HHS Public Access
Author manuscript
Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2020 July 01.

Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2020 January ; 29(1): 39–48. doi:10.1158/1055-9965.EPI-19-0446.

Viruses in Skin Cancer (VIRUSCAN): Study design and baseline characteristics of a prospective clinic-based cohort study

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Abstract

Introduction—Accumulating evidence suggests that cutaneous viral infections are risk factors for the development of keratinocyte carcinomas (KC). The Viruses in Skin Cancer (VIRUSCAN) Study, a prospective cohort study, was established in 2014 to investigate the risk of KC associated with cutaneous human papillomavirus and polyomavirus infection and the possible interaction with ultraviolet radiation exposure (UVR).

Methods/Results—VIRUSCAN incorporates repeated measures of viral infection using multiple markers of infection and quantitative measures of UVR using a spectrophotometer. Participants were recruited between July 14, 2014-August 31, 2017 at the University of South Florida Dermatology Clinic in Tampa, FL. After excluding 124 individuals with prevalent KC at baseline, 1,179 participants (53.2% women, 46.8% men, all ages 60 years and older) were followed for up to four years with routine skin exams occurring every 6–12 months. Here we present the VIRUSCAN Study design, methods and baseline characteristics including demographics, sun exposure behavior, quantitative UVR exposure measurements and cutaneous viral prevalence for the full study cohort.

Conclusions—The VIRUSCAN Study will provide critical temporal evidence needed to assess the causality of the role cutaneous viral infections play in the development of KC, as well as the potential interaction between cutaneous viral infections and UVR exposure.

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Impact—Study findings will be valuable in future development of novel KC prevention strategies.

Keywords

Cutaneous human papillomavirus; epidemiology; non-melanoma skin cancer; polyomavirus; ultraviolet radiation exposure; VIRUSCAN

INTRODUCTION

Keratinocyte carcinoma (KC), comprised of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is the most frequently occurring cancer in the United States (1). KC incidence increased by 35% between 2006 and 2012, and an estimated 5.4 million KC cases were diagnosed in 2012. Despite its low metastatic potential and mortality rates, KC results in over 2,000 deaths annually in the United States (2). Furthermore, individuals are frequently diagnosed with multiple KCs, requiring multiple surgeries throughout their lifetimes and resulting in significant patient morbidity and substantial economic burden at the national level (3, 4). Established host risk factors for KC include older age, male sex and sun-sensitive skin likely to freckle and burn (5, 6). Ultraviolet radiation (UVR) is an environmental risk factor for KC, with intermittent and childhood UVR associated with increased risk of BCC (7, 8) and chronic sun exposure associated with SCC (7). Immunologic deficiencies and chronic immunosuppression are also linked to the development of KC, particularly SCC (9, 10). The continued increase in KC incidence, despite general awareness of the harms of sun exposure (1), underscores the need to identify additional modifiable risk factors that may lead to the development of novel prevention strategies.

Several epidemiological studies have observed KC to be associated with markers of cutaneous viral infections, including cutaneous human papillomaviruses (cuHPV) (11–14) and Merkel cell polyomavirus (MCV), a cutaneous human papillomavirus (HPyV) (15). CuHPV infections are particularly common in immunodeficient (16–18) and immunosuppressed individuals (19–21), but are also observed in immunocompetent populations, with cuHPV infection occurring early in life: 55–70% cuHPV DNA prevalence has been reported for infants and children up to 4 years old with similar prevalence rates observed among their parents (22, 23). CuHPV seroprevalence increases with age, with rates of 32%, 58%, and 60% observed in children ages 1–14, young adults ages 15–34, and older adults ages >34, respectively (24). CuHPV DNA prevalence has also been shown to increase with age (25, 26). While there are no established risk factors for cuHPV infection, previous studies have reported associations between cuHPV prevalence and UVR exposure (27, 28), light skin phenotypes (29, 30), male gender (29, 31, 32) and smoking (29, 30). Similar to cuPHV, HPyV infections also occur in early childhood (33), with MCV seroprevalence rates increasing with age: 40%, 85%, 90% in ages 1–4, 15–19, 50–79, respectively (34). While seroprevalence rates suggest most adults have been exposed to cuHPV and MCV at some point in their lifetime, and presumably cleared, DNA-based markers of infection indicate that infections can be newly acquired in adulthood (27, 35).

Findings between cuHPV infection and KC have been most consistently observed for cuHPV types in genus β ("β-HPV") and cutaneous SCC (36). Experimental studies have identified multiple signalling pathways disrupted by β-HPV oncoproteins, with both in vitro (37–40) and mouse models (41–43) demonstrating the cooperation between β-HPV infection and UVR in SCC development. In humans, cuHPV infections are more likely to be detected in tumors that occur in sun exposed areas of the body (28). A few epidemiologic studies have sought to investigate the interaction between UVR exposure and β-HPV infection by examining SCC risk in subgroups of β-HPV seroreactivity and skin phenotype (11, 32) or past self-reported UVR exposure (44). While positive interactions were observed, these studies were limited by subjective UVR measurements and reliance on single time point assessments of both UVR exposure and β-HPV seroreactivity. Furthermore, no studies have investigated the potential interaction between UVR and infection with cuHPV types in other genera.

The Viruses in Skin Cancer (VIRUSCAN) Study is a prospective cohort study being conducted at the Moffitt Cancer Center and the University of South Florida Dermatology Clinic, in Tampa, Florida, to investigate the risk of KC associated with cuHPV/HPyV infections. The primary study aims are to estimate baseline prevalence of type-specific cuHPV/HPyV infections using multiple biospecimens, determine the risk of incident KC associated with baseline infections, and evaluate UVR as a potential cofactor in virus-associated KC risk. Furthermore, longitudinally banked biospecimens will be used to estimate the risk of incident KC associated with incident and persistent cuHPV/HPyV infection and investigate the concordance between virus types present prior to KC diagnosis and viral DNA detected in subsequent incident tumors. The VIRUSCAN Study addresses several research needs, as it is one of the few prospective studies to incorporate repeated measures of cuHPV/HPyV infection, multiple biomarkers of cuHPV/HPyV infection and quantitative measurements of UVR exposure. Here we describe the VIRUSCAN Study design, methods and baseline characteristics.

