REVIEW

Ultraviolet light and ocular diseases

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Abstract The objective of this study is to review the association between ultraviolet (UV) light and ocular diseases. The data are sourced from the literature search of Medline up to Nov 2012, and the extracted data from original articles, review papers, and book chapters were reviewed. There is a strong evidence that ultraviolet radiation (UVR) exposure is associated with the formation of eyelid malignancies [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)], photokeratitis, climatic droplet keratopathy (CDK), pterygium, and cortical cataract. However, the evidence of the association between UV exposure and development of pinguecula, nuclear and posterior subcapsular cataract, ocular surface squamous neoplasia (OSSN), and ocular melanoma remained limited. There is insufficient evidence to determine whether age-related macular degeneration (AMD) is related to UV exposure. It is now suggested that AMD is probably related to visible radiation especially blue light, rather than UV exposure. From the results, it was concluded that eyelid malignancies (BCC and SCC), photokeratitis, CDK, pterygium, and cortical cataract are strongly associated with UVR exposure. Evidence of the association between UV exposure and development of pinguecula, nuclear and posterior subcapsular cataract, OSSN, and ocular melanoma remained limited. There is insufficient evidence to determine whether AMD is related to UV exposure. Simple behaviural changes, appropriate clothing, wearing hats, and UV blocking spectacles, sunglasses or contact lens are effective measures for UV protection.

Keywords Ultraviolet light · Sunlight · Ocular disease · Eyelid tumur · Pterygium · Cataract · Age-related macular degeneration · Melanoma · Sunlight protection

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Introduction

The human eye is exposed daily to ultraviolet radiation (UVR). The main UVR source is the sun. A spectrum of ophthalmic disease is believed to have an association with acute and cumulative UVR exposure. Today, human exposure to UVR is increasing because ozone depletion and global climate changes are influencing surface radiation levels [1]. In addition, the increasing life expectancy and lifestyle changes would lead to increased leisure activities in ultraviolet (UV)-intense environments. This has broad public health implications, as an increased burden of UV related ocular disease is to be expected. The purpose of

this review article is to evaluate the association between the ocular disease and the UVR exposure.

Ultraviolet radiation

UVR is electromagnetic radiation in the waveband 100–400 nm. The visible light range is from 400 to 700 nm. The infrared light range is from 700 to 1,200 nm. UVR contains more energy than visible or infrared light and consequently has more potential for biological damage. The UV spectrum can be further divided into three bands: UV-A (315–400 nm), UV-B (280–315 nm) and UV-C (100–280 nm) [2]. As sunlight passes through the atmosphere, all UV-C and approximately 90 % of UV-B radiation are absorbed by ozone, water vapur, oxygen and carbon dioxide [2]. Therefore, the UVR reaching the Earth's surface is largely composed of UV-A with a small UV-B component, the former having a ten-fold higher concentration [2]. When UV reaches the eye, the proportion absorbed by different structures depends on the wavelength (Table 1 [3]). The shorter wavelengths are the most biologically active, and are mostly absorbed at the cornea. The longer the wavelength, the higher the proportion that passes through the cornea to reach the lens and retina. In general, the cornea absorbs wavelengths below 300 nm while the crystalline lens absorbs light below 400 nm [4]. Though the cornea's absorption properties remain constant, the lens's changes throughout our life. The lens of a young child transmits light at 300 nm (peak transmittance is at 380 nm), while that of an older adult starts at 400 nm (peak transmittance at 575 nm). The retina and uvea absorb light between 400 and 1,400 nm [4].

Fig. 1 a Image of left lower lid BCC; b image of right nasal pterygium; c image of right nasal pinguecula; d image of photokeratitis: fluorescein stain showing damaged cells in green (courtesy of Dr. A Cullen, University of Waterloo, Canada); e image of CDK with many amber droplets over the inferior half of the cornea, distributed on an area of band-shaped microdroplet haziness (courtesy of Dr. J Urrets-Zavalia, University of Cordoba, Argentina. Reprint permission from Cornea 26(7):800–804, Fig. 1); f left cortical cataract, g image of dry AMD; and h image of wet AMD

Effect of UVR on eyelid

Basal cell carcinoma (BCC) (Fig. 1a) and squamous cell carcinoma (SCC) are the two common malignant tumurs of the eyelid. BCC accounts for approximately 90 % of all eyelid malignancies. It is generally found on the lower eyelid (50–65 %), followed by medial canthus (25–30 %), upper eyelid (15 %) and lateral canthus (5 %) [5]. SCC accounts for approximately 9 % of all periocular cutaneous tumours [5].

There is evidence linking eyelid malignancies to UV-B exposure. It has been demonstrated that there is a direct correlation with the incidence BCC and SCC and the latitude. The closer an individual is to the equator, the greater the UV energy to which they are exposed [6]. The evidence of UV-B as a carcinogen is stronger for SCC. Gallagher et al. [7] found an increased risk of developing SCC with chronic occupational sun exposure in the 10 years prior to diagnosis [odds ratio (OR) = 4.0; 95 % CI 1.2–13.1]. The South European study also demonstrates a trend to increased incidence of SCC with the lifetime occupational exposure (OR = 1.6; 95 % CI 0.93–2.75) [8]. In a study of watermen in the United States, the individual annual and cumulative exposure to UV-B were positively associated with the occurrence of SCC, but not with that of BCC [9].

