AMERICAN ACADEMY OF OPHTHALMOLOGY®

Prevalence of and Associated Factors for Eyelid Cancer in the American Academy of Ophthalmology Intelligent Research in Sight Registry

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Purpose: To estimate the prevalence of eyelid cancers in the American Academy of Ophthalmology Intelligent Research in Sight (IRIS) Registry and evaluate the associated factors.

Design: Retrospective IRIS Registry database study.

Participants: All patients in the IRIS Registry between December 1, 2010, and December 1, 2018, with International Classification of Disease, ninth and 10th revisions, codes for eyelid cancers (basal cell carcinoma [BCC], squamous cell carcinoma [SCC], malignant melanoma [MM], sebaceous carcinoma/other specified malignant neoplasm [SBC], melanoma in situ [MIS], and unspecified malignant neoplasm [UMN]).

Methods: The prevalence of each eyelid cancer type was estimated overall and by age group, sex, race, ethnicity, and smoking status. The associations between any eyelid cancer (AEC) or each cancer type and possible risk factors were examined using univariate and multivariate logistic regression models.

Main Outcome Measures: Prevalence of and associated factors for each eyelid cancer type.

Results: There were 82 136 patients with eyelid cancer identified. The prevalence of AEC was 145.1 per 100 000 population. The cancer-specific prevalence ranged from 87.9 (BCC) to 25.6 (UMN), 11.1 (SCC), 5.0 (SBC), 4.1 (MM), and 0.4 (MIS) per 100 000 population. The prevalence of AEC and each cancer type increased with increasing age (all $P < 0.0001$), and the prevalence of AEC, BCC, SCC, and MM was higher in males (all $P < 0.0001$), MIS ($P = 0.02$). The prevalence of BCC, SCC, MM, SBC, and AEC was highest in Whites versus that in patients of any other race (all $P < 0.0001$). In the multivariate logistic regression model with associated risk factors (age, sex, race, ethnicity, and smoking status), AEC was associated with older age groups ([< 20 years reference {ref.}]; odds ratio [95% confidence interval]: 20–39 years: 3.35 [1.96–5.72]; 40–65 years: 24.21 [14.80–39.59]; and > 65 years: 42.78 [26.18–69.90]), male sex (female [ref.]; 1.40 [1.33–1.48]), White race (inverse associations with African Americans [0.12 {0.09–0.16}], Asians [0.19 {0.13–0.26}], others [0.59 {0.40–0.89}]), and ethnicity (non-Hispanic [ref.]; Hispanic: 0.38 [0.33–0.45]; unknown: 0.81 [0.75–0.88]). Active smoking (never smoker [ref.]) was associated with AEC (1.11 [1.01–1.21]), BCC (1.27 [1.23–1.31]), SCC (1.59 [1.46–1.73]), and MM (1.26 [1.08–1.46]).

Conclusions: This study reports the overall and cancer-specific prevalence of eyelid cancers using a large national clinical eye disease database. Smoking was found to be associated with AEC, BCC, SCC, and MM, which is a new observation. This epidemiologic profile of on-eyelid cancers is valuable for identifying patients at a higher risk of malignancy, allocating medical resources, and improving cancer care. *Ophthalmology Science 2023;3:100227*

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Eyelid cancer represents a relatively common neoplasm reported in ophthalmic practice. In a population-based epidemiologic study using a medical records linkage system in Minnesota, United States (US), 174 patients with newly diagnosed eyelid cancer were identified over a 15-year period, and an incidence rate of 15.7 cases per 100 000 population per year was found for all eyelid cancers.[1] Another population-based study using cancer registry data from Taiwan to evaluate 1166 patients with eyelid cancer over 21 years showed that the annual incidence rate rose from 15 per 100 000 in 1979 to 51 per 100 000 in 1999.[2] In these studies, the cohort sizes were too small to determine the actual incidence of each specific eyelid cancer, and risk factors and sociodemographic associations were not evaluated.

Although studies on discrete diagnostic groups, such as eyelid melanoma alone, exist,[3] the available data on the

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prevalence and demographic characteristics of eyelid cancers are based on data from a number of tertiary care centers and are limited by referral biases and the demographic characteristics of the local and referral communities compared with data from national clinical registries.[4–6] Thus, the frequency and characteristics of each eyelid cancer may vary depending on an institution's reporting nature or geographic region. Age, male sex, cigarette smoking, and excessive exposure to ultraviolet light have been suggested as possible risk factors for basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma (MM) eyelid cancers[5,7]; however, robust data on such risk factors are scarce. Understanding the role of demographics is critical for clinical assessment, and identification of associated risk factors may help modify these risk factors.

The American Academy of Ophthalmology Intelligent Research in Sight (IRIS) Registry is the world's largest electronic health record-based single medical specialty registry and includes deidentified data on demographic records and tobacco use status from > 422 990 000 visits from approximately 71 900 000 unique patients (as of January 2022).[8] The availability of the IRIS Registry provides an opportunity to simultaneously study rare conditions (and associated diagnoses) on a larger scale than previously possible, as demonstrated by recent publications that investigated the visual outcomes of age-related macular degeneration, the incidence of endophthalmitis after cataract surgery, and ophthalmic adverse effects of checkpoint inhibitors.[9–11] The aim of this study was to leverage the IRIS Registry to evaluate the overall and cancer-specific prevalence of eyelid cancers by age, sex, race, ethnicity, smoking, geographic region, and laterality.

Methods

Data Source and Environment

The methods of data collection and aggregation of the IRIS Registry database have been previously described.[12] Access to American Academy of Ophthalmology IRIS Registry data was given to selected academic centers as participants of IRIS Registry Analytic Center Consortium, and the version of the database used was Rome (version 2). This study was conducted in accordance with the Declaration of Helsinki. Given the use of deidentified data, this project was exempted from review by the Wills Eye Hospital Institutional Review Board. The database was queried using Structured Query Language (SQL) (PostgresSQL, version 8.0.2), and all analyses were performed in the Amazon Web Services Virtual Private Cluster environments.

Study Population and Prevalence Estimation

All patients in the IRIS Registry with a diagnosis of eyelid cancer or those who had undergone a procedure for the treatment of eyelid cancer between December 1, 2010, and December 1, 2018, were considered for these analyses. In the IRIS Registry and by the nature of this database, we could not confirm that these were incidence rates; therefore, we included all cases and reported them as prevalence rates. The patients were categorized by eyelid cancer type based on relevant International Classification of Disease (ICD), ninth and 10th revisions, codes (Table S1, available at www.ophthalmologyscience.org/). International Classification of Disease-9 and ICD-10 codes were used to classify the patients. The prevalence numerator was calculated as the number of patients with ≥ 1 diagnosis of eyelid cancer between 2010 and 2018, while the denominator consisted of all patients in the IRIS Registry with ≥ 1 diagnosis or 1 procedure (of any kind) during the same time frame. The patients were labeled as having multiple cancers if they had ≥ 2 different types of eyelid cancers (in any eye) during the time frame. Both the numerator and denominator omitted patients with missing information about sex and patients with missing information about their year of birth. For patients included in the numerator, their age was calculated as the difference between the year of their first diagnosis of eyelid cancer and their year of birth, and for patients without eyelid cancer, the age was calculated as the difference in the year of their last diagnosis observed between 2010 and 2018 (or procedure if no diagnosis was found) and the year of their birth. The group without eyelid cancer was observed until the last follow-up date to ensure that the patients in this group did not develop eyelid cancer at any point. Race and ethnicity were listed as separate variables in the IRIS Registry database; thus, both were reported. The prevalence rate of each eyelid tumor was calculated within each race category. All prevalence estimates and ensuing statistical analyses were patient based and not eye based.

Statistical Analysis

The data of the prevalent cohort were presented as percentage or per 100,000 population and stratified by age (< 20, 20–39, 40–65, and > 65 years), sex (female and male), race (White, African American, Asian, unknown, and other), ethnicity (Hispanic, non-Hispanic, and unknown), and smoking status (never, former, and active). Laterality (right versus [vs.] left) and eyelid location (upper vs. lower) were defined based on ICD-10 codes (Table S1).

