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Original Article

Correlation between ocular tumor distribution and age based on analysis of pathological specimens

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Abstract: Objective: To analyze the distribution of benign and malignant eyelid tumors and their relationship with age, and to provide a reference for clinical diagnosis and treatment. Methods: A retrospective review was conducted on 1,056 patients with eyelid tumors. Clinicopathological data were collected to evaluate the histopathological characteristics and anatomical site distribution of the tumors. The association between age and the distribution of benign and malignant eyelid tumors was analyzed. Results: Among the 1,056 patients with eyelid tumors, 754 (71.40%) cases were benign, whereas 302 (28.60%) cases were malignant. The upper eyelid was the most affected site (44.03%), followed by lower eyelid (41.95%). In patients aged 0-19 years, all tumors were benign. The proportion of malignant tumors increased with age and reached 45.21% in those aged ≥80 years (χ^2=149.333, P<0.001). Significant differences in tumor types were observed among different age groups (χ^2=59.431, P<0.001). Male sex was predominant (64.90%) among patients with malignant tumors. Most malignant tumors were moderately differentiated (45.70%), and dermal infiltration was the most common pattern (51.66%). The proportion of deep infiltration was significantly higher in patients aged ≥60 years (44.88%) than in those <60 years (17.53%) (χ^2=21.357, *P*<0.001). Moreover, the proportion of tumors invading the meibomian glands or orbital tissues was higher in the lower eyelid (28.06%) compared with other sites (χ^2=14.092, *P*=0.003). Conclusion: The type and malignancy of eyelid tumors are closely related to age, gender, and tumor location, while the depth of malignant tumor infiltration is associated with age and anatomical site.

Keywords: Eyelid tumors, pathological analysis, benign tumors, malignant tumors, age, correlation

Introduction

Eyelid tumors are a common group of ocular disorders. Epidemiological studies have shown a gradual upward trend in the incidence of eyelid tumors over the past few decades, which may be attributed to multiple factors such as environmental factors, population aging, and advancements in diagnostic techniques [1]. Eyelid tumors not only affect the ocular appearance but, more importantly, malignant lesions may invade adjacent tissues and structures, causing complications such as visual disturbances and ocular motility disorders. In extreme instances, distant metastasis may pose a serious threat to the patient's life [2]. Thus, accurate differentiation between benign and malignant eyelid tumors is essential for adequate treatment selection and prognosis assessment.

Clinically, common benign eyelid tumors include nevi, papillomas, chalazia, and hemangiomas, while malignant tumors are mainly basal cell carcinoma (BCC), meibomian gland carcinoma, and squamous cell carcinoma. However, distinguishing benign from malignant eyelid lesions based on clinical appearance is challenging due to atypical or overlapping presentations. For example, early symptoms of meibomian gland carcinoma often resemble chalazion, which may result in misdiagnosis and delayed treatment [3]. Consequently, systematic investigation of the distribution patterns of benign and malignant eyelid tumors and their association with age may improve diagnostic accuracy and provide a solid basis for early intervention.

Although previous studies have focused on eyelid tumors, their relatively small sample size lim-

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ited comprehensive assessment of tumor distribution and age-related patterns [4]. In this context, we conducted a large-sample retrospective study on 1,056 patients with pathologically confirmed eyelid tumors to evaluate the distribution characteristics of benign and malignant eyelid tumors and their relationship with age. With an expanded sample size, this study may accurately reflect age-specific trends in benign and malignant eyelid tumors and provide more clinically relevant data.

Materials and methods

Research subjects

Medical records of 1,056 patients with eyelid tumors, confirmed by pathological examination after surgical resection from January 2021 to December 2024 at the West China Hospital of Sichuan University, were retrospectively reviewed. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of West China Hospital, Sichuan University. Given the retrospective nature of this analysis, individual informed consent was waived.

Inclusion criteria: Patients with histopathologically confirmed eyelid tumors and complete clinical data, including age, sex, tumor location, and pathological diagnosis. Exclusion criteria: incomplete clinical data; presence of other malignant tumors or systemic malignancies; and a history of eyelid surgery or radiotherapy which might interfere with diagnosis or analysis of the current lesion.

Pathological specimen processing

All eyelid tumor specimens were fixed immediately after excision in 4% neutral formaldehyde solution for 12-24 hours to preserve tissue morphology and structure. The fixed specimens were then dehydrated through graded ethanol solutions (70%, 80%, 95%, and 100%), cleared in xylene, and embedded in paraffin. Paraffin-embedded blocks were cut at a thickness of 4-5 μm using a microtome, mounted on glass slides, and stained with hematoxylin-eosin (HE). Hematoxylin stained cell nuclei blue, while Eosin stained the cytoplasm red, allowing clear visualization of the histological structures for accurate pathological diagnosis.

Data collection

Clinical and pathological data of patients were collected, including demographic information (age and sex), tumor locations (upper eyelid, lower eyelid, inner canthus, and outer canthus), and pathological diagnosis (specific benign and malignant tumor subtypes).

