Vitamin D and calcium intakes and breast cancer risk in pre- and postmenopausal women[1–3]

Laura N Anderson, Michelle Cotterchio, Reinhold Vieth, and Julia A Knight

ABSTRACT

Background: Some evidence suggests that vitamin D may reduce breast cancer risk. Despite the biological interaction between vitamin D and calcium, few studies have evaluated their joint effects on breast cancer risk.

Objective: The objective was to evaluate the associations and potential interaction between vitamin D and calcium (from food and supplements) and breast cancer risk in a population-based case-control study.

Design: Breast cancer cases aged 25–74 y (diagnosed 2002–2003) were identified through the Ontario Cancer Registry. Controls were identified by using random digit dialing; 3101 cases and 3471 controls completed epidemiologic and food-frequency questionnaires. Adjusted odds ratios (ORs) and 95% CIs were estimated by using multivariate logistic regression.

Results: Vitamin D and calcium intakes from food only and total combined intakes (food and supplements) were not associated with breast cancer risk, although the mean intake of vitamin D was low. Vitamin D supplement intake >10 μg/d (400 IU/d) compared with no intake was associated with a reduced risk of breast cancer (adjusted OR: 0.76; 95% CI: 0.59, 0.98). No categories of calcium supplement intake were significantly associated with reduced breast cancer risk, but a significant inverse trend was observed ($P = 0.04$). There were no significant interactions involving vitamin D, calcium, or menopausal status.

Conclusions: No associations were found between overall vitamin D or calcium intake and breast cancer risk. Vitamin D from supplements was independently associated with reduced breast cancer risk. Further research is needed to investigate the effects of higher doses of vitamin D and calcium supplements. *Am J Clin Nutr* doi: 10.3945/ajcn.2009.28869.

INTRODUCTION

Breast cancer is the most common cancer among Canadian women (1), and few modifiable risk factors have been identified (eg, alcohol consumption, hormone replacement therapy, and obesity among postmenopausal women) (2–4). Several review articles concluded that, despite inconsistencies in the literature and identified areas that still require investigation, low vitamin D intake may also increase breast cancer risk (5–11). One meta-analysis found no overall association between vitamin D, from diet and supplements, and breast cancer risk, but did suggest that an inverse association might exist at higher intakes (12). Vitamin D is synthesized in the skin after sufficient ultraviolet B exposure from sunlight and is found in some foods (eg, fortified milk and fatty fish) and vitamin supplements (13). Vitamin D (from diet and sunlight) is hydroxylated by the liver to the circulating form, ie, 25-hydroxyvitamin D [25(OH)D]—the preferred biomarker for vitamin D. A second hydroxylation in the kidney or in other cells, including breast cells, produces the active hormone 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. The vitamin D receptor is present in many cells, including normal and cancerous breast cells, which enables these cells to respond to 1,25$(OH)_2$D (14–16). Laboratory studies have shown that 1,25$(OH)_2$D promotes cell differentiation and inhibits cell growth (14–17). Some studies of 25(OH)D and breast cancer risk have found an inverse association (18–21), although not all have (22–24).

It is well established that 1,25$(OH)_2$D regulates calcium metabolism and that vitamin D and calcium are found in some of the same foods (eg, vitamin D–fortified milk). Calcium may also have anticarcinogenic properties that include regulation of cell differentiation, proliferation, and apoptosis (25–27). However, results from epidemiologic studies do not strongly support an inverse association between calcium, or more generally dairy products, and breast cancer risk (8, 28–32). The Women's Health Initiative trial—in which postmenopausal women were randomly assigned to 10 μg (400 IU) vitamin D and 1000 mg Ca daily or a placebo—found no reduction in breast cancer risk after a mean follow-up time of 7 y (22). Few observational studies of dietary vitamin D and breast cancer risk have investigated the interaction between calcium and vitamin D (33–35).

Currently, it is unclear whether the possible association between dietary vitamin D and reduced breast cancer risk is confounded or modified by calcium and vice versa. Furthermore,

[1] From Population Studies and Surveillance, Cancer Care Ontario, Toronto, Canada (LNA and MC); the Dalla Lana School of Public Health, University of Toronto, Toronto, Canada (LNA, MC, and JAK); the Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Canada (RV); and the Prosserman Centre for Health Research, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Canada (JAK).

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[3] Address correspondence to LN Anderson, Population Studies and Surveillance, Cancer Care Ontario, 620 University Avenue, Toronto, ON M5G 2L7, Canada. E-mail: laura.anderson@cancercare.on.ca.

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limited evidence suggests that the association between dietary vitamin D and breast cancer risk may (34, 35) or may not (36, 37) differ by menopausal status. The objectives of this study were to evaluate the associations and potential interaction between vitamin D and calcium (from food and supplements) and breast cancer risk in a population-based case-control study of pre- and postmenopausal women in Ontario.

SUBJECTS AND METHODS

Data were collected as part of the Ontario Women's Diet and Health Study—a large population-based case-control study that evaluated various epidemiologic factors and breast cancer risk (38). The study protocols for this study were approved by the University of Toronto Research Ethics Board.

Cases

Cases were women aged 25–74 y with a first pathologically confirmed cancer of the breast identified from the Ontario Cancer Registry and diagnosed between June 2002 and April 2003. The Ontario Cancer Registry is a population-based registry that obtains information from nearly all breast cancer cases in the province in Ontario (39, 40). Physician cooperation was required to contact patients and to obtain contact information and vital status. Consent was obtained for 4109 eligible cases (96%). The average time between diagnosis and interview was 11 mo, with a range (5th to 95th percentile) from 7 to 18 mo.