Smoking status was based on smoking history on or before the first diagnosis of eyelid cancer, along with a hierarchy when necessary. If a patient only had 1 type of smoking status recorded on or before their first diagnosis of eyelid cancer, that patient was assigned to that smoking status group. If a patient had > 1 type of smoking status recorded on or before their first diagnosis of eyelid cancer, the patient's most recent smoking status (relative to their eyelid cancer diagnosis) was used to classify the patient, e.g., "active" or "former." If a patient's most recent smoking status was recorded as "never" after that patient had been classified as active or former, that patient was considered a former smoker. In cases that were still ambiguous (e.g., a patient had 2 different smoking statuses that occurred on the same most recent date), we employed a hierarchical algorithm that favored assigning that patient as a former smoker over never smoker and never smoker over active smoker. This hierarchy was utilized to be conservative with respect to assigning a patient as an active smoker.[13] Patients with missing smoking status (N = 8 618 512) were excluded from the univariate analyses for smoking status as well as the multivariate analyses.

The factors potentially associated with eyelid cancers (age, sex, race, ethnicity. and smoking history) were evaluated by comparing their distributions between cases of eyelid cancer and those without using the chi-square test and Fisher exact test where appropriate and by calculating the odds ratios (ORs) and 95% confidence intervals (CIs) using univariate and multivariate logistic regression. Receiver operating characteristic curves were used to compute the area under the curve (AUC) to assess model fit. All statistical analyses were performed using R, version 3.6.0.

Results

All patients in the IRIS Registry with a diagnosis of eyelid cancer (N = 60 995 367) were evaluated. After excluding patients with unknown or indeterminable age (e.g., diagnosis happened before birth) (N = 4 242 973) and those with missing information about sex (N = 142 020), the final sample size was 56 610 374 patients for analyses.

Prevalence

Among the 56 610 374 patients from the IRIS Registry, 82 136 patients were identified with ≥ 1 eyelid cancer in the IRIS Registry between December 1, 2010, and December 1, 2018. The overall prevalence of any eyelid cancer (AEC) was 145.1 per 100 000 population (Table 1). By type, the prevalence per 100 000 population was highest for BCC (87.9), accounting for over 60% of all cancers, and was 25.6 for unspecified malignant neoplasm (UMN), 11.1 for SCC, 5.0 for sebaceous carcinoma or other specified malignant neoplasm (SBC), 4.1 for MM, and 0.4 for melanoma in situ (MIS). Note that these prevalences belonged to patients having only 1 type of eyelid cancer.

The prevalence of having multiple eyelid cancers was 11.2 per 100 000 population for all cancer types, 9.4 per 100 000 population for multiple eyelid cancers including BCC, 3.4 per 100 000 population for multiple eyelid cancers including SCC, 2.6 per 100 000 population for multiple eyelid cancers including both BCC and SCC, 1.3 per 100 000 population for multiple eyelid cancers including MM, 0.6 per 100 000 population for multiple eyelid cancers including both BCC and MM, and 0.1 per 100 000 population for multiple eyelid cancers including both SCC and MM (Table S3, available at www.ophthalmologyscience.org/). Several remaining combinations were not reported for conciseness.

The mean (standard deviation) age of patients with AEC was 66.7 (12.6) (median, 69.0) years and that of patients without eyelid cancer was 54.3 (21.6) (median, 60.0) years ($P < 0.0001$). When the prevalence of eyelid cancers (per 100 000) was compared across the age groups (< 20, 20−39, 40−65, and > 65 years), the prevalence of BCC (from 1.9 to 15.9, 83.4, and 141.0), SCC (from 0.2 to 1.4, 9.1, and 19.4), MM (from 0.4 to 1.2, 4.1, and 6.0), SBC (from 0.6 to 1.3, 4.7, and 7.7), UMN (from 4.6 to 8.6, 25.4, and 37.5), and AEC (from 8.0 to 29.8, 136.9, and 231.1) was found to increase with increasing age ($P < 0.0001$, $P < 0.0001$, $P < 0.0001$, $P < 0.0001$, $P \leq 0.003$, $P < 0.0001$, $P < 0.0001$, and $P < 0.0001$, for each cancer type, respectively) (Table S4, available at www.ophthalmologyscience.org/ and Fig 1). The prevalence rates of MIS and multiple cancers were lower in the group of patients aged 40 to 65 years (0.4 and 0.5, respectively) than in the group of patients aged > 65 years (9.9−19.0); the prevalence in the 2 youngest age groups (< 20 and 20−39 years) could not be reported because of small numbers in those categories (values < 11).

A comparison by sex (female vs. male) showed a statistically significantly higher frequency of males with BCC (83.0 vs. 94.4), SCC (8.2 vs. 14.9), MM (3.8 vs. 4.5), MIS (0.3 vs. 0.4), and multiple cancers (9.9 vs. 13.1) ($P < 0.0001$, $P < 0.0001$, $P < 0.0001$, $P = 0.02$, and $P < 0.0001$, respectively) (Table S5, available at www.ophthalmologyscience.org/ and Fig 2). There was no difference by sex for patients with UMN ($P = 0.40$) and SBC ($P = 0.25$).

With regard to race, the prevalence of eyelid cancers was highest in Whites for BCC, SCC, MM, SBC, MIS, multiple cancers, UMN, and AEC (all $P \leq 0.003$) (Table S6, available at www.ophthalmologyscience.org/, and Fig 3).

With regard to ethnicity, the prevalence of eyelid cancers was higher in non-Hispanics and patients of unknown ethnicity for all cancer types, except UMN, wherein Hispanics had the highest prevalence rates (at 34.2 per 100 000 population), followed by non-Hispanics (28.1 per 100 000 population), and patients of unknown ethnicity (17.3 per 100 000 population) (Table S7, available at

Table 1. Distribution and Prevalence (with SE) of Eyelid Cancers (by Each Eyelid Cancer and Any Eyelid Cancer) in the Total American Academy of Ophthalmology Intelligent Research in Sight Registry Population of 56 610 374 Patients between 2010 and 2018

Eyelid Cancer Type	Distribution: *Patients with Eyelid Cancer(s) N (%)*		Prevalence: *Per 100 000 Persons (with SE)*	
Basal cell carcinoma	49 730	(61)	87.9	(0.4)
Squamous cell carcinoma	6281	(8)	11.1	(0.1)
Malignant melanoma	2293	(3)	4.1	(0.1)
Sebaceous carcinoma or other specified malignant neoplasm	2800	(3)	5.0	(0.1)
Melanoma in situ	205	(< 1)	0.4	(0.0)
Unspecified malignant neoplasm	14 487	(18)	25.6	(0.2)
Multiple cancers*	6340	(8)	11.2	(0.1)
Any eyelid cancer†	82 136	(100)	145.1	(0.5)

SE = standard error.
*Patients with multiple cancer are those who had ≥ 1 diagnosis of ≥ 2 of the following cancer types: unspecified malignant neoplasm, basal cell carcinoma, squamous cell carcinoma, sebaceous carcinoma or other specified malignant neoplasm, malignant melanoma, or melanoma in situ.
†Patients with any eyelid cancer are those with ≥ 1 diagnosis of any cancer type.

