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Dairy foods and nutrients in relation to risk of ovarian cancer and major histological subtypes

Melissa A. Merritt[1,2,3,*], **Daniel W. Cramer**[1,2], **Allison F. Vitonis**[2], **Linda J. Titus**[4], and **Kathryn L. Terry**[1,2]

[1]Department of Epidemiology, Harvard School of Public Health, Boston, MA

[2]OB/GYN Epidemiology Center, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[3]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA

[4]Department of Community and Family Medicine, Dartmouth Medical School, Hanover, NH

Abstract

Inconsistent results for the role of dairy food intake in relation to ovarian cancer risk may reflect the potential adverse effects of lactose, which has been hypothesized to increase gonadotropin levels, and the beneficial anti-proliferative effects of calcium and vitamin D. Using data from the New England case-control study (1909 cases; 1989 controls) we examined dairy foods and nutrients in relation to risk of ovarian cancer overall, histological subtypes, and rapidly fatal versus less aggressive disease. We used logistic regression and polytomous logistic regression to estimate odds ratios and 95% confidence intervals. In models that were simultaneously adjusted for total (dietary plus supplements) calcium, total vitamin D and lactose, we observed a decreased overall risk of ovarian cancer with high intake of total calcium (Quartile 4 (Q4, >1319 mg/day) *vs.* Quartile 1 (Q1, <655 mg/day), odds ratio (OR)=0.62, 95% Confidence Interval (CI)=0.49 – 0.79); the inverse association was strongest for serous borderline and mucinous tumors. High intake of total vitamin D was not associated overall with ovarian cancer risk, but was inversely associated with risk of serous borderline (Q4, >559 IU/day *vs.* Q1, <164 IU/day, OR=0.51, 95% CI=0.34–0.76) and endometrioid tumors (Q4 *vs.* Q1, OR=0.55, 95% CI=0.39-0.80). We found no evidence that lactose intake influenced ovarian cancer risk, or that risk varied by tumor aggressiveness in the analyses of intake of dairy foods and nutrients. The overall inverse association with high intake of calcium, and the inverse associations of calcium and vitamin D with specific histological subtypes warrant further investigation.

Keywords

dairy foods; calcium; vitamin D; lactose; ovarian cancer

Introduction

Differences in ovarian cancer incidence rates worldwide[1] suggest that lifestyle factors, including diet, may play an important role in risk for this disease. The observation that per

[*]Corresponding author, Melissa A. Merritt, 221 Longwood Avenue, Boston, MA, 02115, Mailstop: BLI 350, Phone: +1 1-617-732-7066, Fax: +1 1-617-732-4899, merritt@jimmy.harvard.edu.

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capita milk consumption and lactase persistence (the ability to digest lactose after childhood) is significantly positively correlated with ovarian cancer incidence worldwide highlights the potential role of dairy food consumption in ovarian carcinogenesis[2]. It has been hypothesized that the galactose component of dairy sugar or lactose might have a toxic effect on oocytes and prematurely raise gonadotropins in a similar manner to that observed in mouse/rat models where high lactose diets led to ovulatory disfunction and hypogonadism[3–5].

Subsequent epidemiologic studies that evaluated consumption of dairy foods or lactose in relation to ovarian cancer risk produced conflicting results with case-control studies generally finding a null association[6] while cohort studies showed a more consistent positive association between high intake of lactose[6–8] and/or skim/low fat milk[7] or milk (all types)[6] and risk of ovarian cancer.

Inconsistencies could be due to the contrasts of intake that were examined, potential differences in the distribution of histological subtypes across studies, or may reflect differences in long term versus recent dairy food consumption or in the types of dairy products consumed and their different nutrient contents. We hypothesized that foods higher in lactose or fats could have a more harmful effect while foods with higher levels of calcium or vitamin D might be beneficial by down-regulation of circulating parathyroid hormone leading to decreased cell proliferation[9, 10]. In this large population-based case-control study of ovarian cancer, we evaluated intake of dairy foods and their components (lactose, calcium, vitamin D) in relation to ovarian cancer risk overall, the main histological subtypes, and rapidly fatal versus less aggressive disease.

Materials and Methods

Study population

Details regarding case and control enrollment in the New England case-control (NECC) study were described previously[11, 12]. Briefly, 3957 women residing in eastern Massachusetts or New Hampshire with a diagnosis of incident ovarian cancer were identified through hospital tumor boards and statewide cancer registries. Of these, 3083 (78%) cases met eligibility criteria and 2203 (71%) were enrolled. This analysis was restricted to 2076 cases with epithelial tumors. Controls were identified through random digit dialing, drivers' license lists and town resident lists. In the first study phase (1992–1997), 420 (72%) and 102 (51%) of the eligible controls identified through random digit dialing and town resident lists, respectively, agreed to participate. In the second (1998–2003) and third (2003–2008) phases, 4366 potential controls were identified of whom 2940 (67%) were eligible; 1362 (46%) declined to participate by phone or by mail via an “opt-out” postcard and 1578 (54%) were enrolled. Controls were frequency matched to cases on age and state of residence. Study participants were interviewed in-person at the time of enrollment about known and putative ovarian cancer risk factors that occurred at least one year before diagnosis (for cases) or enrollment (controls). Institutional review boards at the Brigham and Women’s Hospital and the Dartmouth Medical School approved the study and all participants provided written informed consent.

Tumor histological subtype and behavior (invasive *vs.* borderline) was abstracted from pathology reports that had been reviewed by a gynecologic pathologist. We examined five major histological subtypes of ovarian cancer; serous borderline or invasive, mucinous, endometrioid and clear cell tumors. We also evaluated invasive ovarian cancer cases by tumor aggressiveness (rapidly fatal and less aggressive) based on the time interval between diagnosis and death reported in the National Death Index. Rapidly fatal cases were those who died due to any cause within 3 years (the cause of death was unavailable) and less

aggressive cases were those who died >3 years post-diagnosis or those who were alive at follow-up.

Diet assessment

Dietary intake that occurred at least one year before diagnosis or study enrollment was assessed at the time of enrollment using a semi-quantitative food frequency questionnaire (FFQ)[13, 14] which has been previously shown to provide valid estimates of skim/low fat milk, whole milk and yogurt intake with correlation coefficients between the dietary questionnaire and the 1-week diet records of 0.81, 0.62 and 0.94, respectively[15]. For calcium, correlation coefficients of 0.56 with supplements and 0.51 without supplements were reported between the dietary questionnaire and 1-week diet records[16]. For vitamin D, reported intake via the dietary questionnaire and plasma concentrations of 25-OH vitamin D were moderately correlated (correlation coefficients of 0.35 and 0.25 with and without supplements, respectively)[17].

