·Clinical Research·

Incidence of orbital, conjunctival and lacrimal gland malignant tumors in USA from Surveillance, Epidemiology and End Results, 1973–2009

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Abstract

• AIM: To determine the types and incidence of tumors affecting the orbit, conjunctiva and lacrimal glands and to study the trend line of these tumors in the United States from 1973 to 2009.

• METHODS: We used the publicly available Surveillance, Epidemiology and End Results (SEER) database registries to determine the incidence rates. Age was adjusted to the 2000 US Standard Population. Patients were stratified according to age group, gender, race and histological grouping of tumor lesions. Three age groups were defined: 0–19, 20–49 and ⩾50y. Annual percentage changes were calculated to examine trends.

• RESULTS: The overall age adjusted incidence rate was 3.39 (95% CI: 3.27–3.52) per million person–years. The tumors were more prevalent in age group ⩾50 counting 9.51 (95%CI: 9.11–9.92) per million person–years. Most of the soft tissue sarcomas occurred in the young age with incidence rate of 0.35 (95% CI: 0.28–0.42) per million person–years. Lymphomas were the dominant subtype in the adult population with incidence rate of 5.74 (95%CI: 5.43–6.06) per million person–years. Incidence rates were higher in males than females with an overall rate ratio of 1.31 (95%CI: 1.21–1.41) mainly caused by the increase in carcinoma subtypes. White race had a higher tumor incidence with a rate ratio of 1.47 (95% CI: 1.25–1.73) driven by the higher incidence of most histological subtypes. Orbital tumors showed a higher incidence rate followed by conjunctival and lacrimal gland tumors with incidence rates of 1.59, 1.37 and 0.43 per million person–years respectively. The trend line of overall incidence of tumors showed a significant increase (APC=3.11, 95%CI: 2.61–3.61) mainly due to increase of lymphomas. This increase was higher than the increase of lymphomas at other sites.

• CONCLUSION: Orbital, conjunctival and lacrimal gland malignant tumors differ among children and adults. Over the years there has been a noticeable increase in incidence rates of orbital and lacrimal gland tumors mainly caused by an increase in lymphomas and an apparent increase due to advances in diagnostic techniques. ICD–O–3 topographical coding should be improved to consider the different orbital bones and ocular structures.

• **KEYWORDS:** orbital tumors; incidence; conjunctiva; lacrimal gland
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INTRODUCTION

Orbital lesions are frequently seen at ophthalmology clinics, but malignant forms of such lesions constitute a group of uncommon tumors. Many orbital, conjunctival and lacrimal gland (OCLG) malignant tumors are not at first suspected and thus initially misdiagnosed due to the lack of proper diagnostic methods, presentation to a general ophthalmologist and the lack of knowledge regarding the frequency of such tumors. This lack of knowledge is evident in paucity of literature covering the relative epidemiology and prognosis of these tumors. This study focused on incidence rates of OCLG malignant tumors. Only a few studies have discussed population-based pattern of orbital tumors incidence [1-2]. Most studies have focused on a special histological subtype or a particular age group. Other studies have investigated the population of a certain tertiary referral center-thus possibly showing referral bias[3-5].

In this study, we aimed at discovering the differences in incidence between malignant tumors originating from the OCLG, using data from the Surveillance, Epidemiology and End Results (SEER) Program database of the US National

Cancer Institute (NCI). Data analysis was carried out with a focus on incidence rates according to different histological categories-stratified by site, age, gender, and race.