Preoperative clinical features were also collected, including tumor color (black, brown, skin-colored, red, etc.), shape (regular/irregular), surface condition (smooth, rough, or ulcerated), presence of pain, rapid rumor enlargement (an increase in diameter ≥3 mm within 6 months), and presence of hemorrhage or discharge. Differences in clinical manifestations between benign and malignant tumors were analyzed.

For malignant tumors, additional pathological assessments were performed, including pathological differentiation grading (well-differentiated, moderately differentiated, and poorly differentiated) and infiltration depth. Infiltration depth was classified according to the extent of tumor invasion into the dermal layer, subcutaneous tissue, meibomian glands, and periorbital soft tissues. Furthermore, differences in pathological grade and infiltration depth were further analyzed among malignant tumors stratified by pathological type, age group, and anatomical location.

Statistical analysis methods

SPSS 25.0 statistical software was used for data analyses. Categorical data were presented as case numbers and percentages (%) and compared between groups using the chi-square (χ^2) test. A *P*-value of <0.05 was considered statistically significant.

Results

Histopathological distribution of benign and malignant eyelid tumors

Among the 1,056 patients with eyelid tumors, 754 cases (71.40%) were benign, and 302 cases (28.60%) were malignant. Among benign tumors, nevus was the most common histological type, accounting for 38.33% (289/754), followed by seborrheic keratosis (89 cases, 11.80%), squamous papilloma (86 cases, 11.41%), epidermoid cyst (72 cases, 9.55%), calcifying epithelioma (pilomatricoma) (57 cas-

Table 1. Histopathological distribution of benign and malignant eyelid tumors

Number	Eyelid Tumor	Count	Proportion	Number	Eyelid Tumor	Count	Proportion
	Benign (754 cases)						
1	Nevus	289	38.33%	13	Cyst	6	0.80%
2	Seborrheic Keratosis	89	11.80%	14	Epithelial Cyst	5	0.66%
3	Squamous Papilloma	86	11.41%	15	Papilloma	4	0.53%
4	Epidermoid Cyst	72	9.55%	16	Schwannoma	4	0.53%
5	Calcifying Epithelioma (Pilomatricoma)	57	7.56%	17	Keratoacanthoma	3	0.40%
6	Dermoid Cyst	43	5.70%	18	Lobular Capillary Hemangioma	2	0.27%
7	Hemangioma	30	3.98%	19	Trichoepithelioma	2	0.27%
8	Squamous Epithelial Papillomatous Hyperplasia	13	1.72%	20	Inverted Follicular Keratosis	2	0.27%
9	Benign Cyst	12	1.59%	21	Neurofibromatosis	2	0.27%
10	Cavernous Hemangioma	11	1.46%	22	Fibrolipoma	2	0.27%
11	Capillary Hemangioma	10	1.33%	23	Seborrheic Keratosis	2	0.27%
12	Sebaceous Cyst	8	1.06%	24	-	-	-
	Malignant (302 cases)						
1	BCC	156	51.66%	7	NHL	5	1.66%
2	Meibomian Gland Carcinoma (Sebaceous Gland Carcinoma)	44	14.57%	8	Recurrent Sebaceous Gland Carcinoma	5	1.66%
3	Sebaceous Gland Carcinoma	37	12.25%	9	Recurrent BCC	2	0.66%
4	Malignant Melanoma (MM)	26	8.61%	10	Squamous Cell-BCC	2	0.66%
5	Squamous Cell Carcinoma (SCC)	13	4.30%	11	Cutaneous BCC	2	0.66%
6	Recurrent Meibomian Gland Carcinoma	10	3.31%		-	-	-

BCC: Basal Cell Carcinoma; MM: Malignant Melanoma; SCC: Squamous Cell Carcinoma; NHL: Non-Hodgkin Lymphoma.

es, 7.56%), dermoid cyst (43 cases, 5.70%), and hemangioma (30 cases, 3.98%), among others.

Among malignant tumors, BCC was the most prevalent type, representing 51.66% (156/302). Other malignant tumor types included sebaceous gland carcinoma (37 cases, 12.25%), malignant melanoma (MM) (26 cases, 8.61%), meibomian gland carcinoma (24 cases, 7.95%), meibomian gland carcinoma (sebaceous gland carcinoma) (20 cases, 6.62%), squamous cell carcinoma (SCC) (13 cases, 4.30%), and recurrent meibomian gland carcinoma (10 cases, 3.31%) (**Table 1**). Representative H&E stained images of benign and malignant eyelid tumors are shown in **Figure 1**.

Anatomical site distribution of benign and malignant eyelid tumors

A total of 465 tumors (44.03%) were located in the upper eyelid, including 327 benign cases (70.32%) and 138 malignant cases (29.68%). There were 443 tumors (41.95%) located in the lower eyelid, including 304 benign cases (68.62%) and 139 malignant cases (31.38%). At the medial canthus, 95 tumors (9.00%) were identified, including 76 benign (80.00%) and 19 malignant (20.00%) cases. At the lateral canthus, 53 tumors (5.02%) were observed, consisting 47 benign cases (88.68%) and 6 malignant cases (11.32%). Significant differences were observed in the distribution of benign and malignant tumors across different anatomical sites (χ^2=13.128; P=0.004), with relatively higher proportions of malignant tumors located in the lower eyelid and medial canthus (**Figure 2**).