MATERIALS AND METHODS

Participants and eligibility criteria

Participants were recruited from the University of South Florida Dermatology Clinic, a high volume dermatology clinic in which patients undergo routine total body skin exams for the early detection of skin cancers. University of South Florida Dermatology Clinic patients undergoing total body skin examination are often self-referred, including those who seek treatment of a dermatologic condition and are advised to undergo total body skin examination while they are in the clinic and those who attend the clinic specifically for skin cancer screening.

University of South Florida Dermatology Clinic patients aged 60 or older were eligible to enroll in the VIRUSCAN Study. The recruitment age was restricted to this age group to optimize the number of incident cancers detected during follow-up. Patients with a history of either BCC or SCC were eligible, but patients with a history of both BCC and SCC were excluded to ensure all study participants were naïve to at least one type of KC at baseline. To maximize the generalizability of study findings to broad populations of individuals at risk for KC, no additional exclusion criteria were applied. As such, organ transplant recipients were included but comprised only 1% of the VIRUSCAN Study population and will be excluded from a sensitivity analysis to assess whether associations observed differ from those observed in the full cohort. Eligible patients scheduled to undergo a total body skin examination were identified via daily medical chart reviews and approached for study participation during their clinic visit. The study was approved by the University of South Florida Institutional Review Board, and all participants provided written informed consent.

During the design phase of the VIRUSCAN Study, enrollment was projected to be 1,500 based on historical clinic records. Using this fixed sample size, previously published incidence rates of KC (45), and assuming an alpha error rate of 0.05, power of 80% and false discovery rate of < 10%, the calculated minimal detectable hazard ratios (MDHR) for the association between cuHPV/HPyV infection at baseline and SCC ranged from 1.89 to 2.82 for 40% to 10% of the cohort testing virus-positive at baseline, respectively, and 1.64 to 2.23 for KC overall. Over three years of enrollment, 2,929 patients were approached, of whom 1,303 (44.5%) consented. While the number of enrolled participants was less than projected, the observed SCC and KC incidence rates are trending higher than projected, therefore the final analyses will have more than adequate statistical power to detect the associations of interest.

While there were no differences in the age of participants (mean=69.1 years, SD=6.4) versus non-participants (mean=69.9 years, SD=7.5 P=0.06), females were more likely to enroll in the study than men (52.2% female vs. 47.8% men, P=0.03). Of the 1,303 participants enrolled, 124 (9.5%) underwent biopsies as a result of the baseline total body skin examination that were subsequently determined to be malignant after pathology review. These participants with prevalent KC at baseline (83 SCC, 78 BCC and 1 basosquamous carcinoma) were excluded from follow-up visits. The remaining 1,179 participants were followed for up to four years, depending on the year of enrollment in the study. Follow-up visits coincided with participants' routine total body skin examination appointments at the University of South Florida Dermatology Clinic, the frequency of which varied, depending on the participant's skin cancer risk profile, including skin type, family history of skin cancer and sun exposure history. Typically, participants returned to the clinic every 6–12 months for a total body skin examination. For example, among the 421 participants enrolled in the first year of the study, 87.9% returned to the clinic at least once during the subsequent three years of follow-up, with 69.4% returning at least twice and 53.9% returning three or more times.

Data collection

Table 1 summarizes data and biospecimen collection for VIRUSCAN Study participants at baseline and during follow-up. Variables were broadly classified as patient demographics, skin cancer risk factors, medical history, cutaneous viral infection status, tumor characteristics, and measures of UV exposure.

Questionnaire—Participants completed an electronic questionnaire at baseline that included information on demographics, sun protective behaviors, skin cancer risk factors and medical history (Table 1). Participants unable to complete the questionnaire during the visit were emailed a link to complete the questionnaire online. Non-responders were sent up to five email reminders followed by a final phone call reminder. The overall questionnaire response rate was 97.5%, with no differences observed between the 1,150 participants who completed the questionnaire and the 29 who did not with respect to age (P=0.11) or gender (P=0.58).

Clinical findings of total body skin exams—The outcomes of the total body skin examination conducted at baseline and throughout follow-up were recorded in the study database, including negative findings, instances of actinic keratosis treated with liquid nitrogen (standard practice at the University of South Florida Dermatology Clinic) and biopsies of suspicious lesions. Medical records were reviewed throughout the follow-up period to document histopathological results corresponding to any skin biopsies conducted on participants. Characteristics of those lesions determined to be malignant were recorded in the study database, including tumor size, histology and anatomic location (head, neck, torso, arms, and legs).

UVR exposure assessment

To model the time-dependent dynamic of recent UVR exposure and cutaneous viral infection acquisition and persistence, as well as the interaction between recent UVR exposure and infection associated with subsequent KC development, an objective measure of UVR was needed - one that could be obtained over multiple time points in a manner least burdensome to study participants. As such, a spectrophotometer was used to quantify skin pigmentation at baseline and throughout study follow-up as a proxy for UVR exposure, similar to previous epidemiologic studies (46, 47). Skin pigmentation readings were obtained with the Konica Minolta CM-600D spectrophotometer using the specular component included mode with Spectra Magic NX Lite USB Ver. 2.5 software (48). This instrument measures color on three different axes: lightness on a scale of 0 (black) to 100 (white), axis a, indicating color within the red through green range, and axis b, measuring color within the yellow through blue range, with increasing values on a- and b-axes, indicating saturation of color (49). The instrument was calibrated using a white tile every morning per manufacturer guidelines. Each reading was obtained three times, and the average reading was recorded. The inter-user reliability of the spectrophotometer readings across two VIRUSCAN Study coordinators was determined to be 0.91.