Specific dairy foods that were assessed for this study included skim/low fat milk, whole milk, cream, sour cream, non-dairy coffee whitener, sherbet/ice milk, ice cream, yogurt, cottage/ricotta cheese, other cheeses and butter. Additional food items that are important sources of calcium, including broccoli and leafy green vegetables, also were included in the FFQ. The questionnaire included questions on supplemental vitamin usage; for multivitamins respondents were asked about the number of pills per week and the specific brand and for single supplements respondents were asked about the dosage per day and the duration of use. Dietary nutrient intake (lactose, calcium and vitamin D) was calculated by multiplying the frequency of intake of each food containing the nutrient by the nutrient content of specified portions determined from the food composition values available from the U.S. Department of Agriculture food composition data[18]. In order to provide information about the primary dietary sources of each nutrient, we confirmed that there were similar frequencies of intake of dairy foods in the NECC and the Nurses' Health Study (NHS) which also is comprised of U.S. residents and diet was assessed over a similar time period[7]. In the NHS in 2002, the primary dietary sources of lactose were skim/ low fat milk (63%) and yogurt (15%), the main dietary sources of calcium were skim/low fat milk (29%), fortified orange juice (8%) and hard cheeses (7%), and the major dietary sources of vitamin D were fortified skim/low fat milk (41%) and fish (32%) (S. Tworoger, personal communication). Total (dietary and supplemental) nutrient intake was calculated by summing the contributions of the nutrient from dietary, multivitamin and single supplement sources. Intakes of total and saturated fat were calculated as the sum of the contributions from all foods based on the U.S. Department of Agriculture data and also included margarine and fats used in cooking or baking.

Statistical analysis

Individuals were excluded from the analysis if they did not complete a food frequency questionnaire (n = 134) or if they had an implausibly low or high caloric intake (<500 or >3500 kcals/day) (n = 143). Energy-adjusted nutrient intake was calculated using the residuals from the regression of nutrient intake based on a total caloric intake of 1600 kcal/day[19]. Nutrient quartile cutpoints were calculated based on the distribution of intake among controls. Unconditional logistic regression was used to estimate the odds ratio and 95% confidence intervals for the main effects of dairy foods and nutrients. All multivariable analyses were adjusted for age (continuous), number of pregnancies (continuous), oral contraceptive use (0, >3 months-2 yrs, >2–5 yrs, >5–10 yrs, >10 yrs), tubal ligation (yes, no), family history of ovarian cancer in a first degree relative (yes, no), study center (MA, NH), study phase (1,2,3) and energy intake (continuous). Analyses of lactose intolerance were additionally adjusted for race. To simultaneously evaluate the effects of lactose, total

calcium and total vitamin D, we included all three terms in the same regression model. Additional potential confounders were evaluated but not included in the final models because they did not substantially alter the risk estimates. We calculated Pearson correlation coefficients (r) to assess co-linearity between continuous nutrient variables. Tests for linear trend were performed using the Wald test with a trend variable based on the median number of servings/day for each category of dairy food intake or using a trend variable based on the median value for each quartile (for dairy nutrients). We assessed effect modification by age (< 50, ≥ 50 years), menopausal status (unknown or pre-menopause, post-menopause), body mass index (< 25, ≥ 25), oral contraceptive use (ever/never), parity and median total fat intake (high, low). The *P* for interaction was calculated using a likelihood ratio test to compare models with and without interaction terms.

Polytomous logistic regression (PLR) was used to simultaneously estimate separate risk factor associations across 1) histological subtypes and 2) rapidly fatal versus less aggressive invasive ovarian cancers. For PLR, the likelihood ratio test was used to calculate a *P*-value for heterogeneity comparing a model in which all of the associations were held constant between the case subgroups to a model which allowed only the association of interest to differ between the case subgroups[20]. In all statistical analyses a *P*-value < 0.05 was considered as significant. Analyses were performed using SAS v9.2 (SAS Institute Inc., Cary, NC) and Stata v9 (StataCorp, College Station, Texas).

Results

The final study population included 1909 women with epithelial ovarian cancer (invasive and borderline) and 1989 controls. Cases reported a lower proportion and shorter duration of oral contraceptive (OC) use, were less likely to be parous or to have had a tubal ligation and were more likely to report a family history of ovarian cancer (Table 1). Consumption of selected dairy products (yogurt, cottage/ricotta cheese and hard cheeses) was significant and inversely related to risk of ovarian cancer and all showed a trend ($P \leq 0.02$) of decreasing risk with increasing intake (Table 2, Model 1). Increased consumption of skim/low fat milk also was inversely associated with ovarian cancer risk although only an intermediate category of intake was statistically significant (2–7 times/week *vs.* never/less than monthly, Odds Ratio (OR) = 0.83, 95% CI, 0.70 – 0.97, $P_{trend} = 0.28$). In contrast, we observed an increased risk of ovarian cancer with high intake of whole milk (≥ 2 times/week *vs.* never/less than monthly, OR = 1.43, 95% CI, 1.15 – 1.78, $P_{trend} = 0.002$) or cream cheese (≥ 2 times/week *vs.* never/< monthly, OR = 1.39, 95% CI, 1.09 – 1.77, $P_{trend} = 0.008$). We observed a non-significant positive association between consumption of ice cream and ovarian cancer risk. In additional analyses of dairy foods with a higher fat content (whole milk, hard cheeses, cottage/ricotta cheese, ice cream and cream cheese), additionally adjusting for quartiles of total fat intake (Table 2, Model 2) only minimally altered the risk estimates. Quartiles of total fat and saturated fat intake were not associated with risk of ovarian cancer overall (data not shown).

