Vitamin D and Reduced Risk of Breast Cancer: A Population-Based Case-Control Study

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Abstract

Background: **Vitamin D, antiproliferative and proapoptotic in breast cancer cell lines, can reduce the development of mammary tumors in carcinogen-exposed rats. Current evidence in humans is limited with some suggestion that vitamin D–related factors may reduce the risk of breast cancer. We conducted a population-based case-control study to assess the evidence for a relationship between sources of vitamin D and breast cancer risk.**
Methods: **Women with newly diagnosed invasive breast cancer were identified from the Ontario Cancer Registry. Women without breast cancer were identified through randomly selected residential telephone numbers. Telephone interviews were completed for 972 cases and 1,135 controls. Odds ratios (OR) and 95% confidence intervals (CI) for vitamin D–related variables were estimated using unconditional logistic regression with adjustment for potential confounders.**
Results: **Reduced breast cancer risks were associated with increasing sun exposure from ages 10 to 19 (e.g., OR, 0.65; 95% CI, 0.50-0.85 for the highest quartile of outdoor activities versus the lowest; *P* for trend = 0.0006). Reduced risk was also associated with cod liver oil use (OR, 0.76; 95% CI, 0.62-0.92) and increasing milk consumption (OR, 0.62 95% CI 0.45-0.86 for ≥10 glasses per week versus none; *P* for trend = 0.0004). There was weaker evidence for associations from ages 20 to 29 and no evidence for ages 45 to 54.**
Conclusion: **We found strong evidence to support the hypothesis that vitamin D could help prevent breast cancer. However, our results suggest that exposure earlier in life, particularly during breast development, maybe most relevant. These results should be confirmed.** (Cancer Epidemiol Biomarkers Prev 2007;16(3):422–9)

Introduction

Evidence for the role of vitamin D in the development of various cancers including breast cancer has been accumulating in recent years (reviewed in refs. 1, 2). Vitamin D (cholecalciferol) is produced when skin is exposed to UV light, which converts 7-dyhydrocholesterol to vitamin D (3). Within 48 h, the liver hydroxylates essentially all vitamin D to 25-hydroxyvitamin D (25(OH)D). This has a biological half-life of at least 2 months, and its level is the accepted measure of vitamin D nutritional status (4, 5). The form of vitamin D that is the active, signaling molecule is 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). The enzyme, 25(OH)D-1α-hydroxylase, necessary for this reaction is present not just in the kidney, from which it regulates intestinal calcium absorption, but also in many tissues throughout the body including the breast, in which it serves as a local, paracrine hormone (6, 7). Although the primary source of vitamin D is exposure of the skin surface to 290 to 315 nm of UV radiation, small amounts of vitamin D can also be obtained through a limited number of dietary sources including fortified milk and fatty fish (4, 8).

Initial evidence suggesting the potential for vitamin D to reduce breast cancer risk and mortality arose from ecologic studies relating higher latitude, and therefore lower UVB, to increased breast cancer incidence and mortality (9-11), and from *in vitro* studies showing antiproliferative and proapoptotic effects of $1,25(OH)_2D$ in breast cancer cell lines (reviewed in refs. 12-14). In carcinogen-exposed rats, $1,25(OH)_2D$ or its analogues have been shown to reduce the incidence and size and delay the development of mammary tumors (12-14).

The current analytic epidemiologic evidence is limited. In the first National Health and Nutrition Examination Survey Follow-up Study, a decreased risk of breast cancer was consistently observed for those with higher sun exposure, actinic skin damage, and high dietary or supplemental vitamin D intake, although in most cases, statistical significance was not achieved (15). In an analysis of dietary and supplemental vitamin D in the Nurses' Health Study (NHS) cohort, a higher dietary intake of vitamin D or total intake including supplements was significantly associated with a reduced risk of premenopausal breast cancer (16). A more recent study within this cohort revealed that cases had a significantly lower mean plasma 25(OH)D (prior to diagnosis) compared with controls (17).

To add to the limited, but suggestive evidence regarding the relationship between vitamin D and breast cancer risk, we conducted a population-based case-control study in the province of Ontario, Canada. In this study, we collected information on a wide variety of variables related to vitamin D–relevant sun exposure as well as dietary and supplemental vitamin D. In particular, we focused on exposures during breast development and involution.

Materials and Methods

Case and Control Identification. Women with an invasive first primary breast cancer diagnosed between July 1, 2003 and August 31, 2004 and aged <70 years were identified from the Ontario Cancer Registry. The Ontario Cancer Registry obtains information on nearly all breast cancers diagnosed in residents of the province of Ontario. Only women with a pathology report indicating invasive breast cancer were included and a random sample of ~30% of eligible women were selected for the study. We identified 1,610 eligible women with breast cancer and obtained permission from a physician to contact

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1,350 (84%) of these women. Physicians refused permission for 159 women (10%), no physician could be identified for 52 women (3%), there was no physician response for 32 women (2%), and 17 women (1%) had died. Once physician permission was obtained, we mailed a letter explaining the study and a copy of the questionnaire to each woman. This was followed by a telephone call to arrange a telephone interview. Of the 1,350 women we attempted to contact, 972 (72%) completed the telephone interview. The majority of women not completing the interview (293, 22%), chose not to participate, whereas we were unable to contact 38 (3%), 6 women had died, and for the remaining 41 (3%), there were language or other communication barriers that prevented interview completion.

