Title page

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Title of the paper

Pterygium and conjunctival ultraviolet autofluorescence in young Australian adults: The Raine Study

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The authors have no competing or conflicts of interest

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Abstract and keywords

Background

Sun exposure is associated with several ophthalmic diseases, including pterygium which may develop in adolescence. This study reports the prevalence of pterygium and its associations in a large cohort of young Australian adults. Conjunctival ultraviolet autofluorescence, a biomarker of ocular sun exposure, has recently been characterised in some Australian populations.

Design

Cross-sectional population-based study

Participants

1344 subjects aged 18-22 years in the Western Australian Pregnancy Cohort (Raine) Study

Methods

Standardised colour and ultraviolet autofluorescence photographs of the nasal and temporal conjunctiva were taken, and assessed for presence of pterygium and area of autofluorescence. Sun exposure and protective factors were assessed by structured questionnaire.

Main outcome measures

Area of conjunctival ultraviolet autofluorescence in mm^2 and presence of pterygium

Results

Median total conjunctival autofluorescence was 44.2mm^2 (interquartile range [IQR] $20.2\text{--}69.8\text{mm}^2$). Median conjunctival autofluorescence was higher in nasal than in temporal quadrants (23.8mm^2 vs 18.9mm^2 , $p<0.001$), but did not differ according to age or gender. Higher body mass index was associated with lower levels of autofluorescence. Total autofluorescence increased with increasing time spent outdoors. Prevalence of pterygium was 1.2% (95% CI 0.6-1.8%), and was associated with male gender (odds ratio [OR] 6.71, $p=0.012$). Participants with pterygium had significantly more conjunctival autofluorescence than those without (median 73.4mm^2 vs 44.0mm^2 , $p=0.001$).

Conclusions

Conjunctival ultraviolet autofluorescence is associated with increased time spent outdoors, and increased prevalence of pterygium. The association of this biomarker with other ophthalmohelioses, including cataract, ocular surface squamous neoplasia and eyelid malignancy, has yet to be determined.

Key words

Pterygium, Epidemiology, Conjunctiva, Sunlight

Introduction

Pterygium is a wing-shaped, fibrovascular lesion extending from the bulbar conjunctiva onto the cornea. The first known descriptions of pterygium date from the 4th - 6th century BC, in the Indian surgical text *Susruta Samhita*¹ and in the Hippocratic scripts². *Susruta*'s description of removing the pterygium by scratching with a sharp, round-topped instrument before excision is not dissimilar to the procedure performed today. In modern times, Australia is a world leader in pterygium research with many important clinical³⁻⁶, epidemiological⁷⁻¹² and pathophysiological^{13,14} studies performed by Australian researchers.

Despite these research efforts, and sun protection campaigns from government and non-government organisations^{15,16}, pterygium remains a significant issue in Australia and surrounding territories^{11,17}. Visual impairment can occur through several mechanisms¹⁸, including directly from obscuration of the visual axis or from induced astigmatism¹⁹. With rates of ocular surface neoplasia in excised pterygium around 10-12%^{4,5}, pterygium should not be universally considered a benign condition. Overall, the disease burden associated with pterygium and its treatment is high^{17,20}. There are strong environmental associations with pterygium, including outdoor activity, occupation, latitude and rural lifestyle, providing clear evidence for the role of lifetime ultraviolet light exposure in pterygium pathogenesis^{6,18}.

Ultraviolet radiation is associated with other ophthalmic diseases²¹, including cortical cataract, squamous cell carcinoma of the ocular surface, acute photokeratitis, solar retinopathy, and malignant skin lesions of the eyelids^{20,22}. In contrast, inadequate ultraviolet exposure is associated with deleterious health effects including osteomalacia, osteoporosis and rickets²⁰. Ultraviolet light is not thought to have any direct ocular health benefits, but there is evidence that low levels of outdoor sunlight exposure might have a role in myopia pathogenesis²³.

