Dairy Products and Ovarian Cancer: A Pooled Analysis of 12 Cohort Studies

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Abstract

Background: **Dairy foods and their constituents (lactose and calcium) have been hypothesized to promote ovarian carcinogenesis. Although case-control studies have reported conflicting results for dairy foods and lactose, several cohort studies have shown positive associations between skim milk, lactose, and ovarian cancer.**

Methods: **A pooled analysis of the primary data from 12 prospective cohort studies was conducted. The study population consisted of 553,217 women among whom 2,132 epithelial ovarian cases were identified. Study-specific relative risks and 95% confidence intervals were calculated by Cox proportional hazards models and then pooled by a random-effects model.**

Results: **No statistically significant associations were observed between intakes of milk, cheese, yogurt, ice cream, and dietary and total calcium intake and risk of ovarian cancer. Higher lactose intakes comparing ≥30 versus <10 g/d were associated with a statistically significant higher risk of ovarian cancer, although the trend was not statistically significant (pooled multivariate relative risk, 1.19; 95% confidence interval, 1.01-1.40; P_{trend} = 0.19). Associations for endometrioid, mucinous, and serous ovarian cancer were similar to the overall findings.**

Discussion: **Overall, no associations were observed for intakes of specific dairy foods or calcium and ovarian cancer risk. A modest elevation in the risk of ovarian cancer was seen for lactose intake at the level that was equivalent to three or more servings of milk per day. Because a new dietary guideline recommends two to three servings of dairy products per day, the relation between dairy product consumption and ovarian cancer risk at these consumption levels deserves further examination.** (Cancer Epidemiol Biomarkers Prev 2006;15(2):364–72)

Introduction

Ovarian cancer is the sixth leading cause of cancer and seventh most common cause of cancer death among women worldwide (1), but rates vary substantially by country. Incidence and mortality rates in more developed regions (10.2 per 100,000 and 5.7 per 100,000, respectively) are approximately double those in less developed regions (5.0 per 100,000 and 2.9 per 100,000, respectively; ref. 1). Furthermore, the majority of cases are diagnosed with ovarian cancer at later stages (2-5). Due to the current lack of availability of good screening methods for ovarian cancer and low survival rates among women diagnosed with disease at an advanced stage (6), a better understanding of the etiology of cancer may lead to important reductions in ovarian cancer incidence.

Partly as a result of the large international variation in incidence rates of ovarian cancer, diet has been suggested as a possible risk factor. Dairy foods, such as milk, vary in consumption across the world, where highest consumption is found in developed countries compared with developing countries (7). Dairy foods and some of their constituents, such as lactose and calcium, have been hypothesized to promote the development of ovarian cancer. Higher levels of lactose may affect the ovary and ovarian-pituitary axis through its metabolites (e.g., galactose; refs. 8-11). Galactose, whose main food source is lactose, stimulates gonadotropin secretion that may result in toxicity to oocytes and thus may lead to ovarian failure and cancer (9). High intakes of calcium may increase or decrease ovarian cancer risk. High intakes of calcium may depress 1,25-OH vitamin D, which may result in an increase in cellular proliferation and thus tumorigenesis (12, 13). In contrast, high calcium intakes may protect against carcinogenesis by down-regulating the production of parathyroid hormone, which may reduce mitosis and increase apoptosis (14).

Received 8/3/05; revised 10/26/05; accepted 12/1/05.

Grant support: NIH grants CA098566 and CA55075.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Note: This study was done at Harvard School of Public Health, Boston, Massachusetts.

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doi:10.1158/1055-9965.EPI-05-0484

Although case-control studies have reported conflicting results for dairy foods (8, 15-28) and lactose (3, 8, 20-22, 25, 29-32) in relation to risk of ovarian cancer, the prospective Iowa Women's Health Study (33), Nurses' Health Study (34), and Swedish Mammography Cohort (35) have each shown positive associations between skim milk and lactose intake and risk of ovarian cancer. Furthermore, the Nurses' Health Study and Swedish Mammography Cohort found a stronger positive association between higher lactose intake and specifically risk of serous ovarian cancer (34, 35). Although only occasionally reported, a lower ovarian cancer risk has been observed with higher intakes of vitamin D (21, 32, 36) and calcium (16, 21, 32, 36). Although dietary factors and ovarian cancer risk have been evaluated in case-control settings, few prospective studies have examined diet and ovarian cancer risk, primarily due to the small number of cases of ovarian cancer that have occurred in the individual studies. Due to temporal ambiguity of the diet and cancer association in case-control studies, further prospective assessment of these associations is needed.