Population control women were identified through randomly selected residential telephone number lists for the province of Ontario and were approximately frequency-matched to cases by 5-year age group. In total, we attempted contact with 13,078 telephone numbers. Of these, 706 (5%) numbers were not valid, no contact could be made with 1,211 (9%), and contact was made with 1,761 (13%) households in which no information on potential eligibility could be obtained. There were 7,426 (57%) households with no eligible person available. Of the 1,974 telephone numbers in which an eligible control was identified, 1,376 (70%) potential control women agreed to participate. A letter explaining the study and a copy of the questionnaire was then sent to each of these women and 1,135 (82%) of them completed the telephone interview.

Questionnaire. During the interview, demographic information such as ethnic background and education was collected as well as information on established risk factors such as age at menarche, parity, age at first birth, and breast-feeding. Questions related to vitamin D exposure included those related to sun exposure as well as those related to dietary and supplemental sources of vitamin D. A minimum duration of sun exposure of half an hour was used as significant amounts of vitamin D can be obtained (4, 18) and it is unlikely that durations of less than this could be easily recalled. Most of the vitamin D–related questions were asked with respect to three age groups, 10 to 19, 20 to 29, and 45 to 54 years old. These time periods were chosen to capture exposures during breast development as well as during breast involution occurring around the time of menopause. Sun exposure–related questions included the following (summer was defined as June, July, and August): whether the woman had a job for 1 month or more in which she worked outdoors for a total of at least half an hour between 9 a.m. and 5 p.m. (a list of the jobs was requested along with ages at starting and stopping the job and the months per year and number of years the job was done); whether during the summer she ever did any activities outdoors for at least 30 min in total between 9 a.m. and 5 p.m. at least once a month (a list was provided with the option of adding unlisted outdoor activities) and information on frequency (days per week or month) and duration (number of weeks or months per summer and total number of years) was collected for each activity; on average, in the summer, the number of days per week she spent at least half an hour outdoors including all activities and any other time outside; whether she usually kept her arms and legs covered when she was outside (usually was defined as >50% of the time); whether she usually wore sunscreen when she was outside (and if so, what the usual sun protection factor was); whether her skin usually burned or got darker in the summer; whether in the winter she ever went to a summer climate (and how many years), and whether she had ever used a sunlamp or sun bed (with age when first used, age at last used, and total number of sessions over her lifetime). Respondents were also asked to report their skin color without any tanning from seven categories from very fair to very dark brown/black. There are limited major sources of vitamin D in the diet and questions were asked regarding frequency of intake of milk (number of glasses drunk on average per day, week, or month) and tuna or salmon (number of times per day, week, or month of canned or fresh), as well as whether cod liver oil was taken at least once per week (and at what ages) and what type of vitamin supplements were taken, if any.

Statistical Analysis. Unconditional logistic regression, with the presence of breast cancer as the outcome, was used to generate odds ratios (OR) and 95% confidence interval (CI) estimates and the Armitage test was used to test for trend. All models included age (continuous) and all fully adjusted models included education (less then high school, some college, university degree) and ethnicity (British or Northern European, other European, non-European). Age was taken to be age at diagnosis for cases and age at interview for controls. Known breast cancer risk factors that were significantly associated with the risk of breast cancer in this study were also included as potential confounders. In addition to age, education, and ethnicity, the variables in the fully adjusted models included age at menarche (<12, 12, 13, 14+), first-degree family history of breast cancer (yes/no), ever breast-fed (yes/no), and age at first birth (<20, 20-24, 25-29, 30+, nulliparous). Both parity and age at first birth were significantly related to breast cancer risk. However, as they were highly correlated, age at first birth was chosen because there seemed to be a stronger association. The main variables of interest included number of days per week in which at least half an hour was spent outside (<3, 3-4, 5-6, 7), total number of outdoor activity episodes [of at least half an hour derived from the question described above collecting information on the type of activity as well as frequency and duration during the summer (quartiles)], duration of having a job involving at least half an hour of outdoor work per day (never, 1 year, >1 year), usually keeping arms and legs covered when outside in the summer (no, partial coverage, yes), skin usually burned or darkened in the summer (yes/no), usually used sunscreen in the summer (yes/no), ever took a trip to a summer climate in the winter (yes/no), ever used a sun lamp or sun bed (yes/no), ever took cod liver oil for at least once a week (yes/no), number of glasses of milk per week (none, <5, 5-9, ≥10), number of servings of salmon or tuna per week (none, <1, 1, >1), and use of vitamin supplements (none, supplements without vitamin D, vitamin D or multivitamins). Each reported outdoor activity was also classified as low, moderate, or high intensity based on various sources of information on metabolic equivalents and participation in activities at each intensity level was considered independently (separate models for low-, moderate-, and high-intensity activities). Models were segregated by body mass index (BMI) status (<25 and ≥25 kg/m^2 for BMI 2 years ago and <21 and ≥21 kg/m^2 for BMI at age 18) and menopausal status (premenopausal and postmenopausal). All tests were two-sided with $P < 0.05$ as the criterion for significance. Analyses were conducted using SAS 9.1.

