Advances in Ophthalmology Practice and Research 4 (2024) 128–133

Contents lists available at ScienceDirect

Advances in Ophthalmology Practice and Research

journal homepage: www.journals.elsevier.com/advances-in-ophthalmology-practice-and-research

Full Length Article

Global incidence and prevalence of malignant orbital tumors

Weina Zhang [a], Alexander C. Rokohl [a,b], Yongwei Guo [c], Ke Yao [c], Wanlin Fan [a,**], Ludwig M. Heindl [a,b,*]

[a] Department of Ophthalmology, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany
[b] Center for Integrated Oncology (CIO), Aachen-Bonn-Cologne-Duesseldorf, Cologne, Germany
[c] Eye Center, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

ARTICLE INFO

Keywords:
Orbital tumor
Lymphoma
Malignant
Incidence
Epidemiology

ABSTRACT

Purpose: Aims to provide an overview of the contemporary epidemiology of malignant orbital tumors by analyzing population-based incidence patterns across various regions worldwide.
Methods: In this article, we retrieved orbital malignancy data from the MEDLINE database and analyzed the incidence and prevalence of orbital malignancies worldwide. We performed the literature search by searching on the Mesh terms for malignant orbital tumors ("orbital", "tumor", "lymphoma", "malignant", "cancer", "incidence", and "epidemiology"). All included studies were published between 1993 and 2023 and were written in English.
Results: Ocular or ophthalmic lymphoma most frequently occurred in the orbit, with a prevalence ranging from 47% to 54%. The incidence of malignant orbital tumors was increasing in the USA (2.0 per million (1981–1993), Netherlands (0.86 (1981–1985) to 2.49 (2001–2005) per million) and South Korea (0.3–0.8 per million (1999–2016)), respectively. Ophthalmic lymphoma which includes orbit lymphoma was increasing in Canada (0.17–1.47 per million (1992–2010)), Denmark (0.86 per million (1981–1985) to 2.49 per million (2001–2005)), respectively.
Conclusions: The predominant primary malignant orbital tumor in adults was lymphoma. Ocular or ophthalmic lymphoma most frequently occured in the orbit. The limited data available suggested an increasing trend in the incidence of malignant orbital tumors in each country included, which were mainly attributed to the increase in lymphoma. Generally, incidence rates were found to increase with advancing age, with no difference between males and females.

1. Introduction

The orbit is comprised of various tissues, such as bone, fat, muscle, blood vessels, and neural components. It is divided into four parts: the globe, muscle cone, intraconal space, and extraconal space. A wide range of benign and malignant tumors may involve the orbit, primarily or secondarily, via local extension or distant metastasis (Table 1). Malignant orbital tumors, albeit relatively rare, encompass a spectrum of neoplasms that pose significant challenges in diagnosis and management, leading to a reduced quality of life and even death.[1,2] Among malignant orbital tumors, certain types are more prevalent than others. Lymphomas are malignant tumors originating from B-cells, T-cells, or less commonly, natural killer (NK) cells. They are categorized as Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL). HL originates from B-cells, while NHL comprises various types originating from B-cells, T-cells, and NK-cells, with further subdivisions. HL and NHL can manifest as extranodal lymphomas in the orbit, particularly in adults.[2–6] Olsen TG, et al. described a total of 2211 cases of orbital lymphoma in a 24-year review study.[7] Most cases were demonstrated to be NHL and of B-cell origin, with 2139 cases (97%). Seventy-two cases were of T-cell origin (3%). Olsen TG performed a multicenter retrospective study of orbital lymphoma with other researchers, collecting 797 cases from 7 international eye cancer centers from 1980 through 2017.[8] Four lymphoma subtypes were primarily found: extranodal marginal zone B-cell lymphoma (EMZL) (57%), diffuse large B-cell lymphoma (DLBCL) (15), follicular lymphoma (FL) (11%), and mantle cell lymphoma (MCL) (8%). Generally, orbital lymphoma, comprising less than 1% of all NHL cases, is exceptionally rare.[9] Typically, it presents with proptosis, along with additional systemic symptoms.[10] Rhabdomyosarcoma, a highly aggressive soft tissue tumor derived from primitive mesenchymal cells,

* Corresponding author. Department of Ophthalmology, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany.
** Corresponding author.
E-mail addresses: wanlin.fan@uk-koeln.de (W. Fan), ludwig.heindl@uk-koeln.de (L.M. Heindl).

https://doi.org/10.1016/j.aopr.2024.04.002
Received 20 December 2023; Received in revised form 18 March 2024; Accepted 10 April 2024
Available online 13 April 2024

Table 1
Classification of orbital tumors according to origins and locations.[29]

