Intakes of Calcium and Vitamin D and Breast Cancer Risk in Women

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Background: Animal data suggest the potential anticarcinogenic effects of calcium and vitamin D on breast cancer development. However, epidemiologic data relating calcium and vitamin D levels to breast cancer have been inconclusive.

Methods: We prospectively evaluated total calcium and vitamin D intake in relation to breast cancer incidence among 10 578 premenopausal and 20 909 postmenopausal women 45 years or older who were free of cancer and cardiovascular disease at baseline in the Women's Health Study. Baseline dietary intake was assessed by a food frequency questionnaire. We used Cox proportional hazards regression to estimate hazard ratios and 95% confidence intervals.

Results: During an average of 10 years of follow-up, 276 premenopausal and 743 postmenopausal women had a confirmed diagnosis of incident invasive breast cancer. Higher intakes of total calcium and vitamin D were moderately associated with a lower risk of premenopausal breast cancer; the hazard ratios in the group with the highest relative to the lowest quintile of intake were 0.61 (95% confidence interval, 0.40-0.92) for calcium ($P=.04$ for trend) and 0.65 (95% confidence interval, 0.42-1.00) for vitamin D intake ($P=.07$ for trend). The inverse association with both nutrients was also present for large or poorly differentiated breast tumors among premenopausal women ($P\leq.04$ for trend). By contrast, intakes of both nutrients were not inversely associated with the risk of breast cancer among postmenopausal women.

Conclusions: Findings from this study suggest that higher intakes of calcium and vitamin D may be associated with a lower risk of developing premenopausal breast cancer. The likely apparent protection in premenopausal women may be more pronounced for more aggressive breast tumors.

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EXPERIMENTAL DATA IN ANIMALS have linked calcium and vitamin D intake to breast cancer prevention.[1-4] Female rats fed diets low in calcium and vitamin D developed significantly more experimental mammary tumors than rats fed adequate levels of calcium and vitamin D.[1,4] Increasing dietary calcium and vitamin D intake in female mice also regressed the adverse changes in the mammary gland induced by a high-fat diet.[2,3] Adequate intake of calcium from calcium-rich diets (which may include dairy products and supplements) helps to enhance calcium concentrations to maintain adequate intracellular calcium levels.[5,6] In addition, vitamin D participates in a feedback loop to maintain calcium levels within the regulated range.[7] Vitamin D can be ingested through a few natural food sources such as dairy foods and supplements or obtained through UV radiation for conversion of 7-dehydrocholesterol into vitamin D in the skin. Vitamin D is then hydroxylated in the liver to produce 25-hydroxycholecalciferol, the best indicator for reflecting overall vitamin D status.[8] Circulating 25-hydroxycholecalciferol is further converted into 1,25-dihydroxyvitamin D, the biologically active form of vitamin D that binds to vitamin D receptors in target tissues such as the mammary gland.[9]

Epidemiologic data on the association of intakes of calcium and/or vitamin D with breast cancer risk have been inconclusive. Some[10-15] but not all[16-20] studies reported an inverse association between calcium and/or vitamin D intake and breast cancer risk. It is notable that several[12,15,17,19,20] of these studies lacked information on supplemental calcium and/or cholecalciferol (vitamin D) intake, which may attenuate the overall association with breast cancer risk. Few studies[10,11,19] have also taken into account the strong relatedness between calcium and vitamin D and their similar effects on breast

cancer by examining both nutrients in the analysis. Moreover, because of the potential regulatory role of calcium and vitamin D in estrogen-driven cell proliferation,[21-23] intakes of calcium and vitamin D may have different effects against the development of premenopausal and postmenopausal breast cancer. However, data on the association according to menopause status are sparse. In the present study, we prospectively examined total intakes of calcium and vitamin D from dietary and supplemental sources in relation to breast cancer risk among premenopausal and postmenopausal women from a large cohort study.

METHODS

STUDY COHORT

The Women's Health Study is a recently completed randomized trial evaluating low-dose aspirin and vitamin E therapy for the primary prevention of cancer and cardiovascular disease.[24-26] During 1993 and 1995, 39 876 women 45 years or older who were free of cancer and cardiovascular disease were enrolled in the trial and completed a self-administered questionnaire at baseline about their medical history and lifestyle factors. In the present analysis, we excluded 8389 who provided insufficient dietary information or had biologically uncertain or unknown menopause status. These exclusions left a total of 10 578 premenopausal and 20 909 postmenopausal women.

DIETARY ASSESSMENT

At baseline, participants also filled out a 131-item food frequency questionnaire[27] that asked about the average use of food and beverages during the past 12 months. Participants chose from 9 possible answers ranging from "never or less than once per month" to "6 or more times per day." Participants also reported use of calcium supplements and multivitamins according to duration and dosage. The responses for each food item were then converted into an average daily intake of the food item in servings per day. Nutrient values in foods were computed by multiplying the frequency of responses by the nutrient content of specified portion sizes based on the US Department of Agriculture food composition data[28] and supplemented by food manufacturers. Nutrient intakes were also energy adjusted using the residual methods.[29]

Total intakes of calcium and vitamin D included sources from both diet and supplements. Major dietary sources of both nutrients came mostly from dairy products, which accounted for 53% and 39% of total calcium and vitamin D intake, respectively. Other dietary sources of calcium included pizza (4%), English muffin (3%), orange juice (2%), and bread (2%); other sources of vitamin D included dark fish (9%), tuna mix (5%), cereal (4%), and margarine (4%). Calcium from supplements (22%) was based on individual calcium supplements and multivitamins containing calcium. Vitamin D from supplements (30%) was obtained from multivitamins containing vitamin D. When evaluating the amount of intake from supplements, we also took into account the multivitamin brand.

The reproducibility and validity of calcium and vitamin D intake have been assessed in the Nurses' Health Study. Pearson correlation coefficients between responses from the food frequency questionnaire and those from four 1-week dietary records spaced over a year were 0.56 for total calcium and 0.51 for dietary calcium.[30] Correlation coefficients between vitamin D intake and plasma 25-hydroxycholecalciferol concentrations were 0.35 for total vitamin D and 0.25 for dietary vitamin D.[31]

ASCERTAINMENT OF BREAST CANCER CASES

Every 6 months during the first year and annually thereafter, participants reported on follow-up questionnaires whether they had been diagnosed as having breast cancer. For those who reported a diagnosis of breast cancer and for those who had died, we sought permission to obtain medical records and pathology reports. The end point committee of physicians reviewed and extracted information from the records. During an average 10 years of follow-up, 276 premenopausal and 743 postmenopausal women had a confirmed diagnosis of incident invasive breast cancer.