Age-specific distribution of benign and malignant eyelid tumors

Patients were divided into five age groups: 0-19, 20-39, 40-59, 60-79, and ≥80 years of age. In the 0-19 age group (132 patients), all tumors were benign. In the 20-39 age old group (149 patients), 142 cases (95.30%) were benign and 7 cases (4.70%) were malignant. In the 40-59 age group (310 patients), 220 cases (70.97%) were benign and 90 cases (29.03%) were malignant. In the 60-79 age group (319 patients),

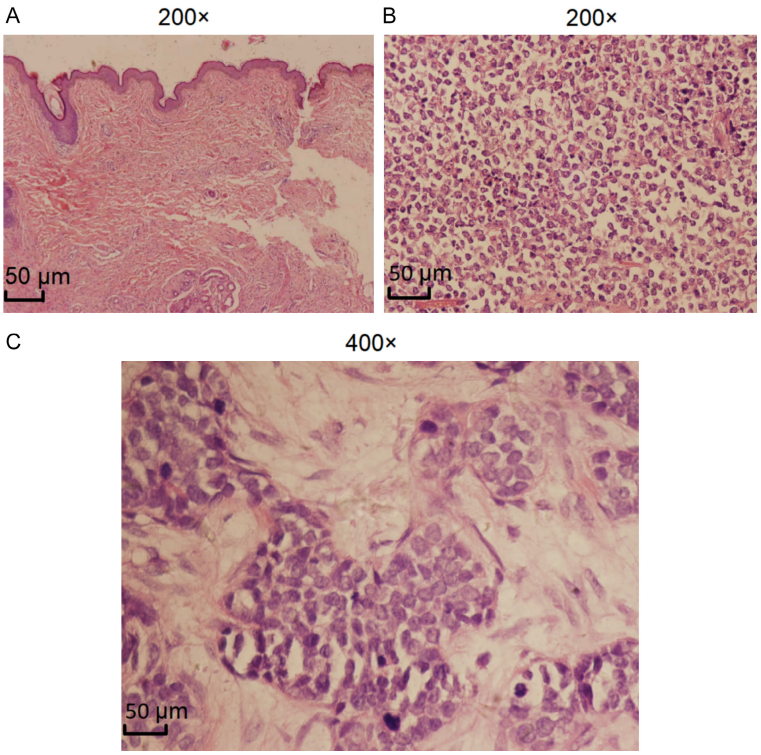

Figure 1. Representative hematoxylin-eosin (HE)-stained images of benign and malignant eyelid tumors. A. Neurofibroma (magnification: ×200); B. Diffuse large B-cell lymphoma (a subtype of non-Hodgkin lymphoma) (magnification: ×200); C. Meibomian gland carcinoma (Sebaceous gland carcinoma) (magnification: ×400).

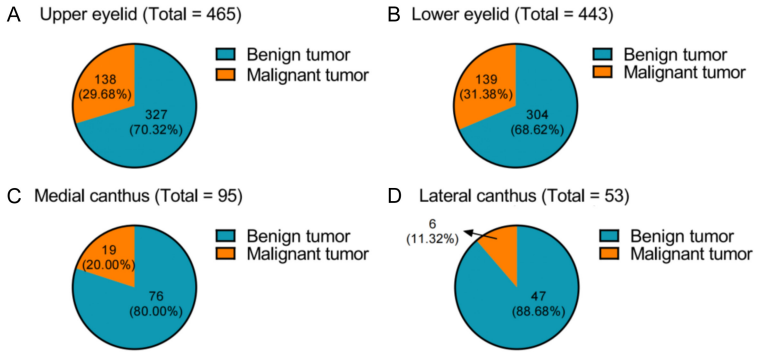

Figure 2. Distribution of benign and malignant tumors at different anatomical sites of the eyelid. A. Upper eyelid; B. Lower eyelid; C. Medial canthus; D. Lateral canthus.

180 cases (56.43%) were benign and 139 cases (43.57%) were malignant. In patients aged ≥80 years (146 patients), 80 cases (54.79%) were benign and 66 cases (45.21%) were malignant. Significant differences were observed in the proportion of malignant tumors across the five age groups (χ^2=149.333, P< 0.001), with the proportion of malignant tumors gradually increasing with age (**Figure 3**).