Optic Nerve and Nerve Sheath
Optic nerve glioma
Optic nerve sheath meningioma
Extraocular extension of retinoblastoma
Extraocular extension of uveal melanoma
Leukemic infiltrate
Metastatic carcinoma
Inflammatory lesions
Extraocular Muscles
Metastatic tumors
Rhabdomyoma
Rhabdomyosarcoma
Lymphoma
Alveolar soft part sarcoma
Thyroid-related myositis
Idiopathic myositis
Inflammation as a component of pseudotumor
Amyloidosis
Carotid artery: cavernous sinus fistula
Lacrimal Fossa
Epithelial tumors
Benign mixed tumor
Adenoid cystic carcinoma
Mixed carcinoma
Adenocarcinoma
Lymphoma
Metastases
Dermoid cysts
Infectious inflammation
Pseudotumor
Orbital Bones
Developmental bone abnormalities/alterations
Axial myopia
Fibrous dysplasia
Osteopetrosis
Craniofacial malformations
Neurofibromatosis
Mass lesions
Epidermoid and dermoid cysts
Hematic bone cyst
Aneurysmal bone cyst
Ossifying fibroma
Mucoceles
Osteosarcoma
Fibrosarcoma
Metastases
Contiguous sinus malignancies
Benign/malignant histiocytosis syndromes
Intraconal Lesions
Benign tumors
Cavernous hemangioma
Hemangiopericytoma
Neurofibroma
Neurilemmoma
Malignant tumors
Malignant hemangiopericytoma
Metastases
Extraconal Lesions
Lymphoid lesions
Lymphoma
Pseudotumor
Leukemia
Metastases
Epidermoids
Capillary hemangioma
Varices
Lymphangiomas
Inflammation from contiguous sinusitis

constitutes one of the most common orbital malignancies in pediatric populations.[2,11,12] Although relatively rare, squamous cell carcinoma can arise within the orbit, often secondary to chronic inflammation or previous radiation exposure.[2] Less frequently than in cutaneous sites, orbital melanoma commonly arises from congenital ocular melanocytosis or a hypercellular blue nevus that affects the orbital tissue and may present with variable clinical features, including pigmented mass or orbital inflammation.[2,13] Due to their rarity, efforts to document the epidemiology of malignant orbital tumors currently rely primarily on small case reports or patient cohorts. Knowledge of orbital tumors' geographic distribution and time trends may help formulate new etiologic hypotheses. The purpose of this paper is to describe and summarize what is known of the contemporary epidemiology of malignant orbital tumors, especially for lymphoma, in terms of incidence and prevalence characteristics in diverse regions of the world on a population-based level.

2. Methods

In this article, we retrieved orbital malignancy data from the MEDLINE database and analyzed the incidence and prevalence of orbital malignancies worldwide. We performed the literature search by searching on the Mesh terms for malignant orbital tumors ("orbital", "tumor", "lymphoma", "malignant", "cancer", "incidence", and "epidemiology"). All included studies were published between 1993 and 2023 and were written in English.

Two primary criteria for inclusion were listed: (1) data were acquired from national registries based on population, and (2) malignant tumors located in the orbit. Considering the restricted data source, this research encompassed study sites ranging from the orbit to the whole eye. Small-scale studies, such as those from a local area, community, or a hospital, were excluded. Raw data from some studies is obtained and graphed in Microsoft Excel 2013 (Microsoft Corp).

3. Results

Only a few studies reported on the epidemiologic information of orbital tumors on a population-based level (Table 2). Most studies examined data from the Surveillance, Epidemiology, and End Results (SEER) database. Developed by the National Cancer Institute, the publicly available SEER program collects valuable data on cancer incidence and survival outcomes in the USA, covering approximately 28% of USA residents.[14] Other studies collected data from the national population-based cancer registry or center. Incidence rates varied among different countries in different periods.

3.1. USA

CE Margo et al. reported 314 cases of primary malignancies in the orbit, including orbital soft tissue and the lacrimal gland, in the Florida cancer registry from 1981 through 1993.[15] The study revealed an average annual incidence of 2.0 per million population for all types of malignancies, showing a steady increase over the 13-year study period (see Fig. 1). Age-standardized incidence rate (ASR) was not used due to no substantial change in age distribution during the study period. The age-specific incidences were initially less than 1.0 per million until the age of 50, gradually increasing each decade. Individuals over 80 years had the highest incidence rate of 10.0 per million (Fig. 2). Gender-specific incidence showed no difference, but there was a significant variance in race-specific incidence, with 2.1 per million whites and 1.5 per million nonwhites. The histopathologic and locational characteristics were further analyzed. Of all the tumors, 85% were from the orbital soft tissue, and the remaining 15% were found in the lacrimal gland. Malignant lymphoma was the most common diagnosis in both sites, accounting for 55% of cases. The average annual incidence of lymphoma was 1.0 per million population. During the last six years, there was a significant increase of 241% with an additional 87 cases reported to the registry compared to the first six years. Correspondingly, the average annual incidence of lymphoma increased by 166%. The increase in orbital malignancies was considered to be due almost entirely to lymphoma (see Fig. 1). Following lymphoma, the most common malignancies in the orbital soft tissue were squamous cell carcinoma, melanoma, and rhabdomyosarcoma, whereas, in the lacrimal gland, they were

