# Association of Cumulative Ultraviolet Radiation Exposure with Prostate Cancer Risk in a Case-control Study of African-American Men

Yasmine M. Kanaan[1,*], Desta Beyene[2], Mohammad Daremipouran[2], Augustine Mireku-Boateng[3], Robert Williams[4], Aaron Jackson[4], George E. Bonney[5], Victor Apprey[5], Marlon G. Daniel[6], Anthony K. Wutoh[6], JoyAnn Phillips Rohan[7], Luisel Ricks-Santi[8] and Robert L. Copeland Jr[9]

[1]*Department of Microbiology, Cancer Center, Howard University College of Medicine, Washington D.C., 20059, USA*

[2]*Cancer Center, Howard University College of Medicine, Washington D.C., 20059, USA*

[3]*Urology Department, Emergency Medicine, Camden, SC 29020, USA*

[4]*Department of Urology, Howard University Hospital, Washington D.C., 20059, USA*

[5]*National Human Genome Center and Department of Community and Family Medicine, Howard University College of Medicine, Washington D.C., 20059, USA*

[6]*Center for Minority Health Services Research, College of Pharmacy, Howard University, Washington D.C., 20059, USA*

[7]*Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, D.C. 20057, USA*

[8]*Department of Pediatrics and Child Health, Howard University College of Medicine, Washington, DC 20059, USA*

[9]*Pharmacology Department, Howard University, Washington D.C., 20059, USA*

**Abstract:** It is well established that exposure to ultraviolet (UV) radiation has beneficial effects in reducing prostate cancer risk. To determine if there is a correlation between UV exposure and prostate cancer risk, we assessed sun exposure in a case-control study of 182 African-American men aged 40 years and older residing in the Metropolitan Washington, DC area. Using data on cumulative exposure per year and adult sunbathing scores derived from a validated questionnaire, analysis revealed significant difference in cumulative sun exposure between cases and controls (p=0.003). Additionally, the outdoor and recreation UV exposures were significantly higher in controls when compared to cases (p=0.003; p=0.03 in age-matched cases and controls). Although the results of conditional logistic regression analysis indicate that there was no association between total UV exposure and risk of prostate cancer after adjusting for age (OR=2.04, 95% CI 0.54-7.70, p=0.29), outdoor UV exposure was associated with decreased prostate cancer risk (OR= 0.31, 95% CI 0.14-0.65, p=0.002). Furthermore, a trend for reduced prostate cancer risk was found among men with early life high sun exposure during childhood ages 0-5 years (OR=0.17, 95% CI 0.03-0.74, p=0.02) and 6-11 years (OR= 0.28, 95% CI 0.07-1.05, p=0.06). Interestingly, this inverse association between prostate cancer risk and early life high sun exposure intensity was also observed among young men at ages 12-17 years although not statistically significant (OR=0.41, 95% CI 0.09-1.95, p=0.26). These findings indicate that UV exposure earlier in life may affect susceptibility to prostate cancer.

**Keywords:** Prostate cancer, Vitamin D, UV exposure, African American.

## INTRODUCTION

Ultraviolet (UV) radiation is a causative factor for the pathogenesis of skin cancer. On the other hand, there are data indicating that UV exposure has beneficial effects and may reduce the risk of various internal cancers, including prostate cancer [1-3]. Furthermore, decreased UV exposure has been found to be associated with increased prostate cancer risk. In particular, it has been shown that lower levels of exposure assessed by parameters including cumulative exposure per year and adult sunbathing were associated with increased prostate cancer risk [4-6]. Although the mechanism for the association of UV exposure and prostate cancer risk is unclear, the vitamin D metabolic pathway may be implicated [7, 8].

Vitamin D is synthesized through an ultraviolet B (UVB) light catalyzed reaction in the skin converting

*Address correspondence to this author at the Department of Microbiology, Cancer Center, Howard University College of Medicine, Washington D.C., 20059, USA; Tel: 202 806 9540; Fax: 202 667 1686;
E-mail: ymkanaan@howard.edu

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7-dehydrocholesterol (7-DHC) into vitamin D. The biologically active form of Vitamin D, Vitamin D3 or cholecalciferol, is formed after several enzymatic reactions. Then, Vitamin D3 binds the Vitamin D receptor (VDR) affecting proliferation and differentiation of many cell types including the prostate [8]. Epidemiological studies report endogenous vitamin D status as the sum of dietary intake and endogenous synthesis. Up to 95% of Vitamin D production is attributable to synthesis from 7-DHC in the skin with sunlight exposure [9].