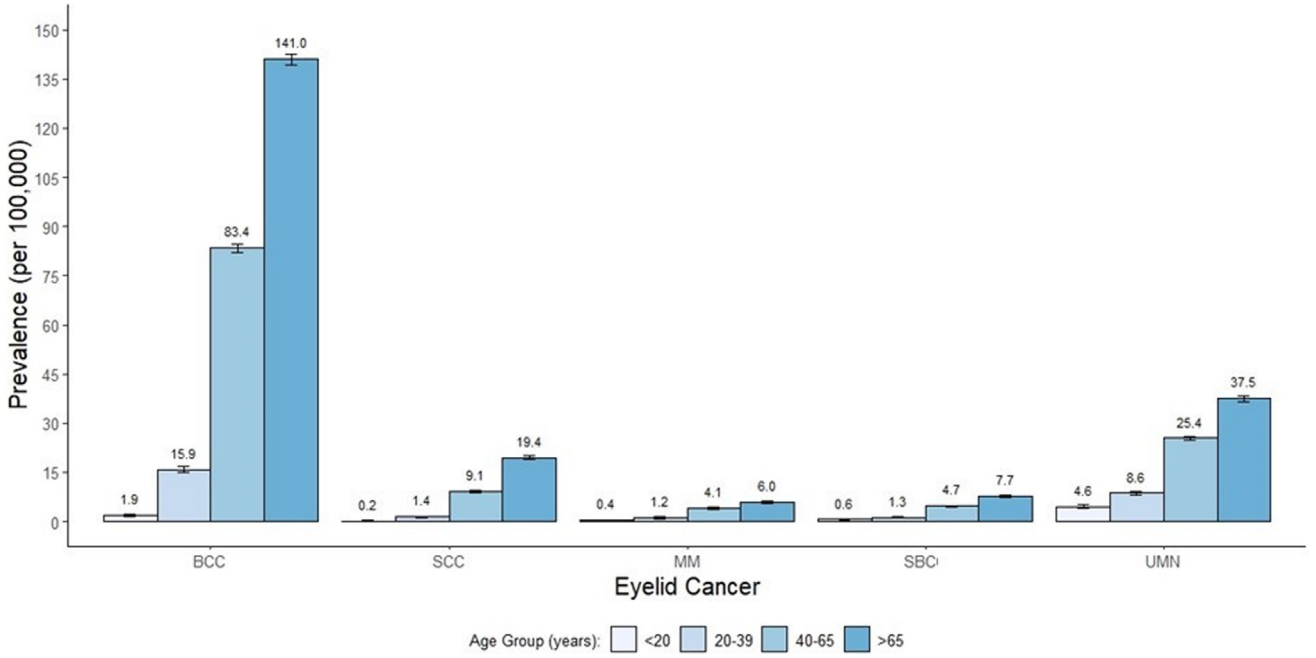

Figure 1. Prevalence (per 100 000 population) of eyelid cancers (with 95% confidence intervals) by age group (in years) in the AAO IRIS® Registry (2010−2018). The rates of any eyelid cancer (patients with ≥ 1 diagnosis of any eyelid cancer type) are as follows: < 20 years (prevalence rate per 10 000 ± standard error): 8.0 ±0.4; 20 - 39 years: 29.8 ± 0.6; 40−65 years: 136.9 ± 0.8; > 65 years: 231.1 ± 1.3. BCC = basal cell carcinoma; MM = malignant melanoma; SBC = sebaceous carcinoma or other specified malignant neoplasm; SCC = squamous cell carcinoma; UMN = unspecified malignant neoplasm.

www.ophthalmologyscience.org/, and Fig 4). There was a statistically significant difference in the distributions of ethnicity among all eyelid cancer types (all $P < 0.0001$), except for MIS ($P = 0.35$).

Laterality

The prevalence of eyelid cancers by laterality (right vs. left) showed a higher rate of left side involvement in UMN (40% vs. 60%) compared with that in all other cancer types (50% vs. 50%, $P = 0.03$) and no difference in laterality in BCC (50% vs. 50%, $P = 0.48$), SCC (45% vs. 55%, $P = 0.24$), MM (50% vs. 50%, $P = 0.21$), MIS (50% vs. 50%, $P = 1.00$), SBC (52% vs. 48%, $P = 0.71$), and multiple cancers (62% vs. 38%, $P = 0.10$).

Associated Factors

AEC. Eyelid cancers classified as AEC were significantly associated with advanced age, male sex, White race, non-Hispanic ethnicity, and former and active smoking in the univariate model. Based on the multivariate analyses (after adjusting for age group, sex, race, ethnicity, and smoking status), older age groups (< 20 years) (reference), 20−39 years [3.35 {1.96−5.72}; $P < 0.0001$], 40−65 years [24.21 {14.80−39.59}; $P < 0.0001$], and > 65 years [42.78 {26.18−69.90}; $P < 0.0001$]), male (vs. female) sex (OR [95% CI], 1.40 [1.33−1.48]; $P < 0.0001$), White race (reference) (inverse associations with African Americans [0.12 (0.09−0.16); $P < 0.0001$], Asians (0.19 [0.13−0.26]; $P < 0.0001$), unknown race (0.60 [0.55−0.66]; $P < 0.0001$), other race (0.59 [0.40−0.89]; $P = 0.01$), Non-Hispanic ethnicity (reference) (Hispanic [0.38 {0.33−0.45}]; $P < 0.0001$), and smoking (active smoker vs. never smoker) (1.11 [1.01−1.21]; $P = 0.03$) were positively associated with all eyelid cancers (Table 2). The AUC for the multivariate model for AEC was 0.70.

Specific Cancer Types (BCC, SCC, and MM). Eyelid cancers classified as BCC were significantly associated with advanced age, male sex, White race, non-Hispanic ethnicity, and former and active smoking in the univariate analyses. The results remained similar in the multivariate analyses (after adjusting for age group, sex, race, ethnicity, and smoking status). Older age groups (using ages < 20 years as the reference group, 20−39 years [6.18 {5.02−7.62}; $P < 0.0001$], 40−65 years [31.76 {26.02−38.77}; $P < 0.0001$], > 65 years [50.49 {41.38−61.62}; $P < 0.0001$]), male (vs. female) sex (OR [95% CI], 1.15 [1.12−1.17]; $P < 0.0001$), and active smoking (vs. never smoker) (1.27 [1.23−1.31]; $P < 0.0001$) were positively associated with BCC. Using White race as the reference group, inverse associations were found with African American (0.05 [0.04−0.06]; $P < 0.0001$) and Asian (0.10 [0.09−0.12]; $P < 0.0001$) patients and patients of unknown (0.72 [0.70−0.74]; $P < 0.0001$) and other race (0.49 [0.42−0.57]; $P < 0.0001$). An inverse association was also identified with Hispanic ethnicity using non-Hispanic ethnicity as the reference group (0.36 [0.35−0.39]; $P < 0.0001$) (Table 3). The AUC for the multivariate BCC model was 0.70.

Eyelid cancers classified as SCC were significantly associated with advanced age, male sex, White race, non-