The energy-adjusted intake of both dietary and total calcium and vitamin D was higher in controls while lactose intake was similar in cases and controls (Table 1). We observed a statistically significant inverse association with ovarian cancer risk with higher intake of both dietary and total (dietary plus supplements) calcium and vitamin D (Table 3, Model 1). The protective effects for intake of total calcium (Quartile 4 (Q4) *vs.* Q1, OR = 0.61, 95% CI, 0.50 – 0.74, $P_{trend} < 0.001$) and total vitamin D (Q4 *vs.* Q1, OR = 0.76, 95% CI, 0.63 – 0.92, $P_{trend} = 0.01$) were slightly stronger than for dietary intake of either nutrient. We observed a non-significant inverse association for high intake of lactose with ovarian cancer risk (Q4 *vs.* Q1, OR = 0.88, 95% CI, 0.73 – 1.05, $P_{trend} = 0.07$). Dietary intake of calcium and lactose were strongly correlated (r = 0.89) as was dietary intake of vitamin D with

lactose or calcium (both correlations r = 0.54). When all three nutrients were included in the same multivariable model (Table 3, Model 2), we observed a similar inverse association for total calcium intake and risk of ovarian cancer (Q4 *vs.* Q1, OR = 0.62, 95% CI, 0.49 – 0.79, $P_{trend} < 0.001$) however the odds ratio for the highest compared with the lowest quartile of total vitamin D intake was attenuated (Q4 *vs.* Q1, OR = 0.93, 95% CI, 0.74 – 1.16, $P_{trend} = 0.75$).

We evaluated the association of intake of total calcium, total vitamin D and lactose with ovarian cancer risk among participants who were < age 50 or ≥ age 50. For participants who were < age 50, any category of calcium intake that was higher than the referent group had a significantly protective effect (e.g., Q4 *vs.* Q1, OR = 0.56, 95% CI, 0.39 – 0.80, $P_{trend} = 0.002$). Among participants who were ≥ age 50, only the highest quartile of calcium intake was significantly protective (Q4 *vs.* Q1, OR = 0.69, 95% CI, 0.54 – 0.87, $P_{trend} < 0.001$) ($P_{int} = 0.01$) (Table 4). Associations were similar for total vitamin D intake with ovarian cancer risk across both age groups ($P_{int} = 0.41$). For lactose intake among participants who were < age 50, we observed a statistically significant inverse association with ovarian cancer risk for any category of intake that was higher than the referent group (e.g., Q4 *vs.* Q1, OR = 0.70, 95% CI, 0.52 – 0.95, $P_{trend} = 0.04$) while there was no association between lactose intake and ovarian cancer risk among participants who were ≥ age 50 ($P_{int} = 0.01$). We observed similar results to those reported using the age 50 cutoff in analyses stratified by menopausal status (pre/dubious menopause *vs.* postmenopausal) (data not shown). In analyses of dairy food and nutrient intake, similar estimates to the overall findings were observed when participants were stratified by parity, OC use, body mass index and median total fat or saturated fat intake (data not shown).

In an earlier report we observed an excess of controls who reported lactose intolerance beginning at an early age (< age 20). Consistent with this finding, we evaluated the association with lactose intolerance beginning before age 20 and found a suggestive inverse association with ovarian cancer risk (OR = 0.72, 95% CI, 0.42 – 1.22). We did not observe any association with ovarian cancer risk for individuals who reported lactose intolerance beginning at or after age 20 (OR = 0.96, 95% CI, 0.75 – 1.22) (data not shown). As a crude measure of lactose intolerance we also asked respondents about their use of lactase enzyme tablets/lactose-free dairy products and observed a non-significant inverse association with reported use of these products (OR = 0.87, 95% CI, 0.67 – 1.12).

We identified significant differences in the risk associations for intake of total calcium and total vitamin D across the histological subtypes (using polytomous logistic regression (PLR) combined with the likelihood ratio test to calculate a *P*-value for heterogeneity, P_{het} (model) ≤ 0.04) (Table 5). The strongest inverse associations for total calcium intake were observed in serous borderline (Q4 *vs.* Q1, OR = 0.41, 95% CI, 0.27 – 0.62, $P_{trend} < 0.001$) and mucinous tumors (Q4 *vs.* Q1, OR = 0.46, 95% CI, 0.29 – 0.72, $P_{trend} < 0.001$). The ORs associated with total calcium intake remained essentially unchanged after additional adjustment for total vitamin D and lactose (data not shown).

The strongest inverse associations for total vitamin D intake were observed in the serous borderline (Q4 *vs.* Q1, OR = 0.51, 95% CI, 0.34 – 0.76, $P_{trend} = 0.001$) and endometrioid tumors (Q4 *vs.* Q1, OR = 0.55, 95% CI, 0.39 – 0.80, $P_{trend} = 0.002$) (Table 5). In the model that was mutually adjusted for all three nutrients, risk estimates for total vitamin D intake were slightly attenuated but remained significantly protective for serous borderline (Q4 *vs.* Q1, OR = 0.61, 95% CI, 0.40 – 0.93, $P_{trend} = 0.02$) and endometrioid tumors (Q4 *vs.* Q1, OR = 0.66, 95% CI, 0.45 – 0.97, $P_{trend} = 0.046$) (data not shown). We observed no difference in the associations between lactose intake and risk of the different histological subtypes of ovarian cancer (P_{het} (model) = 0.66). In analyses assessing intake of individual

dairy foods, ORs for the histological subtypes resembled those for ovarian cancer risk overall (data not shown).

Based on previous suggestions that high intake of dairy-related factors was modestly associated with poorer survival, we evaluated whether the risk associations with dairy food and/or nutrient consumption varied between rapidly fatal and less aggressive invasive cases as compared with controls using the time interval between the date of diagnosis to the date of death to define rapidly fatal (died within 3 years of diagnosis) and less aggressive (died >3 years post-diagnosis or still alive) cases. We observed no statistically significant differences in risk by tumor aggressiveness (rapidly fatal *vs.* less aggressive invasive tumors) in the analyses of intake of dairy foods and nutrients (data not shown). Further adjustment for tumor stage made no difference to the risk associations. In the subset of cases for which detailed chemotherapy data were available (n=946), the majority (90% and 84%) of the rapidly fatal and less aggressive cases, respectively, were treated with a cisplatin and/or carboplatin regimen (data not shown).

