

# Trends in Malignant Lacrimal Gland Tumors And Lacrimal Sac Tumors

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## Research article

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# Abstract

**Background** Malignant tumors of the lacrimal gland and lacrimal sac are rare entities, and their incidence has been decreasing. In this study, the incidence trend was examined in relation to patient demographics of these rare tumors. **Methods** In patient data obtained from the NCI Surveillance Epidemiology and End Results (SEER) database, International Classification of Diseases for Oncology, third edition (ICD-O-3) codes for lacrimal gland and lacrimal sac tumors (C69.5) were used to identify patients with the aforementioned malignancies. Demographic data, tumor size, treatment, and outcomes were analyzed. Tumor–node–metastasis (TNM) staging subgroup analysis was conducted for patients who had received AJCC 6th edition staging at diagnosis. The trend of the incidence rate was calculated per 100,000 person-years by using the joinpoint analysis and age adjusted to the 2000 US standard population (single ages-census P25-1130). All tests of statistical significance were two-tailed, and p-value of <0.05 were considered statistically significant. **Results** The trend of lacrimal gland malignancies has decreased significantly over the years in the white patients. Among the female patients, the incidence rate was significantly lower in female white patients than in the female nonwhite patients. The 5-year survival rate was relatively higher in the patients with lacrimal gland malignancies smaller than 2.5 cm (p-value= .007). The female patients with low socioeconomic status had significantly higher incidence rates (p-value= .041) of lacrimal sac malignancies than did those with high socioeconomic status. **Conclusions** Lacrimal gland and lacrimal sac malignancies have been decreasing overall in recent years in the USA. The trend of lacrimal gland malignancies has decreased significantly over the years in the white patients. Incidence rate vary in gender, race, and socioeconomic status in lacrimal gland and lacrimal sac malignancies. Analysis of lacrimal gland and lacrimal sac malignancy trends improved our knowledge of predisposed populations as well as diagnoses.

## Backgrounds

Malignant tumors of the lacrimal drainage system are rare,<sup>1–3</sup> with an estimated annual incidence of 0.072 per 100,000 people.<sup>4</sup> These tumors have been reported to be associated with high morbidity and mortality,<sup>3,5–9</sup> and early treatment is crucial. However, diagnosis is often delayed because the symptoms, such as epiphora, a palpable mass, are often confused with those of a relatively benign etiology. Thus far, few studies have examined the incidence trends of lacrimal gland and lacrimal sac malignancies in the United States. In this study, the incidence and survival trends of patients with primary malignant tumors of the lacrimal gland and lacrimal sac were examined in a large population by using data from the population-based US National Cancer Institute’s SEER cancer registry.

## Methods

A population-based cohort analysis of patients who had received a diagnosis of primary malignant tumors in the lacrimal gland and lacrimal sac was performed using the case-listing session of the SEER 18 database ([www.seer.cancer.gov](http://www.seer.cancer.gov)). The current

SEER database, managed by the US National Cancer Institute, includes 17 cancer registries. It is an open-access resource for cancer-based epidemiology and survival analyses. The SEER\*Stat software ([seer.cancer.gov/seerstat](http://seer.cancer.gov/seerstat)), version 8.3.5, from the National Cancer Institute was used to identify patients who had received diagnoses of lacrimal gland and lacrimal sac malignancies between January 1, 2009, and December 31, 2015. Moreover, the annual percent change (APC) in rate was quantified using NCI's Joinpoint Regression Program (version 4.6.0). Because data were extracted from a public, deidentified database, this study did not require an approval from an institutional review board.

The database is a widely used cancer registry that covers an estimated 28% of the US population, and African American and Hispanic individuals constitute 23% and 40% of the covered population. Geographic regions covered include San Francisco– Oakland, Connecticut, metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, metropolitan Atlanta, San Jose–Monterey, Los Angeles, Alaska,

rural Georgia, California, Kentucky, Louisiana, New Jersey, and Greater Georgia. Patients with a primary tumor of the lacrimal gland and lacrimal sac from 2009 through 2015, the widest date range available in the latest version of the SEER software, were identified using the primary site label C69.5.