Results

There were 972 cases and 1,135 controls included in the analysis. The distributions of demographic and other characteristics are shown in Table 1. The age distribution of cases and controls was similar, although cases were slightly older. Cases were also slightly less educated and more likely to be of non-European heritage than controls, although only the ethnic differences were significant after adjustment for age and the other variables. As expected, cases were more likely to have a first-degree family history of breast cancer, to have menarche before age 12, to have no children, or to have not breast-fed children compared with controls. Cases were more likely to report having darker skin than controls.

For vitamin D–related exposures between the ages of 10 and 19 (Table 2), cases had a lower frequency of outdoor activities compared with controls (OR, 0.65; 95% CI, 0.50-0.85, for highest versus lowest quartile; P for trend = 0.0006), were less likely to work outdoors (OR, 0.61; 95% CI, 0.46-0.80 for working outdoors for more than 1 year; P for trend = 0.0006), and spent fewer days per week outdoors (OR, 1.49; 95% CI, 1.00-2.22 for <3 days versus 7 days; P for trend = 0.13). Cases were significantly more likely to cover their limbs compared with controls (OR, 1.68; 95% CI, 1.14-2.50). They were significantly less likely to have their skin darken or burn (OR, 1.55; 95% CI, 1.08-2.24 for skin darkening) or to have taken cod liver oil (OR, 0.76, 95% CI, 0.62-0.92). There was a significant inverse association between milk consumption and breast cancer (OR, 0.62; 95% CI, 0.45, 0.86 for 10 glasses per week or more compared with none; P for trend = 0.0004) and there was a marginal significant trend for reduced risk with increasing salmon and tuna servings per week (P = 0.06). Sunlamp use was associated with reduced risk, but not significantly so. There was no evidence of association between sunscreen use and trips to summer climate in winter from ages 10 to 19 and breast cancer. Vitamin supplement use in general was associated with reduced risk.

Table 1. Characteristics of breast cancer cases and population controls

	Cases (N = 972), no. (%)	Controls (N = 1,135), no. (%)
Age (y)		
20-39	67 (7)	116 (10)
40-49	238 (24)	310 (27)
50-59	355 (37)	387 (34)
60-69	312 (32)	322 (28)
Education		
High school or less	389 (40)	389 (34)
Some university or technical school	332 (34)	422 (37)
University graduate	248 (26)	323 (28)
Ethnicity		
Northern European	633 (67)	791 (72)
Mixed or other European	151 (16)	183 (17)
Non-European	156 (17)	132 (12)
Age at menarche (y)		
≤11	216 (22)	212 (19)
12	253 (26)	303 (27)
13	245 (25)	334 (29)
≥14	258 (27)	286 (25)
Age at first birth (y)		
<20	133 (14)	114 (10)
20-24	282 (29)	360 (32)
25-29	243 (25)	322 (28)
≥30	163 (17)	193 (17)
Nulliparous	151 (16)	146 (13)
Number of births		
None	151 (16)	146 (13)
1	152 (16)	165 (15)
2	385 (40)	444 (39)
≥3	284 (29)	379 (33)
Ever breast-fed		
No	503 (52)	497 (44)
Yes	469 (48)	638 (56)
Menopausal status		
Premenopausal	338 (35)	464 (41)
Postmenopausal	593 (61)	613 (54)
Unknown	41 (4)	58 (5)
Hormone replacement ever use		
No	339 (35)	387 (34)
Yes	632 (65)	735 (65)
Family history of breast cancer*		
No	783 (81)	993 (87)
Yes	189 (19)	142 (13)
BMI (at age 18)		
<20	432 (45)	487 (43)
20.1-24.9	469 (48)	555 (50)
25.0+	58 (6)	79 (7)
BMI (2 years prior to reference age)		
<20	69 (7)	80 (7)
20.1-24.9	401 (41)	487 (43)
25.0-29.9	299 (31)	335 (30)
30.0+	199 (21)	225 (20)
Skin color		
Fair	307 (32)	401 (35)
Light	171 (18)	215 (19)
Light medium	365 (38)	430 (38)
Dark medium/brown/black	127 (13)	89 (8)

*Family history defined as breast cancer in mother, sister, or daughter.

There were similar patterns for exposures between the ages of 20 and 29, but in general, the evidence was weaker (Table 3). Significantly reduced risks were observed for any outdoor activity frequency category above the first quartile, but the trend was less clear. The trend was also not as clear for the number of days spent outside. Cases were more likely to keep their limbs covered compared with controls (OR, 1.68; 95% CI, 1.20-2.37) and milk consumption was still significantly associated with reduced risk (OR, 0.63; 95% CI, 0.47-0.83 for 10 glasses per week or more compared with none; P for trend = 0.0006). There was little evidence for association between vitamin D exposure during ages 45 to 54 and breast cancer (Table 4).