STATISTICAL ANALYSIS

We categorized women according to quintiles of intakes of calcium, vitamin D, and other dietary sources of calcium and vitamin D among all women. We also compared mean values or proportions of baseline risk factors for breast cancer across quintiles of total calcium and vitamin D intake.

We calculated person-years of observation for each participant from the date of randomization to the date of confirmed cancer, death from any cause, or March 31, 2004, whichever occurred first. We then used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the development of premenopausal and postmenopausal breast cancer. Analyzed models were adjusted for age and randomized treatment assignment and, in addition, for risk factors for breast cancer assessed at baseline, including body mass index (calculated as weight in kilograms divided by height in meters squared), physical activity, family history of breast cancer in a first-degree relative, history of benign breast disease, age at menarche, parity, age at first birth, multivitamin use, smoking status, alcohol consumption, and total energy intake in premenopausal and postmenopausal women, and age at menopause and postmenopausal hormone therapy in postmenopausal women. When we additionally adjusted, in premenopausal and postmenopausal women, for the presence of a mammogram screening test (yes or no) obtained during the first 12-month follow-up questionnaire, we excluded cases confirmed during the first year of follow-up. For the time-varying analysis of calcium and vitamin D intake, we used Cox proportional hazards regression to calculate HRs and 95% CIs with menopause status updated in 12-, 36-, 60-, and 96-month questionnaires.

Because several dietary factors such as vitamin D, phosphorus, fat, and lactose have been reported to affect calcium absorption, we examined whether these dietary factors (in tertiles) modified the association of calcium intake with breast cancer risk. We also examined the associations, in premenopausal and postmenopausal women, of total intakes of calcium and vitamin D with various tumor characteristics, including hormone receptor (ie, estrogen receptor and progesterone receptor) status, tumor size, lymph node metastasis, and tumor grade. Tests for trend were performed by fitting the median nutrient intake for each quintile as continuous variables in the models. All *P* values were 2 sided.

RESULTS

The mean (SD) intake values of total calcium and vitamin D in this cohort were 1021 (498) mg/d and 353 (244) IU/d, respectively. Premenopausal and postmenopausal women had similar total intakes of calcium and vitamin D (965 vs 1049 mg/d for mean total calcium; 332 vs 364 IU/d for mean total vitamin D). Total intakes of both nutrients were moderately related; the Pearson correlation coefficients were 0.47 and 0.41 in premenopausal and postmenopausal women, respectively. Overall, women who consumed more cal-

Table 1. Age-Adjusted Baseline Characteristics According to Intakes of Total Calcium and Total Vitamin D in the Women's Health Study

Characteristic	Calcium Intake					*P* Value for Trend	Vitamin D Intake*					*P* Value for Trend
	Q1	Q2	Q3	Q4	Q5		Q1	Q2	Q3	Q4	Q5	
No. of participants	6298	6298	6297	6297	6297		6298	6298	6298	6296	6297	
Mean age, y	54.5	54.7	54.9	55.4	56.4	<.001	54.3	54.7	55.3	55.4	56.2	<.001
Mean BMI	26.2	26.3	26.0	25.7	25.2	<.001	26.1	26.1	26.0	25.8	25.4	<.001
History of breast cancer in mother or sister, %	6.4	6.6	6.0	6.3	6.6	.79	6.6	6.6	6.7	6.6	5.6	.07
History of benign breast disease, %	30.3	32.1	32.0	32.6	36.1	<.001	31.6	31.7	33.4	32.1	34.3	.002
Mammogram screening, %†	51.3	57.5	60.5	62.9	67.2	<.001	54.6	58.6	60.4	61.6	64.4	<.001
Postmenopausal, %	66.7	65.5	65.8	65.8	68.5	.02	66.7	66.7	65.0	65.9	68.0	.59
Current users of postmenopausal hormone therapy, %	55.7	59.5	62.2	64.5	71.7	<.001	59.3	60.6	61.5	64.9	67.7	<.001
Current smokers, %	19.7	13.8	10.9	9.3	8.9	<.001	17.4	13.2	10.3	11.1	10.4	<.001
Current users of multivitamins, %	15.1	20.6	28.7	34.3	47.8	<.001	8.6	10.3	13.1	38.6	76.2	<.001
Calcium supplement users, %	5.7	16.3	36.1	56.2	89.5	<.001	23.6	26.0	29.8	48.8	75.9	<.001
Nulliparous women, %	12.6	13.2	13.3	13.4	14.9	.001	12.8	12.9	13.3	14.0	14.3	.002
Mean No. of children among parous women	3.0	2.9	2.9	2.9	2.8	<.001	2.9	2.9	2.9	2.9	2.8	.004
Mean age at first birth, y	24.5	24.6	24.7	24.9	24.8	<.001	24.6	24.6	24.8	24.8	24.6	.47
Mean age at menarche, y	12.5	12.4	12.4	12.4	12.4	.46	12.4	12.4	12.4	12.4	12.4	.20
Mean age at menopause, y	48.1	48.1	48.2	48.3	48.3	<.001	48.1	48.2	48.2	48.3	48.2	.05
Physical activity, kcal/wk	748	912	1016	1064	1126	<.001	807	906	978	1060	1123	<.001
Total calories intake, kcal/d	1630	1766	1785	1844	1623	<.001	1633	1754	1806	1865	1586	<.001
Alcohol intake, g/d	4.9	4.2	3.9	3.9	3.8	<.001	4.8	4.3	3.9	3.7	4.1	<.001
Total fat intake, g/d*	62	59	57	56	54	<.001	61	59	57	56	55	<.001
Phosphorus intake, mg/d*	1114	1254	1339	1431	1479	<.001	1131	1242	1350	1443	1451	<.001
Lactose intake, g/d*	6.3	11.6	16.0	21.2	23.3	<.001	7.3	12.2	17.1	21.9	19.9	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); Q, quintile.
*Nutrient values are based on the energy-adjusted values.
†From the 12-month follow-up questionnaire.

cium and vitamin D were older, leaner, more physically active, and more likely to receive a mammogram screening test, hormone therapy, and multivitamin and calcium supplements, but were less likely to be current smokers (**Table 1**). Women with higher intakes of calcium and vitamin D consumed less alcohol and total fat, but consumed more phosphorus and lactose. Moreover, women who were in the higher calcium and vitamin D intake groups had fewer childbirths.

