Sun Exposure Is Associated with Reduced Breast Cancer Risk among Women Living in the Caribbean: The Atabey Study in Puerto Rico

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ABSTRACT

Background: Though inconsistent, there is evidence that sun exposure is associated with reduced breast cancer risk. Previous studies have been conducted in geographical regions with seasonal variation in UV radiation, including periods of low to no exposure, and among participants mostly of European descent. Puerto Rico has no significant seasonal fluctuation, with continuous exposure to very high UV radiation.

Methods: We conducted a population-based case–control study of breast cancer among women in metropolitan San Juan, Puerto Rico, examining a cumulative sun exposure index (SEI) based on a comparison of reflectance of sun-exposed and non-exposed skin. A chromameter was used to measure skin reflectance and estimate the difference between constitutive (unexposed) and facultative (exposed) skin pigmentation in 307 cases and 328 controls. Breast cancer risk factors were ascertained with interviewer-administered questionnaires. OR and 95% confidence intervals (CI) were estimated with unconditional logistic regression.

Results: Adjusted breast cancer odds were lower for the highest tertile of the SEI ($OR_{adj} = 0.47$; 95% CI, 0.29–0.74). Results were similar within strata of estrogen receptor status. In analyses stratified by constitutive skin pigmentation, among participants with darker skin color, breast cancer risk was lower with more sun exposure ($OR_{adj} = 0.33$; 95% CI, 0.16–0.70).

Conclusions: We found lower risk of breast cancer associated with greater sun exposure in a population living with high, continuous sun exposure. This beneficial finding should be placed in the context of other effects of sun exposure.

Impact: Sun exposure is a modifiable factor that may contribute, directly or indirectly, to lower breast cancer risk.

Introduction

There is growing, although somewhat inconsistent, evidence that chronic sun exposure is associated with breast cancer risk (1–16). In a systematic review and meta-analysis, lifetime sun exposure during the summer of at least 1 hour per day was associated with a reduced risk of breast cancer (pooled RR = 0.84; 95% CI, 0.77–0.91; ref. 9); and in another meta-analysis, sun exposure was associated with risk in a dose-dependent fashion (14). Most studies of this potentially important and modifiable factor have been conducted in North America or Europe, regions with large seasonal variation in sun exposure, and considerable time periods when sun exposure is low (1, 3, 5–7, 11–20). There are few studies conducted in regions closer to the equator (4, 10); additional studies examining breast cancer and sun exposure in regions with higher exposures and less seasonal variation are needed.

Puerto Rico is an archipelago located in the Caribbean Sea, positioned at 18° 15′ N latitude (21). It has no significant seasonal fluctuations, and the climate is characterized by varying but continuous sun exposure year-round (22). San Juan, Puerto Rico, is among the cities with the highest UV index in the United States. The UV Index in Puerto Rico was extreme or very high in 87% of days during 2017 (23). In Puerto Rico, although incidence rates are lower than in the United States, breast cancer is, nonetheless, the leading cause of cancer incidence among women, accounting for 28.6% of the more than 38,000 cancer cases among female residents of Puerto Rico during 2012 to 2016 (24). Further, breast cancer risk is increasing in Puerto Rico, on average 1.5% per year ($P < 0.05$) during 2000 to 2016 (24).

One proposed mechanism explaining, at least part, of the variation in risk with sun exposure is endogenous synthesis of vitamin D with sun exposure. There is evidence, though not consistent, of an association of serum vitamin D status with risk of incident breast cancer; findings of reduced mortality following breast cancer diagnosis associated with vitamin D status are more consistent (25). Most studies of sun exposure and vitamin D in association with breast cancer risk have been limited to women of European ancestry.

There are genetic differences in the vitamin D receptor (26–27) as well as differences in mean serum concentrations of vitamin D by race/ethnicity (28–33). In an analysis in the Multi-Ethnic Cohort Study conducted in Hawaii and Los Angeles, serum 25(OH)vitamin D and 25(OH)vitamin D3 was associated with postmenopausal breast cancer risk among those with European ancestry but not for women from other races or ethnic groups (34). In that cohort, it appeared that there was a threshold effect of serum vitamin D, and that 25(OH) vitamin D was highest in the group with European ancestry (34). There is little

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information regarding Hispanic women and breast cancer risk associated with vitamin D or sun exposure.

