UV Dose Determines Key Characteristics of Nonmelanoma Skin Cancer

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Abstract

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), known as nonmelanoma skin cancer (NMSC), are the most common cancers worldwide. Although many factors are involved in the pathogenesis of NMSC, UV radiation is an important risk factor. A fundamental question in skin cancer research is whether varying doses of total UV radiation influence key characteristics of NMSC. The hypothesis that differences in UV doses influence the BCC/SCC ratio, number of tumors, and anatomic location of the tumor was investigated in 311 participants having 326 tumors and with exposure to a broad range of UV doses. An epidemiologic questionnaire was given to each participant soliciting detailed information on exposure to solar radiation. Environmental UVA and UVB doses were measured continually for 6 years at a permanent UV monitoring station. The total ratio of BCC/SCC was 3.5. Participants who received low and high UV doses had a BCC/SCC ratio of 4.2. Those who received very high UV doses had a ratio of 2.1. A very high UV dose was also associated with the doubling of the total number of tumors per person and a significantly increased risk of having SCC, a more aggressive malignancy. Tumors in sun-exposed areas (on the body) were more common in participants who received high and very high UV doses. The tumors in sun-protected areas were associated with exposure to lower levels of UV. This large-scale population study provides evidence that varying doses of UV radiation have a profound influence on key characteristics of NMSC. (Cancer Epidemiol Biomarkers Prev 2004;13(12):2006–11)

Introduction

Nonmelanoma skin cancer (NMSC) is the most common cancer in the world. It ranks as No. 8 in terms of this decade’s health priorities in the United States (1). NMSC consists of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). BCC is the more common of the two. Although less common, SCC can metastasize, accounting for up to 20% of all deaths from skin cancer (2). Up to 16% of the cutaneous SCC lesions caused by chronic UV exposure and/or preexisting actinic keratosis can metastasize (2, 3). This risk may reach as high as 30% for skin lesions associated with chronic inflammation (4). SCC that occur in the head and neck have the potential for neural involvement and distant metastasis (5). Once SCC metastasizes, the 10-year survival drops 4-fold and the risk for recurrence increases 6.5-fold (6).

Surgical and medical treatments for NMSC are difficult because of the high recurrence rate, the occurrence of multiple lesions, and the location of tumors. Because there are over 1 million new cases of NMSC diagnosed in the US every year, the social and economic burden of treating this disease has increased sharply (7, 8). NMSC is ranked in terms of Medicare expenditures among the top five cancers, incurring an average cost of $426 million per year (7, 8). The majority of NMSC tumors occur in the head, with 30% in the nose (6). Surgical treatment can cause permanent scars and psychological trauma.

Epidemiologic studies have established that exposure to UV radiation is associated with the development of NMSC in sun-exposed areas of the body (9-11). Australians exposed to UV radiation had an increased frequency of facial NMSC (10). Urbach (11) reported that 88% of BCC developed in the head and neck, whereas 68% of SCC occurred in this area. In the face, the majority of tumors developed in areas that received the highest UV exposure (11). The incidence of NMSC which have developed in the trunk and legs have increased in the last decade (12). Other studies have found that the development of truncal tumors is found in genetically susceptible individuals (13, 14). The location of the NMSC is important in the pathogenesis and treatment of the disease. NMSC tumors which occur on the trunk and arms, are at least 4 mm in depth, and have invaded the dermis, could lead to local recurrence and nodal involvement (15). An increased number of SCC tumors and associated changes in the ratio of BCC/SCC are influenced by UV doses (16, 17).

UV radiation is a major risk factor for the development of NMSC. UVA (320-400 nm) and UVB (280-320 nm) both function as initiators and promoters in carcinogenesis as well as immunosuppressors (18-25). UV exposure during childhood and intense intermittent UV exposure are major risk factors for BCC (26). Chronic cumulative UV...
exposure is a major risk factor for SCC (26). UVB causes direct DNA damage and mutations by promoting cyclobutane pyrimidine dimers and 6-4 photoproducts (18-22). UVA stimulates the production of reactive oxygen species and cellular photosensitizers (21). The photosensitized DNA bases induce single-strand breaks, oxidative stress reactions, cyclobutane pyrimidine dimers, and DNA mutations (18, 21, 22).

