Epidemiology of Squamous Cell Conjunctival Cancer

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Abstract

The etiology of squamous cell carcinoma of the conjunctiva (SCCC) is not well known. A possible role of UVB radiation is suggested by an excess of SCCC in tropical countries and by the association between squamous cell skin cancer and exposure to UVB. Human papillomavirus type 16 also may be involved, given that it has been detected in benign and malignant conjunctival lesions and is the primary etiological agent involved in carcinoma of the anogenital tract. To examine the relationship between UVB exposure and SCCC, population-based age-adjusted incidence rates of SCCC and of conjunctival melanoma and squamous cell cancer of the eyelid were plotted against the UVB insolation of each registry site. Incidence data were examined further for patterns of second primary cancers among people with SCCC. SCCC was rare in the United States, with an incidence rate of 0.03 per 100,000 persons, although the rate was approximately 5-fold higher among males and whites. Regression analysis suggested a link between UVB exposure and SCCC rates ($\beta = 2.25$; $r = 0.58$) that was as strong as that for squamous cell carcinoma of the eyelid ($\beta = 2.73$; $r = 0.62$) and much stronger than for conjunctival melanoma ($\beta = 0.28$; $r = 0.02$). Risk of a second malignancy after SCCC was not increased overall (20 observed and 14.1 expected), although a significant excess of salivary gland cancer (4 observed and 0.03 expected) and a borderline excess of lung cancer (6 observed and 2.4 expected) were noted. These observations suggest that UV radiation likely contributes to SCCC development. Additional research is needed to define the other exposures and host susceptibility that likely interact with UV-related genetic damage in the multifactorial development of this rare neoplasm.

Introduction

SCCC[3] is a rare disease in the United States. It usually arises near the limbus, although it can also occur in the forniceal or palpebral conjunctiva. The tumor ranges in color from translucent to pearly white. SCCC is usually nonfatal and seldom metastasizes (1, 2). Surgical excision, sometimes requiring enucleation, usually is curative.

Although the etiology of the disease is not well known (1), exposure to UVB radiation (1–8), infection with HPV (9–12), and AIDS (13–17) have been suggested as possible risk factors. A strong association with UVB exposure is suggested by the greater frequency of the disease in countries that lie near the equator. SCCC accounts for half or more of all the ocular cancers in Afghanistan and Iran (4, 5). Sudan, Senegal, Ethiopia, and Malawi have also reported frequent occurrences of the cancer (6, 7). Newton *et al.* also determined that the incidence of squamous cell eye cancers decreased by approximately 49% for each corresponding 10-degree increase in latitude (18). Furthermore, SCCC is common in patients who are genetically more susceptible to sunlight, particularly those with XP (19). As a possible analogy, a strong association between squamous cell skin cancer and UVB exposure has been established, as shown by an excess of the disease among fair-skinned people and among people who work outdoors and by the direct relationship between the incidence rate of squamous cell skin cancer and the yearly amount of UVB received in the region (7). In particular, squamous cell eyelid cancer has a strong gradient with UVB exposure, which would also suggest an association between SCCC and UVB exposure, given that the eyelid neighbors the conjunctiva.

Infection with HPV type 16 has also been implicated as a risk factor for SCCC (9–11). There are 60 known types of HPV (20). Types 6 and 11 and others have been connected with benign lesions (9–11), whereas types 16 and 18 and other less common types have been associated with malignant tumors (10, 11, 13). HPV type 16 has been associated with anal (21), cervical (22), vulvar (23, 24), esophageal (25, 26), and oral (27, 28) squamous cell cancers. The association between HPV 16 and SCCC has come primarily from examination of conjunctival precancerous and cancerous lesions. McDonnell *et al.* found HPV type 16 DNA in five out of five dysplastic conjunctival lesions and in one invasive carcinoma, and other studies have found HPV type 16 DNA in conjunctival lesions (9, 10). As a noteworthy exception, however, Tuppurainen *et al.* found no HPV type 16 DNA in four conjunctival carcinomas and suggested that either HPV 16 is not a risk factor for SCCC or that other unknown types of HPV are responsible for the disease (12). Exactly how HPV 16 would cause SCCC is not known, although McDonnell *et al.* suggested that the virus might interact with UVB to cause malignant transformation (9). Furthermore, the apparent presence of BPV in precancerous ocular lesions in cattle (29), combined with the failure to detect BPV using serum antibody testing and Southern blotting of cancerous bovine ocular lesions (30), suggests that in cattle, BPV is involved in the formation of precancerous lesions, which then become malignant in the presence of other cofactors. HPV may cause SCCC using a similar mechanism.

