Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2022**; 27(4): 132
https://doi.org/10.31083/j.fbl2704132

Original Research

Age Distribution of 4526 Surgically Excised Specimens of Eye Tumors by Histopathological Examination in China

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Academic Editors: Shikun He and Graham Pawelec
Submitted: 3 January 2022 Revised: 18 February 2022 Accepted: 22 February 2022 Published: 20 April 2022

Abstract

Background: Cumulative evidence suggests that the risk of eye tumors varies among different age groups and populations. The purpose of the present study was to assess the age distribution of eye tumors in China. **Methods**: In this retrospective study, the age distribution of various types of eye tumors was analyzed on surgically excised and histologically confirmed specimens obtained from 4492 patients (4526 eyes), collected between 2001 and 2017. **Results**: Of the 4526 specimens, 3156 eyes (69.7%) had benign eye tumors, while 1370 eyes (30.3%) had malignant tumors. The age-specific incidence of eye tumors was characterized by a bimodal distribution, one peak occurred at age 0–9 years (19.7%) and the other at 50–59 years (14.7%) of age. Malignant eyelid tumors were very rare under the age of 20 years, but increased to 78% of all eyelid tumors by the age of 70 years. Children aged 0–9 years old were 6.5 times as likely to have a malignant eye tumor (95% CI, 4.1–10.4) as those aged 10–19 years. The age-related variation of eye tumors was also observed in the top ten categories of both benign ($p < 0.001$) and malignant types ($p = 0.001$). **Conclusions**: These results showed that age is a major factor determining the type of eye tumor, confirmed by histopathological analysis.

Keywords: age distribution; eye tumor; histopathological examination

1. Introduction

Eye tumors are common eye conditions that may not only affect people's visual acuity, but may also be life-threatening, especially in the case of malignant eye tumors. The prevalence of eye tumors, including benign and malignant types, varies substantially with age, ethnicity, and geographical areas [1–6]. For example, Hu *et al*. [1] reported that the incidence (per million population) of uveal melanoma was 0.3% in Asian, 1.67% in Hispanic, and 6.02% in non-Hispanic white populations. Similarly, a high prevalence of retinoblastoma (RB), but an extremely low prevalence of uveal melanoma, was reported in Africa [2]. In addition, a study in Hong Kong found that basal cell carcinoma was much more common than malignant melanoma [3]. Previous studies of the age distribution of eye tumors in Chinese and other populations based on histological analyses have only focused on specific eye tumors, and no study has evaluated the age distribution of various types of eye tumors confirmed by histologic analysis. For instance, Ohtsuka *et al*. [4] reported 244 orbital tumors and their age distribution, but did not report on any other eye tumors. Wu *et al*. [5] only presented the mean age of periocular basal cell carcinoma in Australia; a similar study on sebaceous cell carcinoma of the ocular adnexa was performed in 30 patients in the United States by Song *et al*. [6]. Age-specific epidemiological data for each type of eye tumor is imperative to guide eye tumor prevention strategies and appropriate interventions in the future. In this study, we analyzed the age-specific data of various eye tumors diagnosed by histopathological examination in the Henan Eye Institute from 2001–2017. To the best of our knowledge, this is the largest retrospective report examining the age distribution of a wide range of eye tumors.

2. Material and Methods

2.1 Patient Information

The Institutional Review Board of Henan Eye Hospital approved our use of human eye tumor specimens. All procedures conformed to the Declaration of Helsinki for research involving human subjects.

A total of 4526 eye tumor specimens from 4492 patients were collected for retrospective histological analysis after surgery, which included penetrating keratoplasty, anterior lamellar keratoplasty, lamellar resection, tumor resection, as well as evisceration, enucleation or orbital exenteration. All surgeries were performed by ocular specialists at the Henan Eye Institute between January 2001 and December 2017. If the tumor recurred, only the earliest

specimen was included. In addition, the following patient details were collected: age at surgery, sex, location of the tumor, medical history, clinical diagnosis, and histopathologic diagnosis. Only the histopathologically confirmed tumor cases were included in this study.

2.2 Tissue Sample Processing

Eye tumor specimens were fixed in 10% neutral buffered formaldehyde and embedded in paraffin. Paraffin sections of 3 μM thickness were stained with hematoxylin and eosin (H&E) for histological analysis. If necessary, immunohistochemical staining was performed to assist the diagnostic process.