Puerto Rico’s geographic location (latitude 18.6 N) provides an excellent photobiological model for studying fundamental aspects of the relationship between UV radiation and NMSC. Normally elevated due to the island’s geographic location, the UV index in Puerto Rico was categorized as “high” for 100 days in 2001 and “very high” for 210 days of that same year (27). Because of its small size (8,960 km$^2$), actual geographic location within the island presumably does not cause much variability in UV dose.

The purpose of this study was to examine how UV radiation is associated with three key characteristics of NMSC: the BCC/SCC ratio, number of tumors, and the anatomic location of the tumors. Previous studies have reported an association between UV radiation and these three characteristics of NMSC (9-11). The findings of this study suggest that these three characteristics associated with NMSC are profoundly influenced by different UV doses.

Materials and Methods

Recruitment of Participants. The institutional review board at Ponce School of Medicine, Ponce Puerto Rico, approved the use of human subjects. Informed consent was obtained from each participant before enrollment. All participants were residents of Puerto Rico and at least 21 years old. The participants had histopathologically confirmed BCC and/or SCC. All cases were diagnosed between February 2000 and November 2003. The participants selected for this study are part of an on-going Research Centers for Minority Institutions NIH-funded case-control study at Ponce School of Medicine that started in the year 2000. In general, the participants were consecutive cases that went on their own to a private dermatology office for examination of skin lesions. At the time of the surgical removal of their tumors, the participants were referred to the study. A consent form and a questionnaire were given to each participant prior to recruitment. The type of cancer, the location of the NMSC when available, and the number of tumors were gathered from pathology reports present, and from medical records after authorization from the informed consent.

Participants included Caucasians and non–Caucasians of all skin types (Fitzpatrick skin-typing classification). A questionnaire was voluntarily completed by each participant, providing detailed information regarding their UV exposure associated with outdoor activities. This included, type of work and hours exposed to UV per week, hobbies, and hours exposed to UV per week, and the duration in years of all activities in which they were exposed to UV radiation. Other factors such as smoking, medical history, cancer history, sunburn, tanning ability, and use of sunblock were also gathered. Use of sunblock was considered if the participants used sunblock with sun protection factor > 15 in most of the occasions they were exposed to sunlight either at work and/or during recreational activities. Exclusion factors for this study included the following: (1) any person with a diagnosis of another cancer including melanoma, (2) any person that received radiotherapy and/or chemotherapy, (3) any person that received a blood transfusion within the last 5 years, (4) any person with a genetic or acquired immunodeficiency, (5) any person with a diagnosis of psoriasis.

UV Measurements. Environmental UVA and UVB data over a 6-year period were obtained with a GUV-511 ground-based radiometer (Biospherical Instruments, Inc., San Diego, CA) at four wavelengths (305, 320, 340, and 380 nm). This instrument is located at the permanent UV monitoring station in the Department of Marine Sciences, University of Puerto Rico, La Parguera. This radiometer records UV data continuously every 5 minutes. The equations of Orce and Helbling (28) were used for spectral reconstruction of the four-band GUV-511 data into daily irradiance in the UV (280-400 nm) range. These data were integrated in time to produce daily UV doses in kJ/m$^2$/d. An integrated approach was used instead of a weighed approach as suggested by CIE Photocarcinogenesis Action Spectrum (NMSC) CIE TC6-32 (2000) because no UV penetration under 300 nm was detected during the 6 years of environmental UV measurements. Although there were differences in cancer susceptibility across the UV spectra, integrating the UV data collected was the best approach because people are exposed to the whole spectra of UV. Also, integrating the UV data is pathophysiologically important because of the photo-interaction that exists between UVA and UVB and the development of erythema and NMSC (29-31).

UV Radiation Classification. The interpretations of the questionnaires were used to estimate the amount of time per day and for how many years each participant was exposed to UV radiation. Three 1-hour periods of continuous UV radiation exposure per week for at least 3 years was designated as the carcinogenic effectiveness between exposure to low and high levels of UV radiation (both UVA and UVB). People who experienced a high level of UV exposure for more than 15 years were classified as having very high UV exposure. These effective doses were estimated from the measured UV doses in Puerto Rico and by using other comparative parameters such as the UV index (27). The UV index is the best next-day predictor reporting the level of harmful ambient solar UV radiation reaching the earth’s surface (Standard CIE S 013/E:2003). At high and very high ranges, it is recommended that people avoid UV exposure between 10:00 a.m. and 4:00 p.m. and if a person must go out into the sun, it is recommended that he or she wear protective clothing and use sunblock (minimum sun protection factor: 15; ref. 27).