To understand the factors driving the development of pterygium and other ophthalmohelioses, research groups must be able to accurately assess individual ultraviolet exposure. This is not straightforward; sun exposure history by questionnaire is inherently subjective and prone to recall bias. Ultraviolet exposure meters are being tested in research settings, but are only able to provide short-term information about current ultraviolet exposure patterns, not the cumulative lifetime exposure that is believed to be of more importance in development of pterygium, ocular surface neoplasia, cataract and eyelid malignancy.

Conjunctival ultraviolet autofluorescence (CUVAF) photography provides an objective, quantifiable measure of ocular ultraviolet exposure^{24,25}. The principle is the same as the Wood's lamp used in dermatology²⁶, whereby areas of actinic damage on the skin are observed to fluoresce under ultraviolet light. The same phenomenon occurs on the conjunctiva (figure 1), and this conjunctival fluorescence can be captured with a camera system and digitally analysed to determine the extent of ocular sun damage²⁴. The technique has been shown to have excellent reliability, with intra- and inter-observer concordance correlation coefficients exceeding 0.900²⁵. The validity of the technique as a biomarker of ocular sun exposure and outdoor time has been demonstrated by correlation with self-reported outdoor time measured by questionnaire, with p_{trend} across categories of outdoor time <0.001 ²⁵.

Distribution of CUVAF has been reported in school-aged children²⁴, in the general adult population of sub-tropical Norfolk Island²⁷ and in a small population of patients with pterygium²⁸. No study has looked exclusively at young adults. This is perhaps the most important age group to target in sun protection research – pterygium has begun to develop in those individuals most at risk, but there remains scope for intervention to prevent development of ultraviolet-related disease later in life. This study looks at the distribution of pterygium and CUVAF in a large cohort of young Australian adults.

Methods

Participants

This study was a cross-sectional analysis of 1328 participants in the Western Australian Pregnancy Cohort (Raine) Study, a population-based longitudinal birth cohort established in 1989^{29,30}. At the 20-year follow-up, participants underwent a comprehensive ophthalmic assessment³¹.

The recruitment and follow-up were performed in Perth, Western Australia, which has a subtropical climate with a latitude of 31°60' south. The cohort participants were predominantly of Caucasian ethnicity; 90.3% had a Caucasian mother, 90.0% had a Caucasian father, and for 85.5% both parents were Caucasian.

Inclusion and exclusion criteria for the initial recruitment of the Raine cohort have been previously published²⁹. There were no specific exclusion criteria for the 20-year follow-up. All 2135 active members of the Raine cohort were invited to participate, and of these 1743 (81.6%) agreed to take part. During the 24-month period from March 2010 to February 2012, 1344 (77.1%) underwent the ophthalmic examination.

Ethics approval was obtained from the Human Research Ethics Committee at the University of Western Australia. The study was conducted in accordance with the tenets of the Declaration of Helsinki and informed consent was obtained from all participants.

Conjunctival ultraviolet autofluorescence

High resolution ultraviolet photographs of the nasal and temporal conjunctiva were taken using a specially designed camera system²⁷. A Nikon D100 (Nikon, Melville, New York USA) digital camera with 105mm 147 f/2.8 Micro Nikkor (Nikon, Melville, New York, USA) macro lens was used with an external electronic flash system including UV transmission filters (transmittance range 300-400nm, peak 365nm). The camera, lens and flash system were mounted on a table with an adjustable subject headrest and joystick-controlled camera positioning assembly. Photographs were taken in a dark room so only ultraviolet fluorescence was recorded by the camera.

Analysis was performed using Adobe Photoshop CS4 Extend (Adobe Systems Inc, San Jose, California, USA). Four photographs were analysed for each participant (left and right eyes, nasal and temporal conjunctiva) by one investigator. The area of fluorescence in mm² for each photograph was determined using Photoshop, and added together to produce a total area of fluorescence in mm² for each participant.

Pterygium assessment

High resolution colour photographs of nasal and temporal conjunctiva were taken using a Nikon D100 (Nikon, Melville, New York USA) digital camera with inbuilt flash and 105mm 147 f/2.8 Micro Nikkor (Nikon, Melville, New York, USA) lens. The camera was mounted on a table with an adjustable subject headrest and joystick-controlled camera positioning assembly.

