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Population-Based Incidence of Conjunctival Tumors in Olmsted County, Minnesota

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Abstract

Aim: To determine population-based incidence of conjunctival tumors in Olmsted County, Minnesota.

Methods: The Rochester Epidemiology Project (REP) medical record linkage system was used to identify patients with conjunctival tumors in Olmsted County (1/1/1980–12/31/2015). Records were reviewed for demographics, types of tumors, histopathology, treatment, and clinical course. Incidence rate of all tumors was calculated per 1,000,000 person-years. Poisson regression analysis was used to assess changes in incidence over time.

Results: There were 504 patients with conjunctival tumors, giving an age- and sex-adjusted incidence rate of 125 per 1,000,000 (CI 113.5–135.5). Incidence increased over time ($p < 0.001$). Most tumors (474, 94%) were benign. Of benign lesions, melanocytic lesions accounted for the majority (431, 86%), with adjusted incidence rates of 10.8 (CI 7.7–13.9) for complexion-associated melanosis, 49.7 (CI 42.9–56.6) for nevus, and 44.1 (37.5–50.8) for primary acquired melanosis. Malignant lesions were rare (30, 6%) with 6 cases of melanoma, 21 cases of ocular surface squamous neoplasia (OSSN), 1 case of Langerhans cell histiocytosis, and 2 cases of lymphoma. Adjusted incidence rates of conjunctival melanoma and OSSN were 1.5 (CI 0.3–2.8) and 6.1 (CI 3.5–8.7), respectively. Outcomes for melanoma (mean follow-up 14 years, range 0–34) and OSSN (mean follow-up 4 years, range 0–24) were favorable in 29 cases, with 1 fatality due to metastatic melanoma.

Conclusions: In a population-based setting, most conjunctival tumors are benign, and the majority of lesions are melanocytic. While it is important to remain vigilant for malignancies, most conjunctival lesions in a community-based practice are not life-threatening.

Keywords

conjunctiva; primary acquired melanosis; melanoma; ocular surface squamous neoplasia; tumor; nevus; epidemiology

INTRODUCTION

A wide variety of benign and malignant tumors occur in the conjunctiva.[1 2] While there have been several large series examining conjunctival lesions in the United States, these reports are primarily from tertiary care centers, making them subject to referral bias.[1–4] Given that some lesions can be life-threatening, such as conjunctival melanoma, which carries a 25–30% mortality rate,[5 6] population-based data on the incidence of these tumors is important information for practicing physicians.

Current population-based studies reviewing conjunctival melanoma originate mainly from Scandinavia and estimate the annual incidence to be between 0.06 and 0.52 cases per 1,000,000, with an increasing incidence over the past several decades.[5–10] The incidence of ocular surface squamous neoplasia (OSSN) has ranged from less than 0.1 cases per 1,000,000 in women in North America to 35 per 1,000,000 in Uganda,[11–16] and incidence rates are higher with male sex, residence closer to the equator, and infection with human immunodeficiency virus (HIV).[2 16] Although these prior studies have provided valuable information, a United States population-based study would add important insights to the literature.

The Rochester Epidemiology Project (REP) captures the medical records of nearly all residents of Olmsted County, MN, and therefore affords an excellent opportunity to determine the incidence of conjunctival tumors in a population-based manner in the United States. In this study, we used the REP database to determine the incidence of benign and malignant conjunctival tumors in Olmsted County patients.

MATERIALS AND METHODS

This retrospective study used the REP medical records linkage system, which is a database currently consisting of 148,201 unique residents of Olmsted County, MN, to identify residents with conjunctival tumors. Queries yield only subjects who have authorized medical records review for research. While Mayo Clinic and Olmsted Medical Center provide the majority of medical care in Olmsted County, small independent clinics also participate in the REP, allowing capture of nearly all county residents.[17 18] Private optometry offices are not included. The database is not biased toward patients with health conditions that require more frequent monitoring, and it has excellent agreement for patient status at last contact, date of last contact, and date of death when compared with manual record abstraction.[19 20] This study complied with the Health Insurance Portability and Accountability Act (HIPAA) and was approved by the Institutional Review Boards of Mayo Clinic and Olmsted Medical Center.