The physiological and environmental factors that modify the supply of cutaneous vitamin D3 are levels of UV exposure, skin pigmentation, and genes involved in the synthesis and metabolism of vitamin D. Several studies have shown large geographic gradients for vitamin D status [10, 11] due to latitudinal differences in UV exposure. In general, latitude and seasons of the year affect the cutaneous photosynthetic process in a highly coordinated mutually dependent manner [12]. Since melanin also absorbs the UVB wavelength (~300nm), it has a significant effect on the synthesis of vitamin D3. Melanin acts as a natural sunscreen and limits vitamin D production; thus, vitamin D deficiency in people with darker skin is common. The highest vitamin D3 response to UVB light is seen in Whites followed by Asians and then African Americans [13, 14]. In 1990, Schwartz & Hulka proposed that vitamin D deficiency may underlie the major risk factors for prostate cancer; advanced age, black race, and northern latitudes are risk factors associated with decreased synthesis of vitamin D [15,16]. Notably, mortality rates due to prostate cancer in the U.S. are inversely correlated with UV radiation, and African-Americans have the highest prostate cancer incidence and mortality rate compared to other groups [15]. Lower mortality rates were associated with high residential solar radiation exposure in a case control study based on a death certificate [17].

In this context, skin type is putatively important as it describes the tanning and burning reaction of the skin to sunlight by considering past reaction to UVB reaction [3]. We therefore hypothesize that increased incidence of prostate cancer and mortality in African Americans involves a dynamic interplay of environmental factors such as diet and UV exposure in addition to genetic factors. We propose that individual risk of prostate cancer will increase with low cumulative UV exposure and dark skin while low risk will be associated with high cumulative exposure and light skin in African Americans. The relative effects of these parameters on individual risk will in turn be modulated by other environmental factors and genetic effects. Accordingly, we sought to determine if there is a correlation between UV exposure and prostate cancer risk in a case-control study of African-American men aged 40 years and older residing in the Metropolitan Washington, DC area. We assessed UV exposure, using data on cumulative exposure per year and adult sunbathing score derived from a validated questionnaire.

## MATERIALS AND METHODOLOGY

### Study Population

We recruited 91 African American men aged > 40 years from the Washington, DC area with histologically diagnosed adenocarcinoma of the prostate with a prostate specific antigen (PSA) of > 3.5 ng/ml and a positive digital rectal examination (DRE). We then identified and recruited ninety-one ethnicity matched (African American) controls who were healthy, unaffected regularly screened volunteers with normal DREs and with no history of prostate cancer among first-degree relatives. Detailed information about demographics and medical history was obtained from a structured in-person interview. The participants were consented by the recruiter, and each individual was assigned a unique study identification number. Participants were recruited from the Division of Urology at the Howard University Hospital (HUH) and/or from ongoing free prostate cancer screening programs at the Howard University Cancer Center (HUCC). The Howard University Institutional Review Board (IRB) and Army Surgeon General's Human Subjects Research Review Board (HSRRB) approved the study protocol, and written informed consent was obtained from all of the study subjects. There were no physical, psychological, social, or legal risks involved in the conduct of this study.

### Assessment of UV Exposure

Each participant answered questions from the validated UV exposure questionnaire (UVQ) [18, 19]; shown to be valid and reproducible in skin cancer [20] and renal transplant studies [21]. This questionnaire is designed to calculate the total amount of exposure to UV light from childhood until the current period. Subjects were asked to assess such exposure during the following age categories; 0-5 years, 6-11 years, 12-17 years, 18-29 years, 30-39 years and 40 years-to age at diagnosis of prostate cancer, or age of data collection for the controls. These data were combined to give a total UV exposure in hours per year (hr/year).

The cumulative sunlight exposure of each subject was assessed by a combination of his history of occupational and non-occupational sunlight exposure. In addition to these questions, the subjects were also asked to indicate their sunlight exposure during specified age periods as "low", "moderate", and "high". Age periods were chosen in such a way that they were easily recognizable, namely ranging from 0 - 5 years: baby time, toddler time and infant class, 6 - 11 years: "lower" school period, 12 - 17 years: "middle" school period, 18 - 29: University, first profession etc. The potential sunlight exposure by recreation, vacation and during residence in the tropics was calculated. Sun bathing scores of 0 for low exposure, 1 for moderate exposure, and 2 for high exposure were given to each category. The total cumulative sunlight exposure was calculated by adding the amounts for profession, outdoor recreation, vacation and residence in the tropics.