Distribution of benign and malignant tumor types across different age groups

In the 0-19-year-old group, the most common tumor types were calcifying epithelioma (pilomatricoma) and dermoid cyst, accounting for 43.18% and 31.06% of benign tumors, respectively. Among patients aged 20-39 years, the nevus and epidermoid cyst were the predominant benign tumor types, representing 61.27% and 23.24%, respectively. In the 40-59-year age group, BCC accounted for the highest proportion of malignant tumors (61.11%), followed by malignant melanoma (MM) (23.33%). In the 60-79-year-old age group, BCC and meibomian gland carcinoma (sebaceous gland carcinoma) were the main malignant tumor types, accounting for 64.75% and 15.83%, respectively. In the ≥80 years age group, meibomian gland carcinoma (sebaceous gland carcinoma) and BCC remained the primary malignant tumor types, representing 29.45% and 6.85%, respectively. Overall, the distribution of common tumor types differed across age groups (**Table 2**).

Gender distribution of benign and malignant eyelid tumors across age groups

Among benign tumors, 61.27% (462/754) occurred in females and 38.73% (292/754) in males. In contrast, malignant tumors were more prevalent in males 64.90% (196/302). A significant association was found between sex and the benign or malignant nature of eyelid tumors (χ^2=59.431, P<0.001). In the age groups of 40-59, 60-79, and ≥80 years, the proportion of malignant eyelid tumors was higher in males than in females (**Table 3**).

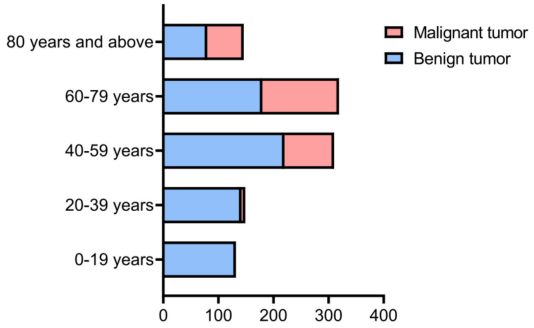

Figure 3. Distribution of benign and malignant tumors in different age groups.

Differences in clinical manifestations between benign and malignant eyelid tumors

Significant differences were observed in the distribution of clinical manifestations between benign and malignant eyelid tumors, with all evaluated clinical features significantly associated with tumor nature (all $P<0.05$) (**Table 4**). In terms of comprehensive appearance assessment (color, shape, and surface characteristics), 72.41% (546/754) of benign tumors presented with uniform color (predominantly brown and skin-colored), regular shape, and smooth surface. In contrast, 68.21% (206/302) of malignant tumors were characterized by uneven color (a mixture of black and dark red), irregular shape, and rough or ulcerated surface. Pain or hemorrhage was observed in only 3.32% (25/754) of benign tumors, while this proportion reached 28.48% (86/302) among malignant tumors. Rapid tumor enlargement was observed in 1.59% (12/754) of benign tumors, whereas 35.10% (106/302) of malignant tumors showed rapid enlargement within a short period.

Pathological grading and infiltration depth of malignant eyelid tumors

Regarding pathological grading, among the 302 malignant tumor cases, 112 cases (37.09%) were well-differentiated, 138 cases (45.70%) were moderately differentiated, and 52 cases (17.22%) were poorly differentiated. In terms of infiltration depth, 156 cases (51.66%) showed invasion of the dermal layer, 98 cases (32.45%) exhibited subcutaneous tissue invasion, 38 cases (12.58%) involved the meibomian glands, and 10 cases (3.31%) extended to the periorbital soft tissues.

Patients aged ≥60 years showed a significantly higher proportion of tumors invading the subcutaneous tissue or deeper layers compared to those younger than 60 years (44.88% [92/205] vs. 17.53% [17/97]; $\chi^2=21.357$, $P<0.001$). Concerning the correlation between tumor location and infiltration depth, the proportion of malignant tumors in the lower eyelid invading the meibomian glands or orbital tissues was 28.06% (39/139). The proportions in the upper eyelid (14.49%, 20/138), inner canthus (5.26%, 1/9), and outer canthus (0.00%, 0/6) were lower than this proportion, which were significantly different ($\chi^2=14.092$, P=0.003) (**Table 5**).

Discussion

In this retrospective analysis of 1,056 histopathologically confirmed eyelid tumor specimens, benign eyelid tumors accounted for 71.40% of all cases, with nevus being the most common subtype, whereas malignant eyelid tumors constituted 28.60%, among which BCC was the predominant histological type. Both the upper and lower eyelids were identified as high-incidence sites for malignant tumors. The proportion of malignant eyelid tumors increased progressively with age, and malignant lesions were more frequently observed in males over 40 years. In addition, the distribution of tumor subtypes varied significantly across different age groups. These findings may contribute to improved clinical diagnosis and treatment of eyelid tumors.

