Risk factors for keratinocyte carcinoma skin cancer in nonwhite individuals: A retrospective analysis

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Background: Because most of the US 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 persons.

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

Methods: Institutional review board—approved retrospective chart review of all nonwhite patients who had received a biopsy-proven diagnosis of skin cancer at Drexel Dermatology during June 2008-June 2015.

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

Limitations: Single-center design and interpractitioner variability of skin examination.

Conclusion: The importance of lesions in photoprotected areas in nonwhite individuals should not go overlooked. However, emphasis should also be placed on active examination of sun-protected areas in nonwhite persons and recognition of the relationship between human papillomavirus 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. (J Am Acad Dermatol 2019;81:373-8.)

Key words: Asian; black; dark skin; epidemiology; ethnic; Hispanic; nonmelanoma skin cancer; smoking.

Keratinocyte carcinoma (KC) is the most common malignancy in the United States and occurs much less frequently in nonwhite populations than white populations. KC and melanoma combined represent 20%-30% of all neoplasms in white persons, 2%-4% of all neoplasms in Asians, and 1%-2% of all neoplasms in

Abbreviations used:

BCC:	basal cell carcinoma
HPV:	human papillomavirus
KC:	keratinocyte carcinoma
SCC:	squamous cell carcinoma
SD:	standard deviation

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black and Asian Indian populations.[1] Basal cell carcinoma (BCC) is the most common KC among white, Hispanic, Chinese, and Japanese populations and squamous cell carcinoma (SCC) is the most common KC among black and Asian Indian populations and is the second most common cutaneous neoplasm in Chinese, Japanese, and white populations.

Although the white population exhibits a greater number of skin cancers overall, the presence of a single skin cancer lesion in a nonwhite individual might be associated with greater morbidity and mortality than one found in a white person. For SCCs arising in areas of chronic scarring, the risk for metastasis is lower in white individuals (1%-4%) than black individuals (20%-40%), and these SCCs tend to be more aggressive in black persons.[2] Although this disparity might be attributable to the inherent aggressiveness of these tumors, differences in survival rates might be due to later diagnosis and socioeconomic factors, such as lack of access to health care, adequate insurance coverage, and 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 to reduce the discrepancy with incidence, morbidity, and mortality among persons of different race/ethnicities.

Despite reports of KC associated with risk factors other than ultraviolet radiation exposure, 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, Pennsylvania. The purpose of this study is to describe associations between specific risk factors and KC in nonwhite populations, with the ultimate goal of creating a risk prediction model that can be used for early diagnosis and treatment.

CAPSULE SUMMARY

- The presence of a single skin cancer lesion is associated with greater morbidity and mortality in nonwhite populations than white populations.
- In nonwhite patients, there should be increased vigilance in sun-protected areas, particularly the anogenital region, during skin examinations, and all patients should be counselled on smoking cessation.

METHODS

An institutional review board—approved retrospective chart review was performed at Drexel Dermatology among all nonwhite individuals who had received a biopsy-proven diagnosis of skin cancer during June 2008-June 2015. In total, 133 patients with skin cancer diagnoses who self-identified as black, Hispanic, or Asian were included in the study. Demographic and clinical characteristics were collected and compared across racial groups. Fitzpatrick type (I-VI) was determined on the basis of patient-reported skin response to sun without sunscreen. Demographics (race, sex) and clinical characteristics (sun exposure, smoking, diabetes, hypertension, hyperlipidemia, immunosuppression) were used to examine differences in age at diagnosis of an SCC or a BCC lesion. These variables might directly correlate with skin cancer risk, confer a state of relative immunosuppression, be associated with the use photosensitizing medications, or affect cell membrane integrity and subsequent cell division.[3] All patients marked as immunosuppressed were on ≤4 immunosuppressive medications for solid-organ transplant (n = 10), were HIV positive (n = 7), or were on immunosuppressive therapy for systemic lupus erythematosus (n = 1) or rheumatoid arthritis (n = 2). Anatomic locations designated as sun-protected included genitals, inguinal fold, gluteal fold, and perianal region. Partially sun-protected locations included lower extremities, chest, abdomen, and back. All other regions were categorized as sun exposed.

Forward, stepwise multiple linear regression was used to find the strongest predictors of age at diagnosis (continuous dependent variable), allowing each predictor to be entered into the equation at a $P < .05$ prediction level of significance. Independent variables included race, sex, sun exposure, smoking, diabetes, hypertension, hyperlipidemia, immunosuppression, and photosensitization (all categorical variables, see Tables I and II for sample sizes). The purpose of this analysis was to find the strongest variables associated with age at diagnosis by using all variables at once, rather than by 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 nonuseful predictors. The same independent variables were then used to predict tumor type (categorical variable) by using a binomial logistic regression. 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 the small population size.

