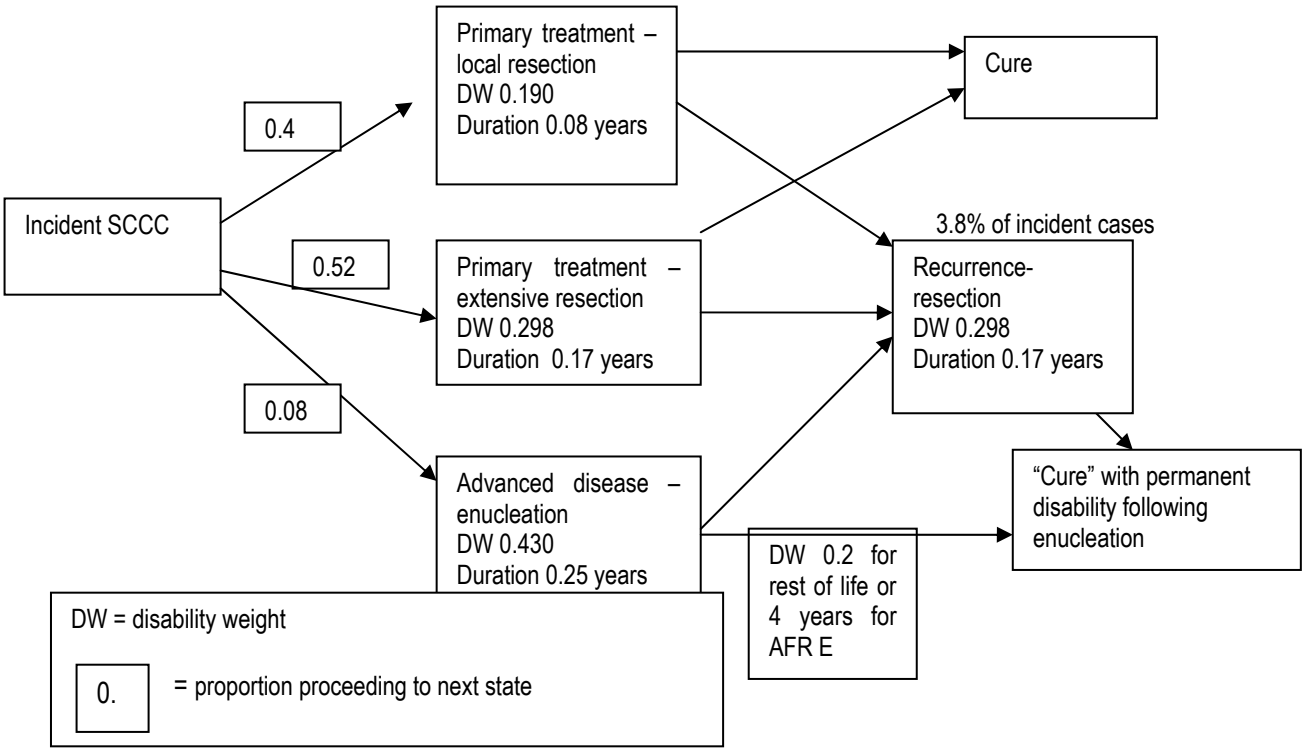
There appears to be no mortality associated with SCCC itself. Treatment is by local resection for localized disease; more extensive resection or enucleation is performed for more extensive disease.

The flow chart of the disease history is outlined in Figure 4.6.

Figure 4.6 Disease model for SCCC - ABC regions



Disease model of SCCC for DE regions



The results of the burden of disease assessment for SCCC for the year 2000 are presented in Tables 4.28 to 4.31.

(*27*)). Further human studies are required to better delineate the role of vitamin D/UVR exposure in disease onset and/or progression.

1.2 Increased susceptibility to infection

There is ample experimental evidence from animal models that exposure to UVR increases susceptibility to a range of infections – Listeria, Schistosoma, Trichinella, and Cytomegalovirus (reviewed in (*28*)). There is biological evidence at least in these animal models of an effect of UVR on immunity at the cellular and the molecular level (*4*). However, there is little evidence of clinically important effects on humans apart from in the reactivation of latent herpes labialis (*29*). There is evidence of increased incidence of viral warts in immunosuppressed patients exposed to UVR (*30*), but although animal models of UVR-induced immunosuppression have raised questions about the effects of UVR on the development or progression of AIDS in HIV positive subjects, human studies have not shown an effect of UVR exposure on HIV progression (*31*). In summary, while there is convincing biological evidence that UVR may have effects on immunity and susceptibility to infection in humans, there is little hard evidence other than in the reactivation of latent herpes labialis.

1.3 Impairment of prophylactic immunization

UVR exposure has been shown to cause local and systemic immune suppression in animal and human studies (*1*). Impairment of contact hypersensitivity to chemicals (nickel, DNCB and diphenylcyclopropenone) has been demonstrated in humans by pretreatment with UVR (*32*). This raises the question of the effect of UVR on the development of an immune response to prophylactic immunization. Sleijffers et al examined the influence of pre-exposure with UVR to the effectiveness of vaccination with hepatitis B. In this cohort study, 97 subjects were irradiated and 94 acted as controls. Pre exposure to UVB induced suppression of NK activity and contact hypersensitivity, but there was no suppression of the antibody response or the cellular immune response to hepatitis B (*33*). A review of the evidence indicates that while there are effects of UVR on response to vaccination, there is no evidence that these are of clinical significance (*34*). Notably, since UVR-induced immunosuppression affects primarily cellular (Th-1) immune responses, further examination is required of the effects of UVR exposure on prophylactic immunization of Th-1 inducing vaccines, e.g. BCG.

1.4 Activation of latent virus infections

1.4.1 Herpes labialis

In animal models and in humans, there is strong circumstantial evidence for the reactivation of herpes virus by exposure to sunlight (*35, 36*). There are few quantitative data on the links between UVR and reactivation of herpes labialis, but sufficient to make a first estimate. Further research will be required before these estimates can be defined with more accuracy.

1.4.2 Papilloma virus

As noted above, there is evidence of increased incidence of viral warts caused by papilloma virus in immunosuppressed patients exposed to sunlight (*37*). Renal transplant recipients exposed to sunlight have an increased risk of development of SCC, which may have human papilloma virus associated with them (*30*). However, there is no evidence to date of an effect of sunlight on papilloma virus infection in humans in the absence of immunosuppression and it is therefore not included in this analysis.

2. Effects on the eyes

2.1 Acute photokeratitis and photoconjunctivitis

There is copious experimental and epidemiological support for a causative role of UVR in the development of acute photokeratitis and photoconjunctivitis (*38-40*). Acute exposure to UVR in settings of high reflectance, such as surroundings covered by snow, is a common cause of photokeratitis (snow blindness) (*41*), with laboratory studies suggesting a mean threshold of UVB for photokeratitis of 3500Jm^{-2} (reviewed in (*41*)).

Occupational exposure to welder's arcs or to metal halide lamps (*42*) can induce photokeratitis in the unprotected eye. UVB blocking contact lenses are able to prevent photokeratitis in laboratory animals (*43*).

2.2 Climatic droplet keratopathy (CDK)

Also called spheroidal degeneration, this is a usually bilateral condition of major significance in certain parts of the world, reducing vision to blindness levels in older people (*41*). It is more common in areas where snowfall persists late into summer as well as in areas of sand and desert at other latitudes. This geographical pattern provides circumstantial evidence of a link with chronic solar exposure, as these surfaces are those of highest UVR reflectance. EHC 160 (*41*) concluded that there was strong evidence that climatic droplet keratopathy is due to environmental factors, but damage by particulate matter could not be excluded. Since 1994 there have been few original research reports on the association between UVR and CDK. Reviews of the association variously conclude that there is insufficient evidence of a causal link (*44*) or very strong evidence (*43*). Cullen accepts the causal association between CDK and chronic UVR exposure as proven (*45*), based on the early studies of Johnson (*46*) and Taylor ((*47*) and provides a biologically plausible explanation for the link, but fails to address the possibly confounding role of damage due to particulate matter. CDK has been used as a proxy for solar damage for the assessment of the association between UVR exposure and cataract (*48*). Animal studies do show biological changes in the cornea exposed to UVR (*43*) but it is not clear that such changes progress to CDK. Reflected UVR (eg from snow, white sand or water) may be more important than direct sunlight (*49*).

