



# Eyelid malignancies in young individuals: clinical peculiarities

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## Abstract

**Objective** The incidence of malignant eyelid tumors is considerably increasing, even in young patients. The purpose of this study was to identify particularities in individuals under 40 years of age affected by eyelid malignancies.

**Methods** Clinical charts of patients under 40 years of age who underwent eyelid tumor excision from 2014 to 2020 in two reference centers, one in Brazil and one in the USA, were reviewed. Demographic and outcome measures included: age, gender, skin phototype, comorbidities, diagnosis, time until diagnosis, lesion location, recurrence and metastasis. In addition, associated characteristics, including chronic sun exposure, intentional tanning (outdoor or artificial), history

of smoking, use of sunscreen, family history of skin cancer and exposure to pesticides or herbicides, were reviewed.

**Results** A total of 24 malignant eyelid tumors from 17 patients were identified. Twelve (70.6%) patients were female, and the most prevalent tumor was basal cell carcinoma (62.5%). Three (17.6%) patients had xeroderma pigmentosum and presented with multiple lesions. Family history of skin cancer was reported by 47% of patients. Prolonged sun exposure was reported by 41.2%; history of smoking and intentional tanning were reported by 23.5 and 17.6%, respectively, and might have played a role in carcinogenesis.

**Conclusions** Although uncommon in young subjects, eyelid malignancies present some peculiarities in individuals under 40 years of age. Our results suggest that women with family history of skin cancer and history of chronic exposure to ultraviolet radiation are at risk. Association with genetic syndromes is also relevant among younger age groups.

**Keywords** Eyelid tumor · Eyelid malignancies · Young individuals

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## Introduction

Non-melanoma skin cancer (NMSC) is the most common form of cancer. Recently, numerous studies report a worldwide increase in its incidence,

particularly for basal cell carcinoma (BCC), due to a combination of factors, such as increased exposure to ultraviolet radiation (UVR), ozone depletion, and the aging population [1–4]. It is estimated that periocular BCCs account for 10% of all BCCs [4]. Periocular BCC can affect patients of all ages, but is most common in elderly, fair-skinned individuals with significant sun exposure [4–6].

An increase in the incidence of NMSCs, especially BCC, in people younger than 40 years of age was also reported [2, 7–10]. Few studies, however, have focused on the particularities associated with eyelid malignancies in a younger population [11]. Periocular malignancies may present differently, behave more aggressively, and pose greater challenges for treatment and repair than malignancies at other sites. Early diagnosis and management of periorbital malignancies is mandatory because of their proximity and potential to invade vital structures such as the orbit, sinuses, and brain [4, 12, 13].

The goal of this study was to identify particularities in individuals under 40 years of age affected by eyelid malignancies. Identifying specific clinical and epidemiological data can help increase awareness in the medical community regarding these cases.

## Methods

This study was performed in compliance with the ethical principles of the Declaration of Helsinki and was approved by the Federal University of São Paulo and University of California San Diego Review Boards.

The clinical charts of patients under 40 years of age, who underwent eyelid malignancy excision from 2014 to 2020 at the Division of Ophthalmic Plastic and Reconstructive Surgery, Department of Ophthalmology and Visual Sciences at the Federal University of S. Paulo/ UNIFESP and at the Division of Ophthalmic Plastic and Reconstructive Surgery, Department of Ophthalmology at the University of California San Diego, were retrospectively reviewed.

*Data recorded include* age, gender, Fitzpatrick skin phototype, comorbidities, diagnosis, location of lesion, margins, recurrence, metastasis, time until diagnosis and risk factors. Additional risk factors also examined were a history of chronic sun exposure, intentional tanning (outdoor or artificial tanning), use

of sunscreen, history of smoking, family history of skin cancer and exposure to pesticides or herbicides.

## Results

A total of 24 malignant eyelid tumors were identified during the studied period in seventeen patients. Twelve (70.6%) patients were female, and the mean age was  $29 \pm 10.3$  years old (range: 8–40 years old). The most prevalent eyelid malignancy was BCC, found in 15 lesions (62.5%). Squamous cell carcinoma (SCC) was observed in 8 lesions (33.3%), and one (4.2%) was identified as basosquamous carcinoma. Three (17.6%) patients had a history of xeroderma pigmentosum (Fig. 1) and presented with multiple lesions, comprising BCC and SCC. Patient 1 presented with several lesions along the study period (at ages 8, 9, and 10 years old). One patient presented with Curry Jones syndrome.

