**Risk Factors for Keratinocyte Carcinoma Skin Cancer In Nonwhite Individuals: A Retrospective Analysis**

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**Abstract**

**Background:** As the majority of the U.S. population will consist of nonwhite individuals by the year 2043, it is essential that both physicians and patients are educated about skin cancer in nonwhite individuals.

**Objective:** To update the epidemiology, investigate specific risk factors, and facilitate earlier diagnosis and intervention of KC in nonwhite individuals

**Methods:** IRB-approved retrospective chart review of all non-white individuals who had received a biopsy-proven diagnosis of skin cancer at Drexel Dermatology from June 2008 to June 2015.

**Results:** Squamous cell carcinoma (SCC) was the most commonly diagnosed skin cancer in Black and Asian populations, while basal cell carcinoma (BCC) was the most common skin cancer in Hispanics. Blacks exhibited the majority of their SCC lesions in sun-protected areas, particularly the anogenital area. On average, current smokers were diagnosed with skin cancer 12.27 years earlier than former smokers and 9.36 years earlier than nonsmokers.

**Limitations:** Single-center design and inter-practitioner variability of skin examination

**Conclusions:**  The importance of photoprotection in nonwhite individuals should not go overlooked. However, emphasis should also be placed on active examination of sun-protected areas in nonwhites and recognition of the relationship between HPV and genital SCC lesions. Smoking cessation should be integrated in dermatologic counseling of all patients. Interventions tailored to each of these ethnic groups are needed.

**Capsule Summary**

* The presence of a single skin cancer lesion in a nonwhite individual may be associated with greater morbidity and mortality than in a White patient.
* Blacks exhibit squamous cell carcinoma in sun-protected areas, particularly the anogenital area, at a higher rate than Asians and Hispanics.
* Emphasize skin examination of sun-protected areas and counsel all patients on smoking cessation.

**Introduction**

Keratinocyte carcinoma (KC) is the most common malignancy in the United States and occurs much less frequently in nonwhite populations compared to Whites. KC and melanoma combined represent 20-30% of all neoplasms in Whites, 2-4% of all neoplasms in Asians, and 1-2% of all neoplasms in Blacks and Asian Indians.1 Basal cell carcinoma (BCC) is the most common KC among Whites, Hispanic, Chinese, and Japanese populations, while squamous cell carcinoma (SCC) is the most common KC in Blacks and Asian Indians and is the second most common cutaneous neoplasm in Chinese, Japanese, and Whites.

Although the White population exhibits a greater number of skin cancers overall, the presence of a single skin cancer lesion in a nonwhite individual may be associated with greater morbidity and mortality than one found in a White patient. Compared to the metastatic rate of squamous cell carcinoma (SCC) arising in areas of chronic scarring in White individuals (1% to 4%), SCC in areas of chronic scarring in blacks tends to be more aggressive and is associated with a 20% to 40% risk of metastasis.2 While this disparity may be attributed to the inherent aggressiveness of these tumors, differences in survival rates may be due to later diagnosis and socioeconomic factors such as lack of access to healthcare, adequate insurance coverage, and lack of transportation.2 In addition to advanced stage at presentation, malignant skin lesions in nonwhite patients often present in an atypical fashion. Our study seeks to raise awareness of the differences in epidemiology, clinical presentation, and prognosis of skin cancers in nonwhite populations in order to reduce the discrepancy between incidence, morbidity and mortality among races.

Despite reports of KC associated with non-ultraviolet-light risk factors, the isolated number of reported cases and the lack of large series in the literature have precluded firm conclusions about epidemiology and risk factors. In the present single-site retrospective chart analysis, we investigate 169 KCs over a span of 8 years and the associations between KC and risk factors in 133 nonwhite participants at the Drexel Dermatology Clinic in Philadelphia, PA. The purpose of the study is to describe associations between specific risk factors and keratinocyte carcinoma in nonwhite populations with the ultimate goal of creating a risk prediction model that can be used for early diagnosis and treatment.

