

# Dairy foods, calcium, and risk of breast cancer overall and for subtypes defined by estrogen receptor status: a pooled analysis of 21 cohort studies

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## ABSTRACT

**Background:** Epidemiologic studies examining the relations between dairy product and calcium intakes and breast cancer have been inconclusive, especially for tumor subtypes.

**Objective:** To evaluate the associations between intakes of specific dairy products and calcium and risk of breast cancer overall and for subtypes defined by estrogen receptor (ER) status.

**Method:** We pooled the individual-level data of over 1 million women who were followed for a maximum of 8–20 years across studies. Associations were evaluated for dairy product and calcium intakes and risk of incident invasive breast cancer overall ( $n = 37,861$  cases) and by subtypes defined by ER status. Study-specific

multivariable hazard ratios (HRs) were estimated and then combined using random-effects models.

**Results:** Overall, no clear association was observed between the consumption of specific dairy foods, dietary (from foods only) calcium, and total (from foods and supplements) calcium, and risk of overall breast cancer. Although each dairy product showed a null or very weak inverse association with risk of overall breast cancer ( $P$ , test for trend  $>0.05$  for all), differences by ER status were suggested for yogurt and cottage/ricotta cheese with associations observed for ER-negative tumors only (pooled HR = 0.90, 95% CI: 0.83, 0.98 comparing  $\geq 60$  g/d with  $<1$  g/d of yogurt and 0.85, 95% CI: 0.76, 0.95 comparing  $\geq 25$  g/d with  $<1$  g/d of cottage/ricotta

cheese). Dietary calcium intake was only weakly associated with breast cancer risk (pooled HR = 0.98, 95% CI: 0.97, 0.99 per 350 mg/d).

**Conclusion:** Our study shows that adult dairy or calcium consumption is unlikely to associate with a higher risk of breast cancer and that higher yogurt and cottage/ricotta cheese intakes were inversely associated with the risk of ER-negative breast cancer, a less hormonally dependent subtype with poor prognosis. Future studies on fermented dairy products, earlier life exposures, ER-negative breast cancer, and different racial/ethnic populations may further elucidate the relation. *Am J Clin Nutr* 2021;114:450–461.

**Keywords:** breast cancer, calcium, cheese, dairy products, diet, milk, pooled analysis, yogurt

## Introduction

Worldwide, breast cancer is the most commonly diagnosed malignancy and the leading cause of cancer death in women, accounting for 2.1 million cases each year and 15% of all cancer deaths (1). Breast cancer is a heterogeneous disease with subtypes based on expression of hormone receptors, indicating different etiologies, clinical characteristics, and survival rates. Hormone-receptor-negative tumors have poorer prognosis and fewer treatment options (2–4). Since these subtypes are less hormonally dependent, any association between dietary exposures and breast cancer risk would be more likely to show up. One challenge in studying hormone-receptor-negative tumors is that they account for <20% of all breast cancers (5), so many studies have inadequate statistical power to analyze them separately.

Dairy products have been hypothesized to influence breast carcinogenesis in conflicting ways. They are the main dietary sources of conjugated linoleic acid, calcium, and vitamin D (in fortified fluid milk and yogurt), all of which have been suggested to have anticarcinogenic properties by regulating cell proliferation, differentiation, and apoptosis (6–9). Dairy products also contain branched chain amino acids and potentially increase circulating insulin-like growth factor 1 (IGF-1) concentrations

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Supplemental Figure 1 and Supplemental Tables 1–10 are available from the “Supplementary data” link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/ajcn/>.

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Abbreviations used: DCP, Diet and Cancer Pooling Project; ER, estrogen receptor; ICD, International Classification of Diseases; IGF-1, insulin-like growth factor 1; PR, progesterone receptor.

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(10), which may promote cell growth, elevate mitotic activity, and increase DNA replication errors (11, 12). Bovine sex hormones and hormone drugs used in dairy management practices (e.g. trenbolone acetate, zeranol, melengestrol acetate) might increase breast cancer risk as well (11, 13). A meta-analysis of 22 prospective cohort studies and 5 case-control studies reported that high total dairy consumption was associated with a modestly lower risk of breast cancer (risk ratio = 0.90, 95% CI: 0.83, 0.98, comparing >600 g/d with <200 g/d) (14). The number of studies reporting on specific dairy products was limited, and results were not reported separately for breast cancer subtypes in that meta-analysis.

To evaluate the associations between intakes of specific dairy products and calcium and risk of female breast cancer overall and for subtypes defined by estrogen receptor (ER) status, we conducted a pooled analysis within 21 cohorts in the Pooling Project of Prospective Studies of Diet and Cancer (Diet and Cancer Pooling Project, DCP).

## Methods

### Study population

The DCP is an international consortium of prospective cohort studies (15). In this study, we analyzed 21 (16–36) cohorts (Table 1, Supplemental Table 1) that met the following inclusion criteria: 1) ≥1 publication on any diet and cancer association; 2) assessed dairy product and calcium intake with a comprehensive long-term (e.g. the past 6 mo or 1 y) dietary assessment tool; 3) validated the dietary assessment tool or a closely related instrument; and 4) included ≥25 incident ER-negative breast cancer cases.

### Assessment of dietary and nondietary factors

Dietary intake was assessed at baseline by a validated study-specific FFQ, generally covering the past year. Total milk, hard cheese, cottage/ricotta cheese, yogurt, and ice cream were examined (see Supplemental Table 2 for the items in each group and the daily intake in each participating cohort). All studies estimated dietary calcium intake (from foods) and 12 studies estimated total calcium intake that also included calcium from multivitamins and other supplements. Dietary and total calcium intakes were energy adjusted using the residual method (37). The Pearson correlation coefficients comparing intakes from the FFQ used in these studies or closely related FFQs with either multiple 24-h recalls or dietary records generally ranged from 0.5 to 0.9 for intake of dairy products (25, 38–44) and 0.5–0.8 for dietary calcium (41, 42, 45–48) (Supplemental Table 1).

Each study collected age, height, and body weight at baseline. Most studies also assessed family history of breast cancer, educational attainment, physical activity, smoking habits, and several reproductive factors (covariate availability for each cohort is summarized in Supplemental Methods).

### Case ascertainment

Breast cancer was defined by International Classification of Diseases 9 (ICD-9) code 174.0 or ICD-10 code C50.