Table 2
Studies involving the incidence and prevalence of malignant orbital tumors on a population-based level in various parts of the world.

Country	Study	No.	Year	Data sources	Study focus	Histological types	Study results
USA	CE Margo, et al.[15]	314	1981–1993	Florida Cancer Data System/SEER	The orbital soft tissue and lacrimal gland	Lymphoma (55%); Squanlous cell carcinoma (11%); Melanoma (8%), rhabdomyosarcoma (5%)	The average annual incidence for all malignancies was 2.0 per million, and 1.0 per million for lymphoma.
	Moslehi R, et al.[16]	893	1975–2001	SEER database	The eye and the adnexa	Non-Hodgkin Lymphoma	In Asians/Pacific Islanders, ASR was 3.3 per million person-years for males and 3.2 for females.
	HassanWM, et al.[19]	2802	1973–2009	SEER database	Orbit, conjunctiva and lacrimal gland	Lymphomas and reticular malignancies; Carcinomas; Soft tissue sarcomas; Melanomas	The overall ASR was 3.39 per million person-years and 2.02 per million person-years for the orbit and lacrimal gland.
	Moustafa GA, et al.[20]	55	2000–2015	SEER database	The ocular adnexal	EMZL (45.5%); DLBCL (9.1%)	The ASR of pediatric (≤18 years of age) ocular adnexal lymphoma was 1.2 per million person-years.
	Rami Darwich, et al.[24]	535	1992–2010	Canadian Cancer Registry; Le Registre Québécois du Cancer	The ocular region	EMZL (73.8%); FL (12.1%); DLBCL (14%)	The ophthalmic lymphoma ASR was 0.65 per million person-years with an average annual increase in the incidence rate of 4.5% per year.
Canada	JH Koopman, et al.[26]	367	1989–2006	Netherlands Cancer Registry	The orbit	Lymphoma (67%); Rhabdomyosarcoma (12%); adenocarcinoma (6%), adenoidcystic carcinoma(5%)	The ASR of malignant orbital tumors was 10.9 per million person-years.
Netherlands	Sjö LD, et al.[25]	228	1980–2005	Eye Pathology Institute Registry; Danish Registry of Pathology; Danish Lymphoma Group Registry.	The ocular region	EMZL (55%), DLBCL (13%), MCL (9%), and FL (8%)	The incidence rates of ophthalmic lymphoma increased from 0.86 (1981–1985) to 2.49 (2001–2005) per million.
Denmark	Holm F, et al.[23]	387	1980–2017	Danish Registry of Pathology	The ocular adnexal	EMZL (55%), DLBCL (13%), MCL (11%), FL (10%).	In the period 1980–1984, the incidence was 0.86 per million, which increased to 3.07 per million in the period 2013–2017.
	Jung SK, et al.[28]	630	1999–2016	Korea Central Cancer Registry	The orbit	EMZL (82.2%), DLBCL (9.2%),	The ASR rates increased from 0.3 to 0.8 per million individuals between 1999 and 2016, with an annual percent change of 6.61%.
South Korea	Olsen TG, et al.[8]	797	1980–2017	7international eye cancer centers	The orbit	EMZL (57%), DLBCL (15%),FL(11%),MCL(8%)	The median age was 64 years, and 51% of patients were male.