Natural skin tone was assessed using spectrophotometer readings of the sun-unexposed underside of the upper arm (i.e. the axilla), with higher readings indicating lighter natural skin tone. As shown in Figure 1, spectrophotometer readings significantly decreased with increasing category of self-reported skin tone (50). The degree of recent tanning in response to recent UVR exposure was measured by calculating the difference between the color readings ($\Delta E \times ab$) on an area of sun-exposed skin (top of the forearm or forehead) and the axilla. These anatomic sites were chosen to correspond with the areas where viral infection measurements were obtained and will be used to model the potential interaction between UVR exposure and cutaneous viral infections. The difference between the sun-exposed pigmentation readings (forearm and forehead) and the sun-unexposed pigmentation readings (underarm) was calculated and used as an objective measure of UVR exposure in response to more recent tanning (48). However, as the exact timing of UVR exposure relative to the spectrophotometer readings is unclear, we administered a questionnaire asking about sun exposures over the past week among a subsample of VIRUSCAN participants (n=159) to validate the spectrophotometer readings as a measure of more recent UVR exposure. The questionnaire included sun exposure and sun protection scales from a questionnaire previously validated against dosimeter-based measures of outdoor time in the past week (51).

Biospecimens

Several biospecimens were obtained for the assessment of cutaneous viral infections. Peripheral blood samples were collected at baseline, processed and stored in aliquots of serum, plasma and mononuclear cells, with serum samples earmarked for the analysis of antibodies to cuHPV and HPyV. Plucked eyebrow hairs and normal forearm skin swabs (52) were collected at baseline and throughout follow-up for the measurement of cuHPV and HPyV DNA. For those 240 study participants who developed KC throughout the follow-up period, formalin-fixed paraffin-embedded tumor tissue sections and tumor tissue slides were obtained from the USF Pathology Department for the measurement of cuHPV/HPyV viral DNA and histopathologic grading, respectively. The study pathologist reviewed each hematoxylin and eosin-stained slide and graded the degree of solar elastosis present (0–3) in the adjacent normal tissues as a measure of cumulative UVR exposure (53, 54). For SCC, the pathologist described the presence of tumor architectural features possibly associated with cuHPV infection, including papillomatosis, hypergranulosis, and crateriform architecture.

Assessment of past and current cutaneous viral infections

Serum samples were analyzed for antibodies to the L1 capsid protein corresponding to 17 β-HPV types and 7 γ-HPV types, as well as antibodies to both the VP1 capsid protein and T-antigens corresponding to 4 cuHPyV types (Supplementary Table S1). Selected types were those shown to be associated with KC in the literature, in addition to the most prevalent types observed in tumor tissues obtained from our previous case-control study (14, 55). Multiplex serology assays were conducted at the German Cancer Research Center in Heidelberg, Germany, using methods previously described (56, 57).

Baseline and follow-up eyebrow hair, skin swab and tumor samples were shipped to the Infections and Cancer Biology Group at the International Agency for Research on Cancer for DNA extraction and genotyping. Multiplex/Luminex PCR-assays were used for the measurement of viral DNA corresponding to 46-β HPV types, 52 γ-HPV types and 5 polyomavirus types (Supplementary Table S1) using methods previously described (52). Analysis of the tumor samples as well as the eyebrow hair and skin swab samples collected throughout follow-up is ongoing. Repeated measures of cutaneous viral infections in the eyebrow hairs and skin swabs will be used to model incident and persistent infections and their association with subsequent KC risk.

Statistical analysis of baseline characteristics

Baseline questionnaire data were largely complete, as <5% of data were missing for each questionnaire item. Given the low rate of missing data, data for select variables were imputed among the 1,150 participants who completed the questionnaire to minimize bias introduced by list-wise deletion of incomplete data. The questionnaire data were complete for age, gender and ethnicity. However, other variables were imputed, including education level, marital status and place of birth, sun protective behaviors and skin cancer risk factors. No medical history-related variables were imputed. The imputation was performed using the multivariate imputation by chained equations algorithm within R, version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria), which imputes data on a variable basis (58). The algorithm specifies an imputation model for each target variable that takes into account all other variables with the assumption that data are missing at random (58). A different type of model was assigned to each variable based on the variables' intrinsic distribution, e.g., continuous (predictive mean match), binary (logistic regression) and unordered categorical (polytomous logistic regression) or ordered categorical (proportional odds model). Five imputed data sets were generated and used to calculate pooled Chi-square p-values for all analyses here that used the imputed baseline questionnaire data.

To better understand how representative the VIRUSCAN Study population is of the general population, demographics, skin cancer risk factors and sun protective behaviors of study participants were compared to the general population, using publically available data from the 2015 National Health Interview Survey (NHIS) (59, 60). The NHIS is a health survey of the non-institutionalized U.S. population conducted annually by the Centers for Disease Control and Prevention (60). The NHIS dataset was restricted to adults ≥60 living in the Southern U.S. for the present analysis, since this age group and geographic region most closely relate to the VIRUSCAN Study population.

The correlation between the spectrophotometer readings obtained at the forearm and forehead were described using Spearman's rank correlation. Associations between the spectrophotometer readings and tertiles of self-reported recent sun exposure and protection scales were examined using logistic regression, adjusted for age and gender. The baseline prevalence of cuHPV/HPyV infection was defined as the proportion of patients whose sample was positive for viral DNA (in the skin swabs and eyebrow hairs) or serum antibodies. Viral prevalence rates were calculated for all beta types tested and by species, type-specific prevalence rates are presented for the eyebrow hair and skin swab samples.

