Sunlight Exposure and Cutaneous Human Papillomavirus Seroreactivity in Basal Cell and Squamous Cell Carcinomas of the Skin

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Background. Ultraviolet radiation exposure may interact synergistically with cutaneous human papillomavirus (HPV) infection in the development of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin.

Methods. To investigate differences in the risk of sunlight-associated BCC and SCC by cutaneous genus-specific HPV serostatus, a case-control study was conducted among 204 BCC and 156 SCC cases who were recruited from a university dermatology clinic and 297 controls who had no history of cancer and screened negative for current skin cancer. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between measures of sunlight exposure and BCC/SCC, stratified by genus-specific HPV serostatus, with adjustment for age and sex.

Results. Sunburn due to cutaneous sensitivity to sunlight exposure ($P = .006$) and poor tanning ability ($P = .003$) were associated with a higher seroprevalence for genus beta HPV types. Poor or no tanning ability was more strongly associated with SCC among individuals who were seropositive for antibodies to cutaneous HPV types in genera alpha (OR, 15.60; 95% CI, 5.40–45.1; $P = .01$ for interaction) and beta (OR, 6.86; 95% CI, 3.68–12.80; $P = .001$ for interaction), compared with individuals who were seronegative for these HPV types.

Conclusions. Seropositivity for HPV types in genera alpha or beta increased the risk of SCC associated with poor tanning ability.

Nonmelanoma skin cancer (NMSC), comprising basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is the most common cancer among white individuals, with >1 million new cases diagnosed annually in the United States alone [1]. Constitutional factors, including light-colored eyes, hair, and skin, as well as older age, male sex, and immunosuppression [2], have been identified as risk factors for BCC and SCC. Ultraviolet radiation (UVR) exposure has been implicated in the etiology of skin cancer and is considered the most important environmental risk for BCC and SCC development [2, 3].

Several lines of evidence suggest that UVR exposure may play a synergistic role along with cutaneous human papillomavirus (HPV) infection in the development of cutaneous NMSC. HPVs belong to a large family of >100 genotypes, including types identified from genera alpha, beta, gamma, mu, and nu that infect cutaneous epithelia [4]. Presence of antibodies against cutaneous HPV types has been associated with SCC in several epidemiologic studies [5–10]; however, results from epidemiologic studies of cutaneous HPV and BCC are less consistent [5–9] and fewer in number. Ultraviolet B radiation has been shown to

Received 17 August 2011; accepted 9 February 2012; electronically published 1 June 2012.

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The Journal of Infectious Diseases 2012;206:399–406

DOI: 10.1093/infdis/jis374

stimulate the promoter activity of HPV types 5 and 8 [11]. In turn, the E6 and/or E7 proteins of genus beta HPV types have been shown to inhibit UVR-induced apoptosis through p53-independent pathways [12, 13], to reduce capacity to repair UVR-induced mutations [14], and to alter the regulation of UVR-activated cell cycle checkpoints.

The goal of the current study was to investigate the potential modifying effects of cutaneous HPV seroreactivity on the associations between sunlight exposure, host susceptibility to UVR exposure, and BCC and SCC.

MATERIALS AND METHODS

Study Design and Population

To investigate differences in sunlight exposure–associated BCC and SCC risk by cutaneous HPV seroreactivity, a clinic-based case-control analysis was conducted. Study procedures have been described previously [15]. Participants were recruited from the dermatology (D) and family medicine (FM) clinics at the University of South Florida (USF), as well as from the Moffitt Cancer Center's Lifetime Cancer Screening and Prevention Center (LCS) clinic. Eligible cases were patients aged 18–80 years who received a diagnosis of histologically confirmed BCC or SCC. Controls were patients who reported no history of any type of cancer at the time of study recruitment and who screened negative for skin cancer, as determined by a full-body skin cancer screening examination conducted by a nurse practitioner. Participation rates for the USF-D, USF-FM, and LCS clinics were 80%, 47%, and 65%, respectively. Study participants and nonparticipants from the USF-FM and LCS clinics differed in mean age by 2 years and had similar sex and race distributions. No significant differences in age or sex were observed between study participants and nonparticipants from the USF-D clinic.

