The Ochsner Journal 10:75–82, 2010

The Role of DNA Repair Capacity in Melanoma Skin Cancer Risk in a Population Chronically Exposed to High Levels of Sunlight

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ABSTRACT

Puerto Rican residents are exposed to some of the highest levels of environmental ultraviolet radiation in the world; paradoxically, the melanoma incidence in Puerto Rico is lower than that of the US mainland. The overall objective of this case-control pilot study was to test the hypotheses that (1) persons with melanoma have a significantly lower DNA repair capacity (DRC) in relation to controls matched by age, (2) decline in DRC is associated with vertical depth of melanoma invasion, and (3) DRC is associated with anatomical tumor location. Controls ($n = 124$) were examined by dermatologists; cases ($n = 62$) were histopathologically confirmed. The mean DRC $\pm$ 1 SE of controls was 6.46% $\pm$ 0.3. Melanoma patients ($n = 62$) had a mean decrease in DRC of 3% (6.25% $\pm$ 0.5), which was not statistically different from controls ($P = 0.697$). No significant differences in DRC were evident in participants with either in situ or malignant melanoma tumors; neither were such differences evident when evaluating anatomical location of tumors (ie, non–sun-exposed versus sun-exposed). DRC generally declined in participants with increased depth of melanoma tumor penetration when compared with controls and those with small in situ tumors. These findings should be examined in a larger-scale population study that includes participants with more advanced metastatic melanoma.

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Key Words: Case-control study, DNA repair capacity, high UV exposure, melanoma, risk factors, skin cancer

The authors do not have any conflicts of interest that require disclosure.

INTRODUCTION

Puerto Rican populations are exposed to very high ultraviolet (UV) radiation levels throughout most of the year.[1] Thus, the general recommendation for preventing the development of melanoma is limiting sun exposure. Even given the average Puerto Rican's frequent exposure to high levels of UV, the incidence of melanoma on the Caribbean island is lower than what is seen on the US mainland. In Puerto Rico, the age-adjusted incidence has increased from 3.5 to 5.5 per 100,000 (estimated), representing a nearly 50% increase over the life of the study (1987–2002).[2,3] This incidence is considerably lower than the US population's reported incidence rate of 28.9 per 100,000 for white males and 18.7 per 100,000 for white females, based on cases diagnosed from 2002 to 2006.[4] Normally elevated owing 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.[1] Puerto Rico (latitude, 18° 15′ N; longitude, 66° 30′ W) provides an excellent photobiologic model for studying fundamental aspects of the relationship between UV radiation and melanoma. Analyzing melanoma among the Puerto Rican population could further elucidate the roles of UV light and of genetics as well as the risk factors involved in the etiology of melanoma.

The depth and anatomical location of the primary melanoma tumor, the tumor's thickness, and the presence and extent of metastatic disease are all factors that determine a given patient's prognosis. Melanoma usually progresses first radially, remaining in situ, and lacking the capacity to invade the dermis; afterward, it grows vertically and becomes metastatically competent.[5] The success of treatment tends toward one of two extremes: At one end lies thin cutaneous melanoma, characterized by a high cure rate; at the other lies metastatic melanoma, with no proven effective therapy.[6] Thus, detecting melanoma in its early stages is critical to reducing morbidity and mortality. Currently, 84% of cases diagnosed are localized at the primary site, while 8% are diagnosed after the cancer has spread to lymph nodes or beyond the primary site.[4] Despite significant advances in prevention, early detection, and

treatment, the worldwide death rate continues to increase steadily.[5,7]

The etiology of melanoma is very complex[8] and involves multiple risk factors. The strongest risk factors for melanoma are a family history of melanoma, having multiple benign or atypical nevi, and having had a previous melanoma. Immunosuppression, sun sensitivity, and exposure to ultraviolet radiation are additional risk factors.[8] Current thinking is that not only environmental factors but also their interactions define the gradient of risk observed within a given population. Recent studies by Riker et al[9] used gene-expression profiling to compare the profiles of primary, nonmelanoma skin cancer and metastatic melanoma. These studies resulted in the identification of several genes that may be involved in the progression and metastatic potential of melanoma. Some of the differentially expressed genes in melanoma metastatic tumors included DNA repair genes.[9]

