ARC Journal of Ophthalmology
Volume 5, Issue 1, PP 21-29
www.arcjournals.org

Eyelid and Conjunctiva Epithelial Tumours: A Review of Risk Factors and Primary Prevention Options

Daniele Oliveira[1,2,*], Diogo Sousa-Martins[3], Alexandra Isabel Rosa[4], Helena Cabral-Marques[5], Cláudia Bacalhau[2], David Martins[2]

[1]*PhD student in Department of Sociopharmacy, Faculty of Pharmacy, University of Lisbon, Portugal*

[2]*Ophthalmologist, Centro Hospitalar de Setúbal and Hospital da Luz Setúbal, Portugal*

[3]*Professor in Department of Sociopharmacy, Faculty of Pharmacy, University of Lisbon, Portugal*

[4]*PhD in Health Sciences from the University of Medicine of the University of Coimbra, Regulatory Affairs Specialist, ELS Solutions, Portugal*

[5]*Professor in Department of Galenic Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Lisbon, Portugal*

Corresponding Author: Daniele Oliveira,** *PhD student in Department of Sociopharmacy, Faculty of Pharmacy, University of Lisbon, Portugal, Ophthalmologist, Centro Hospitalar de Setúbal and Hospital da Luz Setúbal, Portugal.* ***E-mail: *dspo.oftalmo@gmail.com*

Abstract

Introduction: *Skin cancer is one of the most prevalent cancers in the world. This review aims to evaluate current evidence about the appearance of eyelid and conjunctival epithelial tumours, identify risk factors for different types and alert to the importance of primary prevention.*

Materials and Methods: *A systematic literature review was performed by searching the PubMed electronic database. The search was limited to the period between 1990 and 2019 and to articles in Portuguese and/or English.*

Results: *Risk factors associated with the development of eyelid and conjunctiva epithelial tumours were identified. They include: light skin, genetic predisposition, preneoplasic eye lesion and the most relevant risk factor, exposure to sun light, which causes DNA damage by ultraviolet radiation.*

Discussion and Conclusion: *Not all eyelid and conjunctival tumours can be prevented, but some actions may reduce the risk of developing such tumours. Early diagnosis is very important for excellent prognosis. The tumor can be detected on skin during periodical exams and suspicious lesions referred to the ophthalmologist. Nevertheless, there is a dearth of data of sunscreen products suitable for ocular use, which may represent an unmet need to be addressed.*

Keywords: *Eyelid tumours, Conjunctival epithelial tumours, Eye tumour risk factors, Ultraviolet Radiation, Skin cancer.*

1. INTRODUCTION

The eyelid, made up of both skin and mucous membranes, is differentiated into four distinct layers: (i) skin and subcutaneous tissue, (ii) striated muscle (orbicularis oculi), (iii) tarsus and (iv) conjunctiva; while the conjunctiva covers the inner surface of the eyelids and anterior sclera[1,2]. About 5-10% of all skin tumours and 15% of all face tumours have been reported to occur on the eyelid with most of them being of epidermal origin[3–5]. Although about 80% of all eyelid and conjunctiva tumours are benign[6], there are multiple malignant ones that can lead to loss of vision and/or life if not treated. There have been reports of significant increase in the incidence of malignant eyelid tumour over the past two decades[7–10]. Also, epidemiological studies have revealed that certain demographic features such as age, race/ethnicity play a role in the type and frequency of these tumours[1,3,8]. This review seeks to evaluate current evidence about the appearance of eyelid and conjunctival epithelial tumours, identify the risk factors for different types and discuss the importance of early diagnosis. It also seeks to identify conditions that make these tumours easier to treat and to provide knowledge on primary prevention strategies.

2. METHODS

A systematic literature review was carried out by searching the electronic database PubMed. The search was limited to the period between 1990 and 2019 and some articles were eliminated because they were written in a language other than Portuguese or English. This review sought to assess current evidence on the appearance of eyelid and conjunctival epithelial tumours, identify risk factors for different types, and to discuss the importance of early diagnosis. IT also seeks to identify conditions that facilitate the treatment of these tumours and provide knowledge about primary prevention strategies

3. RESULTS

The aetiology, clinical presentation and diagnostics approached of different types of eyelid and conjunctival tumours identified in the literature are discussed below.

