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Pterygium Is a Pre-Malignant Condition: A Systematic Review

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ABSTRACT

In a hot and humid climate Pterygium is one of the common ocular surface disorders. The ultraviolet radiations have been implicated in the pathogenesis of this condition. **Objectives:** To investigate the association between pterygium and ocular surface squamous neoplasia (OSSN) and to determine the prevalence rates of both diseases in varied populations worldwide. **Methods:** The internet search in the selected databases resulted in 420 articles in the first round. The second round of screening of the titles excluded 26 articles ascribed to be duplicates. The third round of evaluation ended with the exclusion of 341 articles because they lacked an association between the pterygium and OSSN. In the final round, 29 studies were excluded according to the inclusion and exclusion criteria. **Results:** A total of 12492 pterygia samples were reported in 24 studies. Most of the studies had been conducted in hot and temperate climates. Out of these twenty-four, three studies were from areas of low UV Radiation like Canada, while six were from the USA, three were from South America, four studies were from Australia and New Zealand, three were from Europe, and one each was from South East Asia, the Middle East, and Far East Asia and Africa. **Conclusions:** There is a paucity of homogeneity in the reported data on the correlation of pterygium and OSSN. Such studies will delineate the relationship between patients with pterygium and suspected OSSN and will provide predictive information to care for public health issues in these countries.

INTRODUCTION

The pterygium is a triangular sheet of thickened conjunctiva, sub-tenon tissue, and new abnormal blood vessels creeping into the cornea. This condition is more prevalent in inhabitants of hot and temperate climates. It reveals the response of conjunctival tissues to chronic dryness and extended exposure to sun rays [1]. Among the three types of ultraviolet radiations, A, B & C, UV B (wavelength 280 to 315 nm) is considered to be the major risk factor leading to the formation of pterygium [2]. Pterygium is associated with a histopathological alteration of pterygium, which is elastotic degeneration of the conjunctiva. It is brought about by the loss of sub-epithelial collagen and is substituted with abnormal material that stains for elastin. Bowman membrane of the cornea is dissolved, and there is dyskeratotic alteration of the epithelial cells that are positioned above the tissues [3].

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Ocular surface squamous neoplasia (OSSN) is one type of ocular surface epithelial growth. It is between the dysplasia of grades I, II, and III and invasive carcinoma of the conjunctiva, squamous type [4]. The pathophysiological etiology of OSSN is multifactorial, although overexposure to UV radiation is considered a primary risk factor of OSSN. OSSN and pterygium have similar risk factors, such as age, race, exposure to ultraviolet radiation, geographical location, etc. Considering that patients with pterygium experienced unsuspected OSSN, the clinical features are not quite different compared to those who had no cancerous lesion in their pterygia [5]. These two clinical conditions mimic the ocular location, clinical appearances, and symptomatology. So, most ophthalmologists can ignore benign clinical conditions like pterygium with invasive ocular surface neoplasia. The purpose of this study was to systematically review the literature that reported an association between pterygium and ocular surface squamous neoplasia in patients operated for pterygium and to find out the prevalence rates of both diseases in varied populations worldwide. Clinically, it is very difficult to differentiate between pterygium and OSSN, as they involve the same age groups and their symptoms are mostly similar. Most of the recent studies have reported a low rate of histologically confirmed OSSN in the specimen retrieved as pterygium tissue. This was documented in cohorts of patients residing close to the equator and having maximum exposure to UV radiation [2]. Due to the close association between these two conditions, the routine histological examination of the excised pteryigum tissue has been suggested to avoid a pre-malignant condition like OSSN in hot and windy regions to prevent overlooking a pre-malignant condition [3].

This study aimed to investigate the association between pterygium and ocular surface squamous neoplasia (OSSN) and to determine the prevalence rates of both diseases in varied populations worldwide.