### Statistical Analyses

The SAS software (SAS Institute Inc., Cary, NC) was used for the analysis. Specifically, conditional logistic regression modeling was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) associated with sun exposures and prostate cancer, adjusting for age. UV numeric variables (e.g., weeks of sun exposure) were

analyzed as both continuous and categorical variables with study participants categorized by quartiles.

## RESULTS

### Description of the Human Participants

A case-control study of African-American men aged 40 years and older residing in the Metropolitan Washington, DC area was conducted to determine if there is a correlation between UV exposure and prostate cancer risk. Ninety-one affected African-American men with histologically diagnosed adenocarcinoma of the prostate and race matched controls were recruited into the study. The characteristics of the study population are listed in Table **1**. Specifically the mean age of the cases and controls was 65 (±9) and 59 (±10) ($p<0.0001$), respectively. Most of the cases were in age groups 60-69 years (46 %) whereas age group 50-59 years was the highest (42 %) among controls. In the cases the mean age at diagnosis was 65 years, (range=40-89) and the mean/median Gleason score was 6 (range=4-10). PSA level were obtained from the Urology Department at HUH and the Prostate Screening program at HUCC. The mean PSA levels were 1.2 ng/ml and 10.3 ng/ml for the controls and cases respectively. As expected, the number of patients with PSA level ≤ 4.0 ng/ml was higher in controls than cases (89 % and 49 % respectively). However, there were a few controls with PSAs higher than 4.0 ng/ml (n=7). Cases and controls did not significantly differ in terms of residence (data not shown).

**Table 1. Selected Characteristics of Prostate Cancer Patients and Control Subjects**

| Characteristics | Cases N=91 | Controls N=91 | *p-value* |
|---|---|---|---|
| Mean Age[a] | 65± 9 | 59± 10 | 0.26 |
| Age at Diagnosis | | | |
| ≤65 | 49 (54%) | | |
| >65 | 42 (47%) | | |
| Age Group (%) | | | |
| 40-49 | 4 (4%) | 15 (16%) | <0.01 |
| 50-59 | 20 (22%) | 39 (42%) | <0.01 |
| 60-69 | 42 (46%) | 24 (26%) | <0.01 |
| ≥70 | 25 (27%) | 14 (15%) | <0.01 |
| PSA level (%) [b] | | | |
| ≤ 4.0 ng/ml | 42 (49%) | 58 (89%) | <0.01 |
| 4.1-9.9 ng/ml | 24 (28%) | 6 (9%) | <0.01 |
| 10.0-19.9 ng/ml | 6 (7%) | 1 (2%) | <0.01 |
| 20.0 - ≥ 100 ng/ml | 14 (16%) | 0 | <0.01 |
| Gleason Score no. (%) | | | |
| ≤4 | 3 (5%) | | |
| 5 | 6 (10%) | | |
| 6 | 30 (49%) | | |
| 7 | 16 (26%) | | |
| 8 | 3 (5%) | | |
| 9 | 2 (3%) | | |
| 10 | 1 (2%) | | |

[a]Plus-minus values are means ±SD.
[b]Prostate specific antigen (PSA) levels were obtained at the time of diagnosis for case subjects and at the time of study enrollment for control subjects.

### Cumulative UV Exposure

Occupational and physical activities were used as surrogates for sunlight exposure as they quantified exposure in those who are engaged in work with walking, labor work, or hard work or those who did not engage in any outdoor physical activities. The mean UV exposure was calculated for environmental factors (professional, outdoor, recreation, and residence) in un-matched and age-matched cases and controls (Table **2**). The lifetime cumulative sun exposures were 25,380 hrs in cancer cases and 26,453 hrs in controls ($p=0.007$). Outdoor exposure was also significantly higher in age-matched controls when compared to the cases ($p=0.001$). Exposure related to profession, recreation, and residence did not demonstrate statistically significant differences between the groups ($p=0.54$, 0.79, and 0.61, respectively). However, the means of total UV exposure, serum vitamin D levels, supplemental vitamin D, diet vitamin D, and tanning potential were higher in controls than cases (data not shown).

