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Original Contribution

Ultraviolet Sunlight Exposure During Adolescence and Adulthood and Breast Cancer Risk: A Population-based Case-Control Study Among Ontario Women

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Recent studies suggest that vitamin D may be associated with reduced breast cancer risk, but most studies have evaluated only dietary vitamin D intake. The associations among ultraviolet radiation from sunlight, factors related to cutaneous vitamin D production, and breast cancer risk were evaluated in a population-based case-control study conducted in Ontario, Canada, between 2003 and 2004 ($n = 3{,}101$ cases and $n = 3{,}471$ controls). Time spent outdoors was associated with reduced breast cancer risk during 4 periods of life (>21 vs. ≤6 hours/week age-adjusted odds ratio (OR) = 0.71, 95% confidence interval (CI): 0.60, 0.85 in the teenage years; OR = 0.64, 95% CI: 0.53, 0.76 in the 20s–30s; OR = 0.74, 95% CI: 0.61, 0.88 in the 40s–50s; and OR = 0.50, 95% CI: 0.37, 0.66 in the 60s–74 years). Sun protection practices and ultraviolet radiation were not associated with breast cancer risk. A combined solar vitamin D score, including all the variables related to vitamin D production, was significantly associated with reduced breast cancer risk. These associations were not confounded or modified by menopausal status, dietary vitamin D intake, or physical activity. This study suggests that factors suggestive of increased cutaneous production of vitamin D are associated with reduced breast cancer risk.

breast neoplasms; case-control studies; sunlight; vitamin D

Abbreviations: CI, confidence interval; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio; UV-A, ultraviolet A; UV-B, ultraviolet B.

It has been hypothesized that vitamin D, a potentially modifiable factor, may reduce the risk of multiple cancer types including breast cancer (1, 2). Vitamin D is produced in the skin through the conversion of 7-dehydrocholesterol to previtamin D_3 following sufficient exposure to ultraviolet B (UV-B) radiation from sunlight. This process is dependent upon many extrinsic factors that affect UV-B radiation (e.g., geographic location, time of day, and season) and intrinsic, person-specific factors (e.g., time spent outdoors, sun protection practices, skin color) (3, 4). Vitamin D is also found in supplements and a few foods (e.g., fatty fish, fortified milk) (5). Vitamin D from sun, diet, and supplements undergoes hydroxylation in the liver to the circulating form 25-hydroxyvitamin D (25(OH)D). Breast cells, among other cells in the body, are capable of locally converting 25(OH)D to the active hormone 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), which has been shown in laboratory studies to have anticarcinogenic properties (6–8).

Ecologic studies suggest that higher latitude (inversely correlated with sun exposure) and lower UV-B irradiance are positively associated with breast cancer incidence (9) or mortality (10–12). Several observational studies (13–21) and 2 meta-analyses (22, 23) have reported some inverse associations between vitamin D intake (from diet or supplements) and breast cancer risk, often among specific subgroups only. Although not without limitations, serum 25(OH)D is considered to be the best measure of vitamin D and reflects both dietary sources and cutaneous production. Meta-analyses have found no association between prediagnosis serum 25(OH)D levels and breast cancer risk (24, 25), although an inverse association was found when case-control studies with postdiagnosis 25(OH)D measures were included (23–25).

Despite the production of vitamin D in the skin following sunlight exposure, fewer studies have evaluated the association between sun exposure variables and breast cancer risk

(13, 19, 26–28), and all except for one study (28) reported some inverse associations with breast cancer risk. No previous breast cancer studies have created one measure of vitamin D from sunlight that combines person-specific factors (e.g., time outdoors, skin color, or sun protection practices) and environmental sun exposure. To address these gaps in the literature, we evaluated the associations between breast cancer risk and variables related to the production of vitamin D from sunlight (time spent outdoors, ultraviolet radiation at the residence, skin color, and sun protection practices). Variables were evaluated individually and as a combined novel solar vitamin D score for 4 age periods of exposure among women in a population-based case-control study in Ontario, Canada.

MATERIALS AND METHODS

Study design

The Ontario Women's Diet and Health Study has been described previously (29). Women between the ages of 25 and 74 years with a first pathologically confirmed cancer of the breast between 2002 and 2003 were identified from the Ontario Cancer Registry. Physician consent was obtained to contact 4,109 (96%) cases, and 3,101 (75%) of these women completed the study (2003–2004). Controls were recruited from Ontario households by using random digit dialing methods and were frequency age-matched 1:1 to cases. A total of 4,352 households with eligible women were identified, and 3,420 women completed the study (79%). Ethics approval for this study was obtained from the University of Toronto Research Ethics Board.

Exposure variables

Study participants completed a 20-page mailed risk factor questionnaire and a modified Block 1998 Food Frequency Questionnaire (30, 31). We have previously reported on the association between vitamin D intake from food and supplements and breast cancer risk (21). Ethnicity or racial background was used as a proxy for skin color. The overwhelming majority (90%) of study participants were of Caucasian ethnicity and, thus, skin color was categorized as Caucasian versus non-Caucasian (6% Southeast or South Asian, 2% black, 1% aboriginal, and <2% other). Other variables related to sun exposure (weekday time outdoors, weekend time outdoors, sun protection, and location of residence) were measured at 4 periods of life: teenage years, 20s–30s, 40s–50s, and 60s–75 years.

