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Usual consumption of specific dairy foods is associated with breast cancer in the Roswell Park Cancer Institute Databank and BioRepository

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Abbreviations:

BMI	body mass index
DBBR	Databank and BioRepository
ER+/-	estrogen receptor positive/negative
FFQ	food frequency questionnaire
OR	odds ratio
CI	confidence interval
RPCI	Roswell Park Cancer Institute

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ABSTRACT

Background. Dairy foods are complex mixtures which include nutrients and non-nutrient substances that could potentially influence cancer etiology, including breast cancer.

Objective. The purpose of this study was to examine associations between the types and quantity of dairy foods consumed and breast cancer among women participating in the Roswell Park Cancer Institute (RPCI) Data Bank and BioRepository (DBBR) between 2003 and 2014.

Methods. Archived clinical and questionnaire data were obtained from the DBBR from 1,941 women diagnosed with breast cancer between December 2003 and October 2014, and 1237 control participants. Intakes of dairy foods were queried with a self-administered food frequency questionnaire and grouped into monthly intakes of total dairy, milk, yogurt, low-fat cheese, other cheese, and sweet dairy. Odds ratios (OR) and 95% confidence intervals (CI) were estimated with unconditional logistic regression adjusting for age, race, BMI, menopausal status, energy intake, type of milk usually consumed, cigarette smoking status, and family history of breast cancer.

Results. Total dairy intakes were associated with a non-significant 15% reduction in breast cancer risk (p=0.11). Higher intakes of yogurt were associated with reduced risk of breast cancer (OR 0.61, 95% CI 0.46-0.82) and higher intakes of American, cheddar, and cream cheeses were associated with a marginally significant increased risk (OR 1.53, 95% CI 0.99-2.34; p=0.05). Associations with dairy foods were mixed when stratified by estrogen receptor status, and in general reflected those of overall breast cancer. However, we observed positive associations between milk intake and risk of ER- breast cancer (OR 1.58, 95% CI 1.05-2.37) and inverse associations between sweet dairy and ER+ breast cancer (OR 0.52, 95% CI 0.29-0.95).

Conclusions. Specific dairy foods may contribute to breast cancer risk in women, although risk varies by source of dairy. Future studies are warranted to confirm the protective potential of yogurt in this cancer.

INTRODUCTION

Several lines of evidence suggest that calcium and vitamin D containing foods, particularly dairy, may be important in the etiology of several cancers (1). Vitamin D, as measured by circulating levels of 25-hydroxyvitamin D, has been inversely associated with risk of colorectal cancer, and to a lesser degree with risk of breast cancer (2), yet evidence for associations with calcium intake has been inconsistent (1). Despite some supporting evidence from observational studies, supplemental low dose vitamin D and calcium was not shown to be preventive against breast cancer incidence in the Women's Health Initiative (WHI) (2,3). Aside from studies of vitamin D and calcium as single nutrients, evidence for dairy products in association with breast cancer risk is also variable, and dependent upon dose, dairy food form, and period of consumption (youth vs. adult) (4). This complexity is probably not unexpected, as dairy foods are complex mixtures and include several nutrients and non-nutrient substances that could potentially influence cancer etiology, through either increases or decreases in risk. Healthy lifestyle factors that may accompany dairy food consumption could further confound the associations, although to our knowledge, this has not been directly documented in the literature. To better understand these complex relationships and to facilitate the synthesis of evidence-based dietary recommendations, more epidemiologic studies are necessary. The purpose of this study was to examine the associations between the types and quantity of dairy foods consumed and breast cancer among women participating in the Roswell Park Cancer Institute Data Bank and BioRepository between 2003 and 2014.

METHODS

Archived clinical and questionnaire data were obtained from the Data Bank and BioRepository (DBBR) at Roswell Park Cancer Institute (RPCI) from 1941 women diagnosed with breast cancer between December 2003 and October 2014, and 1237 control participants.