We investigated the association between intakes of dairy foods and nutrients with risk of ovarian cancer in a pooled analysis of 12 cohort studies (33-35, 37-45). Given that the effect of dairy foods and nutrients may vary by risk factors for ovarian cancer, we also considered whether these associations differed by menopausal status, parity, oral contraceptive use, and postmenopausal hormone use. Additionally, because particular histologic subtypes of ovarian cancer resemble different gynecologic tissue (46), behave different clinically (47), and may have genetic differences (47), individual histologic subtypes may be associated with different etiologies. Thus, we examined associations between intakes of dairy foods and nutrients separately with endometrioid, mucinous, and serous ovarian cancers.

Materials and Methods

Population. A pooled analysis of the primary data from 12 prospective cohort studies (33-35, 37-45) based in North America and Western Europe was conducted in The Pooling Project of Prospective Studies of Diet and Cancer. Two of these studies, Canadian National Breast Screening Study and the Netherlands Cohort Study, were analyzed as case-cohorts because the investigators of these two studies have processed questionnaires for only a sample of noncases. The methods have been described in detail elsewhere.[18] To be included in the ovarian cancer analyses, each study needed a minimum of 50 incident ovarian cancer cases, an assessment of usual food and nutrient intake and validation of the dietary assessment tool or a closely related instrument. The studies that met these criteria were the Adventist Health Study, Breast Cancer Detection Demonstration Project Follow-up Study, Canadian National Breast Screening Study, Cancer Prevention Study II Nutrition Cohort, Iowa Women's Health Study, the Netherlands Cohort Study, New York State Cohort, New York University Women's Health Study, Nurses' Health Study (part a—NHSa and part b—NHSb), Nurses' Health Study II, Swedish Mammography Cohort, and Women's Health Study as shown in Table 1. The follow-up of the Nurses' Health Study was divided into two sections, where part (a), NHSa, followed individuals from the completion of the 1980 food frequency questionnaire to 1986, and part (b), NHSb, followed individuals from the completion of the 1986 food frequency questionnaire to 2002. The follow-up time for the Nurses' Health Study was divided into two separate time periods to take advantage of the expanded food frequency questionnaire administered in 1986. The standard theory of survival data has established that blocks of person-time in different time periods are asymptotically uncorrelated regardless of the extent to which they are derived from the same people (48). Thus, pooling estimates from these two time periods, and the cases that arise within them, produces estimates and estimated SEs that are as valid as those from a single combined period. The total study population consisted of 553,217 women among whom 2,132 developed invasive epithelial ovarian cancer.

Exclusions. In addition to applying the exclusions that each study had predefined for their cohort, we excluded individuals if they had a prior cancer diagnosis other than nonmelanoma skin cancer at baseline, had a bilateral oophorectomy before baseline, or if they had $\log_e$-transformed energy intakes beyond three SDs from the study-specific $\log_e$-transformed mean energy intake of their respective population. The Adventist Health Study (37) and New York State Cohort (42) did not obtain information on oophorectomy at baseline, and thus we were not able to exclude individuals who had a bilateral oophorectomy before baseline in these studies.

Exposure Assessment. Usual frequency of consumption of dairy foods (total milk, whole milk, low-fat milk, hard cheese, cottage cheese, yogurt, and ice cream) was estimated at baseline from study-specific food frequency questionnaires. All dairy foods were analyzed in gram units to take into account differences in portion sizes across studies. Whole milk, low-fat milk, skim milk, buttermilk, and evaporated milk contributed to the total milk summary measure. Hard cheese included cheese (type unspecified), hard cheese, high-fat cheese, and low-fat cheese, whereas yogurt comprised yogurt and low-fat yogurt. Three studies, which have assessed correlations between measurement of dairy products, cheese, and milk from a food frequency questionnaire and 24-hour recalls or food records, have shown reasonable correlations that were >0.63 (49), 0.47 (50, 51), and 0.60 (50, 51), respectively.