All patients diagnosed with any type of conjunctival lesion between January 1, 1980 and December 31, 2015 were identified by searching the REP database for 25 unique H-ICDA, 8 unique ICD-9, and 24 unique ICD-10 codes (eTable 1). Cases were only included if diagnoses were made or confirmed by an ophthalmologist or optometrist, and if they represented benign or malignant tumors. Because our initial search criteria were broad, we reviewed all cases to ensure all tumors were included while excluding degenerative lesions,

conjunctivitis, cysts, phlyctenules, pingueculae, pterygia, granulomata, and depositions. For study inclusion purposes, complexion-associated melanosis was defined as bilateral diffuse pigmentation in a patient of any age with no documentation of change in lesion appearance over time; conjunctival nevus was defined as a single well-circumscribed, cystic lesion or, if non-cystic, required patient age to be 30 years or younger at the time of initial diagnosis; and primary acquired melanosis was defined as single or multiple, unilateral, non-cystic, flat pigmented lesions first documented in white patients older than age 30, or if age 30 or younger required a prior eye exam with no noted lesions. During medical record review, data were collected regarding patient demographics, past medical history, ocular findings, clinical impression, treatment, and histopathology when available. Tumors were categorized based on the histopathologic diagnosis or the clinical diagnosis when histopathology was not available.

Lesions were divided into benign and malignant. While benign melanocytic lesions, such as primary acquired melanosis, can transform into malignant melanoma, these lesions were classified as benign in this study and followed for transformation into melanoma during the study period. Malignant tumors were categorized as melanocytic (malignant melanoma), premalignant/malignant epithelial (OSSN), lymphoma, or Langerhans cell histiocytosis. When available, biopsy specimens of malignant lesions and primary acquired melanosis with atypia were retrieved and reviewed by an ophthalmic pathologist (DRS) to confirm and better characterize diagnoses. The age- and sex-adjusted incidence rate of all conjunctival tumors was calculated, as were the specific incidence rates for melanoma, OSSN, and each additional subtype of tumor that had 20 or more cases, by dividing the number of new cases by the number of patients at risk per unit time, given by the population in Olmsted County during the years studied. Statistical Analysis System 9.4 (SAS, Cary, NC, USA) was used to calculate 95% confidence intervals (CI) for incidences. Results are reported as cases per 1,000,000 person-years, and are age- and sex-adjusted to the 2010 United States general population rates. When applicable, the Poisson regression test was used to analyze changes in incidence over time.

RESULTS

There were 3,369 patients in the REP database diagnosed with a conjunctival lesion between January 1, 1980 and December 31, 2015. Medical record review confirmed the presence of a conjunctival lesion in 919 cases. Of these, we excluded 173 pingueculae, 173 cysts, 50 pterygia, 15 granulomata, 3 phlyctenules, and 1 case of chronic conjunctivitis. This yielded 504 cases of conjunctival tumor, of which 248 (49%) were in males. Most patients were white (388, 76%), with 50 (10%) Asian, 30 (6%) black, 39 (8%) other races, and 2 (<1%) with unknown race. The age- and sex-adjusted incidence rate of all conjunctival tumors was 125 per 1,000,000 (CI 113.5–135.5), and this increased over the course of the study period from 36.8 (CI 23.6–49.9) in the 1980s, to 153.6 (CI 129.0–178.5) in the 1990s, to 170.9 (CI 148.2–193.6) from 2000–2009 (Figure 1). Although the incidence appeared to decrease to 109.0 (CI 87.2–130.8) between 2010 and 2015, the increasing trend across the entire period (1980 to 2015) was significant ($p < 0.001$). In men and women, the adjusted incidence rates of all types of conjunctival tumors were 130.9 (CI 114.3–147.4) and 120.1 (CI 105.3–134.9), respectively.