DBBR control participants had no reported history of cancer, and were recruited from those who were accompanying cases (friends and family members), were community volunteers, or were employees of RPCI. Controls were randomly selected from this pool of healthy participants and frequency matched on 10 year age strata to cases. The DBBR is a shared resource at Roswell Park Cancer Institute that provides biospecimens and linked data for studies of cancer etiology and prognosis (5). The protocol for DBBR was approved by the RPCI Institutional Review Board and all participants provided signed informed consent. Demographics, anthropometrics, medical history, lifestyle variables, and food habits were ascertained with a self-administered extensive epidemiologic questionnaire, and clinical characteristics for women with breast cancer were obtained from the RPCI tumor registry through linkage with DBBR. We excluded women with energy intakes <2092 kJ/d or >18828 kJ/d (n=119), leaving 1857 cases and 1202 controls for analyses.

As part of the self-administered questionnaire, participants completed a detailed food frequency questionnaire, which queried the usual frequency of consumption in the year prior to diagnosis of 110 foods and beverages. Nutrient intake was calculated from the FFQ using USDA food composition data and standard nutrient calculation algorithms. Dairy foods queried on the FFQ included fluid milk, yogurt, cheese (American, cheddar, or cream cheese), low fat cheese, ricotta or cottage cheese, ice cream, low-fat frozen desserts, and pudding. Dairy foods were classified according to nutrient content and culinary use, and were expressed as servings per month calculated from the FFQ as the product of frequency of use and portion size summed across group members. Separate questions were not queried for milk by fat content; rather, a single qualitative question was included that asked what types of milk were usually consumed that allowed multiple choices to be recorded but did not capture the proportion of each milk consumed. Therefore, we were unable to examine associations with milk by fat content. Monthly dairy consumption was categorized to represent typical daily serving sizes, and ranges varied according to dairy group. Dairy intakes were not normally distributed; therefore, dairy consumption was evaluated as categorical variables.

Statistical methods. Statistical analyses were conducted with SAS 9.3 for Windows (Cary, NC). All tests were two-sided and considered statistically significant at $p < 0.05$. Menopause was defined as self-reported cessation of menses either as natural menopause or hysterectomy with bilateral oophorectomy. Differences in characteristics between cases and controls were assessed with standard descriptive statistics: differences in continuous characteristics between cases and controls were assessed with Student's t-tests and with Pearson's chi square for categorical variables. Odds ratios (OR) and 95% confidence intervals (CI) for the associations of breast cancer with each dairy group and total dairy were estimated with unconditional logistic regression adjusting for age (continuous), race (Caucasian/other), BMI (continuous), menopausal status (pre- or postmenopausal), energy intake (continuous), type of milk usually consumed (nonfat, low-fat, whole, or non-dairy milk), cigarette smoking status (never, former, current), and family history of breast cancer (yes/no). Although unadjusted ORs were similar to the adjusted estimates, adjustment for the above variables slightly strengthened the observed associations. In the interest of clarity, only the adjusted estimates are presented. Additional covariates (education, food groups other than dairy, alcohol, physical activity, other lifestyle variables) were assessed for inclusion, but did not substantially modify the risk estimates. Analyses were conducted for breast cancer overall and further assessed by estrogen receptor status (ER+ and ER-). If data for ER status were missing, those cases were excluded for that analysis. Finally, as stratification by menopausal status is conventional in breast cancer research, we had initially conducted stratified analyses. However, estimates were similar between pre- and postmenopausal women; therefore, overall breast cancer estimates are presented herein.

RESULTS

The descriptive characteristics of the women with breast cancer and healthy controls selected from the RPCI DBBR and included in this analysis are shown in **Table 1**. Among pre- and postmenopausal women, those with breast cancer tended to be older than those without breast cancer (mean±SD 45.5±5.9 vs. 44.7±5.9 years and 64.6±8.9 vs. 62.3±8.6 years, pre-and postmenopausal cases and controls, respectively). Postmenopausal women with breast cancer had higher mean BMI compared to postmenopausal women without breast cancer (29.2±6.4 vs. 28.4±6.1, kg/m^2). Age at menarche was comparable between cases and controls but cases were less likely than controls to have never had children. Premenopausal cases were more likely to be never smokers compared to premenopausal controls, whereas postmenopausal cases were more likely to be current smokers compared to postmenopausal controls. As expected, family history of breast cancer was higher among women with breast cancer compared to those without breast cancer.

The clinical characteristics of women with breast cancer are detailed in **Table 2**. The majority of breast cancer was stage 2 or lower, among both pre- and postmenopausal women. ER- cancers were present in 20.0% of premenopausal and 16.3% of postmenopausal women. Approximately 25% of tumors were PR-. HER2 status was positive in 12.8% of premenopausal and 7.2% of postmenopausal women.