2.3 Histopathological Examination

All stained tissue sections were reviewed by two ocular pathologists (ophthalmologists with a specialization in ocular pathology). The tumors were classified as either benign or malignant. The primary diagnosis of eye tumor was further categorized based on anatomic locations into: eyelid, keratoconjunctival, orbit, intraocular, and scleral tumors. To assess the age distribution of various eye tumors, age was grouped into 10-year intervals following our previous publication [7].

2.4 Statistical Analysis

We used descriptive statistics (frequency percentage, mean, standard deviation) to describe the distribution of eye tumors by type, location, and age. We performed the χ^2 test to compare the differences in the frequency distribution of various tumors across age groups, locations, and malignant potential. All the statistical analysis was performed using SPSS version 25 (IBM Corp., Armonk, NY, USA), A two-sided $p < 0.05$ was considered to be statistically significant.

3. Results

A total of 4526 eyes (4492 patients) were included in the analysis. An almost equal representation of right and left eyes (2266 and 2260 specimens, respectively) was observed. Patients were evenly distributed between men (2169, 48%) and women (2323, 52%). The age of patients with an eye tumor ranged from 1.5 to 90 years, with a mean age of 38.8 years.

Histopathological review showed that the most common eye tumor was eyelid tumor (1440 specimens, 31.8%), followed by orbit tumor (1423 specimens, 31.4%), keratoconjunctival tumor (1176 specimens, 26.0%), intraeye tumor (482 specimens, 10.7%), and scleral tumor (5 specimens, 0.1%) (Fig. 1, Table 1). Among all eye tumors, 3156 (69.7%) were benign and 1370 (30.3%) were malignant (Table 1).

In general, the percentage of eye tumors was the highest at age 0–9 years (19.7%), and decreased to 8.31% at age 10–19 years, 7.9% at age 20–29 years, increased to 10.3% at age 30–39 years, peaked at age 50–59 years (14.7%), remained high at age 60–69 years (14.3%), decreased at age 70–79 years (8.3%), and reached the lowest at age 80–90 years (2.1%) (**Supplementary Table 1**). There were two peaks for the incidence of malignant eye tumors, one occurring at age 0–9 and the other at 60–69 years, based on the number of patients with a tumor, and one occurring at age 0–9 years and the other at 80–90 years, based on the percentage of patients with a tumor (Fig. 2a and Fig. 2b). With the age group 10–19 years as the reference group, children 0–9 years of age were 6.5 times as likely to have a malignant eye tumor (95% confidence interval (CI) 4.1–10.4). After age of 10 years, the odds of having a malignant eye tumor increased with age (Fig. 3).

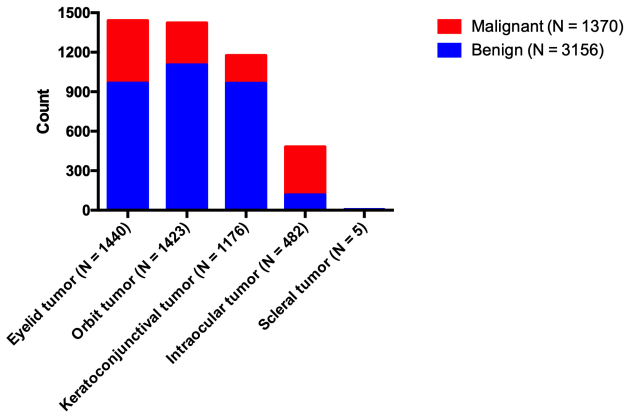

Fig. 1. The location of the distribution of the eye tumors. Red indicated the malignant eye tumors and blue represent benign eye tumors. Orbit, eyelid and keratoconjunctival tumor were the top tree benign eye tumors; while the malignant top 3 eye tumors were eyelid, intraocular and obit tumor. There was a significant difference in the location of tumors in both benign (Wald 28 = 80.7, $p < 0.0001$) and malignant tumors (Wald 28 = 209.2, $p < 0.0001$).