There were no apparent differences in the results between premenopausal and postmenopausal women and also between BMI subgroups according to BMI 2 years ago or at age 18 (data not shown). As there were differences in the proportion who were non-European among cases and controls, although the majority in both groups were European, we also restricted the analysis to Europeans only. Again, there were no major differences in the results (data not shown). Finally, we coded all the outdoor activities as low, moderate, or high intensity (Table 5). Overall, it does not seem that the reduced risk observed to be associated with outdoor activities was primarily associated with the degree of physical activity involved, but there was some suggestion of a stronger effect associated with a higher degree of physical activity.

Discussion

In this population-based case-control study, we found evidence to support an inverse association between vitamin D–related variables and breast cancer in women up to age 69. However, the observed relationship depended on the timing of exposure. In this study, there was consistent evidence of reduced risks associated with sun exposure and dietary sources of vitamin D (milk, salmon and tuna, and cod liver oil) during adolescent development. Some evidence was also observed for exposures occurring during ages 20 to 29, but there was little evidence of a relationship between perimenopausal exposures and breast cancer.

Sun exposure is a major source of vitamin D with evidence from both *in vitro* and *in vivo* studies that high levels of vitamin D can be obtained from less than a minimal erythemal dose (slight reddening of the skin) of sunlight (4, 18). Vitamin D production also reaches a maximum, and this can occur in half an hour in light-colored skin, although longer is required for darker skin (19). At northern latitudes, this only occurs during the summer (20), and clothing coverage also reduces levels of vitamin D (21). We did not find any relationship with trips to a summer climate during winter, although the frequency and duration of such trips may have had a limited effect on long-term levels of 25-hydroxyvitamin D. Some types of fish also contain significant amounts of vitamin D, including salmon and tuna (~360 and 200 IU per serving, respectively; NIH Office of Dietary Supplements), although it was rarely eaten more than once a week in our population. Fortified milk contains ~100 IU per cup, but the true value can vary (22).

Table 2. ORs and 95% CIs for an association between vitamin D–related exposure variables at ages 10 to 19 (sun exposure and dietary vitamin D) and breast cancer in cases and controls

	Cases (%)	Controls (%)	OR* (95% CI)	OR† (95% CI)
Days outside per week‡				
<3	68 (7)	47 (4)	1.69 (1.15-2.49)	1.49 (1.00-2.22)
3-4	64 (7)	62 (5)	1.26 (0.87-1.81)	1.23 (0.85-1.80)
5-6	130 (14)	185 (13)	0.86 (0.67-1.10)	0.82 (0.63-1.06)
7	700 (73)	835 (74)	1.00	1.00
P for trend				0.13
Outdoor activity episodes§				
<828	266 (29)	263 (24)	1.00	1.00
828-1,295	238 (26)	265 (24)	0.90 (0.71-1.16)	0.87 (0.67-1.12)
1,296-2,039	218 (24)	287 (26)	0.76 (0.59-0.97)	0.74 (0.57-0.96)
2,040+	181 (20)	285 (26)	0.65 (0.50-0.83)	0.65 (0.50-0.85)
P for trend				<0.0006
Outdoor job				
Never	809 (83)	846 (75)	1.00	1.00
1 y	67 (7)	114 (10)	0.65 (0.47-0.89)	0.69 (0.50-0.96)
≥1 y	96 (10)	175 (15)	0.58 (0.44-0.75)	0.61 (0.46-0.80)
P for trend				<0.0001
Limbs covered				
No	730 (76)	937 (83)	1.00	1.00
Partial	160 (17)	149 (13)	1.36 (1.06-1.73)	1.36 (1.06-1.75)
Yes	73 (8)	49 (4)	1.85 (1.27-2.70)	1.68 (1.14-2.50)
P for trend				0.0008
Skin burned/darkened				
No	82 (9)	59 (5)	1.65 (1.16-2.33)	1.55 (1.08-2.24)
Yes	881 (91)	1,073 (95)	1.00	1.00
Sunscreen use				
No	895 (94)	1,051 (94)	1.00	1.00
Yes	58 (6)	73 (6)	1.01 (0.70-1.45)	1.04 (0.72-1.51)
Sun trip in winter				
No	779 (86)	907 (80)	1.00	1.00
Yes	127 (14)	180 (16)	0.91 (0.70-1.73)	1.00 (0.77-1.30)
Sunlamp Use				
No	912 (94)	1,036 (91)	1.00	1.00
Yes	60 (6)	99 (9)	0.72 (0.52-1.01)	0.81 (0.57-1.14)
Cod liver oil use				
No	618 (64)	682 (61)	1.00	1.00
Yes	342 (36)	444 (39)	0.77 (0.64-0.93)	0.76 (0.62-0.92)
Milk (glasses/wk)				
None	119 (12)	85 (7)	1.00	1.00
<5	129 (13)	110 (10)	0.89 (0.61-1.30)	0.95 (0.64-1.41)
5-9	224 (23)	266 (23)	0.62 (0.45-0.87)	0.67 (0.48-0.95)
≥10	500 (51)	674 (59)	0.54 (0.40-0.74)	0.62 (0.45-0.86)
P for trend				0.0004
Intake of salmon or tuna per week				
None	273 (28)	286 (25)	1.00	1.00
<1	269 (28)	267 (24)	1.05 (0.83-1.33)	1.10 (0.86-1.41)
1	285 (29)	382 (34)	0.77 (0.61-0.97)	0.82 (0.65-1.04)
>1	145 (15)	200 (18)	0.76 (0.58-0.99)	0.86 (0.64-1.14)
P for trend				0.06
Supplement use				
Vitamin D or multivitamins	145 (15)	252 (22)	0.60 (0.48-0.76)	0.62 (0.49-0.79)
Other vitamin supplements	69 (7)	129 (11)	0.54 (0.40-0.73)	0.53 (0.39-0.73)
None	758 (78)	754 (66)	1.00	1.00