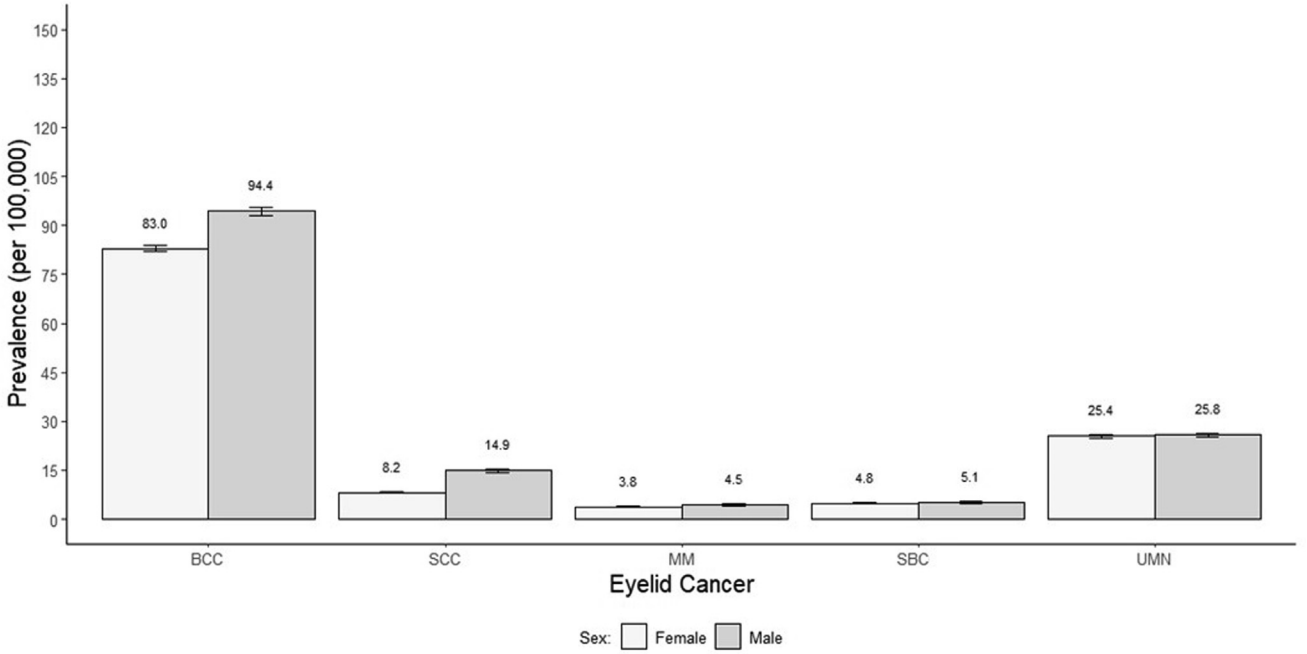

Figure 2. Prevalence (per 100 000 population) of eyelid cancers (with 95% confidence intervals) by sex in the AAO IRIS® Registry (2010–2018). The rates of any eyelid cancer (patients with ≥ 1 diagnosis of any eyelid cancer type) are as follows: female (prevalence rate per 10 000 ± standard error): 132.5 ± 0.7; male: 158.2 ± 0.8. BCC = basal cell carcinoma; MM = malignant melanoma; SBC = sebaceous carcinoma or other specified malignant neoplasm; SCC = squamous cell carcinoma; UMN = unspecified malignant neoplasm.

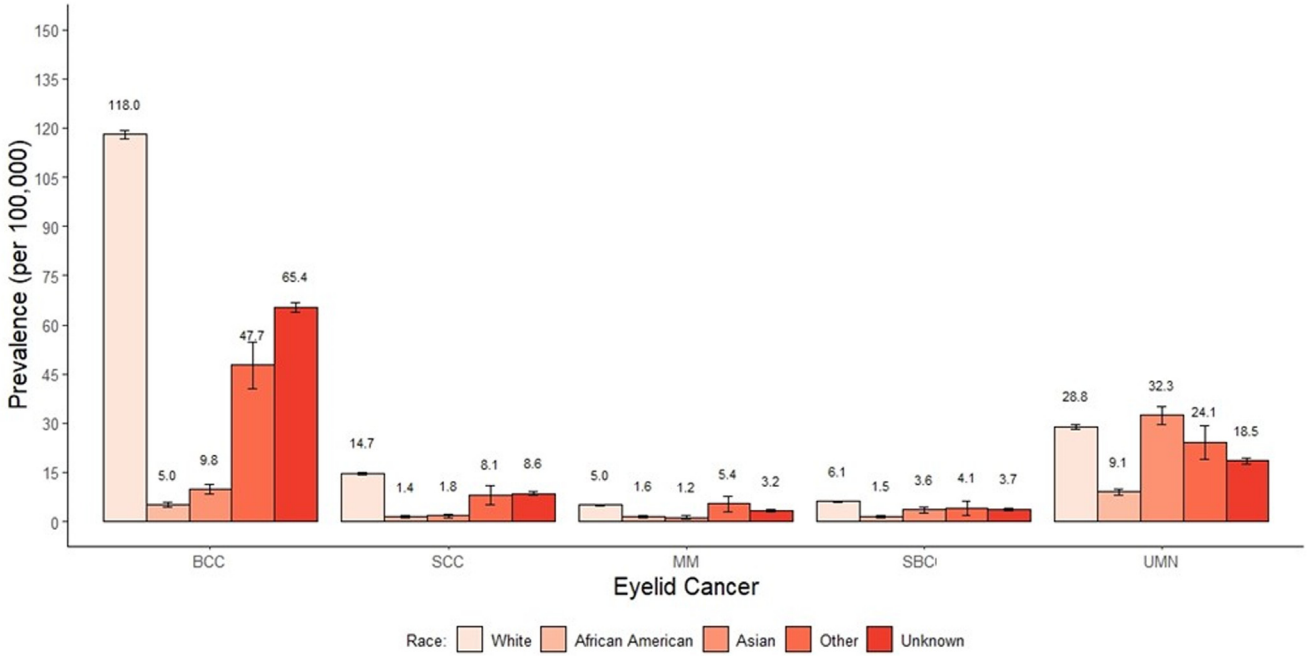

Figure 3. Prevalence (per 100 000 population) of eyelid cancers (with 95% confidence intervals) by race in the AAO IRIS® Registry (2010–2018). The rates of any eyelid cancer (patients with ≥ 1 diagnosis of any eyelid cancer type) are as follows: White (prevalence rate per 10 000 ± standard error): 188.6 ± 0.8; African American: 20.3 ± 0.7; Asian: 51.2 ± 1.8; other: 97.2 ± 5.1; unknown: 106.4 ± 0.9. BCC = basal cell carcinoma; MM = malignant melanoma; SBC = sebaceous carcinoma or other specified malignant neoplasm; SCC = squamous cell carcinoma; UMN = unspecified malignant neoplasm.

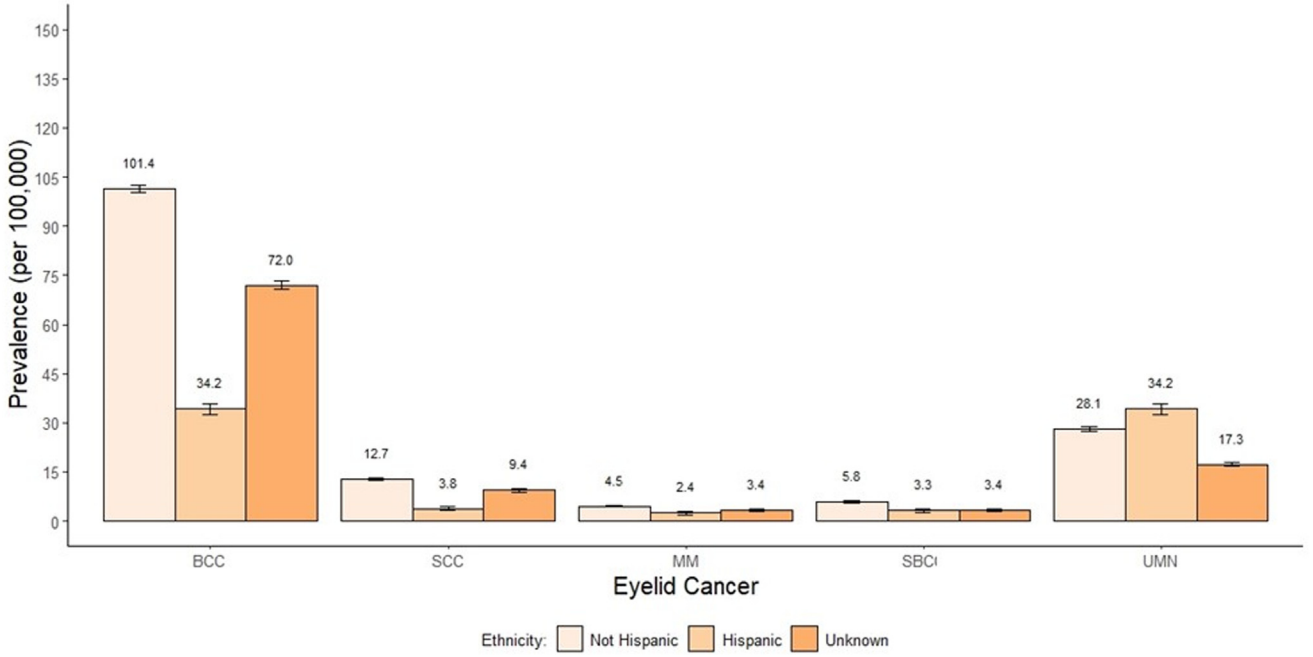

Figure 4. Prevalence (per 100 000 population) of eyelid cancers (with 95% confidence intervals) by ethnicity (in years) in the AAO IRIS® Registry (2010–2018). The rates of any eyelid cancer (patients with ≥ 1 diagnosis of any eyelid cancer type) are as follows: non-Hispanic (prevalence rate per 10 000 ± standard error): 166.5 ± 0.7; Hispanic: 82.8 ± 1.4; unknown: 113.9 ± 0.9. BCC = basal cell carcinoma; MM = malignant melanoma; SBC = sebaceous carcinoma or other specified malignant neoplasm; SCC = squamous cell carcinoma; UMN = unspecified malignant neoplasm.