Eyelid Tumours

The diagnosis of eyelid tumours is challenging due to a varied forms of clinical presentation and biology/histopathology[11].. Several types of eyelid tumours have been identified in the literature and classified into three distinct groups, that is; benign, pre- malignant and malignant tumours[2]. Some benign eyelid lesions such as Actinic Keratosis and Lentigo Malign are considered as pre-malignant squamous cell carcinoma and melanoma. A brief description of the epidemiology and clinical presentation of some malignant eyelid tumours are presented below.

a. Basal Cell Carcinoma or Basalioma

Basal Cell Carcinoma (BCC) is the most common form of malignant cutaneous cancer in humans constituting about 85% of all malignant epithelial eyelid tumours. It is slow-growing, rarely metastasizing and associated with significant morbidity due to invasion and destruction of adjacent areas. It arises in the basal cells in the deepest layer of the epidermis. About 10% of BCCs have been found to occur in the eye area (Fig. 1.)[12–14]. In the eyelid, the most frequent location for BCC is the inferior lid, in the middle third. Tumours involving the medial canthus can invade the orbit and sinuses[14]. Males are the most affected and 95% of the cases occur between 40 and 79 years of age (mean age, 60 years). Prevalence of recurrence is about 4.2% in the short-term and 8.7% in follow-up higher than 5 years[14,15]. The clinical types of BCC are presented in Table 1.

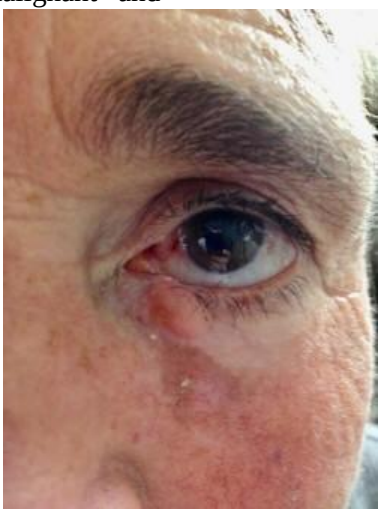

Fig1. *Basal Cell Carcinoma*

Table1. *Clinical types of Basal Cell Carcinoma [5]*

Main Clinical Types of BCC	**Signs**
Nodular or nodule-ulcerative	Classic basal cell carcinoma, shiny, firm, indurated nodule with dilated blood vessels. Nodule may resemble non-cancerous, chalazion-like lesions
Pigmented	Increased concentration of melanin, may be mistaken for a melanoma
Cystic	Dome-shaped, cystic nodule
Infiltrative/sclerosing	Originates in the epidermis but invades the dermis, margins are not delineated, simulates chronic blepharitis
Ulcerative	Large lesion with central necrosis

If detected early, BCCs are treatable and potentially curable. However, the larger the tumour growth, the larger the area to be excised in order to achieve clear margins. The decision of the most appropriate surgical strategy will be based on the size of the lesion, location, adjacent tissues, preservation of eyelid function, eye protection and aesthetic satisfactory result[16].

b. Squamous Cell Carcinoma

Squamous cell carcinoma **(**SCC) is the second most common type of eyelid tumours, constituting about 5-10 % off all eyelid malignancies. Epidemiological studies have estimated incidence rates of about 0.09 - 2.42 cases per 100 000 population[17,18]. It originates from the squamous cells of the skin. It is usually presented as a hard ulcerated nodule which develops crusting erosions and is frequently found on the lower eyelid. Metastasis may occur eventually when natural defences are compromised by immunodeficiency[19,20]. SCC predominantly occurs on the lower lid followed by the medial canthus and lateral canthus. Majority of those affected are 60 years or older, with men two to three times more likely to be affected than women. If detected early and treated adequately by complete excision with histological confirmation of tumour clearance[17], SCCs have excellent prognosis. However, mortality rates as high as 40% have been reported[21].

c. Melanoma

Melanomas are the least frequent type skin cancer and has been reported to have the worst prognosis and highest mortality rates[20,22]. While cutaneous melanoma originates from malignant melanocytes, the eyelid variant (Fig. 2) specifically originates from the periocular lentigo maligna and has been reported to often metastasize into regional lymph nodes with similar characteristics as those of cutaneous and conjunctival melanoma[23,24]. While epidemiological data is sparse, eyelid melanoma is thought to represent about 1 in 350 cases of all cutaneous melanoma or less than 1 % of all eyelid tumours[24,25]. Eyelid melanoma predominantly affects the lower lid and can also affect the eyelid margins thereby worsening prognosis[2]. Table 2 presents the main clinical types of melanoma.