Abbreviations: EMZL: extranodal marginal zone B-cell lymphoma; DLBCL: diffuse large B-cell lymphoma; MCL: mantle cell lymphoma; FL: follicular lymphoma; ASR: Age-standardized incidence rate

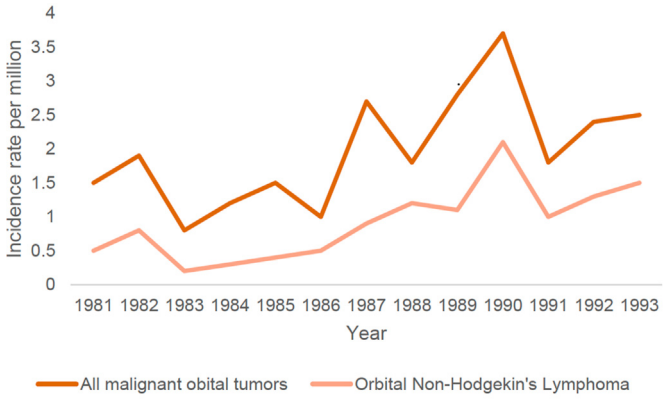

Fig. 1. Annual incidence rates per million population of all malignant orbital tumors and orbital lymphoma, respectively, 1981–1993.[15]

squamous cell carcinoma and adenoid cystic carcinoma. The occurrence of rhabdomyosarcoma was responsible for 55% of malignancies in people below the age of 21 years, heavily weighting the cumulative incidence for children and the young.

Moslehi R et al. examined primary ocular NHL incidence patterns (including eye and the adnexa) from the SEER database from 1975 to 2001.[16] The ocular adnexa refer to the structures surrounding the eye, comprising the eyelids, conjunctiva, orbital soft tissue, and lacrimal apparatus.[5] Among the 893 cases, 457 cases (51%) arose from the orbit and 106 cases (12%) from the lacrimal gland. The overall ASR of ocular NHL was 16.7 per million person-years, rising with advancing age but showing no gender discrepancy. By contrast, other extranodal and nodal NHL occurred predominantly in males. Specific orbital morbidity was not reported. According to different races/ethnicities, for both sexes, Asians/Pacific Islanders exhibited the highest rates of ocular NHL, followed by whites, and the lowest rates were among blacks and American Indians/Alaska natives (see Fig. 3). This higher incidence among Asians/Pacific Islanders compared with Caucasians was consistent with other reports documenting a higher frequency of ocular lymphoproliferative tumors in Asian populations when compared with western countries.[17,18] A steady and rapid increase was also found in the rates, with annual increases of 6.2% and 6.5% among white males and females, respectively.

Hassan WM and colleagues used the SEER database to determine the incidence rates of malignant tumors in the orbit, lacrimal gland, and conjunctive from 1973 to 2009.[19] The overall ASR was 3.39 per million person-years. Age specifically, the incidence rate was lowest among individuals aged 0–19, at 0.56 per million person-years, while the highest incidence rate of 9.51 per million person-years was observed in those aged 50 and above. In adults, lymphomas emerged as the predominant subtype, with an incidence rate of 5.74 per million person-years.

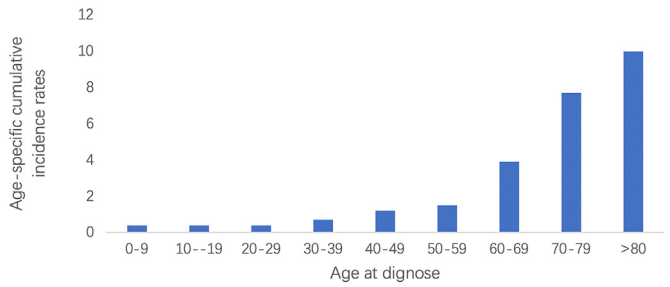

Fig. 2. Age-specific incidence rates per million population of all malignant orbital tumors, 1981–1993.[15]

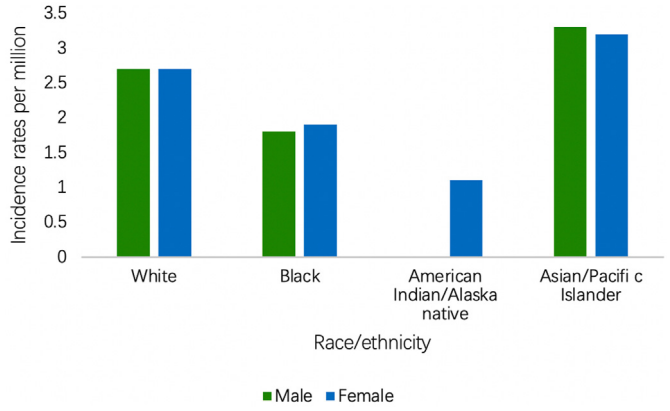

Fig. 3. Age-standardized incidence rates of ocular NHL by sex and Race/ethnicity in the USA, 1992–2001. Rates were per million and adjusted to the 2000 US Standard Population; Confidence intervals are 95% for rates.[16]

However, soft tissue sarcomas, particularly embryonal rhabdomyosarcoma, were predominantly observed in the younger population, with an incidence rate of 0.35 per million person-years. When categorized by location, orbital tumors exhibited a statistically higher ASR of 1.59 per million person-years compared to lacrimal gland tumors (0.43 per million person-years) and conjunctival tumors (1.37 per million person-years). The APC was calculated in this study. The trend line for the overall tumor incidence studied exhibited a significant increase over the years (APC = 3.11), dominantly due to an increase in lymphomas. This finding was in line with the discovery of the previous study.[15] Regarding histologic features, lymphomas, and reticular malignancies exhibited the highest ASR in both the orbit and lacrimal gland (Fig. 4). A subgroup analysis focusing on lymphoma subtypes indicated a notable increase in mature B-cell non-Hodgkin's lymphoma over time, with an APC of 5.82 (Fig. 5).