Four photographs for each participant (left and right eyes, nasal and temporal conjunctiva) were assessed for presence or absence of pterygium (figure 2).

Sun exposure and protection behaviour

Time spent outdoors in summer (none, less than ¼ of the day, ½ of the day, greater than ¾ of the day), location of leisure time in winter (mostly indoors, ½ and ½, mostly outdoors), and frequency of use of hats and sunglasses when outdoors in the sun (never, seldom, ½ of the time, usually, always), were determined by questionnaire completed at the time of the eye examination.

Body mass index (BMI)

BMI was calculated from height (cm) and weight (kg) measured at the time of the eye examination.

Statistical analysis

Total CUVAf was analysed in quartiles and in increments of 10mm². Continuous variables were assessed for normality and summarized using mean (standard deviation) or median (interquartile range [IQR]) as appropriate. Differences between categorical variables were assessed with the chi-squared test. Differences between continuous variables were assessed with the Mann-Whitney U Test. Trends across categories were assessed using Cuzick's non-parametric test for trend. Statistical significance was set at p<0.05. Statistical analyses were undertaken in Stata 10.1 for Macintosh (Stata-Corp, College Station, 2009).

Results

Distribution of conjunctival ultraviolet autofluorescence

Of 1344 participants who attended the eye examination, 16 were excluded due to inadequate or incomplete CUVAf photographs. 1328 participants (98.8%) were included in this analysis. The mean age of participants at the time of the examination was 20.0 years (standard deviation 0.45, range 18.3-22.1 years). 684 participants (51.5%) were male. When comparing cohort participants who attended the eye examination with those who did not, there was no clinically relevant difference in age (mean age [January 2014] 22.98 years vs 23.03 years, p=0.047) or gender (males 51.5% vs 50.1%, p=0.45). Those who attended the eye examination were more likely to be of Caucasian ancestry (85.4% vs 80.1%, p<0.001).

Total CUVAf was non-normally distributed (skewness = 0.66, kurtosis = 3.17). Median total CUVAf was 44.2mm² (interquartile range 20.2-69.8mm²). 47 participants (3.5%) had no detectable CUVAf, and the highest total CUVAf measurement was 180.3mm².

There was no difference in median CUVAf between right eyes and left eyes (22.3mm² vs 22.6mm², p=0.661). Median CUVAf was higher in nasal quadrants than in temporal quadrants (23.8mm² vs 18.9mm², p<0.001). The season in which the eye examination was performed showed no association with measured CUVAf (data not shown).

Associations with conjunctival ultraviolet autofluorescence

Median total CUVAf was higher in males than females; however, this was not statistically significant (45.6mm² vs 43.2mm², p=0.079). There was no association between age and total CUVAf (p=0.170), however the spread of participant ages was small.

BMI was inversely associated with total CUVAf (-0.39mm² per unit BMI, 95% CI -0.75 to -0.03, p=0.035). This remained significant after adjustment for age, gender and height (-0.38mm², 95% CI -0.74 to -0.02, p=0.033). Obese participants (BMI > 30) had significantly lower median total

ultraviolet autofluorescence than non-obese participants (36.5mm² [IQR 14.7 – 61.3] vs 45.2 mm² [IQR 21.0 – 71.2], p=0.004).

Total CUVAF increased with increasing time spent outdoors in summer and winter, p trend <0.001 (figure 3).

There was no association between frequency of wearing sunglasses and total CUVAF. There was a positive association between wearing a hat and total CUVAF, with increasing median total CUVAF as frequency of hat wear increased (p trend = 0.031).

Participants with no detectable CUVAF (n=47) spent less time outdoors than participants with detectable CUVAF. 30.3% of participants with no CUVAF spent half or more of the day outside, compared with 51.6% of the rest of the cohort (p=0.016). There was no difference in gender or obesity between the groups.