SUBJECTS AND METHODS

The SEER database is a publicly available database covering cancer cases in the United States. This database collects patient information, including demographics, tumor site, morphology, and stage as well as treatment course and follow up survival data. In the database race is coded into three categories; White, African American, and "other" (American Indian native, Asian/Pacific). The "other" race category refers to a heterogeneous group of patients each comprising a small patient population and hence was removed during analysis. SEER data cover almost 28% of US inhabitants. Information from this data could be extrapolated from to make conclusions regarding the entire US population[6]. Cases in the current study were obtained from nine SEER registries collected over the period between 1973 and 2009. The SEER's nine registries are the Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah registries. Data for cases diagnosed from 1973 and later are available in these registries with the exception of the Seattle-Puget Sound and Atlanta registries. These two joined the SEER program in 1974 and 1975, respectively. The nine registries used in this study cover approximately 10% of the US population. Population denominators used to calculate rates were extracted from the NCI data. NCI data modifies the population data produced by the US Census Bureau's Population estimate program based on a collaboration with the National Center of Health Statistics [7]. The SEER*Stat program was used to calculate frequencies, incidence rates and trends over time [7]. The database was accessed for data extraction in August 2013. Tumor sites of interest were identified and coded using the ICD-O3 codes as follows: C69.0, conjunctival; C69.5, lacrimal gland and C69.6, orbital. Similar histological subtypes were combined together into 4 groups in addition to a fifth group of rare and other unclassified malignant tumors. Only cases with known age and malignant behavior were included. Population was divided into 3 age categories: 0-19, 20-49 and ⩾50 years of age. Incidence rates were calculated per 1 000 000 person-years and age adjusted to the 2000 US Standard Population (single ages-Census P25-1130); confidence intervals (CIs) were set as 95% for rates and trends. Percentage changes were calculated using one year for each endpoint. Annual percentage changes (APC) were calculated using the weighted least-squares method. The APC were calculated based on the whole study duration. The principles outlined in the Declaration of Helsinki (2008) were followed.

RESULTS

The number of patients identified as having OCLG tumors were 2802 patients. The overall age-adjusted incidence rate for OCLG malignant tumors was 3.39 (95%CI: 3.27-3.52) per million person-years. The ⩾50 age group had the highest incidence rate of 9.51 per million person-years (95% CI: 9.11-9.92), while the 0-19 age group had the lowest incidence rate of 0.56 per million person-years (95% CI: 0.47-0.66). Incidence rates of different histological subtypes differed significantly between age groups. In the 0-19 age group, soft tissue sarcomas comprised the most common histological category with an incidence rate of 0.35 per million person-years (95%CI: 0.28-0.42). However, in the ⩾50 age group, the histological subtypes with the highest incidence rate were lymphomas at a rate of 5.74 per million person-years (95%CI: 5.43-6.06). Table 1 summarizes the more common histological subtypes found in each of the three age groups. Males had a statistically significantly higher rate ratio for the overall incidence of OCLG malignant tumors-compared to females of 1.31 (95% CI: 1.21-1.41). This increase was mainly caused by the increase in carcinoma subtypes in males [rate ratio 2.8 (95%CI: 2.36-3.32)].

There was a statistically significantly higher incidence rate among Whites compared to African Americans with a rate ratio of 1.47 (95%CI: 1.25-1.73). This higher incidence was noted in most histological subtypes, especially melanomas and carcinomas. The rate ratio for melanomas in the White population compared to African Americans was 3.75 (95% CI: 1.87-9.29), while that of carcinomas was 1.5 (95%CI: 1.08-2.14). Table 1 displays rate ratios of different histological subtypes according to gender and race.

The incidence rate was statistically significantly higher for orbital tumors at 1.59 per million person-years (95% CI: 1.50-1.68) compared with conjunctival tumors at 1.37 per million person-years (95%CI: 1.30-1.46) and lacrimal gland tumors at 0.43 per million person-years (95%CI: 0.39-0.48). When the incidence rate of each histological category was stratified according to site, carcinomas and melanomas were statistically significantly higher in conjunctiva than orbit and lacrimal glands. While for lymphomas, the orbit incidence rate was statistically significantly higher than the conjunctival and lacrimal gland rates. More details about the incidence rates according to site are available in Table 2.