The relation between calcium and vitamin D intake and breast cancer was modified by menopause status (multivariate *P* values for interaction were .04 and .08 for calcium and vitamin D intake, respectively). Premenopausal women who consumed more total calcium and vitamin D were at a lower risk of developing breast cancer; the multivariate HRs (95% CIs) in the highest quintile group relative to the lowest one were 0.61 (0.40-0.92) for total calcium (*P* = .04 for trend) and 0.65 (0.42-1.00) for total vitamin D intake (*P* = .07 for trend). Additional adjustment for mammogram screening test in premenopausal women did not substantially change the associations (multivariate *P* values were .06 and .11 for calcium and vitamin D intake, respectively). The results were also unchanged when we simultaneously adjusted for both nutrients in the model (data not shown). For time-varying analyses with updated menopause status (n = 115 premenopausal cases), the results were unchanged for total calcium intake (multivariate *P* = .06), although the association between vitamin D intake and breast cancer risk was attenuated (multivariate *P* = .20). Separate analysis of calcium intake from diet or from supplements showed a nonsignificant inverse association with premenopausal breast cancer (**Table 2**). There was also a nonsignificant inverse association between vitamin D from a supplemental source and premenopausal breast cancer (Table 2).

Total intakes of calcium and vitamin D were not inversely associated with breast cancer in postmenopausal women (Table 2). Additional adjustment for mammogram screening test did not appreciably change the associations (data not shown). The results were unchanged for time-varying analysis with updated menopause status (n = 866 postmenopausal cases), or when both nutrient intakes were simultaneously adjusted for in the multivariate model (data not shown). No significant association was observed in this group of women when we performed an analysis of nutrient intakes from dietary or supplemental sources (Table 2). Both nutrient intakes were also not inversely associated with breast cancer risk in postmenopausal women according to use of hormone therapy or the type of hormone therapy (estrogen alone, estrogen plus progestogen, and other regimens) (data not shown).

Intake of dairy products was nonsignificantly and inversely associated with premenopausal breast cancer

Table 2. Hazard Ratios and 95% CIs of Invasive Breast Cancer According to Quintiles of Intakes of Calcium, Vitamin D, and Dairy Products in the Women's Health Study*

	Premenopausal Women			Postmenopausal Women		
Intake	No. of Cases	Model 1, HR (95% CI)†	Model 2, HR (95% CI)‡	No. of Cases	Model 1, HR (95% CI)†	Model 2, HR (95% CI)‡§
Total calcium						
Q1	70	1 [Reference]	1 [Reference]	128	1 [Reference]	1 [Reference]
Q2	65	0.91 (0.65-1.27)	0.84 (0.59-1.19)	151	1.18 (0.94-1.50)	1.21 (0.95-1.54)
Q3	44	0.63 (0.44-0.93)	0.60 (0.41-0.88)	134	1.03 (0.81-1.31)	1.09 (0.85-1.40)
Q4	59	0.90 (0.63-1.27)	0.79 (0.55-1.14)	157	1.17 (0.92-1.48)	1.21 (0.95-1.55)
Q5	38	0.70 (0.47-1.04)	0.61 (0.40-0.92)	173	1.16 (0.92-1.45)	1.17 (0.92-1.50)
P value for trend		.13	.04		.33	.35
Calcium from diet						
Q1	60	1 [Reference]	1 [Reference]	141	1 [Reference]	1 [Reference]
Q2	57	0.92 (0.64-1.33)	0.89 (0.62-1.29)	153	1.09 (0.87-1.37)	1.09 (0.86-1.38)
Q3	61	0.97 (0.68-1.38)	0.91 (0.63-1.31)	153	1.10 (0.87-1.38)	1.14 (0.90-1.44)
Q4	44	0.71 (0.48-1.04)	0.69 (0.46-1.03)	150	1.07 (0.85-1.34)	1.11 (0.88-1.41)
Q5	54	0.87 (0.60-1.26)	0.84 (0.57-1.22)	146	1.03 (0.82-1.30)	1.10 (0.86-1.39)
P value for trend		.29	.24		.99	.56
Calcium supplements						
None	191	1 [Reference]	1 [Reference]	408	1 [Reference]	1 [Reference]
<500 mg/d	55	0.82 (0.61-1.10)	0.73 (0.52-1.00)	190	1.01 (0.85-1.20)	1.01 (0.84-1.22)
≥500 mg/d	30	0.82 (0.56-1.21)	0.71 (0.47-1.07)	145	1.07 (0.89-1.29)	1.05 (0.86-1.30)
P value for trend		.27	.11		.48	.63
Total vitamin D						
Q1	77	1 [Reference]	1 [Reference]	107	1 [Reference]	1 [Reference]
Q2	55	0.75 (0.53-1.06)	0.74 (0.52-1.05)	167	1.52 (1.19-1.93)	1.53 (1.19-1.96)
Q3	47	0.63 (0.44-0.91)	0.59 (0.41-0.86)	168	1.49 (1.17-1.90)	1.52 (1.19-1.96)
Q4	50	0.71 (0.50-1.01)	0.59 (0.40-0.88)	151	1.33 (1.03-1.70)	1.45 (1.12-1.88)
Q5	47	0.76 (0.53-1.09)	0.65 (0.42-1.00)	150	1.21 (0.95-1.55)	1.30 (0.97-1.73)
P value for trend		.27	.07		.77	.52
Vitamin D from diet						
Q1	54	1 [Reference]	1 [Reference]	121	1 [Reference]	1 [Reference]
Q2	74	1.42 (1.00-2.02)	1.39 (0.98-1.99)	129	1.04 (0.81-1.34)	1.07 (0.83-1.38)
Q3	52	1.01 (0.69-1.48)	0.99 (0.67-1.46)	169	1.33 (1.06-1.69)	1.33 (1.04-1.69)
Q4	48	0.94 (0.64-1.39)	0.91 (0.61-1.35)	165	1.28 (1.02-1.62)	1.30 (1.02-1.66)
Q5	48	1.05 (0.71-1.55)	1.02 (0.69-1.53)	159	1.18 (0.93-1.49)	1.22 (0.95-1.55)
P value for trend		.47	.40		.13	.09
Vitamin D from supplements						
None	197	1 [Reference]	1 [Reference]	517	1 [Reference]	1 [Reference]
<400 IU/d	35	0.84 (0.58-1.20)	0.72 (0.47-1.09)	94	0.90 (0.73-1.13)	0.95 (0.73-1.22)
≥400 IU/d	44	0.96 (0.69-1.34)	0.76 (0.50-1.17)	132	0.87 (0.72-1.05)	0.87 (0.68-1.12)
P value for trend		.85	.41		.16	.31
Total dairy products						
Q1	63	1 [Reference]	1 [Reference]	150	1 [Reference]	1 [Reference]
Q2	46	0.77 (0.53-1.12)	0.65 (0.44-0.97)	171	1.14 (0.91-1.41)	1.18 (0.94-1.48)
Q3	55	0.87 (0.61-1.25)	0.74 (0.51-1.08)	129	0.86 (0.68-1.09)	0.91 (0.72-1.17)
Q4	58	0.90 (0.63-1.29)	0.70 (0.48-1.04)	152	1.01 (0.81-1.27)	1.05 (0.82-1.34)
Q5	54	0.85 (0.59-1.22)	0.64 (0.42-0.95)	141	0.97 (0.77-1.23)	1.07 (0.82-1.39)
P value for trend		.66	.09		.60	.83