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[3] The abbreviations used are: SCCC, squamous cell carcinoma of the conjunctiva; HPV, human papillomavirus; XP; xeroderma pigmentosum; BPV, bovine papillomavirus; SEER, Surveillance, Epidemiology, and End Results; O:E, ratio of observed:expected cases; CI, confidence interval.

Each of these hypotheses, UVB exposure, genetic susceptibility, and HPV infection, would have implications for understanding carcinogenesis, which is seldom, if ever, a single-step process. Understanding the interactions of host and environmental characteristics can lead to better means of diagnosis, prevention, and treatment. Identification of risk factors for SCCC could lead to appropriate identification of at-risk populations, counseling and evaluation, and intervention for individuals or their environment.

Materials and Methods

Since 1973, the National Cancer Institute has monitored cancer incidence in approximately 10% of the United States population through the SEER program (15), which includes data from nine population-based cancer registries. All persons in the SEER regions are under continuous follow-up (31). The data are compiled annually. Populations are counted at each decennial census and interpolated each year. Tumors are histologically confirmed and staged as *in situ* or invasive. Should a subject be diagnosed with multiple tumors of the same or different types while they are living in an area covered by a SEER registry, the tumors are recorded as having occurred in a single person, facilitating the use of second and multiple tumor searches.

The investigation used data from nine SEER registries that covered the metropolitan areas of San Francisco/Oakland, Atlanta, Detroit, and Seattle, as well as the states of Hawaii, Utah, Connecticut, Iowa, and New Mexico. All tumors diagnosed between 1973 and 1990 were used. The International Classification of Diseases for Oncology site code was 190.3 for conjunctiva; the histology codes for squamous cell carcinoma were 8052, 8070–8072, 8074, and 8430. The number of cases of SCCC were tabulated, and age-specific as well as age-adjusted rates of the cancer overall at each SEER site were obtained using the Cancer Incidence and Surveillance System (KISS) program. For comparison, conjunctival melanoma (histology codes 8720–8780) was examined similarly, and squamous cell eyelid cancer was examined using previously reported data that covered all the SEER regions except for Hawaii (7). Conjunctival melanoma was chosen because previous studies had linked intraocular melanoma to UVB exposure (32, 33). SCCC and conjunctival melanoma are rare among nonwhites, making the corresponding incidence rates more unstable. Therefore, most analyses were limited to whites. Among whites, Anglo and Hispanic ethnic groups could be reliably determined and analyzed separately only for New Mexico. At all sites, the male: female incidence ratios were compared for SCCC, squamous cell eyelid cancer, and squamous cell skin cancer by z test, assuming a Poisson distribution. Because of the scarcity of female cases, some analyses were limited to males.

Since 1974, the National Cancer Institute in collaboration with Temple University and the National Oceanic and Atmospheric Administration has maintained Robertson-Berger meters at several airports in major United States cities to monitor the amount of UVB radiation reaching those cities (34). The study used the specific meter measurements for San Francisco/Oakland, Atlanta, Detroit, and Seattle, and measurements for the following cities to approximate the UVB index for their respective states that participated in SEER: Albuquerque for New Mexico, Mauna Loa for Hawaii, Des Moines for Iowa, and Salt Lake City for Utah. With the UVB index for each registry (Table 1), the age-adjusted incidence rates of squamous cell cancer and melanoma of the conjunctiva at each site were plotted against the UVB index on a log-log scale. The results were analyzed by weighted regression, using the Statistical Analysis System. Due to the small number of cases at each SEER site, the age-adjusted rates may be unstable. Therefore, the linear regression was weighted by the number of cases at each site, giving more influence to the age-adjusted rates at sites where more cases were found. The association between UVB and SCCC incidence was estimated by the slope of the regression (β), and the fit of the model was estimated by the correlation coefficient (R^2). The linear model was extrapolated to predict the incidence rates for a high-risk area, Kampala, Uganda, and the prediction was compared against the current (post-AIDS) and average (pre-AIDS) incidence of SCCC in Kampala (14). The UVB index for Kampala was estimated with the following equation (35):

Table 1 UVB insolation indices of cancer registries

Site	UVB	log UVB
Seattle, WA	101	2.004
Connecticut	108	2.033
Detroit, MI	110	2.041
Iowa	125	2.097
Utah	147	2.167
San Francisco, CA	151	2.179
Atlanta, GA	160	2.204
New Mexico	197	2.294
Hawaii	277	2.442
Kampala, Uganda[a]	340 –357	2.531

[a] Measurement for Kampala is estimated as described in "Materials and Methods."

$$\text{UVB index} = 1{,}500{,}000 - 50{,}000 \times (L - 37.9) + 105 \times (A - 1{,}500)$$

In this equation, L is the latitude of Kampala in degrees, and A is the altitude in feet above sea level. Using an atlas, the latitude of Kampala was found to be 0.19 degrees north, and its altitude to be between 1640 and 3281 feet above sea level.