Thus although there is circumstantial (geographic) evidence of a causal contribution UVR exposure to the development of CDK and some epidemiological evidence (*46, 47*), the evidence seems insufficient at this time to conclude a causal relationship of CDK with UVR.

2.3 Pterygium

EHC 160 concluded that there was insufficient evidence to link pterygium to UVR – any associations may be due to confounding of observed associations by exposure to particulate matter (*41*). Mackenzie et al demonstrated a RR of 17.2 for pterygium associated with spending most of the time outdoors in childhood (*50*). There is a negative latitudinal gradient for pterygium but it is also common in arctic and sub arctic environments (*51*). Threlfall et al examined associations between pterygia and UV exposure in a case control study with 150 cases who had had surgical removal of pterygium. Using a complex estimate of daily ocular solar radiation dose (calculated from climatic data, time spent outdoors not under shade and the use of hats and spectacles), there was a strong link between pterygia and UVR exposure (OR = 6.8, 95% CI 2.6-19.7 for the highest quarter of exposure) (*52*). The strongest associations were found when adjustment was made for the use of hats and sunglasses, and preliminary analysis of possible confounders such as particulate matter suggested that these had only a weak effect. McCarty et al reported on the epidemiology of pterygium in Victoria, Australia. The independent risk factors for pterygium in this large case control study were age, male sex, rural residence and lifetime ocular exposure (OR = 1.63, 95% CI 1.18-2.25) (*53*). The attributable risk of sunlight and pterygium was 43.6% (*54*). Recent studies with pterygium epithelial cells provide biological support for the causal role of UVB in pterygium development (*55*).

In the studies reviewed in EHC 160, it was not possible to exclude exposure to particulate matter as a confounder of the association between UVR exposure and development of pterygia. However, both of the recent epidemiological studies reviewed above found an independent association with ocular UVR exposure, after adjustment for exposure to particulate matter. Threlfall et al's finding of a dose-response relationship between ocular UVR exposure and presence of pterygium provides further evidence of a causal association between UVR exposure and development of pterygium.

2.4 Pinguecula

Pingueculae are fibro-fatty degenerative changes of the interpalpebral conjunctiva. They share similar pathological changes to those of actinic elastosis of the skin, suggesting that sunlight may be a causative element. However, there is limited epidemiological evidence for an association with UVR. In the Chesapeake Bay watermen study, Taylor et al showed a weak association with UVA and UVB exposure (*47*). Earlier work by Johnson et al found a correlation between pinguecula and severity of CDK in Labrador (*46*), and Norn reported a geographical variation in pinguecula with higher prevalence in Arabs living near the Red Sea than in Eskimos from Greenland or Caucasians in Copenhagen (*56-58*). More recently, Nakaishi et al reported a significant association between occupational motorcycle driving and the prevalence of pinguecula, lending support to a causation related to exposure to particulate matter (*59*). Tang et al demonstrated an association between pinguecula and cumulative occupational sunlight exposure, but there was no control for confounding by exposure to particulate matter (*60*). The evidence thus far is limited and further studies will be required to

clarify the role of UVR in the development of pinguecula, particularly to separate the effects of exposure to UVR and to particulate matter.

2.5 Squamous cell carcinoma of the cornea and conjunctiva

These conditions usually present in the interpalpebral fissure (*61*), an area likely to be exposed to UVR. These corneal neoplasms are rare but are markedly more common in patients with Xeroderma pigmentosa, a recessively inherited syndrome characterized by sunlight sensitivity and a defect in DNA repair of UV-induced damage (*61*). Lee et al reported a case-control study in Australia examining the risk factors for the development of ocular surface epithelial dysplasia, a spectrum of diseases of which cancer of the cornea and conjunctiva is the most serious (*62*). Increased risk of SCCC was found with fair skin (OR = 5.4 95% CI 1.1 – 25.6), propensity to sunburn (OR = 3.8, 95% CI 0.7 – 19.7), history of previous skin cancers removed (OR = 15.0, 95%CI 2.0 – 113.6) and outdoor living in the first 6 years of life at less than 30 degrees from the equator (OR = 7.5, 95% CI 1.8-30.6). The case numbers in the study were necessarily small, hence the wide confidence intervals. There is geographical support for causation by UVR, with a clear latitudinal gradient in incidence (*63*). Guex – Grosier et al reported three cases of corneal intra-epithelial neoplasia in individuals who wore soft contact lenses and had exposure to high intensity UVR (*64*). Kusewitt et al were able to induce corneal tumours in almost 100% of grey short-tailed South American opossums exposed three times weekly to UVR for periods of a year or more (*65*). The evidence is compelling for a causal relationship between UVR and cancer of the cornea and conjunctiva, and some quantitative information is available. These outcomes were therefore included in this analysis.

2.6 Lens opacity (cataract)

The three major types of cataract are cortical, nuclear and posterior subcapsular, but many cataracts are of a mixed type. While the distinction between the types is not always clearly made in (particularly older) epidemiological studies, the etiology of the different cataract types may be quite different and they are here considered separately.

2.6.1 Nuclear cataract

EHC 160 assessed the evidence for nuclear cataract as showing no association between nuclear cataract and UVR exposure (*41*). Hammond et al studied genetic and environmental factors in the occurrence of nuclear cataracts in monozygotic and dizygotic twins and concluded that there was a strong genetic component to nuclear cataract – genetic factors explained 48% of the variance, age 38 % and unique environmental effects, 14% (*66*). Of the studied environmental effects, smoking was thought to have the greatest contribution. A recent Australian study suggests that there is an increased risk of nuclear cataract with high occupational sun exposure at ages 20-29 years (OR = 5.24, 95% CI 2.19-12.6) (*67*). A similar pattern was not seen for sun exposure at other ages. This somewhat unusual age-pattern of exposure will require further investigation before UVR exposure can be considered as causal for the development of nuclear cataract.

2.6.2 Posterior subcapsular cataract (PSC)

The conclusion of the EHC 160 review was that there was inadequate evidence available to link PSC cataract in humans to chronic UVB exposure, although there was sufficient evidence of a link between PSC cataract and UVB exposure in animals.

Using a measure of sun exposure based on residential history and recalled amount of time in the sun (little, moderate or much), Collman et al found an association of sunlight exposure and posterior subcapsular cataract that was similar in strength to that between cortical cataract and sunlight exposure (OR= 1.52, 95% CI 0.28-5.44 for the highest exposure) (*68*).

Despite high ocular UVR exposure in the Chesapeake Bay watermen study, there were too few PSC cataracts to analyse associations with UVR exposure (*69*). In a group likely to have similar high ocular exposure, Hong Kong fishermen, the number of PSC cataracts was again very low compared with nuclear or cortical cataract (*70*). If there was an association between excess UVR exposure and PSC cataracts one might expect that populations such as these, that are likely to have high ocular UVR exposure might have a high prevalence of PSC cataract, but the reverse is apparent.

The India –US Case-control Study on age-related cataract showed a decreased risk of all types of cataract with increased lifetime cloud cover (and by inference, decreased UVR exposure) at the place of residence (OR = 0.78, 95% CI 0.68-0.9) (*71*).

In the Italian-American Cataract Study, UVR exposure was assessed by occupational exposure, use of a hat in the summertime and leisure activities in the sunlight. Analysis of the results revealed a decreased risk of PSC cataract with increasing occupational exposure and leisure time exposure to sunlight, but a positive association with the use of a hat in summer (*72*). The latter observation of increased risk of PSC cataract with the wearing of a hat in summer was thought to be explainable if wearing a hat in summer was a proxy for increased exposure. However, the lack of a positive association of PSC cataract with the other measures of UVR exposure is perhaps stronger evidence against a causative relationship of PSC cataract with UVR exposure.

There was no association between occupational exposure to sunlight and PSC cataract in the Lens Opacities Case-Control study (*73*). In the Beaver Dam Eye study, a measure of average annual ambient UVB light exposure was constructed for each individual based on years of residence in a region weighted by the total ambient UVB light present in that area, as a ratio of the level of such light present for one year in Wisconsin (*74*). There was no association of UVR exposure as measured by this method with PSC cataract in either sex.

Rosmini et al created a summary sunlight index as the measure of sunlight exposure and found no association between any PSC cataract and the sunlight score (*75*). Notably, the number of PSC cataracts was small compared to nuclear or cortical cataracts, but there was a dose-response relationship between the sunlight index and mixed cortical and PSC cataracts.