Pterygium

Prevalence of pterygium in either eye was 1.2% (95% CI 0.6-1.8%). Three participants had bilateral pterygium; the other 13 participants had unilateral pterygium. In most cases the pterygium occurred on the nasal conjunctiva, with only two pterygia observed on the temporal conjunctiva.

Pterygium was more common in males than females, 2.0% (95% CI 1.0-3.1) vs 0.3% (95% CI 0.0-0.7), p=0.004. The odds of having pterygium was higher in males than females (OR 6.71 [95% CI 1.51-29.90], p=0.012). Age was not significantly associated with pterygium (OR 1.22 per year [95% CI 0.43-3.50], p=0.706).

Median total CUVAF was higher in participants who had pterygium than those who did not, 73.4mm² (IQR 48.3-94.7) vs 44.0mm² (IQR 20.2-69.0), p=0.001. There was no difference in median CUVAF between male and female participants with pterygium (73.4mm² vs 77.5mm², p=0.874). For every 10mm² increase in CUVAF, odds of pterygium increased by 23% (OR 1.23 [95% CI 1.09-1.39], p=0.001).

When CUVAF was considered in quartiles, each additional quartile was associated with two and a half times the odds of pterygium (OR 2.52, 95%CI 1.39-4.60, p trend = 0.002). In the lowest quartile (least CUVAF) there were no participants with pterygium. The second and third quartiles each had three participants with pterygium, while the highest quartile (most CUVAF) had ten participants with pterygium (p trend < 0.001).

61.5% of participants with pterygium reported spending half the day or more outdoors in summer compared with 50.8% of participants without pterygium, however the difference was not statistically significant (p=0.441).

Height, weight and level of education showed no significant association with pterygium.

When BMI was assessed as a continuous variable, there was no association with pterygium (OR 0.92, 95% CI 0.80-1.04, p=0.189). There was a significant difference in rates of overweight/obesity, with 6.3% of participants with pterygium meeting criteria for overweight/obesity (BMI > 25) compared with 33.8% of participants without pterygium (chi-square p=0.020). When obesity (BMI > 30) was considered alone, the difference was not significant (chi-square p=0.128).

Discussion

In this population of young Australian adults, pterygium was present in 2% of males (1 in 50) and 0.3% of females (1 in 330). Prevalence of pterygium is known to increase with age, and it is likely that rates of pterygium in this cohort will increase as the participants pass into later adulthood. Epidemiological studies of pterygium in Australia have found a wide range of prevalence estimates, related to differences in the age, ethnicity and latitude of the study population. The National Trachoma and Eye Health Program⁷ looked at all ages, and found a pterygium prevalence of 1.1% in the non-Aboriginal population and 3.4% in the Aboriginal population. More recently the Central Australian Ocular Health Study⁸ reported pterygium prevalence of 9.3% in Aboriginal adults. The Melbourne Visual Impairment Project⁹, Blue Mountains Eye Study¹⁰ and Norfolk Island Eye Study (NIES)¹¹ reported pterygium prevalence of 2.8%, 7.3% and 10.9% respectively, reflecting the decreasing latitude of the study population (37°S, 33°S and 29°S). Worldwide, prevalence estimates of pterygium vary according to study location and demographics. A recent meta-analysis looked at data from 20 population-based studies published in English and Chinese and found an overall pooled prevalence of 10.2%³².

This study also describes the population distribution of CUVAF. The NIES²⁷, which looked at 641 individuals aged 15 to 89 years, is the only other large study to have reported distribution of CUVAF. Median total CUVAF in the NIES was 28.2mm², much lower than the median total CUVAF of 44.2mm² observed in this study. Geographic differences in ultraviolet exposure are unlikely to explain the discrepancy; Perth and Norfolk Island both have subtropical climates and are located at similar latitudes (31°S and 29°S, respectively).