**Methods**

An IRB-approved retrospective chart review was performed at Drexel Dermatology from June 2008 to June 2015 of all non-white individuals who had received a biopsy-proven diagnosis of skin cancer. In total, this represented 133 patients of self-identified Black, Hispanic, or Asian origin with a skin cancer diagnosis. Demographic and clinical characteristics were collected and compared across racial groups. Fitzpatrick type (I-VI) was determined based on patient-reported skin response to sun without sunscreen. Demographics (race, gender) and clinical characteristics (sun exposure, smoking, diabetes, hypertension, hyperlipidemia, immunosuppression) were used to examine differences in age of diagnosis of a skin lesion. These variables either directly correlate with skin cancer risk, confer a state of relative immunosuppression, are associated with the use photosensitizing medications, or impact cell membrane integrity and subsequent cell division.3 All patients marked as immunosuppressed were on up to four immunosuppressive medications for solid organ transplant recipients (N=10), HIV positive (N=7), or were on immunosuppressive therapy for SLE (N=1) or RA (N=2). A forward stepwise multiple linear regression was used to find the strongest predictors of age of diagnosis, allowing each predictor to be entered into the equation at a *p*< .05 prediction level of significance. The purpose of this analysis was to find the strongest variables of use for understanding the age of diagnosis using all variables at once, rather than individual *t*-tests. A simultaneous regression of the same data produced the same significant predictors, with only a small addition to *R*2 due to the addition of many non-useful predictors. Anatomical locations designated as sun-protected included: genitals, inguinal fold, gluteal fold, and perianal region. Partially sun-protected included: lower extremity, chest, abdomen, and back. All other regions were categorized as sun-exposed. A Fisher’s Exact test was calculated on the significant predictors from this analysis (race, sun exposure) to determine the effects of each variable on tumor type while controlling for small *N*. Effect size *d* values were added to show the strength of the difference between categorical groups.

**Results**

Demographics

 The cohort consisted of 133 nonwhite patients with 169 total malignant cutaneous lesions. Forty-eight of the patients identified as Black, 68 as Hispanic, and 17 as Asian (Table 1). The Asian population self-identified as Fitzpatrick skin types II-IV, while Hispanic and Black populations self-identified as skin types III-IV and V-VI, respectively. The majority of patients were female (54.9%), nonsmoker (65.4%), nondiabetic (63.9%), hypertensive (76.7%), hyperlipidemic (53.4%), and immunocompetent (85.0%) (Table 2). The 169 lesions comprised 61 BCC, 102 SCC, and 5 melanoma, and 1 porocarcinoma. Melanoma and porocarcinoma were excluded from analysis due to their sample sizes. The average age of skin cancer diagnosis was 68.9 years.

Overall Model for Tumor Type

A forward stepwise regression determined that race and anatomical distribution of skin lesions were correlated with the type of tumor diagnosed in a patient (*χ2* = 50.16, df 12, *p*< .001, Nagelkerke*R2* = 0.36).

Race and Tumor Type

Black and Asian patients were significantly more likely to be diagnosed with SCC than BCC (p < 0.05, SE = 0.55), while Hispanic patients were equally likely to be diagnosed with either tumor type. The Black population presented a total of 57 skin cancers in 48 patients, including 8 BCC (14.0%), 47 SCC (82.5%), and 2 melanomas (3.5%) (Table 1). In the Asian population, we found 20 skin cancers in 17 patients with 6 BCC (30.0%) and 14 SCC (70.0). In the Hispanic population, there were 92 skin cancers in 68 patients with 47 BCC (51.1%), 41 SCC (44.6%), 1 porocarcinoma, and 3 melanomas.

Anatomical Distribution and Tumor Type

A Fisher’s Exact test demonstrated a relationship between sun-exposed anatomic areas and tumor type (p < 0.001, Cramer’s V = 0.43). Using standardized residuals, sun protected (SP) and partially sun exposed (PSE) areas showed significantly less BCC, while sun exposed (SE) areas showed equal rates of BCC and SCC diagnoses.

Interaction between Race and Anatomical Distribution

The large majority of Hispanic and Asian patients demonstrated malignancy in sun exposed areas, 83.7% (N = 77) and 85.0% (N = 17) respectively, compared to 28.1% (N = 16) of Black patients. Forty-two percent of malignant lesions (N = 24) in Black patients were in PSE areas, and 29.8% (N = 17) occurred in SP areas. Black patients exhibited 80.9% (N = 38) of SCC and SCCIS lesions in partially exposed or sun-protected areas. In comparison, Hispanic and Asians exhibited 24.4% (N = 10) and 21.4% (N = 3) of SCC and SCCIS lesions in partially exposed or sun-protected areas.