Hispanic ethnicity, and former and active smoking in the univariate analysis. When adjusted for confounding factors (age group, sex, race, ethnicity, and smoking status), older age groups (using ages < 20 years as the reference group, 20–39 years [4.98 {2.58–9.61}; $P < 0.0001$], 40–65 years [32.69 {17.55–60.89}; $P < 0.0001$], and > 65 years [66.97 {35.98–124.63}; $P < 0.0001$]), male (vs. female) sex (OR [95% CI], 1.80 [1.71–1.91]; $P < 0.0001$), and active smoking (vs. never smoker) (1.59 [1.46–1.73]; $P < 0.0001$) remained positively associated with the development of SCC in the multivariate analyses. Using White race as the reference group, inverse associations were found with African American (0.10 [0.07–0.13]; $P < 0.0001$) and Asian (0.16 [0.11–0.23]; $P < 0.0001$) patients and patients of unknown (0.72 [0.66–0.79]; $P < 0.0001$) and other race (0.63 [0.42–0.94]; $P = 0.02$). An inverse association was also found with Hispanic ethnicity (vs. non-Hispanic) (0.32 [0.27–0.38]; $P < 0.0001$) (Table 4). The AUC for the multivariate model for SCC was 0.74.

Eyelid cancers classified as MM were significantly associated with advanced age, male sex, White race, non-Hispanic ethnicity, and former and active smoking in the univariate model. Based on the multivariate analyses (after adjusting for age group, sex, race, ethnicity, and smoking status), older age groups (using ages < 20 years as the reference group, 20–39 years [2.82 {1.58–5.05}; $P = 0.0005$], 40–65 years [10.38 {6.11–17.63}; $P < 0.0001$], and > 65 years [14.87 {8.77–25.23}; $P < 0.0001$]), male (vs. female) sex (OR [95% CI], 1.20 [1.09–1.32]; $P < 0.0001$), and active smoking (vs. never smoker) (1.26 [1.08–1.46]; $P \leq 0.003$) were positively associated with MM. Using White race as the reference group, inverse associations were found with African American (0.40 [0.31–0.52]; $P < 0.0001$) and Asian (0.32 [0.20–0.50]; $P < 0.0001$) patients and patients of unknown race (0.70 [0.60–0.82]; $P < 0.0001$). An inverse association was also found with Hispanic ethnicity (vs. non-Hispanic) (0.61 [0.49–0.76]; $P < 0.0001$) (Table 5). The AUC for the multivariate model for MM was found to be 0.67.

The summary of associations from the multivariate analyses for each tumor type (BCC, SCC, MM, SBC, MIS, UMN, and MC) is presented in Table 6.

Discussion

The advent of "big data" has allowed researchers around the world and across industries to mine large data sets for associations that seemed impossible only a decade ago, and the health care sector is no exception to this data revolution. Since 2016, the IRIS Registry has offered ophthalmologists and clinician scientists the opportunity to better understand the natural history of ophthalmic diseases, treatment practices and outcomes, and the prevalence of a variety of eye diseases, particularly those that are rare.[8] To our knowledge, this is the first eyelid cancer study to evaluate both the overall and cancer-specific prevalence and associated factors related to select eyelid cancers, including BCC, SCC, MM, MIS, and SBC.

Table 2. Univariate and Multivariate Logistic Regression Models for AEC and Risk Factors in the American Academy of Ophthalmology Intelligent Research in Sight Registry (2010–2018)*

Factor		Patients without AEC† N (%)	Patients with AEC† N (%)	Univariate OR	Univariate 95% CI	Univariate P Value	Multivariate OR‡	Multivariate 95% CI	Multivariate P Value
Age group (yrs)	< 20	6 046 811 (11)	481 (1)	[Reference]			[Reference]		
	20–39	7 494 403 (13)	2235 (3)	3.75	(3.40–4.14)	**< 0.0001**	3.35	(1.96–5.72)	**< 0.0001**
	40–65	21 333 955 (38)	29 255 (36)	17.24	(15.75–18.86)	**< 0.0001**	24.21	(14.8–39.59)	**< 0.0001**
	> 66	21 653 069 (38)	50 165 (61)	29.13	(26.62–31.86)	**< 0.0001**	42.78	(26.18–69.9)	**< 0.0001**
Sex	Female	32 303 044 (57)	43 758 (53)	[Reference]		—	[Reference]		
	Male	24 225 194 (43)	38 378 (47)	1.17	(1.15–1.19)	**< 0.0001**	1.40	(1.33–1.48)	**< 0.0001**
Race	White	33 226 488 (59)	62 787 (76)	[Reference]			[Reference]		
	African American	4 012 585 (7)	813 (1)	0.11	(0.11–0.12)	**< 0.0001**	0.12	(0.09–0.16)	**< 0.0001**
	Asian	1 638 090 (3)	839 (1)	0.29	(0.27–0.31)	**< 0.0001**	0.19	(0.13–0.26)	**< 0.0001**
	Unknown	12 777 857 (23)	13 604 (17)	0.6	(0.59–0.62)	**< 0.0001**	0.60	(0.55–0.66)	**< 0.0001**
	Other	368 850 (1)	359 (< 1)	0.55	(0.5–0.61)	**< 0.0001**	0.59	(0.4–0.89)	**0.01**
Ethnicity	Not Hispanic	36 211 187 (64)	60 378 (74)						
	Hispanic	4 504 368 (8)	3734 (5)	0.34	(0.3–0.4)	**< 0.0001**	0.38	(0.33–0.45)	**< 0.0001**
	Unknown	15 812 683 (28)	18 024 (22)	0.58	(0.55–0.62)	**< 0.0001**	0.81	(0.75–0.88)	**< 0.0001**
Smoking status	Never smoker	33 365 554 (59)	41 717 (51)	[Reference]			[Reference]		
	Former smoker	10 234 237 (18)	18 187 (22)	1.42	(1.40–1.45)	**< 0.0001**	0.96	(0.90–1.02)	0.22
	Active smoker	4 324 686 (8)	7481 (9)	1.38	(1.35–1.42)	**< 0.0001**	1.11	(1.01–1.21)	**0.03**

AEC = any eyelid cancer; CI = confidence interval; OR = odds ratio.
*Bold *P* values indicate statistical significance ($P < 0.05$). Univariate *P* values computed using logistic regression assessing the association between each factor and having an eyelid tumor or not.
†Patients with any eyelid cancer are those with at ≥ diagnosis of any cancer type.
‡Multivariate *P* value assesses the association between each factor and having any eyelid tumor adjusting for all other factors presented above (age group, sex, race, ethnicity, and smoking status).