Although we were unable to examine associations between breast cancer and milk by fat content, adjustment for types of milk usually consumed significantly affected the majority of the estimates and thus was included in all models. In our sample, preference was distributed as follows: 14% drank no milk, 24% usually drank nonfat milk, 20% usually drank 2% milk, 11% usually drank 1% milk, 4% usually drank whole milk, and 27% drank various combinations of milk types (data not shown).

Odds ratios and 95% confidence intervals for associations between dairy intakes and breast cancer are shown in **Table 3**. For total dairy, women in the highest vs. lowest category of intake (≥42 svg/mo vs <14 svg/mo) had a marginally significant 15% lower risk of breast cancer (OR 0.85, 95%CI 0.68-1.06; p=0.11). The inverse association between total dairy intake and breast cancer appeared to be mainly attributable to higher yogurt intakes (OR 0.61, 95% CI 0.46-0.82). Contrary to our observations between yogurt and breast cancer, we observed a marginally significant 53% increased risk of breast cancer associated with higher 'other cheese' (American, cheddar, cream cheese) intakes (OR 1.53, 95% CI 0.99-2.34; p=0.05). No associations were observed with the remaining dairy groups and breast cancer in these data.

Associations between intakes of total dairy and specific dairy foods and ER+ and ER- breast cancer are shown in **Table 4**. We observed a borderline significant 18% reduction in the risk of ER+ cancer among women with highest vs. lowest total dairy intakes (OR 0.82, 95% CI 0.64-1.04; p=0.10). Similar to breast cancer risks overall, yogurt intake was statistically significantly negatively associated with risk of both ER+ and ER- breast cancer (OR 0.65, 95% CI 0.48-0.89 and OR 0.61, 95% CI 0.38-0.99, ER+ and ER- respectively). However, the estimates were comparable supporting no effect of ER status on the observed associations (p for heterogeneity=0.73). Intakes of lowfat cheese were inversely associated with risk of ER- breast cancer (OR 0.54, 95% CI 0.29-0.99), although the estimates were not statistically significantly different from those associated with ER+ breast cancer (p for heterogeneity=0.23). Associations between milk intake and ER status were significantly different (p for heterogeneity=0.04) with no associations observed for ER+ breast cancer, but increased risks of ER- breast cancer (OR 1.58, 95% CI 1.05-2.37). Finally, we observed significant heterogeneity in associations between sweet dairy foods and ER status (p=0.01) wherein higher intakes were inversely associated with ER+ breast cancer (OR 0.52, 95% CI 0.29-0.95), but appeared to increase risk of ER- breast cancer, although this association was not statistically significant (OR 1.55, 95% CI 0.89-2.70).

DISCUSSION

In a recent meta-analysis, total dairy and yogurt consumption were inversely associated with breast cancer risk, especially among premenopausal women (4). Similarly, in this hospital-based case-control study of usual adult dairy consumption and breast cancer, we observed total dairy consumption to be negatively associated with breast cancer, and especially ER+ cancer. Whereas milk consumption was weakly negatively associated with breast cancer overall, higher intakes were strongly positively associated with ER- postmenopausal breast cancer. Unexpectedly, consumption of sweetened dairy foods (pudding, low-fat frozen yogurt, and ice cream) was inversely related to ER+ breast cancer.

Dairy foods are important sources of several nutrients that could favorably impact cancer risk, including vitamin D, calcium, conjugated linoleic acid, butyrate, and other nutrients and phytochemicals, but also contain substances, such as IGF-1 and other growth hormones, that may adversely affect risk (6,7). In the Nurses' Health Study (NHS), calcium and vitamin D were inversely related to breast cancer incidence among premenopausal women (8). Multivariable relative risk (RR) for highest calcium intake versus lowest calcium intake was 0.80, 95% CI 0.58-1.12. When further separated into dairy versus nondairy calcium, dairy calcium was associated inversely with risk. Consumption of >800 mg of calcium versus <200 mg of calcium had a RR of 0.69, 95% CI=0.48 to 0.98. Total vitamin D intake was also associated with lower risk of breast cancer in premenopausal women (RR 0.72, 95% CI 0.55-0.94) in the NHS.