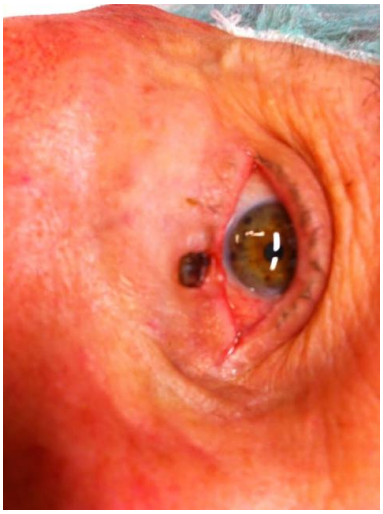

Fig2. *Melanoma*

Table2. *Clinical types of Melanoma*

Main Clinical Types of Melanoma	Signs
Superficial spreading	Arises in white-skinned individuals. The most common type, from pigmented cell (melanocytes), crosses the basement membrane
Nodular	Arises within superficial spreading melanoma and proliferates more deeply
Lentigo malign melanoma	Pre-malignant lesion associated with melanoma of the conjunctiva

Early diagnosis by excisional or incisional biopsy is essential to avoid metastasis. Treatment strategy in the majority of the cases is done through a surgical approach. The eyelid tumour size, location and histological type is important to estimate the prognosis and the best surgical technique[12]. Some of the warning signs for eyelid malignant lesions that can be detected during clinical examinations are listed in Table 3.

Table3. *Warning signs of eyelid malignant lesions*

Palpation shows involvement of deeper structures
Simultaneous ulcer, haemorrhage, and crust
Central ulcer
Loss of eyelashes
Telangiectatic vessels
Pigmentary changes

Some of the surgical procedures for treating eyelid melanomas include:

Wide Surgical Excision and Subsequent Eyelid Reconstruction

This surgery consists in the removal of the entire tumour with a 3mm margin outside the tumour[13]. During surgery, frozen section control can be done by a pathologist to study the biopsied margin fragments. Accordingly, with the pathologist's anatomopathological diagnosis, the surgeon adjusts the excision until an excised fragment is tumour-free. Wide excision may improve survival in patients depending on the melanoma's stage[5].

The Eyelid surgery procedures reconstructs both anterior lamella (skin and muscle) and the posterior lamella (tarsal plate and conjunctiva). For small lesions, less than one-third of the eyelid can be closed directly after a pentagon resection. If necessary, a lateral cantholysis or semi-circular flap (Tenzel) can be performed. For larger lesions, over half of the eyelid can be closed by Mustarde's cheek rotation flap, used to repair upper and lower eyelids lesions, Hughes tarsoconjunctival flap used to repair lower eyelid lesions, Cutler-Beard reconstruction indicated for upper eyelid lesions[14].

Exenteration

This is mostly performed for orbital invasion by tumours and involves removal of the globe and orbital contents. The exenteration may be significantly higher when the initial surgery does not include margin-controlled excision[15].

Radiotherapy, Cryotherapy, Chemotherapy and Immunotherapy

These are useful individual co-treatment strategies like topical Imiquimod 5%, an immunomodulator drug which produces apoptosis of tumour cells due to the increase of cytokine, especially Il-10[26]. Patients with eyelids SCC and malignant melanoma should be evaluated for evidence of metastasis from orbital extension and lymph node spread[11].

Conjunctival Tumours

Conjunctival tumours are the most frequent eye tumours and can be classified as benign, premalignant or malignant. While the conjunctival is made up of a wide variety of cells, most of its tumours originate from conjunctival cells. Other rare forms of conjunctival tumours have been reported to be of epithelial and melanocytic origins, or through the invasion of the conjunctiva by tumours from surrounding structures such as eyelid, orbit and eyeballs. Due to specific clinical features which makes them readily visible, they can be easily diagnosed. The three most important tumors of the conjunctiva are squamous neoplasia of the ocular surface (OSSN), melanocytic and lymphoma[27,28].

a) Ocular Surface Squamous Neoplasia (OSSN)

Ocular surface squamous neoplasia (OSSN) is the most common form of ocular surface tumour, covering a broad spectrum of conjunctival and corneal epithelial lesions such as non-invasive conjunctival and corneal intra-epithelial dysplasia and invasive squamous cell carcinoma[29,30]. OSSN arises at the junction between the cornea and the conjunctiva and clinically presents with irritation, raised gelatinous mass and leucoplakia. While OSSN is found in all races, it is more common in Caucasian populations and predominantly affects the male population. In Caucasian patients, the tumour is typically yellow-pink in colour, while in African patients, it's often pigmented brown[31,32]. Therapeutic approaches to OSSN includes surgical excision, cryotherapy, photodynamic therapy, radiotherapy, topical/injection chemotherapy, immunotherapy, and antiviral medications[29,33–35].