The proportion of malignant eyelid tumors in this study was 28.60%, which is higher than 12.9% reported in a Turkish study involving 251 patients [5]. This difference may be attributable to differences in sample size, UV exposure, and genetic background among populations. Consistent with previous reports by Levinkron et al. [6] (9.2%) and Ulas et al. [7] (23%), BCC was the most common malignant eyelid tumor in this study. In terms of anatomical site distribution, malignant tumors were more frequently located in the lower eyelid than in the upper eyelid, a conclusion consistent with the study by Oliveira et al. [8], which reported that BCC - accounting for 90.9% of all malignant eyelid tumors - predominantly involved the lower eyelid. With respect to age-related patterns, the proportion of malignant tumors increased gradually with increasing ages and

Table 2. Distribution of benign and malignant tumor types in different age groups

Age group	Eyelid tumor type	Count	Proportion	Age group	Eyelid tumor type	Count	Proportion
0-19-year group (n=132)	Benign tumor (n=132)			60-79 years (n=319)	Benign tumor (n=180)		
	Calcifying Epithelioma (Pilomatricoma)	57	43.18%		Nevus	92	51.11%
	Dermoid Cyst	41	31.06%		Seborrheic Keratosis	83	46.11%
	Epidermoid Cyst	26	19.70%		Keratoacanthoma	3	1.67%
	Hemangioma	6	4.55%		Inverted Follicular Keratosis	2	1.11%
	Nevus	2	1.52%		Malignant tumor (n=139)		
20-39-year group (n=149)	Benign tumor (n=142)				BCC	90	64.75%
	Nevus	87	61.27%		Meibomian Gland Carcinoma (Sebaceous Gland Carcinoma)	22	15.83%
	Epidermoid Cyst	33	23.24%		Recurrent Meibomian Gland Carcinoma (Sebaceous Gland Carcinoma)	9	6.47%
	Sebaceous Cyst	8	5.63%		SCC	7	5.04%
	Squamous Papilloma	5	3.52%		MM	5	3.60%
	Hemangioma	4	2.82%		Recurrent BCC	2	1.44%
	Dermoid Cyst	2	1.41%		Squamous Cell-BCC	2	1.44%
	Fibrolipoma	2	1.41%		Cutaneous BCC	2	1.44%
	Trichoepithelioma	1	0.70%	80 years and above (n=146)	Benign tumor (n=80)		
	Malignant tumor (n=7)				Nevus	15	18.75%
	SCC	3	42.86%		Cavernous Hemangioma	11	13.75%
	Meibomian Gland Carcinoma (Sebaceous Gland Carcinoma)	3	42.86%		Hemangioma	11	13.75%
	BCC	1	14.29%		Capillary Hemangioma	10	12.50%
40-59-year group (n=310)	Benign tumor (n=220)				Epidermoid Cyst	8	10.00%
	Nevus	93	42.27%		Cyst	6	7.50%
	Squamous Papilloma	79	35.91%		Benign Cyst	4	5.00%
	Squamous Epithelial Papillomatous Hyperplasia	10	4.55%		Schwannoma	4	5.00%
	Hemangioma	9	4.09%		Squamous Epithelial Papillomatous Hyperplasia	3	3.75%
	Benign Cyst	8	3.64%		Lobular Capillary Hemangioma	2	2.50%
	Seborrheic Keratosis	6	2.73%		Neurofibromatosis	2	2.50%
	Epidermoid Cyst	5	2.27%		Squamous Papilloma	2	2.50%
	Epithelial Cyst	4	1.82%		Papilloma	1	1.25%
	Papilloma	3	1.36%		Epithelial Cyst	1	1.25%
	Seborrheic Keratosis	2	0.91%		Malignant tumor (n=66)		
	Trichoepithelioma	1	0.45%		Meibomian Gland Carcinoma (Sebaceous Gland Carcinoma)	43	29.45%

Malignant tumor (n=90)			BCC	10	6.85%
BCC	55	61.11%	NHL	5	3.42%
MM	21	23.33%	Recurrent Meibomian Gland Carcinoma (Sebaceous Gland Carcinoma)	6	9.09%
Meibomian Gland Carcinoma (Sebaceous Gland Carcinoma)	13	14.44%	SCC	2	1.37%
SCC	1	1.11%	-	-	-

SCC: Squamous Cell Carcinoma; BCC: Basal Cell Carcinoma; MM: Malignant Melanoma; NHL: Non-Hodgkin Lymphoma.

Table 3. Gender distribution of benign and malignant tumors in different age groups

Age	Total (n=1056)	Female (n=568)			Male (n=488)			χ^2	*P*
		n	Benign tumor (n=462)	Malignant tumor (n=106)	n	Benign tumor (n=292)	Malignant tumor (n=196)		
0-19-year group	132	82	82 (100.00%)	0 (0%)	50	50 (100.00%)	0 (0%)	-	-
20-39-year group	149	87	84 (96.55%)	3 (3.45%)	62	58 (93.55%)	4 (6.45%)	0.213	0.645
40-59-year group	310	171	143 (83.63%)	28 (16.37%)	139	77 (55.40%)	62 (44.60%)	29.657	<0.001
60-79-year group	319	160	105 (65.63%)	55 (34.38%)	159	75 (47.17%)	84 (52.83%)	11.047	0.001
≥80 years	146	68	48 (70.59%)	20 (29.41%)	78	32 (41.03%)	46 (58.97%)	12.818	<0.001

Table 4. Differences in the distribution of clinical manifestations between benign and malignant eyelid tumors