Eleven (45.8%) lesions were located in the lower eyelid (Fig. 2), five (20.8%) in the upper eyelid, five (20.8%) in the medial canthus. One (4.2%) lesion involved the upper and lower eyelids, and the malar region (Fig. 3), one (4.2%) involved the upper and lower eyelids, and the lateral canthus, and one (4.2%), involved the upper, lower lids, and orbit.

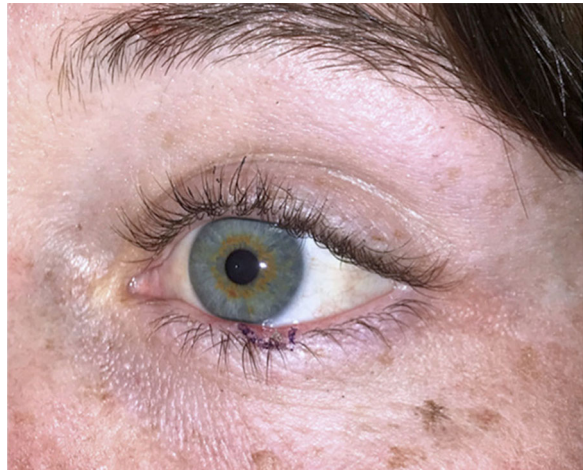
The mean time frame from lesion appearance until surgery was 30 months (41.4 months in S. Paulo and 18.6 months in California) and mean follow-up time was 19.5 months. One recurrence was noted in the patient who presented with basosquamous carcinoma; metastasis was not observed in any patient. Table 1 shows patients demographics and tumor characteristics.

Family history of skin cancer was reported by 8 (47%) patients, while chronic sun exposure (history of outdoor job and/or childhood in low latitude—northeastern states in Brazil) was reported by 7 (41.2%) patients; history of smoking and intentional tanning were reported by 4 (23.5%) and 3 (17.6%) patients, respectively. Regarding use of sunscreen, 7 (41.2%) reported none/ minimal use and 5 (29.4%), occasional use. Exposure to pesticides or herbicides was not reported by any patient from this series. Table 2 shows characteristics associated with the patients from this series.

**Fig. 1** Squamous cell carcinoma in a young patient with xeroderma pigmentosum



**Fig. 2** Basal cell carcinoma in a 28-year-old female patient



**Fig. 3** Pigmented basal cell carcinoma in a female patient with history of outdoor working



**Table 1** Patients demographics and tumors characteristics

Case	Age at diagnosis	Gender	Skin phototype	Associated syndromes	Diagnosis	Location	Recurrence or metastasis	Time until diagnosis (months)
I1	8y	M	IV	XP	SCC BCC solid	LUL LLL	No	15
I11	9y	M			SCC invasive	RLL	No	
I111	10y	M			SCC SCC	RLL LLL	No	
2	38y	F	IV	No	BCC	R Medial canthus	No	60
3	15y	F	V	XP	SCC	LLL	No	1
4	30y	F	II	No	BCC solid	LLL	No	24
5	33y	F	II	No	BCC solid	LLL	No	48
6	34y	F	IV	No	BCC solid	LUL, LLL, malar region	No	120
7	36y	F	II	No	BCC solid	LLL	No	60
8	38y	M	II	No	SCC	LLL	No	13
9	28y	F	IV	CJS	BCC nodular	RUL	No	4
10	16y	F	II	No	BCC nodular	R medial canthus	No	36
11	31y	F	II	No	BCC nodular	RUL,RLL, lateral canthus	No	Prior surgery for BCC
12	34y	M	II	No	SCC infiltrative	LLL	No	24
13	10y	F	IV	XP	BCC and SCC	Multiple lesions: RUL, LUL, both medial canthi	Yes, after 3 months	60
14	40y	M	III	No	BCC nodular	RUL	No	6
15	36y	M	II	No	Basosquamous infiltrative	RUL,RLL,orbit	No	8
16	38y	F	II	No	BCC nodular	R medial canthus	No	6
17	28y	F	I	No	BCC nodular	LLL	No	5

y—years; F—female; M—male; BCC—basal cell carcinoma; SCC—squamous cell carcinoma; CJS—Curry Jones syndrome; XP—xeroderma pigmentosum; R—right; LLL—left lower lid; LUL—left upper lid; RLL—right lower lid; RUL—right upper lid