Next, we used site-specific data items (SSDIs) to discriminate between the lacrimal sac and lacrimal gland. The following primary data were extracted from the database for analysis: age at diagnosis, sex, race, socioeconomic status, marital status, tumor extent, and tumor size from both extent of disease and collaborative stage coding methods, tumor grade, tumor TNM stage, treatment methods, and 5-year survival in months. Well-differentiated and moderately differentiated histological subtypes were grouped as low-grade tumors, whereas poorly differentiated and undifferentiated histological subtypes were grouped as high-grade tumors. Lymphomas and melanomas were excluded.

The trend of the incidence rate examined using the joinpoint analysis was calculated per 100,000 person-years and age adjusted to the 2000 US standard population (single ages-census P25–1130); confidence intervals were set as 95% for rates and trends. Percentage changes were calculated using one year for each endpoint. APCs were calculated using the weighted least-squares method. APCs were calculated on the basis of the entire study duration. Because data were extracted from a public, identified database, this study did not require approval from an institutional review board. Statistical analyses were performed using SPSS (version 20, SPSS Inc, Chicago, IL, USA). Because data was extracted from a public, deidentified database, this study did not require an institutional review board approval.

## Results

### Lacrimal gland malignancy

In total, 114 patients with lacrimal gland malignancies were included in the study. Table 1 summarizes baseline patient demographics. In the patient population, 55% and 45% were male and female patients,

respectively, and 32% and 68% were white and nonwhite patients, respectively. The overall mean patient age at diagnosis was 56

± 18 years. Radiation therapy was administered to 63% of the patients, and 87% of the patients underwent surgery. Chemotherapy was administered to 24% of the patients. Among the patients with malignancies with adequate tumor staging data, the staging of 32% and 53% of the tumors was I or II and III or IV, respectively. Among the patients with data of histological tumor grades, 27% had well- or moderately differentiated tumors and 26% had poorly or undifferentiated tumors. The trend line of lacrimal gland malignancies showed a significant decrease over the years in the white patients. The average APC (AAPC) was statistically significant ( $-11.8$ ,  $p$ -value

$=.046$ ) (Table 2).

The incidence rate was significantly lower in the white female patients than in the nonwhite female patients (0.013 vs 0.024,  $p$ -value = .023); however, no significant difference was observed between the white and nonwhite male patients (0.023 vs

0.029,  $p$ -value = .492). No significant difference was observed in the lacrimal gland malignancy incidence rate when we stratified the population for analysis by sex and socioeconomic status. The 5-year survival rate in the patients with lacrimal gland malignancies was significantly higher in the subgroup p1 + p2 than in the subgroup p3 + p4 (91% vs 59%,  $p$ -value = .007). Regarding the mortality trend, overall, a decreasing trend was observed in APC ( $-4.5$ ,  $p$ -value = 0.094) (Table 3)

## Lacrimal sac malignancy

In total, 49 patients with lacrimal sac malignancies were included in the study. Table 1 summarizes baseline patient demographics. The study population comprised 53% and 47% male and female patients, respectively, and 31% and 69% white and nonwhite patients, respectively. The overall mean patient age at diagnosis was  $64 \pm 16$  years. Radiation therapy was administered to 65% of the patients, and 84% of the patients underwent surgery. Chemotherapy was administered to 14% of the patients. Among the patients with adequate tumor staging data, 14% and 65% of the malignancies were staged as I or II and III or IV, respectively. Among the patients with histological tumor grade data, 39% had well- or moderately differentiated tumors and 27% were poorly differentiated or undifferentiated tumors. A nonsignificant decrease was observed in the incidence rate of lacrimal sac malignancies.(table 4.) No

significant differences were noted in the survival rate and mortality in the subgroups after stratification by age, sex, and race (white or nonwhite). The female patients with low socioeconomic status had a significantly higher incidence rate than those with high socioeconomic status (0.004/100,000 vs 0.002/100,000,  $p$ -value = .041), whereas no significant difference was observed in the male patients with different socioeconomic status.