Measurement of long-term sun exposure poses some difficulties, particularly in regions with large seasonal variation. Proxy measures of sun exposure in the existing epidemiologic literature have included residence location (5, 7, 11, 17–18, 35), occupational time outdoors (6–7, 11), and/or self-report of time spent outdoors (1–2, 4, 6, 10, 12–13, 15–16, 19, 36). Also included in the assessment of sun exposure and breast cancer risk have been self-report of other behaviors such as time sunbathing, use of tanning salons, usual clothing coverage while outdoors, and sunscreen use (2, 10, 15–16). John and colleagues (12) measured a sun exposure index (SEI; ref. 37), directly measuring skin color difference for skin exposed and unexposed to sunlight in a multi-ethnic population in San Francisco. Among women with lighter skin color, they found decreased risk of advanced breast cancer, but not localized disease, associated with greater sun exposure (12). Although there are important advantages to the use of the SEI as a more objective measure, concerns remain because of intra-individual variation in measures over time depending on seasonal variation.

We are reporting the results of a population-based case–control study in Puerto Rico. This study, conducted in a region with little seasonal variation, and high and consistent sun exposure year-round, provides insight regarding the effects of high sun exposure. Further, this study of a Hispanic population provides information on a population with considerable variability in skin color. Using the SEI, an objective measure of sun exposure, we examined the association of sun exposure with breast cancer risk.

Materials and Methods

Study design

The Atabey Study is a population-based case–control study of breast cancer in the metropolitan area of San Juan in Puerto Rico, described in detail previously (38). Briefly, cases were 315 women with incident, primary, pathologically confirmed breast cancer, ages 30 to 79 years, diagnosed between 2009 and 2014, all residents of the San Juan Metropolitan Area. Controls were 348 women, ages 30 to 79 years, frequency matched to cases by age and municipality. The current analyses included 307 cases and 328 controls with data for the exposure of interest. This study was approved by the Institutional Review Board of the University of Puerto Rico Medical Sciences Campus and of the University at Buffalo. All study participants provided written informed consent.

Exposure of interest

Measurements were made of constitutive pigmentation of skin not directly exposed to the sun on the interior area of the upper inner arm, near but sufficiently removed from the axilla. Facultative pigmentation of skin directly exposed to the sun was measured on the dorsal area of the left hand at the corner of the 90-degree angle formed between the extended thumb and index finger. Care was taken to avoid superficial markings (moles, hairs, uneven freckling) on the skin. A calibrated colorimeter, the chroma meter Konica Minolta CR-400 (39), was utilized to take objective measures of skin color in triplicate at each site for each participant. Trained research nurses at the Puerto Rico Clinical and Translational Research Consortium (currently known as Hispanic Alliance for Clinical & Translational Research in Puerto Rico) measured skin pigmentation using a standardized protocol. A SEI was calculated as described by Lock-Andersen and colleagues (37), using the chroma meter L^* value (0 = perfect black; 100 = perfect white) as a percentage derived from the difference between the facultative and the constitutive measures divided by the constitutive measure multiplied by 100. A small number of negative values were set to zero. The average of two measures was used to estimate skin pigmentation in both exposed and nonexposed skin areas.

Other study variables

Data on breast cancer risk factors, including age at interview, education, body mass index (BMI), history of benign breast disease, family history of breast cancer, parity, age at menarche, menopausal status, age at menopause, and estrogen receptor (ER) status, was collected through a structured, interviewer-administered questionnaire (38).