## Discussion

Eyelid malignancies are commonly seen in an ophthalmology practice [11, 12, 14]. The incidence of cutaneous malignancies is increasing in younger patients, including eyelid malignancies [7–10]. Our results suggest that eyelid malignancies present some particularities in younger patients. In these individuals, genetic susceptibility and chronic sun exposure appear to play a crucial role in the pathogenesis of skin cancer, imparting risk of carcinogenesis at an earlier stage. Geography also plays a role due to differing amounts of atmospheric ultraviolet exposure [15, 16]. Also, association with genetic syndromes, such as

xeroderma pigmentosum is more frequent in this age group.

It is known that amount of ambient ultraviolet radiation (UVR) varies greatly with geography of residence. Living in high ultraviolet exposure locations is associated with increased risk for non-melanoma skin cancer, such as BCC and SCC [15, 16]. A significant percentage of total lifetime UVR exposure is believed to occur during childhood and early adulthood. In addition, early UVR exposure has been shown to be more associated with development of skin cancer than similar exposure later in life [17–19]. One study evaluated the relationship between place of residence at birth, adolescence and age 30 and risk of development of multiple skin tumors. They

**Table 2** Risk factors associated with the patients from this series

Case	Family history of skin cancer	Residence in low latitude	History of outdoor job	Length of outdoor work (years)	Use of sunscreen	Intentional tanning	History of smoking	Exposure to pesticides or herbicides
1	No	No	No	N/A	Occasional	No	No	No
2	No	No	No	N/A	None or minimal	No	No	No
3	Yes	No	No	N/A	Occasional	No	No	No
4	No	No	No	N/A	None or minimal	No	No	No
5	No	During childhood	No	N/A	None or minimal	Yes (outdoor)	No	No
6	No	During childhood	Yes	17	None or minimal	Yes (outdoor)	Yes	No
7	No	During childhood	No	N/A	n/a	No	No	No
8	Yes	During childhood	Yes	15	None or minimal	No	Yes	No
9	No	No	No	N/A	Occasional	No	No	No
10	Yes	No	No	N/A	Occasional	No	No	No
11	Yes	No	No	N/A	Almost always	No	No	No
12	Yes	No	Yes	10	Almost always	No	No	No
13	No	No	No	N/A	None or minimal	No	No	No
14	Yes	No	Yes	n/a	Almost always	Yes (outdoor)	Yes	No
15	Yes	No	No	N/A	None or minimal	No	Yes	No
16	Yes	No	No	N/A	Almost always	No	No	No
17	No	No	Yes	5	Occasional	No	No	No

N/A—not applicable; n/a—not available

found a significant association between consistent residence in medium- or high-UVR places and an increased risk of non-melanoma skin cancer later in life [15]. In the present study, 50% of patients treated in Brazil reported spending their childhood in north-eastern Brazilian cities, even closer to the equator, and therefore associated with high ultraviolet exposure and incremental risk of NMSCs later in life.

Because the amount of UVR exposure is challenging to quantify, place of residence has been used as an alternative for assessing UVR exposure [15]. To measure the amount of UVR reaching a geographic zone, an international unit known as UV index was introduced by the National Weather Service. The

index is based on latitude, altitude, time of day, ozone concentration, cloud coverage, and haze [20]. The two study centers (S. Paulo and California) are locations associated with considerable UVR. Moreover, having an outdoor occupation in high UV index locations likely increases the risk of developing eyelid malignancies [21].

We observed that 47% of our patients reported family history of skin cancer, suggesting that genetic susceptibility plays a key role in the pathogenesis of eyelid malignancies in young subjects. A decrease in DNA repair capacity was found to be greater in young patients who had non-melanoma skin cancer (NMSC) when compared to age-matched controls [22].

Environment and behavior must obviously play a role in the impact of family history.

