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The epidemiology of ocular surface squamous neoplasia in a Veterans Affairs population

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Abstract

Purpose—To evaluate the epidemiology of ocular surface squamous neoplasia (OSSN) and its associated risk factors in a South Florida Veterans Affairs Hospital population.

Design—Retrospective case-control study.

Participants: 28 confirmed cases of OSSN from 24,179 veterans who received care at the Miami Veterans Affairs Healthcare System (VA) and affiliated satellite eye clinics between March 1, 2007, and March 1, 2012.

Methods: Data extracted from the veterans administration database comprised of demographic information and medical diagnosis information (based on International Classification of Disease (ICD-9) codes).

Main Outcome Measures: The period prevalence of OSSN and identification of factors associated with the presence of disease.

Results—The period prevalence of OSSN in our population was 0.1%. Studied risk factors included ultra-violet (UV)-related dermatologic diseases (melanoma, squamous and basal cell cancer, and actinic keratosis), UV-related ocular conditions (pterygium). human immunodeficiency virus (HIV) seropositivity, human papilloma virus (HPV)-related diseases, and tobacco use. The presence of a skin malignancy (squamous cell carcinoma (SCC) and/or basal cell carcinoma (BCC)) and pterygium were found to be significantly associated with the presence of OSSN (odds ratio (OR) 4.40, 95% confidence interval (CI) 2.03–9.55, p <0.0005 and OR 16.2 95% CI 7.11–36.9, p <0.0005, respectively).

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Conclusions—The presence of neoplasias and ocular conditions related to sun exposure were the most important risk factors for the presence of OSSN in a South Florida VA population consistent with previous epidemiological reports worldwide.

Keywords

ocular surface squamous neoplasia; epidemiology; sun associated neoplasias

Introduction

Ocular surface squamous neoplasia (OSSN) encompasses the entire spectrum of pre-cancerous squamous epithelium dysplasia (mild, moderate, severe, carcinoma-in situ) to invasive squamous cell carcinoma (SCC) of the conjunctiva and cornea.[1–6] OSSN is presumed to be a rare disease entity in the United States (US), but there are no epidemiological studies evaluating its prevalence to date. However, a study using the United States National Cancer Institute's registries estimated the annual incidence of conjunctival SCC among Caucasians to be 0.03/100 000.[7]

OSSN has been more extensively studied in sub-tropical zones such as sub-Saharan African nations and Australia where it is believed to be more common. Templeton studied the incidence of conjunctival SCC in 4 tribes in Uganda, Africa, between 1961 to 1966 and found an incidence 0.13/100 000.[8] A more recent study evaluated the incidence of disease over time and found a 3 fold increase in the incidence of conjunctival SCC in 1995–1997 compared to in the 1960s.[9] In Brisbane, Australia, the average incidence of OSSN from 1980 through 1989 was found to be 1.9/100 000.[10]

The demographic profile of patients with OSSN appears to be different between developed and developing countries. In the United States and Australia, patients are typically Caucasian males in their sixth decade of life[3, 7, 11–14], while studies from sub-Saharan Africa describe blacks of more equal gender distribution with a mean age of diagnosis in the mid-to-late 30s.[6, 15–19] Furthermore, the course of disease appears indolent in the United States compared to Africa where it has been stated to be more aggressive.[17, 20]

One explanation for the different epidemiologic manifestations of disease may be differences in immune status of the studied populations. In the United States, a minority of patients with OSSN are immunocompromised[2] while Waddell et al found 78% of Malawians with OSSN were human immunodeficiency virus (HIV) positive.[16] Other noted risk factors for OSSN include sun exposure, cigarette smoking and human papilloma virus (HPV) infection. Solar damage manifested by elastosis on histopathology was associated with 83% of OSSN specimens (n=42) in an American study[2] and is seemingly more evident among SCC of the conjunctiva with solar injury present in 92% to 100% of samples.[13, 16] Data on HPV and OSSN are inconclusive with one study finding no HPV in OSSN samples[4] and others finding HPV in all samples.[2, 21]

Since its induction in 1997, the computerized patient record system (CPRS) within Veterans Health Information Systems and Technology Architecture (VistA) employed by the Veterans Health Administration (VHA) has streamlined the electronic patient record.[22, 23]

As an integrated national healthcare information system, CPRS serves as a useful tool for retrospective epidemiological research by providing national and local databases.[23, 24] The Veterans Health Administration (VHA) typically serves a mature population who receive all of their medical care within the VA system, furnishing an excellent data set to study the prevalence of diseases common among an elderly population.[24] This study aimed to assess the epidemiology of OSSN in a south Florida veteran population to fill in the knowledge gap with regards to the prevalence and risk factors of OSSN in a western population.