The distribution of location-specific eye tumors varied significantly across age groups in both benign eye tumors (Fig. 4a, $p < 0.001$) and malignant eye tumors (Fig. 4b, $p = 0.001$) (see **Supplementary Table 1**).

Among benign eye tumors, 66.7% (2104 eyes) were in the top ten (Fig. 5), while 34.1% (1537 eyes) were in the top five. For malignant tumors, 81.0% (1102 eyes) were in the top ten (Fig. 6), and 60.7% (832 eyes) were in the top five.

Among all benign eyelid tumors, there were significant differences in the distribution across age groups (see **Supplementary Table 2**). The malignant eyelid tumors peaked at age 60–69 years (30.0%) and remained high (25.5%) at age 70–79 years. There were significant differences in the percentage of malignant eyelid tumors across age groups (see **Supplementary Table 3**; $p < 0.01$).

Orbit tumors were the second most common eye tumors; 17.4% orbit tumors occurred at age 0–9 years and its incidence peaked at age 40–49 years (21.5%) (see **Supplementary Table 4**). There was a significant difference

Table 1. Distribution of ocular tumor by tumor location (n = 4526 eyes, 4492 patients).

Tumor group	Eyes (Column %)	Benign tumor (Column %)	Malignant tumor (Column %)
Eyelid tumor	1440 (31.8%)	966 (30.6%)	474 (34.6%)
Orbit tumor	1423 (31.4%)	1104 (35.0%)	319 (23.3%)
Keratoconjunctival tumor	1176 (26.0%)	964 (30.5%)	212 (15.5%)
Intraocular tumor	482 (10.7%)	117 (3.7%)	365 (26.6%)
Sclera tumor	5 (0.1%)	5 (0.2%)	0
Total (eyes)	4526 (100%)	3156 (69.7%)	1370 (30.3%)

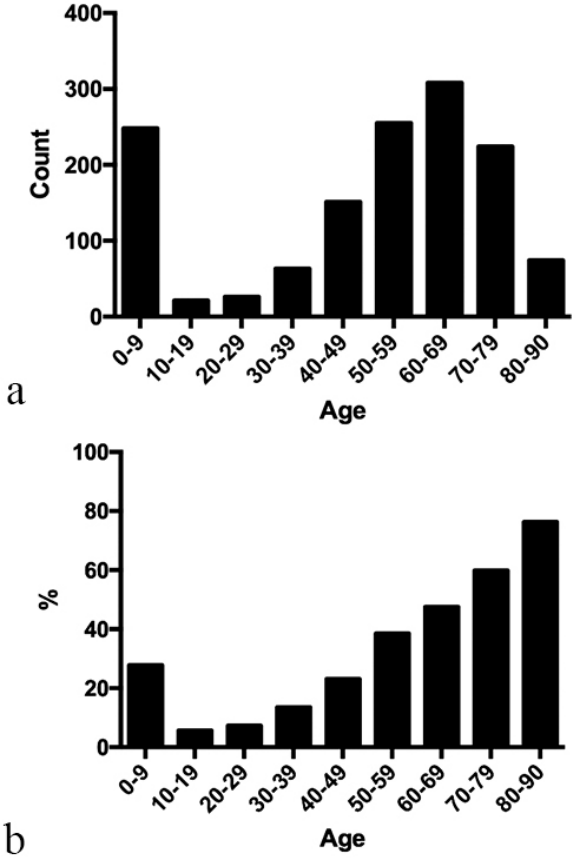

Fig. 2. The counting numbers and percentage of malignant eye tumors in different age groups. (a) Counting numbers of malignant eye tumors in different age groups. Age 0–9 years and 60–69 years were the two peaks of the incidence of malignant eye tumors. (b) The percentage of malignant eye tumors in different age groups. Age 0–9 years was the first peak of the incidence of malignant eye tumors, the lowest incidence was shown in age 10–19 years and then gradually increases and reaches its second peak by age 80–90 years.

in the distribution of benign orbit tumors across age groups ($p < 0.001$). In contrast to benign orbit tumors, the highest percentage of malignant orbit tumors was found at age 80–90 years (24.1%). There was a significant difference in the percentage of malignant orbit tumors across age groups (see **Supplementary Table 5**; $p = 0.005$).