Defects in DNA repair capacity (DRC) are an important risk factor in melanoma.[10,11] The discovery of xeroderma pigmentosum (XP)[12] has provided a human genetic disease model for the critical importance of DNA repair in skin carcinogenesis. Because of the DRC deficiency that occurs in individuals who suffer from XP, UV damage is amplified, specifically in those genes involved in the nucleotide excision repair (NER) pathway. At least 8 different genes are involved in the NER process, and genetic variants of these genes alter DNA repair and thus might serve as biomarkers of susceptibility to melanoma.[13] Moreover, direct molecular evidence of UV involvement in *PTEN*, a tumor suppressor gene, has been reported in xeroderma pigmentosa melanoma.[14] Two studies[15,16] have shown that deficiency in DNA repair mechanisms or higher mutagen sensitivity, as assessed by the induction of chromatid breaks, may have an important mechanistic function in the development of melanoma. Two previous studies[11,17] of the role of DRC on melanoma risk have provided seemingly conflicting conclusions (see discussion). These studies further solidify the role of UV damage and faulty DNA repair in the pathogenesis of melanoma.

The overall objective of the present case-control pilot study was to test the hypothesis that patients with melanoma skin cancer have a significantly lower DRC in relation to controls matched by age. We also hypothesized that DRC is associated with vertical depth (Breslow thickness) of melanoma invasion, deeper invasions tending to have lower DRCs. Finally, we examined whether DRC is significantly different in melanoma tumors that have been removed from sun-exposed areas versus those taken from sun-protected areas, as well as in 2 tumor types, in situ versus malignant melanoma.

MATERIALS AND METHODS

Study Subjects

The institutional review board at the 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 were at least 21 years of age. The participants had histopathologically confirmed primary cutaneous melanoma. All cases were diagnosed between September 2000 and May 2006. The participants recruited for this study were part of a large-scale population case-control skin cancer study sponsored by the Research Centers in Minority Institutions-National Institutes of Health (RCMI-NIH) Program at the Ponce School of Medicine (grant 2G12RR003050-20). The participants were generally consecutive case patients who had been referred by their dermatologists at the time of the surgical removal of their tumors. An 8-page, epidemiologic questionnaire soliciting risk factors was administered to each participant; individuals provided information regarding UV exposure associated with occupational and recreational outdoor activities.[1,18] Other information, such as smoking, medical history, cancer history, sunburns, use of sunblock, and tanning ability, was also gathered.

Study participants included whites and nonwhites of all skin types I–IV (Fitzpatrick skin typing classification). Participants included persons with the following skin types: type I, severe burning, no tanning; type II, moderate burning, mild tanning; type III, mild burning, moderate tanning; and type IV, no burning, intense tanning. Exclusion factors included persons with metastatic melanoma, any other type of cancer including nonmelanoma skin cancer, psoriasis, a prior cancer history, treatment with chemotherapy or radiotherapy, receipt of any blood transfusions within the last 5 years,[19–21] and the presence of a genetic or acquired immunodeficiency.

Tumor Characteristics

Clinical data as to the type of cancer and the location of the melanoma tumor were gathered from pathology reports and medical records after authorization from participants. Participants with melanoma were classified according to the tumors' pathologic characteristics: in situ (localized) or as malignant melanoma with corresponding skin tumor depth (mm).

Host-Cell Reactivation Assay for Measurements of DNA Repair Capacity

DRC was measured in lymphocytes isolated from participants by using the host-cell reactivation assay and a luciferase reporter gene, as previously described.[18] DRC was calculated on the basis of

luminescence units, as the percentage of residual luciferase gene expression (percentage luciferase activity) remaining after the repair of damaged plasmid DNA compared with undamaged plasmid DNA (100%).

Statistical Analysis

A χ^2 test was used to compare the differences between control and case participants in terms of risk factors. DRC was analyzed as a continuous variable without data transformation. Independent Student's *t* tests were used to evaluate the significance of the differences in DRC. Because DRC generally declines with increasing age (for both control and patient participants), all DRC data were adjusted for age.