Materials and Methods

Patient Population

The study population included all patients who received care at the Miami Veterans Affairs Healthcare System (VA) and affiliated satellite eye clinics between the dates of 3/1/2007 and 3/1/2012. Nearly all patients were former active-duty military personnel now residing in or near Miami, FL. However, this population does not include or represent all former military personnel.

Data Collection

All data was extracted from the Veterans Affairs administrative database by a VA-employed programmer and reported in spreadsheet format. The information obtained included demographic information (date of birth, gender, race, ethnicity, combat history, tobacco use) and medical diagnosis information (based on International Classification of Disease, 9th edition, Clinical Modification (ICD-9CM) codes). The diagnosis of OSSN, as well as that for any risk factors of interest was queried via ICD9-CM codes as described above. The risk factors investigated in this study were chosen because they have been proposed to increase the likelihood of developing OSSN. These included: ultra-violet (UV) related dermatologic diseases (melanoma, squamous and basal cell cancer, and actinic keratosis), UV related ocular disease (pterygium), HIV seropositivity, HPV-related diseases (condyloma acuminata, anal/cervical dysplasia), vitamin A deficiency, and relative immune-compromised state (diabetes mellitus). OSSN diagnosis was verified by review of patient records. Due to changes in ICD-9CM codes during the time-period studied and variability among eye care providers of a given diagnosis for a single ailment, a number of codes were used for each diagnosis and risk factor. Those used can be found in table 1.

Statistical Analysis

Descriptive statistics were used to summarize our patient population. All statistical analyses were performed using Microsoft Excel 2010 (Redmond, Washington) and SPSS 20.0 (SPSS Inc, Chicago, IL) statistical packages. Continuous variables were compared between the groups using an independent t-test and categorical variables were compared using the Fisher exact test. Logistic regression analysis was used to evaluate the effect of various risk factors for OSSN, represented by an odds ratio. A 95% confidence interval was used, with a p-value < 0.05 being considered statistically significant. This Miami Veterans Administration Institutional Review Board approved the retrospective review of charts for this study. The methods adhered to the tenets of the Declaration of Helsinki and were Health Insurance Portability and Accountability Act (HIPAA)-compliant.

Results

Prevalence of OSSN in a South Florida VA population

During the five year study period, 24,179 veterans were examined in the eye clinic at the Miami VA and surrounding clinics. Using ICD-9CM codes, 126 potential OSSN cases were identified. From this list, 98 were excluded after chart review revealed a diagnosis other than OSSN (conjunctival melanoma, benign neoplasm of the choroid, conjunctival nevus, pingueculae, pterygia, and other suspicious conjunctival masses). Twenty-eight cases of OSSN were diagnosed by pathology (n=27) or successful response to empiric treatment (n=1). The calculated period prevalence for OSSN among our patient population during the time-period studied was 0.1% (n=28/24,179).

The effect of demographics on the risk of OSSN

The mean age of the patient population was 66 years with a standard deviation (SD) of 15 years. Nearly all patients were male (94%), and most were Caucasian (66%) although 17,252 patients were without documented race. African Americans accounted for 34% while Asian and Indian races accounted for <1% each (Table 2). No demographic factors were associated with an increased risk of OSSN (Tables 2 and 3). Previous or current tobacco use was very common among both the OSSN and control population, however, its use was not a significant risk factor for OSSN (p=0.39).

The effect of medical conditions on the risk of OSSN

Among all risk factors investigated, a diagnosis of squamous and/or basal cell carcinoma (both sun related malignancies) was found to be a significant risk factor for OSSN (OR 4.40, p<0.001) (Table 3). The pre-cancerous cutaneous lesion, actinic keratosis, was found to elevate the risk of OSSN two-fold although this was not statistically significant (p=0.09). A similar trend was seen with melanoma, another UV-related skin cancer (OR 2.13, p=0.46). The presence of pterygium, a benign ocular lesion associated with sun exposure, was associated with a 16 fold increase in the risk of OSSN (p<0.0005).