To capture the time spent outdoors, participants were asked, ''On a typical weekday (weekend) in the months April–October about how many hours per day did you spend outside?'' (<1 hour, 1–2 hours, 3–4 hours, >4 hours). Sun exposure is not sufficient for the production of vitamin D from November to March in Ontario (32). The variable, ''hours outdoors per week,'' was created by weighting and summing weekday and weekend exposures. To measure sun protection practices, we asked women the following question: ''When in the sun did you wear sunscreen or protective clothing, such as long sleeves, etc.?'' (never, sometimes, always). Women were also asked to report their location of residence during each of the 4 age periods. All women resided in Ontario when they participated in the study, but many lived elsewhere earlier in life. Latitude and longitude were obtained for all cities and provinces/states of residence at the 4 time periods from www.geocoder.ca. There were 1,628 (25%) women who reported only their country or province/state of residence, and they were assigned the coordinates of the most populated city in their country or region. Although rare (<2%), when multiple locations were reported for a given time period, only the first location was used.

Latitude and longitude were used to obtain ultraviolet radiation data from the National Aeronautics and Space Administration's total ozone mapping spectrometer (TOMS) (33). Ground level ultraviolet irradiance data are calculated from this spectrometer's onboard spacecraft instrument measurements of atmospheric ultraviolet radiation, total ozone, surface reflectivity, and cloud cover. Monthly average noontime erythemal ultraviolet radiation for June 2003 was used in this study. These data are weighted by using McKinlay-Diffey erythemal action spectra (34), which weight radiation in the ultraviolet A (UV-A) (315–400 nm) and UV-B (280–314 nm) wavelengths on the basis of the time required to induce erythema (skin reddening). Vitamin D production is dependent upon UV-B exposure only, but data weighted by using the vitamin D-specific action spectra (35) are not currently available. Although vitamin D production does not always correspond directly with erythemal ultraviolet radiation estimates (36), the erythemal action spectra closely approximate the vitamin D action spectra in the summer north of 42° (Ontario, Canada) (37, 38).

Derivation of solar vitamin D score

To derive a solar vitamin D score (i.e., one variable that takes into consideration known determinants of cutaneous vitamin D production), we created an algorithm based on the available literature on determinants of cutaneous production of vitamin D. Weighted proportions based on the knowledge that darker skin color and use of sun protection practices limit vitamin D production were applied to ''ultraviolet hours per week'' (the product of erythemal ultraviolet and weekly time spent outdoors). It has been estimated that people with highly pigmented (darker) skin colors in comparison with lighter require at least 3 times the amount of sunlight to produce equivalent vitamin D (4, 39), although estimates range from upward to 5 to 10 times (40). Sunscreen and clothing use both have the potential to block all vitamin D production. It seems unlikely, however, that most women apply a complete application of sunscreen (i.e., a thorough full body application prior to going outdoors with frequent reapplication) (41) or fully cover up with clothing. Elsewhere, sunscreen use has not been found to predict 25(OH)D levels (42, 43), but coverage of arms and legs does significantly predict lower 25(OH)D levels (42). Therefore, we assigned women who reported ''never'' using sunscreen or protective clothing the full value of their vitamin D score, and women who reported ''sometimes'' and ''always'' were assigned weighting factors of two-thirds and

one-third, respectively. This algorithm was applied to each of the 4 age periods of exposure: solar vitamin D score ($mW/m^2 \times$ hours) = ultraviolet hours per week ($mW/m^2 \times$ hours) $\times$ skin color weight $\times$ sun protection weight. If ethnicity = "Caucasian," then skin color weight = 1; if ethnicity = "non-Caucasian," then skin color weight = one-third; if sun protection use = "never," then sun protection weight = 1; if sun protection use = "sometimes," then sun protection weight = two-thirds; if sun protection use = "always," then sun protection weight = one-third.

Detailed sensitivity analyses were conducted to evaluate a range of other plausible weighting values and all subsets of variables included in the algorithm. Moreover, we evaluated the use of a previously published predicted plasma 25(OH)D score that includes dietary vitamin D, supplemental vitamin D, body mass index, race, physical activity (included as a proxy for time spent outdoors), and region of residence (44). This score was developed from a multiple linear regression model among a subset of men with 25(OH)D measures in the Health Professionals Follow-Up Study (44) and has been applied to women in the Nurses' Health Study (45, 46).

Statistical analysis

Age-adjusted odds ratios and 95% confidence intervals were calculated by using unconditional logistic regression. Statistical analysis was conducted by using SAS, version 9.1, statistical software (SAS Institute, Inc., Cary, North Carolina). All tests were 2 sided, and statistical significance was defined as $P < 0.05$. Tests for linear trend were calculated by treating the median intake for each exposure category as a continuous variable in the age-adjusted models. Each variable contributing to vitamin D from sun (i.e., skin color, time spent outdoors, sun protection, and ultraviolet radiation) was assessed on its own in addition to the derived solar vitamin D score. For the derived solar vitamin D score, odds ratios were calculated for each of the 4 age periods of exposure, recent exposure only (exposure during the current age period), and a cumulative measure of lifetime ultraviolet exposure. The cumulative lifetime score was created by classifying exposure as high (greater than the median) or low (less than the median) at each age period and combining all periods.