*ORs with 95% CIs adjusted for reference age.
†ORs with 95% CIs adjusted for reference age, ethnicity, family history in first-degree relatives, ever breast-fed, education, age menarche, and age at first birth.
‡Number of days outside for at least half an hour during the summer (June, July, and August).
§Number of outdoor activity episodes derived from reported outdoor activities done for at least 30 min between 9 a.m. and 5 p.m. at least once per month during June, July, and August along with frequency (days per week or month) and duration (number of years).

Fortification of milk with vitamin D has been mandatory in Canada only since 1975, but did occur voluntarily prior to this. Cod liver oil has been a traditional source of vitamin D, particularly for children, and the amount received was ~400 IU per teaspoon (8).

The epidemiologic evidence to date regarding vitamin D and breast cancer has been recently reviewed (1, 2). In the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, measures of sunlight exposure and dietary vitamin D intake were consistently associated with reduced risk of breast cancer, although the power was limited and many of the estimates did not reach statistical significance (15). In the NHS cohort, there was evidence of decreasing risk associated with increasing dietary or total vitamin D intake, but only in premenopausal women (16). Consistent with the present study, a highly significant inverse trend was observed between the number of glasses of milk consumed and breast cancer, again in premenopausal women only. We did not observe differences between premenopausal and postmenopausal women; however, we only observed a relationship with milk consumption in adolescence and early adulthood. In the NHS study, women with premenopausal cancer would more likely be reporting consumption earlier in adulthood compared with the postmenopausal cases. Consistent with this pattern is the weaker evidence for an association between milk drinking, dietary vitamin D, or total vitamin D, and breast cancer among postmenopausal women in the Cancer Prevention Study II Nutrition Cohort, although the relationship seemed to be stronger in estrogen receptor–positive cases (23). Also in the NHS, cases had lower circulating 25(OH)D levels compared with controls in a nested study, although the trend across quintiles was not quite significant (17). However, the majority of these women were postmenopausal.

Both the original NHS and the NHS II assessed diet during high school in some participants. In the NHS I, there was no relationship (relative risk estimates close to 1.00) between the number of glasses of milk consumed during adolescence and breast cancer (24). The relationship between milk consumption and breast cancer was not specifically reported for NHS II (25). Dietary vitamin D intake was not associated with breast cancer in either study, but it was not clear whether additional sources of vitamin D, such as cod liver oil, were included. Vitamin D was not a primary variable of interest in either analysis.

Accuracy of recall is always a concern in any case-control study. The reproducibility of sun exposure–related questions has been examined in a number of studies over time periods ranging from a few weeks to several years (26-28). In general, these studies have found evidence that sun exposure and outdoor activities, both recent as well as in childhood and adolescence, could be reasonably consistently recalled. The most recent study also compared questionnaire responses to circulating levels of 25(OH)D and showed significant relationships between reported time in the sun and outdoor activities over the past 3 years and 25(OH)D levels (28). It should be

Table 3. ORs and 95% CIs for an association between vitamin D–related exposure variables at ages 20 to 29 (sun exposure and dietary vitamin D) and breast cancer in cases and controls