Abbreviations: CI, confidence interval; HR, hazard ratio, Q, quintile.

*Intake ranges of calcium in the quintile groups were <617, 617 to <789, 789 to <1026, 1026 to <1366, and ≥1366 mg/d for total calcium; <557, 557 to <677, 677 to <802, 802 to <998, and ≥998 mg/d for calcium from diet; and 0, >0 to 499, and ≥500 mg/d for calcium supplements. Intake ranges of vitamin D in the quintile groups were <162, 162 to <230, 230 to <333, 333 to <548, and ≥548 IU/d for total vitamin D; <142, 142 to <193, 193 to <245, 245 to <319, and ≥319 IU/d for vitamin D from diet; and 0, >0 to 400, and ≥400 IU/d for vitamin D supplements. Intake ranges of dairy products in the quintile groups were <0.93, 0.93 to <1.43, 1.43 to <2.07, 2.07 to <3.13, and ≥3.13 servings/d.

†Adjusted for age (in years) and randomized treatment assignment (aspirin vs placebo or vitamin E vs placebo).

‡Adjusted for variables denoted in model 1 and additionally for body mass index (calculated as weight in kilograms divided by height in meters squared) (<25, 25 to <30, and ≥30), physical activity (total expenditure in kilocalories per week, in quartiles), family history of breast cancer in a first-degree relative (yes or no), history of benign breast disease (yes or no), age at menarche (≤11, 12, 13, or ≥14 years), parity (0, 1-2, 3-4, or ≥5 children), age at first birth (≤19, 20-24, 25-29, or ≥30 years), multivitamin use (never, past, or current), smoking status (never, past, or current), alcohol consumption (never, 0.1 to <5, 5 to <15, or ≥15 g/d), and total energy intake (kilocalories per day, in quintiles).

§Adjusted for variables denoted in model 1 and additionally for age at menopause (<45, 45 to <50, 50 to <52, and ≥52 years) and baseline postmenopausal hormone therapy (never, past, or current).

Table 3. Hazard Ratios and 95% CIs of Invasive Breast Cancer According to Quintiles of Total Calcium by Tumor Characteristics in the Women's Health Study*

	Premenopausal Women			Postmenopausal Women		
Tumor Characteristic	No. of Cases	Model 1, HR (95% CI)†	Model 2, HR (95% CI)‡	No. of Cases	Model 1, HR (95% CI)†	Model 2, HR (95% CI)‡§
Estrogen receptor positive						
Q1	53	1 [Reference]	1 [Reference]	104	1 [Reference]	1 [Reference]
Q2	45	0.83 (0.56-1.24)	0.78 (0.52-1.17)	116	1.12 (0.86-1.46)	1.12 (0.85-1.47)
Q3	33	0.63 (0.41-0.97)	0.60 (0.38-0.94)	112	1.06 (0.81-1.38)	1.10 (0.83-1.44)
Q4	44	0.88 (0.59-1.32)	0.78 (0.51-1.19)	119	1.08 (0.83-1.41)	1.10 (0.84-1.45)
Q5	31	0.75 (0.48-1.16)	0.64 (0.40-1.03)	151	1.23 (0.96-1.58)	1.23 (0.94-1.61)
P value for trend		.35	.14		.12	.17
Estrogen receptor negative						
Q1	13	1 [Reference]	1 [Reference]	16	1 [Reference]	1 [Reference]
Q2	16	1.19 (0.57-2.47)	1.09 (0.52-2.31)	27	1.73 (0.93-3.21)	1.84 (0.98-3.45)
Q3	10	0.77 (0.34-1.76)	0.70 (0.30-1.64)	16	1.01 (0.50-2.01)	1.15 (0.57-2.32)
Q4	12	1.07 (0.50-2.32)	0.96 (0.43-2.14)	34	2.09 (1.16-3.80)	2.29 (1.23-4.28)
Q5	7	0.72 (0.29-1.82)	0.68 (0.26-1.77)	16	0.90 (0.45-1.80)	0.94 (0.45-1.98)
P value for trend		.46	.41		.65	.78
Progesterone receptor positive						
Q1	49	1 [Reference]	1 [Reference]	96	1 [Reference]	1 [Reference]
Q2	43	0.86 (0.57-1.29)	0.81 (0.53-1.24)	104	1.09 (0.82-1.43)	1.10 (0.83-1.47)
Q3	28	0.57 (0.36-0.91)	0.55 (0.34-0.88)	92	0.94 (0.71-1.25)	0.98 (0.73-1.32)
Q4	38	0.82 (0.54-1.26)	0.72 (0.46-1.13)	97	0.96 (0.73-1.28)	1.00 (0.75-1.35)
Q5	28	0.73 (0.46-1.16)	0.62 (0.38-1.02)	133	1.18 (0.91-1.54)	1.17 (0.89-1.56)
P value for trend		.25	.09		.24	.30
Progesterone receptor negative						
Q1	15	1 [Reference]	1 [Reference]	23	1 [Reference]	1 [Reference]
Q2	17	1.10 (0.55-2.19)	1.01 (0.50-2.04)	38	1.67 (0.99-2.80)	1.66 (0.98-2.81)
Q3	14	0.94 (0.46-1.95)	0.89 (0.46-1.88)	31	1.34 (0.78-2.29)	1.40 (0.81-2.42)
Q4	18	1.30 (0.65-2.57)	1.17 (0.57-2.38)	55	2.30 (1.41-3.74)	2.24 (1.34-3.72)
Q5	10	0.90 (0.40-2.00)	0.83 (0.36-1.92)	32	1.20 (0.70-2.05)	1.22 (0.69-2.15)
P value for trend		.90	.81		.65	.64
Tumor ≤2 cm						
Q1	50	1 [Reference]	1 [Reference]	93	1 [Reference]	1 [Reference]
Q2	44	0.86 (0.57-1.29)	0.82 (0.54-1.24)	107	1.16 (0.88-1.53)	1.21 (0.91-1.62)
Q3	32	0.64 (0.41-1.00)	0.62 (0.40-0.98)	99	1.05 (0.79-1.39)	1.15 (1.85-1.54)
Q4	48	1.02 (0.69-1.51)	0.93 (0.61-1.41)	113	1.16 (0.88-1.53)	1.22 (0.91-1.64)
Q5	30	0.77 (0.49-1.21)	0.71 (0.44-1.14)	134	1.24 (0.95-1.61)	1.27 (0.95-1.69)
P value for trend		.54	.38		.14	.17
Tumor >2 cm						
Q1	16	1 [Reference]	1 [Reference]	30	1 [Reference]	1 [Reference]
Q2	19	1.15 (0.59-2.24)	1.00 (0.50-2.00)	39	1.30 (0.81-2.09)	1.24 (0.77-2.01)
Q3	11	0.69 (0.32-1.49)	0.60 (0.27-1.33)	27	0.88 (0.52-1.48)	0.85 (0.50-1.45)
Q4	10	0.67 (0.31-1.48)	0.54 (0.24-1.24)	38	1.20 (0.74-1.93)	1.18 (0.72-1.93)
Q5	6	0.50 (0.19-1.27)	0.33 (0.12-0.95)	36	1.02 (0.63-1.65)	1.00 (0.60-1.68)
P value for trend		.06	.01		.85	.90