A positive association between PSC cataract and UVB exposure is reported by Taylor et al (*76*) using a derived measure of personal ocular UVB exposure in a case-control study undertaken in the same area as the Chesapeake Bay Watermen study.

In the Salisbury Eye Evaluation Project, West et al examined relationships between annual ocular UVB doses and cataract in white and African-American populations in Maryland. There was no association between UVB exposure and PSC cataract in either race (*77*).

This lack of association was supported in the Melbourne Visual Impairment Study. While cortical cataract showed a significant association with increased average annual ocular UVB exposure, PSC cataract was associated with increased age, rural location, and use of thiazide diuretics, vitamin E intake and myopia (*78*).

Finally, the POLA study, undertaken in Sete, southern France found no significant association between PSC and average annual ambient solar radiation exposure, while confirming the positive relationship of UVB exposure to cortical cataract (*79*). Professional exposure to sunlight was associated with an excess risk of PSC cataract (OR = 1.75, 95% CI 1.10-2.80).

While some studies have suggested a positive association between PSC cataract and UVB exposure using a number of different measures of UVB exposure, the weight of the evidence (particularly more recently) suggests that PSC cataract is not associated with increased UVB exposure, and PSC has not been included in this burden of disease analysis.

2.6.3 Cortical cataract

In the 1994 WHO review (*41*), most studies indicated some association between cortical cataract and UVR exposure. Taylor et al studied Chesapeake Bay watermen and found a relative risk for presence of cortical cataract for the highest sun exposure category that was three times that for the lowest exposure category (*69*). Subsequent data from the Beaver Eye study suggested that the increased risk might be confined to men (*74*). West et al reported results from a large nested case control study in Maryland in which a detailed model of sun exposure was used to assess sun exposure since age 30, with adjustment for wearing of hats and glasses, average UVR and cloud cover (*77*). There was a higher prevalence of cortical opacity with higher UVR exposure (OR (highest quartile of UV exposure cf. lowest) = 1.57, 95% CI 1.04 – 2.38). Smoking, education and alcohol use were not significantly related to cortical opacity. The association of UVR with cortical cataract was further supported by the findings of McCarty et al in the Visual Impairment study in Victoria, Australia (*78*). There was a statistically significant increased risk of cortical cataract (OR = 1.44, 95% CI 1.21 – 1.73). Further studies of the association between UVR exposure and cortical cataract are summarized in the accompanying tables.

Recent research focuses on the biological processes involved, including the effects of timing and of repeated exposure (*80*), age of exposure (*81*), the role of UVA in cataract genesis (*82*), and protective mechanisms (*83*).

The evidence of an association between presence of cortical cataract and past ocular UVR exposure is largely consistent across a number of well-conducted, large studies. Cortical cataract is included in this analysis.

2.7 Ocular melanoma

EHC 160 reviewed a number of epidemiologic and geographic studies on the risk factors for uveal melanoma and concluded that there was insufficient evidence of a causal association with excessive UVR exposure. In particular, there was no convincing latitudinal gradient for uveal melanoma in the US, Canada or Australia and inconsistent findings relating place of birth to uveal melanoma. There was no statistically significant association between ocular melanoma and a personal history of skin cancer.

In a comparison of age-standardized mortality rates for cancers of the eye and those for cutaneous malignant melanoma (CMM) in England and Wales, Dolin et al found that while rates for CMM increased three-fold from 1950/54 to1985/89 those of uveal melanoma stayed relatively constant (*84*). Holly et al demonstrated an increased risk of uveal melanoma in occupational groups who had intense exposure to ultraviolet light (OR3.0; 1.2-7.8), welding exposure (OR = 2.2; 95% CI 1.3-3.5) and asbestos exposure (OR = 2.4, 95% CI 1.5-3.9) (*85*).

In Queensland, Australia, Pane and Hirst found that risk factors in for ocular melanoma included personal history of cutaneous melanoma (OR = 2.42. 95% CI 0.88-6.62), other skin cancers (OR = 1.52, 95% CI 0.99-2.35), and family history of ocular melanoma (OR = 6.89, 95% CI 0.7-67.38) (*86*). Protective factors included olive or black skin, brown iris colour, high resistance to sunburn and wearing prescription sunglasses. Sunglass wearing and cumulative lifetime ocular UVB exposure were not associated with ocular melanoma.

A recent case-control study in France examined occupational exposure to UVR, both solar and artificial (*87*). While there was an increased risk of ocular melanoma in occupational groups exposed to artificial UVR, there was no increased risk in outdoor occupational groups. Interestingly, this study showed a dose-response relationship with job duration among welders, and an increased risk among male cooks, and female metal workers and material handling operators. This raises the question of whether it is the exposure to UVR in welders that is the causal exposure or something else in the welding process.

Another recent large case-control study from Australia found that eye color was the strongest independent predictor of choroidal and ciliary body melanoma (*88*). Risk was greater for grey, hazel, and blue eyes than brown eyes, and was also increased with decreasing ability to tan, increasing numbers of nevi on the back and with squinting as a child. Such findings strengthen the case for a genetic risk but are consistent with some causal effect of UVR. This study also examined sun exposure and uveal melanomas. Their findings suggest an association of choroid and ciliary body melanoma with occupational sun exposure (mainly in men), with less convincing results of an association with total exposure and no evidence of association with ambient solar irradiance.

In a recent meta-analysis of the evidence, risk of ocular melanoma was increased with exposure to welding (OR = 2.05, 95% CI 1.20 – 3.51) but not with measures of outdoor leisure time (OR = 0.86, 95% CI 0.71 – 1.04), or latitude of birth (OR = 1.08, 95% CI 0.67 – 1.74) (*89*). Occupational sunlight exposure had a borderline non-significant association with the development of uveal melanoma (OR = 1.37, 95% CI 0.96 – 1.61).

In the opinion of the working group, at this stage there is insufficient evidence of a causal relationship with excessive ambient UVR exposure to include ocular melanoma in this analysis.

2.8 Acute solar retinopathy

Also known as phototoxic retinopathy or eclipse retinopathy, acute solar retinopathy has been recognized as a cause of acute loss of vision for many years. It is usually described following sun-gazing or looking at the sun during a solar eclipse, but there have been increasing reports of a similar burn to the retina related to lengthy exposure to light from an operating microscope during eye surgery (*90*). There is such a strong temporal relationship between the intense solar exposure and the retinopathy that we can conclude a causal relationship between the two. Most cases of acute solar retinopathy recover their vision loss over weeks or months, but a few will go on to permanent visual impairment, usually a central scotoma (*91-93*). Despite strong evidence of a causal association with UVR exposure, acute solar retinopathy was not included in this analysis, as it is a sporadic disorder, for which there are insufficient global incidence data from which to derive burden of disease estimates.

2.9 Macular degeneration

There is circumstantial evidence of a link between excess UVR exposure and acute macular degeneration (AMD). For example, Young noted that AMD occurs in the precise region of the eye that would be preferentially damaged by bright light and that both ocular melanin and cataractous lens appear to protect the retina against AMD (*94*).

Bressler's review of the associations between AMD and UVR exposure concluded that the evidence was limited and inconsistent, while there was evidence of positive associations between AMD and cigarette smoking and between AMD and cardiovascular disease (*95*). In a recent examination of the links between ocular UVR exposure and AMD, Loeffler et al examined the association between AMD and other ocular changes possibly induced by UVR, pinguecula and scleral plaque (*96*). There was a significant association between scleral plaque and AMD (and no significant association between pinguecula and AMD). This provides some support for a causative role of exposure to solar radiation in the development of AMD, provided one accepts that solar radiation has a causative role in the development of scleral plaque.

In a comprehensive review of the literature on AMD in 2001, Penfold et al cite the risk factors for AMD, in order of importance, as age and then smoking, with hypertension implicated in causation of the wet form (*97*). Ultraviolet radiation as a causative factor is not considered.

The evidence linking excess ocular UVR exposure to AMD appears tenuous. It seems likely that smoking and cardiovascular disease are important causative factors, with more research required on the associations with UVR exposure and micronutrient levels. While not included in this burden of disease analysis, causative links between excess UV exposure and AMD should be further evaluated in future burden of disease assessments.