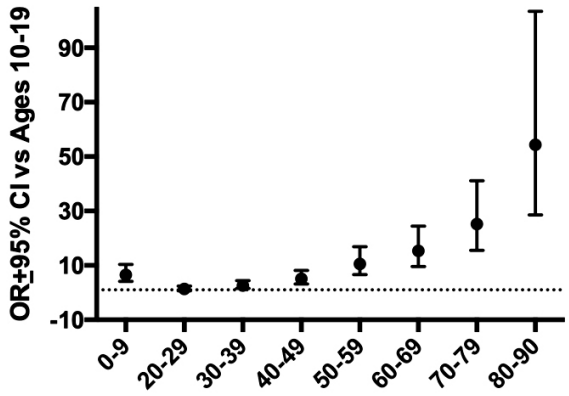

Fig. 3. The Odds Ratio (OR) and 95% confidence intervals of having a malignant eye tumor by age group. Reference group was ages 10–19 years because the incidence of tumors in young children (<age 10) breaks from monotonic pattern after age 10, as it was shown in Fig. 2b. All of the other age groups had significantly higher risk of malignancy than those aged 10–19 years.

The third most common eye tumor in our study was a keratoconjunctival tumor. The frequency distribution of benign keratoconjunctival tumors varied across age groups (see **Supplementary Table 6**, $p < 0.01$). The highest percentage of malignant keratoconjunctival tumors was seen at age 60–69 years (see **Supplementary Table 7**), The percentage of malignant keratoconjunctival tumors sharply reduced by the age 10–19 years, and was at the lowest at 80–90 years. There was a significant difference in the distribution of malignant keratoconjunctival tumors across age groups (see **Supplementary Table 7**).

Intraocular tumors were found to be the fourth most common eye tumor in this study. In general, the percentage of benign intraocular tumors was high for 0–9 years' (16.2%), 50–59 years' (17.1%), and 60–69 years' (15.4%) age groups, but its percentage was low among 70–79 years (4.3%), and ≥80 years (0.9%) groups. The difference in the distribution of benign intraocular tumor varied across age groups (see **Supplementary Table 8**; $p = 0.02$). The highest percentage of malignant intraocular tumors appeared in the age group of 0–9 years (60.3%) (Fig. 4). The distribution of malignant intraocular tumor significantly varied across age groups (see **Supplementary Table 9**; $p < 0.01$).

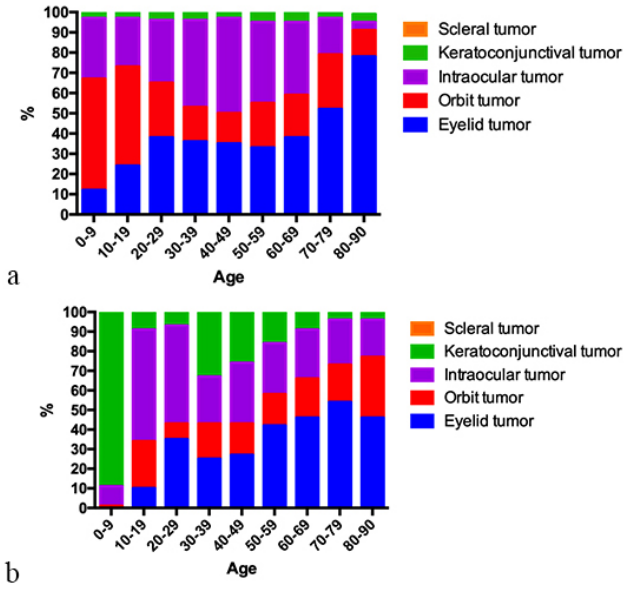

Fig. 4. The age distribution of eye tumors. (a) The age distribution of benign eye tumors. Orbit tumors have a much higher incidence in younger ages from 0–9 to 10–29 years, while eyelid tumors incidence increases with age and over age 80 year it accounts for 78%. Intraocular tumors are most common eye tumor between the ages of 30 and 70, representing an incidence between 40%–47% in those age groups. There is no much variability of the incidence of keratoconjunctival benign tumor cross age. (b) The age distribution of malignant eye tumors. In children less than 10 years of age, the most prevalent malignant tumor is keratoconjunctival tumor (89%). This type of tumor represents about one-third of the tumors in age 30–49 years. The incidence of malignant eyelid tumors, which were very rare under the age of 20 increases across adulthood. The prevalence of intraocular tumors is highest in teenagers and young adults (age 10–29 years). The peak incidence of orbit tumors is seen in age 80–90 years.