RESULTS

Descriptive profile and generalizability of the cohort

Baseline demographics, skin cancer risk factors and sun protective behaviors of the VIRUSCAN Study participants are presented in Table 2, compared to those of the general Southern United States population as measured by the NHIS population. VIRUSCAN Study participants were more likely to have sun-sensitive skin than the NHIS population. For example, 4.2% of VIRUSCAN participants reported no change to their skin after one hour sun exposure as compared to 17.9% of the NHIS population (Table 2). The VIRUSCAN

Study participants were also more likely to report skin cancer risk factors such as use of tanning beds, a history of skin cancer and former smoking. Interestingly, 66.4% and 75.2% of VIRUSCAN Study participants reported use (always/often/sometimes) of sunscreen and hats as compared to 47.6% and 42.4% of the NHIS population, respectively.

Spectrophotometer readings of recent UVR exposure

A strong, intra-individual correlation was observed between the spectrophotometer readings obtained at the forearm and forehead (Figure 2; rho=0.61; $P < 0.001$). Further analysis of baseline skin pigmentation readings revealed greater variation in the forearm spectrophotometer readings (median= 12.63, IQR=7.46) as compared to the forehead readings (median=10.76, IQR=6.03). Based on past-week exposure, individuals in the highest tertile of self-reported sun exposure were 2.5 times more likely to have a higher than median forearm spectrophotometer readings compared to those in the lowest tertile of sun exposure (Table 3; odds ratio (OR) 2.48, 95% CI: 1.01, 6.33, *P-trend*=0.06), after adjustment for age and sex. Similarly, when a ratio of the summary measures of sun exposure and sun protective behaviors was considered, a positive trend was observed between tertiles of the ratio and high versus low forearm spectrophotometer readings (Table 3; $OR_{\text{tertile 3 vs 1}}$=2.89, 95% CI: 1.24, 6.95, *P-trend*=0.01). No associations were observed with the forehead spectrophotometer readings (Supplemental Table S2).

Baseline prevalence of cutaneous viral infections

Based on the completed analysis of baseline samples obtained from the 370 VIRUSCAN Study participants enrolled in the first year of the study who were eligible for follow-up, the prevalence of cuHPV and HPyV was consistently higher in skin swabs than eyebrow hairs, with strong virus-type specific correlations across eyebrow hairs and skin swabs in terms of prevalence, degree of infection and number of types (52). When expanding the analysis to include baseline samples obtained from all VIRUSCAN Study participants eligible for follow-up, similar findings were observed, with higher cuHPV and HPyV prevalence in skin swabs compared to eyebrow hairs and strong type-specific viral prevalence across both sample types (Figure3). For example, DNA corresponding to at least one β-HPV type was detected in the skin swabs of 95.6% of participants and in the eyebrow hairs of 64.4% of participants, with the same trends observed for β-species 1 and 2 (80.5% and 41.2% vs. 90.1% and 53.0%, respectively). Similarly, the γ-HPV prevalence was also higher in the skin swabs (75.6%) than in the eyebrow hairs (29.7%). HPyV prevalence rates followed the same pattern with 82.1% of swabs showing infection and only 35.8% of eyebrow hairs. The type-specific cuHPV and HPyV prevalence rates for VIRUSCAN Study participants are presented in Supplementary Table S3. β-HPV types with the highest prevalence rates in both the skin swab and eyebrow hair were types 5 (36.6% and 14.3%), 38 (47.4% and 18.4%) and 110 (35.7% and 13.3%), with types 4 (18% and 3.1%), 50 (15.3% and 3.5%), and SD2 (19.3% and 4.1%) being the most prevalent γ-HPV types (Figure 3). Additionally, among the subset of cuHPV/HPyV types tested in serology, the seroprevalence was 73.6% for any β-HPV, 57.3% for any γ-HPV and 98.6% for any HPyV.

DISCUSSION

The VIRUSCAN Study is the first prospective cohort study to assess the association between cutaneous viral infections and KC using multiple, repeated markers of viral infection and quantitative measures of ultraviolet radiation exposure. In this manuscript, we present detailed information on the design, methods and baseline characteristics of the VIRUSCAN Study. VIRUSCAN Study participants are at higher risk for skin cancer than the general population, but tend to be more conscious of skin health, engaging in sun protection and undergoing routine skin cancer screening exams. Therefore, this population is ideal for assessing the VIRUSCAN Study aims as we expect to observe a large number of incident KC cases throughout the follow up period.

The spectrophotometer-based skin pigmentation readings obtained at two anatomic sites (forehead and forearm) were highly correlated, although forearm readings varied more than forehead readings, perhaps reflecting differences in sun protective behaviors, as 50.7% of participants used hats always/often to protect their forehead but only 31.8% of participants used long sleeves always/often to protect their forearms (Table 2). Measuring exposure at the forearm maybe a better surrogate for overall sun exposure than forehead measurements, further evidenced by the positive associations observed between forearm spectrophotometer measurements and self-reported recent sun exposure that were not observed for forehead spectrophotometer measurements. Taken together, these results confirm that spectrophotometer based measurements of skin pigmentation are objective measures that may be useful for tracking an individual’s recent sun exposure over time in relation to other time-dependent biomarkers of disease risk and may be useful in future epidemiologic studies seeking to incorporate recent measures of UVR exposure.