On the other hand, the Women's Health Initiative, a large randomized trial of vitamin D and calcium in postmenopausal women, did not show a beneficial effect of supplementation of these nutrients on breast cancer risk in women already consuming supplements (3), a common practice among postmenopausal women. However, associations with dairy foods and breast cancer were not assessed in WHI, and, to our knowledge, clinical trials testing the impact of dairy foods on cancer risk have not been conducted. Given that dairy foods are complex mixtures of nutrients and non-nutrient substances that could be negatively as well as positively associated with risk, an examination of whole foods rather than single nutrients is warranted.

Whereas dairy foods may be important contributors of nutrients with anti-carcinogenic potential, inverse associations may be partly explained by healthier lifestyle adopted by those who consume low fat dairy products. These factors could include tobacco avoidance, being physically active, use of dietary supplements, and interest in health promoting behaviors, although the literature is sparse concerning documentation of these associations. However, adjustment for lifestyle factors such as physical activity did not have a large impact on our observed estimates, and we were unable to examine dairy consumption according to fat content, as our FFQ was not designed to query this level of detail. However, adjustment for usual type of milk consumed was an important covariate and suggests that part of our associations could be due to reduced fat consumption from low-fat dairy products as the majority of milk consumed was nonfat or reduced fat.

Despite fluid milk consumption providing the largest contribution to total dairy intake in our study (R^2=0.72), we observed fairly substantial inverse associations with yogurt consumption. Yogurt provides nutrients and non-nutrient compounds beyond those found in fluid milk, including probiotics and prebiotics that could promote a healthy gut bacterial community structure (9). The gut bacterial community has been implicated in both innate as well as adaptive immunity, which suggests that dysbiosis may contribute to suboptimal immune function and subsequent disease development (10,11). Therefore, it is possible that higher yogurt consumption may be favorably impacting immune function and subsequent cancer risk.

Contrary to our expectations, we observed inverse associations between intakes of sweet dairy foods and ER+ breast cancer, although no associations with breast cancer overall. The sweet dairy group included ice cream, frozen yogurt, low-fat frozen desserts, and pudding, and therefore contributed primarily to added sugar intakes. Higher sugar intakes could increase insulin secretion which has been associated with cancer etiology; therefore, one would expect a positive association between intakes of these foods and breast cancer. Furthermore, intake of these foods was low and did not contribute a large proportion of the variation in total dairy intakes ($R^2 \leq 0.04$). Although there may be unknown mechanisms responsible for this finding, it is also possible that it is due to chance.

Whereas the majority of associations between dairy intake and breast cancer in this study were inverse, a strong positive association was noted between high vs low consumption of milk and ER- postmenopausal breast cancer. Fluid milk is relatively high in IGF-1 as a consequence of growth hormones used to increase milk production (12). As IGF-1 and the estrogen receptor participate in substantial cross-talk, positive associations would be more likely between ER+ breast cancer and dairy, which is contrary to our current findings (13-15). Alternately, milk protein consumption has been shown to increase postprandial hyperinsulinemia which could potentially increase cell growth and proliferation, independent of the estrogen receptor (16).

The current study is subject to limitations common in hospital-based case-control studies. Case-control studies may be susceptible to recall bias if the cases are more likely than controls to remember an exposure. Both cases and the majority of controls were recruited at RPCI or at cancer-focused community events and participants completed the questionnaire at home. Whereas the controls did not have a cancer diagnosis, many were family members or friends of non-breast cancer patients seeking care at RPCI, and thus may also be more aware of the role of diet in cancer etiology, thus reducing the differential recall between the groups.

Another possible limitation is that all cases were patients of RPCI and all controls were friends, relatives or community members of the surrounding area. Therefore, the results may not be generalizable to all women, but should be generalizable to the western New York catchment area.

Dietary intake was queried with a self-administered FFQ which included the majority of commonly consumed dairy foods. Accurate completion of an FFQ requires averaging of estimated intake of a fairly large number of foods and therefore, intake could be under- or over-estimated by this method. Measurement of absolute intake was not a goal of our study; rather we ranked participants on reported intake, which is standard epidemiologic methodology. Dairy intake in our sample was comparable to that reported in NHANES (17) and we are confident that intake estimates are adequate for United States populations. Finally, although the time period of interest was specified to be in the few years before diagnosis, this may not be the relevant time period for breast cancer development, particularly if growth hormones are of interest. Timing of dairy consumption was examined in the meta-analysis by Zang et al, and childhood consumption was not strongly associated with subsequent breast cancer risk (4).