METHODS

This systematic review was conducted according to the guidelines provided by the Cochrane Handbook of Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA)[6, 7]. The studies were included in the systematic review based on the following inclusion criteria: 1) Patients with Pterygium; 2) Morphological and Histopathology reported the presence of OSSN, conjunctival intraepithelial neoplasia (CIN), squamous cell carcinoma (SCC), or dysplasia; 3) experimental or observational studies; and 4) no restriction on the time of follow-up. The studies were excluded if they were 1) reported a different outcome of interest, i.e., Primary acquired melanosis (PAM) or Conjunctival melanosis; 2) not in the English Language; 3) Conference abstracts; and 4) Case reports, dissertations, and letters to the editor. Scientific database search engines like PubMed, Embase, and Cochrane Library were analyzed to find the researcher's work until December 2023 using the following search terms: 'ocular surface squamous neoplasia', OSSN, 'Squamous intraepithelial neoplasia', 'Conjunctival intraepithelial neoplasia', CIN, 'Squamous cell carcinoma', SCC, Carcinoma, Neoplasia, Pterygium. For reference, the EndNote online system was selected. Two authors independently conducted the screening, and discrepancies were resolved after discussion. After removing duplicates, the studies were evaluated based on title and abstract. Full-text reviews were then conducted, and the final studies included in the systematic review were selected. Forward and backward citations of the included studies were also used to search for the relevant articles. Data regarding the baseline characteristics of the included studies and outcomes of interest were extracted. The outcomes included the histopathology of pterygium and the incidence of OSSN, CIN, SCC, and dysplasia. The web search in database systems like PubMed, Embase, and Cochrane Library systematically resulted in 420 articles in the first round. During the second round of screening, due to the duplicate titles, 26 articles were excluded. The third round of evaluation ended with the exclusion of 341 articles due to a lack of association of the pterygium with OSSN. By using online selected database systems systematically, 53 complete texts were retrieved. In the final round, articles were further assessed according to inclusion and exclusion criteria. This resulted in the exclusion of 14 articles due to different populations, no outcome was found in 7 reports, and conference proceedings in 4 and 4 non-English language reports were also excluded (Figure 1).

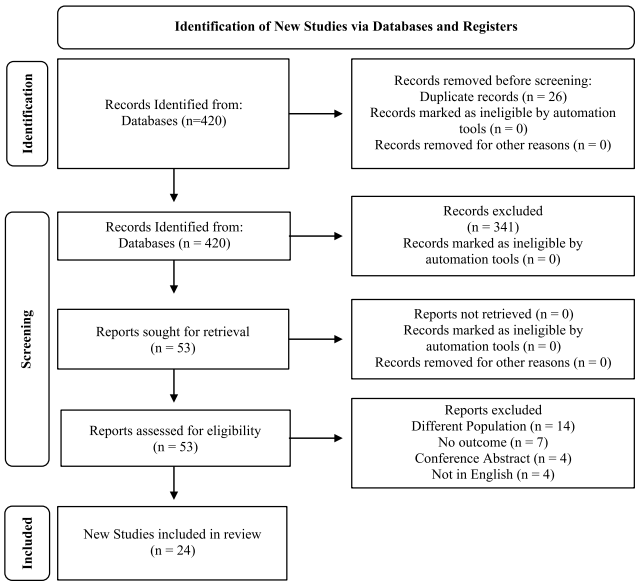

Figure 1: Systematic Search Following PRISMA Guidelines

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RESULTS

A total of 12462 pterygia samples were reported in twenty-four studies. Most of the studies had been conducted in hot and temperate climates. Of these twenty-four, three studies were from areas of low UV Radiation like Canada, while six were from the USA, three were from South America, four studies were from Australia & New Zealand, three were from Europe, and one each was from South East Asia, the Middle East, and Far East Asia and Africa. The publication time varied from as early as 1969, Sevel and Sealy, to the report published in 2023 [8-31]. Similarly, Yeung *et al.* presented 8 years' survey with a mean age of 52.0 years, with a male preponderance of 54% to 46% female [13]. Moreover, Galor *et al.* reported that demographic data showed a higher incidence of pterygia without malignancy in the younger age group, whereas pterygium associated with OSSN was found in the older age group. They also reported that males outnumbered female patients [14]. Whereas McClellan *et al.* and Oellers *et al.* retrospectively analyzed the pterygium tissues and documented a very low prevalence of OSSN in patients of sixty years and above [15, 16]. Artornsombudh demonstrated a mean age of 56.6 ± 11.7 years and a female-to-male ratio of 3:7 for OSSN-associated pterygium [17]. In addition to the other confounding factors, the main factor that had a causative association between pterygium and OSSN was over-exposure to ultraviolet radiation. Cameron's theory found ten percent higher rates of the disease associated with OSSN at 30 degrees' equator latitude. They coined the term Pterygium Belt, which included different countries around the equator that fall in this region. Regarding the co-occurrence of pterygium and OSSN, the largest group of 2005 patients was reported by Segev *et al.* with 1.2 % having OSSN. However, they found both CIN and OSSN in their retrospective study. Similarly, Segev *et al.* studied 682 cases and showed 0 % cases of OSSN [18]. On the other hand, Barros *et al.* found a 40.6% association of OSSN in pterygium, followed by Clear *et al.* who reported 30% cases [19]. These studies revealed that no supporting data currently exist to support the human papillomavirus (HPV) and human immunodeficiency virus (HIV) as etiological agents causing pterygium-associated OSSN (Table 1).