(continued)

(Table 2). When we further excluded nonwhite women (5.0% of the total population) from the analysis, the association between dairy product intake and premenopausal breast cancer became marginally significant; the new HRs (95% CIs) in the higher 4 quintiles were 0.66 (0.44-0.99), 0.72 (0.49-1.07), 0.70 (0.47-1.04), and 0.60 (0.39-0.91) (*P* = .06 for trend). However, no significant results were obtained for intake of low- or high-fat dairy products (data not shown). Dairy products were not shown to be related to postmenopausal breast cancer.

We further observed no effect modification by intakes of fat and lactose on the relation between calcium intake and breast cancer risk (data not shown). However, phosphorus intake modified the relation, in premenopausal and postmenopausal women, between calcium intake and breast cancer with an opposite direction (*P* value for interaction was .02 in premenopausal and postmenopausal women); a nonsignificant inverse association was seen among premenopausal women in the lowest tertile of phosphorus intake but among postmenopausal women in the highest tertile. In addition, we observed a significant interaction between calcium and vitamin D intake and development of postmenopausal breast cancer (*P* = .005 for interaction). There was a nonsignificant inverse association between calcium intake and postmenopausal breast cancer risk in the group with the highest tertile of vitamin D intake; the multivariate HRs in the higher 4 quintile groups were 0.91 (0.51-1.63), 0.64 (0.36-1.12), 0.82 (0.49-1.37), and 0.65 (0.39-1.08) (*P* = .11 for trend). However, the joint relationship of calcium and

Table 3. Hazard Ratios and 95% CIs of Invasive Breast Cancer According to Quintiles of Total Calcium by Tumor Characteristics in the Women's Health Study* (cont)

	Premenopausal Women			Postmenopausal Women		
Tumor Characteristic	No. of Cases	Model 1, HR (95% CI)†	Model 2, HR (95% CI)‡	No. of Cases	Model 1, HR (95% CI)†	Model 2, HR (95% CI)‡§
Negative lymph node metastasis						
Q1	45	1 [Reference]	1 [Reference]	92	1 [Reference]	1 [Reference]
Q2	49	1.07 (0.71-1.60)	1.00 (0.66-1.52)	110	1.20 (0.91-1.58)	1.21 (0.91-1.61)
Q3	32	0.71 (0.45-1.12)	0.68 (0.43-1.09)	95	1.02 (0.76-1.35)	1.04 (0.77-1.40)
Q4	42	0.99 (0.65-1.51)	0.88 (0.57-1.38)	113	1.17 (0.89-1.54)	1.17 (0.88-1.57)
Q5	32	0.90 (0.57-1.42)	0.80 (0.49-1.29)	115	1.07 (0.81-1.41)	1.05 (0.79-1.41)
P value for trend		.65	.36		.87	.96
Positive lymph node metastasis						
Q1	21	1 [Reference]	1 [Reference]	25	1 [Reference]	1 [Reference]
Q2	12	0.55 (0.27-1.13)	0.50 (0.24-1.04)	34	1.38 (0.82-2.31)	1.45 (0.84-2.49)
Q3	9	0.43 (0.20-0.95)	0.40 (0.18-0.89)	33	1.31 (0.78-2.20)	1.55 (0.90-2.66)
Q4	17	0.86 (0.46-1.64)	0.74 (0.38-1.47)	34	1.32 (0.79-2.21)	1.57 (0.91-2.70)
Q5	5	0.32 (0.12-0.84)	0.27 (0.10-0.75)	47	1.66 (1.02-2.69)	1.96 (1.16-3.31)
P value for trend		.08	.06		.07	.02
Well-differentiated tumors						
Q1	14	1 [Reference]	1 [Reference]	23	1 [Reference]	1 [Reference]
Q2	18	1.25 (0.62-2.51)	1.17 (0.57-2.42)	29	1.26 (0.73-2.18)	1.22 (0.70-2.14)
Q3	11	0.79 (0.36-1.75)	0.73 (0.32-1.65)	33	1.41 (0.83-2.39)	1.37 (0.80-2.37)
Q4	12	0.91 (0.42-1.98)	0.74 (0.33-1.67)	30	1.23 (0.72-2.13)	1.19 (0.68-2.08)
Q5	17	1.57 (0.78-3.20)	1.27 (0.60-2.72)	49	1.80 (1.09-2.95)	1.60 (0.95-2.69)
P value for trend		.28	.66		.02	.11
Moderately differentiated tumors						
Q1	25	1 [Reference]	1 [Reference]	54	1 [Reference]	1 [Reference]
Q2	22	0.86 (0.48-1.52)	0.87 (0.49-1.57)	56	1.04 (0.72-1.52)	1.12 (0.76-1.66)
Q3	15	0.60 (0.32-1.14)	0.63 (0.33-1.21)	50	0.91 (0.62-1.34)	1.00 (0.67-1.49)
Q4	30	1.27 (0.75-2.16)	1.27 (0.72-2.24)	70	1.24 (0.87-1.76)	1.32 (0.90-1.93)
Q5	11	0.57 (0.28-1.15)	0.52 (0.24-1.10)	81	1.29 (0.91-1.82)	1.39 (0.96-2.02)
P value for trend		.42	.31		.06	.04
Poorly differentiated tumors						
Q1	24	1 [Reference]	1 [Reference]	33	1 [Reference]	1 [Reference]
Q2	16	0.65 (0.35-1.22)	0.57 (0.29-1.10)	35	1.08 (0.67-1.73)	1.08 (0.66-1.75)
Q3	11	0.46 (0.23-0.94)	0.43 (0.21-0.91)	35	1.05 (0.65-1.69)	1.12 (0.69-1.81)
Q4	8	0.36 (0.16-0.79)	0.33 (0.15-0.76)	39	1.14 (0.72-1.82)	1.22 (0.75-1.97)
Q5	8	0.43 (0.19-0.96)	0.44 (0.19-1.02)	23	0.61 (0.36-1.04)	0.62 (0.35-1.10)
P value for trend		.02	.04		.06	.11