The groups' mean DRC values (cases, controls) were compared by means of a 2-tailed Student's *t* test.[22] Adjustments, odds ratios (ORs), 95% confidence intervals, and tests for trend were computed by use of multiple logistic regression models, including matching variables (ie, age and sex) as independent variables.[22] Univariate analyses were used to compare the distribution of demographic characteristics, comorbid conditions, sunlight sensitivity, and others between the 2 groups of participants. All tabulations, age adjustments, and statistical analyses were performed with the SPSS Statistical Package, version 17, for Windows (SPSS, Chicago, IL) on a personal computer.

RESULTS

Characteristics of Study Population

The population studied included 186 participants either with or without melanoma (controls), ranging in age from 20 to 95 years (Table). Controls consisted of 124 individuals without skin cancer, all Hispanic (76 female and 48 male participants), with a mean age of 57.5 years. The melanoma patient group was composed of 62 participants, all Hispanic (Puerto Ricans), 34 females and 28 males, with a mean age of 57.8 years. The Table also presents a summary of key risk factors for melanoma in the population studied.

DNA Repair Capacity

The mean age-adjusted DRC for the control participants in the population studied was 6.46% $\pm$ 0.3 (n = 124) (Figure 1). Participants (n = 62) with melanoma had a mean age-adjusted decrease of 3% in their DRC (6.25% $\pm$ 0.5) in comparison with the controls. This difference was not statistically significant ($P = 0.697$) (Figure 1). When DRC was divided by sex, there were no differences between cases and controls in males ($P = 0.747$) or females ($P = 0.476$) (Table). Because DRC is influenced by age, controls and cases were separated by decade of age and compared. No statistical differences ($P > 0.05$) in terms of DRC were evident in the 6 age groups that were compared (data not shown).

The association between the DRC of the participants with in situ melanoma tumors and that of patients with malignant melanoma was analyzed (Figure 2). The DRC of the patients with malignant melanoma was 6.59%, which was 2% higher than controls but not statistically significantly different ($P = 0.855$). The DRC of the participants with in situ melanoma was 5.57%, which was 11% lower than that of the controls, but again, not statistically significant ($P = 0.855$). The slight decline in DRC of patients with melanoma was sometimes associated (Breslow index groups 4 and 6) with an increased depth of melanoma tumor penetration when compared with controls and with patients with localized (in situ) tumors (Figure 3). The DRC of the melanoma participants (n = 2) with tumors more than 4 mm in depth was 1.47%, which was 77% lower than that of controls and was statistically significant ($P = 0.046$), despite the small sample size.

The association between DRC and the anatomical location of the tumor in terms of sun exposure was examined. DRC was not significantly reduced in patients (n = 35) with tumors in sun-protected areas ($P = 0.789$) or in patients (n = 25) with tumors in sun-exposed areas of the body ($P = 0.475$) when compared with control participants. However, when in situ cases and malignant melanoma cases were subdivided into anatomical location, patients with malignant melanoma in sun-exposed areas had a 38% reduction in DRC when compared to the controls, which was borderline significant ($P = 0.055$) (Figure 4). Those patients with malignant melanoma in sun-protected areas had a 4% increase in DRC, which was not significant ($P = 0.931$). Patients with in situ melanoma in sun-protected areas (n = 18) did not experience a significant reduction in their DRC (Figure 4). Those with tumors in sun-exposed body parts (n = 17) had a 6% increase in DRC, which was not significant ($P = 0.681$).

DISCUSSION

With its moderate sample size (n = 186), data from this case-control pilot study suggest that a low DRC does not appear to be a significant risk factor for melanoma in general in the population studied. This contrasts to what we previously reported for nonmelanoma skin cancer (NMSC)[18] for this population, in which a decline in DRC was associated with a significant risk for NMSC. DRC generally declined for participants with an increased depth of melanoma tumor penetration when compared with controls and persons with localized (in situ) tumors. However, the

Table. Characteristics of Controls and Melanoma Patients (Cases) Studied in Puerto Rico in Terms of DNA Repair Capacity (DRC)