b) Melanocytic Tumours

Conjunctival melanocytic tumours includes nevus, melanosis, melanoma and primary acquired melanosis (PAM)[36]. While ocular melanoma corresponds to about 5% of all melanomas, melanocytic tumours represents about 12% of all conjunctival tumours. The conjunctival melanoma is rare, pigmented or non-pigmented, with an increased incidence over the past two decades due to a more intense UV/solar radiation exposure[36–38]. The diagnosis of this conjunctiva tumour is made by clinical observation and biomicroscope examination.

Visible lesions observed in routine ophthalmologic examination is an important factor for early stage detection of the disease, follow-up and relapses (even after excision) with surgical excision of the total lesion being the treatment of choice. It can be performed with simple local excision with at least 3mm of free margin or associated with cryotherapy, topical chemotherapy, radiotherapy, enucleation and exenteration when there is invasion of the orbit[39]. Patients with conjunctival melanoma are required to be monitored for metastatic disease by a systemic oncologist[40].

Lesions of the bulbar conjunctiva (Fig. 3) may be benign or malignant. Histologically, the ocular conjunctiva is similar to other membranes of the human body formed by epithelium and stroma, but it is the only one that suffers the damage of solar radiation, a factor predisposing to the appearance of some neoplasms.

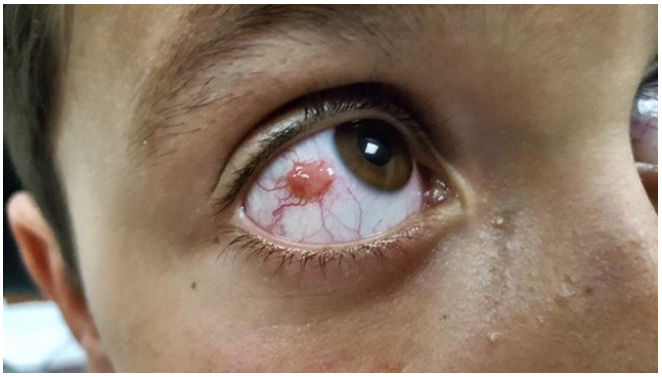

Fig3. *Lesions of the bulbar conjunctiva (melanocytic nevus)*

Primary Acquired Melanosis (PAM) lesion develops in middle-aged or elderly caucasians clinically appearing between 50-70 years of age as a subtle, unilateral pigmentation that is distributed throughout any part of the conjunctiva. The coloration is irregular, ranging from lack of pigmentation to dark brown. The lesion is flat (unlike nevi), can be moved freely over the globe and is considered a precursor of conjunctival melanoma[41]. The histological patterns of PAM are very varied, and depending on the nuclear characteristics, we can distinguish:

1. **PAM without Atypia** - Appears generally in the 4th decade of life. Very low risk of malignancy. It is probably a pre cursor of PAM with atypia.
2. **PAM with Atypia** - The mean age of onset is in the 5th decade of life. Progression to melanoma occurs in 13% of cases.

About 60% of all conjunctival melanoma arises from PAM and treatment options typically depends on the extent or magnitude of the lesion[41].

c) Lymphoma

Conjunctival lymphomas represents about 25 to 30% of all ocular adnexal lymphomas[42,43]. They are mainly B-cell non-Hodgkin lymphomas (NHLs) derived malignant neoplasms and can be classified into four main subtypes: extranodal marginal zone lymphoma (EMZL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL)[44]. Conjunctival lymphomas is considered a disease of the middle aged and the elderly and is characterized by a sessile salmon-pink painless patch with or without visible intrinsic tumour vessels. Because they are often hidden in the superior or inferior fornices of the conjunctiv, they may be difficult to detect clinically. Depending on the subtype, presence or absence of systemic lymphoma and the size; treatment options typically includes a combination of one or more of excision, cryotherapy, incisional biopsy and external beam radiation therapy[42,44].