Benign Conjunctival Lesions

Most conjunctival tumors were benign ($n = 474$, 94%, Table 1). Mean follow-up for all benign tumors was 8 ± 8 years (mean $\pm$ standard deviation; range, 0–36 years).

Benign lymphoid hyperplasia and primary acquired melanosis were classified as benign but can be considered to be premalignant. There were 3 cases of primary acquired melanosis with mild atypia and none with severe atypia. No benign lesions progressed to malignancy.

Benign Melanocytic Conjunctival Lesions—The adjusted incidence of complexion-associated melanosis was 10.8 per 1,000,000 person years (CI 7.7–13.9), with an overall increase in incidence rate over the study period ($p < 0.001$, Figure 1). The adjusted incidences for men and women, respectively, were 8.3 (CI 4.3–12.1) and 13.3 (CI 8.5–18.1). None of these lesions showed clinically-appreciable changes over time, with follow-up of 6 ± 8 years (range, 0–29 years).

The adjusted incidence rate of conjunctival nevus was 49.7 per 1,000,000 person years (CI 42.9–56.6), with adjusted rates of 54.8 (CI 44.3–65.4) and 45.6 (CI 36.6–54.6) for men and women, respectively. The incidence rate increased over the study period ($p < 0.001$, Figure 1). Mean available follow-up was 6 ± 7 years (range 0–35), with 59 patients (28%) having less than 1 year of follow-up, 58 (28%) having 1–5 years, 44 (21%) having 6–10 years, 19 (9%) having 11–15 years, and 30 (14%) having >15 years. No nevus had documented growth or malignant transformation during the available follow-up period.

The adjusted incidence rate of primary acquired melanosis was 44.1 per 1,000,000 person years (CI 37.5–50.8) with overall increasing incidence over time ($p < 0.001$, Figure 1). Adjusted incidence rates for men and women, respectively, were 40.6 (CI 31.4–49.9) and 47.0 (CI 37.5–56.4). Due to lack of clinical suspicion, only 18 cases (10%) were biopsied. Three biopsies revealed mild atypia (low-risk), with no biopsies showing atypia of greater severity (high-risk). Mean available follow-up was 9 ± 8 years (range 0–27), with 32 patients (18%) having less than 1 year of follow-up, 39 (22%) having 1–5 years, 36 (21%) having 6–10 years, 31 (18%) having 11–15 years, and 36 (21%) having >15 years. No patient with primary acquired melanosis progressed to malignant melanoma.

Malignant Conjunctival Lesions

Malignant lesions accounted for 30 (6%) tumors with most being squamous in origin (Table 1). All lesions were primary, and recurrences are indicated in Tables 2 and 3 for conjunctival melanoma and OSSN respectively.

Malignant Melanocytic Conjunctival Lesions—The adjusted incidence rate of conjunctival melanoma in this population was 1.5 per 1,000,000 person years (CI 0.3–2.8). There were too few cases to ascertain a change in incidence over time, with 1 case diagnosed in 1982, 4 in the 1990s, and 1 in 2012 (Figure 1). The adjusted incidence rate for men was 2.9 (CI 0.2–5.6) and for women was 0.4 (CI 0.0–1.1). After mean follow-up 14 years (range 0–34) 5 patients (83%) did well, but 1 patient (17%) required exenteration for recurrence with orbital involvement and later died from metastatic disease (Table 2, eFigure 1).

Premalignant or Malignant Conjunctival Epithelial Lesions—The adjusted incidence rate of OSSN was 6.1 per 1,000,000 person years (CI 3.5–8.7), and the incidence rate appeared to remain stable over time (Figure 1). Adjusted incidence rates for men and women were 12.4 (CI 6.8–28.0) and 1.0 (CI 0.0–2.4), respectively. After mean follow-up of 4 years (range 0–24), 1 patient had recurrent disease, and no patient developed ocular or orbital invasion or metastases (Table 3).