Abbreviations: CI, confidence interval; HR, hazard ratio; Q, quintile.

*Total calcium intake ranges for quintile categories are the same as those in Table 2. The available number (percentage among the total) of cases with information on estrogen receptor status, progesterone receptor status, lymph node metastasis, tumor size, and grade were 976 (96%), 961 (94%), 962 (94%), 982 (96%), and 1019 (100%), respectively.

†Adjusted for variables denoted in Table 2.

‡Adjusted for variables denoted in Table 2.

§Adjusted for variables denoted in Table 2.

vitamin D intake to premenopausal breast cancer risk was not significant ($P=.16$ for interaction).

Additional analysis of total calcium intake carried out according to tumor characteristics among premenopausal women showed that higher intake of total calcium was marginally associated with a lower risk of progesterone receptor–positive and more aggressive breast tumors, including larger tumors (>2 cm), those with positive lymph nodes, or poorly differentiated breast tumors (**Table 3**). By contrast, total calcium intake was not inversely associated with postmenopausal breast cancer according to various tumor characteristics; positive associations were seen between calcium intake and tumors with positive lymph node metastasis and between calcium intake and moderately differentiated breast tumors (Table 3).

Similar to the findings of total calcium intake and premenopausal breast cancer, vitamin D intake was inversely associated with risk of estrogen receptor–positive, progesterone receptor–positive, larger (>2 cm), and poorly differentiated breast tumors (**Table 4**). When we evaluated the association with combined estrogen and progesterone receptor status of breast tumors, we found a marginally inverse association with estrogen receptor–positive/progesterone receptor–positive tumors in premenopausal women ($P=.07$ for trend). However, no inverse associations could be observed with total vitamin D intake among postmenopausal women according to tumor characteristics; a marginally positive association was observed in postmenopausal women between vitamin D intake and moderately differentiated tumors (Table 4).

Table 4. Hazard Ratios and 95% CIs of Invasive Breast Cancer According to Quintiles of Total Vitamin D by Tumor Characteristics in the Women's Health Study*

	Premenopausal Women			Postmenopausal Women		
Tumor Characteristic	No. of Cases	Model 1, HR (95% CI)†	Model 2, HR (95% CI)‡	No. of Cases	Model 1, HR (95% CI)†	Model 2, HR (95% CI)‡§
Estrogen receptor positive						
Q1	59	1 [Reference]	1 [Reference]	87	1 [Reference]	1 [Reference]
Q2	38	0.68 (0.45-1.02)	0.67 (0.44-1.02)	131	1.46 (1.11-1.92)	1.47 (1.12-1.94)
Q3	37	0.65 (0.43-0.97)	0.61 (0.40-0.94)	139	1.51 (1.15-1.97)	1.51 (1.15-2.00)
Q4	40	0.73 (0.49-1.10)	0.59 (0.38-0.92)	121	1.30 (0.99-1.71)	1.40 (1.05-1.87)
Q5	32	0.67 (0.43-1.03)	0.53 (0.31-0.88)	124	1.22 (0.93-1.61)	1.28 (0.93-1.76)
P value for trend		.19	.03		.90	.57
Estrogen receptor negative						
Q1	15	1 [Reference]	1 [Reference]	14	1 [Reference]	1 [Reference]
Q2	14	0.98 (0.47-2.02)	0.95 (0.45-1.97)	25	1.76 (0.92-3.39)	1.94 (0.99-3.84)
Q3	9	0.63 (0.27-1.43)	0.56 (0.24-1.29)	24	1.71 (0.88-3.30)	1.94 (0.97-3.87)
Q4	8	0.59 (0.25-1.39)	0.58 (0.24-1.44)	27	1.89 (0.99-3.60)	2.28 (1.15-4.54)
Q5	13	1.11 (0.53-2.34)	1.30 (0.53-3.15)	19	1.24 (0.62-2.48)	1.47 (0.66-3.30)
P value for trend		.85	.62		.92	.60
Progesterone receptor positive						
Q1	53	1 [Reference]	1 [Reference]	81	1 [Reference]	1 [Reference]
Q2	36	0.71 (0.47-1.09)	0.72 (0.47-1.10)	111	1.34 (1.00-1.78)	1.39 (1.03-1.86)
Q3	32	0.62 (0.40-0.97)	0.59 (0.38-0.93)	111	1.30 (0.98-1.73)	1.32 (0.98-1.77)
Q4	35	0.71 (0.47-1.09)	0.57 (0.35-0.92)	108	1.25 (0.94-1.67)	1.36 (1.00-1.84)
Q5	30	0.69 (0.44-1.09)	0.55 (0.32-0.94)	111	1.18 (0.89-1.57)	1.23 (0.88-1.72)
P value for trend		.24	.04		.85	.58
Progesterone receptor negative						
Q1	19	1 [Reference]	1 [Reference]	19	1 [Reference]	1 [Reference]
Q2	16	0.88 (0.45-1.71)	0.84 (0.43-1.65)	43	2.20 (1.28-3.78)	2.16 (1.23-3.78)
Q3	11	0.60 (0.29-1.27)	0.55 (0.26-1.17)	50	2.53 (1.49-4.29)	2.63 (1.52-4.54)
Q4	13	0.76 (0.37-1.54)	0.73 (0.34-1.54)	38	1.90 (1.09-3.29)	2.10 (1.17-3.74)
Q5	15	1.01 (0.51-2.00)	1.08 (0.48-2.42)	29	1.33 (0.75-2.38)	1.48 (0.76-2.88)
P value for trend		.84	.79		.41	.87
Tumor ≤2 cm						
Q1	59	1 [Reference]	1 [Reference]	81	1 [Reference]	1 [Reference]
Q2	36	0.64 (0.42-0.97)	0.64 (0.42-0.97)	115	1.39 (1.04-1.84)	1.40 (1.04-1.87)
Q3	32	0.56 (0.36-0.86)	0.54 (0.35-0.83)	124	1.46 (1.10-1.93)	1.53 (1.15-2.05)
Q4	39	0.72 (0.48-1.07)	0.63 (0.40-0.98)	114	1.33 (1.00-1.76)	1.50 (1.11-2.03)
Q5	38	0.79 (0.53-1.19)	0.74 (0.46-1.22)	112	1.20 (0.90-1.60)	1.31 (0.94-1.83)
P value for trend		.71	.43		.95	.35
Tumor >2 cm						
Q1	17	1 [Reference]	1 [Reference]	22	1 [Reference]	1 [Reference]
Q2	15	0.93 (0.46-1.86)	0.86 (0.42-1.75)	44	1.93 (1.16-3.23)	1.93 (1.15-3.23)
Q3	14	0.86 (0.42-1.74)	0.76 (0.37-1.59)	37	1.58 (0.93-2.69)	1.47 (0.86-2.53)
Q4	9	0.58 (0.26-1.31)	0.43 (0.18-1.04)	34	1.44 (0.84-2.46)	1.44 (0.82-2.51)
Q5	7	0.52 (0.22-1.27)	0.31 (0.11-0.89)	33	1.27 (0.74-2.19)	1.31 (0.71-2.43)
P value for trend		.08	.02		.64	.93