	Cases (%)	Controls (%)	OR* (95% CI)	OR† (95% CI)
Days outside per week‡				
<3	161 (17)	128 (11)	1.49 (1.15-1.93)	1.40 (1.07-1.84)
3-4	106 (11)	148 (13)	0.85 (0.65-1.12)	0.86 (0.65-1.14)
5-6	132 (14)	209 (19)	0.74 (0.58-0.95)	0.72 (0.56-0.93)
7	557 (58)	645 (57)	1.00	1.00
P for trend				0.17
Outdoor activity episodes§				
<480	251 (28)	230 (21)	1.00	1.00
480-869	206 (23)	291 (26)	0.65 (0.50-0.83)	0.65 (0.50-0.85)
870-1,319	227 (25)	285 (26)	0.72 (0.56-0.92)	0.72 (0.55-0.93)
1,320+	207 (23)	293 (27)	0.64 (0.49-0.82)	0.65 (0.50-0.85)
P for trend				0.005
Outdoor job				
Never	893 (92)	1,043 (92)	1.00	1.00
1 y	33 (3)	40 (4)	1.04 (0.65-1.67)	1.06 (0.65-1.74)
≥1 y	46 (5)	52 (5)	1.11 (0.74-1.68)	1.22 (0.80-1.86)
P for trend				0.35
Limbs covered				
No	696 (72)	875 (77)	1.00	1.00
Partial	176 (18)	192 (17)	1.16 (0.92-1.46)	1.13 (0.89-1.42)
Yes	93 (10)	67 (6)	1.75 (1.26-2.44)	1.68 (1.20-2.37)
P for trend				0.004
Skin burned/darkened				
No	76 (8)	79 (7)	1.15 (0.83-1.60)	1.06 (0.75-1.49)
Yes	888 (92)	1,056 (93)	1.00	1.00
Sunscreen use				
No	751 (79)	836 (74)	1.00	1.00
Yes	205 (21)	290 (26)	0.85 (0.68-1.04)	0.89 (0.72-1.11)
Sun trip in winter				
No	626 (67)	731 (66)	1.00	1.00
Yes	313 (33)	379 (34)	1.02 (0.85-1.23)	1.05 (0.86-1.28)
Sunlamp Use				
No	869 (89)	981 (86)	1.00	1.00
Yes	104 (11)	154 (14)	0.86 (0.65-1.13)	0.88 (0.66-1.18)
Cod liver oil use				
No	945 (98)	1,101 (98)	1.00	1.00
Yes	15 (2)	25 (2)	0.70 (0.36-1.33)	0.61 (0.31-1.21)
Milk (glasses/wk)				
None	163 (17)	126 (11)	1.00	1.00
<5	193 (20)	187 (16)	0.83 (0.61-1.13)	0.81 (0.57-1.11)
5-9	251 (26)	320 (28)	0.62 (0.46-0.82)	0.64 (0.48-0.87)
≥10	365 (38)	502 (44)	0.57 (0.43-0.74)	0.63 (0.47-0.83)
P for trend				0.0006
Intake of salmon or tuna per week				
None	158 (16)	177 (16)	1.00	1.00
<1	304 (31)	324 (29)	1.04 (0.80-1.36)	1.07 (0.81-1.41)
1	299 (31)	390 (34)	0.83 (0.64-1.08)	0.90 (0.68-1.19)
>1	211 (22)	244 (22)	0.95 (0.72-1.26)	1.04 (0.77-1.40)
P for trend				0.77
Supplement use				
Vitamin D or multivitamins	271 (28)	404 (36)	0.65 (0.53-0.79)	0.67 (0.54-0.82)
Other vitamin supplements	149 (15)	222 (20)	0.64 (0.50-0.81)	0.69 (0.53-0.88)
None	552 (57)	509 (45)	1.00	1.00

*ORs with 95% CIs adjusted for reference age.
†ORs with 95% CIs adjusted for reference age, ethnicity, family history in first-degree relatives, ever breast-fed, education, age menarche, and age at first birth.
‡Number of days outside for at least half an hour during the summer (June, July, and August).
§Number of outdoor activity episodes derived from reported outdoor activities done for at least 30 min between 9 a.m. and 5 p.m. at least once per month during June, July, and August along with frequency (days per week or month) and duration (number of years).

Table 4. ORs and 95% CIs for an association between vitamin D–related exposure variables at ages 45 to 54 (sun exposure and dietary vitamin D) and breast cancer in cases and controls

	Cases (%)	Controls (%)	OR* (95% CI)	OR† (95% CI)
Days outside per week‡				
<3	120 (16)	93 (11)	1.45 (1.07-1.97)	1.29 (0.94-1.76)
3-4	123 (16)	137 (16)	1.01 (0.77-1.34)	1.00 (0.75-1.33)
5-6	115 (15)	145 (17)	0.89 (0.68-1.18)	0.86 (0.65-1.15)
7	414 (53)	462 (56)	1.00	1.00
P for trend				0.27
Outdoor activity episodes§				
<270	82 (11)	86 (11)	1.00	1.00
270-599	141 (18)	149 (20)	1.00 (0.68-1.46)	1.01 (0.68-1.50)
600-1,076	213 (33)	268 (30)	0.83 (0.58-1.18)	0.80 (0.55-1.15)
1,077+	271 (38)	309 (38)	0.91 (0.64-1.28)	0.91 (0.64-1.31)
P for trend				0.59
Outdoor job				
Never	728 (91)	795 (90)	1.00	1.00
1 y	15 (2)	20 (2)	0.82 (0.41-1.64)	0.82 (0.41-1.64)
≥1 y	60 (7)	74 (8)	0.89 (0.62-1.28)	0.89 (0.62-1.28)
P for trend				0.47
Limbs covered				
No	441 (57)	507 (60)	1.00	1.00
Partial	184 (24)	191 (23)	1.11 (0.87-1.41)	1.13 (0.88-1.45)
Yes	152 (20)	144 (17)	1.23 (0.95-1.60)	1.22 (0.93-1.60)
P for trend				0.13
Skin burned/darkened				
No	102 (13)	93 (11)	1.22 (0.90-1.64)	1.24 (0.91-1.68)
Yes	678 (87)	749 (89)	1.00	1.00
Sunscreen use				
Yes	377 (47)	411 (55)	0.73 (0.60-0.89)	0.78 (0.64-0.96)
No	466 (53)	368 (45)	1.00	1.00
Sun trip in winter				
No	432 (52)	376 (49)	1.00	1.00
Yes	402 (48)	411 (51)	0.89 (0.73-1.08)	0.93 (0.76-1.13)
Sunlamp use				
No	681 (85)	733 (82)	1.00	1.00
Yes	122 (15)	156 (18)	0.88 (0.67-1.14)	0.84 (0.64-1.11)
Cod liver oil use				
No	770 (97)	845 (96)	1.00	1.00
Yes	23 (3)	37 (4)	0.70 (0.41-1.19)	0.69 (0.40-1.19)
Milk (glasses/wk)				
None	152 (19)	153 (18)	1.00	1.00
<5	186 (24)	188 (22)	1.00 (0.74-1.35)	0.95 (0.69-1.30)
5-9	215 (27)	249 (29)	0.87 (0.65-1.16)	0.85 (0.63-1.15)
≥10	230 (29)	264 (31)	0.87 (0.66-1.16)	0.90 (0.67-1.21)
P for trend				0.42
Intake of salmon or tuna per week				
None	69 (9)	69 (8)	1.00	1.00
<1	228 (29)	244 (28)	0.94 (0.64-1.37)	0.98 (0.66-1.45)
1	228 (29)	291 (34)	0.77 (0.53-1.13)	0.84 (0.57-1.24)
>1	258 (33)	250 (29)	1.02 (0.70-1.48)	1.19 (0.81-1.77)
P for trend				0.20
Supplement use				
Vitamin D	76 (9)	99 (11)	0.82 (0.58-1.16)	0.84 (0.59-1.19)
Multivitamins	347 (43)	376 (42)	0.99 (0.79-1.24)	0.99 (0.79-1.25)
Other vitamin supplements	124 (15)	144 (16)	0.92 (0.68-1.23)	0.86 (0.63-1.17)
None	256 (32)	270 (30)	1.00	1.00