To evaluate whether cancers with known risk factors were linked to SCCC, the SEER system was used to track any second primaries occurring among persons diagnosed with SCCC between 1973 and 1992. The person-years at risk were calculated separately for males and females by 5-year age groups, from 2 months after the date of SCCC diagnosis to the diagnosis of the second primary, or death, or until December 31, 1992, whichever came first. The number of expected cases for each second primary site was calculated by multiplying the person-years at risk by age-, sex-, and calendar year-specific incidence rates from the SEER database. The O:E ratio, with 95% CIs assuming a Poisson distribution, was calculated.

Results

There were 124 cases of SCCC and 93 cases of conjunctival melanoma reported to SEER between 1973 and 1990. The majority of SCCC cases were among white males, who accounted for 92 (64%) of SCCC cases. There were only 17 SCCC cases among white females, 7 among blacks, and 5 in other racial groups. Racial data were missing for three SCCC cases. The age-adjusted annual incidence rate of SCCC was 0.03/100,000 among whites of both sexes and was significantly higher among white males (0.05/100,000) than among white females (0.01/100,000; $P < 10^{-4}$). Although the incidence rates for SCCC were similar to those for conjunctival melanoma and much lower than those for squamous cell eyelid

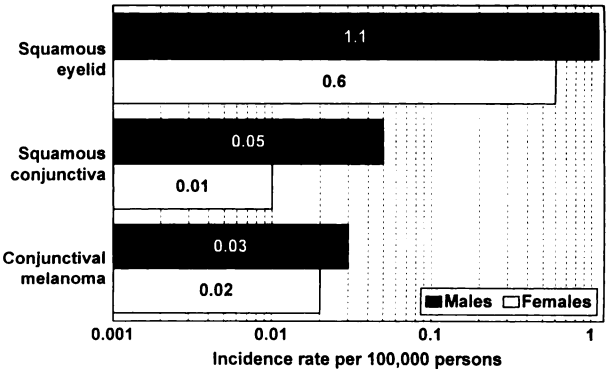

Fig. 1. Male and female incidence rates of SCCC, squamous cell eyelid cancer, and conjunctival melanoma. Data for SCCC and for conjunctival melanoma cover the years 1973–1990 and are from SEER. Data for squamous cell eyelid cancer are from Scotto *et al.* (7) and cover the year 1978.

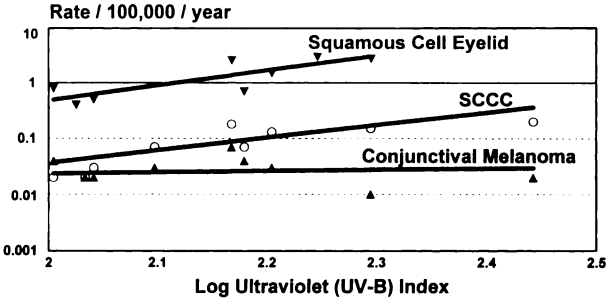

Fig. 2. Log-log plot of the relationship of UVB index to the age-adjusted incidence rates of SCCC (○), squamous cell eyelid cancer (▼), and conjunctival melanoma (▲). The slope of the regression line for SCCC was 2.25 (R^2 = 0.58). For squamous cell eyelid cancer, the slope of the line was 2.73 (R^2 = 0.62). For conjunctival melanoma, the slope was 0.28 (R^2 = 0.02).