All study participants were asked to complete a self-administered questionnaire that included questions on demographic and constitutional characteristics, lifestyle factors, and measures of sunlight exposure and to provide a blood sample for cutaneous HPV antibody measurement. A total of 204 subjects with BCC, 156 subjects with SCC, and 297 controls had available questionnaire data and cutaneous HPV antibody results. Participants who reported a race other than white or who had missing data on race were excluded from the current study analysis. All participants provided written informed consent. All study procedures were approved by the institutional review board at the University of South Florida.

Measurement of Antibodies to Cutaneous HPV Types

At the time of study enrollment, blood was drawn into serum separator tubes with clot activators, using a sterile needle. Following centrifugation, serum was aliquoted into cryovials, stored at −80°C, and shipped on dry ice to the Deutsches Krebsforschungszentrum [German Cancer Research Center] for analysis. Samples were analyzed for antibodies to the major capsid protein L1 for 7 types in genus alpha (2, 3, 7, 10, 27, 57, and 77), 17 types in genus beta (5, 8, 9, 15, 17, 20, 23, 24, 25, 36, 38, 49, 75, 76, 92, 96, and 107), 8 types in genus gamma (4, 48, 50, 65, 88, 95, 101, and 103), and 1 type each in genus mu (1) and genus nu (41), using a detection method based on glutathione-*S*-transferase (GST)–capture enzyme-linked immunosorbant assay, as described in Sehr et al [16, 17], in combination with fluorescent bead technology (Luminex), as recently described elsewhere [18]. In brief, full-length viral proteins were expressed in bacteria in fusion with an N-terminal GST domain. Glutathione cross-linked to casein was coupled to fluorescence-labeled polystyrene beads, and GST fusion proteins were affinity purified on the beads directly in a 1-step procedure. Bead types of different colors and with different antigens were mixed and incubated with human sera. Antibodies bound to the beads via the viral antigens were stained by biotinylated anti-human immunoglobulin and streptavidin–R-phycoerythrin. Beads were analyzed in a Luminex analyzer that identifies the bead color—and, thus, the antigen carried by the bead—and quantifies the antibodies bound to viral antigen via the median R-phycoerythrin fluorescence intensity of ≥100 beads of the same internal color.

Statistical Analysis

Differences in the distributions of demographic and skin cancer risk factors, as well as genus-specific HPV seroreactivity between NMSC cases and controls, were tested using the χ^2 test. Risk factors included cutaneous sensitivity to 1 hour of sunlight exposure in the summer for the first time without sunscreen (sunburn with or without blistering, mild sunburn that turns to a tan, tan, or no change in skin color), tanning ability from repeated sunlight exposure (unable to tan, tan after working at it, tan easily), history of blistering sunburn (yes or no), and cumulative sunlight exposure in early life (low or high). To measure cumulative sunlight exposure in early life (ie, before 30 years of age), a median value was applied to each category of hours of sunlight exposure (<1 hour = 0.5, 1–2 hours = 1.5, 3–4 hours = 3.5, and 5–6 hours = 5.5) experienced on a weekday and weekend day during the summer in different periods (ie, ages 13–19 years, 20–29 years, and 30–39 years). The median values applied to weekday and weekend day hours of exposure were first summed for each age period and then summed across the 3 age periods and divided into 2 categories, low and high. Analyses involving cumulative sunlight exposure in early life were restricted to participants who were ≥40 years of age. These factors are collectively referred to as "sun-related factors" below.

Logistic regression models were used to calculate odds ratios (OR) and 95% confidence intervals (CIs) for the associations between sun-related factors and BCC and SCC.

Confounding by constitutional, demographic, lifestyle, and skin cancer risk factors was assessed. With the exception of age and sex, inclusion of additional cofactors did not alter the calculated estimates by >10%. Thus, final models included only age and sex as covariates.