Table 1: An Association of Pterygium with Premalignant Ocular Surface Neoplasia After Histopathology

Sr. No.	References	Design	Country	Gender M/F	Mean Age (y)	Tissue Studied	Cases (n)	Pathology	Cases (%)
1	[8]	Retrospective	South Africa	NA	NA	Pterygium	100	SCC, CIN	19
2	[9]	Retrospective	Malawi	NA	NA	Pterygium and Pinguecula	224	OSSN	30
3	[10]	Retrospective	USA	NA	NA	Pterygium	92	CIN	4.35
4	[11]	Retrospective	Australia	293/240	50	Pterygium	533	OSSN	9.8
5	[12]	Retrospective	Australia	62/35	50 ± 15	Pterygium	100	OSSN	5.0
6	[13]	Survey	Canada	482/411	52	Pterygium	1127	OSSN	0
7	[14]	Retrospective	USA	282/108	61	Pterygium	396	OSSN	4.1
8	[15]	Retrospective	USA	22646/1533	66 ± 15	Pterygium	590	OSSN	1.3
9	[16]	Retrospective	USA	1054/951	60	Pterygium	2005	OSSN	1.7
10	[17]	Prospective	Thailand	144/338	56.5 ± 17	Pterygium	498	OSSN	1.8
11	[18]	Retrospective	Israel	402/280	56	Pterygium	682	OSSN	0
12	[19]	Prospective	Brazil	17/15	49.21	Pterygium	32	OSSN	40.6
13	[20]	Retrospective	Canada	116/99	53.4 ± 15.5	Pterygium	215	OSSN	2.33
14	[21]	Retrospective	Greece	96/62	67.2 ± 12.1	Pterygium	158	CIN	2.53
15	[22]	Retrospective	Australia	3/1	62	Pterygium	4	SCC	NA
16	[23]	Retrospective	Taiwan	928/859	65.2 ± 14.2	Pterygium	1787	CIN	0.22
17	[24]	Retrospective	Brazil	117/60	52	Pterygium	177	CIN, SCC	11.29
18	[25]	Retrospective	Columbia	313/148	31.8 ± 12.1	Pterygium	461	Dysplasia, CIS	14.96
19	[26]	Retrospective	Canada	141/94	56	Pterygium	149	SCC	20.81
20	[27]	Retrospective	Turkey	36/39	55	Pterygium	75	Dysplasia	65
21	[28]	Retrospective	USA	174/174	58 ± 12	Pterygium	348	OSSN	0.29
22	[29]	Retrospective	USA	300/204	54.0 ± 11.1	Pterygium	504	OSSN	3.57
23	[30]	Prospective	New Zealand	113/97	58 ± 16.2	Pterygium	174	OSSN	2.3
24	[31]	Retrospective	UK	9/3	60.25	Pterygium	2061	CIN, SCC	0.6

n: number; NA: not available; M: male; F: female; y: years; SCC: Squamous cell carcinoma; CIN: conjunctival intraepithelial neoplasia; PAM: Primary acquired melanosis