Statistical analyses

Participants were assigned to categories of sun exposure based on the distribution of the controls to tertiles or to two groups defined by the median value of the controls. Categorical variables were compared using chi-square tests and continuous variables by *t* tests. OR and 95% confidence intervals (95% CI) for associations of sun exposure with risk of breast cancer were estimated using unconditional logistic regression. All analyses were adjusted for other known breast cancer risk factors [age, education, BMI, age at menarche, parity, season (summer: May–October and Winter: November–April), history of benign breast disease, and family history of breast cancer, and age at menopause (postmenopausal only)]. Statistical analyses were conducted using the IBM SPSS Statistics for Windows, Version 27.0 (40).

Results

Characteristics of cases and controls by the SEI are shown in **Table 1**. Those with higher cumulative sun exposure were older among both cases and controls. SEI categories for cases did not differ by education but among controls, those with lower SEI had more years of education. Cases with higher SEI were more likely to have a family history of breast cancer; there was no difference among controls. Premenopausal cases and controls were more likely to have a lower SEI, but no difference was observed among postmenopausal participants.

Odds of breast cancer associated with the SEI are shown in **Table 2**. Compared with the lowest SEI, odds of breast cancer for participants with higher sun exposure were significantly lower (OR_{adj} = 0.47; 95% CI, 0.29–0.74) for those with higher SEI. This inverse association with SEI was also observed by constitutive skin pigmentation categories. Stratifying participants by constitutive skin color at the median level among the population controls, allowed us to reduce the effect of the potential behavior confounder of sun exposure avoidance by women with lighter skin color. Among those with darker skin pigmentation, the odds of breast cancer for those with the darkest skin compared with lighter skin pigmentation was 0.33 (95% CI, 0.16–0.70). Although not statistically significant, there was also a protective effect associated with increased sun exposure for those with lighter skin pigmentation.

Of 307 breast cancer cases, 232 (75.6%) had data on ER status. The risk of breast cancer associated with SEI, stratified by ER status, is shown in **Table 3**. A reduced risk was observed for higher SEI and CIs, regardless of ER status (ER+: OR = 0.56; 95% CI, 0.37–0.86; ER−: OR = 0.39; 95% CI, 0.20–0.78). The sample size was small for the stratified analyses and the CIs were wide.

Table 1. Descriptive characteristics of study participants by case-control status and SEI, Atabey Breast Cancer Study in Puerto Rico, 2009–2014.

Characteristics	Cases		Controls	
	Low SEI* (*n* = 170)	High SEI* (*n* = 135)	Low SEI* (*n* = 164)	High SEI* (*n* = 164)
Age (years)	55.8 (10.5)a	61.9 (10.7)a	49.1 (12.6)d	58.9 (12.5)d
Education (*n*, %)	13.8	13.3	13.5e	11.6e
BMI	30.2 (5.8)	29.5 (6.1)	31.5 (8.6)	31.0 (5.9)
Previous benign breast disease (*n*, % of yes)	78 (46%)	67 (50%)	41 (25%)	44 (27%)
Family history of breast cancer (*n*, % of yes)	29 (17%)b	36 (27%)b	13 (8%)	15 (9%)
Age at menarche (years)	12.2 (1.7)	12.2 (1.6)	12.4 (1.7)	12.6 (1.9)
Number of births	1.9 (1.5)	2.2 (1.4)	2.3 (1.5)	2.7 (1.7)
Menopausal status (*n*, %)				
Pre-	60 (35%)c	24 (18%)c	86 (52%)f	42 (26%)f
Post-	110 (65%)	111 (82%)	78 (48%)	122 (74%)
Age at menopause (years) among postmenopausal women	47.1 (7.2)	47.8 (6.6)	46.3 (6.9)	47.2 (5.8)

Note: Values for continuous variables are mean (SD); for categorical variables, values are numbers (percentages). Two-sided comparisons of means between the low SEI and high SEI were computed by *T* test for continuous and by χ^2 test for categorical variables. Results with the same letter (inline) were significantly different ($P < 0.05$).

*SEI = [(facultative − constitutive) / constitutive] 100. Median SEI (i.e., 11.61) among all controls was used to define the high/low groups.