Controls

Random digit-dialing methods were used to identify eligible controls among households in Ontario and were frequency-matched (1:1) within 5-y age groups to the identified cases, described in detail elsewhere (38). Only one woman from each household was randomly selected for inclusion in the study. Approximately 25,250 households were telephoned; ≈17,000 of these households were ineligible (eg, no woman between the ages of 25 and 74 y with no history of breast cancer), 2000 did not answer the phone, and 2000 refused (eligibility of these households is unknown). Of the 4352 households for which an eligible woman was identified, 250 women refused, and 4102 women (94%) agreed to participate.

Data collection and response rate

Cases and controls were mailed an epidemiologic questionnaire and food-frequency questionnaire (FFQ). The epidemiologic questionnaire consisted of 79 questions and collected information on lifestyle, reproductive, and medical history factors. These questionnaires were completed and returned by 3101 cases (75% response rate) and 3471 controls (80% response rate).

Measurement of vitamin D and calcium

A modified Block FFQ measured 178 foods and supplements and requested data on both frequency of consumption and portion size for all foods and frequency and duration of use for supplements. The validity and reliability of the Block FFQ have been assessed in a random sample of Ontario women (41). The reliability was high; the nondeattenuated Pearson correlation coefficient for vitamin D was 0.76 (95% CI: 0.66, 0.83) and for calcium was 0.80 (95% CI: 0.71, 0.86). The validity of the FFQ, compared with a 24-h recall, was also moderately high for vitamin D (deattenuated Pearson correlation coefficient: 0.54; 95% CI: 0.29, 0.79) and for calcium ($r = 0.71$; 95% CI: 0.35, 1.00) (41). Cases and controls were asked about their consumption of food and supplements 2 y before the time of questionnaire to reduce any bias due to changes in diet after cancer diagnosis. Nutrient analysis was conducted by using the Block Dietary Data Systems with nutrient values from the US Department of Agriculture Nutrient Database for Standard Reference and national data on food consumption (third National Health and Nutrition Examination Survey and the Continuing Survey of Food Intakes by Individuals II) (42, 43). In the modified version of the FFQ used for this study, 2 questions were added to better capture vitamin D intake: type of fish most often consumed (fatty or white fish) and use of vitamin D supplements or cod liver oil. The nutrient analysis specific to vitamin D was modified to account for these additional items and food fortification differences between Canada and the United States. Calcium supplement use, alone or combined with something else, was measured; however, data on combined calcium plus vitamin D supplements were not available.

Derived variables from the Block nutrient analysis were obtained for daily intake of vitamin D and calcium, from all foods and from supplements (single-product supplements, multivitamins, or cod liver oil for vitamin D). A combined total intake measure (foods plus supplements) was also created. In addition to the derived total nutrient values for vitamin D and calcium (from foods, supplements, and total), the following individual foods rich in vitamin D and/or calcium and vitamin supplement sources were individually examined: milk, fish, margarine, single-product supplement measures of vitamin D (or cod liver oil) and calcium (alone or combined with something else), and regular one-a-day multiple vitamins. Individual food intakes were calculated as servings per day, week, or month (depending on the frequency of consumption).

Measurement of other variables

The following variables were tested as potential confounders: marital status, education, ethnicity, body mass index (BMI), smoking status, pack-years smoked, breastfeeding history, breastfed as an infant, age at menarche, oral contraceptive use, oral contraceptive duration, parity, age at first live birth, age at menopause, hormone replacement therapy (HRT; postmenopausal women only), duration of HRT, history of benign breast disease, family history of breast cancer, screening mammogram, alcoholic drinks, dietary fat intake, calorie intake, phytoestrogen intake, physical activity (strenuous, moderate, and daily) at selected periods of life (teenage years, 20–39 y, 40–59 y, and 60–75 y), and sun-exposure variables (time spent outdoors, location of residence, skin color, and sun protection practices) at selected periods of life (teenage years, 20–39 y, 40–59 y, and 60–75 y).

Statistical data analysis

Unconditional logistic regression analysis was used to obtain age-adjusted odds ratios (ORs) and 95% CIs for all vitamin D and

calcium variables (at both the food and nutrient level). Age was calculated as age at diagnosis for breast cancer cases and age at midpoint of recruitment for controls. Confounders were defined as any variable that changed the OR of the exposure variable by >10% when added to the model (44). None of the variables met our definition of a confounder; however, to be conservative, we also constructed multivariate models that adjusted for age, education, age at menarche, age at first live birth, parity, menopausal status, breast cancer in first-degree relative, total energy intake, BMI, pack-years smoked, moderate physical activity during ages 20–30 y, moderate physical activity during ages 40–59 y, time spent outdoors per week during ages 20–39 y, time spent outdoors per week during ages 40–59 y, total calcium intake (included in the models of vitamin D variables only), and total vitamin D intake (included in the models of calcium variables only). Test for linear trend was calculated by treating the median intake for each exposure category as a continuous variable in the age-adjusted and fully adjusted logistic regression models. Tests for multiplicative interactions were calculated by using the likelihood ratio test. To assess the interaction between vitamin D and calcium, calcium was categorized into 2 categories: high and low intakes (because calcium and vitamin D intakes were highly correlated, which resulted in small numbers in the extreme categories, eg, lowest vitamin D and highest calcium). Stratified results are presented by calcium intake and menopausal status. Interactions between vitamin D or calcium intake and BMI and hormone replacement were also tested. Statistical significance was defined as a P value <0.05, and all tests were 2-sided. All statistical analyses were conducted by using SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Overall, 6572 (3101 cases and 3471 controls) women completed the questionnaires. The mean (± SD) age of the study participants was 56 ± 11 y. Most of the women in this study (90%) were white, and many had postsecondary education (46% of cases and 49% of controls). The characteristics of the cases and controls and age-group adjusted ORs for selected factors that may be associated with breast cancer risk or vitamin D status are shown in **Table 1** and were described previously (38).