Dimension of tumor symptoms	Symptom presentation	Total cases with this symptom presentation	Benign tumors (n=754)	Malignant tumors (n=302)	χ^2	*P*
Comprehensive appearance (Color+Morphology+Surface)	Uniform/Regular/Smooth	642	546 (72.41%)	96 (31.79%)	149.317	<0.001
	Heterogeneous/Irregular/Rough or Ulcerated	414	208 (27.59%)	206 (68.21%)		
Pain or bleeding	Present	111	25 (3.32%)	86 (28.48%)	145.127	<0.001
	Absent	945	729 (96.68%)	216 (71.52%)		
Rapid growth in a short period	Present	118	12 (1.59%)	106 (35.1%)	243.921	<0.001
	Absent	938	742 (98.41%)	196 (64.9%)		

Table 5. Distribution of pathological grading and infiltration depth in malignant eyelid tumors

Analytical dimension	Classification	Number of cases (n)	Constituent ratio (%)	χ^2	*P*
Pathological grading distribution	Well-differentiated	112	37.09%	-	-
	Moderately-differentiated	138	45.70%	-	-
	Poorly-differentiated	52	17.22%	-	-
Invasion depth distribution	Dermal invasion	156	51.66%	-	-
	Subcutaneous tissue invasion	98	32.45%	-	-
	Tarsal gland invasion	38	12.58%	-	-
	Periorbital soft tissue invasion	10	3.31%	-	-
Association between age and invasion depth	≥60 years old (Subcutaneous or deeper invasion)	92/205	44.88%	21.357	<0.001
	<60 years old (Subcutaneous or deeper invasion)	17/97	17.53%		
Association between location and invasion depth	Lower eyelid (Tarsal gland/Orbital tissue invasion)	39/139	28.06%	14.092	0.003
	Upper eyelid (Tarsal gland/Orbital tissue invasion)	20/138	14.49%		
	Medial canthus (Tarsal gland/Orbital tissue invasion)	1/19	5.26%		
	Lateral canthus (Tarsal gland/Orbital tissue invasion)	0/6	0.00%		

reached its peak in patients aged ≥80 years, corroborating the association between aging and increased risk of cancer. Regarding sex distribution, malignant eyelid tumors were more common in males than in females among patients over 40 years, suggesting that older males are at a higher risk of malignant eyelid tumors. Collectively, these finding indicate that both sex and age play important roles in the development of malignant eyelid tumors.

Notably, this study systematically analyzed differences in clinical manifestations between benign and malignant eyelid tumors. A comprehensive assessment of the appearance, pain or bleeding, and rapid tumor enlargement over a short period showed potential in distinguishing benign from malignant lesions. Most benign tumors had a uniform color, regular outline, and smooth surface. In contrast, malignancies typically exhibited heterogeneous pigmentation, irregular outline, and rough or ulcerated surfaces. These differences may reflect underlying tissue architectural disruption caused by uncontrolled proliferation of malignant cells [9]. Early identification of these symptoms may facilitate preliminary differentiation at primary medical institutions. Histopathological analysis further revealed that well-differentiated and moderately differentiated malignant tumors accounted for 37.09% of all malignant eyelid tumors, indicating that the majority of malignant eyelid tumors exhibited a high degree of differentiation and less aggressive biological behaviors, an important aspect of good prognosis. Over half the malignant tumors were confined to the dermal layer, while 32.45% invaded the subcutaneous or deeper tissues. According to the report by Gąsiorowski et al. [4], this pattern is associated with a relatively low risk of orbital invasion. However, deeper infiltration was more frequently observed in patients aged over 60 years and in tumors located on the lower eyelid. Therefore, extended surgical resection is recommended for elderly patients with malignant tumors of the lower eyelid to minimize local recurrence [10].

The age-related distribution and anatomical predilection of eyelid tumors are likely attributable to multifactorial pathophysiological mechanisms, including cumulative UV exposure, cellular senescence, and repair anomalies, hormonal alterations, and site-specific anatomical traits. As an exposed facial region, the eyelid is chronically irradiated by ultraviolet B (UVB), which induces DNA damage in epidermal cells through the formation of cyclobutane pyrimidine dimers (CPDs) and 6-4 photoproducts (6-4PPs) [11]. With advancing age, nucleotide excision repair (NER) capacity in skin keratinocytes declines, eventually leading to the accumulation of unrepaired DNA damage and subsequent gene mutations [12]. The Patched 1 (PTCH1) gene inactivation has been strongly implicated in the pathogenesis of BCC. UVB-

induced mutations within the exons of PTCH1 alleviate the suppression of Hedgehog signaling pathway and promote aberrant cell proliferation. Moreover, lower eyelid and medial canthus receive higher UVB exposure due to irradiation angles. The thinner skin and high density of sebaceous glands in these regions may further increase susceptibility to malignant transformation [13, 14].