Participants were classified as seropositive or seronegative for antibodies to each individual cutaneous HPV type, measured on the basis of HPV type–specific cut points assigned as described elsewhere [6, 19]. Cutaneous HPV types were then grouped by genus. Overall genus-specific seropositivity was calculated as the proportion of participants who tested positive for antibodies to at least one of the types in that genus. Genus-specific seropositive participants were compared to participants who tested negative for all types in that genus. The χ^2 test was used to describe differences in the distributions of genus-specific HPV seropositivity across sun-related factors among cases and controls. The associations between sun-related factors and BCC and SCC were stratified by genus-specific HPV serostatus (seropositive or seronegative), and stratum-specific ORs and corresponding 95% CIs were estimated. Statistical significance of multiplicative interactions between genus-specific seroreactivity and sun-related factors as they related to BCC and SCC was tested by placing an interaction term for the product of genus-specific seroreactivity and each sun-related factor in the logistic regression models. Bonferroni correction of P values was used to account for multiple comparisons, reducing the statistical significance level for genus-specific results to $P < .01$ for the beta coefficient corresponding to the interaction term. All analyses were conducted using the SAS statistical software package (version 9.2; SAS Institute).

RESULTS

Compared with controls, NMSC cases were significantly more likely to be male, to be older, to burn from sunlight exposure, and to exhibit diminished ability to tan (Table 1). Additionally, SCC cases reported higher levels of cumulative sunlight exposure ($P = .03$) as compared to controls (Table 1). Seroprevalence was highest for cutaneous genus beta HPV types for SCC cases (73.1%) and controls (60.3%), followed by genus gamma (62.8% and 52.2% in SCC cases and controls, respectively) (Table 1). Statistically significant case-control differences in HPV seropositivity were observed for HPV types in genus alpha and BCC ($P = .01$), genus beta and SCC ($P = .01$), and genus gamma and both BCC ($P = .0002$) and SCC ($P = .03$). Similar differences between controls and cases with BCC or SCC were not observed for the single HPV types in genera mu or nu (Table 1).

Associations between sun-related factors and BCC and SCC are presented in Table 2. Cutaneous sensitivity to sunlight exposure (duration, ≥1 hour) resulting in sunburn, poor tanning ability, and history of blistering sunburn were statistically significantly associated with both BCC and SCC. Cumulative sunlight exposure was associated with SCC; a similar association was not observed for BCC.

Differences in genus-specific HPV seropositivity by sun-related factors within BCC and SCC case groups and the control group are presented in Tables 3 and 4. Among SCC cases, seroprevalence for HPV types in genus beta was significantly associated with a propensity to burn when exposed to sunlight ($P = .006$; Table 3) and an inability to tan after repeated sunlight exposure ($P = .003$; Table 4). Cutaneous HPV seropositivity did not differ significantly by cumulative sunlight exposure or history of blistering sunburn among BCC and SCC cases or controls (data not shown).

Given that cutaneous sensitivity to sunlight exposure and tanning ability were associated with HPV seropositivity, associations between these 2 sun-related factors and BCC and SCC were stratified by genus-specific HPV serostatus to investigate potential effect modification. Associations between propensity to sunburn and BCC and SCC were relatively similar across categories of cutaneous HPV serostatus, with none of the interaction terms being statistically significant (Table 5). Poor tanning ability was associated with a statistically significant increased risk of SCC among those who were seropositive to genus alpha HPV types, whereas a more modest risk of SCC (OR, 2.53; 95% CI, 1.43–4.46) was observed among those who were seronegative to HPV types in genus alpha. Additionally, the association between poor tanning ability and SCC was significantly greater among individuals seropositive for genus beta HPV (OR, 6.86; 95% CI, 3.68–12.80) than among individuals seronegative for this genus (OR, 1.39; 95% CI, .59–3.31) (Table 5). Both interactions were statistically significant ($P = .01$ for genus alpha; $P = .001$ for genus beta) (Table 5). No significant interactions were observed between sun-related factors and seropositivity for HPV types in genera gamma, mu, or nu in relation to either BCC or SCC.

DISCUSSION

A case-control study was conducted to investigate the potential modifying effects of cutaneous HPV seroreactivity on the associations between skin cancer risk factors and BCC and SCC of the skin. Sun-related factors were associated with BCC and SCC in the current study population. Cutaneous sensitivity to sunlight exposure that resulted in sunburn and poor tanning ability were associated with a higher seroprevalence for genus beta HPV types. The associations between poor tanning ability and SCC were significantly greater among those who were seropositive for HPV types in genus alpha and genus beta. It is unclear why the sun-related factors associated with cutaneous HPV seropositivity differed from those related to the association between cutaneous HPV and NMSC.