3. Effects on the skin

3.1 Cutaneous Malignant Melanoma

There is little doubt from the epidemiologic literature that UVR has a causative relationship with development of malignant melanoma. Evidence includes: - a positive association between melanoma incidence and residence at lower latitudes; a decreased risk of melanoma in those who migrated in childhood, from an area of low UVR to an area of high UVR (compared to those born in the area of high UVR and still resident there); a body site distribution which mirrors those areas of the body usually exposed to sunlight; a correlation with freckling and development of melanocytic naevi; a correlation with other evidence of solar skin damage (wrinkling, solar keratoses); the very low incidence of melanoma in people with black skin, and an increased risk (OR of the order of 1.5) with a history of intermittent sun exposure and sunburn (reviewed in (*41, 98*). Cutaneous malignant melanoma is included in this analysis of the global burden of disease due to ultraviolet radiation.

3.2 Cancer of the lip

This disorder includes cancer of the vermilion border of the lip and the adjacent mucous membrane, but excludes cancer of skin adjacent to the lip. There is some evidence for UVR exposure as a causal risk factor for this disease, including: most occur on the lower lip which has a higher sun exposure than the upper lip; incidence is higher in men than women and higher in white populations than in black or Asian populations; incidence is lower in migrants from areas of low UVR to areas of high UVR (compared to those born in the area of high UVR) and higher in rural than urban dwellers and in those with outdoor occupations.

There is an increased risk of cancer of the lip following SCC of the skin (*99*) and actinic cheilosis may progress to SCC of the lip, similar to the association between solar keratoses and SCC (*100*).

Few epidemiological studies have adequately controlled for confounding by tobacco or alcohol which are known risk factors for oral cancers. Furthermore, a recent review suggested that cancer of the lip has a complex causation due to the interaction of a number of factors (*101*).Further research is required before there is sufficient evidence of a causal role for ultraviolet radiation in causation of cancer of the lip and before the risk attributed to UVR exposure can be determined.

3.3 Squamous cell carcinoma of the skin

There is convincing epidemiologic and biological evidence of a causal association of UV exposure (particularly occupational exposure) to development of squamous cell carcinoma of the skin (SCC) and it was thus included in this analysis. The evidence includes: increased risk in those with light complexion and increased sensitivity

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1.4 Reactivation of latent viral infections							
Perna et al., 1987 (*255*)	USA	Experimental N = 5 Age = 26 - 45	UV irradiation	Reactivation of herpes simplex virus infection	Site-specific UV irradiation resulted in reactivation of infection in 8 out of 13 attempts after a mean of 4.4 days. Some patients appear more susceptible to UV-induced reactivation than others.		
Young et al., 1988 (*35*)	Wisconsin, USA	Case-control Cases: n = 139 Controls: n = 283 Age = 17+years	Outdoor job during childhood Severe facial sunburns Severe facial sunburns	Recurrent herpes labialis Recurrence rate		OR = 1.77 OR = 1.64 OR = 1.55	1.14 – 2.70 1.11 – 2.41 0.97 – 2.50

Table A1.3 Summary of reviews of UVR effects on the eyes

2. Effects on eyes		
Bergmanson and Soderberg, 1995 (*43*)	Review	Little light reaches the retina (absorbed by cornea and lens). Experimental evidence of damage due to both low and high intensity UVR. Good evidence for UVR causation of Photokeratitis. Chronic exposure may cause climatic droplet keratopathy (spheroid degeneration). Insufficient evidence to conclude a causal relationship between pinguecula and UVR exposure. Strong experimental and epidemiological evidence for a causal role of UVR exposure in pterygium. Increased risk of cataract, particularly cortical cataract with excessive UVR exposure (experimental and epidemiological evidence). Some evidence for an association with AMD but inconclusive. UVR exposure important for development of SCCC.
Dolin and Johnson, 1994 (*44*)	Review	Sufficient evidence that photokeratitis is caused by exposure to high dose solar radiation, occurring after 200 seconds of unattenuated exposure to 295-315nm UVR. CDK may be caused by solar radiation (limited evidence), but not specifically UVR. Particulate injury (sand, ice) may be important. Pinguecula similar pathologically to actinic keratosis of the skin. Conclude limited evidence for a role of UVR exposure in the causation of pinguecula. Limited evidence of an association between sunlight exposure and development of pterygium; role of UVR exposure unclear. Limited evidence for an association between UVR exposure and conjunctival neoplasms. Insufficient evidence for a causal association between UVR exposure and cataract. UVR exposure is probably not the cause of exfoliation syndrome. Insufficient evidence of a causal association between naturally occurring solar exposure and ocular melanoma. Little evidence of an association between acute macular degeneration and history of UVR exposure.
Taylor, 1989 (*256*)	Review	Association of UVR exposure and cataract is biochemically plausible via photo-oxidation of free or protein-bound tryptophan, photosynthetic processes involving activated species of oxygen, disruption of the membrane-cation transport system or damage to nucleic acids in lens epithelial cells. Experimental studies also supportive. Some support from epidemiological studies. Some indirect evidence of an association between AMD and UVR exposure.
Taylor, 1989 (*257*)	Review	Chesapeake Bay watermen study provided epidemiological evidence for an association between UVR exposure and cortical cataract, pterygium and climatic droplet keratopathy. Other studies have indicated an association between UVR exposure and PSC. While there is experimental support for a role of UVB in age-related macular degeneration there is little epidemiological support.
Young and Sands, 1998 (*258*)	Review	UVR exposure associated causes solar keratopathy, BCC of the eyelid, SCCC, pingueculae, pterygia, climatic droplet keratopathy, cataracts (all types), solar retinopathy, possibly AMD and uveal melanoma.
2.1 Acute photokeratitis and photoconjunctivitis		
Bergmanson, 1990 (*38*)	Experimental	UVR exposure of the primate cornea caused significant destruction of the epithelium and stromal swelling.
Kennedy et al., 1997 (*39*)	Experimental	Acute UV irradiation of human corneal stromal cells results in the production of IL-1, IL-6, IL-8 and TNF-α which may be responsible for UV-mediated corneal inflammation.
Sliney, 1987 (*40*)		Daily radiant UVB exposure to the cornea is less than the mathematically weighted safety limit occupational exposure limit of the American Conference of Governmental Industrial Hygienists – thus photokeratitis from outdoor daylight is rare. Reflected levels of UVR from light sand should be sufficient to cause a threshold photokeratitis within exposure periods of 6-8 hours.
2.2 Climatic droplet keratopathy		
Cullen, 2002 (*45*)	Review	Chronic exposure to UVR causes climatic droplet keratopathy with visual impairment, by depositing material in the superficial stroma and Bowman layer, possibly by photochemically altering diffusible plasma proteins reaching the cornea.
Sliney, 1999 (*49*)	Review	Epidemiological studies assessing the role of UVR in the causation of eye diseases may produce inconsistent findings due to lack of precision in the estimate