RESULTS

Demographics

The cohort consisted of 133 nonwhite patients with 169 total malignant cutaneous lesions; 48 patients identified as black, 68 as Hispanic, and 17 as Asian (Table I). The Asian population self-identified as Fitzpatrick skin types II-IV, and Hispanic and black populations self-identified as skin types III-IV and V-VI, respectively. Most patients were female (54.9%), nonsmokers (65.4%), nondiabetic (63.9%), hypertensive (76.7%), hyperlipidemic (53.4%), and immunocompetent (85.0%) (Table II). The 169 lesions comprised 61 BCCs, 102 SCCs, 5 melanomas, and 1 porocarcinoma. The black population included 48 patients with a total of 57 skin cancers, including 8 BCCs (14.0%), 47 SCCs (82.5%), and 2 melanomas (3.5%). In the Asian population (n = 17), we found 20 skin cancers: 6 BCCs (30.0%) and 14 SCCs (70.0%). In the Hispanic population (n = 68), there were 92 skin cancers: 47 BCCs (51.1%), 41 SCCs (44.6%), 3 melanomas, and 1 porocarcinoma. Melanoma and porocarcinoma were excluded from statistical analysis because of their small sample sizes; all data regarding age at diagnosis refer to SCC and BCC lesions. The average age at skin cancer diagnosis in the overall cohort was 68.9 (95% confidence interval 67.01-70.96) years, in black persons 66.95 (standard deviation [SD] 13.09) years, Hispanic persons 70.12 (SD 14.09) years, and Asian persons 69.60 (SD 7.30) years. There were no statistical differences among these ages as examined by independent *t* tests (black vs Hispanic $P = .15$, Hispanic vs Asian $P = .44$, and Asian vs black $P = .87$).

Effect of smoking, immunosuppression, hypertension, and sex on age at diagnosis

Forward stepwise regression determined that smoking, immunosuppression, and hypertension were correlated with age at diagnosis ($P < .001$, $R^2 = 0.19$). Table III shows the mean differences and regression significance values of the significant variables. To interpret categorical predictors, individual group descriptive statistics (mean [SD]) along with Cohen d effect sizes are provided to gauge the size of the differences between groups. Cohen d is a standardized measure of the differences between groups and can be interpreted as similar to a Z score. Current, former, and nonsmokers showed significant differences with respect to age at skin cancer diagnosis. Analysis of the relationship between smoking and skin cancer indicated that current smokers had skin cancer diagnoses at significantly younger ages (60.23 [10.72] years) than both former smokers (72.50 [SD 10.53] years, $P < .001$, Cohen d = 1.16) and never smokers (69.59 [SD 13.67] years, $P < .001$, Cohen d = 0.71). Current smokers had skin cancer diagnoses 12.27 years earlier on average than former smokers and 9.36 years earlier than never smokers.

Immunosuppressed patients were diagnosed at a younger age (65.21 [SD 8.93] years) than nonimmunosuppressed patients (69.61 [SD 13.64] years, $P < .01$, Cohen d = 0.34). Hypertensive patients were more likely to have diagnoses later (71.25 [SD 11.88] years) than nonhypertensive patients (61.75 [SD 14.52] years, $P < .001$, Cohen d = 0.76). All other predictors were nonsignificant.

Overall model for tumor type

The same demographic and risk variables were used to predict type of tumor, BCC (n = 61) or SCC (n = 102), in a binomial logistic regression. The overall model was a significant predictor of tumor type ($\chi^2 = 50.16$, degrees of freedom 12, $P < .001$, Nagelkerke $R^2 = 0.36$). The model correctly predicted 63.93% of the BCC tumors and 82.35% of the SCC tumors (75.46% overall correct classification). All predictors are presented in Table IV; logarithmic odds are given as the effect size to gauge the size of the predictor.

Race and tumor type

Race was a significant predictor in the overall model of tumor type; therefore, a follow-up Fisher's exact test was performed to examine these results ($P < .001$, Cramer V = 0.37). Cramer V is an effect size, similar to a correlation, provided to gauge the importance of the effect. We then used the standardized residuals to determine which categories were more or less likely to receive a diagnosis by tumor type. Black and Asian patients were significantly more likely to have SCC diagnoses than BCC diagnoses, and Hispanic patients were equally likely to receive SCC and BCC diagnoses.