Seropositive HIV was present in 7% of OSSN cases (OR 2.11, p=0.31). The ages of the two patients with HIV and OSSN were 54 and 61 years, which was not significantly different from the mean age of patients with OSSN and no HIV. The other risk factors investigated including HPV, atopic eczema, and vitamin A deficiency were not found to significantly elevate the risk of OSSN in our population, but were all found to have an odds ratio greater than 1 (Table 3). Interestingly, the presence of diabetes mellitus was associated with a decreased risk of OSSN (OR 0.33, p=0.02).

All OSSN cases during the study period were controlled locally by standard surgical excision with cryotherapy or medically with topical interferon. One patient with previously treated conjunctival intraepithelial neoplasia recurred during the study period and subsequently was enucleated and exenterated secondary to invasive orbital SCC. No cases of OSSN were associated with nodal or distant metastases.

Discussion

The period prevalence of OSSN in our study population was 0.1%. Our mean age of OSSN was analogous to other immune-competent populations worldwide[2, 4, 11–14] and more than 20 years older than mean ages of immune-compromised populations.[6, 16–18] Comparable with other US studies, whites were disproportionately afflicted in our population, with African Americans less likely to develop OSSN.[2, 11]

This study is one of the first to examine risk factors for OSSN in a population with an appropriate control group. We found that the presence of malignancies and ocular abnormalities associated with sun exposure were the strongest risk factors for disease, suggesting that sun exposure is an important risk factor for OSSN in our population.

As OSSN is not a common disease, our analysis is limited by the number of cases (n=28). For this reason, we quantified the likely range of risk estimates with 95% confidence intervals. From this, we can infer that an additional decade of age conferred no more than an additional 22% of risk. Race, ethnicity, and tobacco use may not increase the risk of OSSN at all but neither can we rule out an increased risk of between 3 and 5 fold. The importance of a control group is demonstrated when evaluating, for example, tobacco use as a risk factor of OSSN. The basis for previous data implicating the role of tobacco use in the development of OSSN comes from studies which evaluated the frequency of exposure in a population with disease (e.g. 5 of 11 cases of conjunctival SCC in Victoria, Australia, were known smokers).[13] While diagnosed tobacco use disorder was named in 71% of patients with OSSN (20 of 28), it was also named in 64% of patients without OSSN. This stresses the importance of having a control group when evaluating epidemiologic risk factors.

As with all studies, this work has limitations which need to be considered when interpreting the study results. The largest restriction for this study was utilization of ICD-9CM codes to assess for the presence of risk factors. While ICD-9CM codes may be relatively specific for some conditions, they can be fairly nonspecific for others. This is especially true in men where no routine HPV testing is currently employed and reliance on subjective coding under-represents its true presence. Furthermore, the data selected for conditions such as skin cancer represent a surrogate measure of sun exposure. While certainly correlated, a quantification of an individual’s historical UVB exposure would have been more accurate. Similarly, our data reflecting cigarette smoking described only previous or current smoking en masse without information regarding pack year history. Furthermore, our population of Veterans Affairs Hospital patients may not be representative of other US populations. Our study strengths include investigating a South Florida population with presumed high cumulative UV-B exposure and historic potential for seropositive HIV. Our greatest asset was the ability to use the administrative database not only to describe those with OSSN, but to evaluate and define risk factors of a defined population.

This study suggests that in a South Florida population, sun exposure (as measured by the surrogates of sun related neoplasias and pterygium) is an important risk factor in the development of OSSN. Unlike studies out of Africa, in our population, immune status was not found to be a significant risk factor and diabetes paradoxically was associated with a

decreased risk of disease. Given the very high average UV Index exposure level in Miami during our study period as reported by the National Oceanic and Atmospheric Administration (ftp://ftp.cpc.ncep.noaa.gov/long/uv/cities) and the exposure of veterans to sun during their active service, it is prudent to screen for OSSN during annual comprehensive eye examinations to prevent ocular morbidity, especially persons living in high sun exposure regions.