Several studies have found increased BCC rates among women younger than 40 [2, 7–9]. Numerous studies correlate the use of tanning beds with higher rates of BCC in this population [7, 9, 23, 24]. In the present study, women comprised 70% of cases; however, indoor tanning was not reported by any patient. In Brazil, indoor tanning has been banned since 2009 and in California, it is prohibited in minors, suggesting that other risk factors are associated with the higher rate of eyelid malignancies. One possible explanation could be a higher awareness of skin cancer and increased surveillance in women with medical attention being sought sooner than with men [12]. Leffell et al. [25] reported that aggressive subtypes of BCC were higher for patients aged 35 years or younger, and that difference was significant among women but not among men. The reason for a greater female proportion observed in the periocular region among younger age groups is unclear. It may be that hormones and use of cosmetics and makeup by women could be associated and further studies are necessary in order to better understand these differences.

In young patients, it is important to highlight the possible coexistence of genetic syndromes, such as xeroderma pigmentosum, Gorlin-Goltz syndrome and others, such as Curry Jones syndrome, which are associated with a higher risk of developing non-melanoma skin neoplasms [10, 26]. Four patients in this series presented with genetic syndromes: xeroderma pigmentosum (3 patients) and Curry Jones syndrome (1 patient). Xeroderma pigmentosum can predispose to both BCC and SCC, as observed in the patients in this series. In this series, BCC was observed in 62.5% of cases, followed by SCC (33.3%). Excluding patients with xeroderma pigmentosum, SCC is rare among young individuals. A European study reported that only 3.6% of SCCs were detected in patients under 50 years of age [27].

Because eyelid malignancies are most commonly seen in the elderly, the diagnosis in young adults or children may be considered unlikely or misdiagnosed by general ophthalmologists [11]. This fact might explain the delayed diagnosis in younger individuals, in comparison with diagnosis in older patients. In the present study, average period until treatment was 30 months. Nerad et al. [11] observed that periocular malignant lesions were ignored for several years,

averaging 4.3 years, while Murray and Cannon [28] reported an average lapse of 6.1 years from the onset of disease to establishment of a tissue diagnosis in children and young adults.

In addition to UV exposure and genetic susceptibility, other risk factors may be associated with the development of skin cancer, such as cigarette smoking [9, 10, 29]. This association seems to be stronger for SCC [30]. In this paper, smoking was reported by 23.5% of patients; among the five patients who presented SCC, one had history of smoking.

Some differences between the two study centers were observed: in the Brazilian center, Fitzpatrick phototypes varied from II to V, while in the American center, skin phototypes varied from I to IV. Average time from lesion appearance to surgery was 41.4 months in S. Paulo and 18.6 months in California. This difference may reflect the lack of specialized tertiary centers in remote areas in Brazil, with consequent delay for the patient to reach specialized centers, which contributes even more to a delayed diagnosis. It is important to highlight that the Brazilian center is a public service that receives referred patients from secondary centers from across the country. Moreover, patients who do not have access to health insurance and private care constitute the great majority of patients seen in this center.

This study is primarily limited by its sample size. In addition, populations from both study centers are not homogenous. Further studies involving different centers and epidemiological studies are needed to confirm these findings for eyelid malignancies among younger patients.

## Conclusions

Although uncommon in younger age groups, eyelid malignancies present some unique clinical characteristics in individuals under 40 years of age. Our results suggest that individuals with family history of skin cancer and history of exposure to ultraviolet radiation are at risk to develop eyelid malignancies at a younger age. Because multiple NMSCs can result in significant morbidity and healthcare cost, methods to increase public awareness regarding preventive measures and early diagnosis are essential. In addition, individuals who develop skin cancer are at risk to develop additional malignancies, thus periodic skin cancer

screening is mandatory, especially in individuals living in higher UV index locations. Interventions should be directed toward encouraging daily sun-screen use in outdoor settings as a preventative measure in young adults, even those without malignancy.

**Author Contributions** DFB: acquisition, analysis, and interpretation of data; drafting the work; final approval. MHO: design and conception of the study; analysis, and interpretation of data; critical revision for important intellectual content; final approval. DOK: acquisition, analysis and interpretation of data; critical revision for important intellectual content; final approval. CYL: acquisition, analysis and interpretation of data; critical revision for important intellectual content; final approval. FL: analysis and interpretation of data; critical revision for important intellectual content; final approval. THO: design and conception of the study; analysis, and interpretation of data; critical revision for important intellectual content; final approval.

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#### Declarations

**Conflict of interest** The authors declare that there is no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the UNIFESP (#1333/ 2020) and UCSF (#210647) IRBs and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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