The current findings for SCC are consistent with those from 2 of 3 previous studies [8, 9, 20, 21]. Among participants in a

Table 1. Distribution of Demographic and Skin Cancer Risk Factors Among Cases With Cutaneous Basal Cell Carcinoma (BCC) or Squamous Cell Carcinoma (SCC) and Controls

Variable	Controls (n = 297)	BCC Cases (n = 204)	P^a	SCC Cases (n = 156)	P^a
Age (years)					
Mean (SD)	55.2 (11.7)	62.6 (12.0)	<.0001	64.7 (9.8)	<.0001
18–39	28 (9.4)	7 (3.4)		3 (1.9)	
40–49	54 (18.2)	24 (11.8)		10 (6.4)	
50–59	104 (35.0)	42 (20.6)		28 (18.0)	
60–69	83 (28.0)	60 (29.4)		63 (40.4)	
70–80	28 (9.4)	71 (34.8)	<.0001	52 (33.3)	<.0001
Sex					
Male	111 (37.4)	123 (60.3)		100 (64.1)	
Female	186 (62.6)	81 (39.7)	<.0001	56 (35.9)	<.0001
Cutaneous sensitivity					
Mild sunburn turns to tan/tan	177 (60.0)	80 (40.0)		65 (42.8)	
Sunburn/blistering	118 (40.0)	120 (60.0)	<.0001	87 (57.2)	.001
Tanning ability					
Tan easily	173 (59.3)	96 (48.5)		56 (36.8)	
Tan after working at it/unable to tan	119 (40.8)	102 (51.5)	.02	96 (63.2)	<.0001
History of blistering sunburn					
No	92 (31.3)	52 (25.7)		35 (23.0)	
Yes	202 (68.7)	150 (74.3)	.18	117 (77.0)	.07
Cumulative sunlight exposure					
Low	82 (32.5)	51 (28.7)		31 (22.0)	
High	170 (67.5)	127 (71.4)	.39	110 (78.0)	.03
Genus Alpha					
Negative	193 (65.0)	109 (53.4)		96 (61.5)	
Positive	104 (35.0)	95 (46.6)	.01	60 (38.5)	.47
Genus Beta					
Negative	118 (39.7)	65 (31.9)		42 (26.9)	
Positive	179 (60.3)	139 (68.1)	.07	114 (73.1)	.01
Genus Gamma					
Negative	142 (47.8)	64 (31.4)		58 (37.2)	
Positive	155 (52.2)	140 (68.6)	.0002	98 (62.8)	.03
Genus Mu					
Negative	202 (68.0)	126 (61.8)		94 (60.3)	
Positive	95 (32.0)	78 (38.2)	.15	62 (39.7)	.10
Genus Nu					
Negative	263 (88.6)	180 (88.2)		136 (87.2)	
Positive	34 (11.4)	24 (11.8)	.91	20 (12.8)	.67

Data are no. (%) of subjects, unless otherwise indicated.

[a]By the χ^2 test, for comparison with controls.

case-control study from Queensland, Australia, it was observed that the joint effects of genus beta HPV seropositivity and skin susceptibility to sunlight exposure, specifically fair skin and a propensity to burn, resulted in a statistically significantly greater risk of SCC than either risk factor alone [21]. Similarly, a multicenter case-control study [20] observed a statistically significant interaction between lighter skin phototype and genus beta seropositivity among residents of the Netherlands who had SCC [20]. In contrast, among residents of Italy and Australia in the same multicenter study, no statistically significant interactions were observed between skin phototype and genus beta seropositivity in persons with SCC [20]. Furthermore, a population-based case-control study from New Hampshire [8, 9] observed no effect modification of the association between SCC and cutaneous sensitivity to sunlight exposure by genus beta HPV seropositivity. For comparative purposes, no previously published study has presented similar results with cutaneous HPV types outside of genus beta or among BCC cases.