**TABLE 1** Characteristics by cohort study<sup>1</sup> in the breast cancer analyses in the Pooling Project of Prospective Studies of Diet and Cancer

Cohort <sup>2</sup>	Country	Baseline cohort size <sup>3</sup>	Year(s) of recruitment	Median follow-up (y)	No. of breast cancer cases		
					Total	ER-positive	ER-negative
BCDDP	USA	42,061	1987–1989	8.7	1305	793	166
BWHS	USA	52,576	1995	13.0	670	416	254
CARET	USA	6000	1985–1994	12.3	367	193	31
CLUE II	USA	8279	1989	16.5	288	198	50
CNBSS	Canada	45,185	1980–1985	16.5	1240	367	125
CPS II	USA	74,137	1992–1993	9.8	2999	1835	323
CTS	USA	100,067	1995–1999	8.1	2696	1930	343
IWHS	USA	34,584	1986	18.9	1849	1329	238
JPHC I	Japan	21,609	1990–1992	14.5	289	111	69
MCCS	Australia	22,456	1990–1994	13.4	799	493	171
MEC	USA	92,435	1993–1997	10.7	3308	2169	543
NHS a	USA	88,618	1980–1982	6.5	1122	528	255
NHS b <sup>4</sup>	USA	68,394	1986	19.9	4467	3075	757
NHS II	USA	93,778	1991–1993	12.0	1331	846	303
NIH-AARP	USA	200,049	1995–1997	7.5	5972	2322	464
NLCS	Netherlands	62,573	1986	6.6	2013	700	183
NYUWHS	USA	13,257	1985	17.1	919	392	121
ORDET	Italy	9044	1987–1992	12.5	283	206	67
PLCO	USA	28,292	1993–2002	9.1	1090	858	137
SMC	Sweden	60,950	1987–1990	16.9	2605	1605	384
WHS	USA	38,385	1992–1995	10.1	1177	937	187
WLHS	Sweden	47,514	1991–1992	15.3	1072	737	196
Total		1,141,849			37,861	22,040	5367

<sup>1</sup>For each study, information on the study population, dietary assessment method, and the validation study of the dietary assessment method, as well as the reference(s), are provided in Supplemental Table 1.

<sup>2</sup>BCDDP, Breast Cancer Detection Demonstration Project Follow-up Study; BWHS, The Black Women's Health Study; CARET,  $\beta$ -Carotene and Retinol Efficacy Trial; CLUE II, CLUE II: Campaign Against Cancer and Heart Disease; CNBSS, Canadian National Breast Screening Study; CPS II, Cancer Prevention Study II Nutrition Cohort; CTS, California Teachers Study; ER, estrogen receptor; IWHS, Iowa Women's Health Study; JPHC I, Japan Public Health Center-Based Study Cohort I; MCCS, Melbourne Collaborative Cohort Study; MEC, Multiethnic Cohort; NHS a, Nurses' Health Study (part a); NHS b, Nurses' Health Study (part b); NHS II, Nurses' Health Study II; NIH-AARP, NIH-AARP Diet and Health Study; NLCS, Netherlands Cohort Study; NYUWHS, New York University Women's Health Study; ORDET, Hormones and Diet in the Etiology of Breast Cancer Study; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SMC, Swedish Mammography Cohort; WHS, Women's Health Study; WLHS, Women's Lifestyle and Health Study.

<sup>3</sup>Cohort size reflects the size after application of study-specific exclusion criteria and further exclusion of participants with energy intakes beyond 3 SDs of their  $\log_e$ -transformed study-specific mean energy intake and history of cancer diagnosis at baseline (except for nonmelanoma skin cancer); the Netherlands Cohort Study was analyzed as a case-cohort study, and the above exclusions were not applied to its baseline cohort size.

<sup>4</sup>The Nurses' Health Study (NHS) was analyzed as 2 separate cohorts [1980–86, NHS (a); 1986–2006, NHS (b)] to utilize the comprehensive dietary assessment administered in 1986. As a result, the participants in the Nurses' Health Study (b) were not added into the total baseline cohort size because the participants in this study were included in the Nurses' Health Study (a).

Incident invasive breast cancer cases were identified by follow-up questionnaires and subsequent review of medical records, through linkage to cancer registries, or by both methods. Some cases were also identified using linkage to mortality registries. Follow-up generally exceeded 90% for the studies (15). Estrogen and progesterone receptor status (ER status obtained for 85% and PR status obtained for 80% of all cases) was identified through cancer registries, pathology reports, medical records, or laboratory determinations. Cases with borderline hormone receptor status (<1% among those with ER data) were considered as positive for that hormone receptor.

## Ethics

Each included study and the consortium were approved by their respective Institutional Review Board.

## Statistics

The primary aims for the study were to assess the associations of dairy product and calcium intake and risk of female breast cancer overall and of breast cancer subtypes defined by ER status; as secondary analyses we examined breast cancer subtypes defined jointly by ER and PR status. We analyzed the primary participant-level data in each cohort. The Netherlands Cohort Study was analyzed as a case-cohort study (49), as required by its study design. The Nurses' Health Study was separated into 2 cohorts (1980–1986 Nurses' Health Study a; 1986–2006 Nurses' Health Study b) because of the more detailed dietary assessment after 1986 compared with 1980.

We excluded women who reported total energy intake outside of 3 SDs from the mean  $\log_e$ -transformed energy intake in that study and who had been diagnosed with any cancer other than nonmelanoma skin cancer prior to baseline. The 10 studies that



did not measure supplemental calcium intake were excluded from analyses of total calcium intake.

The associations for dairy products, dietary calcium, and total calcium intake and risk of breast cancer overall and for subtypes defined by ER status and by ER/PR status jointly were evaluated for each study using Cox proportional hazards regression. Dairy product and calcium intakes were modeled using categories defined by common absolute intake cut points. Calcium intake was modeled using study-specific quintiles as well. Most of the dairy products evaluated were comprised of a limited number of items and had relatively discrete intake distributions, thus we did not model them using quantiles. For each participant, we calculated person-years of follow-up from the age at baseline questionnaire return to the age of diagnosis of incident breast cancer, death, loss to follow-up, or end of follow-up, whichever occurred first. We used age at baseline and year of baseline questionnaire return as stratification factors to account for age, calendar time, and time since study entry. In multivariable analyses, we adjusted for established and suspected breast cancer risk factors (see [Table 2](#) for specific variables and categorization) directly in the model for studies with >200 cases of the outcome of interest (i.e. overall breast cancer, ER-positive tumors, and ER-negative tumors); otherwise we included propensity scores ([50](#), [51](#)). We created missing indicator variables for confounders with missing values (the proportion of missing data was generally <10% for all covariates). We evaluated the main exposures for divergence from the proportional hazards assumption by examining figures of Schoenfeld residuals ([52](#)) and did not find evidence of significant violation.

We pooled the study-specific HRs using random-effects models ([53](#)). Between-studies heterogeneity was evaluated using the  $Q$  ([53](#)) and  $I^2$  statistics ([54](#)).

To test for a linear trend across categories of intake for each participant, we assigned the study-specific median value of their exposure category, modeled that variable as a continuous variable, and tested the coefficient using the Wald test. We compared nonparametric regression curves using restricted cubic splines with the linear model using the likelihood ratio test ([55](#)) to test for nonlinearity in the associations for dairy products, dietary calcium, and total calcium. As the  $P$  value test for nonlinearity exceeded 0.05 for all associations, we also conducted analyses in which we modeled dairy food and calcium intakes as continuous variables.