Most studies estimated nutrient intakes using the food composition method (52), but the New York State Cohort used the ''regression weight'' method to estimate nutrient values (42). The regression-residual method (52) was used to adjust nutrient intakes to an energy intake of 1,600 kcal/d. Intake of calcium from diet was estimated from their food frequency questionnaires in all studies, whereas vitamin D from diet was estimated from their food frequency questionnaires in most studies. Because only half of the studies included in our analyses had calculated lactose intake, we calculated lactose intake in the remaining studies. Specifically, the values of lactose from dairy products and foods containing dairy products (e.g., pizza) were based on the Nutrition Data System created by the University of Minnesota Nutrition Coordinating Center (53). A summary score was generated for lactose for each study in which the lactose content (per 100 g) for a given food item (e.g., milk, cheese, and pizza) was multiplied by the grams consumed of that item and then summed over all food items containing lactose. Among those studies that had previously calculated lactose intake [Canadian National Breast Screening Study, Iowa Women's Health Study, the Netherlands Cohort Study, New York State Cohort, Nurses' Health Study (NHSa and NHSb), Nurses' Health Study II, Swedish Mammography Cohort, and Women's Health Study], our calculated lactose intake from the Nutrition Data System was highly correlated with the lactose intake data provided by the original study investigators (median Pearson's correlation across studies = 0.99, minimum correlation across studies = 0.80). When analyzing lactose data, study-specific estimates were used, if available.

[18] Smith-Warner SA, Spiegelman D, Ritz J, et al. Methods for retrospective pooling of results of studies: the Pooling Project of prospective studies of diet and cancer. Am J Epidemiol, in press.

Table 1. Daily mean intakes of dairy nutrients and foods by cohort study in the ovarian cancer analyses in the Pooling Project of Prospective Studies of Diet and Cancer

Cohort	Follow-up years	Baseline cohort size*	No. cases	Mean (SD) intake									
				Dietary calcium (mg/d)	Total calcium† (mg/d)	Lactose (g/d)	Dietary vitamin D (IU/d)	Total vitamin D† (IU/d)	Total milk (g/d)‡	Hard cheese (g/d)‡	Cottage cheese (g/d)‡	Yogurt (g/d)‡	Ice cream (g/d)‡
AHS	1976-1988	18,402	53	833 (124)	880 (139)	18 (14)	—	—	419 (349)	8 (8)	35 (36)	—	—
BCDDP	1987-1999	32,885	142	862 (369)	1,186 (2,979)	19 (14)	206 (122)	341 (279)	260 (269)	13 (20)	11 (22)	—	19 (36)
CNBSS§	1980-2000	49,613	223	673 (253)	—	8 (7)	—	—	200 (199)	22 (23)	14 (27)	29 (61)	10 (17)
CPS II	1992-2001	61,202	278	884 (379)	1,136 (584)	19 (13)	197 (119)	342 (258)	277 (265)	11 (14)	—	44 (71)	7 (19)
IWHS	1986-2001	28,486	208	748 (285)	1,029 (483)	15 (11)	223 (111)	382 (292)	275 (265)	11 (13)	19 (31)	12 (39)	11 (19)
NLCS§	1986-1995	62,412	208	869 (259)	—	14 (7)	—	—	187 (153)	23 (18)	10 (26)	53 (57)	—
NYSC	1980-1987	22,550	77	828 (209)	873 (220)	15 (9)	203 (68)	371 (227)	137 (87)	—	—	—	—
NYU	1985-1998	12,401	65	810 (307)	888 (327)	14 (11)	—	—	202 (243)	17 (22)	15 (26)	38 (61)	19 (32)
NHSa	1980-1986	80,195	120	722 (298)	731 (310)	14 (11)	167 (107)	279 (262)	215 (241)	14 (15)	21 (34)	21 (54)	13 (20)
NHSb	1986-2002	59,538	315	718 (254)	1,056 (492)	13 (10)	182 (100)	319 (243)	221 (230)	13 (13)	17 (25)	28 (55)	13 (18)
NHS II	1991-2002	91,502	52	787 (271)	910 (381)	16 (11)	223 (109)	351 (231)	268 (255)	12 (12)	9 (16)	31 (55)	8 (12)
SMC	1987-2003	61,103	287	913 (255)	—	16 (10)	162 (51)	—	156 (130)	27 (19)	—	104 (108)	7 (10)
WHS	1993-2004	32,466	104	729 (258)	940 (442)	14 (10)	217 (104)	324 (216)	215 (222)	9 (11)	10 (17)	36 (64)	7 (13)

NOTE: Studies that have a ''—'' did not estimate that nutrient or did not ask on their questionnaire about the consumption of that food item.