Table 2. Association Between Sunlight Exposure–Related Factors in Cases With Cutaneous Basal Cell Carcinoma (BCC) or Squamous Cell Carcinoma (SCC) and Controls

		BCC Cases (n = 204)		SCC Cases (n = 156)	
Sunlight-Related Factor	Controls, No. (%) (n = 297)	No. (%)	OR (95% CI)[a]	No. (%)	OR (95% CI)[a]
Cutaneous sensitivity					
Mild sunburn turns to tan/tan	177 (60.0)	80 (40.0)	1.00 (reference)	65 (42.8)	1.00 (reference)
Sunburn/blistering	118 (40.0)	120 (60.0)	2.75 (1.84–4.11)	87 (57.2)	2.39 (1.53–3.74)
Tanning ability					
Tan easily	173 (59.3)	96 (48.5)	1.00 (reference)	56 (36.8)	1.00 (reference)
Tan after working at it/unable to tan	119 (40.8)	102 (51.5)	2.23 (1.48–3.34)	96 (63.2)	4.09 (2.52–6.64)
History of blistering sunburn					
No	92 (31.3)	52 (25.7)	1.00 (reference)	35 (23.0)	1.00 (reference)
Yes	202 (68.7)	150 (74.3)	1.59 (1.04–2.46)	117 (77.0)	1.79 (1.08–2.96)
Cumulative sunlight exposure					
Low	82 (32.5)	51 (28.7)	1.00 (reference)	31 (22.0)	1.00 (reference)
High	170 (67.5)	127 (71.4)	1.21 (.77–1.89)	110 (78.0)	1.85 (1.08–3.15)

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; OR, odds ratio; SCC, squamous cell carcinoma.

[a]Values are adjusted for age and sex.

Cutaneous HPV seroreactivity has been associated with NMSC in several epidemiologic studies [5–10]. It is hypothesized that UVR exposure may interact synergistically with cutaneous HPV in NMSC development. However, the pathway by which cutaneous HPV and UVR exposure are associated with NMSC remains unclear. A source of local immune suppression within the skin is UVR from sunlight exposure. UVR has been shown to suppress the cell-mediated immune response in mice [22], and it is hypothesized that UVR may have a similar effect among humans, thus creating a microenvironment that favors cutaneous HPV replication. By analogy, the cytotoxic T-lymphocyte response has been shown to play a role in the persistence and clearance of HPV type 16 infection and subsequent regression of detected cytological abnormalities [23–25]. If cell-mediated immunity plays a similar role in cutaneous HPV infections, a diminished cytotoxic

Table 3. Cutaneous Sensitivity to Sunlight Exposure, by Genus-Specific Human Papillomavirus Seropositivity, Among Cases With Basal Cell Carcinoma (BCC) or Squamous Cell Carcinoma (SCC) and Controls

	Controls (n = 297)		BCC cases (n = 204)		SCC cases (n = 156)	
Cutaneous Sensitivity, by Genus Seropositivity	No. (%)	*P*[a]	No. (%)	*P*[a]	No. (%)	*P*[a]
Alpha						
Mild sunburn turns to tan/tan	60 (33.9)		37 (46.3)		24 (36.9)	
Sunburn/blistering	43 (36.4)	.65	57 (47.5)	.86	35 (40.2)	.68
Beta						
Mild sunburn turns to tan/tan	103 (58.2)		52 (65.0)		40 (61.5)	
Sunburn/blistering	75 (63.6)	.36	83 (69.2)	.54	71 (81.6)	.006
Gamma						
Mild sunburn turns to tan/tan	89 (50.3)		58 (72.5)		41 (63.1)	
Sunburn/blistering	66 (55.9)	.34	80 (66.7)	.38	54 (62.1)	.90
Mu						
Mild sunburn turns to tan/tan	48 (27.1)		28 (35.0)		24 (36.9)	
Sunburn/blistering	47 (39.8)	.02	49 (40.8)	.41	36 (41.4)	.58
Nu						
Mild sunburn turns to tan/tan	16 (9.0)		10 (12.5)		10 (15.4)	
Sunburn/blistering	18 (15.3)	.10	14 (11.7)	.86	10 (11.5)	.48

[a]By the χ^2 test. Table percentages are row percentages. They were calculated by dividing the number of individuals in each category (i.e., Mild sunburn turns to tan/tan or Sunburn/blistering) that were genus-specific HPV seropositive by the total number of individuals in that category.