In prespecified stratification analyses, we investigated whether the associations of interest varied by menopausal status at diagnosis using a previously described algorithm ([56](#)) (premenopausal, postmenopausal), age at diagnosis (<64, ≥64 y), BMI (<25, ≥25 kg/m<sup>2</sup>), region (North America, other), and follow-up years (<5, ≥5 y) using a mixed-effects metaregression model ([57](#)). We used a contrast test to obtain the  $P$  value, test for common effects of breast cancer subtypes defined by ER status and ER/PR status ([58](#)) (details in Supplemental Methods).

For each study that evaluated calcium intake in their validation study, we corrected for the bias in the estimated HRs due to measurement error in calcium intake ([16–19](#), [21](#), [23–25](#), [27–33](#)), using a regression calibration method ([59](#), [60](#)).

For all tests of statistical hypotheses, 2-sided Wald 95% CIs were calculated, and 2-sided  $P < 0.05$  were considered statistically significant. All analyses were conducted using SAS software versions 9.2–9.4 (SAS Institute).

## Results

After applying the inclusion and exclusion criteria ([Supplemental Figure 1](#)), across the 21 prospective studies with maximum follow-up ranging from 8 to 20 y, 37,861 incident cases of invasive breast cancer (22,040 ER-positive and 5,367 ER-negative breast cancer cases) were diagnosed among 1,141,849 women ([Table 1](#), Supplemental Table 1).

Dairy product and calcium consumption varied substantially across studies. Median dietary calcium intake ranged from 490 to 853 mg/d. Median total calcium intakes ranged from 675 to 1173 mg/d (Supplemental Table 2). Dietary calcium intake was highly correlated with total milk intake (median Pearson correlation coefficient across studies = 0.74) and reduced-fat milk intake (median Pearson correlation = 0.73); correlations for total calcium intake with these 2 food items were weaker. Very weak correlations were observed between calcium and other dairy products ([Supplemental Table 3](#)).

Only multivariable results are presented because results from age-adjusted models were similar. For all dairy products evaluated, null or very weak associations were observed for risk of breast cancer overall with pooled multivariable HRs comparing the highest with the lowest category ranging from 0.95 to 1.01 across the dairy products ([Table 2](#), [Supplemental Table 4](#)). When we expanded the highest category of total milk to ≥500 g/d, the pooled HR did not decrease further (data not shown).

When we estimated associations for subtypes of breast cancer defined by ER status ([Table 2](#)), differences between ER-positive and ER-negative tumors were suggested only for yogurt and cottage/ricotta cheese consumption, with statistically significant inverse associations being observed for ER-negative tumors only. The pooled HRs comparing ≥60 g/d with <1 g/d yogurt intake were 0.90 (95% CI: 0.83, 0.98) for ER-negative tumors and 0.98 (95% CI: 0.94, 1.03) for ER-positive tumors ( $P$ , test for common effects by ER status = 0.07) ([Table 2](#), [Figure 1](#)). Similarly, higher cottage/ricotta cheese consumption was associated with a 15% lower risk of ER-negative (pooled HR comparing ≥25 g/d to <1 g/d = 0.85, 95% CI: 0.76, 0.95) but not ER-positive breast cancer (pooled HR = 0.96, 95% CI: 0.90, 1.02;  $P$ , test for common effects by ER status = 0.07) ([Table 2](#), [Figure 2](#)). When intakes were modeled as continuous variables, we did not observe significant associations for any dairy product with risk of breast cancer overall ([Figure 3](#)) or for subtypes defined by ER ([Supplemental Table 5](#)) or joint ER/PR status ([Supplemental Table 6](#)).

Dietary calcium intake showed a significant inverse trend with risk of breast cancer overall ( $P$ , test for trend = 0.004), although the result for the highest intake category (≥1400 mg/d) was not statistically significant ([Table 3](#)). Weak inverse associations were also observed when dietary calcium intake was modeled using study-specific quintiles (pooled HR comparing quintile 5 with 1 = 0.95, 95% CI: 0.91, 0.98,  $P$ , test for trend = 0.001, [Supplemental Table 7](#)) or as a continuous variable (pooled HR for a 350 mg/d increment = 0.98, 95% CI: 0.97, 0.99, [Figure 4](#)). After correcting for measurement error, the pooled age- and energy-adjusted HR for a 350 mg/d increment of dietary calcium intake changed from 0.98 (95% CI: 0.96, 0.99) to 0.95 (95% CI: 0.91, 0.98) for overall breast cancer. Results for dietary calcium intake were similar in magnitude when we limited the

**TABLE 2** Pooled multivariable<sup>1</sup> adjusted HRs and 95% CIs for intake of dairy products and risk of breast cancer overall and for subtypes defined by estrogen receptor (ER)<sup>2</sup> status

Dairy group <sup>3</sup>	Categories of intake (g/d)				<i>P</i> <sub>trend</sub> <sup>4</sup>	<i>P</i> <sub>het</sub> <sup>5</sup>	<i>I</i> <sup>2</sup> <sup>6</sup>	<i>P</i> <sub>com</sub> <sup>7</sup>
	Pooled HR (95% CI)							
	Reference	Category 1	Category 2	Category 3				
<b>Total milk<sup>8</sup></b>								
No. cases	4774	12,235	9150	10,740				
(ER+/-)	(2835/740)	(7039/1784)	(5366/1234)	(6204/1412)				
Total	1.00 (Ref)	0.97 (0.94, 1.01)	0.99 (0.95, 1.03)	0.95 (0.91, 0.98)	0.02	0.72	<1%	
ER+	1.00 (Ref)	0.97 (0.92, 1.02)	1.00 (0.94, 1.06)	0.95 (0.90, 1.00)	0.13	0.40	5%	0.91
ER-	1.00 (Ref)	1.01 (0.92, 1.11)	0.99 (0.89, 1.09)	0.95 (0.85, 1.05)	0.25	0.37	7%	
<b>Hard cheese<sup>9</sup></b>								
No. cases	7369	24,602	3934	1675				
(ER+/-)	(3792/946)	(14,833/3577)	(2252/560)	(974/241)				
Total	1.00 (Ref)	1.02 (0.98, 1.06)	0.99 (0.93, 1.06)	1.01 (0.93, 1.10)	0.76	0.29	13%	
ER+	1.00 (Ref)	1.05 (1.00, 1.10)	1.00 (0.92, 1.10)	1.03 (0.93, 1.15)	0.82	0.36	8%	0.84
ER-	1.00 (Ref)	0.96 (0.88, 1.04)	0.94 (0.81, 1.09)	1.00 (0.78, 1.29)	0.56	0.18	23%	
<b>Cottage/ricotta cheese<sup>10</sup></b>								
No. cases	13,217	10,373	3277	3596				
(ER+/-)	(7271/1883)	(6202/1377)	(1945/448)	(2073/474)				
Total	1.00 (Ref)	0.99 (0.96, 1.02)	0.96 (0.92, 1.00)	0.97 (0.93, 1.01)	0.19	0.53	<1%	
ER+	1.00 (Ref)	1.00 (0.96, 1.04)	0.96 (0.90, 1.03)	0.96 (0.90, 1.02)	0.10	0.35	9%	0.07
ER-	1.00 (Ref)	0.91 (0.85, 0.99)	0.93 (0.79, 1.10)	0.85 (0.76, 0.95)	0.07	0.47	<1%	
<b>Yogurt<sup>11</sup></b>								
No. cases	14,616	10,146	3675	6997				
(ER+/-)	(8534/2189)	(5846/1344)	(2049/513)	(4163/961)				
Total	1.00 (Ref)	0.98 (0.96, 1.01)	0.97 (0.93, 1.01)	0.96 (0.92, 0.99)	0.01	0.25	17%	
ER+	1.00 (Ref)	0.99 (0.96, 1.03)	0.96 (0.91, 1.02)	0.98 (0.94, 1.03)	0.20	0.94	<1%	0.07
ER-	1.00 (Ref)	0.92 (0.86, 0.99)	0.93 (0.84, 1.03)	0.90 (0.83, 0.98)	0.02	0.62	<1%	
<b>Ice cream<sup>12</sup></b>								
No. cases	11,359	17,381	3749	2406				
(ER+/-)	(6757/1494)	(10,294/2568)	(2264/582)	(1449/345)				
Total	1.00 (Ref)	1.01 (0.98, 1.04)	1.03 (0.99, 1.07)	1.00 (0.95, 1.05)	0.96	0.71	<1%	
ER+	1.00 (Ref)	1.00 (0.96, 1.04)	1.02 (0.97, 1.08)	0.99 (0.92, 1.06)	0.53	0.32	12%	0.53
ER-	1.00 (Ref)	1.03 (0.96, 1.11)	1.12 (0.99, 1.26)	1.04 (0.90, 1.21)	0.42	0.25	17%	