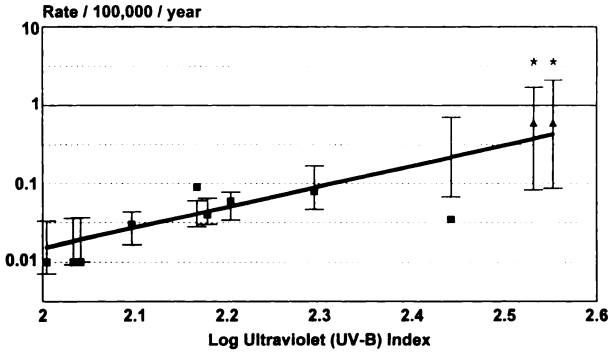

Fig. 3. Log-log plot of the relationship of UVB index to the incidence of SCCC at locations in the United States and in Kampala, Uganda before the AIDS epidemic and during recent years (13). United States incidence rates (■) were modeled by linear regression and extrapolated to the UVB index at Kampala. The incidence of SCCC in Kampala prior to the AIDS epidemic (▲) was close to the extrapolated value, although the post-AIDS incidence rate (*) lay outside of the 95% CI interval (*error bars*) of the estimate.

Table 2 Observed and expected second primary cancers following SCCC

Cancer site	Observed	Expected[a]	O:E	95% CI
All sites	20	14.1	1.4	0.9–1.9
All buccal	5	0.4	12.8	4.1–29.8
Major salivary glands	4	0.03	117.6	31.6–301.1
Oropharynx	1	0.04	23.2	0.3–129.2
All digestive	2	3.5	0.6	0.1–2.1
Rectum	1	1.6	0.6	0.01–3.5
Liver, gall bladder	1	0.6	1.6	0.02–8.8
All respiratory	6	2.7	2.3	0.8–4.9
Lung	6	2.4	2.5	0.9–5.4
All female genital	0	0.2	0	0–20.1
Cervix	0	0.02	0	0–157.0
Testis	0	0.01	0	0–381.5
Prostate gland	4	3.6	1.1	0.3–2.9
Non-Hodgkin's lymphoma	1	0.4	2.5	0.03–13.8
Lymphatic/hematopoietic system	1	1.0	1.0	0.01–5.5
Skin melanoma	1	0.2	4.4	0.06–24.6

[a] Expected cases estimated from U.S. SEER population. 95% CI on the O:E ratio calculated by Poisson distribution.

cancer, the 5-fold excess of SCCC for males was higher than that for squamous cell eyelid cancer (1.8-fold) and conjunctival melanoma (1.5-fold; Fig. 1). In New Mexico, the only registry with consistent identification of white ethnicities, the SCCC rate was significantly higher among Hispanic whites (0.6/100,000) than among Anglo whites (0.09/100,000; $P < 0.05$). Using all SEER sites, the incidence of SCCC among nonwhites (0.004/100,000) was significantly lower than among whites (0.06/100,000; $P < 0.01$).

UVB Exposure. The log-log plots of age-adjusted incidence rate *versus* UVB index were modeled by linear regression for squamous cell eyelid cancer, SCCC, and conjunctival melanoma among white males (Fig. 2). Predictably, the regression line for squamous cell eyelid cancer was steep (β = 2.73), and accurately explained the regressions (R^2 = 0.62), thus showing a strong correlation between incidence of squamous cell eyelid cancer and UVB exposure. As expected, the rates of squamous cell eyelid cancer were higher than the rates of SCCC, but the slope and fit of the regression line for SCCC (β = 2.25; R^2) = 0.58) were almost identical to those for squamous cell eyelid cancer. In contrast, the regression line for conjunctival melanoma was relatively flat (β = 0.28) and fit poorly (R^2 = 0.02).

The log-log plot of age-adjusted incidence rates of SCCC among whites of both sexes *versus* the UVB index was modeled for the United States SEER data and then extrapolated to compare predicted and reported incidence rates of SCCC for Kampala, Uganda. Whites of both sexes were included, because the rates for Kampala encompassed both sexes. The extrapolation of the SEER regression line slightly underestimated both the current (post-AIDS) and average (pre-AIDS) rates of SCCC in Kampala, although the average rate fell within the 95% CI of the projected point (Fig. 3).

Second Malignancies. Twenty of the patients with SCCC developed multiple primary tumors. Table 2 shows the distribution of the second primary tumors by anatomical location. Overall, patients with SCCC were not at a significantly higher risk for contracting second primary cancers (O:E, 1.4; 95% CI, 0.9–1.9). No HPV-related cancers in either the male or female genital areas were found, but SCCC was so rare among females that nearly zero cases were expected. The upper 95% confidence limit for cancer of the cervix after SCCC was 157 (Table 2). The only cancer with a statistically significant excess was salivary gland cancer (O:E, 117.6; 95% CI, 31.2–301.1), although a nonsignificant excess of lung cancers (O:E, 2.5; 95% CI, 0.9–5.4) was present.