 The next analysis looked to see if there was a statistical difference in the anatomic distribution of BCC and SCC between different ethnic groups. There was no significant pattern of anatomical distribution of BCC lesions between the different ethnic groups (p = 0.19, V = 0.18), as the BCC tumor type is predominantly found in sun-exposed areas, regardless of race. However, there was a significant difference in the anatomic distribution of SCC lesions between different ethnic groups (p < .001, Cramer’s V = 0.43). Black patients were more likely to develop tumors in PSE and SP areas than Hispanic and Asian patients. Hispanic patients were more likely to develop tumors in SE areas.

Effect of Smoking, Immunosuppression, Hypertension and Gender on Age of Diagnosis

A forward stepwise regression determined that smoking, immunosuppression, and hypertension were correlated with the age of diagnosis (p < 0.001, R2 = 0.19). Current, former, and nonsmokers showed significant differences with respect to age of skin cancer diagnosis. Analysis of the relationship between smoking and skin cancer indicated that current smokers (M = 60.23, SD = 10.72) were diagnosed with skin cancer at significantly younger ages than both former smokers (M = 72.50, SD = 10.53, p < .001, d = 1.16) and patients who had never smoked (M = 69.59, SD = 13.67, p < .001, d = 0.71) (Figure 1). Current smokers were diagnosed with skin cancer 12.27 years earlier on average than former smokers and 9.36 years earlier than nonsmokers.

Immunosuppressed patients were diagnosed at a younger age (M = 65.21, SD = 8.93) than non-immunosuppressed patients (M = 69.61, SD = 13.64, p < 0.01, d = 0.34). Hypertensive patients (M = 71.23 years, SD = 11.88) were more likely to be diagnosed later than non-hypertensive patients (M = 61.75 years, SD = 14.52, p < 0.001, d = 0.76). Gender and hyperlipidemia were non-significant predictors of both age and type of tumor.

**Discussion**

Our study highlights the most notable risk factors for KC in our nonwhite population. As UV exposure remains the primary risk factor for BCC in both white and nonwhite individuals, nonwhite groups naturally exhibit lower incidences of cutaneous malignancy because increased epidermal melanin acts as an intrinsic SPF against UV damage.2,4 Thus, other factors must contribute to skin cancer in nonwhite individuals, especially those with minimal sun exposure or with lesions in anatomical locations of constant sun protection.

Analyzing the difference between races may elucidate these factors. Though we acknowledge the role of Fitzpatrick skin type (FST) in skin cancer risk, a distinct entity from race, FST is limited by exclusive use by dermatologists. Our study evaluates race rather than FST as racial differences play an important role in skin cancer risk and is universally utilized by both dermatologists and non-dermatologic practitioners. Our analysis showed that race had a statistically significant effect on cancer type when controlling for sun exposure, smoking status, diabetes, hypertension, hyperlipidemia, and immunosuppression. SCCs were the most common KC in Black (82.5%) and Asian (70.0%) patients, while BCCs (51.1%) were the most common skin cancer in Hispanics (Table 1). A study by Loh et al. examined the prevalence of KC among Asian and Hispanic patients over a five-year period. In their cohort, 61.4% of Hispanics had BCC and 38.6% had SCC while 66.7% of Asian patients had BCC and 33.3% had SCC. They found that race was a significant predictor for KC location but not type; however, the study did not include Blacks.5

Moreover, our study showed a relationship between race and location of SCC lesions. The Black population exhibited 80.9% of SCC lesions in areas of partial or full sun protection, more than three times the proportions exhibited by the Hispanic and Asian populations, 24.4% and 21.4% respectively. The majority of these lesions were in the groin and anogenital region. Rather than sun exposure, there may be a confounding variable contributing to these lesions such as behavioral or genetic differences. Another possibility is a partial or full viral etiology. Though the exact pathogenic mechanism remains unclear, Human Papillomavirus (HPV) may contribute carcinogenic potential to SCC lesions in immunocompetent and especially immunocompromised patients.6,7 A study by Nadhan et al. demonstrates that up to 67% of SCC lesions found in the anogenital area of nonwhite transplant patients carried high-risk HPV subtypes 16, 18, 31, and 33.8 The study suggests investigating the utility of HPV vaccination for the prevention of SCC in transplant patients. Our findings suggest the vaccination’s utility in preventing SCC may extend to all nonwhite patients.