The trend line of disease showed significant increase over the years. The annual percent change (APC) was a statistically significant 3.11 (95% CI: 2.61-3.61). This increase was mainly caused by an increase in lymphoma subtypes (APC=4.8, 95% CI: 3.8-5.82). APC was also statistically significant for melanomas and carcinomas but at lower percent increase. Trend analysis stratified according to gender showed that there was no statistically significant difference between both genders. When the trend was stratified according to race, APC could not be computed for African Americans due to the small sample size. Table 3

Table 1 Common histology according to gender, race and age groups

Histology	Statistic	Gender			Race			Age category			
		M	F	Rate ratio	White	African American	Rate ratio	0-19	20-49	⩾50	Total (all age groups)
Carcinomas	Rate[1]	1.27	0.45	2.8[a]	0.80	0.54	1.5[a]	0.02	0.34	2.31	0.79
	95%CI	1.15-1.4	0.39-0.52	2.36-3.32	0.74-0.87	0.38-0.74	1.08-2.14	0.01-0.05	0.28-0.4	2.11-2.51	0.73-0.85
	Count	439	209		554	41		6	126	516	648
Melanomas	Rate	0.48	0.39	1.22	0.47	0.13	3.75[a]	0.03	0.21	1.18	0.43
	95%CI	0.41-0.56	0.34-0.46	0.98-1.51	0.42-0.53	0.05-0.25	1.87-9.29	0.02-0.07	0.17-0.26	1.04-1.33	0.39-0.48
	Count	177	180		328	8		9	80	268	357
Soft tissue sarcomas	Rate	0.15	0.15	1.05	0.15	0.15	0.98	0.35	0.05	0.11	0.15
	95%CI	0.12-0.2	0.11-0.19	0.74-1.50	0.12-0.18	0.09-0.25	0.57-1.74	0.28-0.42	0.03-0.08	0.07-0.16	0.13-0.18
	Count	70	67		106	18		91	22	24	137
Lymphomas and reticular malignancies	Rate	1.92	1.94	0.99	1.90	1.46	1.31[a]	0.09	0.72	5.74	1.93
	95%CI	1.78-2.08	1.81-2.07	0.90-1.10	1.8-2.01	1.18-1.78	1.06-1.63	0.06-0.14	0.63-0.81	5.43-6.06	1.83-2.02
	Count	692	888		1307	103		25	261	1294	1580
Other rare and unclassified malignancies	Rate	0.12	0.08	1.52	0.1	0.07	1.47	0.06	0.07	0.17	0.09
	95%CI	0.08-0.16	0.05-0.11	0.94-2.43	0.08-0.13	0.03-0.14	0.66-3.59	0.03-0.1	0.04-0.1	0.12-0.24	0.08-0.12
	Count	44	36		68	8		16	27	37	80
Total	Rate	3.94	3.01	1.31[a]	3.43	2.34	1.47[a]	0.56	1.39	9.51	3.39
	95%CI	3.74-4.16	2.85-3.17	1.21-1.41	3.29-3.57	1.99-2.73	1.25-1.73	0.47-0.66	1.27-1.51	9.11-9.92	3.27-3.52
	Count	1422	1380		2363	178		147	516	2139	2802

[1]Rates are per 1 000 000 and age-adjusted to the 2000 US Standard Population (19 age groups-Census P25-1130) standard; Confidence intervals (Tiwari mod) are 95% for rates and ratios. [a]The rate ratio indicates that the rate is significantly different from the rate for the other comparison group (P<0.05).