<sup>1</sup>Multivariable model includes race/ethnicity (white, African American, Hispanic, Asian), education (<high school, high school, >high school), BMI (<23, 23 to <25, 25 to <30, ≥30 kg/m<sup>2</sup>), height (<1.60, 1.60 to <1.65, 1.65 to <1.70, 1.70 to <1.75, ≥1.75 m except Japan Public Health Center-Based Study Cohort I: <1.50, 1.50 to <1.55, 1.55 to <1.60, 1.60 to <1.65, ≥1.65 m), alcohol consumption (0, >0 to <5, 5 to <15, 15 to <30, ≥30 g/d), energy intake (kcal/d, continuous), smoking status (never, past, current), physical activity (low, medium, high), age at menarche (<11, 11/12, 13/14, ≥15 y except Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: <10, 10/11, 12/13, ≥14 y), the combination of menopausal status and hormone replacement therapy use [premenopausal women and among postmenopausal women separate categories for never, past, and current users of hormone replacement therapy, except in the California Teachers Study, Canadian National Breast Screening Study, Multiethnic Cohort, New York University Women's Health Study (NYUWHS), Hormones and Diet in the Etiology of Breast Cancer Study, Swedish Mammography Cohort, and Women's Lifestyle and Health Study where the combination was modeled as premenopausal women and among postmenopausal women separate categories for never and ever users of hormone replacement therapy], oral contraceptive use (ever, never), parity (0, 1 to 2, ≥3, except for NYUWHS 0, ≥1), age at first birth (≤25, >25 y), history of benign breast disease (yes, no), family history of breast cancer (yes, no). Age in years and year of questionnaire return were included as stratification variables.

<sup>2</sup>ER: estrogen receptor.

<sup>3</sup>Total milk group included skim milk, 1% milk, 2% milk, whole milk, buttermilk, evaporated milk; hard cheese contained hard cheese, high-fat cheese, low-fat cheese, cheddar cheese, feta cheese, and unspecified cheese; cottage/ricotta cheese contained cottage and ricotta cheese; yogurt included high-fat and low-fat yogurt but not frozen yogurt.

<sup>4</sup>*P*<sub>trend</sub>: the *P* value, test for trend was calculated using the Wald test statistic.

<sup>5</sup>*P*<sub>het</sub>: the *P* value, test for between-studies heterogeneity for the highest category was calculated using the *Q* statistic.

<sup>6</sup>*I*<sup>2</sup> for the highest category.

<sup>7</sup>*P*<sub>com</sub>: the *P* value, test for common effects for different subtypes defined by estrogen receptor status for the highest category was calculated using the Wald test statistic.

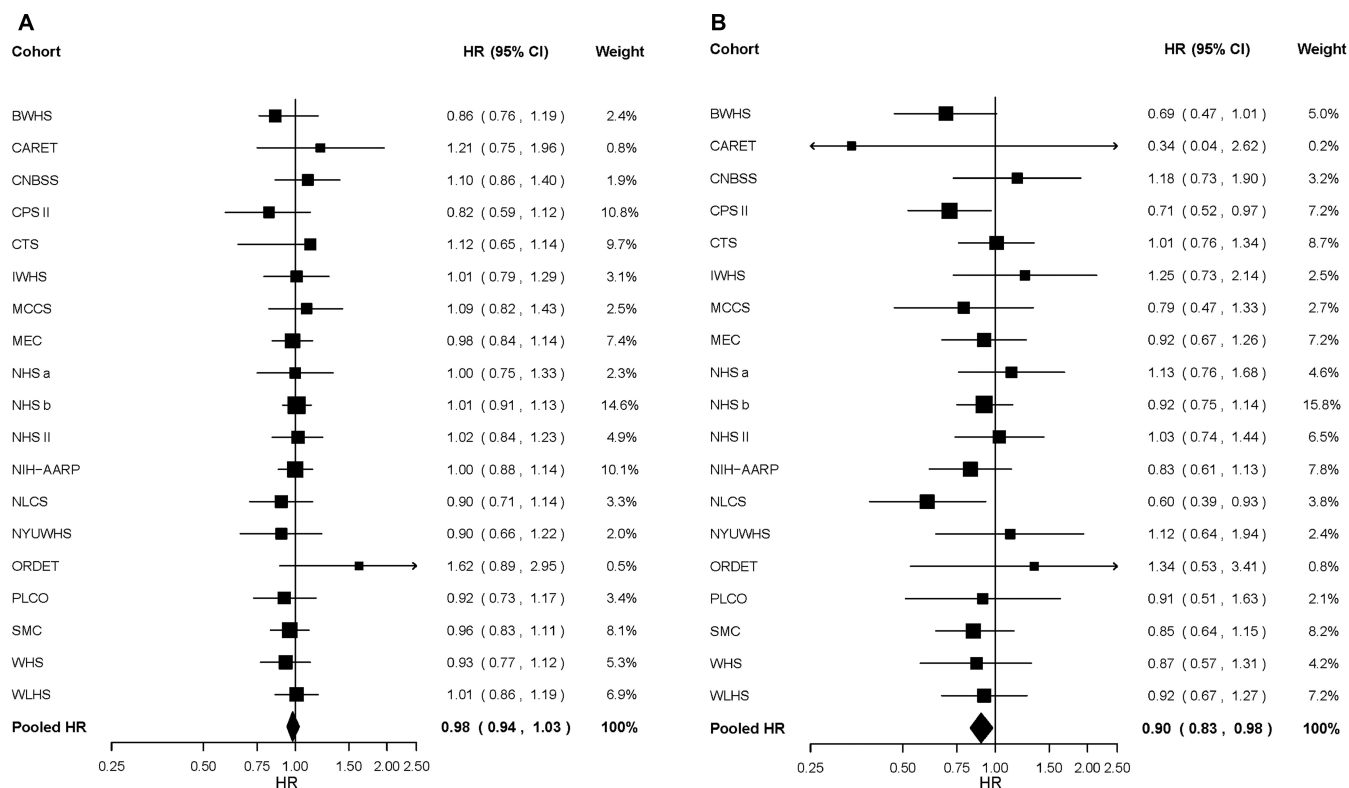
<sup>8</sup>The intake of total milk for reference, category 1, category 2, category 3 is 0, 1–124.9, 125–249.9, ≥250 g/d, respectively.