No significant ORs were observed between milk, margarine, dairy, or fish intake and breast cancer risk (**Table 2**). However, OR point estimates increased with milk intake (P for trend = 0.04). Single-product vitamin D supplements or cod liver oil were used by only 13% of cases and 14% of controls, and, although no categories of frequency or duration of use were significantly associated with breast cancer risk, a significant inverse dose-response relation was observed between frequency of supplement use and breast cancer risk (P for trend = 0.04). Calcium supplement use was more common (33% of cases and 35% of controls) and, similar to vitamin D supplement use, none of the categories of intake for either frequency or duration were significant, but the OR point estimates decreased with frequency of calcium supplement use (P for trend = 0.04). Neither frequency nor duration of multivitamin use was associated with breast cancer risk.

Results for the vitamin D and calcium nutrient-level variables (intake from foods only, supplements only, and total combined)

TABLE 1
Distribution of selected characteristics and age group–adjusted odds ratio (OR) estimates in 3101 breast cancer cases and 3471 controls in the Ontario Women's Diet and Health Study[1]

Variable	Cases	Controls	Model 1[2]
	n (%)	*n* (%)	
Age group[3]			
25–39 y	181 (6)	316 (9)	NA
40–44 y	278 (9)	367 (11)	
45–49 y	380 (12)	482 (14)	
50–54 y	504 (16)	512 (15)	
55–59 y	511 (16)	470 (14)	
60–64 y	450 (15)	471 (14)	
65–69 y	439 (14)	508 (15)	
70–74 y	358 (12)	345 (10)	
Breast cancer in a first-degree relative			
No	2389 (77)	2973 (86)	1.00
Yes	635 (21)	415 (12)	1.86 (1.63, 2.13)
Age at menarche			
≤11 y	594 (20)	615 (18)	1.00
12 y	753 (25)	823 (25)	0.95 (0.81, 1.10)
13 y	846 (28)	973 (29)	0.90 (0.80, 1.04)
≥14 y	782 (26)	939 (28)	0.86 (0.74, 0.99)
Age at menopause[4]			
≤45 y	572 (19)	727 (21)	1.00
45–49 y	511 (17)	550 (16)	1.15 (0.98, 1.36)
≥50 y	987 (33)	888 (26)	1.37 (1.19, 1.59)
Premenopausal	957 (32)	1237 (36)	1.15 (0.95, 1.38)
Parity			
Nulliparous	543 (18)	404 (12)	1.00
1	421 (14)	413 (12)	0.75 (0.62, 0.91)
2–3	1677 (55)	2068 (61)	0.57 (0.49, 0.66)
>4	415 (14)	524 (15)	0.53 (0.44, 0.64)
Pack-years smoked			
Never smoker	1572 (52)	1791 (52)	1.00
≤4	360 (13)	409 (12)	1.04 (0.88, 1.21)
5–12	336 (12)	365 (11)	1.09 (0.92, 1.28)
13–25	388 (14)	424 (13)	1.03 (0.88, 1.20)
≥26	393 (14)	432 (14)	0.97 (0.83, 1.13)
BMI[5]			
≤24.9 kg/m^2	1344 (44)	1535 (45)	1.00
25.0–29.9 kg/m^2	1012 (33)	1171 (34)	0.94 (0.84, 1.05)
≥30 kg/m^2	723 (24)	740 (21)	1.06 (0.93, 1.20)
Moderate physical activity, age 20–39 y			
0–3 times/mo	316 (11)	322 (10)	1.00
1–2 times/wk	698 (23)	722 (22)	1.00 (0.83, 1.21)
3–5 times/wk	1044 (35)	1261 (38)	0.85 (0.71, 1.01)
>5 times/wk	913 (31)	1021 (31)	0.90 (0.75, 1.08)
Moderate physical activity, age 40–59 y			
0–3 times/mo	408 (13)	375 (11)	1.00
1–2 times/wk	654 (22)	711 (21)	0.84 (0.70, 1.00)
3–5 times/wk	1115 (37)	1179 (35)	0.85 (0.73, 1.00)
>5 times/wk	669 (22)	800 (24)	0.75 (0.63, 0.90)
Age not yet reached	181 (6)	316 (9)	NA

[1] NA, not available.
[2] Age group–adjusted ORs (and 95% CIs) were calculated by using multivariate logistic regression.
[3] Age at cancer diagnosis for cases and age on 15 November 2002 for controls.
[4] Women were classified as premenopausal if they had a menstrual period within 12 mo of their diagnosis or referent date.
[5] BMI weight 2 y previous (kg) divided by height^2 (in m).