Moustafa, GA et al. reported the incidence and clinicopathological characteristics of ocular adnexal NHL in the pediatric (≤18 years) population.[20] Using the SEER database, 55 tumors in 54 children were identified, with a median diagnosis age of 13 years. The ASR was 0.12 per million person-years between 1973 and 2015. Pediatric males and blacks had a higher tendency to develop ocular adnexal NHL. Overall, the conjunctiva was the most common primary site (49.1%), followed by the orbit (38.2%), lacrimal gland (9.1%), and eyelid (3.6%). Conversely, the orbit was the most commonly affected anatomical structure in adults.[14,21–23]

3.2. Canada

In Canada, Darwich R et al. observed that the Canadian ASR of ophthalmic lymphoma was 0.65 per million person-years during 1992–2010.[24] The average annual crude incidence rate overall was 0.90 per million person-years. An average annual increase occurred from 0.17 per million person-years in 1992 to 1.47 in 2010, equivalent to a rise of 4.5%.[24] The mean age of diagnosis was 65 years, and no sex predilections were found. It was shown that the most common site for all ophthalmic lymphoma was the orbit (47%), followed by the conjunctiva (33%) and the lacrimal gland (13%). No orbital-specific incidence data were available in this study. Notably, incidence rates in different Canadian provinces and cities were estimated to vary from east to west. The highest incidence was observed in cities situated within the province of British Columbia, which boasts the highest proportion of Asian-Canadians (25%) among all provinces.

3.3. Denmark

Sjö LD et al. analyzed data from three population-based registries to study patients diagnosed with ophthalmic lymphoma between 1980 and 2005.[25] The majority of patients were elderly, with a median age of 69 years. Differences in incidence among genders were not statistically significant. Depending highly on age, the incidence rates increased progressively each decade until maximum.[25] The incidence rate of ophthalmic lymphoma in the entire Danish populace rose from 0.86 (1981–1985) per million to 2.49 (2001–2005) per million. This upward trend remained consistent after adjusting for differences in age distribution. During the 26 years, there was a statistically significant annual average rise of 3.4% across all age groups, primarily driven by an increase in MALT lymphoma incidence. The predominant subtype of

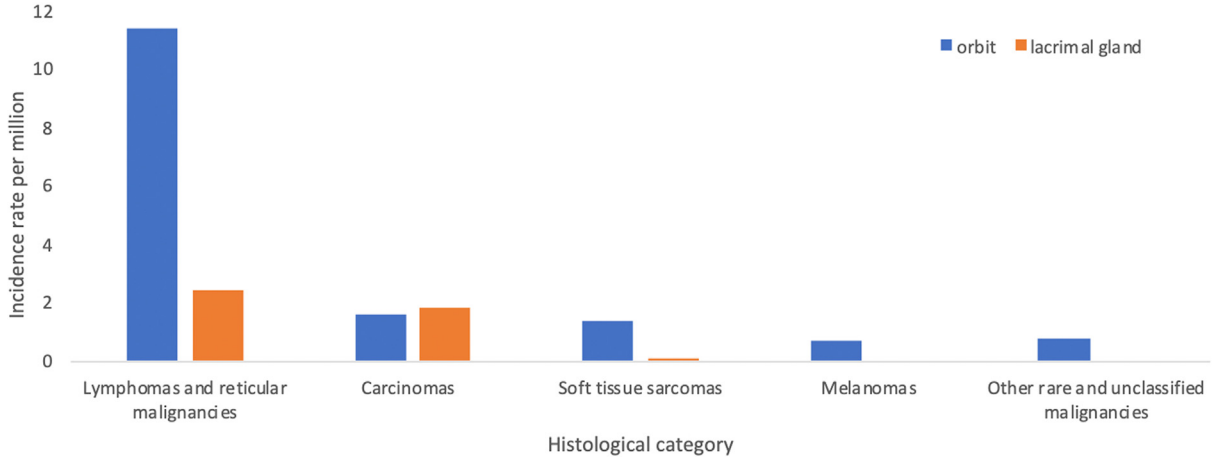

Fig. 4. Age-standardized incidence rates of malignant tumors in orbit and lacrimal gland according to the histological category in the USA, 1973–2009.[19] Rates were per million and age-adjusted to the 2000 US Standard Population standard; Confidence intervals are 95% for rates.