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Table 1

ICD-9CM codes used for diagnosable risk-factors investigated in the study population

Risk Factor	ICD9CM Code
OSSN	190.3, 224.3, 239.89
Tobacco use	305.1, v15.82, 649, 989.84, E869.4
BCC and SCC	173
Melanoma	172
Cancer (any type)	140–239
Actinic keratosis	702.0
Diabetes mellitus	250.0–250.9
Atopic eczema	691.8
HIV	795.71, V65.44, 079.53, v08, 042
HPV-related disease	078.1, V73.18, 079.4, 230.5, 230.6, 233.1, 233.31, 233.32, 569.44, 622.10, 622.11, 622.12, 623.0, 624.01, 624.02, 795.00–795.19, 796.7
Vitamin A deficiency	264, 264.7, 264.8
Pterygium	372.4

OSSN = ocular surface squamous neoplasia; BCC = basal cell carcinoma, SCC = squamous cell carcinoma, HIV = human immunodeficiency virus, HPV = human papilloma virus

Table 2

Demographics and risk-factor diagnoses of the study population

	Patient Population	OSSN	No OSSN	P-value
n	24,179	28	24,151	
Demographics				
Age (±SD), years	66 (±15)	67 (±8)	66 (±15)	0.92
Gender (female), n (%)	1533 (6%)	0	1533 (6%)	0.26
***Race*, n (%)**				
White	4535 (66%)	8 (73%)	4527 (66%)	0.96
Black	2363 (34%)	3 (27%)	2360 (34%)	
Asian	8 (0.1%)	0	8 (0.1%)	
Indian	21 (0.3%)	0	21 (0.3%)	
Missing	17,252	17	17,235	
***Ethnicity*, n (%)**				
Non-Hispanic	6007 (87%)	10 (91%)	5997 (87%)	1.00
Hispanic	920 (13%)	1 (9%)	919 (13%)	
Missing	17,252	17	17,235	
Tobacco use, n (%)	15361 (64%)	20 (71%)	15341 (64%)	0.43
Combat, n (%)	2562 (11%)	4 (14%)	2558 (11%)	0.53
Diagnoses				
Skin malignancy (BCC or SCC), n (%)	2716 (11%)	10 (36%)	2706 (11%)	0.001
Melanoma, n (%)	413 (2%)	1 (4%)	412 (2%)	0.38
Any cancer	11691 (48%)	15 (54%)	11706 (48%)	0.58
Actinic keratosis, n (%)	3972 (16%)	8 (29%)	3964 (16%)	0.12
Diabetes mellitus	10939 (45%)	6 (21%)	10933 (45%)	0.01
Atopic eczema, n (%)	648 (3%)	1 (4%)	647 (3%)	0.53
HIV, n (%)	850 (4%)	2 (7%)	848 (4%)	0.26
HPV, n (%)	753 (3%)	1 (4%)	752 (3%)	0.59
Vit. A deficiency, n (%)	21 (0.1%)	0	21 (0.1%)	1.00
Pterygium	590 (2.4%)	8 (29%)	582 (2%)	<0.0005

BCC = basal cell carcinoma, SCC = squamous cell carcinoma, Vit. = Vitamin, HPV = human papilloma virus, HIV = human immunodeficiency virus; SD=standard deviation

Table 3

Logistic regression analysis of risk factors for OSSN among the study population

	Odds ratio[b]	95% CI	P-value
Demographics			
Decade of Age	1.00	0.82−1.22	0.92
Race (black v. white)	0.72	0.19−2.71	0.63
Ethnicity (H v. NH)	0.65	0.08–5.10	0.68
Tobacco use[a]	1.44	0.63–3.26	0.39
Combat[a]	1.41	0.49–4.06	0.53
Diagnoses			
Skin malignancy (BCC or SCC)[a]	4.40	2.03–9.55	<0.0005
Melanoma[a]	2.13	0.29–15.74	0.46
Any cancer	1.23	0.59–2.59	0.59
Diabetes mellitus	0.33	0.13–0.81	0.02
Actinic keratosis[a]	2.04	0.90–4.63	0.09
Atopic eczema[a]	1.35	0.18–9.92	0.77
HIV[a]	2.11	0.50–8.91	0.31
HPV[a]	1.15	0.16–8.49	0.89
Pterygium	16.2	7.11–36.9	<0.0005

OSSN= ocular surface squamous neoplasia; H = Hispanic, NH = non-Hispanic, BCC = basal cell carcinoma, SCC = squamous cell carcinoma, HPV = human papilloma virus, HIV = human immunodeficiency virus, CI = confidence interval,

[a] odds ratios presented as presence of risk factor versus absence of risk factor

[b] Univariable analysis