The least common eye tumor in our study was a sclera tumor (n = 5). Interestingly, all scleral tumors were benign and accounted for 0.1% of all eye tumors and 0.2% of all benign eye tumors. Scleral tumors included four cases of scleral cyst and one case of a scleral osseous choristoma. All scleral tumors occurred before the age of 30 years.

4. Discussion

Cumulative evidence suggests that the risk of eye tumors varies among different populations and age groups. Therefore, it is important to study the epidemiological characteristics of eye tumors, including their distribution across different populations, geographical regions, and age. This information is critical to devise a sound strategy for the medicare system, especially for the appropriate prevention, diagnosis, and treatment of eye tumors. Furthermore, epidemiological details of a large sample will be helpful in building a large glocal database and will enable precision medicine. In this study, we evaluated the details of eye tumors with respect to their location, malignant potential, and age distribution, using 4526 specimens collected at the Henan Eye Institute over 17 years (2001–2017). This study provides the largest sample of eye tumors for epidemiological studies in the Chinese population; particularly, the age distribution of various eye tumors by location and type of malignancy.

We found that the most common eye tumor was eyelid tumor (31.8%), followed by orbit tumor (31.4%), keratoconjunctival tumor (26.0%), intraocular tumor (10.7%) and scleral tumor (0.1%). This finding is similar to a report from Philippines [8] that showed that the highest percentage of eye tumors was seen in the eyelid (34%), followed, however, by intraocular tumors (25%), the incidence of which is much higher than that in our study (10.7%). In addition, eye surface tumors only accounted for 16% of eye tumors in Philippines, which is much lower than our result (26.0%). In the United Kingdom, intraocular tumor is the most commonly diagnosed primary ocular malignancy, as against eyelid tumor or orbit tumor [9]. A study in sub-Saharan Africa found intraocular tumors to be the leading eye tumor [10]. Interestingly, in southern India, the lacrimal sac tumor is the second most common eye tumor [11]. Taken together, our data and previously published data suggest a wide variation in the dominant location of eye tumors among different populations and areas.

Besides the variation in the location of eye tumors in our study, we also found that the occurrence of eye tumors varied from age 0 to 90 years. Eye tumors occurred at the age of 0–9 years (891 eyes, 19.7%), followed by 50–59 years (663 eyes, 14.6%), and 40–49 years (645, 14.5%), and with $\geq$80 years being the least common. Our finding was similar to a report from Nigeria that reported 21.6% of eye tumors at the age of 0–9 years [12]. However, our results are different from those of a study in the UK, in which 30% of eye tumors occurred at an age of 0–9 years [9]. The difference of the prevalence of eye tumors among age groups in different populations may reflect differences in the geography, population, and methods of diagnosis of eye tumors. In our study, the diagnosis of all cases was confirmed by ocular pathologists. Taken together, these results suggest that during the formulation of relevant eye- care policies, attention should be paid to age groups with a higher risk of specific eye tumors.

We found that malignant eye tumors were closely related to age; the occurrence of malignant tumors increased with age for almost all malignant eye tumors except retinoblastoma. The mechanism for the increasing risk of malignant eye tumor with age may be similar to that for other malignancies—likely due to accumulation of cellular DNA damage over time and abnormal epigenetic factors [13–15].

The eyelid tumor was the most common eye tumor in our study. The top three benign eyelid tumors (nevus,