Discussion

In this updated analysis of the NECC[21] (including 1909 cases and 1989 controls), we evaluated the association of intake of dairy foods and nutrients (including calcium and vitamin D) in relation to ovarian cancer risk overall and assessed whether these associations differed among the histological subtypes of ovarian cancer. Consistent with previous case-control studies[9, 22–24], we observed that high intake of skim/low fat milk was significantly inversely associated with ovarian cancer risk. Among three additional case-control studies that evaluated consumption of any type of milk, two studies reported an inverse association between high milk intake and ovarian cancer risk[25, 26] and the third study found no association[27]. In contrast, three cohort studies reported a suggestive but non-significant increased risk of invasive ovarian cancer with high consumption of skim/low fat milk[7, 28] or any type of milk[29] while another cohort study[30] and a pooled analysis of 12 cohort studies[8] found no association with intake of any type of milk. In separate analyses of whole milk, we observed that high intake was associated with significantly increased risk of ovarian cancer. This finding is consistent with previous case-control studies[23, 24] and some[7] but not all[8, 31] cohort studies.

We found that high intake of yogurt and ricotta/cottage cheese was significantly inversely associated with ovarian cancer risk. In contrast, previous case-control and cohort studies reported no association between consumption of yogurt and/or ricotta/cottage cheese and ovarian cancer risk[7–9, 22, 29, 30] and one study[23] reported an elevated risk with increasing consumption of full fat (but not low fat) yogurt. We were unable to distinguish low fat from full fat yogurt in our study. We observed that high consumption of hard cheeses was significantly inversely associated with risk of ovarian cancer. This result is consistent with the Nurses' Health Study[7] but not with other studies that reported no association[8, 9, 28–30] or an increased risk[23] with high cheese intake. To our knowledge this was the first report that high intake of cream cheese was associated with increased ovarian cancer risk. The increased risk that we observed for selected high-fat foods was unlikely to be due to their fat content because total fat and saturated fat intake alone were not associated with ovarian cancer risk in our study. There have been conflicting findings regarding the association between total fat intake and ovarian cancer risk; a meta-analysis of seven case-control and one cohort study[32] and a recent report from the NIH-AARP Diet and Health Study[33] found significantly increased risk with high total fat intake while a pooled analysis of 12 cohort studies found no association with total fat intake[34].

A component of dairy foods that has been hypothesized to increase ovarian cancer risk is lactose (and its metabolite galactose) through toxic effects on the ovarian germ cells leading to subsequent gonadotropin stimulation of the ovaries[35]. In support of this, most[7, 8, 28, 29] but not all[30, 31] cohort studies reported a positive association between lactose intake and ovarian cancer risk and two of these studies reported a stronger association for serous invasive tumors[7, 29]. In contrast, case-control studies, including the current report, have found little evidence for an association between lactose intake and ovarian cancer risk[6, 21, 23, 36–39] and one study reported a significant inverse association[9]. We did not observe differences in the association with lactose intake across the histological subtypes.

It has been suggested that differences in the association between lactose intake and ovarian cancer risk in case-control and cohort studies may relate to the time periods measured by the dietary questionnaire (i.e., recent diet in case-control studies versus long-term or baseline diet in cohort studies)[6]. Although we were unable to evaluate diet in an earlier life period in our study, we observed a non-significant but suggestive inverse association with ovarian cancer risk among individuals who reported symptoms of lactose intolerance that began before the age of 20 and did not observe an association if symptoms began at or after age 20. Considering that lactose intolerant women are likely to consume less lactose, this finding suggests that decreased lactose intake early in life may reduce ovarian cancer risk although further studies are needed to confirm this finding.

We also evaluated intake of calcium and vitamin D in relation to ovarian cancer risk and identified a significant inverse association and dose-response with higher dietary or total (diet plus supplements) intake of either nutrient. We observed a stronger protective effect for total calcium and total vitamin D as compared with dietary intake of either nutrient alone and attributed this to the higher intake among individuals who use supplements. Due to the high correlations observed for these dairy nutrients, it was difficult to identify independent associations with ovarian cancer risk. Nevertheless, in models that were mutually adjusted for total calcium, total vitamin D and lactose intake, the statistically significant inverse association with total calcium intake remained unchanged, while the association with total vitamin D intake was attenuated and no longer significant. Findings of an inverse association between dietary and/or total calcium intake and ovarian cancer risk are consistent with some[9, 31] but not all[28] previous studies, and a pooled analysis of cohort studies found no association[8]. We also observed that the association with calcium intake was influenced by the participant's age. For women aged ≥ 50 only the highest quartile of calcium intake was significantly inversely associated with ovarian cancer in women, while any intake higher than the referent category was protective for ovarian cancer in younger (< 50 years) women, possibly due to the role of estrogens in enhancing intestinal calcium absorption[40].

In our data total calcium was inversely associated with serous borderline and mucinous tumors. Higher levels of calcium intake have been postulated to reduce ovarian cancer risk by inhibiting the release of parathyroid hormone which may have pro-tumorigenic effects by stimulating IGF-1[9, 10]. Our observation that mucinous tumors showed a strong inverse association with total calcium intake was of interest because intestinal type mucinous ovarian tumors have been recognized[41] and recent studies have suggested that advanced stage ovarian mucinous carcinomas could be metastases from the colorectum[42] and the protective effects for colorectal cancer with increased calcium intake are well established[43]. Together these observations suggest that calcium intake may influence the risk of developing a mucinous neoplasm regardless of the primary tumor site, although these results require further confirmation.

We also found that high intake of total vitamin D was inversely associated with risk of serous borderline and endometrioid tumors. Complementary to our results, a pooled analysis of four studies (including the current study) found that the *VDR Fok1* polymorphism, leading to reduced functionality of the *VDR*, was strongly associated with increased risk of serous borderline and endometrioid tumors[44]. However, a recent pooled analysis of five additional studies observed an increased risk of ovarian cancer (all types) among carriers of the variant *VDR Fok1* allele but they did not observe a difference in the association by tumor histology[45]. In contrast to our findings, the pooled analysis of cohort studies reported a non-significant positive association between total vitamin D intake and risk of endometrioid ovarian cancer[8]. We speculated however that the inverse association between vitamin D intake and endometrioid ovarian cancer risk is biologically plausible based on the known increased risk for endometrioid ovarian tumors with a higher body mass index (BMI)[46, 47]. A recent pooled analysis found a stronger inverse association between circulating 25-hydroxyvitamin D levels and ovarian cancer risk among women with a BMI ≥ 25[48]. Further studies are needed to evaluate whether a high vitamin D intake may be important for the prevention of endometrioid ovarian tumors among women with a higher BMI.