(continued)

COMMENT

In this prospective cohort, higher intakes of total calcium and vitamin D were moderately associated with a lower risk of breast cancer among premenopausal women, and the lower risk was more pronounced in more aggressive breast tumors. However, intakes of calcium and vitamin D were not inversely associated with postmenopausal breast cancer, and the associations were unchanged by tumor characteristics.

In the main analysis, we found that higher intakes of calcium and vitamin D were moderately associated with a lower risk of breast cancer among premenopausal women, although the inverse association was not present after menopause. Consistent with our observations, 2 female cohort studies examining premenopausal and postmenopausal women reported an inverse association of calcium and vitamin D intake with breast cancer risk[10] or breast density[32] only among premenopausal women. The recent Women's Health Initiative randomized trial of calcium plus vitamin D therapy also found no reduction in risk of breast cancer among postmenopausal women taking 1000 mg/d of elemental calcium and 400 IU/d of 25-hydroxyvitamin D_3.[33] However, 2 other cohort studies reported an inverse association with breast cancer risk[11] or breast density levels[34] among postmenopausal women, although 1 of the 2 studies found no risk reduction in breast cancer with higher vitamin D intake.[11] Another nested case-control study reported moderate risk reduction of breast cancer among older women

Table 4. Hazard Ratios and 95% CIs of Invasive Breast Cancer According to Quintiles of Total Vitamin D by Tumor Characteristics in the Women's Health Study* (cont)

	Premenopausal Women			Postmenopausal Women		
Tumor Characteristic	No. of Cases	Model 1, HR (95% CI)†	Model 2, HR (95% CI)‡	No. of Cases	Model 1, HR (95% CI)†	Model 2, HR (95% CI)‡§
Negative lymph node metastasis						
Q1	57	1 [Reference]	1 [Reference]	74	1 [Reference]	1 [Reference]
Q2	37	0.68 (0.45-1.03)	0.68 (0.45-1.04)	115	1.51 (1.13-2.03)	1.54 (1.14-2.08)
Q3	33	0.60 (0.39-0.92)	0.58 (0.37-0.89)	125	1.61 (1.20-2.14)	1.65 (1.22-2.22)
Q4	40	0.76 (0.51-1.13)	0.64 (0.41-1.00)	109	1.38 (1.03-1.86)	1.51 (1.10-2.06)
Q5	33	0.71 (0.46-1.09)	0.62 (0.37-1.03)	102	1.19 (0.88-1.61)	1.21 (0.86-1.72)
P value for trend		.34	.12		.66	>.99
Positive lymph node metastasis						
Q1	17	1 [Reference]	1 [Reference]	24	1 [Reference]	1 [Reference]
Q2	15	0.92 (0.46-1.84)	0.85 (0.42-1.70)	43	1.76 (1.07-2.90)	1.85 (1.11-3.08)
Q3	10	0.61 (0.28-1.32)	0.53 (0.24-1.17)	35	1.43 (0.85-2.40)	1.49 (0.87-2.54)
Q4	9	0.58 (0.26-1.30)	0.51 (0.22-1.20)	37	1.49 (0.89-2.48)	1.71 (0.99-2.93)
Q5	13	0.96 (0.47-1.98)	0.91 (0.37-2.22)	34	1.27 (0.75-2.14)	1.66 (0.90-3.04)
P value for trend		.86	.74		>.99	.31
Well-differentiated tumors						
Q1	20	1 [Reference]	1 [Reference]	22	1 [Reference]	1 [Reference]
Q2	11	0.57 (0.27-1.20)	0.52 (0.25-1.09)	39	1.72 (1.02-2.91)	1.62 (0.95-2.76)
Q3	12	0.62 (0.30-1.26)	0.53 (0.26-1.10)	37	1.58 (0.93-2.69)	1.48 (0.86-2.55)
Q4	17	0.92 (0.48-1.76)	0.57 (0.28-1.17)	33	1.39 (0.81-2.39)	1.45 (0.83-2.54)
Q5	12	0.75 (0.36-1.53)	0.44 (0.19-1.03)	33	1.27 (0.74-2.19)	1.34 (0.72-2.47)
P value for trend		>.99	.14		.82	.77
Moderately differentiated tumors						
Q1	27	1 [Reference]	1 [Reference]	45	1 [Reference]	1 [Reference]
Q2	21	0.82 (0.46-1.44)	0.87 (0.49-1.56)	57	1.24 (0.84-1.83)	1.27 (0.84-1.91)
Q3	17	0.65 (0.36-1.20)	0.69 (0.37-1.28)	68	1.44 (0.99-2.10)	1.58 (1.07-2.33)
Q4	20	0.80 (0.45-1.43)	0.85 (0.45-1.60)	67	1.40 (0.96-2.05)	1.60 (1.07-2.39)
Q5	18	0.83 (0.45-1.50)	0.99 (0.49-2.02)	74	1.42 (0.98-2.06)	1.59 (1.03-2.46)
P value for trend		.71	>.99		.13	.06
Poorly differentiated tumors						
Q1	24	1 [Reference]	1 [Reference]	22	1 [Reference]	1 [Reference]
Q2	16	0.70 (0.37-1.31)	0.68 (0.36-1.30)	49	2.18 (1.32-3.60)	2.19 (1.32-3.64)
Q3	10	0.43 (0.21-0.90)	0.41 (0.19-0.86)	39	1.72 (1.02-2.90)	1.73 (1.02-2.95)
Q4	9	0.41 (0.19-0.88)	0.38 (0.17-0.86)	31	1.35 (0.78-2.33)	1.45 (0.82-2.56)
Q5	8	0.42 (0.19-0.93)	0.36 (0.14-0.98)	24	0.97 (0.54-1.73)	1.13 (0.59-2.18)
P value for trend		.02	.02		.06	.44