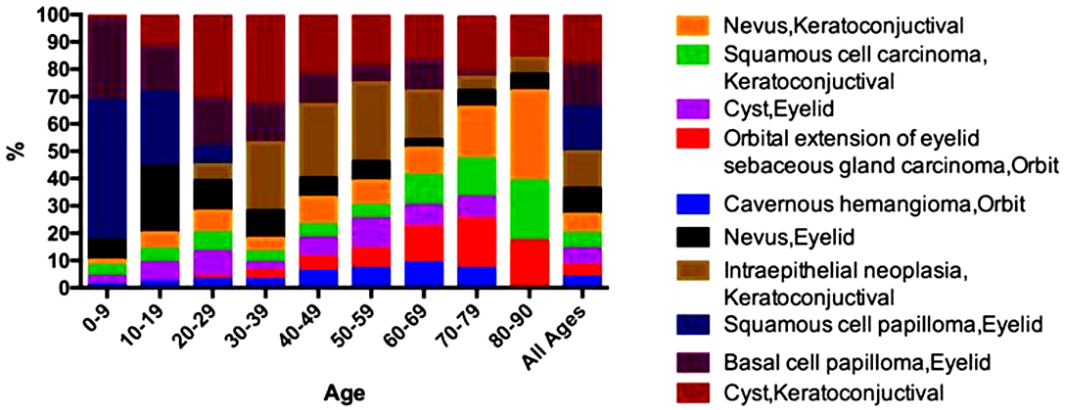

Fig. 5. The incidence of top 10 benign eye tumors in different age groups. Of benign tumors, 67% (N = 2104) were included in the top 10, while 48.7% (N = 1537) were included in the top 5. Squamous cell papilloma is the dominated benign tumor in early life from age 0–19; most of kertoconjuctival cyst is seen in young adult; the highest prevalence of kertoconjuctival nevus can be found in the age 80–90 years; over all the top 3 benign ocular are basal cell papilloma, kertoconjuctival cyst and squamous cell papilloma.

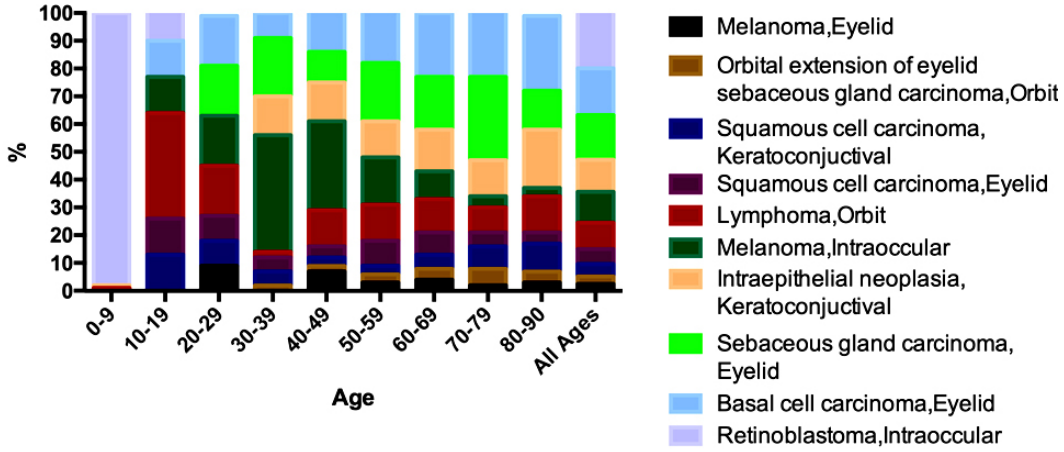

Fig. 6. The incidence of top 10 malignant eye tumors in different age groups. In the age 0–9 years, RB is the major malignant tumor; in teenage and yang adult the most prevalent malignance is orbit lymphoma; the peak age of intraocular melanoma appears in age 30–39 years; notably, the basal cell carcinoma increases with age and reached its peak by age 80–90 years.

squamous cell papilloma, and cyst) occurred in ages ranging from age 0–90 years, but the majority of them were diagnosed at the age of 30–69 years. The peak age for incidence of malignant eyelid tumor was 60–69 years in our study, consistent with a report from California (69 years) [6], Brazil (>60 years) [16], and Australia (68 years) [5]. We found that basal cell carcinoma, sebaceous gland carcinoma, and squamous cell carcinoma accounted for 89% of all malignant eyelid tumors. This finding is similar to a report from Philippines that the basal cell carcinoma (30.6%) was the most common malignant eyelid tumor [8]. The high occurrence of basal cell carcinoma could be attributed to high levels of ultraviolet light exposure [5]. In addition, mutation in the patched 1 gene (*PTCH1*) and overexpression of *EGFR* have been linked to basal cell carcinoma and sebaceous gland carcinoma, respectively [17], suggesting that the gene mutation screening and analysis of *EGFR* expression may be helpful for the diagnosis of these malignant eyelid tumors.