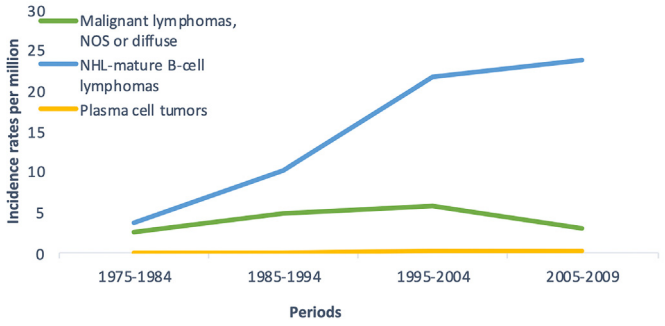

Fig. 5. Age-standardized incidence rates per million people for orbital lymphoma in South Korea from 1999 to 2016.

lymphoma observed was MALT lymphoma, accounting for 55.5% of cases, with the majority situated in the orbit, constituting 56.8% of the total. In addition, A statistically significant increase in incidence rate in the orbital region was found (age-adjusted rate ratio, 1993 to 2005 vs. 1980 to 1992 = 1.6). A more recent study of ocular adnexal lymphoma showed that, in the period 1980–1984, the annual incidence rate for the whole population was 0.86 per million, which increased to 3.07 per million in the period 2013–2017.[23] 387 patients were identified in total, with a median age of 69 years. The orbit was the most common site (54%). Histologically, there was an observable rise in incidence for EMZL, predominantly driving the increase in total ocular adnexal lymphoma incidence rates. However, no increase in incidence was observed for the other three primary subtypes: DLBCL, MCL, and FL.

3.4. Netherlands

In the Netherlands, Koopman JH et al. analyzed the epidemiology of primary malignant orbital tumors from 1989 to 2006, extracting 367 cases from the Netherlands Cancer Registry.[26] The average ASR of malignant orbital tumors is 10 per million person-years, and the incidence showed a slight increase during the 17 years. The most common tumor type was lymphoma, accounting for 67% of cases in both orbital soft tissues (72%) and the lacrimal gland (51%). Rhabdomyosarcoma accounted for 12%, adenocarcinoma for 6%, and adenoid cystic carcinoma for 5%. This histopathological subtype pattern did not differ greatly from studies from other parts of the world.[15,27] The patients' ages ranged from 0 to 93 years, with a median age of 66 years and two age peaks, 0–15 years and 60–80 years. In the younger group, 86% of the tumors were diagnosed as rhabdomyosarcoma, while in the older group, lymphoma (79%) and carcinoma (14%) were more common.

3.5. Republic of Korea

An Asian study conducted in 2021 by Jung SK et al. reported the epidemiological characteristics and temporal trends of orbital lymphoma from 1999 through 2016.[28]

Based on information gathered from the Korea Central Cancer Registry, the research revealed that the ASR of orbital lymphoma throughout an 18-year period amounted to 0.5 per million. This rate, however, was very low in comparison to prior epidemiological investigations. The ASR from 1999 to 2016 rated increased from 0.3 to 0.8 per million individuals, with an increasing APC of 6.61% (see Fig. 5). Furthermore, the research indicated a significantly higher incidence in males compared to females, with a male-to-female ratio of 2.59:1. The majority of orbital lymphomas were of the EMZL subtype (82.2%), followed by DLBL (9.2%), and a few scattered cases of other types (including ML, NK/T cell lymphoma, and FL, which are exceptionally rare). The ASR of EMZL increased from 0.1 to 0.7 per million, with an APC equal to 10.62%.