Table 1 Classification of UV spectrum and absorption by the cornea and aqueous [2, 3]

UV band	Wavelength nm	Availability	% absorbed by cornea	% absorbed by aqueous	% absorbed by lens
UV-A	315–400	Virtually no VU-A absorbed by ozone layer	45 (at 320 nm)	16 (at 320 nm)	36 (at 320 nm)
			37 (at 340 nm)	14 (at 340 nm)	48 (at 340 nm)
UV-B	280–315	Substantial portion absorbed by ozone layer	92 (at 300 nm)	6 (at 300 nm)	2 (at 300 nm)
UV-C	100–280	Almost all absorbed by ozone layer	100	0	0
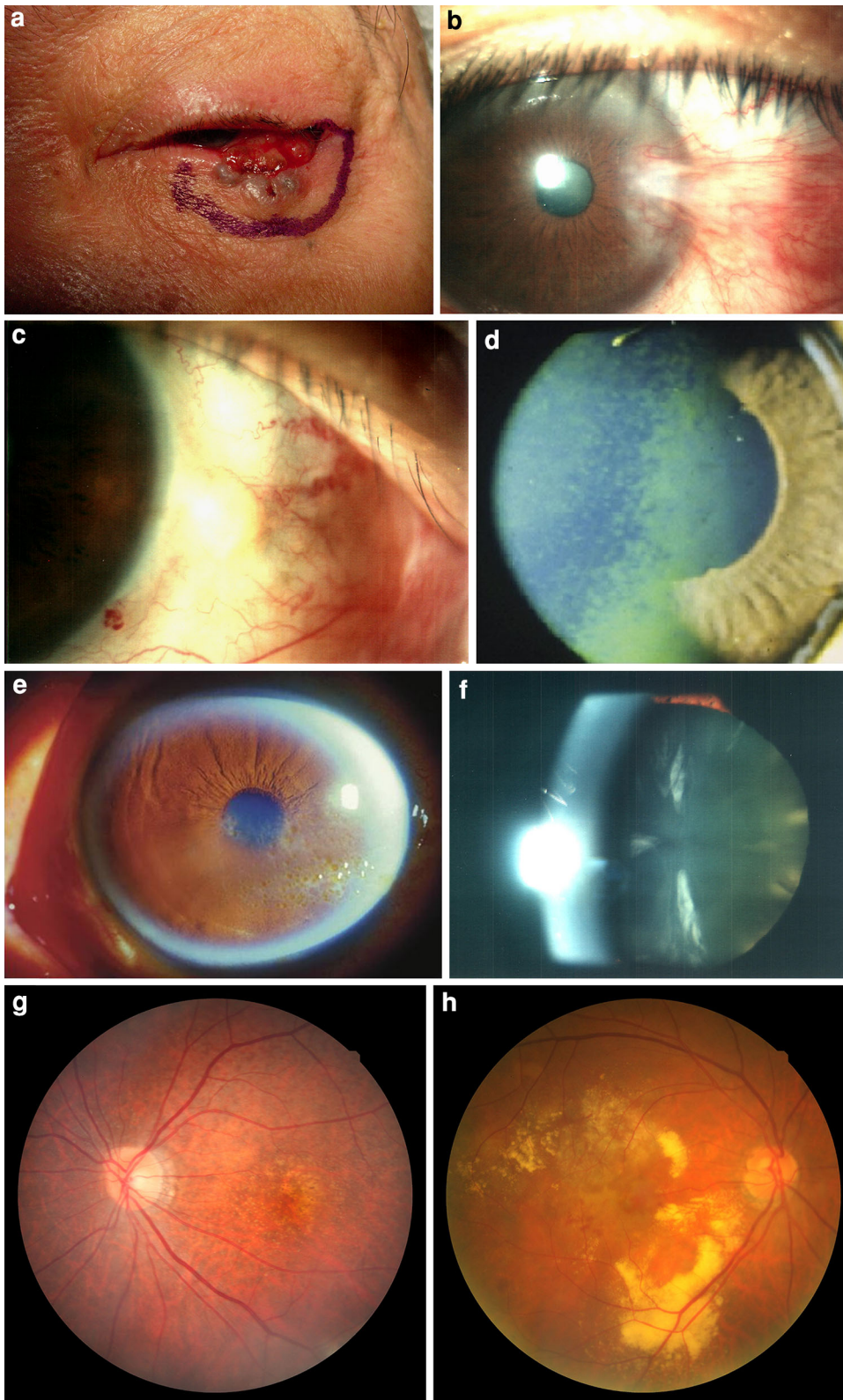
Cumulative sun exposure as the major causative factor in the development of SCC is well established. However, the relationship between UVR and BCC is more complex. It is now suggested that BCC formation may depend more on the severity of UV exposures at the young age rather than cumulative dose over a period of time. An Australian study indicated an elevated risk of BCC with increasing exposure to recreational UVR prior to age of 20 (OR = 3.86, 95 % CI 1.93–7.75) [10]. A similar increased risk (OR = 2.6; 95 % CI 1.1–6.5) with the exposure prior to age of 20 is seen in another Canadian study [11]. In either study, there is no increased risk with exposure in adult life [10, 11]. The South European study also detected an increasing risk of BCC with increasing childhood sun exposure (OR = 1.43; 95 % CI 1.09–1.89) [8]. Two further studies of BCC in Italian populations also found an increasing risk of BCC with beach vocational sunlight exposure prior to age of 20 [12, 13].

The damaging effects of UVR on the skin are thought to be caused by direct cellular damage and alterations in immunologic function. UVR produces DNA damage (formation of cyclobutane pyrimidine dimers), gene mutations, immunosuppression, oxidative stress and inflammatory responses, all of which have an important role in photoaging of the skin and skin cancer [14]. In addition to this, UVR creates mutations to p53 tumor suppressor genes; these genes which are involved in DNA repair or the apoptosis of the cells that have lots of DNA damage. Therefore, if p53 genes are mutated, they will no longer be able to aid in the DNA repair process; as a result, there is dysregulation of apoptosis, expansion of mutated keratinocytes, and initiation of skin cancer [15].

Exposure to UVR on the skin results in clearly demonstrable mutagenic effect. The p53 suppressor gene, which is frequently mutated in skin cancers, is believed to be an early target of the UVR-induced neoplasm [16].

Treatment of eyelid malignancies include complete surgical excision, cryotherapy and radiotherapy [5]. Studies have shown that a simple behaviural change, protection from UV exposure, can lower the incidence of subsequent skin cancer. Reduction in sun exposure by daily use of a sunscreen may reduce the risk of SCC [17].