	DRC Control, %	Control, n	DRC Cases, %	Cases, n
Sex				
Male	5.99	48	6.26	28
Female	6.76	76	6.23	34
Total		124		62
Average age, y (±SD)	57.52 (±16)		57.8 (±15)	
Town				
Coast of Puerto Rico	6.40	114	6.40	52
Center of Puerto Rico	5.12	4	7.47	9
Skin color				
Light	6.45	59	6.47	49
Dark	6.41	61	5.42	13
Freckles				
Some, many	6.12	51	5.90	39
Few, none	6.59	71	6.83	23
Hair color				
Black, brown	6.48	109	6.50	51
Blonde, red	5.45	12	5.05	11
Eye color				
Black, brown, hazel	6.25	95	6.32	48
Green, blue	6.71	22	5.97	14
Burn				
Never	5.17	6	8.86	2
Rarely	5.49	11	5.53	6
Burn lightly	5.89	22	5.46	8
Burn moderately	6.98	30	7.38	11
Burn easily	6.63	51	6.04	35
Tan				
Dark brown	7.94	6	13.44	1
Easily	5.65	39	4.23	11
Moderately	6.37	37	6.55	11
Few times and easily	7.46	19	7.67	27
Never	6.74	17	4.01	12
Work involves sun exposure				
Yes	6.76	35	6.72	21
No	6.25	87	6.00	41
Sport leisure under sun				
Yes	6.43	68	6.29	49
No	6.35	54	6.08	13
Sunblock usage				
Yes	6.71	78	6.49	44
No	5.83	42	5.64	18
Smoking history				
Yes	6.40	37	6.37	37
No	6.34	82	6.16	25
Vitamins				
Yes	5.74	72	6.21	28
No	7.34	48	6.27	34
History of skin cancers in family				
Yes	6.46	12	4.76	11
No	6.39	109	6.57	51
Diagnosis of melanoma while pregnant				
Yes			4.19	17
No			6.93	17
Insolations (sun burns)				
Fewer than 6	6.45	112	6.21	52
6 or more	6.14	8	6.41	10

small sample size of some groups limits statistical interpretation. This is the first study to report that an increased depth of melanoma tumor penetration is associated with a lower DRC, a phenotypic marker of this disease. DRC was influenced by the anatomical location of tumors in terms of sun exposure (protected versus exposed), for which a DRC reduction of 38% was borderline significant in malignant melanoma localized in sun-exposed areas ($P = 0.055$).

It is possible that genetic or other as yet undetermined factors may have a larger influence in determining melanoma risk in the Puerto Rican population studied. Recent studies[23,24] involving haplogroups of 800 mitochondrial DNAs randomly and systematically selected suggest that the Puerto Rican population is genetically mixed, composed primarily of mixed African, European, and Amerindian ancestry. Through natural selection, there might be an abundance of specific genes that can provide protection against melanoma. Although this hypothesis has not been studied, it may provide a biologic explanation as to why this population, despite its chronic exposure throughout the year to high levels of UV, has a lower melanoma incidence than does the US mainland population. Another factor influencing melanoma risk in Puerto Rico could be the chronicity of sun exposure: melanoma has been associated with intermittent intense sun exposure rather than long-

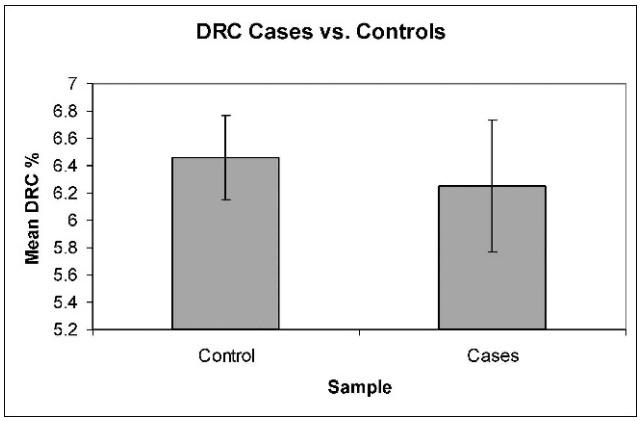


Figure 1. Age-adjusted percentage DNA repair capacity (DRC) of persons in Puerto Rico without skin cancer (n = 124) and with melanoma skin cancer (n = 62). DRC was measured in lymphocytes by using the host-cell reactivation assay with a luciferase reporter gene according to Matta et al.[18] Values are expressed as the mean ± standard error of the mean. Patients with melanoma had a 3% reduction in DRC, as compared to controls, that was not statistically significant ($P = .697$, Student's *t* test).