Potential confounders, evaluated by using the change in odds ratio >10% method (47), included the following: marital status, education, ethnicity, body mass index, smoking status, pack-years smoked, breastfed, lactation, age at menarche, oral contraceptive use, oral contraceptive duration, parity, age at first livebirth, age at last menstruation, duration of hormone replacement therapy use, history of benign breast disease, family history of breast cancer, screening mammogram, alcoholic drinks, dietary fat intake, calorie intake, phytoestrogen intake, physical activity, and both dietary vitamin D and calcium (from food and supplements). Physical activity included strenuous, moderate, and daily activity, during the teenage years, 20s–30s, 40s–50s, and 60s–75 years. It was hypothesized a priori that the effect of vitamin D from sunlight may be modified by menopausal status, vitamin D or calcium intakes from supplements or total intake (food and supplements), body mass index, or smoking status; thus, the statistical significance of these multiplicative interactions was tested by using the likelihood ratio test.

RESULTS

The mean age of women in this study was 56 years. Most women were postmenopausal (68% of cases and 64% of controls), and many women had postsecondary education (46% of cases and 49% of controls). As reported previously, family history of breast cancer, younger age at menarche, lower parity, older age at menopause, and decreased physical activity levels were all positively associated with breast cancer risk (21, 29).

Time spent outdoors was not strongly associated with physical activity, parity, or educational status (all Spearman correlation coefficients (r_s) < 0.26) (data not shown). Increasing time spent outdoors (>21 vs. ≤6 hours/week) was associated with reduced breast cancer risk during the teenage years (odds ratio (OR) = 0.71, 95% confidence interval (CI): 0.60, 0.85); 20s–30s (OR = 0.64, 95% CI: 0.53, 0.76); 40s–50s (OR = 0.74, 95% CI: 0.61, 0.88); and 60s–75 years (OR = 0.50, 95% CI: 0.37, 0.66), all with statistically significant trends (Table 1). Sun protection practices, latitude, and erythemal ultraviolet radiation of residence were not associated with breast cancer risk during any of the 4 age periods. The results did not change substantially after excluding the 1% of women who lived in the Southern hemisphere during at least one life period (wintertime sun exposure) or the 25% of women who reported residence at the country or province/state level only (city was assumed).

The solar vitamin D score was consistently associated with a reduced risk of breast cancer across all 4 age periods of exposure (Table 2). No confounders were identified for any of the models; thus, the age-adjusted only models are presented. The age-adjusted odds ratios comparing the highest with lowest quartile for exposure during the teenage years, 20s–30s, 40s–50s, and 60s–75 years were 0.79 (95% CI: 0.68, 0.91), 0.76 (95% CI: 0.65, 0.89), 0.75 (95% CI: 0.64, 0.88), and 0.59 (95% CI: 0.46, 0.76), respectively, and all trend tests were significant ($P < 0.001$). Interactions between the solar vitamin D score at any age and vitamin D from supplement use were not statistically significant, and stratified analyses do not suggest any effect modification (Table 3). Similarly, no statistically significant interactions were observed with total dietary vitamin D intake, menopausal status, or smoking status (data not shown). Statistically significant interactions were found between the solar vitamin D score during the age period of the 60s–75 and both total calcium intake ($P_{interaction} = 0.02$) and body mass index ($P_{interaction} \leq 0.001$); however, stratified analyses revealed inverse associations among all categories of calcium and body mass index (data not shown).

Sensitivity analyses were conducted by varying assumptions for the solar vitamin D score, and the results changed minimally (Table 4), suggesting that our algorithm was robust to changes. Results from applying the predicted 25(OH)D model (44) to our study yielded a range of

Table 1. Distribution of Breast Cancer Cases and Controls and Odds Ratios for Sun Exposure-related Variables During 4 Age Periods, Ontario Women's Diet and Health Study, 2003–2004