Effects of UVR on conjunctiva and cornea

Pterygium and pinguecula

A pterygium is a hyperplasia of the bulbar conjunctiva, which grows over the cornea (Fig. 1b). It is generally accepted that UV exposure is linked to the formation of pterygia. Early work by Cameron indicated that pterygia occur more commonly where UV intensity is highest. Specifically, a high prevalence of pterygia occurs in an equatorial belt bounded by latitudes 37° north and 37° south [18]. Confirming Cameron's observations, Mackenzie et al. [19] found that those who live at latitude less than 30° during the first 5 years of life have a 40-fold increased risk of developing pterygium. In a study of more than 100,000 Aborigines and non-Aborigines in rural Australia, Moran and Hollows [20] found a strong positive correlation between climatic UVR and the prevalence of pterygium. However, the ocular sun exposure has not been quantified in the study. Mackenzie et al. [19] in their study of Australians also found that time spent outdoors and the development of pterygium were linked. More evidence comes from the Chesapeake Bay study. In that study on 838 watermen in Maryland, the risk of having a pterygium was significantly associated with increased levels of UV-A and UV-B exposure [21]. For those in the highest quartile of annual UV-A and UV-B exposure, the OR for the development of pterygium was 3.06. This study demonstrated pterygium to be associated with wide-band UVR rather than UV-B alone and also demonstrated a dose–response relationship between UVR and pterygium [21].

Pinguecula (Fig. 1c), which is a fibro-fatty degenerative change in the bulbar conjunctiva within the palpebral aperture, is also believed to be related to UVR exposure. Norn [22] reported a high prevalence of pinguecula among Arabs in the Red Sea region. However, the association between pinguecula and UVR appears to be weaker than that of pterygium. In the Chesapeake Bay study, the risk of developing pinguecula was less than that for CDK or pterygium [21]. Thus, a relationship between UVR exposure and pinguecula may exist, but is yet to be established.

Histopathological evidence supports the link between UVR and pterygium and pinguecula formation. Austin et al. found that an important component of both pterygium and pinguecula is abnormal

synthesis and secondary degeneration of elastic fibres. This response shares similarities with sun-induced skin changes [23].

UVR-induced changes in corneal epithelial stem cells were believed to be the driving force behind corneal invasion by the pterygium, leading to subsequent destruction of Bowman membrane and elastosis [24]. Exposure of cells to UVR induces activation of epidermal growth factor receptors and subsequent downstream signaling through the mitogen-activated protein kinase pathways [25, 26], that are partially responsible for expression of proinflammatory cytokines, and matrix metalloproteinases (MMPs) in pterygium cells. MMP-2 and MMP-9 expression by pterygium fibroblasts was found to be significantly increased after the progression of ptergyium, suggesting their role in disease progression [27].

Pterygium is predominantly found on the nasal bulbar conjunctiva. Coroneo et al. [28] offered an explanation for this specific location of the pterygium. They proposed and experimentally demonstrated that tangentially incident light at the temporal limbus travels across the anterior chamber and comes to focus on the opposing corneal side near the nasal limbus [28]. This helps explain why pterygia are most common in the horizontal meridian on the nasal aspect of the cornea, but it does not explain why pterygia are occasionally observed temporally. This unintended refracting power of the peripheral cornea may allow for an up to 20-fold concentration of scattered incident light of UVR [28].

Surgical excision for pinguecula is rarely required. For pterygium growing to cross into the papillary zone or cause discomfort, surgical excision is indicated. Free conjunctival graft, mitomycin C, or radiation therapy have been used to decrease the recurrence of pterygium [29].

Photokeratitis

Acute exposure to UV-B and UV-C produces a painful superficial punctate keratopathy known as photokeratitis. It appears up to 6 h after exposure and resolves spontaneously in 8–12 h [30]. The initial symptoms of photokeratitis are due to lost or damaged epithelial cells leading to a gritty feeling in the eye with photophobia and tearing. Subsequent cornea edema can result in haze or clouding and deterioration of vision. Further UV exposure will result in epithelial

exfoliation which produces excruciating pain. Signs of photokeratitis include conjunctival chemosis, punctate staining of the corneal epithelium, and corneal edema [30] (Fig. 1d).

UV light can accelerate the physiological loss of corneal epithelial cells by two mechanisms, shedding and apoptosis. Animal studies suggested that suprathreshold doses of UV-B radiation disrupt the normal orderly cell shedding process and haemostatic equilibrium of the corneal epithelium [31]. UVR-induced epithelial cell apoptosis has been shown to occur in corneal cells, possibly via activation of potassium channels [32]. As epithelial cells are sloughed, subsurface nerve endings are exposed, which causes the characteristic pain.

Suprathreshold UVR exposure from both artificial and natural radiation sources can cause photokeratitis. Photokeratitis from naturally occurring UVB is commonly referred to as 'snow blindness'. This occurs in conditions where the UVR reflectivity of the environment is extremely high, such as during skiing, mountain climbing, or excessive time at the beach [33]. Artificial sources of UVR include the 'welder's flash', which can be caused by even momentary exposure to UV-C and UV-B during arc welding [33].

Climatic droplet keratopathy

CDK is a spheroidal degeneration of the superficial corneal stroma that is generally confined to geographical areas with high levels of UV exposure such as the arctic or tropics [33]. The condition is characterized by deposition of translucent gray material in the areas of the superficial corneas, which are exposed between eyelids, looking under the slit-lamp like minute 'droplets' [34] (Fig. 1e).

The corneal deposits are thought to be derived from plasma proteins, which diffuse into the normal cornea and are photochemically degraded by excessive exposure to UVR [34]. The degraded protein material is then deposited in the superficial stroma, characteristically in a bandlike distribution corresponding to areas of highest UV exposure [34].

CDK is causally associated with chronic UV-A and UV-B exposure. Klintworth [35] has pointed out the opportunities for excessive UVR that exist in all areas where a high prevalence of CDK has been reported. A study conducted on Labrador Canadians also found

a direct link between the severity of the CDK and UV exposure [36].

By studying large numbers of patients, Johnson was able to define the peak of prevalence of CDK occurring between 55° and 56° latitude. He then calculated the total UV flux reflected from ice and snow throughout Labrador, and found it to reach a peak almost exactly at the same latitude, thus establishing the link between UV and the severity of CDK [36]. This association was further strengthened by the Chesapeake Bay watermen study [21]. Of 838 watermen from the Chesapeake Bay, Taylor et al. detected CDK in 162 watermen. The OR for average annual UVB exposure in the upper quartile was 6.36 for CDK. Similar ratios were shown for exposure to UV-A.

CDK may be temporarily treated by superficial keratectomy. However, the definitive treatment involves penetrating keratoplasty [34].