## Discussion

The overall incidence rate of lacrimal gland malignancies exhibited a significant decreasing trend from 2009 through 2015 in white patients. Among the female patients, the white patients had a significantly lower incidence rate than did the nonwhite patients. The patients with a lacrimal gland malignancy size of <2.5 cm had a significantly higher 5-year survival rate than did those with a tumor size of >2.5 cm. Regarding lacrimal sac malignancies, the female patients with low socioeconomic status exhibited a significantly higher incidence rate than did those with high socioeconomic status.

To our knowledge, our study is one of the few studies to describe the incidence trends of malignancies of the lacrimal gland and lacrimal sac in a large number of patients. SEER provides diverse validated databases with appropriate quality control. Besides, SEER database allows study of rare malignancies with great statistical power. We combined ICD codes and SSDIs to discriminate between malignancies of the lacrimal sac and lacrimal gland; however, other studies have overlooked differences in their anatomical locations and have included both types of malignancies by using the same code C69.5.

Two studies analyzing the epidemiology of primary lacrimal gland malignancies

based on the population-based database of the US National Cancer Institute's SEER Program have been published.<sup>5,10</sup> Both the aforementioned studies identified that adenoid cystic carcinoma is the most common malignant epithelial neoplasm of the lacrimal gland.<sup>5,10</sup> Age at diagnosis and surgical treatment are independent determinants of survival in patients with tumors of the lacrimal gland.<sup>5</sup> Tumor histology differs in survival rate and among different sex.<sup>10,11</sup> A Japanese survey on lacrimal gland cancer showed that the pathological diagnosis differed according to sex. According to the survey results, women had a higher rate of pleomorphic adenoma, whereas men had a higher rate of malignant epithelial tumor.<sup>11</sup> The proportion of lacrimal gland cancer diagnosed as lymphoma has steadily increased over time<sup>1,10</sup> and has been associated with more favorable survival rates. Currently, a study on lacrimal sac malignant tumors using the SEER database is not available. Ni et al. retrospectively studied 82 cases of lacrimal sac tumor in a single hospital. Their experience in China found malignant lacrimal sac not as rare as compared with literature and reported a high overall mortality (37.5%), high incidence of lymphatic metastasis (27%), and significant hematogenous metastasis (9.1%). Montalban et al conducted a 15-year retrospective review of malignant lacrimal sac tumor and found a high recurrence rate (29%). Parmar and Rose also conducted a retrospective review and found 40% recurrence.<sup>12</sup> High tumor staging and large size have been associated

with an increase in metastatic risk and low survival rates.<sup>13,14</sup>

One limitation of this study is the lack of laboratory data, timing, and duration of intervention. Furthermore, the SEER database does not cover the entire population. However, SEER provides demographic characteristics that adequately represent the entire US population. In future studies, we

expect to use the National Health Insurance Research Database of Taiwan, which covers 99.9% of the population of Taiwan and provides multicenter data, specific treatment protocols, and treatment duration.

The current study offers longitudinal data on a vast, diverse population of malignant lacrimal gland and lacrimal sac tumors. This epidemiological data regarding patient demographics improves our knowledge of predisposed populations for these diagnoses.

## Conclusion

Lacrimal gland and lacrimal sac malignancies have been decreasing overall in recent years in the USA. Our study revealed that the incidence of the aforementioned malignancies vary with sex, race, and socioeconomic status. The trend of lacrimal gland malignancies has decreased significantly over the years in the white patients. This analysis of lacrimal gland and lacrimal sac malignancy trend improves our knowledge of predisposed populations during diagnosis.

## Declarations

### *Abbreviations*

Not applicable

### *Ethics approval and consent to participate*

Because data was extracted from a public, deidentified database, this study did not require an institutional review board approval.

### *Competing Interests*

The authors declare no Competing Interests.

## Consent form

Not applicable

### *Availability of data and material*

A population-based cohort analysis of patients who had received a diagnosis of primary malignant tumors in the lacrimal gland and lacrimal sac was performed using the case-listing session of the SEER 18 database ([www.seer.cancer.gov](http://www.seer.cancer.gov)).

### *Funding*

Not applicable

## Authors' contributions

'WY Lai' and 'CH Yin' conceived of the presented idea. 'WY Lai' and 'CH Yin' developed the theory and performed the computations. 'CC Lee' and 'YS Lin' verified the analytical methods. 'CC Lee' encouraged 'WY Lai' to investigate and supervised

the findings of this work. All authors discussed the results and contributed to the final manuscript.