To ensure the association between prostate cancer risk and UV exposure parameters were not influenced by imbalances in ages of controls and cases, we studied the effect of exposure in pairs of men matched for age (Table **2**). The mean total, outdoor, and recreation UV exposure was significantly higher in controls than cases ($p=0.003$, 0.003, and 0.03). Again, no significant differences UV exposure related to profession and residence were found in cases compared to controls ($p=0.12$ and 0.89, respectively).

**Table 2. Comparison of Mean for the Environmental Factors in Prostate Cancer Cases and Controls**

| Characteristics | Cases | Controls | *p-value* | *p-value*[a] |
|---|---|---|---|---|
| Age (year) | 65 | 59 | 0.001 | 1.00 |
| Total UV exposure--hr | 25,380 | 26,453 | 0.007 | 0.003 |
| Profession | 9,023 | 7,597 | 0.54 | 0.12 |
| Outdoor | 1,787 | 5,017 | 0.001 | 0.003 |
| Recreation | 12,960 | 12,639 | 0.79 | 0.03 |
| Residence | 1,609 | 1,201 | 0.61 | 0.89 |

[a]Age matched cases and controls.

However, conditional logistic regression modeling only revealed an association between Outdoor UV exposure and prostate cancer risk (OR=0.31, 95% CI 0.14-0.65, $p=0.002$) (Table **3**). No association with prostate cancer was found with total sun exposure (OR= 2.04, 95% CI 0.54-7.70, $p=0.29$), recreation UV exposure (OR= 0.77, 95% CI 0.39-

1.47, p=0.42), or professional UV exposure (OR= 0.59, 95% CI 0.18-1.89, p=0.37).

**Table 3. Association of Environmental Factors, Age Groups and Prostate Cancer Risk Using Conditional Logistic Regression (m/n)**

| Variable<br>Age -- yr | Odds Ratio | 95% CI | *p-value* |
|---|---|---|---|
| 40-49 | 1.00 | | Reference |
| 50-59 | 2.01 | (0.53-7.59) | 0.30 |
| 60-69 | 9.13 | (2.42-34.38) | 0.001 |
| ≥ 70 | 8.73 | (2.15-35.41) | 0.002 |
| Total sun exposure[a] | 2.04 | (0.54-7.70) | 0.29 |
| Outdoor[a] | 0.31 | (0.14-0.65) | 0.002 |
| Recreation[a] | 0.77 | (0.39-1.47) | 0.42 |
| Professional[a] | 0.59 | (0.18-1.89) | 0.37 |

[a]Variables are standardized factors.

### Protective effect of Early- Life Sun Exposure

Risk of prostate cancer in relation to stage of life from ≥5 years to ≤ 40 years was assessed by self-report. Each life stage was assigned a solar radiation level and classified as low, medium, or high. Prostate cancer risk was less evident among men with early life high sun exposure for childhood ages 0-5 years (OR=0.17, 95% CI 0.03-0.74, p=0.02) and 6-11 years (OR=0.28, 95% CI 0.08-1.06, p=0.06). The trend of this inverse association between prostate cancer risk and high sun exposure intensity was also observed in men with childhood ages 12-17 years (OR=0.41, 95% CI 0.09-1.95, p=0.26) of high sun exposure, although it was not statistically significant. Notably, non-significant inverse associations were found among men with moderate sun exposure in all childhood age groups. Interestingly, increased risk of prostate cancer was found to be associated with high sun exposure levels in men with childhood ages 18-29 years (OR=1.54; 95% CI 0.39-6.03, p=0.53), 30-39 years (OR=1.05, 95% CI 0.29-3.85, p=0.95), and ≥40 years (OR=1.33, 95% CI 0.32-5.48, p=0.70), although, these differences were not statistically significant (Table **4**).