<sup>9</sup>The intake of hard cheese for reference, category 1, category 2, category 3 is 0, 1–24.9, 25–49.9, ≥50 g/d, respectively.

<sup>10</sup>The intake of cottage/ricotta cheese for reference, category 1, category 2, category 3 is 0, 1–12.4, 12.5–24.9, ≥25 g/d, respectively.

<sup>11</sup>The intake of yogurt for reference, category 1, category 2, category 3 is 0, 1–29.9, 30–59.9, ≥60 g/d, respectively.

<sup>12</sup>The intake of ice cream for reference, category 1, category 2, category 3 is 0, 1–16.9, 17–33.9, ≥34 g/d, respectively.



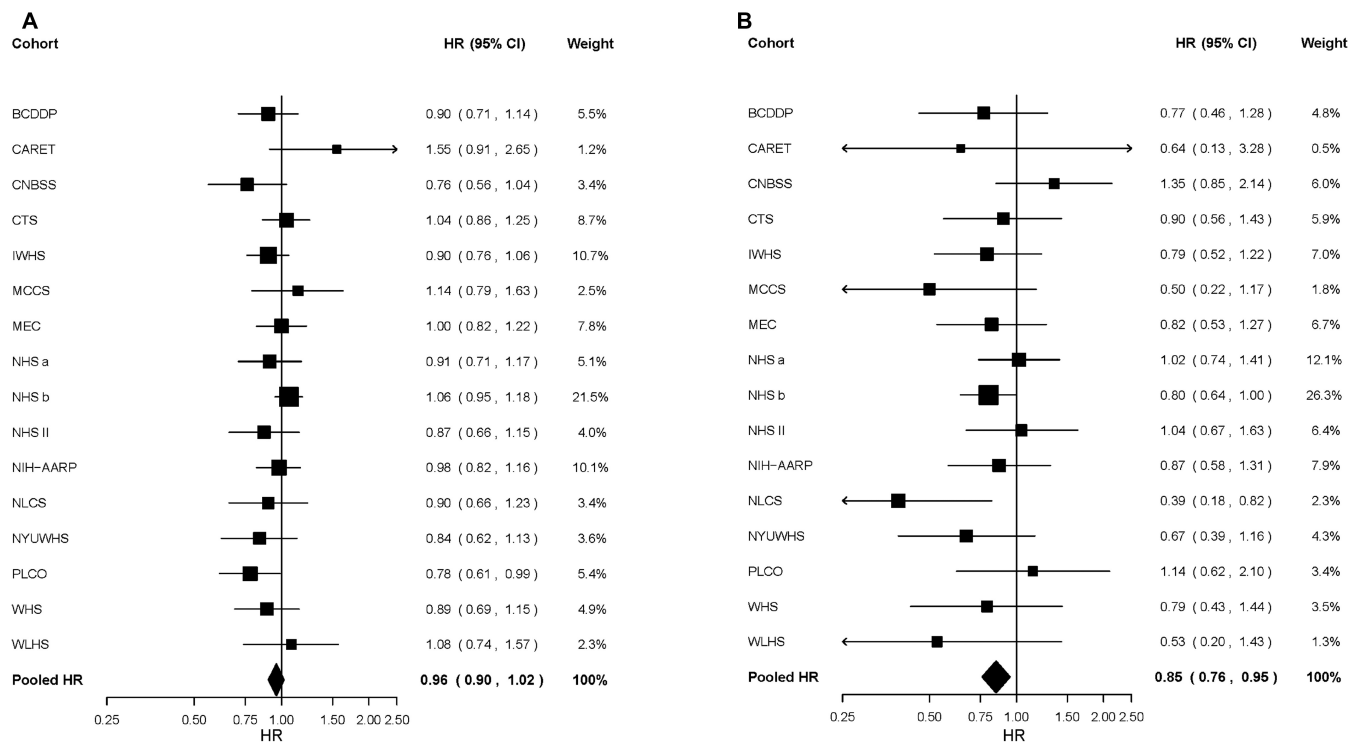
**FIGURE 1** Study-specific and pooled multivariable HRs comparing  $\geq 60$  versus 0 g/d of yogurt intake and risk of (A) estrogen-receptor-positive breast cancer and (B) estrogen-receptor-negative breast cancer. The squares and horizontal lines correspond to the study-specific HRs and 95% CIs for the comparison of  $\geq 60$  g/d to 0 g/d of yogurt intake. The BCDDP (Breast Cancer Detection Demonstration Project Follow-up Study), CLUE II (CLUE II: Campaign Against Cancer and Heart Disease), and JPHC I (Japan Public Health Center-Based Study Cohort I) were excluded from the figure because these studies did not measure yogurt intake. The size of the squares reflects the study-specific weight (inverse of the variance). The diamond represents the pooled multivariable HR and 95% CI. BWHS, The Black Women's Health Study; CARET,  $\beta$ -Carotene and Retinol Efficacy Trial; CNBS, Canadian National Breast Screening Study; CPS II, Cancer Prevention Study II Nutrition Cohort; CTS, California Teachers Study; IWHS, Iowa Women's Health Study; MCCS, Melbourne Collaborative Cohort Study; MEC, Multiethnic Cohort; NHS a, Nurses' Health Study (part a); NHS b, Nurses' Health Study (part b); NHS II, Nurses' Health Study II; NIH-AARP, NIH-AARP Diet and Health Study; NLCS, Netherlands Cohort Study; NYUWHS, New York University Women's Health Study; ORDET, Hormones and Diet in the Etiology of Breast Cancer Study; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SMC, Swedish Mammography Cohort; WHS, Women's Health Study; WLHS, Women's Lifestyle and Health Study.

analyses to only those studies included in the total calcium analyses or when limited to individuals with no supplemental calcium intake (results not shown). The associations between total calcium intake and risk of breast cancer were all weak and statistically nonsignificant when intake was modeled as a categorical variable (Table 3), as quintiles (Supplemental Table 7), or continuously (Figure 4). Results for dietary and total calcium intake did not differ by ER (Table 3) or joint ER/PR subtypes ( $P$ , test for common effects  $>0.4$ , Supplemental Table 8).