Variable	Cases (n = 3,101)		Controls (n = 3,471)		OR[a]	95% CI
	No.	%	No.	%		
Ethnicity (proxy for skin color)						
Caucasian	2,749	89	3,121	90	1.00	Referent
Non-Caucasian	341	11	330	10	1.23	1.05, 1.45
Teenage years[b]						
Use of sun protection						
Never	1,601	54	1,829	55	1.00	Referent
Sometimes	1,234	41	1,354	40	1.06	0.95, 1.18
Always	149	5	169	5	1.03	0.82, 1.31
P_{trend}						0.29
Time outdoors, hours/week[c]						
≤6	365	12	324	10	1.00	Referent
7–12	558	19	549	17	0.90	0.74, 1.09
13–14	505	17	569	17	0.81	0.66, 0.98
15–21	566	19	679	20	0.76	0.63, 0.91
>21	944	32	1,198	36	0.71	0.60, 0.85
P_{trend}						<0.001
Latitude of residence[d]						
≤42.5°N (median = 41.5)	644	22	662	20	1.15	1.00, 1.33
42.6°–43.5°N (median = 43.5)	1,015	35	1,137	35	1.07	0.94, 1.21
43.6°–45.0°N (median = 44.5)	320	11	383	12	0.98	0.83, 1.17
>45.0°N (median = 47.5)	908	31	1,050	32	1.00	Referent
P_{trend}						0.22
Erythemal UV radiation of residence, mW/m^{2}[e]						
10–169 (median = 150)	497	17	575	18	1.00	Referent
170–179 (median = 170)	1,370	47	1,509	47	1.07	0.91, 1.26
180–380 (median = 180)	1,019	35	1,148	36	0.99	0.83, 1.18
P_{trend}						0.73
20s–30s						
Use of sun protection[b]						
Never	1,004	34	1,119	34	1.00	Referent
Sometimes	1,647	56	1,889	57	1.03	0.92, 1.15
Always	270	9	300	9	1.11	0.91, 1.34
P_{trend}						0.31
Time outdoors, hours/week[c]						
≤6	528	18	488	15	1.00	Referent
7–12	758	26	858	26	0.81	0.70, 0.95
13–14	640	22	720	22	0.84	0.71, 0.99
15–21	551	19	576	17	0.88	0.74, 1.05
>21	452	15	655	20	0.64	0.53, 0.76
P_{trend}						<0.001
Latitude of residence[d]						
≤42.5°N (median = 42.5)	531	19	547	18	1.11	0.94, 1.30
42.6°–43.5°N (median = 43.5)	1,276	46	1,414	46	1.03	0.91, 1.17
43.6°–45.0°N (median = 44.5)	272	10	364	12	0.85	0.71, 1.03
>45.0°N (median = 46.5)	686	25	768	25	1.00	Referent
P_{trend}						0.07
Erythemal UV radiation of residence, mW/m^{2}[e]						
10–169 (median = 150)	316	11	358	11	1.00	Referent
170–179 (median = 170)	1,576	57	1,706	55	1.08	0.94, 1.25
180–380 (median = 180)	872	32	1,029	33	1.06	0.91, 1.23
P_{trend}						0.45
40s–50s[f]	2,920		3,155			
Use of sun protection[b]						
Never	501	18	551	18	1.00	Referent
Sometimes	1,529	56	1,736	58	1.00	0.86, 1.15
Always	687	25	697	23	1.11	0.94, 1.31
P_{trend}						0.15

Table continues

Table 1. Continued

Variable	Cases (n = 3,101)		Controls (n = 3,471)		OR[a]	95% CI
	No.	%	No.	%		
Time outdoors, hours/week[c]						
≤6	736	27	766	26	1.00	Referent
7–12	807	30	835	28	1.00	0.87, 1.15
13–14	482	18	566	20	0.89	0.76, 1.04
15–21	422	15	417	14	1.04	0.88, 1.23
>21	286	10	400	13	0.74	0.61, 0.88
P_{trend}						0.007
Latitude of residence[d]						
≤42.5°N (median = 42.5)	365	13	417	14	0.94	0.78, 1.13
42.6°–43.5°N (median = 43.5)	1,480	55	1,516	52	1.05	0.92, 1.21
43.6°–45.0°N (median = 44.5)	325	12	416	14	0.83	0.69, 1.01
>45.0°N (median = 45.5)	541	20	577	20	1.00	Referent
P_{trend}						0.62
Erythemal UV of residence, mW/m^2[e]						
10–169 (median = 150)	152	6	168	6	1.00	Referent
170–179 (median = 170)	1,742	64	1,754	60	1.11	0.88, 1.40
180–380 (median = 180)	817	30	1,004	34	0.91	0.71, 1.15
P_{trend}						0.04
60s–75[g]	1,247		1,224			
Use of sun protection[b]						
Never	202	17	206	16	1.00	Referent
Sometimes	531	46	637	51	0.89	0.71, 1.13
Always	430	37	410	33	1.15	0.90, 1.47
P_{trend}						0.24
Time outdoors, hours/week[c]						
≤6	402	35	366	29	1.00	Referent
7–12	370	32	352	28	0.96	0.78, 1.17
13–14	115	10	143	12	0.74	0.56, 0.99
15–21	171	15	210	17	0.74	0.58, 0.95
>21	93	8	172	14	0.50	0.37, 0.66
P_{trend}						<0.001
Latitude of residence[d]						
≤42.5°N (median = 42.5)	158	13	159	13	1.05	0.79, 1.40
42.6°–43.5°N (median = 43.5)	637	54	622	50	1.09	0.88, 1.34
43.6°–45.0°N (median = 44.5)	162	14	226	18	0.76	0.58, 0.99
>45.0°N (median = 45.5)	230	20	244	20	1.00	Referent
P_{trend}						0.17
Erythemal UV of residence, mW/m^2[e]						
120–179 (median = 170)	787	66	805	64	1.00	Referent
180–380 (median = 180)	400	34	445	36	0.92	0.77, 1.08
P_{trend}						0.29

Abbreviations: CI, confidence interval; NASA, National Aeronautics and Space Administration; OR, odds ratio; UV, ultraviolet.