4. Conclusions

This study highlights the global epidemiology of malignant orbital tumors, emphasizing their frequency, demographic variations, age distribution, and rising incidence rates. Unlike predominantly retrospective published reports and data originating from single centers with inherent biases, national cancer registries, e.g. the SEER, can provide population-based information that better reflects true patterns in disease incidence and epidemiology. Considering the restricted data source, this research encompassed study sites ranging from the orbit to the whole eye. The predominant primary malignant orbital tumor in adults was lymphoma, with a prevalence ranging from 55% to 67%.[15,26] Ocular or ophthalmic lymphoma most frequently occurred in the orbit, with a prevalence ranging from 47% to 54%.[24,25] The median age at diagnosis ranged from 64 to 69 years.[8,25,26] Generally, incidence rates were found to increase with advancing age,[25,28] and there was no difference between males and females.[15,16] Incidence rates also differed among races,[15,16] suggesting environmental factors may be involved in disease. It's challenging to determine and compare the global incidence rates because of variations in data sources, study sites, analyzed time frames, and the different forms of incidence rates examined within each study. Despite these differences, the limited data available suggested an overall increasing trend in the incidence of malignant orbital tumors in each country included. In the USA, there was a significant increase of 241% in orbital malignancies over 13 years, primarily attributed to lymphoma.[15] Similarly, in Denmark, there was a statistically significant annual average rise of 3.4% in the incidence of ophthalmic lymphoma across all age groups, primarily driven by an increase in MALT lymphoma,[25] which were consistent with other studies.[19,20,24] The increase in lymphoma incidence may be real or may be partly due to new and improved diagnostic methods that better diagnose low-grade lymphomas previously diagnosed as pseudolymphoma. Further studies are needed to identify factors that contribute to the rare but rapidly rising orbital malignancy. Notably, it is important to focus on the Southern Hemisphere, where there is a lack of relevant research in those areas.

Study approval

Not Applicable.

Author contributions

The authors confirm contribution to the paper as follows: Conception and design of study: WZ, LMH, YG, KY; Data collection: WZ, ACR; Analysis and interpretation of results: WZ, WF; Drafting the manuscript: WZ; All authors reviewed the results and approved the final version of the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Editorship disclosure

Given their role as Editor-in-Chief, Ke Yao had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Prof. Andrzej Grzybowski.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Thanks to all the peer reviewers and editors for their opinions and suggestions.