Potential limitations of this study include potential differences in the reported diet due to disease status and the highly correlated nature of dairy related nutrients. However, we observed an increased ovarian cancer risk with high intake of certain dairy foods (whole milk, cream cheese) and a decreased risk with others (including consumption of skim/low fat milk, yogurt), indicating that cases did not consistently under- or over-report their dairy food intake. Levels of intake of dairy nutrients were highly correlated which can be problematic in attempts to isolate their mechanistic effects, particularly when lactose is postulated to increase ovarian cancer risk while calcium and vitamin D were inversely associated with risk. To address this issue we evaluated the dairy nutrients simultaneously in the same model, however even using this approach it is possible that residual confounding could explain some of the observed associations. Lastly, we cannot exclude the possibility that components of dairy foods other than lactose, vitamin D or calcium might explain the observed associations with ovarian cancer risk, however these dairy nutrients were selected *a priori* based on their potential role in ovarian carcinogenesis.

In conclusion, we found that high intake of certain dairy foods was inversely associated with ovarian cancer risk (skim/low fat milk, yogurt, cheeses) while increased consumption of other foods (whole milk, cream cheese) was associated with increased risk. Analyses of dairy nutrients identified a significant inverse association with high intake of total calcium (dietary plus supplements) for ovarian cancer risk overall. Furthermore, increased intake of total calcium was significantly inversely associated with risk of serous borderline and mucinous tumors, while high intake of total vitamin D was significantly protective for serous borderline and endometrioid tumors. Future studies are needed to confirm the role of calcium and vitamin D in the prevention of these specific histological subtypes of ovarian cancer. If these findings are confirmed in future studies, increasing intakes of calcium and/or vitamin D may be important factors to consider for the prevention of epithelial ovarian cancer.

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Abbreviations

OR	Odds Ratio
CI	95% confidence interval
NECC	New England case-control
FFQ	study, food frequency questionnaire
PLR	polytomous logistic regression
OC	oral contraceptive
Q1	quartile 1
VDR	etc, vitamin D receptor
BMI	body mass index

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Novelty and impact

Inconsistent results for the role of dairy food intake in relation to ovarian cancer risk may reflect the potential conflicting effects of lactose, which may increase gonadotropin levels, and the beneficial anti-proliferative effects of calcium and vitamin D. We provide evidence of an overall inverse association with high intake of calcium, and identify novel inverse associations for calcium and vitamin D intake with specific histological subtypes of ovarian cancer.

Table 1

Descriptive characteristics of ovarian cancer cases and controls in the New England case-control (NECC) study

Population Characteristics	Cases	Controls
Participants, *n*	1909	1989
Mean (SD)		
Age (yrs) [1]	52.5 (12.3)	52.4 (12.5)
Parity among parous women	2.5 (1.3)	2.7 (1.4)
Duration of breastfeeding (yrs) [2]	0.5 (0.9)	0.7 (1.2)
Duration of oral contraceptive pill use (yrs) [3]	4.7 (4.8)	5.7 (5.0)
BMI (kg/ m^2)	26.4 (6.2)	26.0 (5.5)
Total calories (kcal)	1886.6 (574.0)	1851.3 (563.2)
Num (%)		
Parous	1294 (67.8)	1637 (82.3)
Ever use of oral contraceptives [4]	1002 (52.5)	1263 (63.5)
History of tubal ligation	256 (13.4)	392 (19.7)
Family history of ovarian cancer	90 (4.7)	54 (2.7)
Nutrient intake [5], mean (SD)		
Lactose (g/d)	13.3 (10.0)	13.6 (9.6)
Dietary calcium (mg/d)	694.9 (256.4)	724.2 (255.5)
Total calcium (mg/d)	967.3 (471.5)	1036.0 (499.5)
Dietary vitamin D (IU/d)	177.9 (112.3)	185.8 (154.1)
Total vitamin D (IU/d)	375.9 (281.7)	392.1 (288.8)
Tumor histology, num (%)		
Serous borderline	225 (11.8)	
Serous Invasive	792 (41.5)	
Mucinous	217 (11.4)	
Endometrioid	305 (16.0)	
Clear Cell	243 (12.7)	
Other	90 (4.7)	
Undifferentiated	37 (1.9)	

[1] Cases and controls were frequency-matched on age.

[2] Duration of breastfeeding among parous women.

[3] Duration of oral contraceptive use among ever users.

[4] Ever users used oral contraceptives for >3 months.

[5] Reported values are the energy-adjusted nutrient intake.

Table 2

Adjusted Odds Ratios (ORs) for epithelial ovarian cancer associated with frequency of consumption of dairy foods

Dairy foods and model	Never or <monthly Multivariate OR *1* (95% CI)	1–4 times/month Multivariate OR *1* (95% CI)	2–7 times/week Multivariate OR *1* (95% CI)	>1 time/day Multivariate OR *1* (95% CI)	P_{trend} *2*
Skim/low fat milk (8 oz glass)					
Cases, *n*	536	278	823	251	
Model 1	1.00 (Ref)	0.87 (0.70 – 1.08)	0.83 (0.70 – 0.97)	0.87 (0.70 – 1.09)	0.28
Whole milk (8 oz glass)					
Cases, *n*	1417	232	236		
Model 1	1.00 (Ref)	1.24 (1.00 – 1.53)	1.43 (1.15 – 1.78)		0.002
Model 2	1.00 (Ref)	1.23 (1.00 – 1.52)	1.42 (1.14 – 1.77)		0.003
Hard cheeses (1 slice or 1 oz serving)					
Range *3*	≤ 3/ month	1 time/ week	2–4 times/ week	≥ 5 times/ week	
Cases, *n*	497	373	668	367	
Model 1	1.00 (Ref)	1.07 (0.87 – 1.31)	0.93 (0.78 – 1.10)	0.71 (0.58 – 0.88)	0.0002
Model 2	1.00 (Ref)	1.06 (0.87 – 1.30)	0.90 (0.76 – 1.08)	0.68 (0.55 – 0.85)	<.0001
Yogurt (1 cup)					
Cases, *n*	704	636	553		
Model 1	1.00 (Ref)	0.83 (0.71 – 0.98)	0.65 (0.55 – 0.77)		<.0001
Cottage or ricotta cheese (1/2 cup)					
Cases, *n*	986	766	145		
Model 1	1.00 (Ref)	0.89 (0.78 – 1.03)	0.75 (0.59 – 0.96)		0.02
Model 2	1.00 (Ref)	0.90 (0.78 – 1.03)	0.76 (0.59 – 0.97)		0.02
Ice cream (1/2 cup)					
Cases, *n*	488	1045	356		
Model 1	1.00 (Ref)	1.08 (0.92 – 1.26)	1.15 (0.94- 1.41)		0.24
Model 2	1.00 (Ref)	1.08 (0.92 – 1.26)	1.14 (0.93 – 1.40)		0.29
Cream cheese (1 oz)					
Cases, *n*	828	851	200		
Model 1	1.00 (Ref)	1.13 (0.98 – 1.30)	1.39 (1.09 – 1.77)		0.008

