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Serum calcium and breast cancer risk in a prospective cohort study

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Breast cancer; calcium; molecular epidemiology; cohort study; Vitamin D

Introduction

Laboratory evidence suggests that calcium can inhibit the development of mammary tumors in mice (1,2). Previous epidemiologic studies have suggested an inverse association between dietary calcium intake and breast cancer risk in humans (3-5). Additionally, calcium regulates Vitamin D and parathyroid hormone (PTH), both of which have been proposed to influence breast cancer risk (6,7). A recently reported prospective cohort study found that serum calcium levels were inversely associated with breast cancer risk among premenopausal women, while a positive association was observed among overweight postmenopausal women (8). We have examined the relation between serum calcium and breast cancer risk in a second prospective cohort.

Methods

This analysis was conducted with data from the Beaver Dam Eye Study (9,10), which consists of 4,926 (83.1% of eligible; 2,762 women) residents of Beaver Dam, WI, between the ages of 43 and 86 years who were identified in a private census conducted in 1987-1988. Participants provided a casual blood specimen, were measured for height and weight, and completed a questionnaire including reproductive and menstrual histories, lifestyle factors, health history, and demographics. Serum total and ionized calcium assessment was performed within four hours of the blood draw using an ICA-2 Ionized Calcium Analyzer (Radiometer, Copenhagen) (11).

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Incident cases of breast cancer and dates of diagnosis through August 1, 2007, were identified through linkage with the statewide mandatory tumor registry (Wisconsin Cancer Reporting System). Deaths were recorded via linkage with the National Death Index.

Cox proportional hazards regression was used to estimate the age-adjusted hazard ratio (HR) and 95% confidence interval (CI) for breast cancer risk associated with quartiles of serum calcium. Secondary models were adjusted for potential confounders selected *a priori* on the basis of their known association with breast cancer risk (menopausal status, age at menarche, age at menopause, parity, age at first birth, alcohol consumption, body mass index, education, and postmenopausal hormone use). Tests for trends were conducted by the inclusion of calcium quartile as a continuous variable. Tests for interaction were conducted by the inclusion of cross product terms in the regression models.

Female study participants with a history of cancer at the baseline examination (N=382), those who survived less than one year (N=22) or were diagnosed with breast cancer (N=9) within one year after the baseline examination, and those missing serum calcium measurements (N=2) were excluded, leaving a total of 2,338 women available for analysis.

Results

At the baseline exam, the study population had a mean age of 62.0 years. Mean total calcium was 2.44 mmol/L (range 1.40-3.16 mmol/L) and mean ionized calcium was 1.24 mmol/L (range 0.94-1.66 mmol/L). During 33,470 person-years of follow-up (mean 14.3 years per person), 124 incident cases of breast cancer were diagnosed. There was no overall association between either total or ionized serum calcium and breast cancer risk (Table 1). In analyses limited to the 334 premenopausal subjects, there was no suggestion of a trend in risk with total or ionized serum calcium. Among 1,995 postmenopausal women, there remained no association between breast cancer risk and total or ionized serum calcium.

In analyses of postmenopausal women stratified by median body mass index (BMI) at baseline (27.4 kg/m^2), total serum calcium was not associated with breast cancer risk in either strata, although there was some suggestion that the association between ionized serum calcium and breast cancer incidence varied by BMI (Table 1). Women below the median BMI had a reduced breast cancer risk at higher ionized serum calcium levels, whereas women above the median BMI had an increased breast cancer risk with higher ionized serum calcium levels. However, none of the hazard ratios reached statistical significance and a dose-response trend was not present in either BMI strata. The statistical test for an interaction between BMI and ionized serum calcium was not significant (p=0.15).

Discussion

In this prospective cohort study we found no evidence for an association between breast cancer risk and either total or ionized calcium. There was some suggestion that BMI modified this association among postmenopausal women, but this finding could likely be due to chance.

Only one previous cohort study has evaluated serum calcium in relation to breast cancer risk. Similar to Almquist et al. (8) we found no association between total calcium and breast cancer risk among all subjects or among postmenopausal women overall. However, Almquist et al (8) observed an inverse association between total calcium and breast cancer risk among premenopausal women (HR=0.56; 95% CI: 0.32, 0.99 for quartile 4 vs. quartile 1) and a positive association between total calcium and breast cancer risk among overweight postmenopausal women (HR=2.72; 95% CI: 1.24, 5.94 for quartile 4 vs. quartile 1). We were unable to evaluate breast cancer risk among premenopausal women with any precision, though a negative trend was not suggested. We found no association between total calcium and breast cancer risk among postmenopausal women with high BMI. There was some suggestion of an interaction between ionized calcium and BMI among postmenopausal women; yet neither the individual confidence intervals nor the test for interaction reached statistical significance, suggesting that this could likely be explained by chance.