Discussion

In this population-based case–control study in Puerto Rico, we found lower risk of incident breast cancer associated with greater chronic sun exposure, as objectively measured by the difference between participants' sun exposed and non-sun exposed skin pigmentation (OR = 0.47; 95% CI, 0.29–0.74). These results, in a Hispanic population with varied skin color and relatively consistent sun exposure throughout the year, are consistent with increasing evidence that breast cancer risk is inversely associated with sun exposure (9).

In some studies with self-reported sun exposure associated with decreased risk by age (9, 13) or by geographical region (11). In ecologic studies of breast cancer by region, there is some evidence of a gradient in breast cancer risk by proximity to the equator (10). However, in studies of average UV radiation exposure based on individual participants' residences, most studies have found no evidence of an association with risk (19, 35, 41).

We observed lower risk of breast cancer associated with high sun exposure accumulation among women with darker skin pigmentation, adding to the vitamin D paradox for people with dark skin pigmentation related to bone health: although the darker skinned have lower 25(OH)D levels, they have greater bone density and reduced falls and fractures when compared with the lighter skinned (42–43). Among older Puerto Rican adults living in the Boston area at a significantly higher latitude with marked seasons, 42% of women were classified with vitamin D insufficiency and 11% were classified as vitamin D deficient (44).

We observed lower risk of breast cancer with higher sun exposure independent of ER status (ER+: OR = 0.56; 95% CI, 0.37–0.86; ER−: OR = 0.39; 95% CI, 0.20–0.78). These findings are consistent with other studies, finding no difference in risk associated with sun exposure and/or vitamin D intake with breast cancer by ER status (3, 19, 35). We did not see a difference in breast cancer risk associated with constitutive skin pigmentation when stratified by ER status. However,

Table 2. Risk of breast cancer by SEI, and stratified by constitutive skin pigmentation in the Atabey Breast Cancer Study in Puerto Rico, 2009–2014.

	Cases *n*	Controls *n*	Crude OR (95% CI)	Adj OR[a] (95% CI)
SEI[b]				
Low	121	109	1.00	1.00
Medium	99	110	0.81 (0.56–1.18)	0.64 (0.42–0.98)
High	85	109	0.70 (0.48–1.03)	0.47 (0.29–0.74)
Constitutive skin pigmentation = <63.57; participants with darker skin color				
SEI[b]				
Low	53	54	1.00	1.00
Medium	26	56	0.47 (0.26–0.86)	0.42 (0.21–0.84)
High	24	54	0.45 (0.25–0.84)	0.33 (0.16–0.70)
Constitutive skin pigmentation = ≥63.57; participants with lighter skin color				
SEI[b]				
Low	68	55	1.00	1.00
Medium	73	54	1.09 (0.66–1.80)	0.87 (0.49–1.53)
High	61	55	0.90 (0.54–1.49)	0.64 (0.34–1.21)

[a]ORs and 95% CIs adjusted for age, education, BMI, age at menarche, parity, age at menopause (for postmenopausal women), history of benign breast disease, family history of breast cancer, and season [summer (May–October) and winter (November–April)].

[b]SEI = [(facultative − constitutive) / constitutive] 100.

Table 3. Risk of breast cancer by SEI, constitutive and facultative skin pigmentation for 232 breast cancer cases by ER status and 328 controls. Atabey Breast Cancer Study in Puerto Rico, 2009–2014.

	Cases			Adjusted OR[a] (95% CI)	
	ER+	ER−	Controls	ER+ vs. Controls	ER− vs. Controls
SEI					
Low	102	34	164	1.00	1.00
High	78	18	164	0.56 (0.37, 0.86)	0.39 (0.20, 0.78)

[a]ORs and 95% CIs adjusted for age, education, BMI, age at menarche, parity, age at menopause (for postmenopausal women), previous benign breast disease, family history of breast cancer, and season [summer (May–October) and winter (November–April)].

in the United States, black women are more likely than women of other ethnic groups to have hormone receptor negative and triple-negative breast tumors (45). These differences are likely related to other factors.