A high prevalence of cutaneous viral infections was observed in both skin swabs and eyebrow hairs obtained from VIRUSCAN Study participants, consistent with previous epidemiologic studies of cutaneous viral infections (22, 27). Interestingly, regardless of the cuHPV species, viral prevalence was consistently higher in skin swabs than in eyebrow hairs, with HPyV types following this same pattern. We also observed a strong correlation between type-specific infections across skin swabs and eyebrow hairs. These full baseline viral prevalence results confirm the findings previously reported among a subset of VIRUSCAN Study participants enrolled in year one in which prevalence, as well as number of types and degree of infection, were correlated across skin swabs and eyebrow hairs (52).

The VIRUSCAN Study has some methodologic limitations. The study population is a select group, comprised of older adults residing in a geographic region with high ambient UVR exposure, engaging in sun protective behaviors more often than the general population. Therefore, the generalizability of study findings may be limited. However, if UVR is a necessary cofactor in virus-associated skin carcinogenesis, then examining virus-associated KC risk in populations with higher UVR exposure maximizes the likelihood of observing such associations. Furthermore, should cutaneous viral infections be associated with KC in the VIRUSCAN Study population, then future studies could examine similar associations in populations with lower UVR exposures. Importantly, the VIRUSCAN Study participants would be an ideal target population in which to test novel skin cancer prevention strategies, due to their high skin cancer risk profile and motivation to decrease their risk.

To minimize participant burden, blood samples were only collected at baseline. However, baseline seroreactivity will provide information about past viral infections, while the DNA-based markers of infection in eyebrow hairs and skin swabs will provide insight on current infection. The tumor samples collected were typically small in size since they are screen-detected cancers. However, β-HPV types have been shown to be more prevalent in earlier stages of skin carcinogenesis (61) and therefore, the viral DNA detection may be more feasible in smaller tumors compared to more advanced, larger tumors. We were unable to collect tissue samples from premalignant lesions such as actinic keratosis because the standard treatment protocol at the University of South Florida Dermatology Clinic is cryodestruction. However, incident actinic keratosis lesions are documented throughout follow-up, thus enabling the assessment of actinic keratosis risk associated with baseline viral infections. Finally, while VIRUSCAN Study participants were only followed for up to four years; longer term follow-up may be possible with additional grant funding.

A major strength of the VIRUSCAN Study is the incorporation of repeated measures of UV exposure and cutaneous viral infections that will be used to assess temporal patterns of exposure and their associations with incident KC, as well as acquisition of new viral infection. Additionally, the longitudinal biospecimens were tested for over 100 cutaneous virus types, facilitating the investigation of KC risk associated with persistence of viral infections, an aspect of HPV infection known to be associated with increased risk of other cancers (62). Furthermore, the banked samples will facilitate multi-disciplinary research involving measures of immune function and subsequent cancer development. Finally, our subsample validation study indicates that the spectrophotometer readings yield an objective and quantifiable measure of recent UVR exposure which will be used in the VIRUSCAN study to assess the possible interaction between UVR exposure and cuHPV/HPyV infection in relation to KC risk.

While the VIRUSCAN Study is ongoing, the longitudinal results will provide critical temporal evidence as to the role of cutaneous viral infections in the development of KC, as well as the potential interaction between viral infections and UVR. These findings will inform future KC prevention efforts, such as the development of a vaccine which could serve as a primary prevention strategy among individuals at high risk for KC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

Funding was provided by the National Cancer Institute at the National Institutes of Health (1R01-CA17758), awarded to D.E. Rollison, and supported all authors. This work was supported in part by the Survey Methods and Tissue Cores at the H. Lee Moffitt Cancer Center and Research Institute, a comprehensive cancer center designated by the National Cancer Institute (Grant P30-CA076292).

The authors would like to sincerely thank the USF Dermatology Clinic patients who contributed generously of their time to the VIRUSCAN Study.

Conflicts of interest: Dr. Anna R. Giuliano reports being a Merck & Co, Inc. grant recipient and advisory board member. The remaining authors state no relevant financial disclosures.

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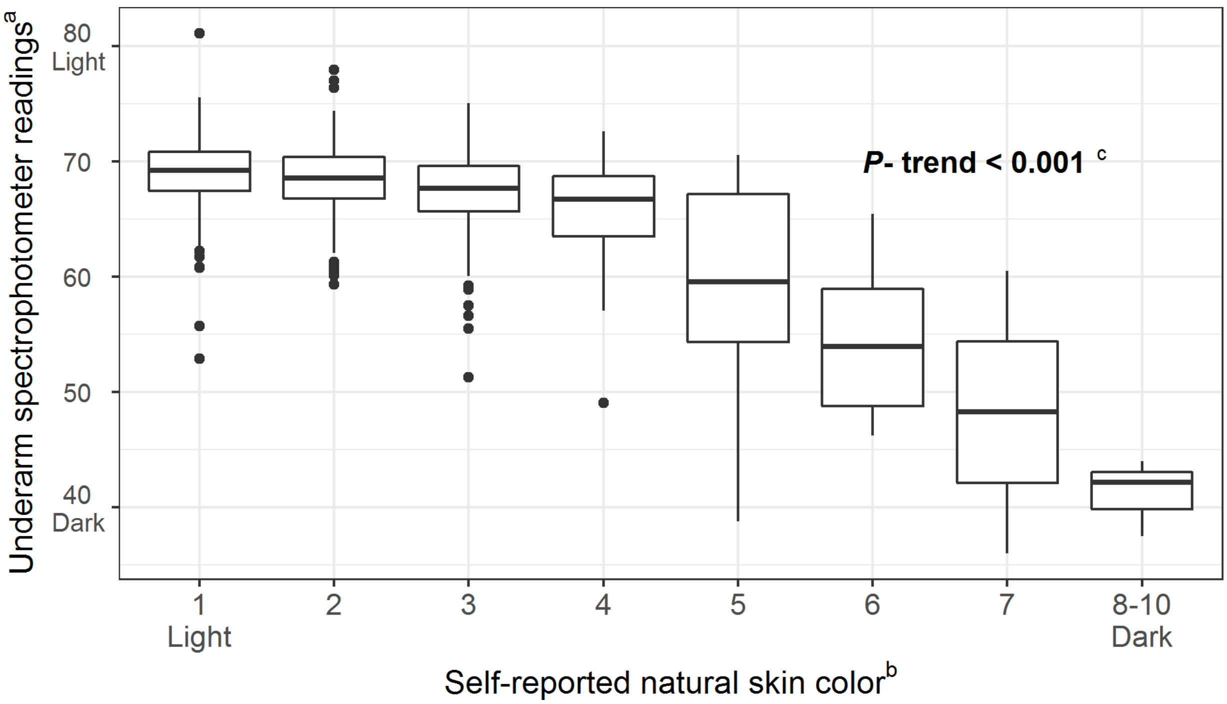