TABLE 2
Distribution of breast cancer cases ($n = 3101$) and controls ($n = 3471$) and odds ratio (OR) estimates for intake of selected foods and supplements (frequency and duration) known to contain vitamin D or calcium among Ontario women

Food/supplement intake (serving size)	Cases	Controls	Model 1[1]	Model 2[2]
	n (%)	*n (%)*		
Glasses of milk (244 g, 8.5 oz)				
<1/wk	780 (26)	879 (26)	1.00	1.00
1–2/wk	447 (15)	573 (17)	0.91 (0.77, 1.06)	0.94 (0.79, 1.12)
3–6/wk	549 (18)	605 (18)	1.06 (0.91, 1.23)	1.10 (0.93, 1.30)
3–6/wk	657 (22)	697 (21)	1.10 (0.96, 1.28)	1.13 (0.97, 1.34)
≥1/d	596 (20)	640 (19)	1.10 (0.95, 1.27)	1.15 (0.97, 1.37)
P for trend	—	—	0.17	0.04
Margarine (5 g, 1 tsp)[3]				
Never or few times per year	996 (33)	1097 (33)	1.00	1.00
<0.5/wk	218 (7)	264 (8)	0.95 (0.77, 1.16)	0.88 (0.70, 1.10)
0.5–5/wk	632 (21)	691 (21)	1.03 (0.89, 1.18)	1.04 (0.89, 1.21)
5–13/wk	867 (29)	975 (29)	0.96 (0.84, 1.09)	0.96 (0.83, 1.10)
≥2/d	274 (9)	303 (9)	0.96 (0.79, 1.15)	0.99 (0.80, 1.27)
P for trend	—	—	0.67	0.79
Tuna (51 g, 1/4 cup)				
Never or few times per year	836 (28)	884 (26)	1.00	1.00
1/mo	521 (17)	557 (16)	0.99 (0.85, 1.15)	1.04 (0.88, 1.24)
2/mo	545 (18)	620 (18)	0.94 (0.81, 1.09)	0.96 (0.81, 1.14)
1/wk	547 (18)	652 (19)	0.89 (0.77, 1.03)	0.92 (0.77, 1.08)
≥2/wk	580 (19)	674 (20)	0.91 (0.78, 1.05)	0.93 (0.78, 1.10)
P for trend	—	—	0.95	0.27
Other fish (43 g, 1/4 cup)[4]				
Never or few times per year	758 (25)	890 (26)	1.00	1.00
1/mo	405 (13)	516 (15)	0.92 (0.78, 1.09)	0.93 (0.78, 1.12)
2/mo	608 (20)	657 (19)	1.07 (0.92, 1.24)	1.09 (0.92, 1.29)
1/wk	839 (28)	877 (26)	1.10 (0.96, 1.26)	1.07 (0.91, 1.25)
≥2/wk	405 (13)	440 (13)	1.05 (0.89, 1.24)	0.96 (0.79, 1.16)
P for trend	—	—	0.98	0.59
Fish type consumed most often				
Did not eat fish or missing	523 (17)	624 (18)	1.00	1.00
White (eg, haddock, cod, sole)	1713 (55)	1865 (54)	1.08 (0.94, 1.23)	1.13 (0.97, 1.33)
Fatty (eg, salmon, mackerel)	865 (28)	982 (28)	1.02 (0.88, 1.19)	1.05 (0.88, 1.25)
P for trend	—	—	0.93	0.88
Frequency of vitamin D supplement use[5]				
Did not use or <1/mo	2701 (87)	2984 (86)	1.00	1.00
≥1/mo to ≤6/wk	114 (4)	137 (4)	0.89 (0.69, 1.15)	0.85 (0.64, 1.14)
Every day	286 (9)	350 (10)	0.84 (0.71, 1.00)	0.84 (0.70, 1.01)
P for trend	—	—	0.03	0.04
Duration of vitamin D supplement use				
Did not use	2730 (88)	3022 (87)	1.00	1.00
≤2 y	123 (4)	135 (4)	0.98 (0.76, 1.26)	0.93 (0.70, 1.23)
3–9 y	162 (5)	201 (6)	0.83 (0.67, 1.03)	0.85 (0.67, 1.08)
≥10 y	86 (3)	113 (3)	0.78 (0.59, 1.04)	0.83 (0.61, 1.14)
P for trend	—	—	0.03	0.08
Frequency of calcium supplement use[6]				
Did not use or <1/mo	2064 (67)	2269 (65)	1.00	1.00
≥1/mo to ≤6/wk	247 (8)	298 (9)	0.89 (0.74, 1.07)	0.91 (0.74, 1.11)
Every day	790 (25)	904 (26)	0.88 (0.78, 0.99)	0.88 (0.77, 1.00)
P for trend	—	—	0.02	0.04
Duration of calcium supplement use				
Did not use	2182 (70)	2400 (69)	1.00	1.00
≤2 y	248 (8)	332 (10)	0.80 (0.67, 0.95)	0.75 (0.62, 0.92)
3–9 y	457 (15)	473 (14)	0.98 (0.85, 1.14)	1.00 (0.85, 1.17)
≥10 y	214 (7)	266 (8)	0.81 (0.67, 0.98)	0.84 (0.68, 1.04)
P for trend	—	—	0.05	0.14
Frequency of multivitamin use				
Did not use or <1/mo	1930 (62)	2179 (63)	1.00	1.00
≥1/mo to ≤6/wk	343 (11)	380 (11)	1.05 (0.90, 1.23)	1.10 (0.92, 1.31)
Every day	828 (27)	912 (26)	1.00 (0.89, 1.11)	0.99 (0.87, 1.12)
P for trend	—	—	0.99	0.95

(Continued)

TABLE 2 (*Continued*)

Food/supplement intake (serving size)	Cases	Controls	Model 1[1]	Model 2[2]
	n (%)	*n* (%)		
Duration of multivitamin use				
Did not use	2023 (65)	2256 (65)	1.00	1.00
≤2 y	297 (10)	320 (9)	1.05 (0.89, 1.25)	0.99 (0.82, 1.19)
3–9 y	444 (14)	539 (16)	0.91 (0.79, 1.05)	0.95 (0.81, 1.11)
≥10 y	337 (11)	356 (10)	1.01 (0.86, 1.19)	0.99 (0.83, 1.18)
P for trend	—	—	0.57	0.66

[1] Age group–adjusted ORs (and 95% CIs) were calculated by using multivariate logistic regression. (Note: 39 variables were evaluated as potential confounders, and none were identified as confounders, ie, their inclusion in the model did not change the OR >10%.)