Table 3. Univariate and Multivariate Logistic Regression Models for BCC and Associated Risk Factors in the American Academy of Ophthalmology Intelligent Research in Sight Registry (2010–2018)*

Factor		*Patients without BCC N (%)*		*Patients with BCC N (%)*		Univariate OR	Univariate 95% CI	Univariate P Value	Multivariate OR†	Multivariate 95% CI	Multivariate P Value
Age group (yrs)	< 20	6 047 179	(11)	113	(0)	[Reference]			[Reference]		
	20–39	7 495 446	(13)	1192	(2)	8.51	(7.02–10.32)	**< 0.0001**	6.18	(5.02–7.62)	**< 0.0001**
	40–65	21 345 396	(38)	17 814	(36)	44.66	(37.14–53.71)	**< 0.0001**	31.76	(26.02–38.77)	**< 0.0001**
	> 66	21 672 623	(38)	30 611	(62)	75.58	(62.87–90.87)	**< 0.0001**	50.49	(41.38–61.62)	**< 0.0001**
Sex	Female	32 319 970	(57)	26 832	(54)	[Reference]	—	—	[Reference]	—	—
	Male	24 240 674	(43)	22 898	(46)	1.14	(1.12–1.16)	**< 0.0001**	1.15	(1.12–1.17)	**< 0.0001**
Race	White	33 249 995	(64)	39 280	(82)	[Reference]	—	—	[Reference]	—	—
	African American	4 013 196	(8)	202	(0)	0.05	(0.04–0.05)	**< 0.0001**	0.05	(0.04–0.06)	**< 0.0001**
	Asian	1 638 769	(3)	160	(0)	0.09	(0.08–0.11)	**< 0.0001**	0.1	(0.09–0.12)	**< 0.0001**
	Unknown	12 783 090	(25)	8371	(17)	0.61	(0.59–0.62)	**< 0.0001**	0.72	(0.7–0.74)	**< 0.0001**
	Other	369 033	(1)	176	(0)	0.44	(0.38–0.51)	**< 0.0001**	0.49	(0.42–0.57)	**< 0.0001**
Ethnicity	Not Hispanic	36 234 780	(64)	36 785	(74)	[Reference]	—	—	[Reference]	—	—
	Hispanic	4 506 561	(8)	1541	(3)	0.34	(0.32–0.35)	**< 0.0001**	0.36	(0.35–0.39)	**< 0.0001**
	Unknown	15 819 303	(28)	11 404	(23)	0.71	(0.7–0.73)	**< 0.0001**	0.87	(0.84–0.89)	**< 0.0001**
Smoking status	Never smoker	33 382 018	(70)	25 253	(62)	[Reference]	—	—	[Reference]	—	—
	Former smoker	10 241 311	(21)	11 113	(27)	1.43	(1.4–1.47)	**< 0.0001**	0.98	(0.96–1.01)	0.17
	Active smoker	4 327 569	(9)	4598	(11)	1.4	(1.36–1.45)	**< 0.0001**	1.27	(1.23–1.31)	**< 0.0001**

BBC = basal cell carcinoma; CI = confidence interval; OR = odds ratio.
*Bold *P* values indicate statistical significance ($P < 0.05$). Univariate *P* values computed using logistic regression assessing the association between each factor and having an eyelid tumor or not.
†Multivariate *P* value assesses the association between each factor and having any eyelid tumor adjusting for all other factors presented above (age group, sex, race, ethnicity, and smoking status).

Table 4. Univariate and Multivariate Logistic Regression Models for SCC and Associated Risk Factors in the American Academy of Ophthalmology Intelligent Research in Sight Registry (2010–2018)*

Factor		*Patients without SCC N (%)*	*Patients with SCC N (%)*	Univariate *OR*	Univariate *95% CI*	Univariate *P Value*	Multivariate *OR*†	Multivariate *95% CI*	Multivariate *P Value*
Age group (yrs)	< 20	6 047 279 (11)	13 (< 1)	[Reference]	–	–	[Reference]	–	–
	20–39	7 496 536 (13)	102 (2)	6.33	(3.55–11.27)	**< 0.0001**	4.98	(2.58–9.61)	**< 0.0001**
	40–65	21 361 258 (38)	1952 (31)	42.51	(24.64–734)	**< 0.0001**	32.69	(17.55–60.89)	**< 0.0001**
	> 66	21 699 020 (38)	4214 (67)	90.34	(52.41–155.71)	**< 0.0001**	66.97	(35.98–124.63)	**< 0.0001**
Sex	Female	32 344 144 (57)	2658 (42)	[Reference]	–	–	[Reference]	–	–
	Male	24 259 949 (43)	3623 (58)	1.82	(1.73–1.91)	**< 0.0001**	1.80	(1.71–1.91)	**< 0.0001**
Race	White	33 284 376 (59)	4899 (78)	[Reference]	–	–	[Reference]	–	–
	African American	4 013 344 (7)	54 (1)	0.10	(0.08–0.13)	**< 0.0001**	0.10	(0.07–0.13)	**< 0.0001**
	Asian	1 638 900 (3)	29 (< 1)	0.13	(0.09–0.19)	**< 0.0001**	0.16	(0.11–0.23)	**< 0.0001**
	Unknown	12 790 365 (23)	1096 (17)	0.64	(0.60–0.68)	**< 0.0001**	0.72	(0.66–0.79)	**< 0.0001**
	Other	369 179 (1)	30 (< 1)	0.61	(0.42–0.87)	**0.006**	0.63	(0.42–0.94)	**0.02**
Ethnicity	Not Hispanic	36 266 951 (64)	4614 (73)	[Reference]	–	–	[Reference]	–	–
	Hispanic	4 507 929 (8)	173 (3)	0.30	(0.26–0.35)	**< 0.0001**	0.32	(0.27–0.38)	**< 0.0001**
	Unknown	15 829 213 (28)	1494 (24)	0.74	(0.70–0.79)	**< 0.0001**	0.90	(0.84–0.98)	**0.01**
Smoking status	Never smoker	33 404 289 (70)	2982 (58)	[Reference]	–	–	[Reference]	–	–
	Former smoker	10 250 945 (21)	1479 (29)	1.62	(1.52–1.72)	**< 0.0001**	1.01	(0.95–1.08)	0.73
	Active smoker	4 331 469 (9)	698 (14)	1.81	(1.66–1.96)	**< 0.0001**	1.59	(1.46–1.73)	**< 0.0001**

CI = confidence interval; OR = odds ratio; SCC = squamous cell carcinoma.
*Bold *P* values indicate statistical significance ($P < 0.05$). Univariate *P* values computed using logistic regression assessing the association between each factor and having an eyelid tumor or not.
†Multivariable *P* value assesses the association between each factor and having any eyelid tumor adjusting for all other factors presented above (age group, sex, race, ethnicity, and smoking status).

Prevalence

Eyelid cancers are the most common malignant neoplasms in ophthalmic practice.[14] The available epidemiologic data on eyelid cancers have been traditionally limited to 1 or 2 eyelid cancer diagnoses, which can be attributed to the lack of an aggregated database of eyelid cancer cases from which meaningful associations can be made.[15,16] The epidemiologic data from tertiary care centers may, thus, be confounded by referral biases, preventing the generalizability of any conclusions reached.[4-6,16]

In this large national IRIS Registry database, we found that the prevalence of AEC, BCC, SCC, MM, SBC, MIS, UMN, and multiple cancers was 145.1, 87.9, 11.1, 4.1, 5.0, 0.4, 25.6, and 11.2 per 100 000 population, respectively. Previous available data were limited to incidence studies, which reported newly diagnosed cases and, as expected, showed consistently lower rates than our prevalence findings, which include all cases available in the registry, making direct comparisons with existing data difficult to interpret.

The reported incidence of eyelid cancers varies widely. In 1999, Cook and Bartley[1] studied medical records in Minnesota and found the incidence rates of BCC, SCC, MM, and AEC to be 14.4, 1.4, 0.1, and 15.7 per 100 000 population, respectively. In another study conducted in Taiwan in 2006, the incidence rate of all eyelid cancers was found to be 32.0 per 100 000 population, double the rate reported by Cook and Bartley[1] less than a decade earlier.[2] More recently, in 2020, Shan et al[17] evaluated 1397 eyelid melanomas in the Surveillance, Epidemiology, and End Results program data and found the incidence to be 0.1 per 100 000 population, a rate consistent with that reported in the Minnesota study. We hypothesized that the difference in the incidence rates across the various studies can be attributed to not only the smaller number of cases but also the different methods for reporting eyelid cancer cases among different institutions in different countries.