Smoking may be a significant additional predictor of KC occurrence in nonwhite patients. Our study showed that smoking had a very large effect (Cohen’s d = 1.16) on age of cancer occurrence. Being a current smoker precipitated earlier cancer occurrence in nonwhite individuals, as much as 12 years. There has been controversy regarding the relationship between smoking and KC; however, recent literature has bolstered the idea that smoking increases the risk of SCC (Odds Ratio 1.61).9 Additional literature states the relative risk of acquiring skin cancer to be as high as 2.0 when compared to nonsmokers after controlling for other risk factors such as age and sun exposure.10 As the vast majority of patients in these studies were white, our study is one of the first to demonstrate this relationship in a nonwhite population. Counseling on smoking cessation should be provided to all patients, white and nonwhite alike.

 Immunosuppressed patients expectedly developed skin cancer earlier than immunocompetent patients, on average by 4.4 years. Interestingly, hypertensive patients were diagnosed with skin cancer 10 years later than non-hypertensive patients. This is particularly surprising as we would expect the opposite as hydrochlorothiazide, a commonly used anti-hypertensive medication, has been shown to be related to photosensitivity. We cannot explain this finding and it may warrant further exploration with a larger cohort.11

**Limitations**

 Limitations of our study include inter-practitioner variability in thoroughness of genital examinations, most likely leading to under-diagnosis of genital lesions. Furthermore, this is a single center study and a small sample size, both of which contribute to a lack of generalizability.

**Conclusion**

Given the role of ultraviolet radiation in BCC and some SCC development, the importance of photoprotection in nonwhite individuals should not go overlooked. However, emphasis should also be placed on active examination of sun-protected areas in all nonwhites, especially Blacks, and exploration of the relationship between HPV and genital SCC lesions. Smoking cessation should be integrated in dermatologic counseling of all nonwhite patients. Given the increasing Hispanic, Black, and Asian demographics in the United States, interventions that address the unique risk factors of each of these groups are needed.

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**Abbreviation and Acronym List**

BCC – basal cell carcinoma

SCC – squamous cell carcinoma

SCCIS – squamous cell carcinoma in situ

KC – keratinocyte carcinoma

SLE – Systemic Lupus Erythematosus

RA – Rheumatoid Arthritis

HIV – Human Immunodeficiency Virus

SP – Sun Protected

SE – Sun Exposed

PSE – Partially Sun Exposed

FST – Fitzpatrick skin type

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| **Table 1. Demographics** |
|  | **Black** | **Hispanic** | **Asian** |
| **Total N** | 48 | 68 | 17 |
| **Gender (%)** |  |  |  |
| Male | 18 (37.5) | 31 (45.6) | 11 (64.7) |
| Female | 30 (62.5) | 37 (54.4) | 6 (35.3) |
| **Age of Dx (SD)** | 66.95 (13.09) | 70.12 (14.09) | 69.60 (7.30) |
| **CA Type (%)** |  |  |  |
| BCC | 8 (14.0) | 47 (51.1) | 6 (30.0) |
| SCC | 47 (82.5) | 41 (44.6) | 14 (70.0) |
| Other | 2 (3.5) | 4 (4.3) | 0 |
| Total Lesions | 57 | 92 | 20 |
| **CA Location** |  |  |  |
| Sun Exposed | 16 (28.1) | 77 (83.7) | 17 (85.0) |
| Partially Sun Exposed | 24 (42.1) | 14 (15.2) | 3 (15.0) |
| Sun Protected | 17 (29.8) | 1 (1.1) | 0 |

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| **Table 2. Risk Factors** |
|  | **Black** | **Hispanic** | **Asian** |
| **Total N** | 48 | 68 | 17 |
| **Smoking (%)** |  |  |  |
| Current | 7 (14.6) | 8 (11.8) | 3 (17.6) |
| Former | 12 (25.0) | 13 (19.1) | 3 (17.6) |
| Never | 29 (60.4) | 47 (69.1) | 11 (64.8) |
| **Diabetes (%)** |  |  |  |
| Yes | 14 (36.8) | 27 (39.7) | 7 (41.2) |
| No | 34 (70.8) | 41 (60.3) | 10 (58.8) |
| **Hypertension (%)** |  |  |  |
| Yes | 37 (77.1) | 52 (76.5) | 13 (76.5) |
| No | 11 (22.9) | 16 (23.5) | 4 (23.5) |
| **Hyperlipidemia (%)** |  |  |  |
| Yes | 23 (47.9) | 41 (60.3) | 7 (41.2) |
| No | 25 (52.1) | 27 (39.7) | 10 (58.8) |
| **Immunosuppression (%)** |  |  |  |
| Yes | 12 (25.0) | 4 (5.9) | 4 (23.5) |
| No | 36 (75.0) | 64 (94.1) | 13 (76.5) |