[a] Age group adjusted (note: 39 variables were evaluated as potential confounders, and none was identified as a confounder; i.e., their inclusion in the model did not change the OR >10%).

[b] Protective clothing or sunscreen. Odds ratios were adjusted for age and time spent outdoors at the same age period of exposure.

[c] Time spent outdoors from May to September only.

[d] Geocoded on the basis of location lived reported as city and province/state (e.g., Toronto, Ontario = 43.7°N).

[e] Monthly average local noon erythemal UV radiation for June 2003 obtained from NASA's total ozone mapping spectrometer.

[f] Age 40 years not reached by 181 (6%) cases and 316 (10%) controls.

[g] Age 60 years not reached by 1,854 (61%) cases and 1,324 (63%) controls.

predicted values from 39 to 87 nmol/L, similar to the ranges reported in the Health Professionals Follow-up Study and the Nurses' Health Study. The association between predicted 25(OH)D and breast cancer risk was also statistically significant (highest vs. lowest quintile OR = 0.84, 95% CI: 0.72, 0.98) (Table 5).

Table 2. Distribution of Breast Cancer Cases and Controls and Odds Ratios for Derived Proxy Measures of Vitamin D From Sunlight During 4 Age Periods, Recent Exposure Only, and Cumulative Life Exposure, Ontario Women's Diet and Health Study, 2003–2004

Solar Vitamin D Score[a]	Cases (n = 3,101)		Controls (n = 3,471)		OR[b]	95% CI
	No.	%	No.	%		
By specific age period						
Teenage years, mW/m^2 × hours (n = 5,924)						
Q1 (≤1,425)	797	29	780	25	1.00	Referent
Q2 (1,426–2,295)	743	27	804	26	0.90	0.78, 1.03
Q3 (2,296–3,570)	696	25	855	27	0.80	0.70, 0.93
Q4 (>3,570)	557	20	692	22	0.79	0.68, 0.91
P_{trend}						<0.001
20s–30s, mW/m^2 × hours (n = 5,579)						
Q1 (≤957)	718	27	739	25	1.00	Referent
Q2 (958–1,514)	497	19	528	18	0.95	0.81, 1.12
Q3 (1,515–2,430)	862	33	979	33	0.89	0.77, 1.02
Q4 (>2,430)	546	21	710	24	0.76	0.65, 0.89
P_{trend}						<0.001
40s–50s, mW/m^2 × hours (n = 5,263)						
Q1 (≤617)	665	26	623	23	1.00	Referent
Q2 (618–1,178)	560	22	615	22	0.85	0.72, 0.99
Q3 (1,179–1,785)	754	30	841	31	0.82	0.71, 0.95
Q4 (>1,785)	541	21	664	24	0.75	0.64, 0.88
P_{trend}						<0.001
60s–75, mW/m^2 × hours (n = 2,257)						
Q1 (≤589)	295	27	257	22	1.00	Referent
Q2 (590–1,178)	313	29	300	26	0.91	0.72, 1.14
Q3 (1,179–1,767)	285	26	318	27	0.78	0.62, 0.98
Q4 (>1,767)	197	18	292	25	0.59	0.46, 0.76
P_{trend}						<0.001
Cumulative (n = 6,159)[c]						
Low at all age periods	874	30	878	27	1.00	Referent
Low at 3 age periods	639	22	682	21	0.93	0.81, 1.08
Low at 2 ages and high at 2	602	21	716	22	0.84	0.72, 0.96
High at 3 age periods	573	20	667	21	0.81	0.70, 0.94
High at all age periods	219	8	309	10	0.63	0.51, 0.78
P_{trend}						<0.001
Recent, mW/m^2 × hours (n = 5,805)[d]						
Q1 (≤589)	692	25	669	22	1.00	Referent
Q2 (590–1,178)	799	29	856	28	0.90	0.78, 1.04
Q3 (1,179–1,603)	624	23	711	23	0.84	0.72, 0.98
Q4 (>1,603)	619	23	838	27	0.72	0.62, 0.84
P_{trend}						<0.001

Abbreviations: CI, confidence interval; OR, odds ratio; Q, quartile; UV, ultraviolet.

[a] Average weekday and weekend hours spent outdoors per week multiplied by erythemal UV radiation of residence weighted for skin color and sun protection practices. Refer to Materials and Methods for more details.

[b] Adjusted for age group.

[c] Exposure at all 4 age periods was classified as high (>50th percentile) or low (<50th percentile) and added for all age periods reached.

[d] Exposure during age period when questionnaire was completed.