Abbreviations: AHS, Adventist Health Study; BCDDP, Breast Cancer Detection Demonstration Project Follow-up Study; CNBSS, Canadian National Breast Screening Study; CPS II, Cancer Prevention Study II Nutrition Cohort; IWHS, Iowa Women's Health Study; NLCS, the Netherlands Cohort Study; NYSC, New York State Cohort; NYU, New York University Women's Health Study; NHSa, Nurses' Health Study (part a); NHSb, Nurses' Health Study (part b); NHS II, Nurses' Health Study II; SMC, Swedish Mammography Cohort; WHS, Women's Health Study.

*Baseline cohort size was determined after specific exclusions (i.e., had a prior cancer diagnosis other than nonmelanoma skin cancer at baseline, had a bilateral oophorectomy before baseline, or had $\log_e$-transformed energy intakes beyond 3 SDs from the study-specific $\log_e$-transformed mean energy intake of the population).

†Total calcium and vitamin D intake includes dietary and supplemental sources.

‡Milk: 1 8 oz serving is equivalent to 245 g; hard cheese: 1 oz serving is equivalent to 28 g; cottage cheese: 1 0.5 cups serving is equivalent to 105 g; yogurt: 1 cup serving is equivalent to 227 g; ice cream: 1 0.5 cups serving is equivalent to 66g.

§The Canadian National Breast Screening Study and the Netherlands Cohort Study are analyzed as case-cohort studies so the baseline cohort size does not reflect the above exclusions.

Use of multivitamins and single supplements, including calcium and vitamin D, was also ascertained in several studies. If available, total (supplemental and dietary) vitamin D and calcium intakes were calculated by summing the contributions of that nutrient from dietary, multivitamin, and single supplement sources. Because the Adventist Health Study and the New York State Cohort had not estimated the amount of calcium in multivitamins, we estimated the contribution of calcium for multivitamin users as 130 mg/d (the calcium value for generic multivitamins that was used in the Nurses' Health Study) to derive total calcium intake from foods and supplements. Studies have observed good correlations of calcium intake measured from a food frequency questionnaires and 24-hour recall or diet record, ranging from 0.46 to 0.72 (49, 50, 54-58).[19]

Information on nondietary factors was collected on the baseline self-administered questionnaires within each individual study. The majority of studies obtained information on other known and suspected risk factors for ovarian cancer, including several reproductive factors, body mass index (BMI), smoking status, and physical activity.

Outcome Assessment. Participants were followed from the date of the baseline questionnaire until date of diagnosis of ovarian cancer, date of death, date the participant moved out of the study area (if applicable), or end of follow-up, whichever came first. Invasive epithelial ovarian cancer was ascertained by self-report with subsequent medical record review (34, 44, 45), cancer registry linkage (33, 35, 39, 41, 42), or both (37, 38, 40, 59). Some studies also obtained incident outcome and mortality information from death registries (33, 34, 38, 40, 42, 44, 59, 60). Invasive epithelial ovarian cancer was defined by International Classification of Diseases-9 code 183.0 or International Classification of Diseases-10 code C56. Borderline and nonepithelial ovarian cancer cases were not included as cases. Histologic information was ascertained from the International Classification of Diseases for Oncology morphology codes (61) or the histologic information supplied by individual studies.