In our study, orbit tumor was the second most common eye tumor accounting for 31.4% of all eye tumors; the majority (89.3%) of benign orbit tumors occurred at the age of 0–39 years. The percentage of malignant orbit tumors increased with age, starting from 50–79 years and reaching its peak (93.3%) at age 80–90 years. We found that the most common benign orbit tumors in young patients were cyst and hemangioma, while the most common orbit tumors in older patients were lymphoma and melanoma, suggesting that benign orbit tumors were more common than malignant tumor in young patients, while malignant tumors were more predominant in older age groups [18].

Interestingly, a striking difference was found in the distribution of orbit tumors among different populations. In the current study, malignant lymphoma accounted for

32.9% of all orbit tumors. However, Bonavolontà *et al.* [19] found that malignant lymphomas only accounted for 12% of 2480 orbit tumors in Italy, and similar results were published in other reports [20–22]. Therefore, the novel finding of this study was that lymphomas were much more common in Chinese populations than in Caucasian. The mechanism of this difference is unknown, but analysis of single nucleotide polymorphisms in DNA and that of epigenetic factors using approaches such as epigenome-wide association studies may provide insights.

Keratoconjunctival tumors were the third most common eye tumor in our study, accounting for 26.0%; the majority were benign (82%) and typically occurred in the age range of 0–9 years (77.1%), These tumors were extremely uncommon after 30 years of age. The majority (26.0%) of cases of squamous cell papilloma occurred in the age range of 0–9 years. On the other hand, the majority of nevus (28.4%) occurred at age 10–19 years. We found that 79% of malignant keratoconjunctival tumors were diagnosed after the age of 50 years and peaked at age 60–69 years, suggesting that age is one of the major risk factors for the development of malignant keratoconjunctival tumors. The susceptibility to malignant keratoconjunctival tumor has been linked to the mutations of several genes, including *FGFR3*, *PIK3CA* and *HRAS* [23]. Therefore, screening for these genes may be useful for populations vulnerable to malignant keratoconjunctival tumors.

Intraocular tumors were the fourth most common tumor in the study. The majority (75.7%) of these tumors were malignant, and largely occurred at age 50–69 years. Because benign intraocular tumors may affect visual acuity and may become malignant, close monitoring of patients with benign intraocular tumors is recommended. Among malignant intraocular tumors, retinoblastoma was the most common malignancy (60.3%) in the current study. Moreover, 99.6% of retinoblastoma cases occurred in those younger than 10 years old, and it was hardly seen after 20 years, consistent with findings from the USA [24] and other countries. However, a report from Nigeria [22] showed that retinoblastoma accounted for 84% of all enucleated eyes from children, which is lower than our finding and those of other reports. This difference may reflect the variability in the sampling, diagnostic approach, and population characteristics.

Clinically, retinoblastoma is one of the most critical intraocular tumors, *RB1* gene mutation is known to cause retinoblastoma, and carriers of this *RB1* mutation may also have a higher risk of developing cancers in other tissues; therefore, early diagnosis and treatment are extremely important. At present, it is suggested that if a family member carries an *RB1* gene mutation or has a history of retinoblastoma, the test for *RB1* gene mutation should be performed in other children in the same family. More recently, it was reported that genomic cell-free DNA analysis of the aqueous humor in retinoblastoma could be used for predicting the possibility of eye salvage [25]. Thus, this epidemiological study in the age distribution of retinoblastoma is essential for the development of a suitable strategy for the early diagnosis and treatment of RB.

In our study, melanoma was the second most common malignant intraocular tumor in adults. In contrast to the age distribution of retinoblastoma that occurred very early in life (99.6%, of patients were $<$10 years old), 54.9% of primary intraocular melanoma occurred at age 30–49 years. Our result was similar to those of two previous reports, with respect to the prevalence and age distribution of melanoma [26,27]. However, a few other reports have demonstrated the variation in melanoma risk among different populations. In a report from Philippines, only 8% of intraocular tumors were diagnosed as uveal melanoma [7], much lower than that reported in our study (33.4%). In addition, the incidence of uveal melanoma was extremely low in Africa [12], but particularly high in Caucasians such as northwestern European populations [28,29]. The mechanism for these variations is still under investigation, and is likely due to gene mutation; for example, the *BAP1* gene located on chromosome 3 and miRNA-506-514 cluster, hsa-miR-592, and hsa-miR-199a-5p, all play important roles in predisposition to melanoma [30,31]. Researches have shown that *BAP1* gene carriers are more likely to develop uveal melanoma and have a higher risk of tumor spread. Therefore, genetic screening should be performed in individuals susceptible to melanoma or metastasis of intraocular melanoma [32–34].