Figure 1.

Association between underarm spectrophotometer reading and self-reported natural skin color in the VIRUSCAN Study, Tampa, FL, 2014–2017. A strong positive correlation was observed between the baseline underarm spectrophotometer readings and self-reported natural skin color.

[a]Lower values of the underarm spectrophotometer readings represent darker skin pigmentation.

[b]Self-reported natural skin color was assessed with the New Immigrant Survey Color Scale which included images of hands in a variety of skin shades categorized as ranging from 0 to 10, with 0 representing the lightest skin and 10 representing the darkest skin.

[c]The Jonckheere-Terpstra test was used to determine if a trend existed between underarm spectrophotometer readings and self-reported natural skin color.

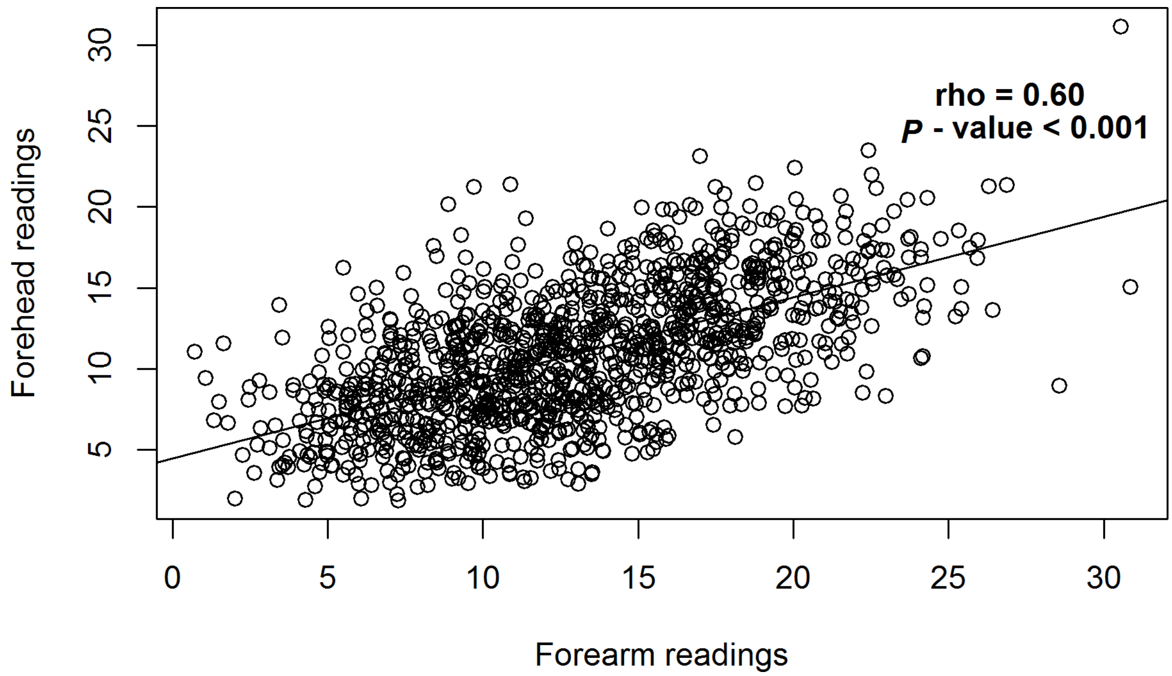

Figure 2.
Correlation between forearm and forehead spectrophotometer readings in the VIRUSCAN Study, Tampa, FL, 2014–2017. A strong positive correlation was observed between the baseline forearm and forehead spectrophotometer readings.
[a]Rho and *P* value were calculated using Spearman correlation.