Statistical Analysis. The BCC/SCC ratio was calculated from the total number of BCC and SCC cases in the population studied. Univariate analyses were used to
compare the distribution of UV dose and the three NMSC characteristics being studied. Because older people are at higher risk for NMSC and participants with skin types I/II have a higher risk of NMSC than skin types III/IV, all calculations were adjusted for skin type and age. An independent sample Student’s t test was used to evaluate the significance of the characteristics studied. Logistic regression analysis adjusted for skin type and age were used to calculate odds ratios. Statistical significance was established as a P value < 0.05, based on a two-tail distribution. All tabulations, adjustments, and statistical analyses were performed with software (SPSS Statistical Package, Version 12.0 for Windows, SPSS, Chicago, IL).

**Results**

**UV Radiation Dose.** The mean cumulative of the total UV dose was 1,160 kJ/m²/d during 6 years. On a typical day (vernal equinox), the UV dose per hour varied from 42.5 to 210.8 kJ/m² during an 8-hour period (9:00 a.m. to 5:00 p.m.). Three, 1-hour periods (9:00 a.m. to 5:00 p.m.) of continuous UV exposure a week corresponded to a minimum of 184 kJ/m² (± 24 SE) per week (Table 1). The cumulative carcinogenic effectiveness for exposure to high and very high UV levels were 29,000 kJ/m² (± 3,700) and 145,000 kJ/m² (± 18,700), respectively (Table 1). The number of participants that received low, high, and very high UV doses was 74, 168, and 69, respectively.

**Population Characteristics.** The 311 participants with NMSC had a total of 326 tumors excised at the time of enrollment. Fifteen participants had two tumors excised at the time of enrollment. Approximately 75% to 80% of the pathology reports and/or medical records revealed the identity of the body part where the biopsy or the surgical removal of the tumor came from and how many lesions each participant had. Pathology reports and/or medical reports enumerating the quantity of tumors were obtained for 251 participants. Tumor location was described in 254 of the pathology reports. Participants were mostly consecutive cases with histopathologically diagnosed NMSC. The participants were not preselected and every person that met the criteria for the study was enrolled in the study. Participants had basal or squamous tumors ranging in size from 0.1 cm to over 3 to 4 cm. Their age ranged from 21 to 100 years of age. There were 213 and 98 participants with skin types I/II and II/IV, respectively. Participants exposed to low, high, or very high UV doses used sunblock in 25%, 28%, and 21%, respectively. There were 53% males and 47% females in the study. Males and females groups were correspondingly exposed to 47%, 54%, 56% and 53%, 46%, 44% to low, high, or very high UV doses, respectively.

**BCC to SCC Ratio.** There were 254 BCC (53% males) and 72 SCC (58% males) cases (3:5:1 ratio) in the population studied (Fig. 2). The BCC/SCC ratio for participants who received low, high, and very high UV doses was 4:2:1, 4:2:1, and 2:1:1, respectively (Fig. 1).

**UV Radiation and Tumor Number.** Each participant had 2.1 tumors on average. Participants with low and high exposure to UV levels did not differ significantly (P > 0.05) in the number of tumors: participants exposed to low UV levels averaged 1.6 tumors per person, whereas the group exposed to high UV levels averaged 1.8. The group exposed to very high UV radiation had an average of 3.5 tumors per person (Fig. 2). The difference between the very high UV radiation group and the other two groups was statistically significant (P < 0.05). Logistic regression analysis in the population studied showed that the risk of developing a second tumor increased 13% in participants that received very high UV doses (P = 0.004).

**UV Radiation and Tumor Location.** Sun-exposed areas of the body were considered the head, neck, and outer surface of the arms, including the shoulder. The rest of the body was considered sun-protected. During leisure activities, some participants received direct UV exposure in sun-protected areas of the body. Because the proportion of these participants were nearly equally distributed along the three groups, no distinctions were made in the classification. Seventeen participants had tumors in both sun-exposed and protected locations. The participants that had tumors in both areas were not considered for statistical analysis. More females (65%) developed NMSC in sun-protected areas, whereas more males (56%) developed NMSC in sun-exposed areas of the body. There was no statistical significance (P > 0.05) difference in terms of gender between the groups. Tumors in sun-exposed body parts (n = 174) were 2.7 times more frequent than in sun-protected body parts (n = 63). The percentages of tumors that developed in sun-exposed areas were 36% (20/56; low UV doses), 85% (113/134; high UV doses), and 87% (41/47, very high UV doses; Fig. 3). The differences between the participants exposed to low UV doses and either the participants exposed to high or very high UV doses were statistically significant (P < 0.05). No differences were found between the participants exposed to low or very high UV doses. Logistic regression analysis showed that participants with NMSC who received high or very high UV doses had 7.7 times the risk of developing their tumor in sun-exposed areas (P value < 0.001; odds ratios 7.7, 95% confidence interval 4.2-14.2).