**Table 4. Age Groups Stratified by Sunbathing Score and Risk of Prostate Cancer**

| Age Period (Years) | Cases No. (%) | Controls No. (%) | Odds Ratio | 95% CI | *p* Value |
|---|---|---|---|---|---|
| 0-5 (years) | | | | | |
| Low exposure[a] | 22 (26) | 24 (30) | 1.00 | | Reference |
| Moderate exposure[b] | 36 (42) | 30 (38) | 0.44 | (0.11 - 1.71) | 0.24 |
| High exposure[c] | 27 (32) | 26 (33) | 0.17 | (0.03 - 0.74) | 0.02 |
| 6-11 (years) | | | | | |
| Low exposure | 11 (13) | 9 (11) | 1.00 | | Reference |
| Moderate exposure | 35 (41) | 32 (40) | 0.76 | (0.24 - 2.41) | 0.64 |
| High exposure | 39 (46) | 40 (49) | 0.28 | (0.08 - 1.06) | 0.06 |
| 12-17 (years) | | | | | |
| Low exposure | 6 (7) | 4 (5) | 1.00 | | Reference |
| Moderate exposure | 33 (38) | 30 (37) | 0.74 | (0.16 - 3.24) | 0.69 |
| High exposure | 47 (55) | 47 (58) | 0.41 | (0.09 - 1.95) | 0.26 |
| 18-29 (years) | | | | | |
| Low exposure | 7 (8) | 7(9) | 1.00 | | Reference |
| Moderate exposure | 33 (38) | 40 (49) | 0.83 | (0.19 - 3.55) | 0.80 |
| High exposure | 46 (54) | 34 (42) | 1.54 | (0.39 - 6.03) | 0.53 |
| 30-39 (years) | | | | | |
| Low exposure | 14 (16) | 10 (12) | 1.00 | | Reference |
| Moderate exposure | 38 (44) | 46 (57) | 0.44 | (0.13 - 1.51) | 0.19 |
| High exposure | 34 (40) | 25 (31) | 1.05 | (0.29 - 3.85) | 0.95 |
| ≥ 40 (years) | | | | | |
| Low exposure | 21 (25) | 19 (24) | 1.00 | | Reference |
| Moderate exposure | 38 (44) | 44 (54) | 0.49 | (0.17 - 1.43) | 0.19 |
| High exposure | 27 (31) | 18 (22) | 1.33 | (0.32 - 5.48) | 0.70 |

[a]sunbathing score=0, [b] sunbathing score=1, [c] sunbathing score=2.

## DISCUSSION

This study revealed significant differences in cumulative sun exposure between cases and controls. Additionally, this study demonstrated that outdoor and recreation UV exposures were significantly higher in controls when compared to cases. Furthermore, a trend for reduced prostate cancer risk was found among men with early life high sun exposure during childhood ages 0-5 years and 6-11 years. Our hypothesis that the risk of prostate cancer is inversely correlated with the availability of UV radiation in African American men is supported by the findings from this study and concurs with results in other populations [5, 15, 22, 23].

It is well established that there is an association between UV exposure, vitamin D, and the risk of prostate cancer [3, 9, 17]. Similarly, we showed that total UV exposure was associated with case status. Early on, Schwartz and Hanchette [21] presented ecologic data from 3073 United States counties showing an inverse association between prostate cancer mortality and UV, where the mortality was significantly lower in the South [5]. Others have also found that cumulative, outdoor occupations and skin type reduce the risk of advanced stage tumors [1, 24-26]. However, in our study, only outdoor exposure had significant association with reducing risk of prostate cancer while occupational (professional), recreational, and total sun exposure was not associated with prostate cancer risk. It is possible that the assessment of occupational exposure used as a surrogate measure of sun exposure in our study was not as sensitive as the measure used by Luscombe *et al.,* [25]. It should be noted that they did the study on individuals with less pigmentation and more UVB exposure resulting in a higher level of vitamin D synthesis.

In a separate study, Bodiwala *et al.,* found that living abroad in a hot climate for 6 months or more was not linked with risk of prostate cancer [3]. The reason why this parameter was not associated with prostate cancer risk is not clear though it may be related to the relationship between the extent of exposure to UVB and cutaneous synthesis of vitamin D. Vitamin D synthesis is influenced by the length of UVB exposure, latitude, outdoor or recreational exposure, age, and skin type. Other factors that may influence cutaneous vitamin D synthesis include the ability to mount a pigmentation response to UVB since increased melanin production may reduce UV-mediated synthesis of previtamin D3 [12, 27]. Adult sunbathing is also an important factor in determining prostate cancer risk because it involves exposure of larger areas of the body. Exposure of the torso and legs to sub-erythemic doses of UVB results in greater increases in serum vitamin D levels than exposure of the head, neck or arms [28]. Usual residence in a high solar radiation region or being born in the South was associated with reduced risk in the National Health and Nutrition Examination Survey I follow-up study [29].