In a previous study using the same measure of sun exposure as we did, there was some evidence that increasing SEI was associated with decreased risk of breast cancer. That study was conducted in the San Francisco Bay area, where results could have been affected by seasonal variation in sun exposure (12). In the Atabey study in Puerto Rico, there is less variation in sun exposure related to season. Although there is some evidence of UV exposure differences for winter and summer even in this tropical location, in a study in a Puerto Rican research center, UV radiation was high even in the winter (22). Although all our analyses were adjusted for season, findings were similar without that adjustment.

There are plausible mechanisms linking sun exposure with breast carcinogenesis. The sun provides natural ultraviolet radiation which is defined by the wavelength ranges in nanometers as ultraviolet A (UVA, 315–399 nm), ultraviolet B (UVB, 280–314 nm), and ultraviolet C (UVC, 100–279 nm; ref. 46). One proposed mechanism explaining at least part of the variation in breast cancer risk with sun exposure is endogenous synthesis of vitamin D requiring UVB radiation to begin the process from 7-dehydrocholesterol in the skin (34). Endogenous vitamin D synthesis is, however, downregulated with aging (47) and increasing adiposity (48). OR calculations were adjusted by age and BMI.

Sun exposure may also have other biological effects not related to vitamin D. These include effects on blood nitric oxide levels, insulin resistance, circadian rhythms, inflammation, and obesity (49–52), which may also factor into breast cancer risk. There is also evidence that sun exposure is associated with lower breast density, particularly when significant sun exposure occurs earlier in life (53).

In evaluation of the findings from this study, their strengths and limitations need to be considered. Among the strengths, sun exposure for this study was assessed using an objective measure of skin reflectance with calibrated specialized equipment, using a standardized protocol implemented by trained research nurses. The SEI has a lower likelihood of both differential and nondifferential misclassification and recall bias, particularly in a tropical environment with less seasonal variation. A potential source of nondifferential misclassification includes biological differences among the women in their response to the same amount of sun exposure. Although the SEI is an integration of sun exposure over time, it is nonetheless a snapshot of cumulative sun exposure at the time of the interview and could differ over an individual's lifetime, another source of potential nondifferential misclassification. There is the possibility that there were chances in behavior among the breast cancer cases that included changes in sun exposure; likely such changes though would bias the findings toward the null. As in any case–control study, although selection bias remains a concern, the response rate for this study was relatively high for both cases (71.3%) and population-controls (64.7%; ref. 38). Sample size was an important limitation. Nonetheless, we had sufficient power to detect significant associations. Residual confounding is always a concern in any epidemiologic study. Although we adjusted all the analyses for known breast cancer risk factors, other unmeasured confounders could potentially impact the findings.

This study complements the existing evidence regarding sun and breast cancer risk by providing data on Hispanic women living in a tropical climate. To our knowledge, Atabey is the first population-based study of breast cancer epidemiology in Puerto Rico (38) that provides insights regarding cancer risk among Hispanic women living in a climate with considerable and relatively consistent year-round sun exposure. Our findings of reduced risk of breast cancer associated with greater cumulative sun exposure is consistent with findings in other populations. Replication in a larger sample is desirable. These beneficial findings should be placed in the context of other effects of sun exposure.

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Authors' Contributions

C.M. Nazario: Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, investigation, methodology, writing–original draft, project administration. **R.V. Rosario-Rosado:** Conceptualization, data curation, formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **M. Schelske-Santos:** Conceptualization, investigation, methodology, writing–review and editing. **I. Mansilla-Rivera:** Conceptualization, data curation, formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **F.A. Ramírez-Marrero:** Conceptualization, formal analysis, funding acquisition, investigation, methodology, writing–review and editing. **J. Nie:** Data curation, formal analysis, methodology. **P. Piovanetti-Fiol:** Conceptualization, investigation, methodology, writing–original draft. **J. Hernández-Santiago:** Data curation, supervision, validation, writing–review and editing. **J.L. Freudenheim:** Conceptualization, formal analysis, funding acquisition, investigation, methodology, writing–review and editing.

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