The associations between total milk, hard cheese, cottage/ricotta cheese, yogurt, dietary calcium, and total calcium intake and risk of overall, ER-positive, and ER-negative breast cancer generally did not vary significantly by BMI, menopausal status, or age at diagnosis. Some differences by region and follow-up time were noted (Figures 3 and 4, Supplemental Tables 5 and 9). For example, the following associations were modified by region: hard cheese intake and risk of ER-positive breast cancer ( $P$ , test for interaction = 0.03), cottage/ricotta cheese and risk of ER-negative breast cancer ( $P$ , test for interaction = 0.001), and dietary calcium and risk of ER-negative breast cancer ( $P$ , test for interaction = 0.02) where stronger associations were observed among cohorts outside of North America. A suggestively stronger association was also observed for total milk intake and risk of ER-negative breast cancer among cohorts outside of North America ( $P$ , test for interaction = 0.06). The associations for dietary and total calcium did not vary by total vitamin D intake ( $P$ , test for interaction  $>0.19$ , results not shown). When we examined supplemental calcium intake stratified by tertiles of dietary calcium intake, no evidence of an interaction was found for the association between supplemental calcium intake and risk of breast cancer ( $P$ , test for interaction = 0.86, results not shown).

**Discussion**

In this pooled analysis, we found null or very weak inverse associations for the consumption of total milk, yogurt, hard cheese, cottage/ricotta cheese, ice cream, dietary calcium, and total calcium with risk of overall and ER-positive breast cancer. For ER-negative breast cancer, modest inverse associations were observed for yogurt and cottage/ricotta cheese consumption when modeled as categorical variables. Results were generally



**FIGURE 2** Study-specific and pooled multivariable HRs comparing  $\geq 25$  versus 0 g/d of cottage/ricotta cheese intake and risk of (A) estrogen-receptor-positive breast cancer and (B) estrogen-receptor-negative breast cancer. The squares and horizontal lines correspond to the study-specific HRs and 95% CIs for the comparison of  $\geq 25$  g/d to 0 g/d of cottage/ricotta cheese intake. The BWHS (The Black Women's Health Study), CLUE II (CLUE II: Campaign Against Cancer and Heart Disease), CPS II (Cancer Prevention Study II Nutrition Cohort), JPHC I (Japan Public Health Center-Based Study Cohort I), ORDET (Hormones and Diet in the Etiology of Breast Cancer Study), and SMC (Swedish Mammography Cohort) were excluded from the figure because these studies did not measure cottage/ricotta cheese intake. The size of the squares reflects the study-specific weight (inverse of the variance). The diamond represents the pooled multivariable HR and 95% CI. BCDDP, Breast Cancer Detection Demonstration Project Follow-up Study; CARET,  $\beta$ -Carotene and Retinol Efficacy Trial; CNBSS, Canadian National Breast Screening Study; CTS, California Teachers Study; IWHS, Iowa Women's Health Study; MCCS, Melbourne Collaborative Cohort Study; MEC, Multiethnic Cohort; NHS a, Nurses' Health Study (part a); NHS b, Nurses' Health Study (part b); NHS II, Nurses' Health Study II; NIH-AARP, NIH-AARP Diet and Health Study; NLCS, Netherlands Cohort Study; NYUWHS, New York University Women's Health Study; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; WHS, Women's Health Study; WLHS, Women's Lifestyle and Health Study.

consistent across studies and population subgroups defined by menopausal status at diagnosis, age at diagnosis, and BMI.

A previous meta-analysis of cohort and case-control studies showed a modest inverse relation between dairy consumption and overall breast cancer risk and stronger inverse associations for yogurt and low-fat dairy products (14). Of the 17 cohorts in that meta-analysis examining diet during mid to later adulthood, 7 were included in our pooled analysis but had 1–7 y longer follow-up. The meta-analysis included 10 studies that did not compute total energy intake, did not measure long-term usual diet covering the past 6 mo or 1 y, or did not validate the dietary assessment tool, thus these cohorts were not included in our study as they did not meet our inclusion criteria. Our study included another 14 cohorts that had not previously examined dairy products and breast cancer, minimizing the influence of publication bias, a common limitation of meta-analyses of the published literature (61, 62). The meta-analysis did not examine breast cancer subtypes, whereas our study showed stronger associations for yogurt and cottage/ricotta cheese intake with risk of ER-negative than ER-positive breast cancer.

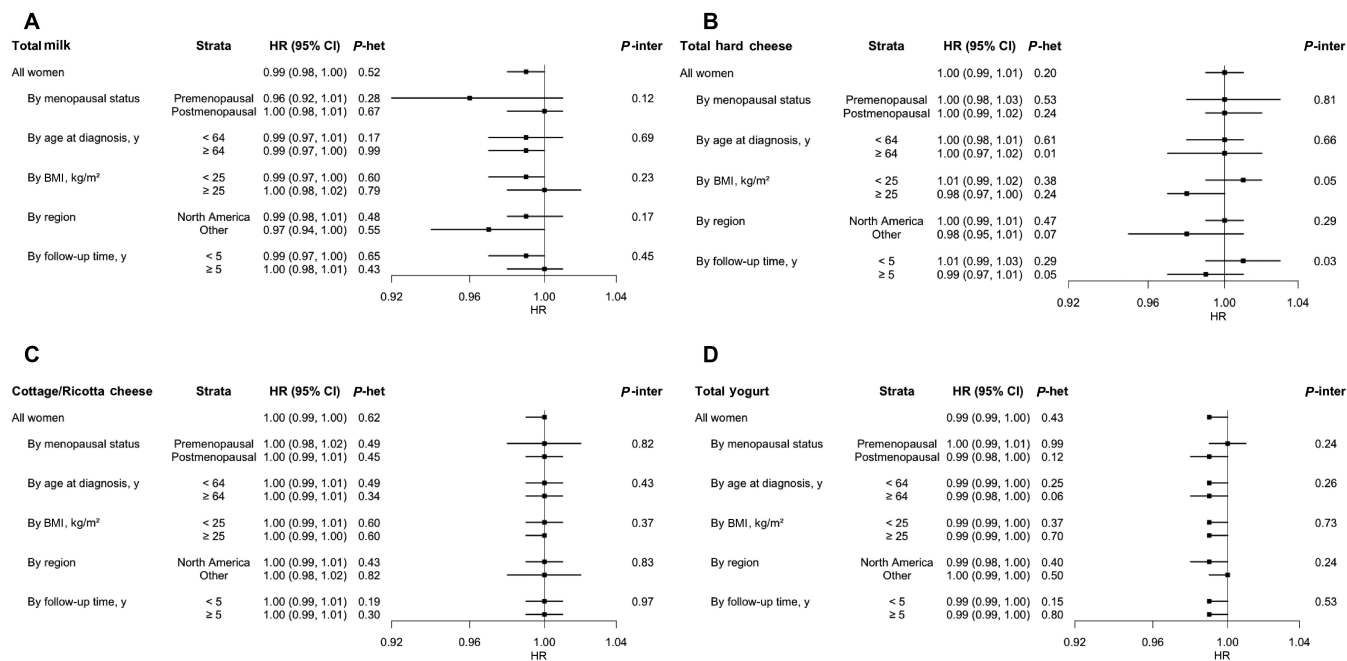
There are a few explanations for the inverse association observed for yogurt intake. Yogurt consumption does not increase