Risk Factors and prevention of Eyelid and Conjunctival Cancer – The invisible enemy

Several risk factors have been identified for different types of eyelid and conjunctiva tumours discussed above. The main risk factors found in the literature are:

a) Human Papilloma Virus (HPV) Infection: HPV infection is associated with the development of Non-Melanoma Skin Cancer (NMSC). The virus has tropism for epithelial cells, having an important role in the carcinogenic process of host epithelial cells in immunocompromised patients through the inhibition of tumor suppressor genes[45,46].

b) Xeroderma Pigmentosum: Xeroderma Pigmentosum is an autosomal recessive genetic disease that affects the genes responsible for DNA repair after damage caused by UV radiation. This deficiency leads to the appearance of multiple NMSCs in the exposed areas. It is necessary to avoid exposure to sunlight[47].

c) Immunossupression: Patients undergoing treatment with immunosuppressants are subject to a higher incidence of NMSC due to the accumulation of drug metabolites in cells, and these, under the action of UV rays, undergo DNA mutations and by deficiency in apoptosis (protective response to damage caused by UV radiation avoiding survival of the damaged cell) of the mutant cells by the immunosuppressive effect itself [48].

Environmental Risk Factors

Over the past few decades, ozone depletion and global climate change have led to higher levels of human exposure to ultraviolet (UV) light or irradiation from the sun, and increased incidence of several types of eyelid and conjunctival tumours[49,50]. Despite the increased use of sunscreen as skin protection, 80% of all human BCC cases develop in regions of the head and neck which are more exposed to the sun, while 20% of all skin cancers occur in the eyelids with 50% in the lower eyelid. It's been suggested that main reason why eyelid tumours predominantly affects the lower lid is because of light reflection by the cornea onto the lower lid margin compared to the upper lid that's protected by the eyebrow[14,51]. Short-wavelength UV radiation (290-320nm) is considered the greatest risk factor in BCC, SCC, OSSN, Melanoma etc. Some studies have demonstrated the increased incidence of SCC and other tumours with each 10-degree reduction in latitude due to exposure to greater UV-B energy[49,52,53]. Also, outdoor recreational activities and occupations such as golfing, fishing and construction have been implicated in increased incidence of these tumours. In BCC, SCC, OSSN etc., UV-B damages DNA and its repair systems thereby modulating genetic alterations that leads to these tumours. The mechanism of UV-B induced tumour formation influences the eventual type of eyelid tumour. For instance, the severity of UV exposures at young age rather than cumulative exposure over a period of time has been implicated in BCC[49,54]. Other environmental factors such as photosensitizing drugs, chemicals, cigarette smoke etc. are elucidated in Table 4[40,55].

Table4. *Risk factors for eyelid and ocular conjunctival tumours*

Eye Tumour		Environmental risk factors	Other risk factors	References
Eyelid Tumours	Basal Cell Carcinoma	UV radiation		
	Squamous cell carcinoma	Smoking Exposure to polycyclic hydrocarbons and arsenic Geographic region	Genetic skin disorders like xeroderma pigmentosum, etc. Human papilloma virus infection Immunosuppression	[48,56]
	Melanoma	Outdoor activities		
Conjunctival Tumours	Ocular Surface Squamous Neoplasia			
	Melanocytic Tumours			
	Lymphoma			

Phenotypic Risk Factors

Phenotypic characteristics such as age, gender, skin colour, family history, actinic damage are recognised risk factors with huge potentials for increasing susceptibility to eyelid and conjunctival tumours. As discussed above, different types of eyelid and conjunctival tumours display specific age and gender patterns. It has been suggested that the distinct male predominance may represent increased occupational sunlight exposure by males, rather than a genetic predisposition[19]. Perhaps, the most important and widely recognised phenotypic risk factor is the skin colour. Eyelid and conjunctival tumours disproportionately affects Caucasians or fair/white skinned individuals and light-coloured eyes) [49,52,55,56]. Often, the complex interplay between environmental and phenotypic characteristics complicates the aetiology of these tumours. For instance, the risk of eyelid tumours like SCC and conjunctival tumours like OSSN are higher in fair/white skinned individuals live near the equator[29,40]. As formerly mentioned, cutaneous BCC represents one of the most common

malignancies in the Caucasian population worldwide[57]. However, the prevalence and incidence of some non-melanoma skin cancers are difficult to estimate because of the absence of registries[58]. A meta-analysis has suggested an elevated risk of developing BCC and SCC after a non-melanoma skin cancer[59]. Table 4 presents the cutaneous eyelid tumour risk factors among Caucasian populations.