**Discussion**

This populational study shows that UV dose influences three important characteristics of NMSC, the BCC/SCC ratio, and the location, as well as the number of tumors. These findings provide valuable dose-response data concerning UV radiation exposure effects that can provide the basis for future mechanistic studies. Using the UV index and estimating UV by dosimeters, previous studies in human populations have established the

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**Table 1. The carcinogenic effectiveness of the different total UV (UVA+UVB) classifications based on the 6-year (1998-2003) environmental UV doses collected in La Parguera, Puerto Rico**

<table>
<thead>
<tr>
<th>UV Classification</th>
<th>kJ/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly dosage</td>
<td></td>
</tr>
<tr>
<td>Low UV dose</td>
<td>184</td>
</tr>
<tr>
<td>High UV dose</td>
<td>&gt; 29,000</td>
</tr>
<tr>
<td>Very high UV dose</td>
<td>29,000-145,000</td>
</tr>
<tr>
<td></td>
<td>&gt; 145,000</td>
</tr>
</tbody>
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correlation between UV radiation and NMSC (10, 32). However, this study provides a directly measured estimate of the carcinogenic effectiveness for each of the three NMSC characteristics studied. Three, 1-hour periods of continuous UV exposure per week for at least 3 years was established as the effective dose for a high UV exposure in the population studied. The UV dose in 1 week corresponded to 184 kJ/m²; however, considering the UV variation throughout a day, this dose can be as high as 630 kJ/m². The high intensity of UV exposure may cause significant DNA damage as well as mutations. Animal studies have shown that skin changes and DNA mutations usually occur before any erythema is visible (33, 34). The amount of DNA damage and the appearance of NMSC are strongly influenced by the intensity or duration of UV exposure (33-36). UV results gathered in this study from Puerto Rico are comparable to UV results obtained at similar latitude in the southern hemisphere (Jujuy, Argentina) with the same instrument (28).

The BCC/SCC ratio found in this study (3.5:1) was similar to the BCC/SCC ratio reported in two studies in Puerto Rico and in Baltimore, MD (37, 38). A key finding is that the BCC/SCC ratio decreased in those participants who had received very high UV doses. A minimal total of 145,000 kJ/m² was the carcinogenic effectiveness level for a decrease in the BCC/SCC ratio of the participants studied. Those participants who had received low and high UV doses had a 4.2:1 BCC/SCC ratio, which was twice that of those in the group who received very high UV doses (2.1:1 BCC/SCC). This difference was statistically significant and clinically relevant. In animal models, there is an increased number of SCC and actinic keratosis (premalignant lesions of SCC) with an increasing dose of UV radiation. This is related to the increased accumulation of DNA damage and mutations in the p53 gene (35, 36). The data presented suggests that as the years of exposure to high UV levels increase, more SCC tumors develop. The number of SCCs...
doubled in participants who received very high UV doses, suggesting an increased risk for developing metastatic skin tumors. This may be caused by an increase in the incidence of SCC as UV doses increase. This finding supports the previously cited animal and human studies which have shown that chronic UV exposure is an important risk factor in the development of SCC.

Another key finding is that the number of NMSC tumors doubled in participants receiving very high UV doses. The cumulative UV dose needed to significantly increase the number of tumors was at least 145,000 kJ/m². This represents the effective UV dose required for doubling the amount of NMSC tumors in the population studied. Although our results showed that SCC increased in the participants exposed to very high UV, the increase in SCC alone could not explain the doubling in the number of NMSC tumors. Exposure to very high UV levels resulted in an increase in the numbers of both BCC and SCC, although the increase was more pronounced in SCC. Exposure to very high UV levels resulted in a 13% increase in the risk of developing a second tumor. This was statistically significant and was associated with the increase in the number of tumors per participant found.