In conclusion, we found inverse associations between total dairy intake and yogurt intake with breast cancer and positive associations between other cheese and breast cancer, as well as between milk and ER- breast cancer. Our study suggests that specific dairy foods may influence breast cancer risk, although the direction of the associations vary by food source. Future studies are also warranted to explore the mechanisms by which yogurt could contribute to risk reduction for breast cancer.

Authors contributions to manuscript. SEM, JH, and CBA designed and conducted research; SEM and JH analyzed data, wrote the manuscript, and had primary responsibility for final content; SEM, JH, CWB, EHW, SY, and CBA contributed to review and refinement of manuscript after initial analyses. All authors have read and approved the final manuscript.

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Table 1. Descriptive characteristics of breast cancer cases and controls, Roswell Park Cancer Institute Data Bank and BioRepository, 2003-2014[§]

	Premenopausal		Postmenopausal	
	Cases n=601	Controls n=470	Cases n=1256	Controls n=732
	Mean±SD			
Age, years	45.5±5.9*	44.7±5.9	64.6±8.9**	62.3±8.6
BMI, kg/m2	27.0±6.3	27.4±6.0	29.2±6.4	28.4±6.1
	n (%)			
Age at menarche, years				
≤11	96 (16.0)	94 (20.0)	259 (20.6)	146 (20.0)
12	202 (33.6)	153 (32.6)	390 (31.1)	230 (31.4)
13	177 (29.5)	123 (26.2)	356 (28.3)	212 (29.0)
14	60 (10.0)	61 (13.0)	140 (11.2)	81 (11.1)
15	36 (6.0)	20 (4.3)	57 (4.5)	29 (4.0)
≥16 or never had period	30 (5.0)	19 (4.0)	54 (4.3)	34 (4.6)
Age at first birth				
Nulliparous	133 (22.1)*	131 (27.9)	203 (16.2)*	134 (18.3)
≤19	53 (8.8)	57 (12.1)	205 (16.3)	80 (10.9)
20-24	149 (24.8)	100 (21.3)	466 (37.1)	258 (35.3)
25-29	140 (23.3)	102 (21.7)	250 (19.9)	175 (23.9)
30-34	99 (16.5)	58 (12.3)	99 (7.9)	64 (8.7)
≥35	27 (4.5)	22 (4.7)	33 (2.6)	21 (2.9)
Smoking status				
Never	353 (58.7)**	262 (55.7)	613 (48.8)*	387 (52.9)
Former	166 (27.6)	144 (30.6)	531 (42.3)	300 (41.0)
Current	82 (13.6)	64 (13.6)	112 (8.9)	45 (6.2)
Family history of breast cancer				
No	471 (78.4)**	403 (85.7)	950 (75.6)	603 (82.4)
Yes	130 (21.6)	67 (14.3)	306 (24.4)	129 (17.6)

[§]Excludes women with implausible dietary data

Differences between cases and controls assessed with Student's t-test for continuous variables and Pearson's chi-square for categorical variables; *p<0.05, **p<0.01

Table 2. Clinical characteristics of women with breast cancer, Roswell Park Cancer Institute Data Bank and BioRepository, 2003-2014

	Premenopausal (n=601)	Postmenopausal (n=1256)
	n (%)	
Stage		
0	92 (15.3)	156 (12.4)
1	225 (37.4)	591 (47.1)
2	181 (30.1)	318 (25.3)
3	65 (10.8)	80 (6.4)
4	10 (1.7)	25 (2.0)
Unknown/Missing	28 (4.7)	86 (6.9)
Estrogen receptor status		
Negative	120 (20.0)	205 (16.3)
Positive	413 (68.7)	880 (70.1)
Missing	68 (11.3)	171 (13.6)
Progesterone receptor status		
Negative	149 (24.8)	341 (27.2)
Positive	384 (63.9)	745 (59.3)
Missing	68 (11.3)	169 (13.5)
HER2		
Borderline	0	2 (0.2)
Negative	374 (62.2)	818 (65.1)
Positive	77 (12.8)	90 (7.2)
Missing	150 (25.0)	346 (27.6)