Table 2 Incidence rates according to site and histological category

Site	Statistic	Carcinomas	Melanomas	Soft tissue sarcomas	Lymphomas and reticular malignancies	Other rare and unclassified malignancies	Total
C69.0-conjunctiva	Rate[1]	0.45	0.35	0	0.55	0.02	1.37
	95%CI	0.41-0.5	0.31-0.4		0.5-0.6	0.01-0.03	1.3-1.46
	Primary tumors	311	246	0	410	12	979
	Second tumors[2]	60	48	0	46	1	155
	Total count	371	294	0	456	13	1134
C69.5-lacrimal gland	Rate	0.18	0	0.01	0.24	0	0.43
	95%CI	0.15-0.21	0-0.01	0-0.02	0.21-0.27	0-0.01	0.39-0.48
	Primary tumors	137	3	8	166	3	317
	Second tumors	12	0	0	33	0	45
	Total count	149	3	8	199	3	362
C69.6-orbit, NOS	Rate	0.16	0.07	0.14	1.14	0.08	1.59
	95%CI	0.13-0.19	0.06-0.09	0.12-0.17	1.06-1.21	0.06-0.1	1.5-1.68
	Primary tumors	105	50	121	785	60	1121
	Second tumors	23	10	8	140	4	185
	Total count	128	60	129	925	64	1306
Total	Rate	0.79	0.43	0.15	1.93	0.09	3.39
	95%CI	0.73-0.85	0.39-0.48	0.13-0.18	1.83-2.02	0.08-0.12	3.27-3.52
	Primary tumors	553	299	129	1,361	75	2417
	Second tumors	95	58	8	219	5	385
	Total count	648	357	137	1,580	80	2802

[1]Rates are per 1 000 000 and age-adjusted to the 2000 US Standard Population (19 age groups-Census P25-1130) standard; Confidence intervals (Tiwari mod) are 95% for rates and ratios; [2]"Second tumors" means that they are the second neoplasms after a primary one (later primary neoplasms). The primary neoplasms for those second tumors might be of different histology and/or in different sites.

shows the APC for each histological category, with further analysis stratified by race and gender. Subgroup analysis of the trend in lymphoma subtypes was done. Table 4 shows a significant rise of mature B-cell non-Hodgkin's lymphoma over years (APC=5.82, P<0.01). Incidence rates of different histological subtypes and the overall incidence rates across the years are displayed in Figure 1.

DISCUSSION

OCLG malignant tumors are more predominant among adults. The 0-19 age group had the highest incidence rate of

Table 3 APC in each histological category stratified by gender and race

Histology	Statistic	Gender		Race white	Total
		M	F		
Carcinomas	APC[a]	0.66	0.89	1.02[b]	0.80[b]
	95%CI	-0.32 to 1.65	-0.14 to1.93	0.36-1.68	0.14-1.46
Melanomas	APC	-[c]	-[c]	1.41[b]	1.28[b]
	95%CI	-[c]	-[c]	0.35-2.49	0.19-2.39
Lymphomas and reticular malignancies	APC	4.45[b]	4.95[b]	4.60[b]	4.80[b]
	95%CI	3.25-5.66	3.77-6.15	3.63-5.59	3.80-5.82
Total	APC	2.61[b]	3.47[b]	3.03[b]	3.11[b]
	95%CI	1.9-3.33	2.83-4.12	2.51-3.55	2.61-3.61

[a]APC: Annual percent change is calculated using weighted least squares method; [b]The confidence interval indicates that the annual percent change is statistically significant different than zero; [c]Statistics could not be computed here beside soft tissue sarcomas, other rare and unclassified malignancies and African American race due to small sample size.

Table 4 Incidence rates of lymphoma broad groupings over years

Year of diagnosis	Lymphoma broad grouping (rate)		
	Malignant lymphomas, NOS or diffuse	NHL-mature B-cell lymphomas	Plasma cell tumors
APC	1.27 (P=0.12)	5.82 (P<0.01)	
1975-2009	0.44	1.51	0.02
1975-1984	0.27	0.39	0
1985-1994	0.49	1.03	0.01
1995-2004	0.58	2.19	0.03
2005-2009	0.31	2.39	0.03

APC: Annual percent change. Rates are per 1 000 000 and age-adjusted to the 2000 US Standard Population (19 age groups-Census P25-1130) standard. Malignant lymphomas as per codes 9590-9599, NHL-mature B-cell lymphomas as per codes 9670-9699 and plasma cell tumors as per codes 9730-9739.