Anatomical distribution and tumor type

A Fisher's exact test demonstrated a relationship between sun-exposed anatomic areas and tumor type ($P < .001$, Cramer V = 0.43). Using standardized residuals, sun-protected and partially sun-exposed areas had significantly fewer BCC diagnoses, and no statistical differences were seen in the total number of BCC and SCC diagnoses in sun-exposed areas.

Table I. Demographics of study population

Characteristic	Black, n = 48	Hispanic, n = 68	Asian, n = 17
Sex, n (%)			
Male	18 (37.5)	31 (45.6)	11 (64.7)
Female	30 (62.5)	37 (54.4)	6 (35.3)
Age at diagnosis, y, mean (SD)	66.95 (13.09)	70.12 (14.09)	69.60 (7.30)
Cancer type, n (%)			
Basal cell carcinoma	8 (14.0)	47 (51.1)	6 (30.0)
Squamous cell carcinoma	47 (82.5)	41 (44.6)	14 (70.0)
Other	2 (3.5)	4 (4.3)	0
Total lesions	57	92	20
Cancer location, n (%)			
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

SD, Standard deviation.

Table II. Risk factors evaluated in study

Risk factor	Black, n = 48, n (%)	Hispanic, n = 68, n (%)	Asian, n = 17, n (%)
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)

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 with 28.1% (N = 16) of black patients. In total, 42% of malignant lesions (n = 24) in black patients were in partially sun-exposed areas, and 29.8% (N = 17) occurred in sun-protected areas. Black patients exhibited 80.9% (N = 38) of SCC and SCC in situ lesions in partially exposed or sun-protected areas. In comparison, Hispanic and Asian patients exhibited 24.4% (n = 10) and 21.4% (n = 3) of these lesions (SCC and SCC in situ) in partially exposed or sun-protected areas, respectively.

In the next analysis, we looked to see if there was a statistical difference in the anatomic distribution of BCC and SCC among the different ethnic groups by using 2 Fisher's exact analyses (1 for each tumor type). There was no significant pattern of anatomic distribution for BCC lesions among the different ethnic groups (P = .19, Cramer V = 0.18); the BCC tumor type was predominantly found in sun-exposed areas, regardless of race. However, there was a significant difference in the anatomic distribution of SCC lesions among the different ethnic groups (P < .001, Cramer V = 0.43). Black patients were more likely to develop tumors in partially sun-exposed and sun-protected areas than Hispanic and Asian patients. Hispanic patients were more likely to develop tumors in sun-exposed areas.

DISCUSSION

Our study highlights the most notable risk factors for KC in a nonwhite population. As ultraviolet light 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 sun-protection factor against ultraviolet light damage.[2,4] Thus, other factors must contribute to skin cancer in nonwhite individuals, especially those with minimal sun exposure or with lesions in anatomic locations of constant sun protection.

Analyzing the differences among races might elucidate these factors. Though we acknowledge the role of Fitzpatrick skin type in skin cancer risk, a distinct entity from race, Fitzpatrick skin type is limited by its exclusive use by dermatologists. Our study evaluates race rather than Fitzpatrick skin type, as racial differences play an important role in skin

Table III. Mean differences and regression statistics for age at skin cancer diagnosis

Predictor	Mean difference (95% CI)	*t* test	*P* value	Cohen d
Hypertension*	9.48 (4.50-14.46)	4.46	< .001	0.76
Current smoker vs former smoker	12.27 (6.50-18.04)	3.76	< .001	1.16
Current smoker vs never smoked	9.36 (2.98-15.74)	3.29	.001	0.71
Immunosuppression	4.40 (0.17-8.64)	2.71	.008	0.34

All factors presented in this table are statistically significant.
CI, Confidence interval.
*Hypertensive patients were more likely to be diagnosed later than nonhypertensive patients. All other factors (current smoker and immunosuppression) correlate with an earlier age at skin cancer diagnosis.

Table IV. Regression statistics for prediction of tumor type

Predictor	*b* (95% CI)	*Z* score	*P* value	Logarithmic OR
Black vs Hispanic	**−1.22 (−2.30 to −0.14)**	**−2.21**	**.03**	**0.30**
Black vs Asian	0.17 (−1.23 to 1.57)	0.24	.81	1.19
Sex	−0.62 (1.48 to 0.24)	−1.42	.16	0.54
Sun-exposed vs partially exposed areas	**1.72 (0.58 to 2.86)**	**2.95**	**.003**	**5.58**
Sun-exposed vs sun-protected areas	17.34 (−1760.85 to 1795.54)	0.02	.98	ND*
Current smoker vs former smoker	0.3 (−1.04 to 1.65)	0.44	.66	1.35
Current smoker vs never smoker	0.54 (−0.68 to 1.77)	0.86	.39	1.72
Diabetes	0.11 (−0.78 to 1.01)	0.25	.80	1.12
Hypertension	−0.05 (−1.01 to 0.91)	−0.10	.92	0.95
Hyperlipidemia	−0.31 (−1.22 to 0.60)	−0.67	.50	0.73
Immunosuppression	0.42 (−0.91 to 1.75)	0.62	.53	1.53
Photosensitized	−0.73 (−1.79 to 0.33)	−1.35	.18	0.48