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## Tables

Table 1. Baseline characteristics of the patients according to lacrimal gland and lacrimal sac cancer from 2009 to 2015,  $n=163$

Variables	Lacrimal gland	Lacrimal sac
	<i>n</i> =114 (%)	<i>n</i> =49 (%)
Age, years (Mean±SD)	56±18	64±16
Gender		
Male	63 (55%)	26 (53%)
Female	51 (45%)	23 (47%)
Race		
White	36 (32%)	15 (31%)
Non-withe	78 (68%)	34 (69%)
pT satge		
T1+T2	37 (32%)	7 (14%)
T3+T4	60 (53%)	32 (65%)
Missing	17 (15%)	10 (21%)
pN satge		
N0	97 (85%)	43 (88%)
N1	11 (10%)	0 (0%)
Missing	6 (5%)	6 (12%)
Grade		
Well+Moderately	31 (27%)	19 (39%)
Poorly+Undifferentiated	30 (26%)	13 (27%)
Unknown	53 (47%)	17 (34%)
Operation		
Yes	99 (87%)	41 (84%)
No	15 (13%)	8 (17%)
Radiotherapy		
Yes	72 (63%)	32 (65%)
No	42 (37%)	17 (35%)
Chemotherapy		
Yes	21 (24%)	7 (14%)
No	87 (76%)	42 (86%)
Marital status		
Married	51 (45%)	26 (53%)
Non-married	47 (41%)	18 (37%)
Unknown	16 (14%)	5 (10%)
Poverty		

< 15%	60 (53%)	30 (61%)
≥ 15%	54 (47%)	19 (39%)

Table 2. Trends of the incidence rate analyzed using the joinpoint analysis based on SEER18, 2009-2015 (2000 US population).

	Trend 1			Trend 2			2009-2015	
	Years	APC	p value	Years	APC	p value	AAPC	p value
<u>Lacrimal gland</u>								
All	2009-2012	-25.8	0.084	2012-2015	25.5	0.134	-3.5	0.350
Age group								
< 65 years	2009-2015	-3.6	0.279				-3.6	0.279
≥ 65 years	2009-2015	-4.6	0.269				-4.6	0.287
Gender								
Male	2009-2011	-41.0	0.089	2011-2015	22.3	0.088	-4.1	0.351
Female	2009-2015	-6.6	0.151				-6.6	0.151
Race								
White	2009-2015	-11.8	0.046				-11.8	0.046
Non-white	2009-2012	-27.4	0.051	2012-2015	35.9	0.055	-0.7	0.450

Table 3. Trend of the mortality rate analyzed using the joinpoint analysis based on SEER18, 2009-2015 (2000 US population).

	Trend		
	Years	APC	p value
<u>Lacrimal gland</u>			
All	2010-2015	-4.5	0.094
Age group			
< 65 years	2010-2015	-5.5	0.230
≥ 65 years	2010-2015	-3.4	0.234
Gender			
Male	2010-2015	3.1	0.394
Female	2010-2015	-8.5	0.176
Race			
White	2009-2015	-11.3	0.084
Non-white	2009-2012	11.9	0.130

Table 4. Trend of the incidence rate analyzed using the joinpoint analysis based on SEER18, 2009-2015 (2000 US population).

	Trend 1		Trend 2		2009-2015	
	Years	APC <i>p</i> value	Years	APC <i>p</i> value	AAPC <i>p</i> value	
<u>Lacrimal sac</u>						
All	2009-2015	-1.5	0.451		-1.5	0.451
Age group						
< 65 years	2009-2015	3.9	0.382		3.9	0.382
≥65 years	2009-2015	-8.5	0.272		-8.5	0.272
Gender						
Male	2009-2015	-5.9	0.341		-5.9	0.341
Female	2009-2015	2.6	0.415		2.6	0.415
Race						
White	2009-2015	-4.1	0.304		-4.1	0.304
Non-white	2009-2015	-1.5	0.461		-1.5	0.461