Ocular surface squamous neoplasia

OSSN is a term for precancerous and cancerous epithelial lesions of the conjunctiva and cornea [37]. It includes dysplasia and carcinoma in situ and SCC. It can also be called corneal (or conjunctival) intraepithelial neoplasia [37].

Exposure to solar UVR has been identified in many studies as a major etiologic factor in the development of OSSN, although human papilloma virus and human immunodeficiency virus also play a role [37].

Templeton reported a high incidence of conjunctival SCC in an African population living in Uganda near the equator [38]. A study in Sudan found a predilection for SCC and other epithelial lesions of the conjunctiva in the north, in contradistinction to the much lower frequency in the south [39]. They ascribed this trend to various environmental factors such as the presence of clouds, rain, the thick equatorial forests and shaded valleys which reduce the effect of UV-B in the south [39]. The rarity of OSSN in Europe and North America [40] and its higher incidence in sub-Saharan African countries [38, 41] and Australia [42], where people are more exposed to sunlight, may be another proof of the important role of solar UVR in the development of OSSN. Later, Newton et al. [43] analyzed different population-based studies and found the geographic distribution of OSSN to be highly correlated with ambient solar UVR levels, as the rate

of OSSN was found to decline by 49 % for each 10° increase in latitude. For instance, in Uganda, there are 12 cases per million per year in contrast to 0.2 cases per million per year in the United Kingdom [43]. Another population-based study investigating the relationship between incidence rates of OSSN and UV-B exposure showed the correlation to be as strong as for UV-B and SCC of the eyelids [40]. Lee et al. [44] reported that outdoor exposure for more than half of the first 6 years of life (OR = 7.5; 95 % CI 1.8–30.6) are important to the development of OSSN, although there are other risk factors including fair skin, pale irides, and the propensity to burn on exposure to sunlight.

UV-B is thought to cause DNA damage and the formation of pyrimidine dimmers. Failure or delay in DNA repair, such as in xeroderma pigmentosum, leads to somatic mutations and development of cancerous cells, including OSSN [45]. This damage to DNA, which also occurs in patents without xeroderma pigmentosum, is probably the explanation for the higher risk for OSSN with long exposure to solar UV light [45].

OSSN should be treated with surgical excision with adequate margin with or without cryotherapy or brachytherapy [37]. More importantly, emphasis should be placed on the prevention of this disease through the use of UV light protection devices such as sunglasses and hats.

Effects of UVR on the lens

Cataract (Fig. 1f) is a clinical syndrome involving an opacification of the crystalline lens that causes reduced vision. Many epidemiological studies investigate the relationship between sunlight and cataract, which is summarized in Table 2 [46–70].

In the 1980s, the solar dose of UVR for different populations was associated with the prevalence of cataract. In the United States, Hiller et al. [46] found a higher cataract-to-control ratio for persons aged 65 or over in locations with longer duration of sunlight. Two studies in Australian Aborigines have also shown a dose–response relation between the prevalence of cataracts and levels of UV-B radiation [47, 48]. A country-wide survey of Nepal in which 30,565 lifelong residents were examined also found a positive correlation between the prevalence of cataracts and the

Table 2 Chronological review of epidemiologic studies on sunlight and cataract [46–70]

Reference	Study population	Sunlight/UV exposure measurement	Cataract measure	Findings in relation to sunlight/UV
Hiller et at. 1977 [46]	US population-based (1) Model reporting area for blindness statistics (MRA) (2) National health and nutrition examination survey 1971–1972	Total annual sunshine hours	(1) Blind from cataract (2) Lenticular opacity + VA ≤ 20/25	Ratio of cataract cases to controls was significantly higher in areas with large amounts of sunlight for people aged 65+
Taylor 1980 [47]	350 Australian Aborigines aged 30+	Latitude, sunlight hours, annual UVR, occupation, total radiation	Opacity with acuity < 6/6	Annual UVR significantly related to cataract in people aged 40+
Hollows and Moran 1981 [48]	(1) 64,307 Australian Aborigines (2) 41,254 non-Aborigines in Australia	Average daily erythmal units of UV-B in 5 geographic zones	Any cataract	(1) Significant positive correlation between UV and cataract for Aborigines aged 60+ ($p < 0.005$) (2) No significant association for non-Aborigine
Chatterjee et al. 1982 [49]	1,269 persons aged 30+ from 3 districts in Punjab	Indoor/outdoor occupation	Senile opacity + VA ≤ 6/18	Age-adjusted cataract prevalence = 17.1 % in indoor workers, 12.5 % in outdoor workers No significant association between UV and cataract was detected
Brilliant et al. 1983 [50]	Probability sample of 30,565 Nepalese in 105 sites in Nepal	Seasonally adjusted average daily sunlight hours	Senile cataract	Cataract prevalence was negatively correlated with altitude ($r = -0.533$, $p < 0.0001$) and positively correlated with average hours of sunlight exposure ($r = 0.563$, $p < 0.0001$)
Wojno et al. 1983 [51]	66 patients aged 60+ at the Medical College of Wisconsin, into 2 groups: (1) patients worn spectacles continuously for 35+ years (2) those never worn spectacles or had worn only reading glasses	Use of spectacles	Sclerotic nuclear lens changes	Spectacle wear had a small but significant effect ($p < 0.1$) on the degree of nuclear sclerosis. Less nuclear sclerotic lens changes developed in spectacle wear group
Perkins 1985 [52]	51 patients admitted for senile cataract extraction, 51 age-, gender-matched controls aged 50–90	Prevalence of pinguecula, outdoor working environment	Senile cataract	No significant association