Table 3. Distribution of Breast Cancer Cases and Controls and Odds Ratios for Derived Proxy Measures of Vitamin D From Sunlight During 4 Age Periods Stratified by Vitamin D Supplement Use, Ontario Women's Diet and Health Study, 2003–2004

Solar Vitamin D Score by Specific Age Period[a]	Vitamin D Supplement Use				$P_{interaction}$
	<400 IU/Day (n = 4,364)		≥400 IU/Day (n = 2,125)		
	OR[b]	95% CI	OR[2]	95% CI	
Teenage years, mW/m^2 × hours (n = 5,924)					
Q1 (≤1,425)	1.00		1.00		0.44
Q2 (1,426–2,295)	0.96	0.81, 1.15	0.79	0.61, 1.00	
Q3 (2,296–3,570)	0.81	0.68, 0.96	0.81	0.64, 1.04	
Q4 (>3,570)	0.79	0.65, 0.95	0.80	0.61, 1.04	
20s–30s, mW/m^2 × hours (n = 5,579)					
Q1 (≤957)	1.00		1.00		0.27
Q2 (958–1,514)	0.94	0.77, 1.14	0.98	0.74, 1.30	
Q3 (1,515–2,430)	0.95	0.80, 1.12	0.77	0.60, 0.98	
Q4 (>2,430)	0.76	0.63, 0.92	0.78	0.60, 1.02	
40s–50s, mW/m^2 × hours (n = 5,263)					
Q1 (≤617)	1.00		1.00		0.15
Q2 (618–1,178)	0.88	0.73, 1.07	0.76	0.58, 1.01	
Q3 (1,179–1,785)	0.91	0.76, 1.10	0.67	0.52, 0.87	
Q4 (>1,785)	0.74	0.61, 0.90	0.75	0.57, 0.99	
60s–75, mW/m^2 × hours (n = 2,257)					
Q1 (≤589)	1.00		1.00		0.31
Q2 (590–1,178)	0.97	0.71, 1.31	0.86	0.60, 1.23	
Q3 (1,179–1,767)	0.93	0.68, 1.26	0.63	0.44, 0.91	
Q4 (>1,767)	0.59	0.43, 0.81	0.60	0.41, 0.89	

Abbreviations: CI, confidence interval; OR, odds ratio; Q, quartile; UV, ultraviolet.

[a] Average weekday and weekend hours spent outdoors per week multiplied by erythemal UV radiation of residence weighted for skin color and sun protection practices. Refer to Materials and Methods for more details.

[b] Adjusted for age group.

DISCUSSION

The results of this large population-based case-control study suggest that time spent outdoors and our derived proxy measure of vitamin D from sun are inversely associated with breast cancer risk. Exposure during all 4 periods of life, cumulative life exposure, and recent exposure were all associated with reduced breast cancer, with the strongest inverse associations observed for exposure during the 60s–75 years. Erythemal ultraviolet radiation, latitude, and sun protection practices were not independently associated with breast cancer risk; however, our sun protection measure was relatively crude, and there was limited variation in the latitude of residence and thus limited variation in erythemal ultraviolet radiation. The majority of study participants resided in the Greater Toronto Area (~43°N latitude). Detailed measures of physical activity were included in our study, yet physical activity was not highly correlated with time spent outdoors. Confounding by known breast cancer risk factors and other variables that may be associated with time spent outdoors (e.g., physical activity, parity, education) was not observed.

Consistent with our findings, time spent outdoors has been associated with reduced breast cancer risk in most previous cohort (13, 27) and case-control (19) studies but not all (26). Sunscreen use, sunburns/skin damage, winter sun trips, or sunlamp/solarium use have generally not been associated with breast cancer risk (13, 19, 28), although usually covering the skin with clothing in the summer was associated with increased breast cancer risk (19). No significant associations were observed between erythemal ultraviolet radiation exposure and breast cancer risk, and previous studies of ultraviolet or solar radiation and breast cancer risk in the United States are inconsistent (13, 27). Non-Caucasian ethnicity, our proxy for darker skin color, was associated with increased breast cancer risk, consistent with the vitamin D hypothesis. The association between ethnicity and breast cancer risk, however, may be explained by many other factors, and our association is inconsistent with US data that suggest breast cancer rates are highest among white women (48). Because the vast majority of women were Caucasian (90%), we were unable to explore this association further. Elsewhere, a sun exposure index, from skin reflectometry measures, was inversely associated

Table 4. Sensitivity Analyses Evaluating a Range of Assumptions to Derive the Solar Vitamin D Score and Corresponding Odds Ratios for the Derived Variables and Breast Cancer Risk, Ontario Women's Diet and Health Study, 2003–2004