[2] Adjusted for age group, education, age at menarche, age at first live birth, parity, menopausal status, breast cancer in first-degree relative, total energy intake (kcal), BMI, smoking (pack-years), moderate physical activity during ages 20–39 y, moderate physical activity during ages 40–59 y, time spent outdoors per week during age 20–39 y, and time spent outdoors per week during ages 40–59 y. ORs (and 95% CIs) were calculated by using multivariate logistic regression.

[3] Intake of margarine (not butter) on foods such as bread or vegetables.

[4] Not fried fish.

[5] Vitamin D as a single-product supplement or cod liver oil.

[6] Calcium as a single vitamin or combined.

are presented in **Table 3**. No confounders were identified. Although the risk of breast cancer was lower in women with a vitamin D intake from supplements >10 μg/d (400 IU/d) than in those with no intake (fully adjusted OR: 0.76; 95% CI: 0.59, 0.98), no dose-response relation was observed between vitamin D supplements and breast cancer risk. No associations were observed between total combined vitamin D intake or vitamin D intake from foods alone and breast cancer risk. No statistically significant associations were observed between calcium and breast cancer risk; however, the OR point estimates decreased with increasing calcium supplement dose (*P* for trend = 0.04).

Vitamin D and calcium were highly correlated with a strong positive correlation observed between the continuous measures from food (Pearson's $r = 0.79$, $P < 0.0001$), supplements ($r = 0.50$, $P < 0.0001$) and total intake ($r = 0.63$, $P < 0.0001$). The interactions between total calcium (high compared with low intake) and all categorical vitamin D variables were not significant (**Table 4**). The odds ratios in the stratified analysis do not appear substantially different, which suggests no effect modification. When the interactions were assessed by using supplemental calcium intake (yes compared with no), which was less highly correlated with all measures of vitamin D, there were still no significant interactions. The relation between calcium and vitamin D was not different between pre- and postmenopausal women (data not shown).

Similarly, no significant interactions between the vitamin D or calcium nutrient-level variables and menopausal status were observed (**Table 5**). There were also no statistically significant interactions, and the ORs did not differ substantially by menopausal status for intakes of milk, margarine, and other fish or for duration and frequency of calcium, vitamin D, or multivitamin use (data not shown). However, a significant interaction was observed between tuna intake and menopausal status ($P = 0.02$); no association was observed among premenopausal women, although a significant inverse association existed among postmenopausal women after a comparison of the highest with the lowest category (OR: 0.78; 95% CI: 0.65, 0.93). Further tests for interactions showed no significant interactions between any of the 3 vitamin D nutrient-level variables and BMI or hormone replacement therapy use (between postmenopausal women only).

DISCUSSION

This study provides some evidence that vitamin D supplement use, but not intake from food alone or combined intake, is independently associated with reduced breast cancer risk. Our data suggest that there may be a threshold at >10 μg/d (400 IU/d) for vitamin D supplements. No significant ORs were observed for calcium intake from foods, supplements, or total combined intake and breast cancer risk; however, a significant inverse trend was observed across categories of calcium supplement use. Measurement of vitamin D or calcium from foods compared with supplements may be more susceptible to misclassification (potentially biasing results toward the null). It is also possible that foods containing vitamin D and calcium contain other detrimental components that counteract the potential benefits from vitamin D (eg, dietary fat in milk) (29, 32). We cannot rule out the possibility that our observed associations were due to chance or residual confounding; however, multivitamin use was not associated with breast cancer risk, which suggested that the associations are not due to residual confounding by other unmeasured healthy lifestyle traits among supplement users.

A recent meta-analysis suggested a trend toward a reduced breast cancer risk at minimum vitamin D intakes of ≥10 μg/d, but no association overall (relative risk: 0.98; 95% CI: 0.93, 1.03) (12). Several large cohort studies (34, 35, 45–47) have all reported some inverse associations between vitamin D intake (from diet and/or supplements) and breast cancer risk, but none have reported significant inverse associations consistently for all sources of vitamin D intake measured or among all women (eg, pre- and postmenopausal). The results of the Women's Health Initiative trial, of breast cancer risk in postmenopausal women randomly assigned to 10 μg vitamin D plus 1000 mg Ca/d or a placebo (HR: 0.96; 95% CI: 0.85, 1.09) (22), were consistent with our results that a vitamin D intake ≤10 μg/d (400 IU/d) was not associated with breast cancer risk. A smaller trial of all

TABLE 3
Distribution of breast cancer cases (n = 3101) and controls (n = 3471) and odds ratio (OR) estimates for derived vitamin D and calcium nutrient intake from food, supplements, and total combined among Ontario women