No patients were immunocompromised or had HIV. All lesions were located on the interpalpebral bulbar conjunctiva.

Other Malignant Conjunctival Lesions—There was 1 case of biopsy-proven Langerhans cell histiocytosis in a 35-year-old patient with 7 months of available follow-up and no systemic Langerhans cell histiocytosis (eFigure 2). There were 2 cases of biopsy-proven lymphoma: 1 follicular lymphoma in a white patient in their eighth decade with known systemic lymphoma and 1 diffuse large B cell lymphoma in a white patient in their sixth decade with no known systemic disease and only 1 month of follow-up.

DISCUSSION

This study provides important population-based data regarding the incidence of conjunctival tumors in the United States. The most frequently encountered tumors were benign melanocytic lesions, including nevus (41% of all conjunctival tumors), primary acquired melanosis (34%), and complexion-associated melanosis (9%). Non-pigmented benign conjunctival tumors were less common, accounting for only 9% (48) of all conjunctival tumors and 10% of benign lesions, similar to results from referral centers.[1 2] Benign conjunctival tumors occurred with similar frequency in men and women except for complexion-associated melanosis (more common in women), which might reflect a tendency for women to have more frequent health maintenance visits than men.[21] Tumors (except for complexion-associated melanosis) were most common in white patients, which is likely a reflection of the demographics of Olmsted County.

Regarding primary acquired melanosis, only 18 cases (10%) were biopsied in this series, with 3 cases having mild atypia. The risk of progression to malignant melanoma for primary acquired melanosis has been reported to range from 0% in lesions without atypia to 13% when severe atypia is present.[22] In this series none of the 174 total cases of primary acquired melanosis progressed to malignant melanoma during the available follow-up period, which was 11 years in 39% of cases and 6 years in 60% of cases. There was evidence of malignant melanoma arising from primary acquired melanosis with atypia in 3 of the patients with conjunctival melanoma, but these cases presented as clinically-suspicious or changing lesions. No other benign tumors in this series transformed into malignancy after mean follow-up of 8 years, providing reassurance that in a population-based setting, most conjunctival lesions, including primary acquired melanosis and nevus without worrisome or changing clinical features, may be observed.

Malignant tumors were most common in middle-aged, white men. As anticipated, malignancies accounted for a much smaller percentage (6%) of all tumors in this population-

based study than in series from tertiary referral centers, where over 15% and, in some cases, greater than one third of all lesions harbored malignancy.[1 2 4] Even though we found few malignancies compared to benign lesions, OSSN (4%) was the fourth most frequently occurring tumor in our study.

The adjusted incidence rate of conjunctival melanoma in this study (1.5 per 1,000,000, CI 0.3–2.8) was similar to adjusted incidence rates in Denmark, which were as high as 2.12 per 1,000,000 (CI 1.23–3.65) in the 2000–2009 time period.[7] This was the expected result given the similar demographics and analogous climate of our population compared to those examined in previously (Table 4).[5–10] Numbers were too small to determine if there was any change in incidence over time in our study. However, other studies reported increasing incidence of conjunctival melanoma, possibly related to better provider reporting and recognition along with increased exposure to ultraviolet radiation.[6–9]

The adjusted incidence rate of OSSN (6.1 per 1,000,000, CI 3.5–8.7) was toward the lower end of the reported range (0.1–35 per 1,000,000),[11–16] which was expected for our North American population with low HIV prevalence (Table 4). Although we had small numbers, the incidence rate of OSSN appeared stable over time, in contrast to the increasing incidences in Uganda and Zimbabwe, which may be on the rise secondary to increased exposure to ultraviolet light as well as increased rates of infection with HIV and papillomavirus.[16 23]

We suspect the increasing incidence of all conjunctival tumors in our population was secondary to improved provider awareness and documentation of benign lesions, as the study design relied on what was reported in the medical records. While other studies reported increasing incidences of conjunctival melanoma, OSSN, and lymphoma,[6 16 23 24] we did not find increasing rates of these specific tumors. Although our incidence rate from 2010–2015 appeared to decrease, we suspect this was an artifact, possibly explained by more patients seeking routine and primary eye care at private optometry offices, which are not captured in the REP database.