Statistical Analysis. Studies were excluded from the analysis of a particular dietary factor if they did not measure intake of that specific dietary exposure or if that item was not consumed in that population. Intakes of dietary antioxidant nutrients were analyzed using two different estimates, one crude nutrient estimate and one adjusted for energy intake by residual analysis. Dietary exposures were modeled continuously and categorically according to absolute cut points based on serving sizes and quantiles defined within each individual study. Relative risks (RR) and 95% confidence intervals (95% CI) were calculated by Cox proportional hazards models for each individual study, and the study-specific RRs were then pooled using a random-effects model (62). The model included stratification by age at baseline (in years) and the year the baseline questionnaire was returned and treated the follow-up time (in years) as the time scale, resulting in a time metric that simultaneously accounts for age, calendar time, and time since entry into the study. Multivariate RRs were adjusted for age at menarche (<13, 13, >13 years), menopausal status at baseline (premenopausal, postmenopausal, dubious), oral contraceptive use (ever, never), menopausal hormone therapy use among postmenopausal women (never, past, current), parity (0, 1, 2, >2), BMI (<23, 23 to <25, 25 to <30, ≥30 kg/m^2), smoking status (never, past, current), physical activity (low, medium, high), and energy intake (continuously), with covariates defined identically across studies. A missing indicator variable was also generated within a study for each covariate, if needed. In general, data on age, education, BMI, smoking status, physical activity, multivitamin use, age at menarche, parity, menopausal status, oral contraceptive use, and postmenopausal hormone use was missing for <10% of each study population.

[19]A. Wolk, personal communication.

For each study, we corrected the RR for calcium and lactose for measurement error using the regression coefficients between dairy nutrient intake estimated by the food frequency questionnaires and by the reference methods that were either multiple diet records or 24-hour recalls (63, 64). We did not calculate measurement error-corrected RRs for vitamin D because intake of this nutrient was not calculated for the reference method in several studies.

SAS software (65) was used for the cohort analyses, and Epicure software (66) was used for case-cohort analyses of the Canadian National Breast Screening Study (39) and the Netherlands Cohort Study (41). Between-study heterogeneity was investigated using the Q test statistic (62). To test whether there was a linear trend in the risk of disease with increasing intake, a continuous variable with values corresponding to the median value for each exposure category was included in the model, and the coefficient for that variable was evaluated using the Wald test. If heterogeneity was present between studies, mixed-effects meta-regression analyses (67) were conducted to evaluate whether there was heterogeneity by follow-up time, number of questions for that particular food item, and age at diagnosis.

Stratified analyses were conducted by menopausal status at baseline (premenopausal, postmenopausal), parity (<1 live births, 1+ live births), oral contraceptive use (ever, never), hormone replacement therapy (ever, never), and study-specific median fat intake (high, low). For each factor of interest, a cross-product term of the ordinal score for the level of each factor and intake of a specific dairy food or nutrient expressed as a continuous variable was included in the model. Participants with missing values of the factor of interest were excluded from these analyses. Separate analyses were conducted for endometrioid, mucinous, and serous subtypes among those studies having >10 cases of the specific histologic subtype. We tested whether results differed across the subtypes using a contrast test (68).

Results

Table 1 presents the study-specific characteristics and daily mean intakes of dairy foods and nutrients. Studies had a maximum follow-up time ranging from 7 years in the New York State Cohort to 22 years in the Nurses' Health Study. The Nurses Health Study II contributed the smallest number of invasive epithelial ovarian cancer cases with 52, whereas the Nurses' Health Study contributed the largest number with 435 cases. Daily mean dietary intakes for dairy foods and nutrients differed across studies, particularly for total calcium, lactose, hard cheese, and yogurt.

The median Pearson correlations for dairy foods and nutrients are shown in Table 2. Lactose intake was highly correlated with total milk (all study-specific correlations exceeded 0.59, median correlation = 0.83), dietary calcium (all correlations >0.69, median = 0.90), and, except for the Swedish Mammography Cohort (r = 0.36), dietary vitamin D (all other correlations >0.73, median = 0.83). Milk intake was also highly correlated with dietary calcium (median = 0.77) and dietary vitamin D (median = 0.71) intake. Weaker correlations were observed between lactose and cheese and yogurt intake.