Vitamin D or calcium intake	Cases	Controls	Model 1[1]	Model 2[2]
	n (%)	*n* (%)		
Total combined vitamin D[3,4]				
<2.5 μg/d	384 (13)	443 (13)	1.00	1.00
2.5–4.9 μg/d	607 (20)	702 (20)	1.02 (0.86, 1.21)	1.01 (0.82, 1.25)
5.0–9.9 μg/d	731 (24)	831 (24)	1.03 (0.87, 1.22)	1.01 (0.81, 1.26)
10.0–14.9 μg/d	708 (23)	734 (21)	1.10 (0.87, 1.22)	1.10 (0.88, 1.37)
≥15.0 μg/d	632 (21)	717 (21)	0.99 (0.83, 1.18)	0.99 (0.78, 1.26)
P for trend	—	—	0.96	0.87
Vitamin D from foods				
<2.5 μg/d	638 (21)	717 (21)	1.00	1.00
2.5–4.9 μg/d	1036 (34)	1182 (34)	1.00 (0.87, 1.14)	0.97 (0.82, 1.14)
5.0–9.9 μg/d	1066 (35)	1197 (35)	1.01 (0.88, 1.15)	1.01 (0.85, 1.21)
≥10.0 μg/d	322 (11)	331 (10)	1.10 (0.91, 1.33)	1.13 (0.88, 1.45)
P for trend	—	—	0.31	0.23
Vitamin D from all supplements[5]				
0 μg/d	1679 (55)	1893 (55)	1.00	1.00
<10.0 μg/d	378 (12)	414 (12)	1.05 (0.90, 1.22)	1.08 (0.90, 1.28)
10.0 μg/d	847 (28)	912 (27)	1.01 (0.90, 1.13)	0.98 (0.85, 1.13)
>10.0 μg/d	158 (5)	208 (6)	0.80 (0.64, 0.99)	0.76 (0.59, 0.98)
P for trend	—	—	0.17	0.11
Total combined calcium[3]				
<500 mg/d	453 (15)	501 (15)	1.00	1.00
500–749 mg/d	539 (18)	641 (19)	0.94 (0.80, 1.12)	0.99 (0.80, 1.22)
750–999 mg/d	472 (15)	504 (15)	1.06 (0.88, 1.26)	1.13 (0.90, 1.43)
1000–1499 mg/d	698 (23)	798 (23)	0.97 (0.82, 1.14)	1.06 (0.85, 1.33)
>1500 mg/d	900 (29)	983 (28)	0.97 (0.83, 1.14)	1.03 (0.82, 1.30)
P for trend	—	—	0.81	0.95
Calcium from foods				
<500 mg/d	771 (25)	833 (24)	1.00	1.00
500–749 mg/d	803 (26)	972 (28)	0.90 (0.79, 1.03)	0.93 (0.78, 1.10)
750–999 mg/d	627 (20)	695 (20)	0.99 (0.86, 1.15)	1.07 (0.88, 1.30)
>1000 mg/d	861 (28)	927 (27)	1.03 (0.90, 1.18)	1.17 (0.95, 1.45)
P for trend	—	—	0.32	0.05
Calcium from all supplements[6]				
0 mg/d	1435 (47)	1612 (47)	1.00	1.00
<1000 mg/d	837 (27)	911 (27)	1.03 (0.91, 1.16)	0.97 (0.82, 1.14)
1000 mg/d	387 (13)	433 (13)	0.92 (0.78, 1.07)	0.86 (0.72, 1.03)
>1000 mg/d	403 (13)	471 (14)	0.88 (0.76, 1.03)	0.85 (0.68, 1.05)
P for trend	—	—	0.05	0.04

[1] Age group–adjusted ORs (and 95% CIs) were calculated by using multivariate logistic regression. (Note: 39 variables were evaluated as potential confounders, and none were identified as confounders, ie, their inclusion in the model did not change the OR >10%.)

[2] Adjusted for age group, education, age at menarche, age at first live birth, parity, menopausal status, breast cancer in first-degree relative, total energy intake (kcal), BMI, smoking (pack-years), moderate physical activity during ages 20–39 y, moderate physical activity during ages 40–59 y, time spent outdoors per week during age 20–39 y, time spent outdoors per week during ages 40–59 y, total calcium intake (included for vitamin D models only), and total vitamin D intake (included for calcium models only). ORs ratios (and 95% CIs) were calculated by using multivariate logistic regression.

[3] From food and supplements.

[4] Vitamin D: 10 μg = 400 IU.

[5] Multivitamins and vitamin D single-product supplements or cod liver oil.

[6] Multivitamins and calcium supplements.

cancer sites combined (few breast cancer cases), in postmenopausal women randomly assigned to receive 27.5 μg/d (1100 IU/d) vitamin D plus 1500 mg Ca/d compared with placebo, observed a significant reduction in cancers (relative risk: 0.40; 95% CI: 0.20, 0.82); a reduction in risk of borderline statistical significance was also observed in those who received calcium only (relative risk: 0.53; 95% CI: 0.27, 1.03) (48).

Only one (36) of the previous large population-based case-control studies of vitamin D intake and breast cancer risk (33, 36, 37) included vitamin D from supplements and found a reduced breast cancer risk associated with vitamin D supplement use earlier in life only (36). In contrast with our null results for dietary vitamin D, other case-control studies of diet only (during adulthood) have found significant inverse associations above the threshold of only 5 μg/d (200 IU/d) among European populations (33, 37).