While informative, our study is not without limitations. Because the population of Olmsted County is predominantly white, results are most reasonably extrapolated to the semi-urban United States white population. Population-based data from Olmsted County are similar to data from other United States communities,[17] and in 2010, 72% of the total United States population was white,[25] supporting this extrapolation. However, the northern latitude of Olmsted County must also be considered, as patients living in the southern part of the United States may have different risk factors, such as increased sun exposure, that could alter the incidence and risk of malignant transformation for some conjunctival lesions. Other limitations of this study include its retrospective nature and reliance on provider recognition and clinical documentation for diagnoses. When biopsies were not performed and no photographs were available, clinical descriptions alone were the basis for diagnosis, which was the case for the majority of benign tumors. Finally, the small number of conjunctival malignancies may have influenced our incidence rates, but we reported confidence intervals that aligned with incidence rates in previous studies. It is also possible that our incidence rates for benign lesions might be underestimated if some patients did not seek medical care,

were unaware of their condition, or were seen at private optometry offices without referral to an ophthalmologist.

This study provides valuable epidemiologic data regarding the incidence rates of conjunctival tumors in the United States. The data are directly applicable to general ophthalmologists encountering conjunctival tumors in a population-based primary eye care setting. While most tumors are benign, with low risk for malignant transformation, subspecialty referrals should be made in the setting of changing appearance or worrisome features.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SYNOPSIS

In a population-based study, the incidence of conjunctival tumors increased between 1980 and 2015. Most tumors (94%) were benign and there was only one fatality from conjunctival melanoma over a 35 year period.

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Fig. 1: Change in incidence rate of conjunctival tumors over time. The incidence rates per million person-years of all conjunctival tumors, complexion-associated melanosis (CAM), nevus, and primary acquired melanosis (PAM) increased from 1980 to 2015 ($p < 0.001$).

Table 1:

Types of conjunctival tumors (504) and patient demographics in Olmsted County, MN.

Type of Tumor	Number of Patients (%)	Histo-pathology Available	Mean Age (years) [Range]	Race					
				Male	White	Asian	Black	Other	Refused
BENIGN	479 (94%)								
Dermoid	6 (1%)	0	14 [13–17]	2	5	0	0	1	0
Dermolipoma	5 (1%)	0	37 [1–54]	1	4	0	0	1	0
Benign epithelial hyperplasia	3 (<1%)	3	56 [42–66]	0	3	0	0	0	0
Hemangioma, acquired sessile	2 (<1%)	1	50 [29–70]	0	2	0	0	0	0
Hemangioma, cavernous	1 (<1%)	0	13	0	1	0	0	0	0
Leiomyoma	1 (<1%)	1	36	0	1	0	0	0	0
Lipoma	1 (<1%)	0	13	1	1	0	0	0	0
Lymphangiectasia	3 (<1%)	0	48 [32–65]	3	3	0	0	0	0
Benign lymphoid hyperplasia	3 (<1%)	3	42 [9–75]	2	3	0	0	0	0
Oncocytoma	1 (<1%)	1	88	1	1	0	0	0	0
Osseous choristoma	1 (<1%)	1	1	1	0	0	0	1	0
Papilloma	16 (3%)	11	40 [10–75]	9	15	1	0	0	0
Melanocytic	431 (86%)								
Complexion-associated melanosis	47 (9%)	0	38 [8–70]	16	0	12	16	19	0
Nevus	210 (42%)	29	40 [1–90]	107	160	24	12	14	0
Primary acquired melanosis	174 (35%)	18	51 [15–99]	78	156	11	2	3	2
MALIGNANT	30 (6%)								
Malignant Melanocytic									
Melanoma	6 (1%)	6	54 [34–83]	5	6	0	0	0	0
Premalignant/Malignant epithelial									
OSSN	21 (4%)	16	67 [29–87]	19	20	1	0	0	0
Other Malignant	3 (<1%)								
Langerhans cell histiocytosis	1 (<1%)	1	35	1	1	0	0	0	0
Lymphoma	2 (<1%)	1	59 [45–73]	1	2	0	0	0	0