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DISCUSSION

This systematic review aimed to investigate the correlation between pterygium and ocular surface squamous neoplasia (OSSN). There are inconsistent reports on the association between pterygium and SSN. Moreover, there is a scarcity of systematic review research findings on the association and its determinants. Therefore, the findings from this systematic review will help eye care professionals design appropriate strategies to reduce the prevalence rates of both of these diseases in varied populations of the world. In the present study, a wide range of differences was reported among the samples sent for histopathology after pterygium excision among the world population, from 0 % by Segev *et al.* to 40.6% by Barros *et al.* [18, 19]. Most of these studies were retrospective, based on the post-operative hospital data. Moreover, the difference might be due to the various age and gender groups that had been studied by the researchers. However, Zoroquiain *et al.* reported that 54% of male were 53.4 ± 15.5 years at diagnosis of the disease. The OSSN was identified in 5 cases (2.33 %), and four of them were female patients. The mean age of patients with both these diseases is reported to be the same [20]. A study conducted by Hirst *et al.* in Queensland, Australia, on the other hand, reported male to female ratio of patients as 1.82: 1.00, and the mean age was 50 years (range 18-85 years) [11]. Moreover, Barros *et al.* reported a median age of 44 years in Brazilian patients (range between 28 and 81 years) [19]. The different socio-economic conditions of the varied geographical locations of the world might explain these variations regarding the gender and age groups of the patients. Nearly all the studies showed a strong correlation between pterygium and OSSN in areas of maximum exposure to the sun and ultraviolet radiation. Zoroquiain *et al.* elaborated a higher number of OSSN in cases of pterygium than expected (2.33%) in Montreal, which has low ultraviolet radiation exposure; these rates were close to rates reported in Sydney and even higher than in Florida [20]. It was reported that snowfall persists late into the spring in Montreal. The ultraviolet rays reflected off might have played a role in the tissue damage. Moreover, Montreal had a multi-ethnic, multi-cultural society, and subjects might have shifted from the region having high ultraviolet exposure [20]. Detorakis *et al.* analyzed the hospital records of the patients between 2000 and 2014. A total of 1787 pterygium cases underwent surgical excision [21]. The mean age of the patients was 65.19 ± 14.21 years. The majority (80.3%) had primary pterygium, while the remaining (20.3%) were diagnosed as recurrent cases. Only 0.2% of cases were provisionally diagnosed as neoplasia on histopathological examination. The authors inferred that the association with OSSN was a remote possibility. However, it was concluded that a detailed history, clinical evaluation, followed by histopathology examination of the surgically excised specimens must be carried out [21]. Besides, a retrospective chart review of patients who had undergone pterygium surgery in Mendoza *et al.* was conducted at the University of Montreal. Between 2010 and 2022, 1559 patients underwent surgery for pterygium, and 854 patients (55) were males. Histopathology examination of 1142 specimens was done, and the majority were pterygium (1105 out of 1142; 97%). It had a surprise discovery of 3 cases of OSSN [22]. Moreover, Hung *et al.* and Lomelí-Linares *et al.* reported CIN and SCC instead of OSSN in the pterygium tissues on histological examination [23, 24]. Similarly, Mejia *et al.* also documented Dysplasia and CIS in the retrospective studies [25]. However, the frequency of OSSN in pterygium is rare in the Canadian population, but it can be clinically difficult to distinguish. It is important to send all pterygium specimens for pathology [26]. Although Suren *et al.* studied the retrieved pterygium tissues and found dysplasia in all cases [27]. Modabber *et al.* reported a retrospective study that out of 348 cases of pterygium. All cases had surgical excision followed by histopathology. Nearly 16% had recurrence, and one case of OSSN was reported in the excised pterygia. Hence, it showed a poor association of pterygium and OSSN in the middle-aged population [28]. This review showed the diversity of the population of nearly all continents of the world, Asia, Europe, Australia, North America, South America, Africa, and Canada. In addition, Zhu *et al.* reported a prevalence of 3.5% cases of OSSN in pterygium tissues of middle-aged USA subjects [29]. In contrary, Hossain *et al.* reported in the retrospective studies a very low frequency of 2.3% cases of OSSN, respectively [30]. In addition, a retrospective study was carried out on pterygia samples received for histopathology, suspected of being pterygium, between 1997 and 2021. The overall prevalence of neoplasia was 0.6%. It was concluded that the rates of unexpected results of finding a malignancy were meager [31]. Pterygium and OSSN have been recognized as closely similar conditions as they share a similar location and symptoms. In addition, had common risk factors such as ultraviolet radiation and a hot, dusty, and windy environment [32]. Vempuluru *et al.* studied the clinical features, anterior segment optical coherence tomography patterns, medical and surgical treatment, and histological diagnosis of ocular surface squamous neoplasia (OSSN) in the specimens [33]. In a meta-analysis, the authors investigated the prevalence rate and various risk factors for the identification of pterygium from OSSN. It was important to adopt the management strategies for these varied conditions [34]. In another study, the authors investigated the pterygia samples using a novel

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autofluorescence technique. They documented that in hot and temperate climate countries like Australia, where due to maximum exposure to u v radiations from the sun, can lead to the development of malignant conditions in the pterygia[35].

CONCLUSIONS

This systematic review depicted that pterygium is not only an elastotic degeneration of the conjunctival tissue, but it represents a pre-malignant ocular surface condition, which is closely associated with high UV exposure, with a measurable risk of occult OSSN across the varied population of the world. The reported wide variations in neoplastic transformation reflected differences in the intensity of ultraviolet exposure, population risk factors, histopathological grading systems, and methodology adopted for the study, but not a true biological inconsistency. It was demonstrated that routinely submitting the excised pterygia tissues for histopathological examination significantly improves early detection of subclinical OSSN, particularly from high-risk regions within the Pterygium Belts. These findings support reclassifying pterygium as a premalignant condition and justify mandatory histopathologic evaluation of excised tissues in high-UV settings.

Authors Contribution

Conceptualization: MSZK
Methodology: MSZK, AS
Formal analysis: MSZK, AMM, CAN, AZKC, AS
Writing review and editing: MSZK, GA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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