Dairy foods and model	Never or <monthly Multivariate OR *1* (95% CI)	1–4 times/month Multivariate OR *1* (95% CI)	2–7 times/week Multivariate OR *1* (95% CI)	>1 time/day Multivariate OR *1* (95% CI)	P_{trend} *2*
Model 2	1.00 (Ref)	1.13 (0.98 – 1.30)	1.38 (1.08 – 1.75)		0.01

1 Model 1 is adjusted for age (continuous), number of pregnancies (continuous), oral contraceptive pill use (0, >3 mnths-2 yrs, >2–5 yrs, >5–10 yrs, >10 yrs), tubal ligation, family history of ovarian cancer in a first degree relative (yes *vs* no), study center (MA, NH), study phase (1,2,3) and total calories. Model 2 (where applicable) is adjusted for all of the factors in model 1 plus quartiles of total fat intake.

2 *P* value, test for trend using a trend variable based on the median number of servings/day for each category of dairy food intake as follows: skim/low fat milk (0, 0.07, 0.79, 2.50), whole milk (0, 0.07, 0.79), hard cheeses (0.07, 0.14, 0.43, 0.79) and yogurt, cottage/ricotta cheese, ice cream and cream cheese (0, 0.07, 0.43).

3 Hard cheeses were categorized differently than the other dairy foods due to differences in the frequency of consumption.

Table 3

Adjusted Odds Ratios (ORs) for epithelial ovarian cancer associated with intake of dairy nutrients

Dairy nutrients [1] and model	Q1 [2] Multivariate OR [3] (95% CI)	Q2 *vs.* Q1 Multivariate OR [3] (95% CI)	Q3 *vs.* Q1 Multivariate OR [3] (95% CI)	Q4 *vs.* Q1 Multivariate OR [3] (95% CI)	P_{trend} [4]
Dietary calcium (mg/d)					
Range	< 543.7	543.7 – 677.5	677.6 – 859.3	> 859.3	
Cases, *n*	565	494	425	425	
Model 1	1.00 (Ref)	0.88 (0.74 – 1.05)	0.75 (0.62 – 0.90)	0.74 (0.62 – 0.89)	<0.001
Total calcium (mg/d)					
Range	< 654.9	654.9 – 924.5	924.6 – 1318.8	> 1318.8	
Cases, *n*	584	465	477	383	
Model 1	1.00 (Ref)	0.76 (0.64 – 0.92)	0.78 (0.65 – 0.94)	0.61 (0.50 – 0.74)	<0.001
Model 2	1.00 (Ref)	0.80 (0.65 – 0.97)	0.79 (0.63 – 0.99)	0.62 (0.49 – 0.79)	<0.001
Dietary vitamin D (IU/d)					
Range	< 105.3	105.3 – 161.0	161.1 – 236.0	> 236.0	
Cases, *n*	507	504	464	434	
Model 1	1.00 (Ref)	0.98 (0.82 – 1.18)	0.90 (0.75 – 1.08)	0.82 (0.68 – 0.99)	0.03
Total vitamin D (IU/d)					
Range	< 163.6	163.6 – 341.4	341.5 – 559.1	> 559.1	
Cases, *n*	546	455	478	430	
Model 1	1.00 (Ref)	0.80 (0.67 – 0.97)	0.81 (0.68 – 0.98)	0.76 (0.63 – 0.92)	0.01
Model 2	1.00 (Ref)	0.89 (0.73 – 1.09)	0.94 (0.77 – 1.16)	0.93 (0.74 – 1.16)	0.75
Lactose (g/d)					
Range	< 6.7	6.7 – 11.4	11.5 – 17.7	> 17.7	
Cases, *n*	518	520	420	451	
Model 1	1.00 (Ref)	1.00 (0.84 – 1.20)	0.81 (0.67 – 0.97)	0.88 (0.73 – 1.05)	0.07
Model 2	1.00 (Ref)	1.06 (0.88 – 1.28)	0.95 (0.77 – 1.16)	1.11 (0.89 – 1.38)	0.41

[1] Total calcium and total vitamin D include intake from multivitamins and supplements (in addition to dietary intake), while the dietary calcium and dietary vitamin D do not.

[2] Q, quartile.

[3]Model 1 is adjusted for age (continuous), number of pregnancies (continuous), oral contraceptive pill use (0, >3 mnths-2 yrs, >2–5 yrs, >5–10 yrs, >10 yrs), tubal ligation, family history of ovarian cancer in a first degree relative (yes *vs* no), study center (MA, NH), study phase (1,2,3) and total calories. Model 2 (where applicable) is adjusted for all of the factors in model 1 plus total calcium (quartiles), total vitamin D (quartiles) and lactose (quartiles).

[4]*P* value test for trend using a trend variable based on the median nutrient value from each quartile category. Medians for nutrient categories based on the distribution in controls are as follows: dietary calcium (461.3 mg/day, 609.3, 752.5, 1017.7), total calcium (531.9 mg/day, 775.9, 1096.7, 1648.2), lactose (4.2 g/day, 9.0, 14.1, 24.2), dietary vitamin D (71.3 IU/day, 134.0, 195.1, 312.5) and total vitamin D (106.7 IU/day, 231.5, 454.2, 694.2).