Another interesting aspect of UV in association to risk of prostate cancer is seasonal UV index alteration. Ginde *et al.,* and other researchers [14, 30-32] showed that the correlation between prostate cancer rates and UV indexes for white men was strongest in the fall and winter, moderate in the spring, while weak or nonexistent in the summer. Studies in Edmonton, Canada, demonstrated that photosynthesis of vitamin D ceases by mid-October and does not resume until mid-April. While, in Los Angeles (34°N) and Puerto Rico (18°N), vitamin D synthesis continues all year [12]. Gordon *et al.,* [33] also showed that the prevalence of vitamin deficiency was highest in African American teenagers during winter.

In our study the recruitment was based on the availability of participants in a non-seasonal basis manner. Washington DC has low latitude (38.9 ° N) which confers low UV index and exposure which may partly explain the high prostate cancer rates. Still, our study did not include men with lifelong residence in a high or low solar radiation region. This may partly explain the reason why our study did not show significant association of prostate cancer risk with residential sun exposure. Also, we found other parameters of exposure, such as sun exposure score (never, moderate, high; scored 0, 1, and 2), were linked with reduced risk. These results indicate that when subjects aged 0-5 and 6-11 years old were highly exposed to UV, they were at lower risk of prostate cancer. Moderate UV exposure in all age groups had inverse association with the prostate cancer risk. Remarkably, it seems that higher exposure to UV in advanced age did not protect against prostate cancer.

Our finding of reduced prostate cancer risk associated with early-life sun exposure was consistent with results from a case-control study conducted in England where several indicators of childhood sun exposure, including sun burns and sunbathing were inversely associated with prostate cancer risk [1]. It had been widely believed that susceptibility to melanoma was restricted to a ''critical period'' in early life because many case-control studies found a damaging effect of sunburns early in life on the risk of melanoma. However, subsequent studies have shown that after controlling for sunburns early in life, sunburns during adulthood also confer increased risk [31, 33]. Although most epidemiologic studies have focused on the role of sunlight/vitamin D exposure in adulthood, it is biologically plausible that exposure to vitamin D in early life also may contribute to reduced prostate cancer risk. The reduction in epithelial cell population, where prostate cancer is typically formed, potentially is one mechanism whereby exposure to vitamin D early in life could reduce the risk. Our results in agree with other findings that high residential solar radiation in the state of birth, a proxy measure for early-life sun exposure, was associated with reduced prostate cancer risk [34-36]. Among men born in a region of high solar radiation the risk was reduced by 51% with a slightly greater risk reduction noted for fatal than for nonfatal prostate cancer, while among men with frequent recreational sun exposure the risk of fatal prostate cancer was reduced by 53%.

In conclusion, we found an association between cumulative measures of UV exposure at ages 0 to 17 years and prostate cancer risk. UV exposure earlier in life was related to reduce prostate cancer risk possibly through the formation of vitamin D3, although there was no association between total UV exposure and low vitamin D status on prostate cancer development. These findings provide evidence that early-life exposure to sunlight is beneficial. Similarly, findings in our study suggest that the window of opportunity for sunlight to alter prostate cancer risk is not

restricted to adulthood. In assessing these study results, it is important to consider the limitations and strengths of the study. The population-based study design, detailed questionnaire data, and disease characteristics are strengths in this study. However, several limitations should be considered when evaluating our results. The reduced the sample size was a limit although the study had enough power to detect differences. However, the small sample size might have affected the ability to detect differences where null results were demonstrated. As in all epidemiologic studies, additional studies are needed to elucidate the underlying biological mechanisms.

## ABBREVIATIONS

| | | |
|---|---|---|
| UV | = | Ultraviolet |
| UVB | = | Ultraviolet B |
| DRE | = | positive digital rectal examination |
| HUH | = | Howard University Hospital |
| HUCC | = | Howard University Cancer Center |
| IRB | = | Institutional Review Board |
| HSRRB | = | Human Subjects Research Review Board |
| UVQ | = | UV exposure questionnaire |
| PSA | = | Prostate specific antigen |

## CONFLICT OF INTEREST

We have no personal or financial conflict of interest and have not entered into any agreement that could interfere with our access to the data on the research, or upon our ability to analyze the data independently, to prepare manuscripts, and to publish them.

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