Table 4. Tanning Ability, by Genus-Specific Human Papillomavirus Seropositivity, Among Cases With Basal Cell Carcinoma (BCC) or Squamous Cell Carcinoma (SCC) and Controls

	Controls (n = 297)		BCC cases (n = 204)		SCC cases (n = 156)	
Tanning Ability, by Genus Seropositivity	No. (%)	P^a	No. (%)	P^a	No. (%)	P^a
Alpha						
Tan easily	67 (38.7)		41 (42.7)		19 (33.9)	
If work at it/unable to tan	35 (29.4)	.10	52 (51.0)	.24	40 (41.7)	.35
Beta						
Tan easily	107 (61.9)		64 (66.7)		33 (58.9)	
Tan after working at it/unable to tan	69 (58.0)	.51	71 (69.6)	.66	78 (81.3)	.003
Gamma						
Tan easily	90 (52.0)		61 (63.5)		32 (57.1)	
Tan if worked at it/unable to tan	64 (53.8)	.77	76 (74.5)	.09	62 (64.6)	.36
Mu						
Tan easily	56 (32.4)		34 (35.4)		17 (30.4)	
Tan after working at it/unable to tan	38 (31.9)	.94	42 (41.2)	.41	43 (44.8)	.08
Nu						
Tan easily	19 (11.0)		12 (12.5)		5 (8.9)	
Tan if worked at it/unable to tan	14 (11.8)	.84	12 (11.8)	.87	15 (15.6)	.24

[a]By the χ^2 test. Table percentages are row percentages. They were calculated by dividing the number of individuals in each category (i.e., Tan easily or Tan if worked at it/unable to tan) that were genus-specific HPV seropositive by the total number of individuals in that category.

T-lymphocyte response caused by UVR may promote the persistence of HPV infection in the skin [26]. In turn, persistent HPV infection may promote tumor progression by interfering with the host response to UVR-induced DNA damage [27–30].

If, in fact, UVR exposure interacts synergistically with cutaneous HPV in NMSC, one would expect to observe significant interactions between cutaneous HPV seropositivity and sun-related factors in relation to BCC and SCC. Poor tanning ability was the only sun-related factor measured that demonstrated statistically significant multiplicative interactions with cutaneous HPV seropositivity, and this was observed in SCC cases only. Pigmentation, characterized by melanin production, is the main photoprotective mechanism in the skin, including the functions of the cell-mediated immune response. Individuals with skin type I, II, or III exhibit low melanin production in the skin and tend to have difficulty tanning when exposed to UVR. This may explain why statistically significant interactions observed between sun-related factors and HPV seropositivity in relation to SCC were observed with poor tanning ability only [31].

The current proposed study has some limitations. Sample sizes were small, which limits stratified analyses and the ability to detect statistically significant interactions. Case-control studies are often subject to recall bias since cases tend to think about their exposures more carefully because they might relate them to their current cancer diagnosis. As such, observed main effects between sun exposure and skin cancer can be subject to recall bias. However, participants in this study did not know their HPV serostatus at the time of questionnaire completion, and therefore the observed interactions between sun-related factors and HPV seropositivity in relation to NMSC should not have been affected by recall bias. In contrast, general difficulties of participants to recall past sun exposures could have resulted in nondifferential misclassification, potentially attenuating the observed associations.

Several study strengths should also be noted. The current study presents cutaneous HPV genus–specific associations outside of genera alpha and beta in a US population. It is the first study to investigate interaction effects between genus-specific HPV seropositivity and multiple measures of sunlight exposure as they relate to both BCC and SCC in a US population. The use of a multiplexed assay to assess seropositivity to multiple cutaneous HPV types is a great strength of the proposed study. The laboratory of one author (M. P.) has been generating most of the serological data in epidemiologic studies of cutaneous HPV published to date [6, 8, 9, 19, 20, 32–34], including the only other study published from the United States [8, 9]. Use of a common assay facilitates the direct comparison of results across studies by eliminating differences due to variation in laboratory techniques.