Our results do not suggest an interaction between calcium and vitamin D intakes, and these 2 variables did not confound each other. Elsewhere, the association between dietary calcium and breast cancer risk was attenuated and was no longer statistically significant after adjustment for vitamin D (33). Although we

TABLE 4
Distribution of breast cancer cases and controls and odds ratio (OR) estimates for vitamin D intake variables stratified by total calcium intake

	Total combined calcium <1000 mg/d			Total combined calcium ≥1000 mg/d			
Vitamin D	Cases (n = 1464)	Controls (n = 1646)	Model 1[1]	Cases (n = 1598)	Controls (n = 1781)	Model 1[1]	P for interaction[2]
	n (%)	*n (%)*		*n (%)*	*n (%)*		
Total combined[3,4]							
<2.5 μg/d	321 (22)	354 (22)	1.00	63 (4)	89 (5)	1.00	0.49
2.5–4.9 μg/d	473 (32)	550 (33)	0.98 (0.81, 1.19)	134 (8)	152 (9)	1.25 (0.84, 1.87)	
5.0–9.9 μg/d	360 (25)	421 (26)	0.96 (0.78, 1.19)	371 (23)	410 (23)	1.30 (0.91, 1.85)	
10.0–14.9 μg/d	229 (16)	243 (15)	1.02 (0.81, 1.30)	479 (30)	491 (28)	1.38 (0.98, 1.96)	
≥15.0 μg/d	81 (6)	78 (5)	1.08 (0.76, 1.53)	551 (34)	639 (36)	1.22 (0.87, 1.72)	
Foods							
<2.5 μg/d	461 (31)	481 (29)	1.00	177 (11)	236 (13)	1.00	0.13
2.5–4.9 μg/d	639 (44)	743 (45)	0.92 (0.78, 1.08)	397 (25)	439 (25)	1.21 (0.95, 1.54)	
5.0–9.9 μg/d	348 (24)	407 (25)	0.89 (0.73, 1.08)	718 (45)	790 (44)	1.24 (1.00, 1.55)	
≥10.0 μg/d	16 (1)	15 (1)	1.11 (0.53, 2.27)	306 (19)	316 (18)	1.33 (1.04, 1.71)	
Supplements[5]							
0 μg/d	1032 (70)	1193 (72)	1.00	647 (40)	700 (39)	1.00	0.64
<10.0 μg/d	178 (12)	190 (12)	1.14 (0.91, 1.43)	200 (13)	224 (13)	0.97 (0.78, 1.20)	
10.0 μg/d	233 (16)	238 (15)	1.08 (0.88, 1.32)	608 (38)	666 (37)	0.97 (0.83, 1.13)	
>10.0 μg/d	21 (1)	25 (2)	0.87 (0.48, 1.57)	143 (9)	191 (11)	0.79 (0.62, 1.01)	

[1] Age group–adjusted ORs (and 95% CIs) were calculated by using multivariate logistic regression.
[2] Likelihood ratio test for age-adjusted model only.
[3] From food and supplements.
[4] Vitamin D: 10 μg = 400 IU.
[5] Multivitamins and vitamin D single-product supplements or cod liver oil.

observed an independent dose-response trend for calcium supplements and reduced breast cancer risk, we cannot rule out the possibility of residual confounding from unmeasured vitamin D intakes; many calcium supplement users also consume vitamin D (usually for bone health), and 19% of calcium supplement users did not report taking vitamin D supplements. Previous studies (33–35) found no interaction between vitamin D and calcium (33, 34) or an interaction between postmenopausal women only (35), such that an inverse association between calcium and breast cancer risk was observed only in the highest category of vitamin D intake. A recent prospective study of serum calcium (with no measures of vitamin D) and breast cancer incidence found an inverse association between premenopausal women only (49). The independent association between calcium and breast cancer risk requires further investigation.

Studies that evaluated the vitamin D–breast cancer relation by menopausal status have reported inconsistent results (34–37). Consistent with previous case-control studies (36, 37), we found no significant interactions. Unfortunately, a small proportion of premenopausal women in our study were taking vitamin D supplements containing >10 μg/d (400 IU/d). In contrast, cohort studies have reported inverse associations between dietary vitamin D intake and breast cancer risk only among premenopausal women (34, 35) and the potential for increased risk among postmenopausal women (35). Some (35, 46, 47) but not all (50) studies of vitamin D and breast cancer risk have reported differences by hormone receptor status. Data on hormone receptor status is not currently available for our study.

Whereas it has been hypothesized that vitamin D exposure during adolescence may be most important, we were unable to examine early-life dietary vitamin D intake, and the current evidence is inconsistent (34, 36, 51, 52). Vitamin D may also have some short-term effects in reducing breast cancer risk (18). Among 2 large cohort studies, the inverse associations between vitamin D and breast cancer were stronger when recent measures of vitamin D (34) or cases only within 5 y of baseline measurements of vitamin D intake were considered (47), which possibly indicates a role for vitamin D in slowing disease progression.

As with all observational studies, the potential for measurement error and other biases may limit internal validity. Sun exposure is the primary source of vitamin D in southern populations; however, this study population resides north of 43° latitude (Ontario, Canada), where sun exposure is insufficient for vitamin D production ≥4 mo of the year (53), and skin is mostly covered up for ≥50% of the year. Most studies in Canadian and other northern populations have found that dietary vitamin D intake is a significant predictor of 25(OH)D (54–58), but not all (59). There is the potential for misclassification, likely nondifferential, resulting from the absence of a complete measure of vitamin D (ie, a composite measure including diet/supplements and sun exposure). Our study did not measure the different forms of vitamin D; however, most intakes would likely be vitamin D_3, which is found in fatty fish and commonly used in supplements and food fortification in Canada, compared with vitamin D_2 from plant sources. Recall bias is likely minimal in this study because there is no obvious reason why cases or controls would differentially recall their recent intake of vitamin D or calcium. Similarly, survival bias is expected to be minimal because there is a high rate of survival among breast cancer cases in Ontario, and women were recruited, on average, within 1 y of diagnosis.