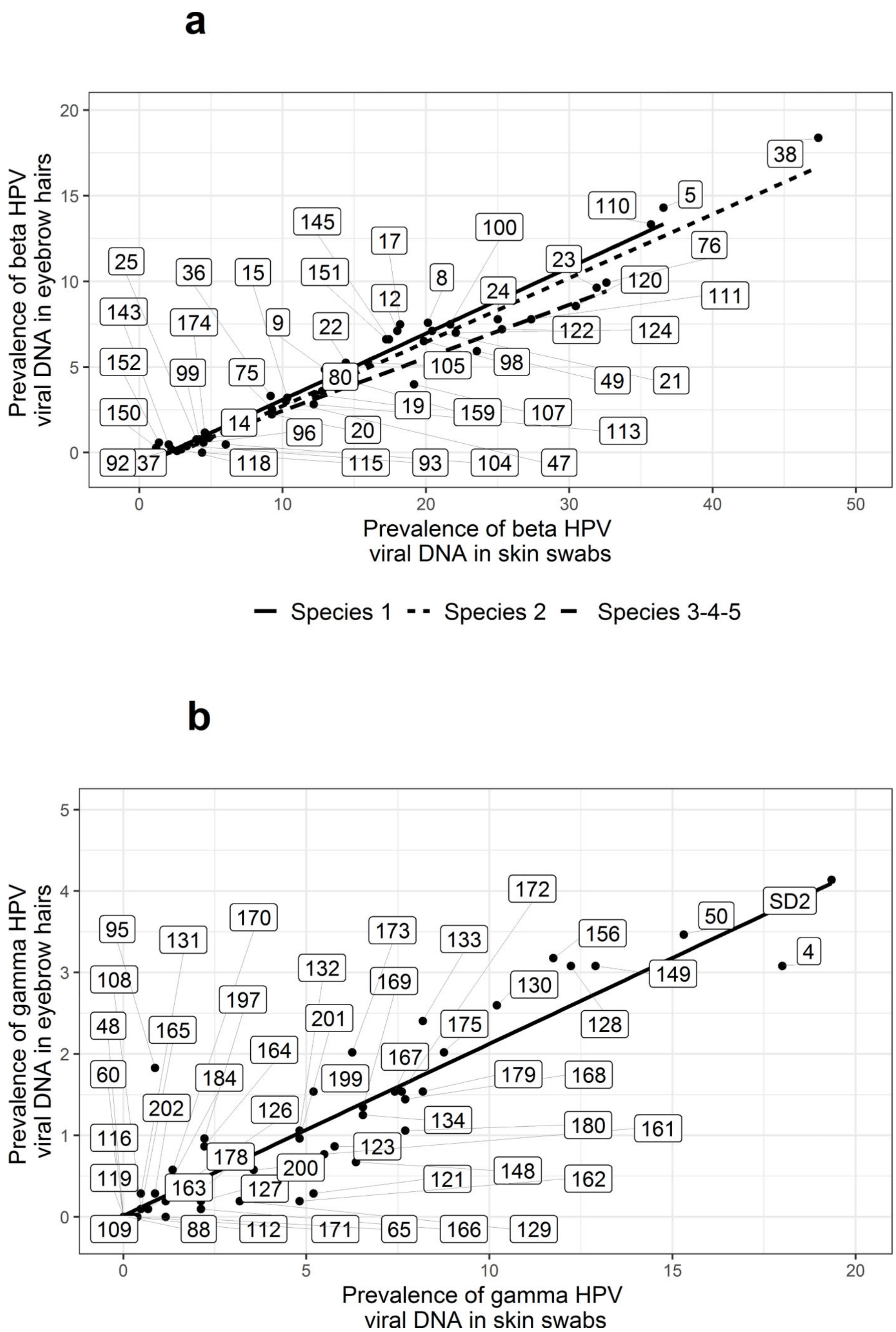

Figure 3.

Cutaneous Human papillomavirus (HPV) prevalence in skin swabs and eyebrow hairs among VIRUSCAN Study participants, Tampa, FL 2014–2017. The scatterplots display the correlation between type-specific HPV viral prevalence in skin swabs (x-axis) and eyebrow hairs (y-axis). The numbers within the rectangles indicate the HPV type tested for both (a) β-HPV types and (b) γ-HPV types.

[a]Rho and *P* value were calculated using Spearman correlation.

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Table 1.

Variables collected in the VIRUSCAN Study, Tampa, FL, 2014–2018.

Source	Variable details	Visit
Study questionnaire		B
Demographics	Gender, age, race, ethnicity, education level, marital status, place of birth	
Sun protection	Use of sunscreen, long sleeves, pants, hats, sunglasses, and sun avoidance	
Sun exposures	Occupational sun exposure, history of sunburn, skin reaction to the sun, use of sunlamps or UV nail dryers	
Phenotypic factors	Eye color, hair color, untanned skin color, number of moles on arm/body	
Skin cancer screening	Number of skin exams per year	
Skin conditions	History of skin biopsies, eczema, psoriasis, acne, vitiligo, actinic keratosis, keratoacanthoma, warts, other skin conditions, treatment for skin conditions	
Cancer history	Melanoma, basal cell carcinoma, squamous cell carcinoma, other skin cancers or other cancers	
Other medical conditions	Organ transplant, Crohn's disease, Type I diabetes, Type II diabetes, heart disease, epidermodysplasia verruciformis, lupus, multiple sclerosis, Sezary syndrome, rheumatoid arthritis, osteoarthritis, xeroderma pigmentosum, asthma/bronchitis/emphysema, gout	
Smoking and alcohol	Smoking and drinking habits	
Steroid medication	Use of oral steroids or steroid creams	
Clinical findings of total body skin examinations	Identification of pre-malignant (actinic keratosis) and malignant lesions (tumor histology, anatomic site [head, neck, torso, arms, legs])	B and FU
Biospecimens		
Blood	HPV/HPyV serum antibodies	B
Eyebrow hair	HPV/HPyV viral DNA	B and FU
Skin swabs	HPV/HPyV viral DNA	B and FU
Tumor Tissue	HPV/HPyV viral DNA, solar elastosis, papillomatosis, hypergranulosis, and crateriform architecture (SCC only)	B and FU
Spectrophotometer	Inner upper arm, forearm and forehead spectrophotometer reading	B and FU
Sun exposure questionnaire	(subsample n=159)	FU
Sun exposure (past week)	Time outdoors, frequency of sunbathing and spending time in the sun sitting or lying	
Sun protection (past week)	Use of sunscreen, clothing, hat and sun avoidance	

Abbreviations: B, baseline visit; FU, follow-up visit.

Table 2.