Table 2 continued

Reference	Study population	Sunlight/UV exposure measurement	Cataract measure	Findings in relation to sunlight/UV
Collman et al. 1988 [53]	Cases and controls aged 40–69 from North Carolina ophthalmic clinic	Average annual sun exposure which incorporated ambient solar radiation and time spent in sun	Cortical, nuclear or PSC opacity	No significant association, although OR were greater than 1.5 for cortical and posterior subcapsular cataract
Taylor et al. 1988 [54]	838 watermen in the Chesapeake Bay	Personal ocular exposure index to UV-A and UV-B incorporating ambient UV and personal behaviour	Wilmer classification: cortical and nuclear grade 2+	OR for cortical cataract = 1.60 for doubling of UV-B exposure. Similar but non-significant finding for UV-A, no significant associations for UV and nuclear cataract
Dolezal et al. 1989 [55]	160 matched pairs of cases and controls aged 40+ from Iowa hospitals and clinics	Residential history, duration of continuous eyeglass wear, average lifetime frequency of sunglass wear, average use of head coverings to shade eyes	Admission for cataract surgery, cataract type	No significant association
Bochow et al. 1989 [56]	168 case–control pairs from Chesapeake Bay ophthalmic practice	Personal ocular exposure index to UV-B incorporating ambient UV-B and personal behaviour	Cataract extraction for PSC opacity	OR = 14.5. Significant association ($p = 0.006$) between UV-B exposure and the presence of PSC cataracts
Mohan et al. 1989 [57]	1,441 hospital-based cases and 549 controls aged 37–62 in India	Average altitude of residence, average lifetime temperature of residence, average lifetime cloud cover of residence, indoor/outdoor occupation, hours working indirect sunlight	Cortical, nuclear and PSC cataract + VA ≤ 6/18	OR = 0.78 for 4 oktas increase in cloud cover and all types of cataract
Leske et al. 1991 [58]	1,380 cases and controls aged 40–79 from Massachusetts Eye Infirmary	Leisure time in the sun, occupational exposure to sunlight, use of hats, sunglasses or spectacles, skin sensitivity to the sun	LOCSI cortical C1b or C2, nuclear N1 or N2, PSC P1 or P2	OR = 0.78 for nuclear and occupational exposure to sunlight, non-significant for other cataract types
Cruickshanks et al. 1992 [59]	4,926 residents aged 43–84 from Beaver Dam, Wisconsin	Annual UV-B exposure index incorporating ambient UV-B and personal behaviour	Cortical, nuclear, PSC opacity	OR = 1.40 for cortical cataract in men, no other significant associations
Wong et al. 1993 [60]	367 fishermen and women aged 55–74 in Hong Kong	Lifetime occupational history, time spent outdoors, use of hats or sunglasses	Cortical, nuclear PSC opacity	Increased, but non-significant OR with increased sun exposure
Rosmini et al. 1994 [61]	1,008 clinic-based patients, 469 controls aged 45–79 from Italy	Sunlight exposure index incorporating time spent outdoors and time spent in shade while outdoors	LOCSI grade N1, P1, C1b or greater	Dose–response relationship found for pure cortical cataracts, non-significant trend for all other cataract types

Table 2 continued

Reference	Study population	Sunlight/UV exposure measurement	Cataract measure	Findings in relation to sunlight/UV
Hirvela et al. 1995 [62]	500 people aged 70+ in Finland	Outdoor occupation	LOCSII NC 0–1, N 0–1, C 0–1, P0	No significant association
Javitt and Taylor 1994 [63]	Medicare claims data in the US for people aged 65+	Latitude in the US which correlates with UV-B	Cataract surgery	Latitude predicts cataract surgery
Burton et al. 1997 [64]	797 Pakistan residents aged 40+ from 2 mountainous villages	Global radiation, outdoor occupation	Lens opacity obscuring red reflex	Male outdoor workers had significantly higher cataract prevalence than male indoor workers in village with lower UV ($p < 0.001$), no difference in village with higher UV
West et al. 1998 [65] (The SEE project)	2,520 Maryland residents aged 65–84	Personal ocular exposure index to UV-B incorporating ambient UV-B and personal behaviour	Wilmer Classification: cortical 3/16+	OR = 1.10 for cortical cataract for each 0.01 increase in Maryland sun-year exposure index
McCarty et al. 2000 [66]	4,744 Australians aged 40+	Personal ocular exposure index to UV-B incorporating ambient UV-B and personal behaviour	Wilmer Classification: cortical and nuclear grad 2+, any PSC	OR = 1.55 for cortical cataract, upper 25 % percentile of UV-B exposure responsible for 10 % of cortical cataract, no significant associations with other types
Delcourt et al. 2000 [67] (POLA Study)	2,584 residents of France aged 60+	Solar ambient radiation, use of sunglasses	LOCS III	OR = 2.5 for cortical cataract, OR = 4.0 for mixed cataract, OR = 4.0 for cataract surgery and higher ambient solar radiation, OR + 0.62 for PSC and use of sunglasses, no significant associations for nuclear cataract
Katoh et al. 2001 [68] (Reykjavik Eye Study)	456 cases and 378 controls	Questionnaires to assess daytime hours spent outside, wear of sunglasses, spectacles and hats, and occupational exposure to sunlight	JCCESG system (Japanese cooperative cataract epidemiology study group system)	Significant association between spending more than 4 h in 20–30 and 40–50 years of age and development of moderate and severe cortical cataract RR for grades II cataract = 2.80 (95 % CI 1.01–7.80) RR for grades III cataract = 2.91 (95 % CI 1.13–9.62)
Neale et al. 2003 [69]	195 cases and 159 controls	Questionnaires to assess lifetime sun exposure history, eyeglasses and sunglasses	Wilmer Classification: cortical 3/16+	Strong positive association of occupational sun exposure between age 20 to 29 years with nuclear cataract (OR = 5.95; 95 % CI 2.1–17.1)
Pastor-Valero et al. 2007 [70]	343 cases and 334 controls of Spanish	Questionnaires to assess outdoor exposure	LOCS II (Lens opacification classification system)	No association or tread between years of outdoor exposure and risk of cataract