		of ocular UVR dose. Most ground surfaces reflect little UVR and greatest UVR exposure may thus occur where ground reflection is high. The role of particulate matter in the causation of CDK is unclear.
Young and Finlay, 1975 (*259*)	Cross-sectional	929 persons in Labrador and Northern Newfoundland. Increasing prevalence and severity of CDK with increasing age, in males and with outdoor occupation. Suggest UVR as the most significant causative factor (based on geographic variation).
2.3 Pterygium		
Cameron, 1965 (*51*)	Review	Good correlation between latitude and prevalence of pterygium. Hot, dry dusty countries have high prevalence, eg North Africa, Arabia, Mexico.
Coster, 1995 (*260*)	Review	Brief review suggests that high UVR exposure particularly in the second or third decade of life is important to pterygium development. Also a genetic predisposition.
Di Girolamo et al., 2005 (*55*)	Experimental	UVB exposure of pterygium epithelial cells was associated with induction of matrix metalloproteinase collagense-1 (MMP-1) and enhancement of the phosphorylated form of ERK1/2 in a time-dependent manner. The finding of specific UVB induced intracellular signaling pathways, supports a role for UVB in pterygium formation.
Hirst, 2000 (*261*)	Review	Increased risk of developing pterygium in subjects who spent the first five years of life at latitudes less than 30° and who spent most of their time outdoors, particularly in the first decade of life. Greater risk associated with working on sand; hazel-green eye colour; red hair; medium skin colour; moderate number of freckles; history of burning when sun-exposed; possible increased risk due to exposure to irritants; possibly HPV infection.
Shimmura et al., 2000 (*262*)	Experimental study	UVR exposed skin is characterized by specific mutations in the tumour suppressor gene p53 and increased telomerase activity (prolonging cell survival). Pterygia tissue shows some increase in telomerase activity but no increase in p53
Wang et al., 2000 (*263*)	Experimental study	Experimental study of tissue from pterygia and normal conjunctival specimens. UV irradiation induced induces mutations resulting in increased tropoelastin in conjunctival fibroblasts similar to that seen in the pinguecula subepithelial connective tissue of pterygia.
2.4 Pinguecula		
Norn, 1979 (*56*)	Cross-sectional	Prevalence of pinguecula in Eskimos in South Greenland was 56%, compared to 41% in Copenhagen, with increasing prevalence with increasing age. Incidence of pinguecula and CDK are correlated in both geographic series but are not correlated with pterygium.
Norn, 1982 (*57*)	Cross-sectional	Prevalence of pinguecula at the Red Sea is 90% - this is consistent with causation by high UVR exposure. Pterygia were equally present at the Red Sea and in Greenland and were quite small.
Norn, 1984 (*58*)	Cross-sectional	Pinguecula present in 60% of Japanese in Kyoto province (ages 0-89) with increasing prevalence with increasing age and male sex. The prevalence is lower than Jordan, higher than in Denmark but similar to that in Greenland. Prevalence was higher in rural than urban dwellers. Pterygium was rare.
2.5 SCCC		
Ateenyi-Agaba, 1995 (*264*)	Cross-sectional	RR for conjunctival tumours associated with HIV infection = 13.0; possible interaction with high UVR exposure
Guex-Crosier and Herbort, 1993 (*64*)	Case reports	Three cases reported with corneal intra-epithelial neoplasia in young adults with a history of contact lens wearing and repetitive exposure to strong ultraviolet light.
Kusewitt et al., 2000 (*65*)	Experimental	UVR exposure of the grey, short-tailed South American opossums (*Mondelphis domestica*) resulted in the formation of corneal tumours of a variety of histologies, but including squamous cell carcinoma of the cornea.
Newton, 1996 (*265*)	Review	SCCC related to HIV seropositivity, previous SCC, and UVR exposure and possibly ocular trauma or ocular HPV infection.
Sun et al., 1997 (*61*)	Review	Evidence for a causal association with UVB exposure: greater frequency of SCCC at low latitude; decreasing incidence with increasing latitude (in a dose-response manner); SCCC more common in patients with xeroderma pigmentosa; association between UVB exposure and SCC of the skin especially SCC of the eyelid. Other likely causative agents: HIV infection and HPV infection.
2.6 Lens opacity		
Ayala et al., 2000 (*80*)	Experimental	Repeated UVR exposure of the lens in rats at different time intervals indicated that the greatest sensitivity for a second UVR exposure occurred where the time from first UVR exposure was three days (compared to 6 hours, 1 day, 9 days and 30 days). When exposures are one month apart the lens is able to undergo physiological repair.
Brian and Taylor, 2001 (*266*)	Review	Risk factors for age-related cataract include UVR exposure, diabetes, therapeutic drugs, smoking and alcohol.
Colitz et al., 2005 (*83*)	Review	There are a number of mechanisms by which the mammalian lens protects and repairs UV-induced damage, including several endogenous anti-oxidants and

		dietary intake of anti-oxidants. Micronutrient poor diets and smoking increase the risk of cataract.
Hockwin et al., 1999 (*267*)	Review	Experimental evidence confirms an important role for UVR in cataractogenesis – acute lens damage from high dose UVR (uncommon) and (chronic lower dose) cocataractogenic promotion of other processes, eg changes in carbohydrate metabolism, oxidative stress etc.
Hodge et al., 1995 (*268*)	Review	Ecologic studies suggest an associated between cataract and UVR exposure, although in one study this was limited to cortical cataracts only. Evidence from case-control studies is more equivocal – some show an association but most consistent results are for cortical cataract.
Hu and Lao, 1987 (*269*)	Cross-sectional	Study from China indicating an inverse association of cataract with latitude and direct association with altitude (10 fold increase in cataract in Zedang – the region of highest latitude).
Taylor et al., 1994 (*244*)	Review	Chesapeake Bay watermen studies show a consistent relationship between individual ocular UVB exposure and risk of both cortical and posterior subcapsular cataract (p = 0.006), but no association with nuclear cataract.
West and Valmadrid, 1995 (*270*)	Review	Cortical and posterior subcapsular cataract most closely associated with environmental stresses including UVR exposure; nuclear cataract particularly associated with smoking.
West, 1999 (*271*)	Review	Ecological studies suggest increased risk of cataract with residence in areas of higher ambient UVR. Increased exposure to UVB association with increased risk of cortical cataract.
Zigman, 2005 (*82*)	Review	UVA irradiance is 1000 times that of UVB in sunlight. Little UVB penetrates the cornea to reach the lens (<2%), as UVA energy is about 30 times that of UVB. UVA penetrates the cornea (approx 50%) to reach the lens. There are a number of potential UVA targets in the lens and some evidence for an important role of UVA exposure.
2.7 Ocular melanoma		
Egan et al., 1988 (*272*)	Review	Conflicting evidence for role of UVR. For: rare in non-white populations. Against: no increase in incidence rate over time; not latitudinal gradient; no increased risk in persons with xeroderma pigmentosa; experimental evidence suggests that virtually no UVA or B is transmitted past the cornea and lens; negative findings from case-control studies.
2.8 Acute solar retinopathy		
Atmaca et al., 1995 (*93*)	Follow-up	Solar retinopathy following a solar eclipse associated with early but not late visual loss.
Eke and Wong, 2001 (*91*)	Case series	Eclipse retinopathy following a solar eclipse in 20 patients – persistent central scotomata at 14 months resolved by 21 months.
Kleinmann et al., 2002, (*90*)	Retrospective trial	Phototoxic retinopathy occurred following cataract surgery, induced by the operating microscope. This may occur during even short duration operations.
Rai et al., 1998 (*273*)	Case series	319 patients with solar retinopathy following sun gazing. Most resolve quickly, but some patients have persistent visual disturbances.
Verma et al., 1996 (*274*)	Case series	21 patients with eclipse retinopathy following unprotected (or insufficient protection) viewing of a solar eclipse. Some associated long-term visual damage.
Wong et al., 2001 (*92*)	Prospective study	Report of 45 patients who suffered acute solar retinopathy after watching a solar eclipse (age 15-82y). 5 patients had detectable retinal changes and reduced vision. 20 patients had visual disturbance mainly resolving over several months.
2.9 Macular degeneration		
Bressler and Bressler, 1995 (*95*)	Review	The evidence for an association between AMD and UVR exposure is limited, inconsistent and conflicting. There are positive associations with smoking and cardiovascular disease.
Penfold et al., 2001 (*97*)	Review	Population studies indicate that after age, the most significant risk factor for AMD is smoking (OR = 3.9).
Loeffler et al., 2001 (*96*)	Histological cross-sectional study	No statistically significant association between presence of pinguecula and AMD. There was a statistically significant association with senile scleral plaque (p = 0.02), but this became non-significant when adjusted for age. These results could support a UVR etiology for AMD but the UVR etiology of both pinguecula and scleral plaque is not established.
Young, 1988 (*94*)	Review	Action spectrum of damage to the retina suggests blue light (wavelength 400-500nm) most important. AMD probably multi-factorial, with a genetic element.