Table 4

Associations between calcium and lactose intake with ovarian cancer risk are influenced by age

	Q1 [2]	Q2 *vs*. Q1	Q3 *vs*. Q1	Q4 *vs*. Q1	
Dairy nutrients [1] and model	**Multivariate OR [3] (95% CI)**	**Multivariate OR [3] (95% CI)**	**Multivariate OR [3] (95% CI)**	**Multivariate OR [3] (95% CI)**	***P* trend [4,5]**
Total calcium (mg/d)					
Range	<654.9	654.9 – 924.5	924.6 – 1318.8	> 1318.8	
Age <50 yrs	1.00 (Ref)	0.56 (0.42 – 0.73)	0.60 (0.45 – 0.80)	0.56 (0.39 – 0.80)	0.002
Age ≥ 50 yrs	1.00 (Ref)	1.00 (0.78 – 1.28)	0.96 (0.76 – 1.22)	0.69 (0.54 – 0.87)	< 0.001
P_{int} [6] = 0.01					
Lactose (g/d)					
Range	< 6.7	6.7 – 11.4	11.5 – 17.7	> 17.7	
Age <50 yrs	1.00 (Ref)	0.69 (0.51 – 0.92)	0.60 (0.44 – 0.81)	0.70 (0.52 – 0.95)	0.04
Age ≥ 50 yrs	1.00 (Ref)	1.26 (1.00 – 1.59)	0.96 (0.75 – 1.21)	1.03 (0.81 – 1.29)	0.59
P_{int} [6] = 0.01					

[1] Total calcium includes intake from multivitamins and supplements in addition to dietary calcium.

[2] Q, quartile.

[3] Multivariate models are adjusted for age (continuous), number of pregnancies (continuous), oral contraceptive pill use (0, >3 mnths-2 yrs, >2–5 yrs, >5–10 yrs, >10 yrs), tubal ligation, family history of ovarian cancer in a first degree relative (yes *vs* no), study center (MA, NH), study phase (1,2,3) and total calories.

[4] The reported *P* value (test for linear trend) used a trend variable based on the median nutrient value for each quartile category based on the distribution among controls.

[5] The *P* value for interaction was calculated using the Chi-square test for the difference between the log likelihood for models with and without interactions terms between the trend variables (for total calcium or lactose) and age (<50 *vs.* ≥ 50 yrs). Both *P* values for interaction using the trend variables were non-significant ($P \geq 0.14$).

[6] The *P* value for interaction was calculated using the Chi-square test for the difference between the log likelihood for models with and without interactions terms between quartiles of total calcium or lactose intake (modeled as categorical variables) and age (<50 *vs.* ≥ 50 yrs).

Table 5

Adjusted Odds Ratios (ORs) for ovarian cancer associated with consumption of dairy nutrients by histologic subtype

Dairy nutrients [1]	Controls (N=1989) N (%)	Serous borderline (N=226 [2]) N (%)	Adjusted [3] OR (95% CI)	Serous invasive (N=791 [2]) N (%)	Adjusted [3] OR (95% CI)	Mucinous [4] (N=217 2) N (%)	Adjusted [3] OR (95% CI)	Endometrioid (N=305 [2]) N (%)	Adjusted [3] OR (95% CI)	Clear cell (N=243 [2]) N (%)	Adjusted [3] OR (95% CI)
Dietary calcium (mg/d)											
Q1	497 (25.0)	67 (29.7)	1.00 (Ref)	247 (31.2)	1.00 (Ref)	61 (28.1)	1.00 (Ref)	92 (30.2)	1.00 (Ref)	60 (24.7)	1.00 (Ref)
Q2	497 (25.0)	61 (27.0)	0.92 (0.63 – 1.33)	188 (23.8)	0.77 (0.61 – 0.97)*	51 (23.5)	0.84 (0.57 – 1.25)	95 (31.2)	1.04 (0.76 – 1.43)	63 (25.9)	1.06 (0.73 – 1.54)
Q3	497 (25.0)	51 (22.6)	0.76 (0.51 – 1.12)	176 (22.3)	0.71 (0.56 – 0.90)*	62 (28.6)	1.01 (0.69 1.48)	47 (15.4)	0.51 (0.35 – 0.74)*	65 (26.8)	1.08 (0.74 – 1.57)
Q4	498 (25.0)	47 (20.8)	0.69 (0.47 – 1.03)	180 (22.8)	0.72 (0.57 – 0.91)*	43 (19.8)	0.69 (0.46 – 1.05)	71 (23.3)	0.76 (0.54 – 1.07)	55 (22.6)	0.90 (0.61 – 1.33)
P_{het} (trend)[5] = 0.76			P_{trend}[7] = 0.05		P_{trend}[7] = 0.008		P_{trend}[7] = 0.14		P_{trend}[7] = 0.02		P_{trend}[7] = 0.57
P_{het} (model)[6] = 0.04											
Total calcium (mg/d)											
Q1	497 (25.0)	81 (35.8)	1.00 (Ref)	230 (29.1)	1.00 (Ref)	66 (30.4)	1.00 (Ref)	92 (30.2)	1.00 (Ref)	66 (27.2)	1.00 (Ref)
Q2	497 (25.0)	65 (28.8)	0.77 (0.54 – 1.10)	171 (21.6)	0.72 (0.56 – 0.91)*	66 (30.4)	0.97 (0.67 – 1.39)	69 (22.6)	0.73 (0.52 – 1.02)	68 (28.0)	0.99 (0.69 – 1.43)
Q3	498 (25.0)	45 (19.9)	0.53 (0.36 – 0.79)*	208 (26.3)	0.87 (0.69 – 1.10)	53 (24.4)	0.77 (0.52 – 1.14)	82 (26.9)	0.86 (0.62 – 1.19)	61 (25.1)	0.89 (0.61 – 1.29)
Q4	497 (25.0)	35 (15.5)	0.41 (0.27 – 0.62)*	182 (23.0)	0.75 (0.59 – 0.95)*	32 (14.8)	0.46 (0.29 – 0.72)*	62 (20.3)	0.64 (0.45 – 0.91)*	48 (19.8)	0.69 (0.46 – 1.02)
P_{het} (trend)[5] = 0.004			P_{trend}[7] < 0.001		P_{trend}[7] = 0.09		P_{trend}[7] < 0.001		P_{trend}[7] = 0.04		P_{trend}[7] = 0.04
P_{het} (model)[6] = 0.02											
Lactose (g/d)											
Q1	497 (25.0)	68 (30.1)	1.00 (Ref)	214 (27.1)	1.00 (Ref)	60 (27.7)	1.00 (Ref)	80 (26.2)	1.00 (Ref)	61 (25.1)	1.00 (Ref)
Q2	497 (25.0)	66 (29.2)	0.97 (0.67 – 1.39)	211 (26.7)	0.98 (0.78 – 1.24)	55 (25.4)	0.92 (0.62 – 1.35)	92 (30.2)	1.15 (0.83 – 1.59)	57 (23.5)	0.93 (0.63 – 1.37)
Q3	497 (25.0)	44 (19.5)	0.64 (0.43 – 0.96)*	172 (21.7)	0.80 (0.63 – 1.02)	55 (25.4)	0.91 (0.62 – 1.34)	63 (20.7)	0.78 (0.55 – 1.12)	64 (26.3)	1.04 (0.72 – 1.52)
Q4	498 (25.0)	48 (21.2)	0.71 (0.48 – 1.06)	194 (24.5)	0.91 (0.72 – 1.16)	47 (21.7)	0.79 (0.53 – 1.18)	70 (23.0)	0.88 (0.62 – 1.25)	61 (25.1)	1.01 (0.69 – 1.47)