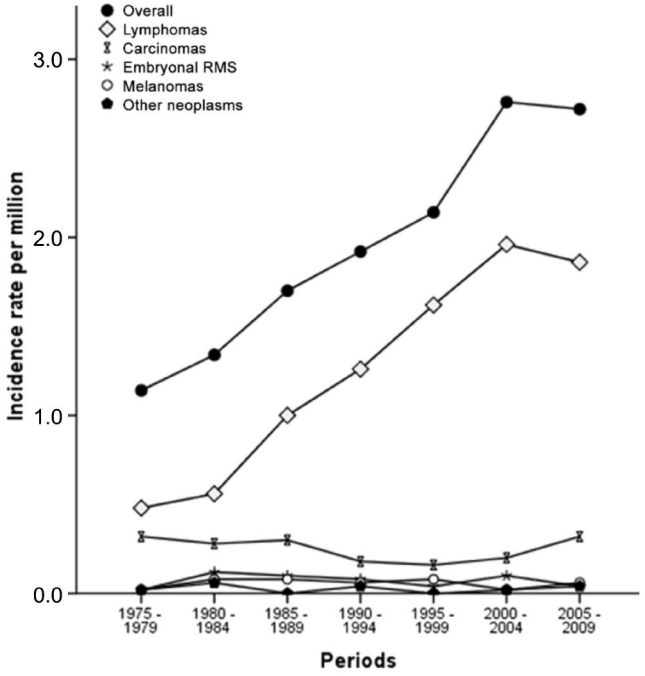

Figure 1 Incidence rates of different histological subtypes and the overall incidence rate across the years from 1975 to 2009
RMS: Rhabdomyosarcoma.

soft tissue sarcomas. This rate was mainly attributed to the high rate of embryonal rhabdomyosarcoma in this age group. According to the Cancer Incidence and Survival in Children and Adolescent Rhabdomyosarcoma the incidence rate is 4.3 cases per million child, with 10% of them being orbital in site (estimated to be 35 cases per year in US)[8].

Another longitudinal study of the years 1942-1959 highlighted 40 (73%) children were diagnosed with embryonal rhabdomyosarcoma (OER) out of a total of 55 children diagnosed with orbital tumors [9]. OER rise embryonically as other rhabdomyosarcomas from fibers imitating smooth muscles [10].

The results of this study are in alignment with others, enabling us to conclude that OER presents commonly in the younger age groups while being extremely rare in adults. Additionally, the results of this study suggest no statistically significant difference in incidence of OCLG soft tissue sarcomas based on gender or race.

Lymphomas have the highest incidence of orbital malignancies. We are able to note a rapidly rising trend with a rise in rate. According to one review of 244 cases of OCLG malignant tumors in Japan, malignant lymphoma was the most common tumor-at 31%- in the >40 age group [4]. This higher incidence rate was possibly due to environmental or racial differences, or due to different techniques of diagnosis of malignant lymphomas. Another study indicated that incidence had tripled within the last 15y [11]. It had been previously thought that this was due to an increase in immunocompromised patients. However the incidence has continued to increase whilst the number of immunocompromised patients have been recently decreasing[11]. Another hypothesis connected this increase to the increase in incidence of infections as with the Epstein Barr virus in HIV negative patients [12]. Moreover, Toxoplasma gondii and Chlamydia psittaci is often detected in cases of B-cell lymphoma [13]. This hypothesis suggests that an antigenic factor is the primary drive for B-cell expression. However, another study of 200 patients above the age of 60 showed that 28% of patients with orbital tumors had lymphoma [14]. The study connected the increased life expectancy in recent years to the higher incidence rates of lymphoma.

The increasing incidence of lymphoma could be partially attributed to new diagnostic methods which better diagnose low grade lymphomas which were previously diagnosed as pseudolymphomas [15]. But several other reviews have

confirmed the unexplained increasing incidence of all subtypes of lymphoma [16-17]. Our data show a steady annual increase of most subtypes of lymphoma in the OCLG which warrants further etiological studies. However, mature B-cell lymphomas showed the only significant increase over years. This is probably the subtype that leads the trends showed in other papers [18-19].