We had 80% power to detect a hazard ratio ≥ 1.7 when comparing breast cancer risk between the fourth and first quartiles of calcium levels. Reduced power among subgroups limited the precision of the stratified results. Additionally, reliance on a single serum calcium measure may have limited our ability to accurately classify calcium status. However, previous studies have demonstrated that short-term and long-term intra-individual variation in serum calcium levels is low (13) and that there is significant tracking of calcium levels over time, such that a woman's rank within a given population remains quite similar over many years (14). In contrast to other measures of exposure (e.g. dietary intake), circulating serum calcium levels reflect the concentration of calcium to which breast tissue is exposed. We were able to evaluate ionized calcium, the physiologically active fraction of calcium in serum (~60% of total serum calcium is non-ionized) (12). Thus, a single serum calcium measurement provides an etiologically-relevant marker for evaluating the influence of calcium exposure on breast cancer risk.

Overall, these finding suggest no relation between serum calcium and breast cancer risk. Future studies would benefit from the consideration of calcium in tandem with related molecules such as PTH and Vitamin D, in addition to BMI.

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Abbreviations

PTH	parathyroid hormone
CI	confidence interval
BMI	body mass index
HR	hazard ratio

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TABLE 1

Hazard ratios and 95% confidence intervals of breast cancer risk according to quartiles of serum calcium.

	Total subjects	No. of cases	Person years*	Incidence per 100,000	HR (95% CI)†	HR (95% CI)‡
All subjects (N=2,338)						
Total serum calcium (mmol/L)						
1.40-2.38	687	39	9,819	397	1	1
2.39-2.44	605	27	8,699	310	0.76 (0.47, 1.26)	0.70 (0.42, 1.17)
2.45-2.52	508	26	7,297	356	0.83 (0.50, 1.37)	0.84 (0.51-1.40)
2.53-3.16	538	32	7,637	419	1.00 (0.62, 1.60)	0.98 (0.60, 1.60)
					$P_{trend} = 0.99$	$P_{trend} = 0.96$
Ionized calcium (mmol/L)						
0.94-1.21	666	39	9,148	426	1	1
1.22-1.23	535	25	7,713	324	0.75 (0.45, 1.24)	0.83 (0.50, 1.40)
1.24-1.25	482	27	7,050	383	0.89 (0.54, 1.47)	0.98 (0.59, 1.63)
1.26-1.66	655	33	9,539	346	0.77 (0.48, 1.23)	0.85 (0.53, 1.38)
					$P_{trend} = 0.37$	$P_{trend} = 0.64$
Postmenopausal women only (N=1,995)						
BMI ≤ 27.4 kg/m^2 (N=992)						
Total calcium (mmol/L)						
1.40-2.38	279	12	3,907	307	1	1
2.39-2.44	264	11	3,708	297	0.87 (0.38, 1.98)	0.69 (0.28, 1.67)
2.45-2.52	224	11	3,204	343	1.07 (0.46, 2.49)	0.88 (0.36, 2.19)
2.53-3.16	225	10	3,139	319	1.13 (0.48, 2.67)	0.97 (0.39, 2.43)
					$P_{trend} = 0.69$	$P_{trend} = 0.93$
Ionized calcium (mmol/L)						
0.94-1.21	238	15	3,091	485	1	1
1.22-1.23	227	8	3,233	247	0.50 (0.21, 1.21)	0.60 (0.24, 1.51)
1.24-1.25	208	9	3,009	299	0.69 (0.29, 1.62)	0.78 (0.32, 1.92)
1.26-1.66	319	12	4,627	259	0.54 (0.25, 1.18)	0.63 (0.27, 1.44)
					$P_{trend} = 0.20$	$P_{trend} = 0.37$
BMI > 27.4 kg/m^2 (N=985)						

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	Total subjects	No. of cases	Person years*	Incidence per 100,000	HR (95% CI)†	HR (95% CI)‡
Total calcium (mmol/L)						
1.40-2.38	252	16	3,414	469	1	1
2.39-2.44	259	10	3,641	275	0.61 (0.26, 1.40)	0.56 (0.24, 1.35)
2.45-2.52	215	13	2,973	437	0.89 (0.42, 1.91)	1.03 (0.46, 2.34)
2.53-3.16	259	17	3,663	464	0.90 (0.45, 1.81)	0.94 (0.44, 1.98)
					$P_{trend} = 0.97$	$P_{trend} = 0.79$
Ionized calcium (mmol/L)						
0.94-1.21	287	14	4,070	344	1	1
1.22-1.23	217	13	3,192	407	1.40 (0.64, 3.07)	1.52 (0.66, 3.51)
1.24-1.25	180	12	2,701	444	1.41 (0.64, 3.11)	1.89 (0.80, 4.45)
1.26-1.66	245	17	3,728	456	1.26 (0.61, 2.59)	1.59 (0.73, 3.47)
					$P_{trend} = 0.55$	$P_{trend} = 0.22$

HR = hazard ratio; CI = confidence interval.

*Total person years for cases and noncases.

†Models are adjusted for age.

‡Models are adjusted for age, menopausal status, age at menarche, age at menopause, parity, age at first birth, alcohol consumption, BMI, education, and postmenopausal hormone use.