3. Discussion and Conclusions

Examining the skin periodically is a simple and easy way to detect these tumours and an ophthalmologist should be consulted if any lesion develop. Urban photoprotection is a great challenge. The use of sunglasses to protect the eyes and eyelids from UV rays are associated with outdoor activities, however, daily solar exposure, during routine activities, such as walking, car or public transport, physical activities in schools and, especially, outdoor workers, is much more harmful to eye health than sporadic exposure[17]. Damage from occasional exposure to solar radiation is potentiated by the air pollution of urban centres[18]. New technological advances have contributed to the development of UV-blocking sunglasses and hats, useful to prevent the majority eyelid and conjunctival tumours. However, the sunscreen used regularly on face, when in close contact with the eyes creates sensitivity concerns. Indeed, there is still a need for sunscreens that do not irritate the eyes. Additionally, there is still a lack in sunscreen products suitable for ocular use. The need of a sunscreen for ocular use should include the development of a stable pharmaceutical formulation with the aim of preventing and protecting the eyes from damage caused by UV radiation that is safe, adapted to the eyes and does not promote eye irritation.

In conclusion, this article reviews the types and risk factors related to the appearance of tumor lesions of the conjunctiva and eyelids. The most important risk factor observed was excessive exposure to solar radiation, which causes oxidative stress, DNA damage and the appearance of eyelid and conjunctiva tumors. Although not all tumors of the eyelid and conjunctiva can be prevented, but there are many procedures that can reduce the risk of developing these lesions. Early diagnosis is very important, since most of the cases detected at an early stage have a good cure rate with less invasive reconstructive surgical treatments and good aesthetic and functional results.

4. Contributions of Authorship

Daniele Oliveira contributed to the conception and design of the work carried out the initial literature search and wrote the first draft of the manuscript. Diogo Sousa-Martins, Alexandra Isabel Rosa and Helena Cabral-Marques contributed to the conception of the work, supervised the first author and provided relevant intellectual inputs. Cláudia Bacalhau and David Martins Contirbuted to the scientific revision.

5. Funding

This work is part of a Ph.D. research project financed by iMed. ULisboa, financed by national funds from FCT/MCTES (UID/DTP/04138/ 2019)

References

[1] Mi JC, Se HB. Clinical analysis of benign eyelid and conjunctival tumors. Vol. 220, Ophthalmologica. 2005. p. 43–51.

[2] Pe'er J. Pathology of eyelid tumors. Vol. 64, Indian Journal of Ophthalmology. 2016. p. 177–90.

[3] Deprez M, Uffer S. Clinicopathological features of eyelid skin tumors. a retrospective study of 5504 cases and review of literature. Am J Dermatopathol. 2009;31(3):256–62.

[4] Yu SS et al. A retrospective study of 2228 cases with eyelid tumors. Int J Ophthalmol. 2018;11(11):1835–41.

[5] Bizarro MB et al. Tumores de localização palpebral, 15 anos de experiência no Centro de Patologia Oftálmica do Centro Hospitalar da Universidade de Coimbra. Rev Soc Port Oftalmol. 2016;40(2).

[6] Obata H et al. Incidence of benign and malignant lesions of eyelid and conjunctival tumors. Vol. 109, Nippon Ganka Gakkai zasshi. 2005. p. 573–9.

[7] Mak ST et al. Malignant eyelid tumors in Hong Kong 1997-2009. Jpn J Ophthalmol. 2011;55(6):681–5.

[8] Mak ST. Eyelid tumours and pseudotumours in Hong Kong. Vol. 19, Hong Kong Medical Journal. 2013. p. 277.

[9] Quigley C et al. National incidence of eyelid cancer in Ireland (2005–2015). Eye. 2019;33(10):1534–9.

[10] Lin HY et al. Incidence of Eyelid Cancers in Taiwan. A 21-Year Review. Ophthalmology. 2006;113(11) :2101–7.

[11] Balasubramanian A, Kannan NS. Eyelid malignancies-always quite challenging. J Clin Diagnostic Res. 2017;11(3):XR01–4.

[12] Carucci JA, Leffell DJ, Pettersen JS. Chapter 115. Basal Cell Carcinoma. In: Fitzpatrick's Dermatology in General Medicine, 8e [Internet]. 2012. Available at: http://access

medicine.mhmedical.com/content.aspx? aid=56 059410

[13] Saleh GM et al. Incidence of eyelid basal cell carcinoma in England: 2000-2010. Br J Ophthalmol. 2017;101(2):209–12.

[14] Shi Y, Jia R, Fan X. Ocular basal cell carcinoma: A brief literature review of clinical diagnosis and treatment. Onco Targets Ther. 2017;10:2483–9.