Statistically significant predictors are bolded.
b, *y*-intercept; *CI*, Confidence interval; *ND*, not done; *OR*, odds ratio.
*The logarithmic OR for sun-exposed vs sun-protected areas was not calculated because the large CI indicated this variable needed to be analyzed with a test that controlled for small population sizes.

cancer risk and is universally utilized by both dermatologists and nondermatologic 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 I). Loh et al examined the prevalence of KC among Asian and Hispanic patients over a 5-year period.[5] In their cohort, 61.4% of Hispanics had BCC and 38.6% had SCC, and 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 black persons.[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, >3 times the proportions exhibited by the Hispanic and Asian populations, 24.4% and 21.4%, respectively. Most these lesions were in the groin and anogenital region. Rather than sun exposure, there might 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) might 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 utility in preventing SCC might extend to all nonwhite patients.

Smoking might be a significant additional predictor of KC occurrence in nonwhite patients. Our study showed that smoking had a very large effect (Cohen d = 1.16) on age at cancer occurrence. Being a current smoker precipitated earlier cancer occurrence in nonwhite individuals, as much as by

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 for 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 with 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.

As expected, skin cancer developed earlier in immunosuppressed patients than immunocompetent patients, on average by 4.4 years. Interestingly, hypertensive patients had skin cancer diagnoses 10 years later than nonhypertensive patients. This finding is particularly surprising; we expected the opposite because hydrochlorothiazide, a commonly used antihypertensive medication, has been shown to be related to photosensitivity. We cannot explain this finding. and it warrants further exploration with a larger cohort.[11]

Limitations

Limitations of our study include interpractitioner variability in the thoroughness of genital examinations, most likely leading to underdiagnosis of genital lesions. Furthermore, this is a single-center study with a small sample size, both of which could 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 nonwhite persons, especially black persons, and the 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.

REFERENCES

1. Gloster HM, Neal K. Skin cancer in skin of color. *J Am Acad Dermatol*. 2006;55(5):741-760.
2. Agbai ON, Buster K, Sanchez M, et al. Skin cancer and photoprotection in people of color: a review and recommendations for physicians and the public. *J Am Acad Dermatol*. 2014;70(4):748-762.
3. McNaughton SA, Marks GC, Green AC. Role of dietary factors in the development of basal cell cancer and squamous cell cancer of the skin. *Cancer Epidemiol Biomarkers Prev*. 2005;14(7):1596-1607.
4. Tadokoro T, Kobayashi N, Zmudzka BZ, et al. UV-induced DNA damage and melanin content in human skin differing in racial/ethnic origin. *FASEB J*. 2003;17:1177-1179.
5. Loh TY, Ortiz A, Goldenberg A, Jiang SI. Prevalence and clinical characteristics of nonmelanoma skin cancers among Hispanic and Asian patients compared with white patients in the United States. *Dermatol Surg*. 2016;42(5):639-645.
6. Arron ST, Jennings L, Nindl I, et al. Viral oncogenesis and its role in nonmelanoma skin cancer. *Br J Dermatol*. 2011;164(6):1201-1213.
7. Purdie KJ, Surentheran T, Sterling JC, et al. Human papillomavirus gene expression in cutaneous squamous cell carcinomas from immunosuppressed and immunocompetent individuals. *J Invest Dermatol*. 2005;125(1):98-107.
8. Nadhan KS, Larijani M, Abbott J, Doyle AM, Linfante AW, Chung CL. Prevalence and types of genital lesions in organ transplant recipients. *JAMA Dermatol*. 2018;154(3):323-329.
9. Leonardi-Bee J, Ellison T, Bath-Hextall F. Smoking and the risk of nonmelanoma skin cancer: systematic review and meta-analysis. *Arch Dermatol*. 2012;148(8):939-946.
10. De Hertog SA, Wensveen CA, Bastiaens MT, et al. Relation between smoking and skin cancer. *J Clin Oncol*. 2001;19:231-238.
11. Pederson SA, Gaist D, Schmidt SA, Holmich LR, Friis S, Pottegard A. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: a nationwide case-control study from Denmark. *J Am Acad Dermatol*. 2017;78(4):673-681.