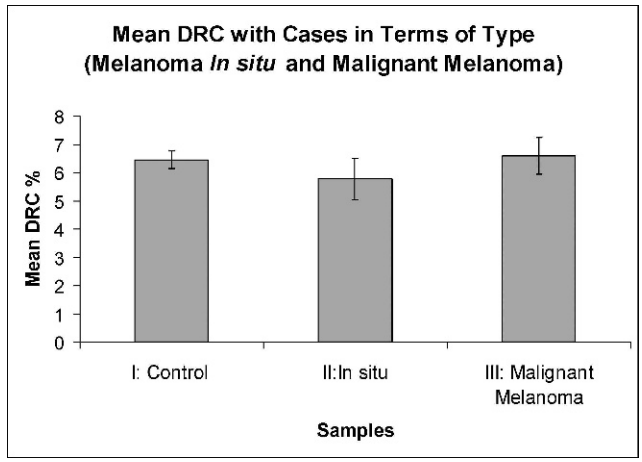


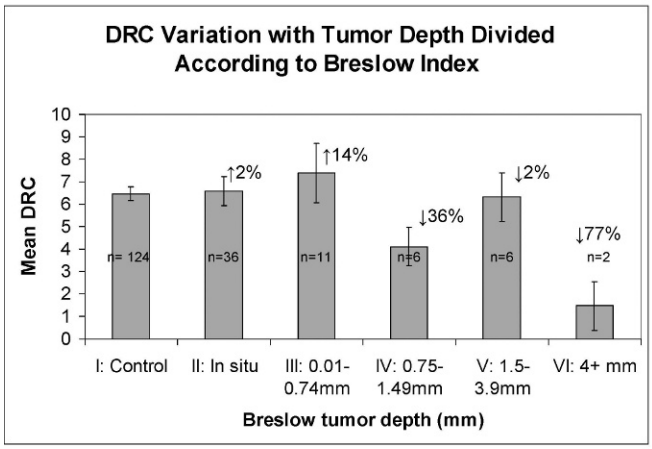
Figure 2. DNA repair capacity (DRC) of controls in terms of their type (in situ and malignant melanoma). Values are expressed as the mean ± standard error of the mean and adjusted by age.

term, constant exposure, such as that received throughout the year in Puerto Rico.[14]

The present study represents the third population study that has examined the influence of DRC in terms of melanoma skin cancer risk. Two previous studies have established different conclusions; this may be a reflection of how cases are selected and the varying ethnicities and genetics in the populations that have been studied. In the Italian study[17] (done with 132 cases and 1,454 age- and sex-matched control subjects), no statistically significant association between melanoma risk and DRC by itself was found (OR = 1.0). However, DRC strongly influenced melanoma risk in persons with a low tanning capacity (OR = 8.6) or dysplastic nevi (OR = 6.7). It is noteworthy that tending to have low DRC did not appear to be a risk factor in the absence of other strong risk factors such as low tanning ability and/or dysplastic nevi. The second study done was a hospital-based case-control study involving a large population of non-Hispanic whites (312 cases, 324 controls). Case patients had a 19% lower mean DRC than did control subjects, which was statistically significant ($P < 0.001$). Wei et al[11] also reported that a dose-response relationship existed between decreased DRC and an increased risk of melanoma. These researchers showed that a decreased DRC is an independent risk factor for melanoma.

Our findings (from an entirely Hispanic population that is routinely exposed to high environmental UV) do not support the hypothesis that persons with melanoma have a DRC that is reduced by any statistically significant degree. The results of our study were obtained primarily from individuals in the early stages of melanoma; on the other hand, Wei et al[11] studied the DRC of people at more advanced stages of the disease. This difference in test subjects may account, as well, for the differences in results. Moreover, the chronic sun exposure received by members of the Puerto Rican population could serve to constantly promote DNA repair in lymphocytes, and thus no statistically significant change can be perceived initially in the earlier stages of disease. In addition, it is important to underscore that both populations were of different ethnicities. One limitation of our study is that we were unable to obtain data on a number of dysplastic nevi. Having done so would have allowed us to compare our findings in light of what Landi et al[17] reported.