It is possible that the age range of participants accounts for some or all of the difference in median CUVAF between these studies. In the NIES there was a significant inverse relationship between CUVAF and age, with less CUVAF observed in older participants. It is not known whether this represents the natural history of the conjunctival autofluorescence phenomenon, or if it is a cohort effect of different ultraviolet exposure patterns between generations. In either case, the Raine study includes only young adults, which is the age group found in the NIES to have the most CUVAF. The relationship between age and CUVAF is interesting; in a cross-sectional study of children aged 3 to 15 years²⁴ CUVAF was found to increase with age, the opposite of the relationship observed in the NIES. It is possible that the young adults in the Raine study represent the peak of the CUVAF age curve. Longitudinal data are needed, and to this end a follow-up assessment of the NIES cohort is planned.

The observation that participants with higher BMI had less CUVAF is interesting and to our knowledge has not previously been reported. On average, obese participants had 20% less CUVAF than non-obese participants (36.5mm² vs 45.2 mm²). It could be speculated that an active, outdoor lifestyle might result in both lower body weight and more sun exposure, compared with a sedentary, predominantly indoor lifestyle. The finding that participants with pterygium were less likely to be overweight or obese than those without pterygium (6.3% vs 33.8%) supports this theory. Caution must be used in interpreting these results, particularly as BMI overall did not show an association with pterygium. Clearly more research is needed in this area.

It is well established that pterygium and ocular surface squamous neoplasia are more common in males than females^{32,33}, attributed to differences in occupational and recreational ultraviolet exposure between genders. Certainly in this study males had more than six times the odds of pterygium than females. It is interesting, then, that although males had slightly more CUVAF than females the difference did not reach statistical significance. This was also the case with self-reported outdoor activity by questionnaire; males spent more time outdoors in summer than females, but the difference was not significant (data not shown). If both CUVAF and questionnaire data suggest that there was little difference in ocular ultraviolet exposure between the genders in this cohort, why was pterygium so much more common in males? It is possible that early-onset pterygium has a particular predilection for males, or perhaps that males are in some way inherently more sensitive to even moderate increases in ultraviolet light exposure.

Increased frequency of wearing sunglasses did not protect against development of CUVAF, even when those with high levels of outdoor activity were considered alone. This is interesting, as current sun-protection guidelines published in a joint position statement from the Royal Australian and New Zealand College of Ophthalmologists and Cancer Council Australia³⁴ recommend wearing close-fitting, wraparound style sunglasses to protect the eyes from ultraviolet radiation. As this study did not differentiate between different styles of sunglasses, no comment can be made about the effect of wraparound sunglasses specifically on CUVAF.

Hats did not confer any protective effect against CUVAF, as has been previously demonstrated for hat wear and pterygium³⁵. Participants who spent more time outdoors had more CUVAF, and were also more likely to wear a hat (data not shown), explaining the observed positive correlation between hat wear and CUVAF.

The nasal conjunctiva had higher levels of CUVAF than the temporal conjunctiva, and was more affected by pterygium, likely due to corneal light-focusing across the anterior chamber^{13,36}. Total CUVAF was significantly higher in participants with pterygium compared with the rest of the cohort, presumably due to higher levels of ocular ultraviolet light exposure. Odds of having pterygium increased with increasing quartile of CUVAF, demonstrating a dose-response relationship. This relationship was also observed in the NIES¹¹, and is of particular interest as it demonstrates that the asymptomatic and essentially invisible phenomenon of conjunctival autofluorescence has a direct link to real-world clinical ophthalmic disease. The relationship of CUVAF to other ophthalmohelioses, including cataract, ocular surface squamous neoplasia and eyelid malignancy has yet to be determined. CUVAF photography may have a role in research into the pathophysiology of these diseases, and has potential for use in health promotion and patient education regarding ocular sun protection.

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Figure legends

Figure 1

Photographs of the nasal conjunctiva

- a) colour image with no visible sun damage
- b) ultraviolet image showing area of autofluorescence

Figure 2

a-d) Colour photographs of a participant with bilateral nasal pterygia

e-h) Ultraviolet photographs of the same participant

Figure 3

CUVAF and participant recall of outdoor time measured by questionnaire

Figures

Figure 1a and 1b

(images uploaded separately)

Figure 2

(compilation image uploaded separately)

Figure 3