[15] Rosner M. Basal Cell Carcinoma. In: Clinical Ophthalmic Oncology. 2007. p. 76–80.

[16] Muzic JG et al. Incidence and Trends of Basal Cell Carcinoma and Cutaneous Squamous Cell Carcinoma: A Population-Based Study in Olmsted County, Minnesota, 2000 to 2010. Mayo Clin Proc. 2017;92(6): 890–8.

[17] Donaldson MJ et al. Squamous cell carcinoma of the eyelids. Br J Ophthalmol. 2002;86(10) :1161–5.

[18] Cook BE, Bartley GB. Epidemiologic characteristics and clinical course of patients with malignant eyelid tumors in an incidence cohort in Olmsted County, Minnesota. Ophthalmology. 1999;106(4):746–50.

[19] Rosner M, Fabian ID. Squamous Cell Carcinoma. In: Clinical Ophthalmic Oncology: Eyelid and Conjunctival Tumors. 2014. p. 43–51.

[20] Yin VT et al. Eyelid and ocular surface carcinoma: Diagnosis and management. Clin Dermatol. 2015;33(2):159–69.

[21] Lober CW, Fenske NA. Basal cell, squamous cell, and sebaceous gland carcinomas of the periorbital region. J Am Acad Dermatol. 1991;25(4):685–90.

[22] Ho M et al. Eyelid tumours and pseudotumours in Hong Kong: A ten-year experience. Hong Kong Med J. 2013;19(2):150–5.

[23] Shields CL, Kels JG, Shields JA. Melanoma of the eye: Revealing hidden secrets, one at a time. Clin Dermatol. 2015;33(2):183–96.

[24] Mancera N, Smalley KSM, Margo CE. Melanoma of the eyelid and periocular skin: Histopathologic classification and molecular pathology. Vol. 64, Survey of Ophthalmology. 2019. p. 272–88.

[25] Pe'er J, Folberg R. Eyelid tumors: Cutaneous melanoma. In: Clinical Ophthalmic Oncology: Eyelid and Conjunctival Tumors. 2014. p. 63–8.

[26] Williams HC et al. Surgery Versus 5% Imiquimod for Nodular and Superficial Basal Cell Carcinoma: J Invest Dermatol. 2017;137(3):614–9.

[27] Shields CL et al. Conjunctival tumors: Review of clinical features, risks, biomarkers, and outcomes - The 2017 J. Donald M. Gass Lecture. Vol. 6, Asia-Pacific Journal of Ophthalmology. 2017. p. 109–20.

[28] Shields CL, Shields JA. Tumors of the conjunctiva and cornea. Surv Ophthalmol. 2004;49(1):3–24.

[29] Lee GA, Hirst LW. Ocular surface squamous neoplasia. Surv Ophthalmol. 1995;39(6):429–50.

[30] Gichuhi S et al. Epidemiology of ocular surface squamous neoplasia in Africa. Vol. 18, Tropical Medicine and International Health. 2013. p. 1424–43.

[31] Tunc M et al. Intraepithelial and invasive squamous cell carcinoma of the conjunctiva: Analysis of 60 cases. Br J Ophthalmol. 1999;83(1):98–103.

[32] Sun EC, Fears TR, Goedert JJ. Epidemiology of squamous cell conjunctival cancer. Cancer Epidemiol Biomarkers Prev. 1997;6(2):73–7.

[33] Kim HJ et al. Giant ocular surface squamous neoplasia managed with interferon alpha-2b as immunotherapy or immunoreduction. Ophthalmology. 2012;119(5):938–44.

[34] Patrick Yeatts PR et al. 5-Fluorouracil for the treatment of intraepithelial neoplasia of the conjunctiva and cornea. Ophthalmology. 2000;107(12):2190–5.

[35] Shields CL, Naseripour M, Shields JA. Topical mitomycin C for extensive, recurrent conjunctival-corneal squamous cell carcinoma. Am J Ophthalmol. 2002;133(5):601–6.

[36] Roth M. Eyelid, Conjunctival, and Orbital Tumors. An Atlas and Textbook, third edition Jerry A Shields, Carol L Shields Wolters Kluwer 2015, 824 pages, $456.00. Clin Exp Optom. 2018;101(4):618–9.

[37] Yu GP et al. Conjunctival melanoma: Is it increasing in the United States? Am J Ophthalmol. 2003;135(6): 800–6.