From a pathologic standpoint, melanoma tumor thickness and ulceration are the two most powerful independent predictors of survival.[25] This is based on the tumor, node, and metastasis staging system revised recently by the Melanoma Staging Committee of the American Joint Committee on Cancer (AJCC). The Committee used prospectively accumulated melanoma data obtained from 13 databases containing pathologic records of 13,581 patients. The AJCC classification of primary lesions is based primarily on microscopic assessment of Breslow tumor thickness.[7] The preliminary findings of this study suggest that the host-cell reactivation assay used to measure DRC can at least discriminate from a localized disease (in situ) to one in which tumor thickness is more pronounced. Our preliminary results showed an increased melanoma tumor penetration associated with a lower DRC, although conclusions are limited by the small sample size of some of the subgroups. It is

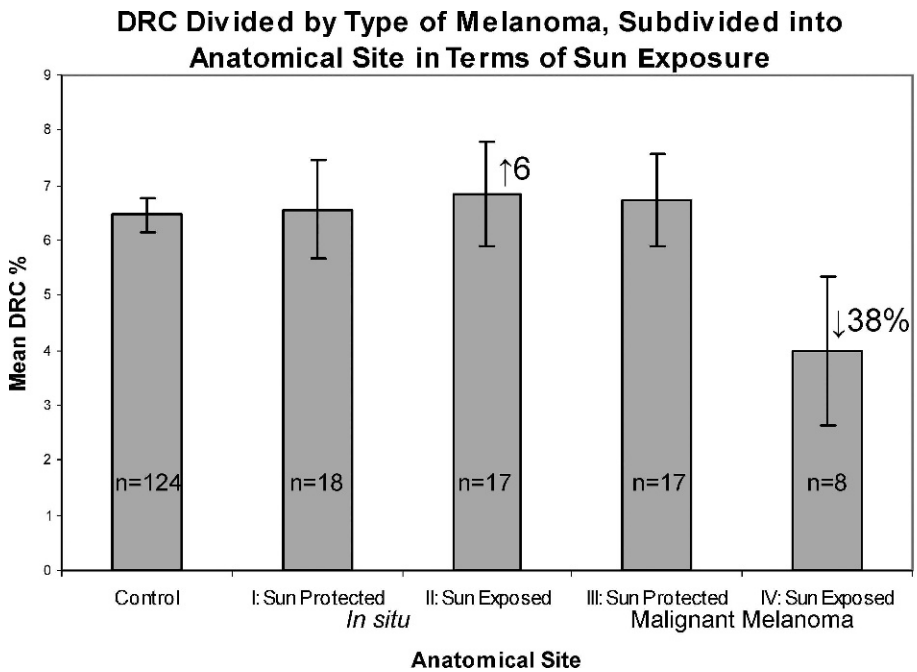


P values
I vs. II
I vs. III
I vs. IV
I vs. V
I vs. VI
II vs. III
II vs. IV
II vs. V p=.866
II vs. VI
III vs. IV
III vs. V
III vs. VI
IV vs. V
IV vs. VI
V vs. VI

Figure 3. DNA repair capacity (DRC) of controls versus cases as a function of tumor depth, based on the Breslow index, with corresponding *P* value obtained through a Student's *t* test.

important to note that most of the melanoma tumors examined in this study fall in the category of thin (0-1 mm) in terms of Breslow depth. In the tumors (n = 14) examined that were of intermediate thickness (>1.0-5.0 mm), DRC was reduced approximately 38% in relation to controls. This contrasts with an average increase of 8% in DRC, relative to controls, in the combined in situ and Breslow index 3 categories. One possible explanation for this seemingly paradoxical variability in DRC is that DNA repair is induced in lymphocytes in the early stages of melanoma, but as the disease progresses (ie, increased tumor penetration), this mechanism becomes progressively impaired or dysregulated.

A broader study with a larger sample size is needed to determine whether this association between melanoma tumor thickness and DRC is also evident in thick (>5.0 mm) and metastatic tumors. This is important because recent studies involving gene-expression profiling of melanoma have shown that the transition from nonmetastatic expression levels to metastatic expression levels occurs as melanoma tumors thicken.[9] This transition in gene expression occurs at different thicknesses for different genes,



P Value
Control vs. I p= .910
Control vs. II p= .681
Control vs. III p=.931
Control vs. IV p= .055
I vs. II p=.834
I vs. III p=.895
I vs. IV p=.122
II vs. III p=.895
II vs. IV p=.103
III vs. IV p=.090

Figure 4. The association between DNA repair capacity (DRC) and the anatomical location of both in situ and malignant melanoma tumors in terms of sun exposure was analyzed. Patients with melanoma skin cancer in sun-exposed areas had a 38% reduction in DRC when compared to controls with borderline significance, *P* = 0.055.

suggesting that the ''transition zone'' represents a critical time for the emergence of the metastatic phenotype.