The relative distribution of frequencies of eyelid cancer diagnoses showed striking differences among studies. In this current study from the IRIS Registry cohort of 82 136 eyelid cancer cases, the majority of the cases were BCC (61%), followed by SCC (8%), MM (3%), SBC (3%), MIS (< 1%), UMN (18%), and multiple cancers (8%). The proportion of BCC cases in our study (61%) was higher than those in studies conducted in Japan (40%)[18] and Thailand (38%)[19] but lower than those reported in Switzerland (86%)[6] and Singapore[20] and similar to those in studies conducted in Korea (68%).[21] The proportion of SBC cases in our study (3%) was identical to that reported in Switzerland[6] but much lower than that reported in Thailand (41%)[19] and India (43%).[22] We suspect that the difference in the proportions of eyelid cancers among different populations in geographically distinct regions might be attributed to a difference in the genotypes of assorted populations (Whites vs. Asians) and differences in the cumulative yearly sun exposure in different latitudes (US and Switzerland vs. Thailand and India). Further studies of eyelid cancers in the

Table 5. Univariate and Multivariate Logistic Regression Models for MM and Associated Risk Factors in the American Academy of Ophthalmology Intelligent Research in Sight Registry (2010–2018)*

Factor		Patients without MM N (%)	Patients with MM N (%)	Univariate OR	Univariate 95% CI	Univariate P Value	Multivariate OR†	Multivariate 95% CI	Multivariate P Value
Age group (yrs)	< 20	6 047 270 (11)	22 (< 1)	[Reference]	–	–	[Reference]		
	20–39	7 496 551 (13)	87 (4)	3.19	(2.00–5.09)	**< 0.0001**	2.82	(1.58–5.05)	**≤ 0.003**
	40–65	21 362 326 (38)	884 (39)	11.37	(7.45–17.36)	**< 0.0001**	10.38	(6.11–17.63)	**< 0.0001**
	> 66	21 701 934 (38)	1300 (57)	16.47	(10.81–25.09)	**< 0.0001**	14.87	(8.77–25.23)	**< 0.0001**
Sex	Female	32 345 590 (57)	1212 (53)	[Reference]	–	–	[Reference]	–	–
	Male	24 262 491 (43)	1081 (47)	1.19	(1.10–1.29)	**< 0.0001**	1.20	(1.09–1.32)	**0.0001**
Race	White	33 287 610 (59)	1665 (73)	[Reference]	–	–	[Reference]	–	–
	African American	4 013 334 (7)	64 (3)	0.34	(0.26–0.44)	**< 0.0001**	0.40	(0.31–0.52)	**< 0.0001**
	Asian	1 638 909 (3)	20 (1)	0.26	(0.17–0.40)	**< 0.0001**	0.32	(0.20–0.50)	**< 0.0001**
	Unknown	12 791 047 (23)	414 (18)	0.69	(0.62–0.77)	**< 0.0001**	0.70	(0.60–0.82)	**< 0.0001**
	Other	369 189 (1)	20 (1)	1.15	(0.74–1.79)	0.53	1.01	(0.58–1.74)	0.97
Ethnicity	Not Hispanic	36 269 923 (64)	1642 (72)	[Reference]			[Reference]		
	Hispanic	4 507 992 (8)	110 (5)	0.54	(0.44–0.65)	**< 0.0001**	0.61	(0.49–0.76)	**< 0.0001**
	Unknown	15 830 166 (28)	541 (24)	0.75	(0.68–0.83)	**< 0.0001**	0.84	(0.74–0.97)	**0.02**
Smoking status	Never smoker	33 406 169 (70)	1102 (62)	[Reference]	–	–	[Reference]	–	–
	Former smoker	10 251 952 (21)	472 (27)	1.40	(1.25–1.55)	**< 0.0001**	1.00	(0.90–1.12)	0.95
	Active smoker	4 331 967 (9)	200 (11)	1.40	(1.20–1.63)	**< 0.0001**	1.26	(1.08–1.46)	**≤ 0.003**

CI = confidence interval; MM = malignant melanoma; OR = odds ratio.
*Bold *P* values indicate statistical significance ($P < 0.05$). Univariate *P* values computed using logistic regression assessing the association between each factor and having an eyelid tumor or not.
†Multivariate *P* value assesses the association between each factor and having any eyelid tumor adjusting for all other factors presented above (age group, sex, race, ethnicity, and smoking status).

White, Asian, and other ethnic populations are essential to better understand the reasons for these different patterns of the occurrence of eyelid cancer.

Risk Factors

In this study, the prevalence of each eyelid cancer type increased with increasing age for BCC, SCC, MM, SBC, and AEC ($P < 0.0001$, $P < 0.0001$, $P < 0.0001$, $P < 0.0001$, and $P < 0.0001$, respectively). Likewise, increasing age was an independent risk factor for all eyelid cancer types (for AEC: age, 20–39 years [OR, 3.35]; age, 40–65 years [OR, 24.21]; and age, > 65 years [OR, 42.78]). Similarly, the prevalence of eyelid cancers in patients younger than 40 years was much lower than that in patients aged ≥ 40 years: BCC (3%), SCC (2%), SBC (5%), MM (5%), and AEC (3%). The higher prevalence in patients of older ages is consistent with that of other skin cancers reported in the literature[23] and other reports on eyelid cancers. Wang et al[24] evaluated 5146 eyelid cancers and found that the incidence of eyelid cancer increased with increasing age and that the mean patient age at the time of diagnosis of BCC, SBC, SCC, and MM was 70, 71, 74, and 71 years, respectively. Quigley et al[25] investigated eyelid cancers in Ireland over an 11-year period and found that the incidence of eyelid SCC rose exponentially with age. The increased risk in older patients could be explained by greater lifetime exposure to known and unknown environmental carcinogens.[26] Advanced age, coupled with a decline in the functionality of the immune system, leads DNA damage to build up over time, raising the risk of eyelid cancers in the elderly population.[26] For this reason, there should be a low threshold of suspicion among ophthalmologists for eyelid lesions that present in older patients, and when in diagnostic doubt, a biopsy or referral to an ocular oncologist or oculoplastic surgeon for evaluation and surgical management is advised.

The prevalence rates (per 100 000 population) were higher in male patients than in female patients in the IRIS Registry: BCC (94.4 vs. 83.0, respectively), SCC (14.9 vs. 8.2, respectively), MM (4.5 vs. 3.8, respectively), and AEC (158.2 vs. 135.3, respectively). These patterns are similar to those reported by Deprez and Uffer[6] and Paavilainen et al.[27] Similarly Cook and Bartley[1] showed that the age-adjusted incidence rate of eyelid cancer was 19.6 and 13.3 per 100 000 population in male and female patients, respectively. In contrast, Kaliki et al[28] evaluated 536 eyelid cancers and found a higher proportion of female patients (57%). The sex-specific disparities in the prevalence of cancer have long been acknowledged because males tend to have outdoor occupations and are more likely to smoke, both of which are risks factors for certain cancers. The sex-specific disparity in the prevalence of eyelid cancer may be attributed to underlying genetic, hormonal, and behavioral differences.[29] Dunford et al[30] evaluated > 4100 cancers using The Cancer Genome

Table 6. Summary of Associations from Multivariate Logistic Regression Models for AEC and Each Specific Eyelid Cancer Type*