The results gathered are supported by findings from animal models which have shown the extent of DNA damage caused by the dose of UV radiation as well as the subsequent progression to skin cancer. In hairless mice, increased DNA damage and p53 mutations are associated with an increasing UV dose (35, 39). Increased UV dose also shortened the latency period for the development of NMSC and was associated with an increase in the number of tumors (35). Sauter et al. (36) describes the grafting of human neonatal skin to mice and their subsequent exposure to various doses of UVB. The number of tumors and the frequency of actinic keratosis and SCCs were higher when UV dose and/or the time of exposure were increased (36). Collectively, these studies indicate that a higher dose of UV radiation resulted in more DNA damage and mutations, which subsequently lead to increased numbers of NMSC tumors, particularly SCC.

The third NMSC characteristic studied was the relationship between UV radiation and the location of tumors. The number of lesions which appeared on sun-exposed areas of the body was higher in participants who received high UV doses. This finding is not surprising because areas exposed to higher UV radiation should have more accumulation of DNA damage and mutations (40, 41). Persons who developed BCC on sun-exposed skin had a higher accumulation of pyrimidine dimers than in sun-protected skin (41). A study done in Australia, in which UV was measured by means of a personal dosimeter, showed that persons exposed to high UV radiation levels for a prolonged time period developed more lesions in the face when compared with any other body part (10). In this study, the head, neck, and the outer surface of the arms were designated as sun-exposed areas. Consequently, these areas are at a higher risk for tumorigenesis. A minimum total UV dose of 29,000 kJ/m² was required for NMSC tumors to become more common in sun-exposed areas. This value was lower than the UV dose required for either doubling the tumor number or decreasing the BCC/SCC ratio.

The development of tumors in sun-exposed areas did not differ between the groups exposed to either high or very high UV levels. Participants in this study, who received high levels of UV, had a 7.7-fold increased risk of developing an NMSC tumor in their head, neck, or outer arms. Due to the increased visibility of these areas of the body, cosmetic surgical repair is usually more expensive because it must provide optimal results. In addition, recurrence rates tend to be higher because treatments are more conservative (6). Increased risk of developing NMSC in sun-exposed areas may ultimately be associated with an increased risk of metastasis because of the higher recurrence rates in sun-exposed areas (6).

A very important finding was that the tumors in sun-protected areas of the body were more common in people who were potentially exposed to low doses of UV radiation. The participants that developed tumors in both areas were not considered for this analysis. The number of tumors in sun-protected areas of the body in participants that received low UV doses was 64% (36/56). The percentages of sun-protected tumors in the high and very high UV exposure groups were 15% and 13%. The difference between low UV exposure group and the other two groups was statistically significant. Although more females developed NMSC in sun-protected areas, no significant difference was found between genders. Ramachandran et al. (13) reported that the development of NMSC exclusively in the trunk of the body is linked to an NMSC subtype that occurs in genetically susceptible individuals. The DNA repair capacity has been established as an independent risk factor for the development of NMSC (37, 38). It is possible that people who develop NMSC in sun-protected areas of the body may have a decreased DNA repair capacity. An alternative hypothesis to explain this may be that UV radiation causes a systemic as well as a local immunosuppressive effect. UV-induced DNA damage releases cytokines that ultimately results in the immunosuppression of T-lymphocytes (22, 24, 25, 42, 43). The recent treatment modality for NMSC with immunotherapy and immunomodulators supports this hypothesis, providing substantial evidence that exposure to UV radiation is not the only factor that causes NMSC (44, 45).

In summary, this study provides evidence in a large-scale human population that different doses of UV radiation influence key characteristics of NMSC. Given that the risk of an invasive and metastatic disease is higher as exposure to UV doses increases, the mortality rate should also increase. The current decrease in the planet’s ozone layer has been associated with higher levels of UV radiation (46). In areas of the world like Argentina where the ozone layer is depleted, people are exposed to higher UV levels and they have a higher incidence of NMSC (46). Consequently, NMSC may become an epidemic disease that affects a large segment of the population. The Centers for Disease Control considers, as a national priority, the need for a task force for reducing exposure to UV and for the prevention of skin cancer (47). The findings and carcinogenic effectiveness obtained in this study for the three NMSC characteristics could contribute to the development of more effective skin cancer prevention programs.
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