*ORs with 95% CIs adjusted for reference age.
†ORs with 95% CIs adjusted for reference age, ethnicity, family history in first-degree relatives, ever breast-fed, education, age menarche, and age at first birth.
‡Number of days outside for at least half an hour during the summer (June, July, and August).
§Number of outdoor activity episodes derived from reported outdoor activities done for at least 30 min between 9 a.m. and 5 p.m. at least once per month during June, July, and August along with frequency (days per week or month) and duration (number of years).

noted that in all these studies, the questions tended to focus on total time in the sun and sun damage to the skin as the original questionnaires were developed for studies of melanoma. In our study, the questionnaire was designed specifically to evaluate vitamin D. As high or even maximal levels of 25(OH)D can be reached in less than half an hour for a light-skinned person with high skin exposure in the sun (i.e., with arms and legs exposed; refs. 4, 18, 19), we did not request total number of hours in the sun, but instead focused on the frequency at which reasonably high levels of vitamin D exposure could be achieved (e.g., number of days or activities per week involving at least half an hour outdoors in the summer). Note that in Ontario, very little vitamin D would be obtained in the winter from sun exposure (20). Although it is unlikely that individuals can recall exactly how much time they spent outside or how much milk they drank, it is likely that we are able to adequately distinguish those who spent very little time outdoors or drank little or no milk from those who spent considerable time outdoors or drank milk on a regular basis.

Biased recall or differential recall between cases and controls is also a concern. Although we cannot be sure that this did not occur, at the time the study was conducted, there was little information regarding vitamin D in the media and none regarding a potential relationship between vitamin D or sun exposure and breast cancer. Most public sun exposure information was related to the dangers of sun exposure with respect to skin cancer. There is also the potential for selection bias in case-control studies. We had some concern regarding the higher proportion of non-Europeans among the case participants compared with control participants (17% versus 12%). Although all models adjusted for ethnicity, we also repeated the analyses in Europeans only and found no difference in the results.

The evidence thus far has been suggestive of an inverse relationship between vitamin D and breast cancer. We now present the results of a relatively large, population-based study that was specifically designed to address the relationship between vitamin D and breast cancer. In this study, we found strong evidence to support the hypothesis that vitamin D could help to prevent breast cancer. We also found that exposures during adolescence, a critical period in breast development, were the most consistently related to breast cancer. This finding, in particular, should be replicated. It is possible that some of the apparent benefit from sun exposure could be due to the increased physical activity associated with outdoor activities, although not all outdoor activities involved exercise. These activities included time spent outdoors sunbathing or at picnics. When we separated the activities into those of low, moderate, and high intensity, an inverse relationship persisted in all three categories. However, it is possible that the combined effect of physical activity and sun exposure could result in greater benefit. This question needs further evaluation.