Of interest was a female who contracted seven tumors

(three SCCC, squamous cell cancers of the lip and tongue, and melanomas of the skin and conjunctiva) between the ages of 10 and 24. The high number of cancers, the early age at which they occurred, and the location of these cancers at sun-exposed sites strongly suggest a diagnosis of XP.

Discussion

The results suggest an association between incidence of SCCC and exposure to UVB radiation. Among white males, the incidence rate of SCCC increases with increasing levels of UVB insolation. The regression line for this association nearly parallels the regression line for squamous cell cancer of the eyelid among white males. These two observations suggest that UVB exposure plays a similar role in the etiology of both cancers. Given the generally accepted causal association between squamous cell cancer of the eyelid and exposure to UVB, our data suggest that a strong relation between UVB and SCCC exists as well. In contrast, the results also suggest that UVB exposure plays a relatively smaller role in the etiology of conjunctival melanoma, as the regression line is nearly flat, suggesting that melanoma incidence increases very little with increasing possible UVB exposure.

The interaction between environmental exposure and host-susceptibility is seen in the etiology of SCCC. Although exposure to UVB seems to play a role in etiology of the cancer, the rarity of the cancer suggests that cofactors involving environment and host susceptibility must be present. Infection with HPV could be a susceptibility factor, because previous studies have indicated that HPV and UVB may interact to cause malignant transformation (9). Our SEER data showed a dearth of HPV-related second malignancies following SCCC, but we could not exclude HPV infection as a major factor for SCCC because of its rarity, especially among women. We did find a significant excess of salivary gland cancers and a nonsignificant excess of lung cancers, suggesting that smoking may play a role in the etiology of SCCC. These results are consistent with a previous study, which also found an excess of smoking-related second primaries following squamous cell skin cancer (36) and with the potential for a direct effect of cigarette smoke on the eye (37). However, these findings should be viewed conservatively, because the low number of person-years following SCCC limits our study's scope and power.

Pigmentation is a host-susceptibility factor that the study examined. Nonwhites and Hispanic whites are at a presumed lower risk for UVB-related cancers than are Anglo whites, as a result of their skin pigmentation. However, two observations in our study ran contrary to this presumption. In New Mexico, the incidence of SCCC among Hispanics was nearly seven times higher than the incidence of SCCC among Anglo whites. Furthermore, the regression line in Fig. 3 suggests similar susceptibility to UVB-induced SCCC in United States whites and in Kampala, Uganda, a population that is virtually all black. Another recent study of UVB and SCCC (18) suggests that tropical dark-skinned populations, such as those in Mali and Zimbabwe, and light-skinned populations, such as those in Western Europe, are equally susceptible. As the conjunctiva is not pigmented, and as whites and nonwhites have similar susceptibility to SCCC, it appears that the strong protective effect of skin pigmentation is limited to skin cancer and does not influence the risk of UVB-related SCCC.

One prominent host-susceptibility factor suggested by the data is heredity. It is already well documented that persons with XP are susceptible to UVB damage, as seen in previously published literature and in a presumed XP case found in the current analysis. It is noteworthy, however, that less than 1% of the SCCC cases had frank XP. It also may be possible that persons who are heterozygous for XP may be more susceptible to SCCC, and to UVB-related cancers in general. The higher incidence of SCCC among males may also point to other genetic, X-chromosome-linked factors. Although an excess among males may be explained by a predisposition of men to remain outdoors more frequently than women, the male:female incidence ratio for SCCC exceeds the male:female incidence ratios of squamous cell skin cancer and squamous cell eyelid cancer, two other UVB-linked cancers.

Given the rarity of SCCC, several factors must be taken into account when considering the results. First, the UVB indices reflect only the maximum possible exposure at a given SEER site. They do not reflect individual exposure to UVB, which allows for several confounding factors. People who are more susceptible to UVB exposure may avoid staying outdoors or preferentially wear sunglasses (8). Also, additional confounding factors may be more common in certain regions. People living in the South, for example, may tend to have occupations which would increase their exposure to UVB. Furthermore, it is possible that the local hospitals may have misdiagnosed the tumor or its histology.

In summary, UVB appears to be important in the development of SCCC. It is equally clear, however, that much more work, perhaps including a case-control study of smoking, occupation, UVB-related variables (8), and genetic susceptibility, is needed to explain why SCCC occurs so rarely with such a ubiquitous exposure as sunlight.

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