This study had several strengths, including a large sample size, population-based recruitment of cases and controls, and high response rates. Overall, the study results do not support an association between vitamin D or calcium from food or total intake and breast

TABLE 5
Distribution of breast cancer cases and controls and odds ratio (OR) estimates for vitamin D and calcium variables stratified by menopausal status among Ontario women

	Premenopausal				Postmenopausal				
Variable	Cases (n = 948)	Controls (n = 1226)	Model 1[1]	P for trend	Cases (n = 2111)	Controls (n = 2196)	Model 1[1]	P for trend	P for interaction[2]
	n (%)	*n (%)*			*n (%)*	*n (%)*			
Vitamin D									
Total combined[3,4]				0.07				0.26	0.41
<2.5 μg/d	112 (12)	166 (13)	1.00		272 (13)	277 (13)	1.00		
2.5–4.9 μg/d	217 (23)	301 (25)	1.09 (0.81, 1.47)		390 (18)	403 (18)	1.00 (0.80, 1.24)		
5.0–9.9 μg/d	260 (27)	351 (29)	1.10 (0.83, 1.47)		472 (22)	482 (22)	1.00 (0.81, 1.24)		
10.0–14.9 μg/d	208 (22)	229 (19)	1.35 (0.99, 1.84)		502 (24)	505 (23)	1.01 (0.82, 1.24)		
≥15.0 μg/d	154 (16)	184 (15)	1.23 (0.89, 1.70)		478 (23)	534 (24)	0.90 (0.73, 1.11)		
Foods				0.11				0.91	0.66
0 μg/d	188 (20)	240 (20)	1.00		451 (21)	477 (22)	1.00		
<10.0 μg/d	325 (34)	452 (37)	0.92 (0.73, 1.17)		711 (34)	732 (33)	1.03 (0.88, 1.22)		
10.0 μg/d	332 (35)	421 (34)	1.00 (0.79, 1.27)		736 (35)	778 (35)	1.01 (0.86, 1.19)		
>10.0 μg/d	106 (11)	118 (10)	1.16 (0.84, 1.61)		216 (10)	214 (10)	1.07 (0.85, 1.34)		
Supplements[5]				0.38				0.04	0.24
0 μg/d	562 (59)	773 (63)	1.00		1117 (53)	1124 (51)	1.00		
<10.0 μg/d	158 (17)	178 (15)	1.24 (0.97, 1.58)		222 (11)	237 (11)	0.94 (0.77, 1.16)		
10.0 μg/d	202 (21)	245 (20)	1.12 (0.90, 1.39)		640 (30)	659 (30)	0.96 (0.84, 1.10)		
>10.0 μg/d	29 (3)	35 (3)	1.07 (0.64, 1.78)		135 (6)	181 (8)	0.74 (0.58, 0.94)		
Calcium									
Total combined[3]				0.04				0.13	0.13
<500 mg/d	133 (14)	190 (15)	1.00		320 (15)	12 (14)	1.00		
500–749 mg/d	191 (20)	277 (23)	1.00 (0.75, 1.34)		348 (16)	366 (17)	0.92 (0.74, 1.14)		
750–999 mg/d	180 (19)	217 (18)	1.19 (0.88, 1.60)		293 (14)	287 (13)	1.00 (0.79, 1.25)		
1000–1499	233 (25)	318 (26)	1.05 (0.79, 1.38)		466 (22)	480 (22)	0.94 (0.77, 1.15)		
>1500 mg/d	214 (23)	229 (19)	1.32 (0.99, 1.77)		687 (33)	756 (34)	0.87 (0.72, 1.05)		
Foods				0.15				0.84	0.36
<500 mg/d	201 (21)	250 (20)	1.00		570 (27)	585 (27)	1.00		
500–749 mg/d	232 (24)	361 (29)	0.80 (0.62, 1.02)		572 (27)	612 (28)	0.96 (0.81, 1.12)		
750–999 mg/d	206 (22)	252 (20)	1.01 (0.78, 1.31)		422 (20)	443 (20)	0.98 (0.81, 1.17)		
>1000 mg/d	312 (33)	368 (30)	1.06 (0.84, 1.35)		550 (26)	561 (25)	1.01 (0.85, 1.19)		
Supplements[6]				0.68				0.02	0.68
0 mg/d	527 (55)	709 (58)	1.00		908 (43)	906 (41)	1.00		
<1000 mg/d	309 (32)	383 (31)	1.09 (0.90, 1.32)		530 (25)	529 (24)	0.99 (0.85, 1.15)		
1000 mg/d	48 (5)	60 (5)	1.03 (0.69, 1.54)		340 (16)	373 (17)	0.89 (0.75, 1.06)		
>1000 mg/d	67 (7)	79 (6)	1.09 (0.77, 1.55)		336 (16)	393 (18)	0.83 (0.70, 0.99)		

[1] Age group–adjusted ORs (and 95% CI) were calculated by using multivariate logistic regression.
[2] Likelihood ratio test.
[3] From food and supplements.
[4] Vitamin D: 10 μg = 400 IU.
[5] Multivitamins and vitamin D single-product supplements or cod liver oil.

cancer risk. However, vitamin D intakes were relatively low in this study and supplemental vitamin D intakes >10 μg/d (400 IU/d) were associated with a reduced breast cancer risk. Future studies are needed among populations with higher intakes, possibly carried out as a chemoprevention/intervention trial. Additional research is also needed to determine whether the association between vitamin D supplements and reduced breast cancer risk varies by timing of exposure, menopausal status, and tumor characteristics (including hormone receptor status and stage of diagnosis).

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