No statistically significant associations with ovarian cancer risk were present by categories of hard cheese, cottage cheese, yogurt, ice cream, and calcium intake (Table 3). No association between higher intake of milk and ovarian cancer risk (pooled multivariate RR, 1.11; 95% CI, 0.87-1.41 comparing 500 to 0 g/d) was observed. When we examined a larger contrast in intake, >750 g/d of milk, a nonstatistically significant higher risk of ovarian cancer was observed (pooled multivariate RR, 1.23; 95% CI, 0.79-1.92), although the number of cases within most studies was <10 (total case N = 58). Results from the multivariate-adjusted models were similar to those from age-adjusted models. A positive association was present for intakes >400 IU/d of dietary vitamin D and risk of ovarian cancer (pooled multivariate RR for 400 to <500 IU/d, 1.56; 95% CI, 1.17-2.08 and pooled multivariate RR for ≥500 IU/d, 1.37; 95% CI, 0.78-2.40) comparing with <100 IU/d. However, the association was not present for total (dietary and supplemental) vitamin D intake and ovarian cancer risk. A statistically significant higher risk of ovarian cancer was observed with higher intakes of lactose (pooled multivariate RR, 1.19; 95% CI, 1.01-1.40, P_{trend} = 0.19) comparing ≥30 g/d (equivalent to ≥3 servings or 750 g milk/d) versus <10 g/d (equivalent to <1 serving or 250 g milk/d). Although the study-specific risk estimates for the ≥30 g/d category compared with the <10 g/d were all nonsignificant (Fig. 1), 8 of the 13 studies included in this analysis reported a higher risk of ovarian cancer with higher lactose intake ($P_{heterogeneity}$ = 0.58).

Table 2. Median Pearson correlations for dairy products and nutrients across all studies included in the ovarian cancer analyses in the Pooling Project of Prospective Studies of Diet and Cancer

	Lactose	Total milk	Whole milk	Low-fat milk	Hard cheese	Cottage cheese	Yogurt	Ice cream	Dietary calcium	Total calcium	Dietary vitamin D	Total vitamin D
Lactose	1.00	0.83	0.21	0.67	−0.08	0.08	0.18	0.02	0.90	0.63	0.83	0.40
Total milk		1.00	0.36	0.84	0.03	0.08	0.07	0.03	0.77	0.54	0.71	0.34
Whole milk			1.00	−0.19	0.03	0.00	−0.02	0.06	0.14	0.03	0.13	0.04
Low-fat milk				1.00	0.01	0.09	0.07	0.01	0.69	0.47	0.68	0.33
Hard cheese					1.00	0.09	0.04	0.09	0.17	0.08	−0.10	−0.04
Cottage cheese						1.00	0.15	0.03	0.14	0.10	0.04	0.04
Yogurt							1.00	0.00	0.28	0.23	0.17	0.13
Ice cream								1.00	−0.01	−0.01	−0.02	−0.02
Dietary calcium									1.00	0.70	0.79	0.39
Total calcium										1.00	0.50	0.47
Dietary vitamin D											1.00	0.47
Total vitamin D												1.00

NOTE: Median correlation value was calculated over all studies that measured that dairy food or nutrient. Studies that did not measure that particular food or nutrient were excluded from that specific analysis. For whole milk, New York State Cohort was excluded; for low-fat milk, New York State Cohort was excluded; for hard cheese, New York State Cohort was excluded; for cottage cheese, Cancer Prevention Study II Nutrition Cohort, New York State Cohort, and Swedish Mammography Cohort were excluded; for yogurt, Adventist Health Study, Breast Cancer Detection Demonstration Project Follow-up Study, and New York State Cohort were excluded; for ice cream, Adventist Health Study, the Netherlands Cohort Study, and New York State Cohort were excluded; for total calcium (dietary + supplemental), Canadian National Breast Screening Study, the Netherlands Cohort Study, and Swedish Mammography Cohort were excluded; for dietary vitamin D, Adventist Health Study, Canadian National Breast Screening Study, the Netherlands Cohort Study, and New York University Women's Health Study were excluded; and for total vitamin D, Adventist Health Study, Canadian National Breast Screening Study, the Netherlands Cohort Study, New York University Women's Health Study, and Swedish Mammography Cohort were excluded. All studies measured lactose, total milk, and dietary calcium.