Dairy nutrients [1]	Controls (N=1989) N (%)	N (%)	Serous borderline (N=226 [2]) Adjusted [3] OR (95% CI)	N (%)	Serous invasive (N=791 [2]) Adjusted [3] OR (95% CI)	N (%)	Mucinous [4] (N=217 2) Adjusted [3] OR (95% CI)	N (%)	Endometrioid (N=305 [2]) Adjusted [3] OR (95% CI)	N (%)	Clear cell (N=243 [2]) Adjusted [3] OR (95% CI)
P_{het} (trend)[5] = 0.49			P_{trend}[7] = 0.04		P_{trend}[7] = 0.33		P_{trend}[7] = 0.27		P_{trend}[7] = 0.22		P_{trend}[7] = 0.84
P_{het} (model)[6] = 0.66											
Dietary vitamin D (IU/d)											
Q1	497 (25.0)	79 (35.0)	1.00 (Ref)	192 (24.3)	1.00 (Ref)	59 (27.2)	1.00 (Ref)	86 (28.2)	1.00 (Ref)	55 (22.6)	1.00 (Ref)
Q2	497 (25.0)	52 (23.0)	0.64 (0.44 – 0.94) *	205 (25.9)	1.05 (0.82 – 1.33)	51 (23.5)	0.85 (0.57 – 1.26)	94 (30.8)	1.07 (0.78 – 1.48)	68 (28.0)	1.21 (0.83 – 1.77)
Q3	497 (25.0)	50 (22.1)	0.62 (0.43 – 0.91) *	221 (27.9)	1.13 (0.89 – 1.43)	55 (25.4)	0.92 (0.62 – 1.35)	61 (20.0)	0.70 (0.49 – 0.99) *	55 (22.6)	0.98 (0.66 – 1.46)
Q4	498 (25.0)	45 (19.9)	0.55 (0.37 – 0.81) *	173 (21.9)	0.87 (0.68 – 1.11)	52 (24.0)	0.85 (0.57 – 1.26)	64 (21.0)	0.72 (0.51 – 1.02)	65 (26.8)	1.14 (0.78 – 1.67)
P_{het} (trend)[5] = 0.06			P_{trend}[7] = 0.004		P_{trend}[7] = 0.26		P_{trend}[7] = 0.53		P_{trend}[7] = 0.02		P_{trend}[7] = 0.73
P_{het} (model)[6] = 0.02											
Total vitamin D (IU/d)											
Q1	497 (25.0)	77 (34.1)	1.00 (Ref)	206 (26.0)	1.00 (Ref)	63 (29.0)	1.00 (Ref)	97 (31.8)	1.00 (Ref)	63 (25.9)	1.00 (Ref)
Q2	497 (25.0)	58 (25.7)	0.73 (0.50 – 1.05)	174 (22.0)	0.81 (0.64 – 1.04)	64 (29.5)	0.98 (0.67 – 1.42)	78 (25.6)	0.77 (0.56 – 1.07)	58 (23.9)	0.89 (0.61 – 1.30)
Q3	497 (25.0)	51 (22.6)	0.62 (0.42 – 0.90) *	218 (27.6)	0.99 (0.78 – 1.25)	44 (20.3)	0.65 (0.43 – 0.98) *	75 (24.6)	0.72 (0.52 – 1.01)	62 (25.5)	0.92 (0.63 – 1.34)
Q4	498 (25.0)	40 (17.7)	0.51 (0.34 – 0.76) *	193 (24.4)	0.92 (0.72 – 1.17)	46 (21.2)	0.71 (0.48 – 1.07)	55 (18.0)	0.55 (0.39 – 0.80) *	60 (24.7)	0.93 (0.64 – 1.36)
P_{het} (trend)[5] = 0.002			P_{trend}[7] = 0.001		P_{trend}[7] = 0.96		P_{trend}[7] = 0.03		P_{trend}[7] = 0.002		P_{trend}[7] = 0.82
P_{het} (model)[6] = 0.04											

*Indicates Odds Ratios that are statistically significant.

[1]Total calcium and total vitamin D include intake from multivitamins and supplements (in addition to dietary intake), while the dietary calcium and dietary vitamin D do not.

[2]A total of 127 cases were excluded from the analysis of histological subtype since these tumors were classified as other or undifferentiated histology.

[3]Models are adjusted for age (continuous), number of pregnancies (continuous), oral contraceptive pill use (0, >3 mnths-2 yrs, >2–5 yrs, >5–10 yrs, >10 yrs), tubal ligation, family history of ovarian cancer (yes *vs* no), study center (MA, NH), study phase (1,2,3) and total calories.

[4] Includes borderline (n = 131, 60%) and invasive (n = 86, 40%) mucinous tumors.

[5] P_{het} (trend) is from the Likelihood-ratio test (based on the chi-square distribution) that compares a model with the same estimate for the association with the exposure of interest (trend variable) across the histological subtypes to a model which allows the association of interest (trend variable) to vary across the histological subtypes.

[6] P_{het} (model) is from the Likelihood-ratio test that compares a model with the same estimate for the association with the exposure of interest (e.g., quartiles 2, 3, 4 of dietary calcium intake) across the histological subtypes to a model which allows the exposure of interest to vary across the histological subtypes.

[7] P_{trend} is the test for trend within each histological subtype (*P* value from the z-test) using a trend variable based on the median nutrient value from each quartile category based on the distribution in controls.