Our results indicate that there is no statistically significant difference in incidence rate of lymphomas according to gender comparable to two recent publications[15,19].

Carcinomas were the second most common histological type in our series. Most patients were above 50 years of age. The majority of cases suffered from squamous cell carcinoma, occurring predominantly in the conjunctiva. We noted that carcinomas show a statistically significantly higher incidence rate in males than females. These findings are inconsistent with the cancer statistics published by the American Cancer Society in 2010, which estimated the number of new cases of eye and orbital tumors to be the same-irrespective of gender [20]. However, Our results are consistent with a skin cancer study conducted at 2002 [21] and another study from the Netherlands [2]. The underlying reason for this may be due to higher sun exposure in males compared with females; possibly due to occupational differences [22]. Another recent study comparing gender impact on incidence of squamous cell carcinoma (SCC) in healthcare workers concluded that male incidence rates were higher than females [23]. It also noted that head and neck SCC were about 48%-60% of total SCC. In addition, it stated that the European standardized rates for male incidence was 22.2 to 35.4 per 100 000 and 7.8 to 20.5 for females. This was confirmed by other studies [24]. Conversely, one study studying association between ultraviolet ray exposure and squamous cell carcinoma showed a higher incidence in females compared to males in many anatomical sites [24]. The later study requires more correlation with demographics, pattern of work and sun exposure habits.

Carcinomas show a higher incidence rate in whites compared with African Americans. Other studies focused mainly on white populations[25].

Melanomas show its highest incidence rate in the ⩾50 age group, whites and in the conjunctiva. Melanomas show no statistically significant difference in incidence rate based on gender. A recent study identified the incidence of ocular melanoma to be 5.6 patients per million person-years-a very low value when compared with cutaneous disease. That study however did not discuss orbital affection [26]. In later study there was a lower age-adjusted incidence of cutaneous and ocular melanomas in women. The increasing incidence of conjunctival melanoma over years was noted by other studies[27] in contrast to ocular melanomas[26,28].

Examining the trend of OCLG malignant tumors reveals a significant increase across the years (Table 3). This increase has been brought about in the form of an increase in lymphomas subtypes. Other histological subtypes have also shown a statistically significant annual percent increase in incidence rates, but this was not as marked as in the case of lymphomas (Figure 1). Incidence rates of lymphomas are already shown to have been increasing at most sites across the years, but at lower rates[29]. A slight drop was observed in the last five years. The higher rates of increase of lymphomas in orbit and lacrimal glands compared with other sites should be further studied. We believe that this study will help ophthalmologists during diagnosis and patient counselling by considering all tumors that affect the ocular adnexa and comparing them together in standardized settings. Furthermore, our findings can be correlated with future systemic prospective studies. Our study carries the limitations of SEER data usage that were described else-where [30-31]. Moreover, ICD-O-3 coding has limited capability of representing eye lid, structures of the eye, adnexa and orbital bones[32].

In summary, primary malignant tumors at OCLG sites comprise numerous histological subtypes. They mainly affect adults, and do so with different histologies than those affecting children. This study concludes that lymphomas are the most common primary malignant orbital tumor in the US, followed by carcinomas, melanomas and rhabdomyosarcomas. The overall trend of orbital malignant tumors has been increasing and this is attributed mainly to the rising incidence rates of lymphomas. Incidence rates differences are observed between genders with a higher overall male incidence due to differences in incidence of carcinomas. There is also a significantly higher incidence rate among Whites compared with African Americans; predominantly due to increased incidence of melanomas and carcinomas among the former. We recommend further studies focusing on demographic and geographic factors, exposure to ultraviolet rays and to carcinogens, and the effect of habits and the role of genetics on incidence rates of OCLG malignant tumors.

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