Table A1.4 Detailed summary of epidemiological studies examining UVR effects on eyes

Study	Location	Design, N, Age	Exposure assessment	Outcome assessment	Adjusted covariates	Measure of effect	95% CI
2.1 Acute photokeratitis and photoconjunctivitis							
Kirschke et al., 2004 (*42*)	Nashville, USA	Cohort	Exposure to damaged metal halide lamps	Development of photokeratitis within 12 hours	Attack rate for persons sitting in an identified high risk area was 46%; some protection from UV-blocking glasses or contact lenses.		
2.2 Climatic droplet keratopathy							
Johnson, 1981 (*46*)	Labrador and northern Newfoundland	Cross-sectional	Latitude of residence	Age of onset and severity of CDK	Peak prevalence, earliest age of onset and greatest severity of CDK was in those living at 55-56 degrees north. This corresponds to the area of highest intensity UVR reflected from ice and snow. Degree of CDK proportional to amount of time spent in outdoor activities such as hunting, trapping.		
2.3 Pterygium							
Ben-Amer, 1989 (*275*)	Libya	Cross-sectional	Housing conditions, trachoma	Pterygium	Association between pterygium, trachoma and poor housing		
Detels and Dhir, 1967 (*276*)	Canada India Thailand Taiwan	Cross-sectional N = 210 (cases); N = 104 (cases); N = 107 (controls) N = 110 (cases) N = 83 (controls) N = 153 (cases) N = 197 (controls)	Occupation as a sawmill worker	Presence of pterygium	Age adjusted prevalence of pterygium: Canada – 12% for East Indian sawmill workers Canada – 2% for white sawmill workers India - 7% for Kurali villagers India - 24% among sawmill workers India – 8% among urban controls Bangkok – 27% among sawmill workers Bangkok – 16% in cotton mill workers Taiwan – 31% among sawmill workers Taiwan – 10% among clothing workers Sawmill work cf other work: p<0.00001; increasing risk with increasing years in the sawmill. Good correlation with latitude but not solar radiation; suggest exposure to particulate matter more important than UVR exposure.		
Goldberg and David, 1976 (*277*)	South Africa	Case-control N = 105 eyes Age: 44 – 79 y	Tear film abnormalities (postulated as on the causal pathway from UVR to pterygium	Pterygium	No significant difference between normal eyes and those with pterygium in tear formation ie if pterygium is caused by UVR this is not mediated by its effect on the tear film		
Hirst, 2000 (*261*)	Australia	Review	Childhood sun exposure: - (latitude <30°) - Time spent outdoors (>50% cf <50%) Adult sun exposure - latitude <30° - Time spent outdoors - working environment (concrete vs indoor	Pterygium	 RR = 36.3 RR = 17.2 RR = 39.5 RR = 5.7 RR = 10.8	 6.7 – 196 6.2 – 47.6 6.7 – 196 3.1 – 10.6 4.1 – 28.1	
Liu et al., 2001 Abstract only, article in Chinese (*278*)	Haikou, China	Prevalence survey	Age, sex	Pterygium		Overall prevalence 7.86% M 6.4%; F 9.4%	
Luthra et al., 2001 (*279*)	Barbados	Cross-sectional study	Sun exposure (occupational, use of sun glasses)	Prevalence of pterygium	Age and sex (protective factors: dark skin, use of sunglasses)	OR = 2.02	1.65 – 2.47

McCarty et al., 2000 (*53*)	Melbourne, Australia	Cross-sectional N = 5147 Age: 40-101 years	Lifetime ocular sun exposure	Pterygium	Age, gender, rural residence	OR = 1.63	1.18 – 2.25
Mackenzie et al., 1992 (*50*)	Brisbane, Australia	Case control	Sandy living environment - 20-29 years - 0-5 years Latitude residence (<30) - 20-29 years - 0-5 years Time spent outdoors - 20-29 years - 0-5 years Did not wear sunglasses	Primary pterygium	Age	 OR = 10.81 OR = 1.6 OR = 39.5 OR = 36.3 OR = 5.7 OR = 17.2 OR = 5.4	 4.1 – 28.1 0.9 – 2.9 2.8 – 560.6 6.7 – 196.0 3.1 – 10.6 6.2 – 47.6 3.3 – 8.7
Moran and Hollows, 1984 (*280*)	Australia	Ecologic	Latitude of residence	Pterygium	Strong positive correlation with latitude		
Nakaishi et al., 1997 (*59*)	Japan	Cross-sectional Exposed: n = 783 Controls: n = 207 Age = 22 - 49	Occupation as a motorcycle policeman	Pinguecula Pterygia	RR (15 yrs driving cf 0) = 2.92 RR (Exposure index – km yrs, 200,000 vs none) = 2.66 Too few to analyse		2.18 – 3.86 2.08 – 3.40
Panchapakesan et al., 1998 (*281*)	New South Wales, Australia	Cross-sectional Pterygium: n = 236 Pinguecula: n = 2521 Age = 49+	Sun-induced skin damage	Pterygium Pinguecula	OR = 2.4 ns		1.5 – 3.8
Saw et al., 2000 (*282*)	Singapore	Case-control Cases: n = 61 Controls: n = 125 Age: 30+	Current sun exposure Sun exposure 5 yrs ago Sun exposure 10 yrs ago	Pterygium	Sex, age, use of spectacles, family history of eye disease, family income	OR = 1.05 OR = 1.27 OR = 1.31	0.83 – 1.34 1.06 – 1.54 1.09 – 1.57
Tang et al., 1999 Abstract only (*60*)	Taipei, Taiwan	Cross-sectional N = 394	Outdoor postal work	Pterygium Pinguecula	As occupational sun exposure increases by one unit, the risks of developing pinguecula and pterygium increase by 2.1% and 0.8% respectively		p<0.05 p<0.05
Taylor et al., 1989 (*47*)	Maryland, USA	Cross-sectional N = 838 Age: 30+	Ocular exposure: UVA_1 (A1) UVA_2 (A2) UVB (B) Av annual UVB UVA_1 (A1) UVA_2 (A2) UVB (B) Av annual UVB UVA_1 (A1) UVA_2 (A2) UVB (B) Av annual UVB	 Pterygium, Pingueculae Climatic droplet keratopathy	Age	 OR = 0.82 OR = 0.86 OR = 0.65 OR = 3.06 OR = 0.29 OR = 0.28 OR = 0.29 OR = 1.40 OR = 1.49 OR = 1.53 OR = 1.26 OR = 6.36	 0.45 – 1.19 0.48 – 1.25 0.33 – 0.98 1.77 – 5.31 0.03 – 0.55 0.02 – 0.54 0.05 – 0.52 0.88 – 2.23 1.07 – 1.92 1.09 – 1.96 0.88 – 1.63 3.46 – 11.68

Threlfall and English, 1999 (*52*)	Perth, Australia	Case-control Cases: n = 150 Controls: n = 135	Av. Latitude of residence, >32° cf <32° Av. Daily hrs sunshine at place of residence Av. Solar radiant energy at residence Av. Daily hrs personal sun exposure (9-5) Av. Daily hrs personal sun exposure (10-2) Av. Daily hrs ocular sun exposure (9-5) Av. Daily ocular radiation dose	Pterygium	Age group, sex	OR = 0.52 OR = 2.63 OR = 2.31 OR = 4.01 OR = 4.84 OR = 4.38 OR = 6.77	0.25 – 1.03 1.49 – 4.71 1.28 – 4.25 1.60 – 10.88 1.98 – 12.74 1.88 – 10.93 2.60 – 19.68
Wong et al., 2001 (*283*)	Singapore	Cross-sectional N = 1232 Age: 40-79	Occupation: Factory/production workers and machine operators Labourers and agricultural workers Smoking status: Y vs N	Pterygium	Age, sex	OR = 3.8 OR =3.2 OR = 1.7	1.9 – 7.5 1.6 – 6.6 1.1 – 2.7
2.5 Squamous cell carcinoma of the cornea and conjunctiva							
Lee et al., 1994 (*62*)	Australia	Case-control N (cases) = 60 N (controls) = 60	Fair skin Propensity to sunburn Pale iris History of previous skin cancers removed High early residential ambient UVR	SCCC		OR = 5.4 OR = 3.8 OR = 1.8 OR = 15.0 OR = 7.5	1.1 – 25.6 0.7 – 19.7 0.9 – 3.8 2.0 – 113.6 1.8 – 30.6
2.6 Cataracts							
AREDS, 2001 (*284*)	USA	Case-control N = 4477 Age: 60-80 yrs	Sunlight exposure (adult average annual ocular UVB exposure)	Cortical cataract Nuclear cataract		OR = 1.33 ns	0.98 – 1.82
Brilliant et al., 1983 (*285*)	Nepal	Cross-sectional N = 873 All ages	Altitude of residence Sunlight hours	Cataract prevalence		r = -0.533 r = 0.563	p<0.0001 p<0.0001
Chatterjee et al., 1982 (*286*)	India	Cross-sectional N = 1269 Age: 30+	Low total protein consumption, low education	Cataract	40% of the excess prevalence of Punjab cataract over that in a US population study could be accounted for by low protein consumption.		
Collman et al., 1988 (*68*)	North Carolina, USA	Case-control Cases: n = 113 Controls: n = 161 Age = 40-69	Sunlight exposure	Cataract		C: OR = 1.53 PSC:OR= 1.52 N: OR = 0.79 M: OR = 1.36	0.21 – 7.19 0.28 – 5.44 0.39 – 1.96 0.36 – 3.72
Cruickshanks et al., 1992 (*74*)	Wisconsin, USA	Cross-sectional N = 4926 Age: 43-84	Average annual ambient UVB exposure	Cataract: Cortical PSC Nuclear	Age	OR=1.36 (M) OR=0.94 (F) OR=1.17 (M) OR=1.10 (F) OR=0.93 (M) OR=0.97 (F)	1.02 – 1.79 0.70 – 1.26 0.79 – 1.73 0.70 – 1.72 0.78 – 1.12 0.78 – 1.20
Delcourt et al., 2000 (*79*).	France	Cross-sectional N = 2584 Mean age=70.4 yr	Annual ambient solar radiation Professional exposure to sunlight Leisure sunlight exposure	Cataract: Cortical (C) Posterior subcapsular (PSC) Nuclear (N) Mixed (M)	Age, sex, education level, oral corticosteroids, cancer, diabetes, smoking	C: OR = 2.48 PSC = ns N: OR = 1.76 M: OR = 3.98 C: ns PSC: OR=1.63 N & M = ns C, N & M: ns PSC: OR=0.62	1.24 – 4.99 0.95 – 3.24 1.98 – 7.98 1.01 – 2.63 0.43 – 0.90