circulating IGF-1 as has been shown for other dairy products (63). Probiotics and fermented dairy products have been shown to boost intestinal microbiome richness, which might increase urinary estrogen excretion (64), induce apoptosis of breast cancer cell lines (65), and counteract dietary and genetic predisposition to mammary cancer in mice (66). Moreover, probiotics have been shown to be enriched in controls compared with breast cancer cases (67).

A lower risk of ER-negative breast cancer was also associated with a higher intake of cottage/ricotta cheese but not hard cheese. This may be attributable to differences in viable bacterial counts between cottage/ricotta cheese and hard cheese that occur during manufacturing and storage (68–70); for example, evidence has shown that the abundance of probiotic strains in low-fat hard cheese decreased over the aging process (71). When we stratified by region, the inverse association for cottage/ricotta cheese intake and ER-negative breast cancer was shown only among studies outside of North America. The regional differences might potentially be due to differences in food regulations, food processing, farming practices, or nutrient content.

Our findings on calcium intake and overall breast cancer risk are consistent with a meta-analysis of 11 prospective





**FIGURE 3** Pooled multivariable HRs and 95% CIs for intake of dairy products and risk of breast cancer stratified by participant characteristics, region, and follow-up time. Pooled multivariable HRs (solid circles) of breast cancer and 95% CIs (horizontal lines) are plotted on a log scale for intake of (A) total milk (per 250 g/d increment), (B) total hard cheese (per 14 g/d increment), (C) cottage/ricotta cheese (per 10 g/d increment), and (D) total yogurt (per 25 g/d increment) stratified by participant characteristics, region, and follow-up time. The *P* value, test for between-studies heterogeneity (*P*-het) was calculated using the *Q* statistic; the *P* value, test for interaction (*P*-inter) was calculated using metaregression.

cohort studies (of which 6 were included in our study) (9). Studies suggest that higher dietary calcium can markedly suppress Western-diet induced hyperproliferation of epithelial cells in mice (72, 73), exert a prodifferentiation effect on mammary gland cells (74), and reduce the incidence of mammary tumors in rats (75). Yet, in the Women's Health Initiative, calcium and vitamin D supplementation was not associated with breast cancer risk (76), nor with mammographic density [higher breast density is associated with higher breast cancer risk (77)] between the intervention and placebo groups (78). However, the low intervention dose, study duration, population studied (>60% were ≥60 y old at baseline), and nonadherence may have contributed to the null findings. Our study and the meta-analysis (9) both found slightly stronger, although still weak, associations for dietary calcium than for calcium from supplements, suggesting a synergistic effect of calcium and other nutrients in dairy foods and/or effects of nutrients in dairy foods that are highly correlated with calcium. It is also possible that supplemental calcium reduces breast cancer risk only among women who are calcium deficient, resulting in supplementation having minimal benefit above and beyond adequate calcium intake from food. Although we do not have a measure of whether women were calcium deficient, the association for supplemental calcium intake with risk of overall breast cancer did not vary across tertiles of dietary calcium intake in our study.

The main strength of our study is that we analyzed the primary participant-level data from 21 prospective cohort studies, which made it possible to harmonize the definitions of the outcomes, exposures, and confounding variables. Harmonization, in turn, reduced potential sources of heterogeneity across studies due to different exposure and covariate definitions and use of different

analytic approaches. Analyzing the participant-level data also permitted more flexibility in the analyses and estimation of finer dose-response relations than possible in meta-analyses of published studies. In addition, the large sample size provided adequate statistical power to examine breast cancer subtypes defined by hormone receptor status, particularly the less common subtypes. Lastly, the adjustments for known breast cancer risk factors minimized the likelihood of residual confounding strongly influencing our results. In fact, despite the differences in the assessment methods used across studies for diet and confounding variables, there was no significant between-study heterogeneity in any of our main analyses.

Our study has limitations. Dietary intakes were inevitably measured with error. However, moderate to high correlations between the measurements by FFQ and by dietary record or similar instruments have been reported in validation studies (25, 38–48). After correcting for measurement error, the association between calcium intake and risk of breast cancer changed only slightly. Misclassification of the exposure and the covariates might exist given that only baseline measurements were available, however, the results stratified by follow-up time indicated little difference across strata. We were not able to estimate consumption during earlier life periods, which could be biologically more relevant (79). A recent study found that adolescent consumption of high-fat dairy products was positively associated with ER-negative-PR-negative breast cancer (80). We also could not further characterize other subtypes including luminal A, B, and basal-like subtypes. Although the amount of missing data was generally low for most of the covariates measured in each cohort study, some covariates were not available in a number of cohorts such as use of menopausal hormone therapy and history of benign



**TABLE 3** Pooled multivariable<sup>1</sup> adjusted HRs and 95% CIs for calcium intake and risk of breast cancer overall and for subtypes defined by estrogen receptor (ER)<sup>2</sup> status

Nutrients	Reference	Categories of intake					P <sub>trend</sub> <sup>3</sup>	P <sub>het</sub> <sup>4</sup>	I <sup>2</sup> <sup>5</sup>	P <sub>com</sub> <sup>6</sup>
		Category 1	Category 2	Category 3	Category 4	Category 5				
Pooled multivariable HR (95% CI)										
<b>Dietary calcium<sup>7</sup></b>										
No. cases	6976	11,699	9394	5268	3194	1327				
(ER+/-)	(3999/1061)	(6899/1708)	(5449/1281)	(3057/717)	(1861/442)	(774/158)				
Total	1.00 (Ref)	0.99 (0.96, 1.02)	0.98 (0.95, 1.02)	0.95 (0.91, 1.00)	0.93 (0.88, 0.99)	0.99 (0.91, 1.07)	0.004	0.19	22%	
ER+	1.00 (Ref)	1.00 (0.96, 1.04)	0.98 (0.93, 1.04)	0.96 (0.91, 1.02)	0.93 (0.86, 1.01)	1.00 (0.91, 1.11)	0.08	0.21	21%	0.71
ER-	1.00 (Ref)	0.99 (0.91, 1.08)	0.97 (0.88, 1.07)	0.96 (0.85, 1.08)	0.97 (0.86, 1.02)	1.04 (0.86, 1.26)	0.18	0.32	11%	
<b>Total calcium<sup>8</sup></b>										
No. cases	2749	5129	4698	3759	3915	5574				
(ER+/-)	(1553/395)	(3006/778)	(2754/666)	(2209/511)	(2351/510)	(3408/684)				
Total	1.00 (Ref)	0.99 (0.95, 1.04)	0.97 (0.93, 1.02)	0.96 (0.92, 1.02)	0.97 (0.91, 1.04)	0.97 (0.91, 1.04)	0.25	0.19	28%	
ER+	1.00 (Ref)	1.02 (0.96, 1.08)	1.00 (0.93, 1.06)	0.98 (0.92, 1.05)	1.01 (0.94, 1.10)	1.01 (0.93, 1.09)	0.80	0.20	26%	0.92
ER-	1.00 (Ref)	1.08 (0.95, 1.22)	1.04 (0.89, 1.22)	1.03 (0.86, 1.23)	1.02 (0.88, 1.18)	1.02 (0.88, 1.17)	0.57	0.82	<1%	