References

1. Tailor TD, Gupta D, Dalley RW, et al. Orbital neoplasms in adults: clinical, radiologic, and pathologic review. *Radiographics*. Oct 2013;33(6):1739–1758. https://doi.org/10.1148/rg.336135502.
2. Shields JA, Shields CL, Scartozzi R. Survey of 1264 patients with orbital tumors and simulating lesions: the 2002 Montgomery Lecture, part 1. *Ophthalmology*. May 2004;111(5):997–1008. https://doi.org/10.1016/j.ophtha.2003.01.002.
3. Bonavolontà G, Strianese D, Grassi P, et al. An analysis of 2,480 space-occupying lesions of the orbit from 1976 to 2011. *Ophthalmic Plast Reconstr Surg*. Mar-Apr 2013;29(2):79–86. https://doi.org/10.1097/IOP.0b013e31827a7622.
4. Markowski J, Jagosz-Kandziora E, Likus W, et al. Primary orbital tumors: a review of 122 cases during a 23-year period: a histo-clinical study in material from the ENT Department of the Medical University of Silesia. *Med Sci Mon Int Med J Exp Clin Res*. Jun 16 2014;20:988–994. https://doi.org/10.12659/msm.890433.
5. Ferry JA, Fung CY, Zukerberg L, et al. Lymphoma of the ocular adnexa: a study of 353 cases. *Am J Surg Pathol*. Feb 2007;31(2):170–184. https://doi.org/10.1097/01.pas.0000213350.49767.46.
6. Stefanovic A, Lossos IS. Extranodal marginal zone lymphoma of the ocular adnexa. *Blood*. Jul 16 2009;114(3):501–510. https://doi.org/10.1182/blood-2008-12-195453.
7. Olsen TG, Heegaard S. Orbital lymphoma. *Surv Ophthalmol*. Jan-Feb 2019;64(1):45–66. https://doi.org/10.1016/j.survophthal.2018.08.002.
8. Olsen TG, Holm F, Mikkelsen LH, et al. Orbital lymphoma-an international multicenter retrospective study. *Am J Ophthalmol*. Mar 2019;199:44–57. https://doi.org/10.1016/j.ajo.2018.11.002.
9. Fitzpatrick PJ, Macko S. Lymphoreticular tumors of the orbit. *Int J Radiat Oncol Biol Phys*. Mar 1984;10(3):333–340. https://doi.org/10.1016/0360-3016(84)90051-8.
10. Briscoe D, Safieh C, Ton Y, et al. Characteristics of orbital lymphoma: a clinicopathological study of 26 cases. *Int Ophthalmol*. Feb 2018;38(1):271–277. https://doi.org/10.1007/s10792-017-0457-y.
11. Shields CL, Shields JA, Nowinski T. *Orbital rhabdomyosarcoma. Taylor and Hoyt's Pediatric Ophthalmology and Strabismus*. 2016:225.
12. Shields CL, Shields JA, Honavar SG, et al. Clinical spectrum of primary ophthalmic rhabdomyosarcoma. *Ophthalmology*. Dec 2001;108(12):2284–2292. https://doi.org/10.1016/s0161-6420(01)00840-5.
13. Roth M, Eyelid Conjunctival, Tumors Orbital. 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):618–619. https://doi.org/10.1111/cxo.12618, 2018/07/01.
14. Cronin KA, Ries LA, Edwards BK. The Surveillance, epidemiology, and End results (SEER) program of the national cancer Institute. *Cancer*. Dec 1 2014;120(Suppl 23):3755–3757. https://doi.org/10.1002/cncr.29049.
15. Margo CE, Mulla ZD. Malignant tumors of the orbit. Analysis of the Florida cancer registry. *Ophthalmology*. Jan 1998;105(1):185–190. https://doi.org/10.1016/s0161-6420(98)92107-8.
16. Moslehi R, Devesa SS, Schairer C, et al. Rapidly increasing incidence of ocular non-hodgkin lymphoma. *J Natl Cancer Inst*. Jul 5 2006;98(13):936–939. https://doi.org/10.1093/jnci/djj248.
17. Ohtsuka K, Hashimoto M, Suzuki Y. High incidence of orbital malignant lymphoma in Japanese patients. *Am J Ophthalmol*. Nov 2004;138(5):881–882. https://doi.org/10.1016/j.ajo.2004.05.069.
18. Cho EY, Han JJ, Ree HJ, et al. Clinicopathologic analysis of ocular adnexal lymphomas: extranodal marginal zone b-cell lymphoma constitutes the vast majority of ocular lymphomas among Koreans and affects younger patients. *Am J Hematol*. Jun 2003;73(2):87–96. https://doi.org/10.1002/ajh.10332.
19. Hassan WM, Bakry MS, Hassan HM, et al. Incidence of orbital, conjunctival and lacrimal gland malignant tumors in USA from Surveillance, Epidemiology and End Results, 1973-2009. *Int J Ophthalmol*. 2016;9(12):1808–1813. https://doi.org/10.18240/ijo.2016.12.18.
20. Moustafa GA, Topham AK, Aronow ME, et al. Paediatric ocular adnexal lymphoma: a population-based analysis. *BMJ Open Ophthalmol*. 2020;5(1):e000483. https://doi.org/10.1136/bmjophth-2020-000483.
21. Sjö LD. Ophthalmic lymphoma: epidemiology and pathogenesis. *Acta Ophthalmol*. Feb 2009;87(1):1–20. https://doi.org/10.1111/j.1755-3768.2008.01478.x. Thesis.
22. Hindsø TG, Esmaeli B, Holm F, et al. International multicentre retrospective cohort study of ocular adnexal marginal zone B-cell lymphoma. *Br J Ophthalmol*. Mar 2020;104(3):357–362. https://doi.org/10.1136/bjophthalmol-2019-314008.
23. Holm F, Mikkelsen LH, Kamper P, et al. Ocular adnexal lymphoma in Denmark: a nationwide study of 387 cases from 1980 to 2017. *Br J Ophthalmol*. Jul 2021;105(7):914–920. https://doi.org/10.1136/bjophthalmol-2019-315637.
24. Darwich R, Ghazawi FM, Rahme E, et al. Epidemiology of ophthalmic lymphoma in Canada during 1992-2010. *Br J Ophthalmol*. Aug 2020;104(8):1176–1180. https://doi.org/10.1136/bjophthalmol-2019-314653.
25. Sjö LD, Ralfkiaer E, Prause JU, et al. Increasing incidence of ophthalmic lymphoma in Denmark from 1980 to 2005. *Invest Ophthalmol Vis Sci*. Aug 2008;49(8):3283–3288. https://doi.org/10.1167/iovs.08-1768.
26. Koopman JH, van der Heiden-van der Loo M, van Dijk MR, et al. Incidence of primary malignant orbital tumours in The Netherlands. *Eye*. Apr 2011;25(4):461–465. https://doi.org/10.1038/eye.2011.9.
27. Lee SB, Au Eong KG, Saw SM, et al. Eye cancer incidence in Singapore. *Br J Ophthalmol*. Jul 2000;84(7):767–770. https://doi.org/10.1136/bjo.84.7.767.
28. Jung SK, Lim J, Yang SW, et al. Nationwide trends in the incidence of orbital lymphoma from 1999 to 2016 in South Korea. *Br J Ophthalmol*. Oct 2021;105(10):1341–1345. https://doi.org/10.1136/bjophthalmol-2020-316796.
29. Char DH. *Tumors of the Eye and Ocular Adnexa. PMPH-USA*. 2001.