Table 2:

Clinical characteristics and follow-up of patients with conjunctival melanoma

Case	Sex	Race	Smoking Status	Age at Diagnosis (years)	Follow-up (years)	Presenting Signs/Symptoms	Location	Initial Treatment	Pathology	Additional Treatment and Outcome
1	M	White	Unknown	37	1	None, found on routine examination	Left plica semilunaris	Excision, cryotherapy	Invasive melanoma *	None, no recurrence
2	M	White	Never	83	3	Itching, pigment on exam 8 months prior with interval growth and thickening	Right inferior bulbar	Excision, cryotherapy	Invasive melanoma arising from PAM with atypia	Exenteration with adjuvant radiation for recurrence with orbital involvement 10 months later; death due to metastatic disease 2 years after exenteration
3	M	White	Unknown	59	15	Patient noted growth of pigmented lesion 3 years prior	Left temporal bulbar	Excision, cryotherapy, conjunctival graft, map biopsies	Invasive melanoma *	None, no recurrence
4	F	White	Former	34	13	Pigment on exam 3 years prior with interval growth	Left temporal bulbar	Excision, cryotherapy	Invasive melanoma arising from PAM with atypia	2 repeat excisions with cryotherapy due to positive margins followed by 1 week of topical mitomycin C, then no further recurrence
5	M	White	Former	41	34	None, found on routine examination	Right temporal bulbar	Excision, cryotherapy	Invasive melanoma *	None, no recurrence
6	M	White	Former	69	10	Pigment on exam 4 months prior with interval growth	Right temporal bulbar	Excision, cryotherapy	Invasive melanoma arising from PAM with atypia	Repeat excision for positive margins 3 times, then no further recurrence

M, male; F, female; PAM, primary acquired melanosis;

* histopathology slides could not be retrieved for review

Clinical characteristics and follow-up of patients with ocular surface squamous neoplasia (OSSN).

Table 3:

Case	Sex	Race	Smoking Status	Age at Diagnosis (years)	Follow-up (years)	Presenting Signs/Symptoms	Location	Initial Treatment	Pathology	Additional Treatment and Outcome
1	M	White	Former	67	2	None, found on routine examination	Right	Excision, cryotherapy	CIN, severity not specified*	Repeat excision with cryotherapy for recurrence 1 year later, then no further recurrence
2	M	White	Unknown	69	1	None, found on routine examination	Left	Excision, cryotherapy	CIS	None, no recurrence
3	M	White	Current	52	0	FB sensation	Left temporal	Excision, cryotherapy	CIS	Repeat excision with cryotherapy due to residual tumor at margins, then no recurrence
4	M	White	Unknown	52	0	None, found on routine examination	Left	Excision, cryotherapy	CIN, severity not specified*	None, no recurrence
5	M	White	Current	71	0	None, found on routine examination	Right	Excision, cryotherapy	CIS	None, no recurrence
6	M	White	Former	76	9	None, found on routine examination	Right temporal	Excision, cryotherapy	CIS	None, no recurrence
7	M	White	Unknown	87	5	FB sensation	Left temporal	Excision, cryotherapy	CIN, severe dysplasia	None, no recurrence
8	M	White	Unknown	77	0	None, found on routine examination	Right	Excision, cryotherapy	CIS	None, no recurrence
9	M	White	Former	81	2	None, found on routine examination	Left temporal	Excision, cryotherapy	CIS	None, no recurrence
10	M	White	Never	62	4	Patient noticed a red spot on eye	Left temporal	Excision, cryotherapy	CIN, moderate dysplasia	Adjuvant topical mitomycin C, no recurrence
11	F	White	Never	62	7	None, found on examination for uveitis	Right nasal	Incisional biopsy	CIN, severe dysplasia	Adjuvant topical mitomycin C, no recurrence
12	F	White	Former	29	1	None found on routine examination	Left nasal	Excision, cryotherapy	CIN, severity not specified*	None, no recurrence
13	M	White	Never	58	4	None, found on routine examination	Right nasal	Excision, cryotherapy	CIN, severe dysplasia	None, no recurrence
14	M	White	Former	82	1	None, found on routine examination	Right nasal	Topical mitomycin C	-	None, no recurrence