<sup>1</sup>Multivariable model includes race/ethnicity (white, African American, Hispanic, Asian), education (<high school, high school, >high school), BMI (<23, 23 to <25, 25 to <30, ≥30 kg/m<sup>2</sup>), height (<1.60, 1.60 to <1.65, 1.65 to <1.70, 1.70 to <1.75, ≥1.75 m except Japan Public Health Center-Based Study Cohort I: <1.50, 1.50 to <1.55, 1.55 to <1.60, 1.60 to <1.65, ≥1.65 m), alcohol consumption (0, >0 to <5, 5 to <15, 15 to <30, ≥30 g/d), energy intake (kcal/d, continuous), smoking status (never, past, current), physical activity (low, medium, high), age at menarche (<11, 11/12, 13/14, ≥15 y except Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: <10, 10/11, 12/13, ≥14 y), the combination of menopausal status and hormone replacement therapy use [premenopausal women and among postmenopausal women separate categories for never, past, and current users of hormone replacement therapy, except in the California Teachers Study, Canadian National Breast Screening Study, Multiethnic Cohort, New York University Women's Health Study (NYUWHS), Hormones and Diet in the Etiology of Breast Cancer Study, Swedish Mammography Cohort, and Women's Lifestyle and Health Study where the combination was modeled as premenopausal women and among postmenopausal women separate categories for never and ever users of hormone replacement therapy], oral contraceptive use (ever, never), parity (0, 1 to 2, ≥3, except for NYUWHS 0, ≥1), age at first birth (≤25, >25 y), history of benign breast disease (yes, no), family history of breast cancer (yes, no), age in years and year of questionnaire return were included as stratification variables.

<sup>2</sup>ER: estrogen receptor.

<sup>3</sup>P<sub>trend</sub>: the P value, test for trend was calculated using the Wald test statistic.

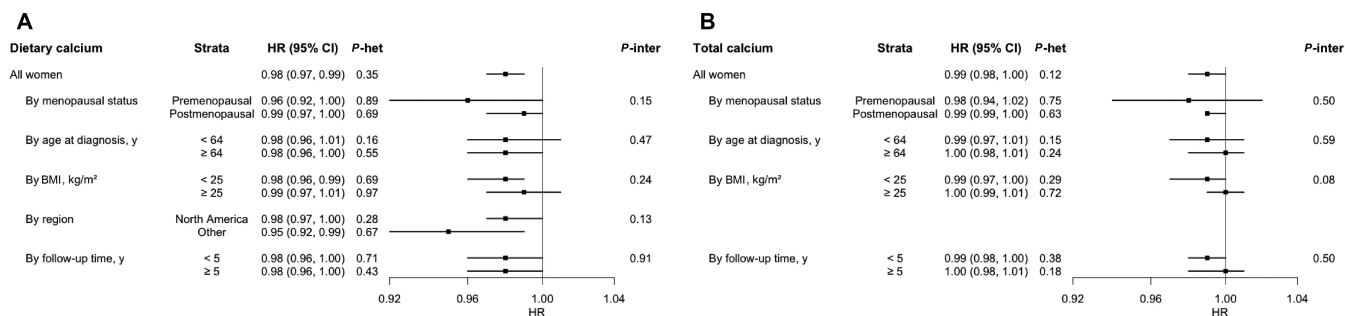
<sup>4</sup>P<sub>het</sub>: the P value, test for between-studies heterogeneity for the highest category was calculated using the Q statistic.

<sup>5</sup>I<sup>2</sup> for the highest category.

<sup>6</sup>P<sub>com</sub>: the P value, test for common effects for different subtypes defined by estrogen receptor status for the highest category was calculated using the Wald test statistic.

<sup>7</sup>The intake of dietary calcium for reference, category 1, category 2, category 3, category 4, and category 5 is <500, 500 to <700, 700 to <900, 900 to <1100, 1100 to <1400, ≥1400 mg/d, respectively.

<sup>8</sup>The intake of total calcium for reference, category 1, category 2, category 3, category 4, and category 5 is <500, 500 to <700, 700 to <900, 900 to <1100, 1100 to <1400, ≥1400 mg/d, respectively.



**FIGURE 4** Pooled multivariable HRs and 95% CIs for calcium intake and risk of breast cancer stratified by participant characteristics, region, and follow-up time. Pooled multivariable HRs (solid circles) of breast cancer and 95% CIs (horizontal lines) are plotted on a log scale for intake of (A) dietary calcium (per 350 mg/d) and (B) total (from foods and supplements) calcium (per 350 mg/d) stratified by participant characteristics, region, and follow-up time. The *P* value, test for between-studies heterogeneity (*P*-het) was calculated using the *Q* statistic; the *P* value, test for interaction (*P*-inter) was calculated using metaregression.

breast disease (Supplemental Methods). However, we do not expect that the unmeasured covariates had a strong influence on the observed associations as the age-adjusted estimates were very similar to the multivariable estimates. Lastly, our study population consisted predominantly of white women. The results might not be applicable to populations of other racial or ethnic compositions.

In summary, although concerns were raised that dairy products might contribute to a higher risk of breast cancer, this international study of over 1 million women suggested that adult dairy consumption is unlikely to be associated with higher risk of this common cancer and that higher fermented dairy product intake could potentially decrease the risk of the ER-negative subtype, if the aforementioned associations were causal. Evaluation of these associations in more racially/ethnically diverse populations and in those with higher fermented dairy product consumption may help elucidate further any relation between dairy foods and breast cancer risk.

We thank Shiaw-Shyuan Yaun and Tao Hou for their contributions to data management and statistical support. The author's contributions were as follows—all authors of this research manuscript: have participated in the planning, execution, and/or analysis of the study, and have read and approved the final manuscript. For each cohort, acknowledgments, and disclaimers are listed in **Supplemental Table 10**. The authors report no conflicts of interest.

## Data Availability

The data described in the manuscript will not be made available because we do not have permission to disclose or release the data from the participating cohorts as specified in their executed data use agreements.

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