Age-related mechanisms underlying cellular senescence and tumor development appear to be stage specific. The high incidence of calcifying epithelioma (pilomatricoma) and dermoid cyst in infants and young children is mainly attributable to abnormal differentiation of hair matrix cells and ectopic epithelial tissue during embryonic development [15]. These tumors are mostly congenital lesions and tend to stabilize gradually with age. The predominance of nevus in young adults is associated with increased proliferative activity of melanocytes [16]. During this life stage, melanocytes are sensitive to hormonal regulation, and although UV exposure begins to accumulate, it has generally not reached the threshold necessary for malignant transformation. The high prevalence of BCC and meibomian gland carcinoma in middle-aged and elderly individuals is closely associated with cellular senescence-related mechanisms, including telomere shortening and p53 gene mutations. Studies have demonstrated that telomere length in skin cells is significantly reduced in individuals over 60 years, accompanied by an increased mutation rate of p53, markedly elevating the risk of malignant tumor development [17, 18]. The increased proportion of meibomian gland carcinoma observed in the population aged ≥80 years may further be related to cellular metabolic disorders caused by the age-related decline in meibomian gland function. Abnormal lipid synthesis in sebaceous gland cells can activate the PI3K/Akt/mTOR signaling pathway, thereby promoting tumor progression [19, 20].

The molecular mechanism underlying sex-related differences in malignant eyelid tumor incidence are likely multifactorial and primarily involves hormonal regulation and sex-specific differences in DNA repair capacity. The higher incidence of malignant tumors in males may be associated with the expression of androgen receptor (AR). AR expression has been detected in meibomian gland carcinoma tissues [21], and androgen-AR binding can activate downstream target genes, thereby promoting cell proliferation [22]. In contrast, the cancer-protective effect of the estrogen receptor β (ERβ) in female skin could minimize the risk [23]. ERβ expression has been reported to be higher in female patients with benign tumors than in male patients; ERβ upregulates BRCA1 expression, thereby enhancing DNA repair capacity [24].

Several limitations should be acknowledged in this study. First, as a single-center retrospective study, selection bias cannot be excluded. Second, crucial clinical data, including cumulative UV exposure and family tumor history, were unavailable, preventing further exploration of the interplay among risk factors. Third, pathological diagnosis was based solely on H&E staining, without immunohistochemical markers (e.g., CK5/6, p63) for carcinoma subtyping, which may have affected diagnostic accuracy of some tumor types. The absence of long-term follow-up data precluded analysis of prognostic outcomes and recurrence-related risk factors. Finally, no molecular analyses were performed, which restricted evaluation of mutation profile-clinical characteristic associations, limiting the depth of mechanistic insight.

Conclusions

Eyelid tumors are predominantly benign, with malignancy increasing with age. Basal Cell Carcinoma and meibomian gland carcinoma are the most common malignancies in elderly patients. The clinical features such as uneven color, irregular shape, rough and ulcerated surface, pain and hemorrhage, rapid tumor enlargement in a short period may assist in differentiating benign from malignant tumors. Malignant tumors are more aggressive in patients above 60 years and in the lower eyelid. The results are clinically relevant. Differential screening and surveillance strategies should be tailored to high-risk groups and anatomical sites. In males over 40 years of age with new lesions on the lower eyelid or medial canthus, malignancy is highly suspected, and timely biopsy is strongly recommended.

Disclosure of conflict of interest

None.

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References

[1] Haseli-Mofrad A, Rajavi Z, Ashtar-Nakhaei P and Mofrad NH. A comprehensive scientometric analysis of eyelid tumor research: co-word mapping and thematic clustering based on scopus data. Int Ophthalmol 2025; 45: 426.

[2] Gniesmer S, Sonntag SR, Schiemenz C, Ranjbar M, Heindl LM, Varde MA, Emmert S, Grisanti S and Kakkassery V. Diagnosis and treatment of malignant eyelid tumors. Ophthalmologie 2024; 121 Suppl 1: 33-39.

[3] Wang W, Wang H, Wu G, Liu X, Zhu L, Tian F and Lin T. Proteomics reveals the regulation of ALG1 expression by lentivirus-mediated THBS1 overexpression and its mechanism in meibomian gland carcinoma. Oncol Lett 2025; 30: 517.

[4] Gąsiorowski K, Gontarz M, Marecik T, Szczurowski P, Bargiel J, Zapała J and Wyszyńska-Pawelec G. Risk factors for orbital invasion in malignant eyelid tumors, is orbital exenteration still necessary? J Clin Med 2024; 13: 726.

[5] Sendul SY, Akpolat C, Yilmaz Z, Eryilmaz OT, Guven D and Kabukcuoglu F. Clinical and pathological diagnosis and comparison of benign and malignant eyelid tumors. J Fr Ophtalmol 2021; 44: 537-543.

[6] Levinkron O, Schwalb L, Shoufani A, Gutovitz J, Krausz J and Briscoe D. Comparison of the clinical characteristics of benign and malignant eyelid lesions: an analysis of 1423 eyelid lesions, compared between ophthalmology department and plastics department. Graefes Arch Clin Exp Ophthalmol 2024; 262: 615-621.

[7] Ulas B, Ozcan A, Sulanc B and Acıkalın A. Evaluation of histopathology results in eyelid tumors: 20-year experience at a Turkish tertiary referral center. J Fr Ophtalmol 2025; 48: 104543.