Table 3. Pooled age and multivariate adjusted RRs and 95% CIs for ovarian cancer according to intake of dairy foods and nutrients

		Categories of intake						$P_{heterogeneity}$*	P_{trend}†
Foods									
Milk‡ (g/d)	Range	0	1-69.9	70-124.9	125-249.9	250-499.9	≥500		
	Cases	214	305	320	673	321	273		
	Age RR	1.00 (Reference)	0.98 (0.81-1.17)	1.07 (0.85-1.34)	1.09 (0.87-1.36)	0.90 (0.73-1.10)	1.10 (0.89-1.36)	0.48	0.20
	MV RR	1.00 (Reference)	0.98 (0.81-1.17)	1.07 (0.84-1.35)	1.09 (0.87-1.36)	0.90 (0.73-1.11)	1.11 (0.87-1.41)	0.30	0.43
Whole§,‖ (g/d)	Range	0	1-124.9	125-249.9	≥250				
	Cases	1,120	428	226	145				
	Age RR	1.00 (Reference)	0.92 (0.82-1.04)	1.01 (0.87-1.18)	0.93 (0.75-1.16)			0.28	0.83
	MV RR	1.00 (Reference)	0.94 (0.83-1.05)	1.04 (0.88-1.21)	0.95 (0.73-1.24)			0.10	0.99
Low-fat§ (g/d)	Range	0	1-124.9	125-249.9	≥250				
	Cases	818	343	449	373				
	Age RR	1.00 (Reference)	1.00 (0.87-1.15)	1.08 (0.93-1.25)	1.07 (0.94-1.23)			0.44	0.38
	MV RR	1.00 (Reference)	0.99 (0.86-1.14)	1.08 (0.93-1.25)	1.07 (0.93-1.23)			0.51	0.38
Hard cheese¶,** (g/d)	Range	0	1-24.9	25-49.9	≥50				
	Cases	191	1,444	253	139				
	Age RR	1.00 (Reference)	1.05 (0.87-1.27)	1.05 (0.74-1.49)	1.24 (0.92-1.68)			0.66	0.51
	MV RR	1.00 (Reference)	1.09 (0.90-1.33)	1.09 (0.77-1.53)	1.30 (0.96-1.78)			0.74	0.38
Cottage cheese††,‡‡ (g/d)	Range	0	1-25.9	26-52.9	≥53				
	Cases	542	668	179	75				
	Age RR	1.00 (Reference)	0.96 (0.85-1.09)	0.91 (0.75-1.12)	0.88 (0.63-1.23)			0.14	0.31
	MV RR	1.00 (Reference)	0.97 (0.85-1.10)	0.92 (0.75-1.13)	0.88 (0.63-1.23)			0.14	0.33
Yogurt¶,§§ (g/d)	Range	0	1-27.9	28-56.9	57-113.9	≥114			
	Cases	800	407	177	197	228			
	Age RR	1.00 (Reference)	0.98 (0.87-1.12)	0.89 (0.75-1.05)	0.90 (0.76-1.07)	1.04 (0.87-1.24)		0.80	0.86
	MV RR	1.00 (Reference)	0.97 (0.85-1.10)	0.87 (0.73-1.04)	0.89 (0.75-1.06)	1.04 (0.86-1.24)		0.75	0.89
Ice cream‖‖ (g/d)	Range	0	1-16.9	17-32.9	33-65.9	≥66			
	Cases	561	862	230	67	33			
	Age RR	1.00 (Reference)	0.98 (0.88-1.10)	1.07 (0.87-1.32)	1.13 (0.83-1.52)	0.85 (0.59-1.23)		0.67	0.82
	MV RR	1.00 (Reference)	1.02 (0.90-1.14)	1.12 (0.90-1.38)	1.18 (0.85-1.63)	0.91 (0.63-1.32)		0.66	0.55
Nutrients									
Dietary calcium¶¶ (mg/d)	Range	<500	500-699.9	700-899.9	900-1,099.9	1,100-1,299.9	≥1,300		
	Cases	287	554	562	354	182	140		
	Age RR	1.00 (Reference)	1.02 (0.88-1.18)	1.06 (0.87-1.28)	1.00 (0.78-1.29)	0.98 (0.79-1.21)	1.17 (0.93-1.47)	0.43	0.33
	MV RR	1.00 (Reference)	1.02 (0.88-1.18)	1.05 (0.89-1.24)	1.00 (0.79-1.27)	0.98 (0.79-1.21)	1.17 (0.93-1.47)	0.53	0.38
Total calcium¶¶,*** (mg/d)	Range	<500	500-699.9	700-899.9	900-1,099.9	1,100-1,299.9	≥1,300		
	Cases	119	251	274	213	169	335		
	Age RR	1.00 (Reference)	1.01 (0.85-1.33)	1.10 (0.87-1.40)	1.08 (0.85-1.36)	1.22 (0.95-1.56)	1.18 (0.90-1.53)	0.27	0.11
	MV RR	1.00 (Reference)	1.05 (0.84-1.30)	1.06 (0.85-1.34)	1.04 (0.82-1.32)	1.16 (0.90-1.48)	1.08 (0.84-1.38)	0.37	0.49
Lactose (g/d)	Range	<10	10-19.9	20-29.9	≥ 30				
	Cases	785	793	344	210				
	Age RR	1.00 (Reference)	1.09 (0.97-1.22)	1.06 (0.91-1.24)	1.21 (1.03-1.42)			0.55	0.17
	MV RR	1.00 (Reference)	1.09 (0.97-1.22)	1.07 (0.91-1.25)	1.19 (1.01-1.40)			0.58	0.19
Dietary vitamin D†††,‡‡‡ (IU/d)	Range	<100	100-199.9	200-299.9	300-399.9	400-499.9	≥ 500		
	Cases	226	699	427	136	71	24		
	Age RR	1.00 (Reference)	1.05 (0.90-1.22)	1.11 (0.94-1.31)	1.07 (0.84-1.36)	1.60 (1.20-2.13)	1.46 (0.80-2.65)	0.15	0.02
	MV RR	1.00 (Reference)	1.05 (0.90-1.23)	1.10 (0.93-1.30)	1.05 (0.83-1.33)	1.56 (1.17-2.08)	1.37 (0.78-2.40)	0.21	0.04
Total vitamin D†††,‡‡‡ (IU/d)	Range	<100	100-199.9	200-299.9	300-399.9	400-499.9	≥500		
	Cases	125	346	252	113	121	339		
	Age RR	1.00 (Reference)	1.20 (0.97-1.48)	1.28 (1.02-1.59)	1.11 (0.80-1.54)	1.33 (1.02-1.72)	1.16 (0.94-1.44)	0.49	0.29
	MV RR	1.00 (Reference)	1.20 (0.97-1.48)	1.26 (1.00-1.57)	1.09 (0.79-1.51)	1.27 (0.98-1.64)	1.12 (0.90-1.38)	0.55	0.60