Abbreviations: CI, confidence interval; HR, hazard ratio; Q, quintile.
*Total vitamin D intake ranges for quintile categories are the same as those in Table 2.
†Adjusted for variables denoted in Table 2.
‡Adjusted for variables denoted in Table 2.
§Adjusted for variables denoted in Table 2.

with high circulating levels of 25-hydroxycholecalciferol, which is more sensitive to dietary intake.[35] Most case-control studies showed no significant association between calcium and/or vitamin D intake and breast cancer risk in middle-aged or older women.[16-19] One study[14] among them evaluating the association according to menopause status found an inverse association between calcium intake and premenopausal breast cancer.

Limited data address the hypothesis that the association between intakes of calcium and vitamin D and breast cancer risk may be stronger for premenopausal than for postmenopausal women. A possible explanation for the evident difference by menopause status may be related to the joint relationship among calcium, vitamin D, and insulinlike growth factors (IGFs).[36,37] In vitro studies have suggested that calcium and vitamin D exert anticarcinogenic effects on breast cancer cells expressing high levels of IGF-I and IGF binding protein 3.[37-40] Calcium, vitamin D, and IGF binding protein 3 have been shown in vitro to interact with each other in promoting growth inhibition in breast cancer cells.[38,39] In addition, vitamin D effectively inhibits IGF-I–stimulated growth of breast cancer cells.[37,40] Because circulating levels of IGF-I and/or IGF binding protein 3 decline with increasing age,[41,42] the interaction between IGF pathways and calcium and vitamin D are likely to be stronger for premenopausal women than for postmenopausal women, leading to greater risk reduction in premenopausal breast cancer.[43]

The observation of a positive association between calcium and vitamin D intake and breast cancer risk in postmenopausal women is unexpected. One possible explanation may be attributable to the bias of the high mammogram screening rates in postmenopausal women. However, this explanation is not supported by our analy-

sis of additional adjustment for the presence of the screening test. It is also possible that the protective effects of calcium and vitamin D against postmenopausal breast cancer occur only when intakes of both nutrients are substantially high, as inadequacy of both nutrients is very common in postmenopausal women.[44,45] Our data suggest that postmenopausal women consuming higher levels of calcium may be at a lower risk of developing breast cancer when the level of vitamin D consumption was also high. It has been suggested that a minimum of 1000 IU/d of vitamin D intake may be necessary to achieve adequate vitamin D concentrations, especially when sunlight exposure is minimal.[46] Accordingly, 400 IU/d of vitamin D from the Women's Health Initiative trial may be insufficient to reach the hypothesized risk reduction. Finally, it is also possible that other factors unknown to us may have contributed to the findings in postmenopausal women.

In this cohort, higher total calcium and vitamin D consumption was moderately associated with a lower risk of more aggressive breast tumors in premenopausal women. In vivo studies have suggested the effectiveness of vitamin D treatment in inhibiting late events of breast tumorigenesis, although similar inhibitory effects were also observed at an early stage.[47,48] In addition, vitamin D has been demonstrated to be effective in both in vivo and in vitro data for treating large breast tumors, mainly through the mechanisms of enhancing apoptosis and reducing proliferation of tumor cells.[49,50] Similar to the protective role of vitamin D, calcium has been shown in in vitro studies to slow the progression of breast cancer through its inhibition of the secretion of proteins responsible for advanced breast tumors, one of which is parathyroid hormone-related protein, a protein that contributes significantly to the metastatic potential in bone.[51] Calcium may also protect against advanced breast cancer through the vitamin D–induced apoptotic pathway.[52] We, however, observed no such protection by calcium and vitamin D against the development of more aggressive breast tumors in postmenopausal women. Our findings need to be confirmed in other studies.

The strengths of this study include the large sample size, the prospective design, the long duration, high follow-up rates in the cohort, and the comprehensive dietary information. We also have a large number of breast cancer cases in this cohort. However, the present study is also limited by several factors. First, nutrient intake was assessed only once at baseline and is subject to measurement error due to random within-person variation. Second, we did not have information about vitamin D intake from sunlight exposure, which is the major source of vitamin D for most people.[53] Our lack of information on sun exposure may have attenuated the true association with vitamin D intake. Finally, our findings may be subject to chance because so many subgroup analyses have been performed.

In conclusion, findings from the present study suggest that higher intakes of calcium and vitamin D from dietary plus supplemental sources may be associated with a lower risk of breast cancer among premenopausal women. The inverse association in premenopausal women may be more pronounced in more aggressive breast tumors. Further investigation is warranted to study the potential utility of calcium and vitamin D intake in reducing the risk of breast cancer.

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