Values Applied in Algorithm[a]				OR[b] Comparing Highest With Lowest Quartile of Exposure			
				Exposure During Ages 20–39 Years		Exposure During Ages 40–59 Years	
Skin Color[c]	Sun Protection Practices[d]	Erythemal UV,[e] mW/m^2	Time Outdoors,[f] hours/week	OR	95% CI	OR	95% CI
A priori-derived score (as reported in Results)							
Caucasian = 1.0 Non-Caucasian = 0.33	Never = 1.0 Sometimes = 0.66 Always = 0.33	As measured (continuous)	Hours/week (continuous)	0.76[g]	0.65, 0.89	0.75	0.64, 0.88
Variations on the score							
Caucasians = 1.0 Non-Caucasians excluded	Never = 1.0 Sometimes = 0.66 Always = 0.33	As measured (continuous)	Hours/week (continuous)	0.79	0.67, 0.93	0.77	0.65, 0.92
Not included	Not included	As measured (continuous)	Hours/week (continuous)	0.79	0.68, 0.91	0.88	0.75, 1.02
Caucasian = 1.0 Non-Caucasian = 0.33	Never = 1.0 Sometimes = 0.66 Always = 0.33	Not included	Not included	0.83[h]	0.71, 0.96	0.85	0.72, 1.01
Caucasian = 1.0 Non-Caucasian = 0.33	Never = 1.0 Sometimes = 0.66 Always = 0.33	As measured (continuous)	Not included	0.77	0.69, 0.89	0.84	0.70, 0.99
Caucasian = 1.0 Non-Caucasian = 0.33	Never = 1.0 Sometimes = 0.66 Always = 0.33	As measured (continuous)	≥1 hour/day = 1.0 <1 hour/day = 0.5	0.83	0.71, 0.96	0.79	0.66, 0.95
Caucasian = 1.0 Non-Caucasian = 0.33	Never = 1.0 Sometimes = 0.66 Always = 0.33	0–120 = 1.0 >120–240 = 1.2 >240–360 = 1.4 >360 = 1.6	Hours/week (continuous)	0.78	0.67, 0.91	0.78	0.67, 0.91
Caucasian = 1.0 Non-Caucasian = 0.33	Never = 1.0 Sometimes = 0.66 Always = 0.33	0–120 = 1.0 >120–240 = 1.2 >240–360 = 1.4 >360 = 1.6	≥1 hour/day = 1.0 <1 hour/day = 0.5	0.82	0.71, 0.96	0.80	0.64, 0.99
Caucasian = 1.0 Non-Caucasian = 0.33	Never = 1.0 Sometimes = 0.9 Always = 0.7	As measured (continuous)	Hours/week (continuous)	0.75	0.64, 0.87	0.85	0.73, 0.99
Caucasian = 1.0 Non-Caucasian = 0.33	Never = 1.0 Sometimes = 0.9 Always = 0.7	0–120 = 1.0 >120–240 = 1.2 >240–360 = 1.4 >360 = 1.6	≥1 hour/day = 1.0 <1 hour/day = 0.5	0.81	0.69, 0.94	0.81	0.65, 1.0
Caucasian = 1.0 Non-Caucasian = 0.80	Never = 1.0 Sometimes = 0.66 Always = 0.33	As measured (continuous)	Hours/week (continuous)	0.75	0.64, 0.87	0.78	0.66, 0.90

Abbreviations: CI, confidence interval; NASA, National Aeronautics and Space Administration; OR, odds ratio; UV, ultraviolet.

[a] Score derived by multiplying the assigned values for skin color, sun protection practices, erythemal UV radiation, and time spent outdoors.

[b] Age group adjusted.

[c] Ethnicity used as a proxy for skin color with Caucasians assumed to have lighter skin color then non-Caucasians.

[d] Self-reported protective clothing or sunscreen use.

[e] Monthly average local noon erythemal UV radiation for June 2003 obtained from NASA's total ozone mapping spectrometer.

[f] Typical number of hours spent outdoors from April to October during weekdays and weekends.

[g] Original solar vitamin D score as proposed a priori.

[h] Categorized as 0–0.33, 0.34–0.66, and ≥0.67 on the basis of distribution of variables. The odds ratio shown is for the comparison of highest with lowest categories.

Table 5. Distribution of Breast Cancer Cases and Controls and Odds Ratios for Predicted Plasma 25(OH)D, Ontario Women's Diet and Health Study, 2003–2004[a]

Predicted 25(OH)D	Cases (n = 3,101)			Controls (n = 3,471)			OR[b]	95% CI
	Mean (SD)	No.	%	Mean (SD)	No.	%		
Per 1-unit increase, nmol/L	66.2 (7.8)			66.7 (7.6)			0.99	0.98, 1.00
Per 25-unit increase, nmol/L	66.2 (7.8)			66.7 (7.6)			0.75	0.64, 0.88
Quintiles								
1 (39–59.9)		657	21		699	20	1.00	
2 (60–65.2)		650	21		696	20	0.97	0.83, 1.13
3 (65.3–68.8)		621	20		665	19	0.96	0.82, 1.12
4 (69–73.2)		594	19		723	21	0.84	0.72, 0.98
5 (73.3–87)		579	19		688	20	0.84	0.72, 0.98

Abbreviations: CI, confidence interval; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio; Q, quintile; SD, standard deviation.

[a] Regression coefficients from a previously developed prediction model for 25(OH)D (refer to reference 44) were applied as follows to the variables in our study: intercept = 90.8; race (white = 0, black and other = −12.8, Asian = −13.3); body mass index (<22 kg/m^2 = 0; 22–24.9 kg/m^2 = −1.0; 25–29.9 kg/m^2 = −4.5; 30–34.9 kg/m^2 = −6.5; ≥35 kg/m^2 = −8.6); quintiles of weekly average moderate and strenuous physical activity during 20s–30s and 40s–50s (Q5 = 0; Q4 = −4.5; Q3 = −7.7; Q2 = −9.0; Q1 = −13.5); dietary vitamin D (≥400 IU/day = 0; 300–399 IU/day = −3.5; 200–299 IU/day = −2.6; 100–199 IU/day = −7.2; <100 IU/day = −10.4); and supplementary vitamin D (≥400 IU/day = 0; 200–399 IU/day = −1.8; 1–199 IU/day = 2.4; <100 IU/day = −2.1). Because all women were living in Ontario, Canada, upon study completion, they were all assigned the value for northern area of residence (Northeast/mid-Atlantic = −6.4).