Exposure to UVR is the most important environmental risk factor for NMSC, and the incidence of NMSC is increasing despite the increased use of sunscreen products. Therefore, there is a need to identify cofactors that may interact with UVR exposure to increase the risk of NMSC, so that novel prevention strategies can be developed. Epidemiologic studies have demonstrated a potential role for cutaneous HPV infection in NMSC development [5–10], and accumulating evidence suggests that cutaneous HPV may interact synergistically with UVR exposure

Table 5. Association Between Sunlight Exposure–Related Factors and Nonmelanoma Skin Cancer, by Genus-Specific Cutaneous Human Papillomavirus (HPV) Serostatus

	BCC (n = 204)			SCC (n = 156)		
Sunlight-Related Factor, by Genus	Seropositive OR (95% CI)[a]	Seronegative OR (95% CI)[a]	P[b]	Seropositive OR (95% CI)[a]	Seronegative OR (95% CI)[a]	P[b]
Cutaneous sensitivity						
Alpha						
Mild sunburn turns to tan/tan	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
Sunburn/blistering	2.39 (1.28–4.47)	2.94 (1.74–4.99)	.55	2.52 (1.17–5.42)	2.32 (1.33–4.02)	.88
Beta						
Mild sunburn turns to tan/tan	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
Sunburn/blistering	2.63 (1.60–4.35)	2.90 (1.48–5.69)	.82	2.75 (1.60–4.75)	1.38 (0.60–3.18)	.14
Gamma						
Mild sunburn turns to tan/tan	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
Sunburn/blistering	2.05 (1.24–3.37)	4.68 (2.30–9.52)	.08	1.95 (1.09–3.50)	3.02 (1.50–6.12)	.35
Mu						
Mild sunburn turns to tan/tan	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
Sunburn/blistering	2.02 (1.05–3.87)	3.19 (1.90–5.36)	.51	1.75 (0.83–3.68)	2.88 (1.62–5.13)	.32
Nu						
Mild sunburn turns to tan/tan	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
Sunburn/blistering	1.23 (0.40–3.76)	3.17 (2.05–4.90)	.12	0.90 (0.26–3.11)	2.77 (1.71–4.49)	.10
Tanning ability						
Alpha						
Tan easily	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
Tan after working at it/unable to tan	4.71 (2.29–9.66)	1.48 (.88–2.48)	.02	15.6 (5.40–45.1)	2.53 (1.43–4.46)	.01
Beta						
Tan easily	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
Tan after working at it/unable to tan	2.94 (1.73–4.98)	1.44 (.75–2.78)	.13	6.86 (3.68–12.8)	1.39 (0.59–3.31)	.001
Gamma						
Tan easily	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
Tan after working at it/unable to tan	2.50 (1.49–4.20)	1.67 (0.85–3.29)	.30	4.42 (2.33–8.38)	3.65 (1.72–7.76)	.61
Mu						
Tan easily	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
Tan after working at it/unable to tan	2.52 (1.28–4.95)	2.10 (1.25–3.54)	.37	6.08 (2.59–14.3)	3.29 (1.80–5.98)	.19
Tanning Ability						
Nu						
Tan easily	1.00 (reference)	1.00 (reference)		1.00 (reference)	1.00 (reference)	
Tan after working at it/unable to tan	2.16 (0.65–7.21)	2.22 (1.44–3.42)	.84	8.58 (1.83–40.3)	3.76 (2.25–6.29)	.33

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; OR, odds ratio; SCC, squamous cell carcinoma.

[a]Values are adjusted for age and sex.

[b]P for interaction between genus-specific HPV seroreactivity and sunlight exposure–related factor.

in NMSC development. However, additional studies are needed, including those that measure infection with HPV types in multiple genera. Identifying how cutaneous HPV infections may influence sunlight exposure–associated risks of NMSC may lead to improved characterization of high-risk individuals and aid in the development of novel prevention strategies.

Notes

Financial support. This work was supported by Florida's James and Esther King Biomedical Research Program (06NIR-08 to D. E. R.).

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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