The diagnosis of uveal melanoma (UM) can be made by regular ophthalmic examination such as ophthalmoscopy, fundus photography, ultrasound, fluorescein fundus angiography and ultrasound biomicroscope; however, it is well recognized that the golden standard for the diagnosis of UM is histopathological analysis. With respect to histopathological features, we found that the most common type of UM was spindle cell type, followed by epithelioid cell type and mixed cell type, consistent with the review by Broggi *et al.* [35] and Kivela *et al.* [36] Because UM is derived from the choroidal layer, the majority of the cells are pigment-rich melanocytes. A number of studies have also shown infiltration by inflammatory cells (macrophages, lymphocytes, and mast cell), though they are not the dominant cell type in UM. In addition, the connective tissue has also been seen in the extra cellular matrix. Immunohistochemical staining often provides valuable information for the diagnosis of UM; common antigens, human melanoma black 45 (HMB45) antigen, S-100 protein, Melan-A, vimentin, and sex determining region Y-box 10 (SOX10), have been recognized in UM tissue. The SOX10 antigen may be more important than other cell markers in the diagnosis of UM, therefore, SOX10 antigen staining should be routinely performed during the histopathological analysis of UM [37].

Computed tomography (CT) and magnetic resonance imaging (MRI) are routinely used to assist the diag-

nosis of UM. CT is able to identify most cases of uveal melanoma, which appear as hyperdense, sharply marginated mushroom-shaped lesions with a convexity toward the vitreous cavity, or present as a limited fusiform thickened eye ring. Typically, UM presents as a mass with high signal intensity on T1-weighted MRI and low signal intensity on T2-weighted MRI. As indicated by Foti *et al.* [38], the application of PET/CT is able to help to determine if the tumor is benign or malignant, the possibility of metastasis, and the response to treatment. MRI, on the other hand, has the advantage of being able to provide high soft tissue contrast and spatial resolution, details of tumor size and extrascleral and orbital extension, as well as functional images [39]. MRI is especially useful for patients with cataract or serious vitreous opacity, and for the evaluation of the treatment for UM [38].

Scleral tumors were the least common eye tumors diagnosed in our study, accounting for only 0.11% of eye tumors, and this finding is consistent with previous studies reporting the rarity of scleral tumors [40–42]. We found that scleral tumors were age-dependent, with 60% of them diagnosed at age 0–9 years, the remaining 40% cases at age 10–29 years, and no case after 30 years, consistent with most literature [40–42]. However, occasionally, the scleral tumors can be seen in 3-month-old [41] to 79-year-old patients [43].

5. Conclusions

In conclusion, the frequency type, malignancy, and location of eye tumors were significantly different across age groups, and age was the major risk factor for malignant eye tumors. Our study also demonstrated that the eyelid was the most common location for eye tumors, and RB and melanoma were the top two malignant intraocular tumors in children and adults, respectively.

Author Contributions

XL (Xiaohua Li) designed the study and wrote the draft of the manuscript; XL (Xiaohua Li) and XL (Xiaohui Liu) made the pathological diagnosis; MY and RY performed the lab experiments; GY performed the statistical analysis; XL (Xiaohua Li) and GY analyzed the data and revised the manuscript.

Ethics Approval and Consent to Participate

The study was approved by the ethics review board of Henan Eye Hospital (Approval No. HNEECKY-2022(14)).

Acknowledgment

We warmly appreciate the suggestion and revision from Benjamin Glasgow (Department of Ophthalmology, UCLA, USA).

Funding

The study was supported by the "23456" project of Henan Provincial People's Hospital (Grant No ZC23456135, ZC20200296).

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.fbl2704132.

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