Table 3. Odds ratios and 95% confidence intervals for associations between total dairy and specific dairy foods and breast cancer, Roswell Park Cancer Institute Data Bank and BioRepository, 2003-2014

Servings/mo	Case	Control	OR (95% CI)
Total dairy			
0-14	424	245	1.00
14-28	457	250	1.10 (0.88-1.38)
28-42	360	241	0.93 (0.73-1.18)
≥42	616	466	0.85 (0.68-1.06)
Milk			
0	495	322	1.00
≤ 14	852	535	0.94 (0.78-1.14)
14-28	250	172	0.88 (0.69-1.13)
≥28	260	173	0.96 (0.75-1.24)
Yogurt			
0	417	196	1.00
≤ 14	1268	843	0.78 (0.64-0.96)
≥14	172	163	0.61 (0.46-0.82)
Lowfat cheese			
0	191	115	1.00
≤ 14	1513	958	0.99 (0.76-1.27)
≥14	153	129	0.84 (0.60-1.19)
Other cheese			
0	82	63	1.00
0-14	1613	1034	1.28 (0.91-1.82)
≥14	162	105	1.53 (0.99-2.34)
Sweet dairy			
0	74	41	1.00
0-14	1537	974	0.89 (0.60-1.33)
14-28	178	136	0.75 (0.47-1.18)
≥28	68	51	0.73 (0.42-1.26)

Odds ratios and 95% confidence intervals estimated with unconditional logistic regression adjusting for age, race, BMI, menopausal status, energy intake, type of milk usually consumed (nonfat, low-fat, whole, or non-dairy milk), cigarette smoking status, and family history of breast cancer

Table 4. Odds ratios and 95% confidence intervals for associations between total dairy and specific dairy foods and breast cancer by estrogen receptor status, Roswell Park Cancer Institute Data Bank and BioRepository, 2003-2014

	Controls (n=1202)	ER positive (n=1293)	OR (95% CI)	ER negative (n=205)	OR (95% CI)	p for heterogeneity
Svg/mo						
Total dairy						
0-14	245	301	1.00	72	1.00	0.24
14-28	250	326	1.11 (0.87-1.42)	70	0.97 (0.66-1.43)	
28-42	241	249	0.91 (0.70-1.18)	64	0.99 (0.66-1.46)	
≥42	466	417	0.82 (0.64-1.04)	119	1.00 (0.68-1.46)	
Milk						
0	322	355	1.00	76	1.00	0.04
≤ 14	535	586	0.90 (0.74-1.11)	142	1.03 (0.74-1.42)	
14-28	172	178	0.87 (0.66-1.14)	46	1.12 (0.74-1.71)	
≥28	173	174	0.88 (0.67-1.16)	61	1.58 (1.05-2.37)	
Yogurt						
0	196	290	1.00	74	1.00	0.73
≤ 14	843	883	0.81 (0.66-1.00)	218	0.72 (0.52-0.98)	
≥14	163	120	0.65 (0.48-0.89)	33	0.61 (0.38-0.99)	
Lowfat cheese						
0	115	125	1.00	40	1.00	0.23
≤ 14	958	1062	1.06 (0.80-1.40)	264	0.82 (0.55-1.23)	
≥14	129	106	0.92 (0.63-1.35)	21	0.54 (0.29-0.99)	
Other cheese						
0	63	58	1.00	13	1.00	0.92
≤14	1034	1125	1.32 (0.90-1.93)	283	1.31 (0.70-2.42)	
≥14	105	110	1.56 (0.97-2.50)	29	1.44 (0.68-3.03)	
Sweet dairy						
0†	41	56	1.00			
0-14	974	1074	0.82 (0.54-1.26)	276	1.00	0.01
14-28	136	124	0.68 (0.42-1.11)	29	0.82 (0.53-1.26)	
≥28	51	39	0.52 (0.29-0.95)	20	1.55 (0.89-2.70)	

Odds ratios and 95% confidence intervals estimated with unconditional logistic regression adjusting for age, race, BMI, menopausal status, energy intake, type of milk usually consumed (nonfat, low-fat, whole, or non-dairy milk), cigarette smoking status, and family history of breast cancer

†Categories collapsed to 0-14, 14-28, and >28 for ER negative cancer