average hours of sunlight when comparing different zones of the country [50]. Studying 367 fishermen in Hong Kong, it was found that the risk for cortical cataract among men aged 40–50 years who spent 5 or more hours per day outdoors, was increased compared with that for men who spent less time outdoors [60]. All these studies suggested that areas with higher solar radiation had higher prevalence of cataract, but using very crude estimation of sunlight exposure only [46, 48, 50, 60]. Later studies, recognizing the need to bring exposure to a personal level, attempted to develop models of personal exposure in a number of ways. The Chesapeake Bay Study was the first study to develop a detailed model of personal ocular exposure to UV-B, and correlate it with a detailed, standardized system for assessment of cataract [54]. It was shown that the risk of cortical cataracts was increased 1.6-fold when the cumulative UVB exposure was doubled. However, no association was found between nuclear cataracts and UV-B exposure or between cataracts and UV-A exposure [54]. In the Beaver Dam Eye study, the relationship between UVR exposure and lens opacities was examined in 4,926 adult subjects [59]. Men with higher estimated UV-B exposure were 1.4 times more likely to have more severe cortical opacities than those with lower estimated exposure. However, the exposures among women were lower than exposures among men, and no association was seen. It was suggested that the risk may be confined to men [59]. Having demonstrated an association between cortical opacity and increasing ocular exposure to UV-B, it was, however, not clear whether this association would still be observed with lower exposures more characteristic of the general population. Salisbury Eye Evaluation (SEE) project was the first study to quantify the levels of ocular exposure to UV-B and visible light for a general population, as opposed to high-risk occupational groups, and to determine the association of these levels of exposure with the risk of cortical opacity separately for women and African Americans [65]. The odds of cortical opacity increased with increasing ocular exposure to UV-B (OR = 1.10; 95 % CI 1.02–1.20). The relationship was similar for women (OR = 1.14; 95 % CI 1.00–1.30) and for African Americans (OR = 1.18; 95 % CI 1.04–1.33). The Pathologies Oculaires Liees al Age (POLA) study of 2,584 participants also found an increased risk of cortical opacities with high ocular exposure to UV-B [67]. It further confirmed that no

particular age is important in determining the risk but rather that the risk is a cumulative risk phenomenon, including all life periods, even childhood. The most convincing data on this association were provided by the studies that quantified individual ocular UV-B exposure and analysed dose response [66]. In the areas with the same level of ambient sunlight, variations in individual behaviour can be a reason for up to a 18-fold difference in UV-B exposure. Sunlight exposure presents an attributable population risk of 10 % for cortical cataract [66]. Review of these epidemiological studies strongly support UV-B as a risk factor for cortical cataract. Although ocular UV-B exposure has also been suggested as a risk factor for nuclear cataract and posterior subcapsular cataract, a positive association has not been shown to this date in large epidemiologic studies, and any role of UVR in the pathogenesis of these types of cataract require further study.

Modern experimental studies have suggested that UV-B induce anterior cortical opacities and later posterior cortical opacities [71]. Microscopically, the cortical opacities correspond to swelling of lens epithelial cells and cortical fibres, until they rupture and thus cause vacuolization of the cortical area. The swelling has been associated with a transient increase of lens water which is related to a sodium–potassium shift. The energy-dependent sodium–potassium ATP-ase that is responsible for maintenance of the sodium–potassium balance over lens cell membranes, has been found to become impaired after exposure to UVR. Extended low dose exposure to UVR has been found to induce changes in lens proteins [71].

Cataract can be surgically removed by a technique called phacoemulsification. Wearing a brimmed hat and UV-B protecting sunglasses and also avoiding direct sunlight at the peak hours of UV-B radiation have been suggested as a powerful measures of primary prevention for cortical cataract [3].

Effects of UVR on retina and choroid

Age-related macular degeneration

Animal studies and case reports in humans have suggested that exposure to intense bright sunlight or UVR may cause changes in the retinal pigment epithelium (RPE) similar to those seen in AMD [72].

In a study, the human RPE cells (ARPE19) was exposed to UV-C. A time dependent apoptosis of ARPE19 cells induced by UV was observed [73]. It is hypothesized that UVR exposure induces DNA breakdown and causes cellular damage through the production of reactive oxygen species, which leads to the activation of MAPK signaling pathways, and subsequent programmed cell death [73].

Another study on the human RPE cells (ARPE19) demonstrated that UVR caused progressive increase in morphologic changes with an increased degradation of the mitochondria (fragmented and merged mitochondria) [74]. Energy level of UVB radiation from 0.2 to 0.4 J/cm^2 induced decreased phagocytotic activity of the RPE cells [74]. A decreased in phagocytic ability may be associated with an increase in RPE melanogenesis, and clinically, RPE hyperpigmentation, a risk factor for the development of AMD [75].

However, epidemiological evidence of the association between sunlight exposure and AMD is mixed, with several case–control studies showing no relationship (Table 3) [72, 76–83].

In the 1980s, Hyman et al. [76] found no association between recreational or occupational exposure to sunlight and AMD. The Eye Disease Case–Control Study Group evaluated crude measures of sunlight exposure, and found no association between exudative AMD and leisure time spent outdoors in summer [79]. Further, in a large Australian case–control study involving 409 cases with 286 controls, Darzins did not find macular degeneration to be associated with cumulative sunlight exposure [80]. In fact, the control group had higher cumulative sunlight exposure; however, patients with macular degeneration did have a higher rate of poor tanning ability and glare sensitivity. Thus, sun avoidance behavior may be a confounding factor which makes the association difficult to assess[80]. In the Chesapeake Bay watermen study, initial analysis did not find a linkage between UVR and macular degeneration [77]; however, reanalysis of the data did find an association between cumulative high energy blue light exposure (but not UV-A and UV-B) and AMD over the previous 20 years [78]. In the cross-sectional population-based Beaver Dam Eye Study, the amount of leisure time spent outdoors in summer was significantly associated with AMD (OR = 2.19; 95 % CI 1.12–4.25), but no association between AMD and estimated ambient

UV-B exposure was found [72]. The authors cautiously concluded that exposure to bright visible light may be associated with AMD. In another Australian population-based study, the Visual Impairment Project, the mean ocular sun exposure over the previous 20 years was not significantly different between people with and without AMD [82]. However, in a recent meta-analysis by Sui et al. [84], which analyzed the epidemiological evidence on the association between sunlight exposure and AMD, suggested that individuals with more sunlight exposure are at a significantly increased risk of AMD (pooled OR = 1.379, 95 % CI 1.091–1.745).