[8] Oliveira D, Ribeiro A, Diniz S, Cabral-Marques H and Sousa-Martins D. Incidence of malignant eyelid tumors: a 6-year period review (2015-2021). The Pan-American Journal of Ophthalmology 2024; 6: 62.

[9] Ranjbar R, Behjatfar M, Teimouri A, Aghaie Fard A, Maniati M and Taheri-Anganeh M. Long non-coding RNAs and microorganism-associated cancers. Cell Biochem Funct 2021; 39: 844-853.

[10] Gigov K, Ginev I and Kavradzhieva P. Mustardé Cheek Rotation-advancement flap: a case-based experience in reconstruction of a large defect of the lower eyelid due to squamous cell carcinoma. Clin Pract 2025; 15: 165.

[11] El Mir J, Fedou S, Thézé N, Morice-Picard F, Cario M, Fayyad-Kazan H, Thiébaud P and Rezvani HR. Xenopus: an in vivo model for studying skin response to ultraviolet B irradiation. Dev Growth Differ 2023; 65: 194-202.

[12] Meyer CA, Nelms B and Schmitz RJ. Nanorate sequencing reveals the Arabidopsis somatic mutation landscape. bioRxiv [Preprint] 2025; 15: 659769.

[13] Ju S, Rokohl AC, Guo Y, Yao K, Fan W and Heindl LM. Personalized treatment concepts in extraocular cancer. Adv Ophthalmol Pract Res 2024; 4: 69-77.

[14] Maturo MG, Rachakonda S, Heidenreich B, Pellegrini C, Srinivas N, Requena C, Serra-Guillen C, Llombart B, Sanmartin O, Guillen C, Di Nardo L, Peris K, Fargnoli MC, Nagore E and Kumar R. Coding and noncoding somatic mutations in candidate genes in basal cell carcinoma. Sci Rep 2020; 10: 8005.

[15] Tauziède-Espariat A, Beccaria K, Dangouloff-Ros V, Sievers P, Meurgey A, Pissaloux D, Appay R, Saffroy R, Grill J, Mariet C, Bourdeaut F, Hasty L, Métais A, Chrétien F, Blauwblomme T, Puget S, Boddaert N and Varlet P; RENOCLIP-LOC. A comprehensive analysis of infantile central nervous system tumors to improve distinctive criteria for infant-type hemispheric glioma versus desmoplastic infantile ganglioglioma/astrocytoma. Brain Pathol 2023; 33: e13182.

[16] Ruiz-Vega R, Chen CF, Razzak E, Vasudeva P, Krasieva TB, Shiu J, Caldwell MG, Yan H, Lowengrub J, Ganesan AK and Lander AD. Dynamics of nevus development implicate cell cooperation in the growth arrest of transformed melanocytes. Elife 2020; 9: e61026.

[17] Zhang L, Huang X, Zhu X, Ge S, Gilson E, Jia R, Ye J and Fan X. Differential senescence capacities in meibomian gland carcinoma and basal cell carcinoma. Int J Cancer 2016; 138: 1442-52.

[18] Richardson RB. p53 mutations associated with aging-related rise in cancer incidence rates. Cell Cycle 2013; 12: 2468-78.

[19] Zhu X, Xu M, Portal C, Lin Y, Ferdinand A, Peng T, Morrisey EE, Dlugosz AA, Castellano JM, Lee V, Seykora JT, Wong SY, Iomini C and Millar SE. Identification of Meibomian gland stem cell populations and mechanisms of aging. Nat Commun 2025; 16: 1663.

[20] Wang C, Lin H, Zhao W, Liang Y, Chen Y and Wang C. MiR-26a-5p exerts its influence by targeting EP300, a molecule known for its role in activating the PI3K/AKT/mTOR signaling pathway in CD8+tumor-infiltrating lymphocytes of

colorectal cancer. Cell Mol Biol (Noisy-le-grand) 2023; 69: 232-241.
[21] Mulay K, Shah SJ, Aggarwal E, White VA and Honavar SG. Periocular sebaceous gland carcinoma: do androgen receptor (NR3C4) and nuclear survivin (BIRC5) have a prognostic significance? Acta Ophthalmol 2014; 92: e681-7.
[22] Wang X, Yan G, Li H, Wang C, Kang Y, Wang S, Liu W, Lin L, Zou R, Zeng K, Wang M, Luan R, Zhou B, Bai Y, Yang D, Ning B, Sun G and Zhao Y. RBAP48 facilitates the oral squamous cell carcinoma process in an androgen receptor-dependent and independent manners. Commun Biol 2025; 8: 829.
[23] Nagandla H and Thomas C. Estrogen signals through ERβ in breast cancer; what we have learned since the discovery of the receptor. Receptors (Basel) 2024; 3: 182-200.
[24] Suba Z. DNA stabilization by the upregulation of estrogen signaling in BRCA gene mutation carriers. Drug Des Devel Ther 2015; 9: 2663-75.