[b] Age adjusted.

with advanced stage breast cancer risk among light-skinned women only (26). Evaluating breast cancer stage was not possible within our study. When we restricted our solar vitamin D score to Caucasians only, the results did not change substantially.

The timing of sunlight exposure may be important to confer any potential benefits of vitamin D for breast cancer risk; breast tissue is undifferentiated prior to first pregnancy and potentially more susceptible to exposures during the period from menarche to first birth (49). Our study results do not suggest that the inverse association between time spent outdoors and breast cancer risk is more pronounced for adolescent exposure. Elsewhere, stronger inverse associations were observed between both sun exposure and dietary vitamin D during adolescence and breast cancer risk (19). Null associations have been observed between breast cancer risk and early life exposures to sunburns, sun vacations and solarium use (28), or region of residence (27).

To the best of our knowledge, no previous study has combined multiple factors to evaluate the association between a composite measure of vitamin D from sunlight and breast cancer risk. Previous studies have evaluated predictors of vitamin D production independently or simultaneously controlling for each other by using multivariate regression (13, 19, 26–28) or conducting some stratified analyses by skin pigment (26), skin type and ethnicity (27), outdoor physical activity intensity (19), or solar radiation (13). Time spent outdoors was associated with breast cancer risk on its own but does not appear to be entirely driving the observed association with the solar vitamin D score; sensitivity analyses indicate that combinations of the other components were also associated with reduced risk. The sensitivity analyses also reveal that the algorithm is relatively robust to variations in the weighting values assigned a priori to the algorithm. It is a limitation of our study that we were unable to validate our novel algorithm used to derive the composite measure of vitamin D from sunlight. Future studies need to determine how well such a measure predicts vitamin D intake from sunlight or 25(OH)D. Previous scores combining only time spent outdoors and amount of skin exposed have been found to predict summertime 25(OH)D levels with correlation coefficients ranging from 0.49 to 0.59 (50, 51). We applied a previously published predictive 25(OH)D score (44) to our study, and the results were similar to our derived solar vitamin D score. The suitability of this predictive 25(OH)D score for our population is unknown, and it explained only 28% of the variation in 25(OH)D in the population in which it was developed (44). Furthermore, this predicted 25(OH)D score does not include any direct measures of sun exposure or time spent outdoors, and some of the reported coefficients are not in the expected direction. Measured 25(OH)D has been associated with reduced breast cancer risk among several case-control studies with postdiagnosis 25(OH)D levels, but not among the few nested case-control or cohort studies (23–25). However, serum 25(OH)D measured either postdiagnosis or via a single prediagnosis measure may not reflect usual vitamin D levels during the relevant period of exposure. Future studies with

repeated prospective 25(OH)D measures or improved validated predicted models are warranted.

There is the potential for misclassification error in this study, and more detailed measures of skin type, sun protection practices, data on sun bed/lamp, wintertime sun holidays, and time of day outdoors may be beneficial. The categories for sun exposure (all >1 hour) measured in this study are beyond that necessary for vitamin D synthesis. It is not realistic, however, to expect study participants to recall their sun exposure with much greater level of accuracy, and this measure does provide us with a relative estimate of high versus low sun exposure. Although our results were independent of many potential confounders (including physical activity), there is always the potential for residual confounding in observational studies. Alternate explanations for the observed association between sun exposure and reduced breast cancer risk have been reviewed (e.g., changes in melatonin, seasonal affective disorder, immunologic effects, or degradation of folic acid by UV-B exposure) (52). Evaluating these hypotheses was not possible within our study, and thus it is not possible to determine if our associations are attributable to vitamin D.

Strengths of this study include its population-based case-control study design, high response rates, and large sample size. This study included a detailed person-specific sun exposure questionnaire, with information on exposure during multiple periods of life, as well as estimated ambient ultraviolet irradiation for each participant. Survival bias is likely minimal in this study, as cases were recruited within 11 months of diagnosis (on average), and 5-year relative survival is nearly 90% among breast cancer cases in Ontario (53). Although measurement error may be of concern in this study, there is no reason to suspect that this would be differential or lead to recall bias; study participants were not aware of the study hypothesis, and data collection occurred prior to any current media attention regarding the vitamin D hypothesis.

In conclusion, time spent outdoors during multiple periods of life and our composite solar vitamin D score were associated with reduced breast cancer risk. Furthermore, the use of a previously published predictive model for plasma 25(OH)D was also associated with reduced breast cancer risk within our study. A score such as that created in this study to derive a composite measure of cutaneous production of vitamin D or to predict 25(OH)D levels may be useful for future population-based studies, and more research is needed to develop and validate such measures. It is plausible that vitamin D production mediates the inverse associations observed between sunlight exposure and breast cancer risk, yet future studies are needed to confirm this hypothesis.

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