The lack of a clear association between UVR exposure and AMD is not surprising, because the lens absorbs almost all UV-B, and only very small amounts of this waveband can reach the retina. Currently, it is suggested that retinal light damage is due to exposure of visible radiation, especially blue light (400–500 nm), rather than UVR. Blue light has been shown to be the portion of the visible spectrum that produces the most photochemical damage to animal RPE cells [33]. In the study of Chesapeake Bay watermen, persons with severe vision-impairing macular degeneration had a statistically greater recent exposure to blue or visible light over the preceding 20 years (OR = 1.36; 95 % CI 1.00–1.85) [78].

The contribution of blue light exposure to AMD incidence and progression is a concern in aphakic and pseudophakic patients who lack the protective effect of the aging crystalline lens. It has been suggested that cataract surgery may increase the development or progression to neovascular AMD or geographic atrophy [33]. In a comprehensive analysis of the pooled data from the Beaver Dam Eye Study and the Blue Mountains Eye Study, comprising 6,019 participants (11,393 eyes), the 5-year risk for development of late-stage AMD in the operated eye following cataract surgery may be 2–5 times higher than that of phakic patients [85]. The possibility that blue light exposure may accelerate AMD after cataract extraction has led to the recent introduction of blue-blocking intraocular lenses, which have been shown to be able to shield RPE cells from the damaging effects of light in vitro in comparison to standard intraocular lenses [86]. Currently, there is no treatment for dry AMD (Fig. 1g), but wet AMD (Fig. 1h) can be treated with the recently introduced intravitreal anti-VEGF therapy [87].

Table 3 Summary of studies between sunlight and AMD [72, 76–83]

Reference	Study population	Study design	Sunlight/UV exposure measurement	ARM severity	Findings in relation to sunlight/UV
Hyman et al. 1983 [76]	228 cases with AMD 237 controls	Case–control study	Questionnaires on occupational, residential and recreational exposure to sunlight	Drusens to AMD	No association between AMD and occupational, residential and recreational exposure to sunlight
West et al. 1989 [77]	838 watermen in Chesapeake Bay, Maryland	Cross-sectional study	Personal ocular exposure index to UV-A and UV-B incorporating ambient UV and personal behaviour	Drusens to AMD	No association between AMD and UV exposure
Taylor et al. 1992 [78]	838 watermen in Chesapeake Bay, Maryland	Cross-sectional study	Personal ocular exposure index to UV-A and UV-B incorporating ambient UV and personal behaviour	Drusens to AMD	Association between blue light exposure and AMD OR = 1.36 (CI 1.00–1.85) No association between UV-A or UV-B and AMD
Eye disease case–control study group 1992 [79]	421 cases with AMD 615 controls	Case–control study	Leisure time in the sun, occupational exposure to sunlight, use of sunglasses	Exudative AMD	No association between AMD and sunlight exposure OR = 1.1; 95 % CI 0.7–1.7, for great amount of summer leisure time versus none or very little summer leisure time spent outdoor)
Cruickshanks et al. 1993 [72]	4,926 residents aged 43–84 from Beaver Dam, Wisconsin	Cross-sectional study	Residential history, time spent outdoors during leisure and work, and use of glasses for distance vision, hats with brims, and sunglasses.	Drusens to AMD	No significant association in women Amount of outdoor leisure time in men was significantly associated with exudative macular degeneration (OR = 2.26) and late maculopathy (OR = 2.19) No association between estimated ambient UVB exposure and AMD
Darzins et al. 1997 [80]	409 Australian with AMD 286 controls without AMD	Case–control study	Personal ocular exposure index to UV-A and UV-B incorporating ambient UV and personal behaviour	Drusens to AMD	Control had greater median annual ocular sun exposure then cases
Delcourt et al. 2001 [81]	2,584 residents of France aged 60+	Cross-sectional study	Solar ambient radiation, use of sunglasses	Drusens to AMD	Subjects exposed to high ambient solar radiation and those with frequent leisure exposure to sunlight had decreased risk of pigmentary abnormalities (OR = 0.61; 0.70) and of early signs of AMD (OR = 0.73; 0.80)

Table 3 continued

Reference	Study population	Study design	Sunlight/UV exposure measurement	ARM severity	Findings in relation to sunlight/UV
McCarty et al. 2001 [82] Visual Impairment Project	3,271 urban residents; 1,473 rural residents in Australia Aged 40+	Cross-sectional study	Personal ocular exposure index to UV-B and visible light incorporating time spent outdoors and ocular protection behaviours	Drusens to AMD	Mean annual ocular sun exposure over the previous 20 years was not significantly different between people with and without AMD ($p = 0.4$)
Khan et al. 2006 [83]	446 cases with end stage AMD 283 spouse controls	Case–control study	Leisure time in the sun, occupational exposure to sunlight, use of hats, sunglasses or spectacles, skin sensitivity to the sun	End stage AMD	No association between AMD and sun exposure or related factors

Uveal melanoma

Uveal melanoma is the most common primary malignant intraocular tumour of adults, with a high incidence of metastasis [88]. Approximately 50 % of affected patients die of their disease within 10–15 years after treatment [88]. Treatment of ocular melanoma depends on its size, location, and stages. Options include brachytherapy, external radiotherapy, transpupillary thermotherapy, trans-scleral local resection, and enucleation [89].

Based on findings with cutaneous melanoma, the melanocyte is believed to undergo malignant transformation from UV light [90]. Melanocytes in the eye might also respond similarly to UV light [91]. The carcinogenic effect of UV light might be more important in children than adults, as the crystalline lens of children allows transmission of UV light to the posterior uvea, whereas the adults lens and cornea filter UV-B and most UV-A [91].