[38] Tuomaala S et al. Conjunctival melanoma: Is it increasing in the United States? [1] (multiple letters). Vol. 136, American Journal of Ophthalmology. 2003. p. 1189–90.

[39] Silas O, Ajetunmobi O, Enwereuzo C. A descriptive study of patterns of conjunctival lesions in Jos, Nigeria: A 10-year retrospective study. Ann Trop Pathol. 2017;8(1):39.

[40] Shields CL et al. Conjunctival melanoma: Risk factors for recurrence, exenteration, metastasis, and death in 150 consecutive patients. Arch Ophthalmol. 2000;118(11):1497–507.

[41] Jovanovic P et al. Ocular melanoma: An overview of the current status. Vol. 6, International Journal of Clinical and Experimental Pathology. 2013. p. 1230–44.

[42] Kirkegaard MM et al. Malignant lymphoma of the conjunctiva. Vol. 60, Survey of Ophthalmology. 2015. p. 444–58.

[43] Sjö LD. Ophthalmic lymphoma: Epidemiology and pathogenesis. Vol. 87, Acta Ophthalmologica. 2009. p. 1–20.

[44] Kirkegaard MM et al. Conjunctival lymphoma-an international multicenter retrospective study. JAMA Ophthalmol. 2016;134(4):406–14.

[45] Ally MS, Tang JY, Arron ST. Cutaneous human papillomavirus infection and basal cell carcinoma of the skin. Vol. 133, Journal of Investigative Dermatology. 2013. p. 1456–8.

[46] Das Graças M et al. Human papillomavirus infection: etiopathogenesis, molecular biology and clinical manifestations * Infecção pelo papilomavírus humano: etiopatogenia, biologia molecular e manifestações clínicas [Internet]. Vol. 86, REVIEW An Bras Dermatol. 2011. Available at: http://www.scielo.br/pdf/abd/ v86 n2/en_v86n2a14.pdf

[47] Brooks BP et al. Ocular manifestations of xeroderma pigmentosum: Long-term follow-up highlights the role of DNA repair in protection from sun damage. Ophthalmology. 2013;120(7):1324–36.

[48] Rünger TM. How different wavelengths of the ultraviolet spectrum contribute to skin carcinogenesis: The role of cellular damage responses. Vol. 127, Journal of Investigative Dermatology. 2007. p. 2103–5.

[49] Yam JCS, Kwok AKH. Ultraviolet light and ocular diseases. Vol. 34, International Ophthalmology. 2014. p. 383–400.

[50] Sliney DH. Ultraviolet Radiation and the Eye BT - Environmental UV Radiation: Impact on Ecosystems and Human Health and Predictive Models. In: Ghetti F, Checcucci G, Bornman JF, editors. Dordrecht: Springer Netherlands; 2006. p. 259–78.

[51] Allali J, D'Hermies F, Renard G. Basal cell carcinomas of the eyelids. Vol. 219, Ophthalmologica. 2005. p. 57–71.

[52] Mehta M, Fay A. Squamous cell carcinoma of the eyelid and conjunctiva. Vol. 49, International Ophthalmology Clinics. 2009. p. 111–21.

[53] Vajdic CM et al. Sun exposure predicts risk of ocular melanoma in Australia. Int J Cancer. 2002;101(2):175–82.

[54] Kricker A et al. Does intermittent sun exposure cause basal cell carcinoma? a case-control study in Western Australia. Int J Cancer. 1995;60(4):489–94.

[55] Verkouteren JAC et al. Epidemiology of basal cell carcinoma: scholarly review. Vol. 177, British Journal of Dermatology. 2017. p. 359–72.

[56] Cassidy PB et al. A phase II randomized placebo-controlled trial of oral n-acetylcysteine for protection of melanocytic nevi against uv-induced oxidative stress in vivo. Cancer Prev Res. 2017;10(1):36–44.

[57] Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Vol. 166, British Journal of Dermatology. 2012. p. 1069–80.

[58] Marzuka AG, Book SE. Basal cell carcinoma: Pathogenesis, epidemiology, clinical features, diagnosis, histopathology, and management. Vol. 88, Yale Journal of Biology and Medicine. 2015. p. 167–79.

[59] Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: A critical review of the literature and meta-analysis. Arch Dermatol. 2000;136(12): 1524–30.

Citation: *Daniele Oliveira, et al. Eyelid and Conjunctiva Epithelial Tumours: A Review of Risk Factors and Primary Prevention Options. ARC Journal of Ophthalmology. 2021; 5(1): 21-29.*