This study also provides insights as to the potential association between DRC and anatomical location of melanoma tumors in terms of sun exposure. An association between sun exposure and melanoma development was postulated nearly 50 years ago.[26] Melanomas develop more commonly on the backs of white males and on the lower legs (from knees to ankles) and backs in females.[7] Although melanomas can occur almost anywhere on the body, they are less common in those body parts that are protected by clothing.[7] However, melanomas can also develop on the soles of the feet and in mucosal areas that are never exposed to sunlight.[10]

DRC was significantly ($P = 0.055$) reduced (mean, 3.99%) in persons ($n = 25$) with malignant melanoma tumors in sun-exposed areas of the body but not ($P = 0.08$) in those (mean, 6.73%; $n = 35$) with tumors in sun-protected body areas when compared with control participants (mean, 6.46%). Wei et al[11] similarly found that patients in Texas with melanoma tumors on sun-exposed skin had statistically significantly ($P = 0.04$) lower DRCs than patients with tumors on nonexposed areas. San Juan, Puerto Rico, has the second highest average UV index number (an indicator of sunlight exposure) when compared with 58 cities in the United States. In 2001, there were 210 days in which the San Juan UV index was at very high levels and 100 days in which it was at high levels.[1] A study by Ramos et al[1] has provided the first dose estimates of environmental UVA and UVB radiation in Puerto Rico, based on 6 years of data from a permanent UV-monitoring station that measures UVA and UVB at 4 wavelengths. The issue of UV dose in relation to melanoma risk gained national attention; the National Cancer Institute issued a press release on July 14, 2002, regarding the study by Fears et al[27] titled ''*Average Midrange Ultraviolet Radiation Flux and Time Outdoors Predict Melanoma Risk*.'' In this study, 718 patients with melanoma (non-Hispanic whites) were recruited from Philadelphia and San Francisco and compared with 945 nonmelanoma participants from the same areas. Fears et al[27] concluded that a 10% percent increase in the average annual intensity of UVB was associated with a 19% increase in the individual's risk for melanoma in men and a 16% percent increase in women, at any age. It is important to consider location; for example, New Orleans receives 20% more UVB each year than Atlanta. These researchers limited the analysis to non-Hispanic whites because the numbers of cases in other racial/ethnic groups were too few for analysis; our study is the first to be performed on an entirely Hispanic population.

Despite exposure to much higher UV fluxes than is seen in most of the US population, the Puerto Rican population has a significantly lower age-adjusted melanoma incidence and mortality than those of the United States.[7,28] In trying to resolve the questions of why and how factors affect geographic incidence rates of melanoma, it is necessary to examine whether environment (such as differing UV radiation levels between countries), genetic predisposition, or both underlie the variation seen in melanoma penetrance rates.[29] To answer these questions, future population studies with large sample sizes are needed to examine how genetic (eg, DRC) and environmental (eg, UV dose) factors interact to influence melanoma risk.

ACKNOWLEDGMENTS

This study was supported by a grant from the RCMI-NIH Program (grant G12RR003050-20) to the Ponce School of Medicine through Dr J. Matta. The following dermatologists referred participants to this study: Limary Aguila, MD, Norma Alonso, MD, Coty Benmaman, MD, Moises Benmaman, MD, Olivia Benmaman, MD, Alma Cruz, MD, Laureano Giraldez, MD (surgeon), José A. Hernández, MD, David Latoni, MD, Luis J. Ortiz, MD, Aida Quintero, MD, Edgardo Rodríguez, MD, Hiram Ruiz Santiago, MD, Rafael Vélez, MD. Dr Lawrence Grossman provided the plasmid for the HCR assay. Mrs Felicita Quintana and Mrs Ivette Lopez are acknowledged for their efforts in patient recruitment. Mrs Hannia Delgado provided crucial administrative support. Additional thanks go to Mr Bob Ritchie of the RCMI Publications Office (grant G12RR003050-25) for editing this manuscript.

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