There is some epidemiological evidence that exposure to UV light is a factor in its etiology. Table 4 summarizes all the important case–control studies evaluating associations between UV exposure and ocular melanoma [92–100]. Tucker et al. [93] compared 444 uveal melanoma patients with controls and found that melanoma patients were more likely to have spent time outdoors gardening, to have sunbathed, and to have used sunlamps. They were less likely to have used some form of eye protection while outside. Holly et al. [95] also reported that the exposure to UV light was a risk factor for uveal melanoma. Perhaps the best evidence for an association between ocular melanoma and sun exposure comes from Australia. A national case–control study of ocular melanoma cases diagnosed between 1996 and mid-1998 demonstrated an increase in risk of the cancer with increasing quartile of sun exposure prior to age 40 (RR in highest quartile = 1.8; 95 % CI 1.1–2.8), after control for phenotypic susceptibility factors [99]. However, Seddon et al. [94] observed that the outdoor work was not a risk determinant for uveal melanoma, in line with Pane and Hirst [97] who did not find cumulative lifetime ocular UV-B exposure to be a risk factor. Exposure to artificial UV light at work has been associated with uveal melanoma. A French case–control study involving 50 patients with uveal melanoma showed an increased risk of uveal melanoma in occupational groups exposed to artificial UV light, such as welders

(OR = 7.3; 95 % CI 2.6–20.1), but occupational exposure to sunlight was not a risk factor [98]. A recent meta-analysis which utilized exposure to welding as a surrogate for intermittent UV exposure detected a significantly elevated risk with exposure (OR = 2.5; 95 % CI 1.2–3.51) [91]. However, outdoor lesion exposure was not found to be a significant risk factor. Chronic occupational UV exposure was of borderline significance (OR = 1.37; 95 % CI 0.96–1.96) [91].

Protection from the sun

There are a number of steps that patients can take to minimize solar radiation exposure to the eyes. Table 5 summarizes the available options for UV protection [101]. The most effective method is avoidance. Cloud cover does not necessarily block UVR, and patients should be counseled to avoid sun exposure even in overcast weather conditions [4]. The World Health Organization and World Meteorological Organization have developed the Global Solar UV index, which provides the public with an estimate of UVR on any given day [2]. The scale ranges from 1 to 11+, and when the UV index is 8 or higher, indoor activities are suggested.

Table 5 Options in UV protection [101]

UV filtering hydrogel contact lenses
UV filtering RGP contact lenses
UV filtering ophthalmic lenses:
Sunglasses with UV filtering coating
Prescription lenses with UV filtering coating
Snow skiing goggles
Sunscreen > spf 15
Hat with broad brim
Limit outdoor exposure to before 1000 and after 1400 hours
Limit time spent in high intensity UV environments
Combination of above

Table 4 Summary of results from case control studies evaluating UV exposure as risk factors in uveal melanoma [92–100]

Reference	Region	No. of cases	Findings in relation to UV exposure
Gallagher et al. 1985 [92]	Canada	87	Sunlight exposure was not found to be as significant risk factor for ocular melanoma
Tucker et al. 1985 [93]	United States	444	Sunbathing: OR = 1.5; 95 % CI 0.9–2.3
			Use of sunlamps: OR = 2.1; 95 % CI 0.3–17.9
			No eye protection in sun: OR = 1.4; 95 % CI 0.9–2.3
			Gardening: OR 1.6; 95 % CI 1.01–2.4
Seddon et al. 1990 [94]	New England	197	Outdoor work was not found to be a significant risk factor for ocular melanoma
Holly et al. 1990 [95]	United States	407	Exposure to UV light: OR = 3.7, $p = 0.003$
			Tendency to sunburn: OR = 1.8, $p < 0.001$
			Light-colored eye: OR = 2.5, $p < 0.001$
			Welding burn: OR = 7.2, $p < 0.001$
Holly et al. 1996 [96]	United States	221	Exposure to artificial UV light: OR = 3.0; 95 % CI 1.2–7.8
			Welding exposure: OR = 2.2; 95 % CI 1.3–3.5
Pane and Hurst 2000 [97]	Queensland, Australia	125	Cumulative lifetime ocular UVB exposure was not found to be a risk factor for ocular melanoma
Guenel et al. 2001 [98]	France	50	Occupational exposure to solar UV light: OR = 0.9, 95 % CI 0.4–2.3
			Exposure to artificial UV light: OR = 5.5; 95 % CI 1.8–17.2
			Welders: OR = 7.3; 95 % CI 2.6–20.1
Vadjic et al. 2002 [99]	Australia	290	Outdoors activity: OR = 1.8; 95 % CI 1.1–2.8
Lutz et al. 2005 [100]	Nine European countries	292	Occupational exposure to sunlight was not associated with increased risk of ocular melanoma

Individuals should also wear appropriate clothing when outdoors. Hats with a wide brim are quite helpful in reducing direct exposure to sunlight [2]. However, such a hat may not shield the indirect UVR, hence potentially 50 % of the UVR may still enter the eyes [101]. Clothing choices are important as thin or wet clothing is less protective than thick clothing, and synthetic materials provide more protection from solar radiation than cotton materials [2].

Contact lenses can be designed to be effective UVR absorbers but contact lenses without a UVR blocker transmit 90 % of the UVR spectrum [71]. Both soft contact lens and rigid gas permeable (RGP) contact lens with UV filter are available. According to American National Standards Institute, UV blocking contact lens must absorb a minimum of 95 % of UVB and 70 % of UVA. In general, soft contact lens offers more protection than a RGP contact lens because the former provides complete corneal and partial conjunctival coverage while the latter only covers a portion of the cornea [71].

Effective UV blocking spectacle lenses provide a good general protection. However, the spectacle lens does not offer complete protection of the eye and its internal structures, since obliquely incident UVR still reaches the eye, either directly or by reflection off of the back surface of the lens [101]. In bright outdoor environments, clear spectacle lenses with UVR filtering coating may not provide adequate comfort. Wearing sunglasses is another good alternative. Ideally, sunglasses should block all UVR and some blue light as well. The American Academy of Ophthalmology suggests that sunglasses should block 99 % of all UVR [2].

Conclusion

Many ocular disease are shown to be associated with UVR exposure.

Eyelid malignancies including BCC and SCC are strongly associated with UVR exposure, which are supported by both the epidemiological and molecular studies.

Photokeratitis are caused by acute UVR exposure, while CDK is associated with chronic UVR exposure. There are also strong evidence that pterygium and cortical cataract are associated with UVR exposure.

However, the evidence of the association between UV exposure and development of pinguecula, nuclear

and posterior subcapsular cataract, OSSN, and ocular melanoma remains limited. There is insufficient evidence to determine whether AMD is related to UV exposure. It is now suggested that AMD is probably related to visible radiation especially blue light, rather than UV exposure. More research is needed to clarify these associations. Simple behavioral changes, appropriate clothing, wearing hats, and UV-blocking spectacles, sunglasses, or contact lens are effective measures for UV protection.

Conflict of interest None.

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