Case	Sex	Race	Smoking Status	Age at Diagnosis (years)	Follow-up (years)	Presenting Signs/Symptoms	Location	Initial Treatment	Pathology	Additional Treatment and Outcome
15	M	White	Former	86	6	None, found on routine examination	Left temporal	Excision, cryotherapy	CIS	Adjuvant topical mitomycin C, no recurrence
16	M	White	Former	75	5	Conjunctivitis	Left nasal	Topical mitomycin C	-	None, no recurrence
17	M	White	Former	79	0	FB sensation	Right temporal	None - patient declined biopsy	-	Lost to follow-up
18	M	White	Former	55	24	Mattering	Left temporal	Excision, cryotherapy	CIN, severity not specified *	None, no recurrence
19	M	Asian	Never	59	0	None, found on examination for vitreous detachment	Left temporal	None - patient no-showed for treatment	-	Lost to follow-up
20	M	White	Former	62	6	FB sensation	Left nasal	Topical mitomycin C	-	None, no recurrence
21	M	White	Unknown	67	17	Growth on eye	Right nasal	Excision, cryotherapy	CIN, severe dysplasia	None, no recurrence

M, male; F, female; FB, foreign body; CIN, conjunctival intraepithelial neoplasia; CIS, carcinoma in situ;

* histopathology slides could not be retrieved for review

Table 4:

Incidence rates of conjunctival melanoma and ocular surface squamous neoplasia (OSSN).

Study	Melanoma					OSSN					High HIV Prevalence	
	Location	Years	Cases (n)	Incidence (per million)	Incidence Increasing	Study	Location	Years	Cases (n)	Incidence (per million)		Incidence Increasing
Norregaard[5]	Denmark	1960–1980	42	0.52 ^a	unknown	Newton[15]	global	1968–1992	unknown	0.00–13.93	unknown	variable
Triay[6]	Sweden	1960–2005	89 men 81 women	0.10–0.74 0.06–0.45	yes yes	Ateenyi-Agaba[16]	Uganda	1970–1991	48	6–35	yes	yes
Larsen[7]	Denmark	1960–2012	138	0.5 adjusted rates 0.75–2.12	yes	Sun[14]	USA	1973–1990	124	0.3	unknown	no
Tuomaala[8]	Finland	1967–2000	85	0.51	yes	Lee[13]	Brisbane, Australia	1980–1989	139	19	unknown	no
Yu[9]	USA	1973–1999	206	0.22–0.43	^b yes	Emmanuel[11]	USA	1995–2006	40	8.4	unknown	no
Hu[10]	USA	1992–2003	168	0.15–0.49	unknown	Furahini[12]	Tanzania	2006–2008	729 suspected cases	22	unknown	yes
Dalvin	Olmsted County, MN, USA	1980–2015	6	1.5	unknown	Dalvin	Olmsted County, MN, USA	1980–2015	21	6.1	no	no

^aCalculated using 42 cases of malignant melanoma plus 13 patients with primary acquired melanosis with atypia.

^bIncidence rates increased in men, whites, and persons older than 40 years.