Dong et al., 2003 (*81*)	Stockholm, Sweden	Experimental (rats)	UVR exposure, age	Development of cataract	UVR-irradiated rats developed cataracts with greater sensitivity in young cf old rats.		
Graziosi et al., 1996 (*287*)	Italy & USA	Cross-sectional element of case-control study N = 731	Sunlight index	Location of cortical opacity (Wedge-shaped cortical opacities markedly more frequent and more severe in the inferior-nasal quadrant of the lens): Inferior lens areal involvement cf superior involvement		OR = 1.73	1.03 – 2.93
Hammond et al., 2000 (*66*)	UK	Twin studies N = 506 twins Age: 50-79	Zygosity Environmental factors	Nuclear cataract	Heritability in nuclear cataract = 48% (95% CI 42 – 54%); remaining variance explained by age (38%, 95% CI 31-44) and unique environmental factors (14%, 95% CI 12-18%).		
Hollows and Moran, 1981 (*288*)	Australia	Cross-sectional N = 105,561	Indigenous status UV zone of residence	Cataract	Significant positive correlation between UVR and cataract prevalence ($p<0.005$) in Indigenous Australians, but not in the non-Indigenous population.		
Italian-American Cataract Study Group, 1991 (*72*)	Italy	Case-control Cases: n = 1008 Controls: n = 469 Age: 45 – 79	Work location in sunlight Leisure time in sunlight	Cataract: cortical (C), posterior subcapsular (PSC), Nuclear (N); Mixed (M)	Sex, education, cortisone use	OR = 1.75 (C); OR = 0.84 (PSC) OR = 0.65 (N) OR =1.75 (M) OR = 1.45 (C) OR = 0.64 (PSC) OR = 1.20 (N) OR = 1.45 (M)	1.15 – 2.65 ns p<0.05 1.09 – 1.93 ns ns
Jonasson et al., 2004 (*289*)	Reykjavik, Iceland	Cohort N = 1045	Time spent outside during weekdays (>4 hours cf seldom) at: Age 20-30 Age 40-50	Cortical cataract		 OR = 2.80 OR = 2.91	 1.01 – 7.80 1.13 – 9.62
Katoh et al., 2001 (*290*)	Iceland	Case-control Cases (I) n = 374 Cases (II) n = 82 Controls: n = 378 Age: >50 years	Sun exposure at ages: 20-30 40-50 Now	Cortical cataract I – grade 1 II – grade 2 and 3		 RR: (I) = 1.19 RR (II) = 2.80 RR (I) = 0.98 RR (II) = 2.91 RR (I) = 0.88 RR (II) = 2.94	 0.66 – 2.15 1.10 – 7.80 0.51 – 1.95 1.13 – 9.62 0.44 – 1.76 0.99 – 8.54
Klein et al., 1995 (*291*)	Beaver Dam, Wisconsin, USA	Cross-sectional Cases: n = 4677 43 – 84 years	Wisconsin Sun Years	Cortical cataract Nuclear sclerosis Posterior subcapsular cataract	Age, wearing glasses, diabetes, smoking, heavy drinking	OR = 0.94 (F); OR = 1.36 (M) OR = 0.97 (F); OR = 0.93 (M) OR = 1.10 (F); OR = 1.17 (M)	0.70 – 1.26 1.02–1.79 0.78 – 1.20 0.78 – 1.12 0.70 – 1.72 0.79 – 1.73
Leske et al., 1991 (*73*)	Massachusetts, USA	Case-control	History of diabetes Smoking Occupational sun exposure	Nuclear (N), cortical (C), or PSC cataract in at least one eye, with loss of visual acuity	Age, sex	OR = 1.47 (PSC) OR = 1.98 (C) OR = 0.47 (N) OR = 1.64 (PSC) OR = 1.10 (C) OR = 2.30 (N) OR = 1.28 (PSC)	0.70 – 3.08 1.25 – 3.13 0.19 – 1.19 0.87 – 3.08 0.78 – 1.84 1.30 – 4.07 0.72 – 2.26

						OR = 0.91 (C) OR = 0.53 (N)	0.64 – 1.30 0.30 – 0.94
Leske et al., 1999 (*292*)	Barbados	Cross-sectional	Diabetes High diastolic BP High waist-hip ratio	Cortical cataract	Age-stratified (<60 and ≥ 60)	OR = 2.23 OR = 1.49 OR = 1.36	1.63 – 3.24 1.00 – 2.23 1.00 – 1.84
Lim et al., 1998 (*293*)	New South Wales, Australia	Cross-sectional	Pinguecula Pterygium (UVR exposure proxies)	Cortical cataract	Age, sex, smoking, high blood pressure, diabetes, steroid use	OR = 1.40 OR = 0.95	1.15 – 1.70 0.69 – 1.31
McCarty et al., 1999 (*78*)	Victoria, Australia	Cross-sectional N = 5147 Age: 40 - 103	Average annual ocular UVB exposure	Cataract	Age, gender, iris colour, diabetes, gout, beta blocker use, myopia, glaucoma	Cortical OR = 1.44 PSC cataract: OR = 1.15	 1.21 – 1.73 0.90 – 1.46
Minassian et al., 1994 (*48*)	Mongolia	Cross-sectional N = 4344 persons (8634 eyes) Age: 40+	CDK (as a marker of high UVR exposure) (present vs absent)	Cataract	Age	40-54 years: OR = 13.19 >54 years OR = 0.53	 1.04 – 167 0.28 – 0.99
Mohan et al., 1989 (*71*)	India	Hospital based Case control	Education, Increasing cloud cover Blood pressure, Cooking fuels (gas vs dung)	Cataract – nuclear, cortical, PSC and mixed	Age, sex, year of examination,	OR = 0.62 (all types) OR = 0.78 (all types) OR = 1.44 (nuclear) OR = 0.62 (cortical and nuclear)	0.40 – 0.98 0.60 – 0.90 1.25 – 1.65 0.40 – 0.98
Neale et al., 2003 (*67*)	Nambour, Australia	Case-control Cases: n = 195 Controls: n = 159	Lifetime occupational sun exposure (high vs very low) Lifetime leisure exposure Occupational sun exposure: 13-19 yrs of age 20-29 yrs of age 30-39 yrs of age 40-49 yrs of age 50-59 yrs of age 60+ yrs of age	Nuclear cataract grade 2.0 or higher	Ages, sex, education, smoking, diabetes, wearing eyeglasses or sunglasses, occupational or leisure sun exposure (where appropriate)	OR = 2.11 OR = 0.84 OR = 2.12 OR = 5.94 OR = 1.15 OR = 0.86 OR = 2.17 OR = 1.38	0.74 – 5.98 0.51 – 1.38 0.84 – 5.41 2.07 – 17.10 0.33 – 3.96 0.28 – 2.62 0.55 – 8.53 0.19 – 10.2
Rosmini et al., 1994 (*75*)	Italy	Case-control Cases: n = 1008 Controls: n = 469 Age: 45 – 79 y	Sunlight index (indoor/outdoor work/leisure)	Cataract: cortical (C), posterior subcapsular (PSC), Nuclear (N); Mixed (M)	Age, sex, educational status, use of hat, parent/sibling with cataract, red blood cell G6PD level	OR=2.26 (C) (significant dose response relationship) PSC = ns N = 1.29 M (Cortical/PSC) = 4.40	1.14 – 4.46 0.38 – 4.35 1.70 – 11.4
Sasaki et al., 1999 (*294*)	Japan (2 sites), Reykjavik, Iceland, Singapore	Cross-sectional & case control N = 884, 301, 993 and 468 respectively Age = >50	Latitude Hours spent outside on weekdays (<4 cf 5+)	 Cortical cataract		Cortical and nuclear cataract less common in Reykjavik. OR = 2.11 (M)	 0.65 – 6.88