Concern is frequently expressed regarding the potential for confusion among the public with respect to the risks and benefits of sun exposure. However, in truth, a recommendation of moderation may be more achievable than compete avoidance (29, 30). Relatively short sun exposure time will maximize vitamin D generation, although the amount of vitamin D produced in a given time depends on the degree of skin coverage and skin color. The use of sunscreen in

Table 5. ORs and 95% CIs for an association between low-, moderate-, and high-intensity outdoor activity episodes at ages 10 to 19, 20 to 29, and 45 to 54, and breast cancer in cases and controls

	Cases (%)	Controls (%)	OR* (95% CI)	OR† (95% CI)
Low-intensity outdoor activity‡				
Ages 10-19				
<1	285 (31)	250 (23)	1.00	1.00
1-98	215 (23)	259 (24)	0.76 (0.59-0.97)	0.80 (0.61-1.04)
99-313	216 (23)	287 (26)	0.69 (0.54-0.88)	0.76 (0.58-0.99)
314+	209 (23)	295 (27)	0.65 (0.51-0.83)	0.69 (0.53-0.91)
Ages 20-29				
<1	295 (32)	302 (27)	1.00	1.00
1-80	188 (20)	237 (21)	0.83 (0.65-1.07)	0.88 (0.68-1.15)
81-240	268 (29)	337 (31)	0.83 (0.66-1.04)	0.90 (0.70-1.14)
241+	179 (19)	229 (21)	0.81 (0.63-1.05)	0.85 (0.65-1.11)
Ages 45-54				
<64	93 (23)	108 (23)	1.00	1.00
64-143	100 (25)	115 (25)	1.01 (0.69-1.49)	1.04 (0.70-1.56)
144-287	97 (24)	116 (25)	0.97 (0.66-1.43)	0.90 (0.60-1.36)
288+	114 (28)	124 (27)	1.07 (0.73-1.56)	1.01 (0.68-1.50)
Moderate-intensity outdoor activity‡				
Ages 10-19				
<295	263 (28)	246 (22)	1.00	1.00
295-672	226 (24)	297 (27)	0.72 (0.56-0.92)	0.70 (0.54-0.90)
673-840	253 (27)	272 (25)	0.87 (0.68-1.12)	0.87 (0.67-1.12)
841+	187 (20)	287 (26)	0.60 (0.47-0.78)	0.58 (0.44-0.76)
Ages 20-29				
<225	275 (29)	236 (21)	1.00	1.00
225-540	234 (25)	292 (26)	0.69 (0.54-0.88)	0.74 (0.57-0.95)
541-840	237 (25)	304 (27)	0.66 (0.52-0.85)	0.68 (0.53-0.88)
841+	191 (20)	280 (25)	0.57 (0.44-0.73)	0.59 (0.45-0.77)
Ages 45-54				
<240	94 (14)	116 (15)	1.00	1.00
240-504	182 (27)	195 (25)	1.14 (0.81-1.60)	1.10 (0.77-1.56)
504-839	144 (21)	170 (22)	1.03 (0.73-1.47)	0.98 (0.68-1.41)
840+	260 (38)	302 (39)	1.04 (0.75-1.44)	0.99 (0.70-1.38)
High-intensity outdoor activity‡				
Ages 10-19				
<141	290 (31)	222 (20)	1.00	1.00
141-416	223 (24)	285 (26)	0.61 (0.48-0.79)	0.62 (0.47-0.80)
417-840	216 (23)	300 (27)	0.56 (0.44-0.72)	0.57 (0.44-0.74)
841+	205 (22)	295 (27)	0.55 (0.43-0.710	0.59 (0.45-0.77)
Ages 20-29				
<1	295 (32)	257 (23)	1.00	1.00
1-120	229 (24)	291 (26)	0.71 (0.56-0.90)	0.75 (0.59-0.97)
121-324	200 (21)	261 (24)	0.68 (0.53-0.88)	0.75 (0.57-0.97)
325+	211 (23)	297 (27)	0.65 (0.51-0.83)	0.70 (0.54-0.90)
Ages 45-54				
<48	67 (15)	72 (13)	1.00	1.00
48-119	80 (18)	87 (16)	0.99 (0.63-1.56)	0.96 (0.60-1.53)
120-269	129 (29)	163 (30)	0.84 (0.56-1.27)	0.77 (0.51-1.18)
270+	174 (39)	224 (41)	0.83 (0.56-1.22)	0.79 (0.53-1.18)

*ORs with 95% CIs adjusted for reference age.

†ORs with 95% CIs adjusted for reference age, ethnicity, family history in first-degree relatives, ever breast-fed, education, age menarche, and age at first birth.

‡Number of outdoor activity episodes derived from reported outdoor activities done for at least 30 min between 9 a.m. and 5 p.m. at least once per month during June, July, and August along with frequency (days per week or month) and duration (number of years) and classified as low, moderate, or high intensity.

adolescence could not be adequately assessed in this study as it was relatively rare in these mostly older women. Sunlamp use is controversial (29), but was also quite rare in the youngest age group in this study. There was an inverse association, but it was not statistically significant for either age 10 to 19 or age 20 to 29. Dietary sources of vitamin D are more limited and generally provide a lower dose. However, sources such as low-fat milk may be useful, particularly in the winter. Fatty fish such as salmon, and to a lesser extent tuna, also contribute vitamin D, but are generally not eaten frequently. We were only able to crudely assess vitamin D supplements other than cod liver oil, and further work on the role of supplements is needed. Interestingly, cod liver oil exhibited a similar inverse association at all ages, although only significant early in life, likely because it was rarely taken in adulthood.

Research into the relationship between breast cancer and vitamin D and vitamin D–related lifestyle factors such as sun and milk consumption create new opportunities in breast cancer prevention in which few potentially modifiable risk factors are known. However, the timing of exposure seems to be important and additional work will be needed to meet the challenge of assessing etiology and prevention earlier in life.

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