	Demographic and Smoking Characteristics				
Eyelid Cancer Modeled†	*Age Group (yrs)*	*Sex*	*Race*	*Ethnicity*	*Smoking Status*
AEC‡	Increasing association with older ages	F < M	Whites have increased association compared with African Americans, Asians, and patients of other and unknown races	Hispanic < non-Hispanic	Never < active No association between never and former
BCC	Increasing association with older ages	F < M	Whites have increased association compared with African Americans, Asians, and patients of other and unknown races	Hispanic < non-Hispanic	Never < active No association between never and former
SCC	Increasing association with older ages	F < M	Whites have increased association compared with African Americans, Asians, and patients of other and unknown races	Hispanic < non-Hispanic	Never < active No association between never and former
MM	Increasing association with older ages	F < M	Whites have increased association compared with African Americans, Asians, and patients of unknown races No association between White and other races	Hispanic < non-Hispanic	Never < active No association between never and former
SBC	Increasing association with older ages	No association	Whites have increased association compared with African Americans and Asians No association between White and other or White and unknown races	Hispanic < non-Hispanic	Never < active No association between never and former
MIS	Increasing association with older ages	F < M	Whites have increased association compared with African Americans and patients of unknown races No association between Asian and White or other and White races	No association	No association
UMN	Increasing association with older ages	F < M	Whites have increased association compared with African Americans, Asians, and patients of unknown races No association between White and other races	Hispanic < non-Hispanic	Never < active No association between never and former
MC§	Increasing association with older ages	F < M	Whites have increased association compared with African Americans, Asians, and patients of other and unknown races	Hispanic < non-Hispanic	Never < active No association between never and former

AEC = any eyelid cancer; BCC = basal cell carcinoma; F = female; M = male; MC = multiple cancer; MIS = melanoma in situ; MM = malignant melanoma; SBC = sebaceous carcinoma or other specified malignant neoplasm; SCC = squamous cell carcinoma; UMN = unspecified malignant neoplasm.
*Symbol < denotes the direction of association (e.g., F < M can be interpreted as: males have an increased association as compared with females).
†Results derived from a multivariate logistic regression model including age, sex, race, ethnicity, and smoking status as predictor variables and each respective eyelid tumor type listed as the response variable.
‡Patients with any eyelid cancer are those with ≥ 1 diagnosis of any cancer type.
§Patients with multiple cancers are those who had ≥ 1 diagnosis of ≥ 2 of the following cancer types: BCC, SCC, MM, SBC, MIS, or UMN.

Atlas and investigated whether there are genes that are more likely to be mutated in male patients than in female patients. They found certain tumor suppressor genes on chromosome X that escape X inactivation (EXITS genes), and the expression of these genes in both X chromosomes in women might provide protection against developing cancers compared with men, who only have 1 copy of chromosome X and, therefore, lack EXITS genes.[30] Therefore, our results demonstrating the higher prevalence of every subdiagnosis of eyelid cancer in males warrant further investigation of the possible role of genetics in eyelid cancers.

White patients were found to be more likely to have BCC ($P < 0.0001$), SCC ($P < 0.0001$), MM ($P < 0.0001$), and SBC ($P < 0.0001$) than African American and Asian patients as well as patients of unknown and other race, an observation consistent with the dermatology literature that showed that the prevalence of skin cancer is relatively low in patients of color. In a previous study of patients with eyelid cancer conducted in the US, 100% of the patients were White.[1] In another study, the risk of the development of eyelid cancer was 6.4 times higher for Whites than for African Americans.[15] Our results are congruent with those published in the literature.[31] This observation is hypothesized to be due to excess melanin in melanocytes and larger melanosomes, which provide extra sun protection in patients of color.[32]

A unique observation in this study is the association of smoking with each type of eyelid cancer. Smoking was

independently associated with AEC (OR, 1.11), BCC (OR, 1.27), SCC (OR, 1.59), and MM (OR, 1.26) after adjusting for other covariates. This finding might be explained by the fumes emitted when a cigarette is smoked, which contains > 7000 chemicals; of these, 70 are either known or suspected carcinogens, including polycyclic aromatic hydrocarbons, heterocyclic compounds, and N-nitrosamines.[33] Based on these findings, it is possible that vapor or particle carcinogens from cigarette smoke induce eyelid malignancies, especially given the proximity of the eyelids, where particulate matter can accumulate. Interestingly, former smoking was not associated with AEC ($P = 0.22$), BCC ($P = 0.17$), SCC ($P = 0.73$), or MM ($P = 0.95$). Peto et al[34] studied patients with lung cancer in the United Kingdom and found that the ratio of risk of lung cancer by 75 years of age was 15.9% in men who were active smokers and 9.9%, 6.0%, 3.0%, and 1.7% for those who quit smoking at 60, 50, 40, and 30 years of age, respectively. It seems that with cessation of smoking, the concentration of carcinogens in the airways and, thus, their potency to cause cancer is diminished the longer the duration of cessation of smoking. This might explain why in our cohort, the risk of eyelid cancer in patients who had stopped smoking was lesser than that in those who were actively smoking because the eyelids of active smokers are still subjected to carcinogenic cigarette fumes on a daily basis.

Although the association between smoking and many types of cancer has been investigated in great detail in the literature, the relationship between smoking and ocular or periocular cancers has received limited attention.[7,35] The association between smoking and eyelid cancers is consistent with the dermatology literature that showed that smoking is associated with cutaneous malignancies.[36] In 1999, Wojno[7] evaluated 112 patients with eyelid BCC and found that smoking was associated with BCC in women but not in men. However, that cohort was small and lacked robust associations. Although the development of eyelid cancers can be multifactorial and has been associated with several risk factors, smoking is a modifiable risk factor that we were able to investigate in this study. Although this association should be confirmed in other studies, it does provide yet another reason for physicians to advise patients against cigarette smoking.

This study aimed to evaluate the prevalence of and associated risk factors for eyelid cancers. The strengths of this study include the use of the IRIS Registry, which included patient data from approximately 3000 ophthalmology practices across the US. The large sample size from a demographically diverse, national clinical database offers estimates of actual prevalence, suggesting a more generalizable database to the US population. The limitations include the inability to capture eyelid cancers not identified by ICD-9 or ICD-10 codes, such as eyelid sweat gland adenocarcinoma. Because the IRIS Registry database did not have an ICD code for eyelid sebaceous carcinoma until 2015, we included "other specified malignant neoplasm" in the SBC category, precluding our ability to study this type separately. In addition, the ICD code-based electronic medical records in the IRIS Registry may not have retrieved data from histologic diagnoses confirmed by biopsy in all cases. Other associations that might have been important were limited in the IRIS Registry, such as ultraviolet exposure, which is important in cutaneous malignancies. Another study limitation was the lack of information on cancer location (upper vs. lower eyelid) and laterality (right vs. left eye) because these data were limited (location information could only be determined for 5% (1801/37 180) of the available patients because of lack of reporting of the necessary ICD-10 digit during coding), and information on laterality was available for 90% (33 478/37 180) of the available patients, reducing meaningful analysis and reporting of results.

In conclusion, using the IRIS Registry, a large national clinical registry of electronic health records, this study identified patients at a high risk of developing eyelid cancer, estimated a clinical setting prevalence, and identified associated risk factors. To our knowledge, the unique association between smoking and AEC as well as each subtype of eyelid cancer (BCC, SCC, MM, and SBC) has not been previously reported. Our findings support that BCC is the most common eyelid cancer in the US, representing 61% of all eyelid cancers. This study also showed that eyelid cancers were associated with older age groups, particularly age > 60 years, male sex, and White race. Health care providers should maintain a high index of suspicion for possible eyelid cancer while examining high-risk patients, such as older White, non-Hispanic men who are active smokers. These data could additionally aid in earlier detection and planning of future health care policies for prevention of eyelid cancer.

Footnotes and Disclosures

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Abbreviations and Acronyms:
AAO = American Academy of Ophthalmolog; **AEC** = any eyelid cancer; **AUC** = area under the curve; **BCC** = basal cell carcinoma; **CI** = confidence interval; **ICD** = International Classification of Disease; **IRIS** = Intelligent Research in Sight; **MIS** = melanoma in situ; **MM** = malignant melanoma; **OR** = odds ratio; **SBC** = sebaceous carcinoma or other specified malignant neoplasm; **SCC** = squamous cell carcinoma; **UMN** = unspecified malignant neoplasm; **US** = United States; **vs** = versus.

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