Demographic Characteristics and Skin Cancer Risk Factors and Protective Behaviors in the VIRUSCAN Study, Tampa, FL, 2014–2017 and the Southern United States Population

Demographic and skin cancer risk factors	VIRUSCAN (n=1,179)		Southern NHIS 2015[c] (n=25,149,699)		p-value[d]
	N	%	n	%	
Age in years					
Mean SD	69.0	6.3	70.2	7.6	< 0.001
Gender					
Female	627	53.2	14,073,280	56.0	0.055
Male	552	46.8	11,076,419	44.0	
Race					
White	1,132	96.1	20,421,079	81.2	< 0.001
Others	46	3.9	4,728,620	18.8	
Ethnicity					
Non-Hispanic	1,115	94.6	22,748,364	90.5	< 0.001
Hispanic or Latino	64	5.4	2,401,335	9.5	
Sunburn in the past 12 months					
No	1,061	92.5	20,241,154	86.1	< 0.001
Yes	86	7.5	3,273,041	13.9	
History of any cancer					
No	565	49.1	19,269,413	76.8	< 0.001
Yes	585	50.9	5,807,869	23.2	
History of skin cancer at study enrollment					
No known skin cancer	687	59.7	5,264,232	90.7	< 0.001
Any type of skin cancer	463	40.3	536,843	9.3	
Smoke status					
Never smoked	586	51.0	13,307,427	53.1	< 0.001[e]
Former smoker	524	45.6	9,180,053	36.6	
Current smoker	38	3.3	2,563,205	10.2	
Reaction to 1 hour sun exposure					
No change	48	4.2	3,430,354	17.9	< 0.001[e]
Tans without sunburn	234	20.4	4,556,119	23.8	
Mild sunburn with tan[a]	488	42.6	4,898,328	25.6	
Sunburn without blisters	315	27.5	4,198,736	21.9	
Blistering sunburn	60	5.2	2,052,810	10.7	
Ever used a sun lamp or tanning bed					
No	905	78.8	1,943,216	97.2	< 0.001[e]
Yes	243	21.2	55,992	2.8	
Sunscreen use[b]					
Always	109	10.5	4,295,888	21.2	< 0.001[f]

Demographic and skin cancer risk factors	VIRUSCAN (n=1,179)		Southern NHIS 2015[c] (n=25,149,699)		p-value[d]	
	N	%	n	%		
Often	265	25.5	2,155,292	10.7		
Sometimes	316	30.4	3,180,984	15.7		
Rarely	221	21.3	2,022,689	10.0		
Never	127	12.2	8,566,555	42.4		
Wore a hat[b]						
Always	245	23.6	3,617,098	17.9	< 0.001[f]	
Often	282	27.1	1,974,467	9.8		
Sometimes	255	24.5	2,965,504	14.7		
Rarely	141	13.6	1,949,292	9.7		
Never	116	11.2	9,650,956	47.9		
Stayed in shade[b]						
Always	109	10.5	4,303,200	21.3	< 0.001[f]	
Often	464	44.7	6,050,002	29.9		
Sometimes	356	34.3	6,119,738	30.2		
Rarely	81	7.8	2,011,929	9.9		
Never	27	2.6	1,762,869	8.7		
Wore protective clothes[b]			**Wore long sleeves**		**Wore long pants**	
Always	83	8.0	2,660,356	13.2	5,605,566	27.8
Often	248	23.8	1,537,657	7.6	2,545,902	12.6
Sometimes	339	32.6	3,404,590	16.9	3,666,794	18.2
Rarely	262	25.2	2,506,741	12.4	1,893,874	9.4
Never	109	10.5	10,027,229	49.8	6,475,233	32.1

Abbreviations: NHIS, National Health Interview Survey; SD, standard deviation; VIRUSCAN, Viruses in Skin Cancer.

[a] The corresponding category for the NHIS data is: burn mildly with some or no tanning.

[b] The sun exposure timeframe differed between the VIRUSCAN questionnaire (if outside in sun for 15 minutes or more) and the NHIS questionnaire (if outside in sun for 1 hour or more) for the sun protection variables.

[c] The NHIS data set was restricted to adults ages 60+ and weighted using the “sampleweight” variable.

[d] P-values were calculated using Chi-square tests without correction for continuity and confirmed by conditional exact tests.

[e] The following variables were tested using a pooled Chi-square test from 5 imputed datasets including: smoke status, reaction to 1 hour sun exposure and ever use a sun lamp or tanning bed.

[f] The following variables were tested using the Cochran-Armitage trend test: sunscreen use, wore a hat and stayed in shade.

Table 3.

Correlation Between Forearm Spectrophotometer Readings and Past-Week Measures of Sun Exposure and Protection Among a Subsample of VIRUSCAN Study Participants (n=159), Tampa, FL, 2014–2017

Questionnaire measurement of exposure/protection		Forearm spectrophotometer readings[a]					
		low (<=11.55)		high (>11.55)		OR	95% CI[b]
		n	%	n	%		
Exposure scale							
	T1	45	56.2	34	43.0	1.00	Referent
	T2	22	27.5	21	26.6	1.03	0.45, 2.32
	T3	13	16.2	24	30.4	2.48	1.01, 6.33
						P-trend[c] = 0.06	
Protection scale							
	T1	29	36.2	30	38.0	1.00	Referent
	T2	26	32.5	26	32.9	0.97	0.42, 2.24
	T3	25	31.2	23	29.1	0.76	0.32, 1.75
						P-trend = 0.54	
Ratio of exposure/protection scales							
	T1	37	46.8	23	29.1	1.00	Referent
	T2	26	32.9	24	30.4	1.14	0.49, 2.61
	T3	16	20.3	32	40.5	2.89	1.24, 6.95
						P-trend = 0.01	

[a]Forearm spectrophotometer readings were dichotomized based on the median value.

[b]Odds ratio and 95% confidence interval were calculated using logistic regression, adjusted for age and gender.

[c]The median score/ratio of each group was used to test the trend between score and spectrophotometer readings, using logistic regression adjusted for age and gender.