			20s – 30s 30s – 40s Present			OR = 1.06 (F) OR = 3.88 (M), OR = 0.93 (F) OR = 2.20 (M), OR = 0.64 (F)	0.57 – 1.97 1.11–13.53 0.51 – 1.71 1.03 – 4.71 0.38 – 1.05
Taylor et al., 1988 (*69*)	Maryland, USA	Cross-sectional N = 838 Mean age: 53 yrs	Av. Annual UVB exposure (Maryland Sun Years)	Cortical cataract Nuclear cataract		OR = 3.30 OR = 0.96	0.90 – 9.97 0.36 – 2.60
West et al., 1998 (*77*)	Maryland, USA	Cohort study N = 2520 Age: 65-84 yrs	Ocular UVB exposure (Maryland sun years)	Cortical cataract	Age, sex, race, diabetes	OR = 1.57	1.04 – 2.38
Wong et al., 1993 (*70*)	Hong Kong	Cross-sectional N = 685 Age: 55-74	Sun exposure score	Cataract of any type, grade 3, 4 or 5	Age, sex	OR = 2.1	0.6 – 7.9
2.7 Ocular melanoma							
Ajani et al., 1992 (*295*)	Boston, USA	Case-control Cases: 197 Controls: 385 Mean age = 59.2	Occupation: Agriculture, forestry, fishing workers Exposure to inks	Uveal melanoma	Age, ancestry, skin colour, moles, use of sunlamps, past income level	OR = 2.02 OR = 2.44	0.61 – 6.73 1.14 – 5.23
Dolin et al., 1994 (*84*)	UK	Ecologic correlation	Mortality rates for CMM over time	Mortality rates for uveal melanoma	Mortality rate of CMM increasing steadily, but not uveal melanoma. Suggest UVR exposure not causative		
Guenel et al., 2001 (*87*)	France	Case-control Cases: n = 50 Controls: n = 479 Age: 35 - 70	Eye burns (5 cf 0) Light eye colour Occupational exposure to artificial UVR (eg welding) Occupational exposure to sunlight	Ocular melanoma	Age, gender	OR = 3.3 OR = 3.0 OR = 5.5 OR (high vs none) = 0.9	1.1 – 9.6 1.4 – 6.3 1.8 – 17.2 0.4 – 2.3
Holly et al., 1990 (*296*)	Western USA	Case-control Cases: n = 407 Controls: n = 870 Age = 20-74	Eye colour (cf brown): - Green, gray, hazel - Blue Vacation outdoors in sunny climate Leisure time outdoors Exposure to UV or black lights Welding burn, snow blindness, sunburn to eye	Uveal melanoma	Age, coffee consumption.	 OR = 2.50 OR = 2.21 OR = 0.84 OR = 0.79 OR = 3.69 OR = 7.17	 1.77 – 3.54 1.58 – 3.09 0.59 – 1.20 0.59 – 1.04 1.57 – 8.70 2.50 – 20.57
Holly et al., 1996 (*85*)	California, USA	Case-control Cases: n = 221 Controls: n = 447 Age: 20-74	Occupation and duration: Sailors (≥6yrs cf 0) Welders (≥11 yrs cf 0)	Ocular melanoma	Age	 OR = 2.7 OR = 1.9	 0.60 – 12.2 1.0 – 3.6
Pane and Hirst, 2000 (*86*)	Queensland, Australia	Case-control Cases: n = 125 Controls: n = 375	Painful sunburns (6+ cf 0) Wearing sunglasses Childhood ocular sun exposure Adult ocular sun exposure Lifetime ocular sun exposure	Ocular melanoma		OR = 0.78 OR = 1.00 OR = 1.18 OR = 0.67 OR = 0.91	0.40 – 1.52 0.64 – 1.56 0.74 – 1.87 0.37 – 1.19 0.50 – 1.65
Schwartz and Weiss, 1988 (*297*)	USA	Ecologic N = 1247 tumours	Season of diagnosis	Uveal malignant melanoma	No significant variation in diagnosis overall or for tumours arising in the choroid. Strong seasonal variation in tumours coded as arising in the eyeball with large, late winter-early spring peak in males and smaller mid-spring peak in females.		

Schwartz and Weiss, 1988 (*298*)	USA	Ecologic N = 763 patients	Place of birth (southern cf northern USA) Av. Daily solar irradiance in state of birth	Ocular melanoma	Age, sex, residence at diagnosis	RR = 1.1 RR = 1.2	0.8 – 1.5 0.6 – 2.2
Seddon et al., 1990 (*299*)	New England, USA	Case-control Cases: n = 197 Controls: n = 385 (population controls)	Northern latitude ancestry Southern residence >5y Use of sunlamps Intense sun exposure Birthplace <40°latitude Outdoor work	Uveal melanoma	Age, no. of moles, freckles, skin colour, eye colour, hair colour, skin reaction to sun	RR = 6.5 RR = 2.8 RR = 3.4 RR = 1.7 RR = 0.2 RR = 0.6	1.9 – 22.4 1.1 – 6.9 1.1 – 10.3 0.9 – 3.0 0.0 – 0.7 0.3 – 1.4
Seddon et al., 1990 (*299*)	USA	Case-control Cases: n = 337 Controls: n = 800 (sibling controls)	Use of sunlamps Intense sun exposure Outdoor work Fluorescent lighting Sunbathing Outdoor hobbies	Uveal melanoma	Age, no. of moles, freckles, skin colour, eye colour, hair colour, skin reaction to sun	RR = 2.3 RR = 2.1 RR = 0.4 RR = 1.7 RR = 0.8 RR = 0.7	1.2 – 4.3 1.4 – 3.2 0.2 – 0.8 1.1 – 2.5 0.5 – 1.2 0.5 – 1.1
Shah et al., 2005 (*89*)		Meta-analysis 133 published reports	Ultraviolet light: Exposure to welding Outdoor leisure time Latitude of birth Occupational UVR exposure	Uveal melanoma		 OR = 2.05 OR = 0.86 OR = 1.08 OR = 1.37	 1.20 – 3.51 0.71 – 1.04 0.67 – 1.74 0.96 – 1.96
Tucker et al., 1985 (*300*)	Philadelphia, USA	Case-control Cases: n = 444 Controls: n = 424	Birth in Southern USA Brown eyes (cf blue) Leisure time outdoors Sunlamp use Gardening Increased vacation sun exposure Frequent sunbathing Eye protection in sun (never cf almost always)	Intraocular malignant melanoma	History of cataracts Age, eye colour	RR = 2.7 RR = 0.6 RR = 1.1 RR = 2.1 RR = 1.6 RR = 1.5 (p for trend=0.01) RR = 1.5 RR = 1.4	1.3 – 5.9 0.4 – 0.8 0.7 – 1.6 0.3 – 17.9 1.01 – 2.4 0.97 – 2.3 0.9 – 2.3 0.9 – 2.3
Vajdic et al., 2002 (*301*)	Australia	Case-control Cases: n = 290 Controls: n = 893 Age: 18-79	Tot. hrs exposure weekdays and weekends Tot. hrs exposure weekdays Tot. hrs exposure weekends Total lifetime occupational exposure Tot recreational hrs. since leaving school Ambient UVR 0-9 yrs	Choroidal and ciliary body melanoma - no consistent association for iris and conjunctival melanomas	Age, sex, place of birth, eye colour, ability to tan and squinting as a child	OR = 1.6 OR = 1.8 OR = 0.8 OR = 1.7 OR = 0.8 OR = 0.8	1.0 – 2.6 1.1 – 2.8 0.5 – 1.3 1.1 – 2.7 0.5 – 1.3 0.5 – 1.3