NOTE: Multivariate RRs were adjusted for age at menarche (<13, 13, >13 years), menopausal status at baseline (premenopausal, postmenopausal, dubious), oral contraceptive use (ever, never), hormone replacement therapy use among postmenopausal women (never, past, current), parity (0, 1, 2, >2), BMI (<23, 23-<25, 25-<30, ≥30 kg/m^2), smoking status (never, past, current), physical activity (low, medium, high), and energy intake (continuously), modeled identically across studies.
Abbreviation: MV RR, multivariate RR.

*P value, test for between-studies heterogeneity is based on the highest category of intake for that food or nutrient.

†P value, test for trend.

‡New York State Cohort was not included in the categories 250 to 499.9 and ≥500 g/d of milk because this study had no cases in that category.

§New York State Cohort was not included in the low-fat or whole-milk analyses because they did not measure consumption of these items separately.

‖Nurses' Health Study II was not included in the category ≥250 g/d of whole milk because this study had no cases in that category.

¶New York State Cohort is not included in the hard cheese or yogurt analyses because they did not measure consumption of these food items.

**Adventist Health Study, Nurses' Health Study (part a) and Nurses' Health Study II were not included in the category ≥50 g/d of hard cheese because this study had no cases in that category.

†† Nurses' Health Study II was not included in the category ≥53 g/d of cottage cheese because this study had no cases in that category.

‡‡ Cancer Prevention Study II Nutrition Cohort, New York State Cohort, and Swedish Mammography Cohort were not included in this analysis because they did not measure consumption of this item.

§§Adventist Health Study and Breast Cancer Detection Demonstration Project Follow-up Study are not included in the yogurt analysis because they did not measure consumption of this food item.

‖‖Adventist Health Study, the Netherlands Cohort Study, and New York State Cohort are excluded from the ice cream analyses because they did not measure consumption of this food item. Nurses' Health Study II and Women's Health Study were not included in the category ≥66 g/d of ice cream because this study had no cases in that category.

¶¶Adventist Health Study was not included in the analysis of dietary or total calcium because this study had no cases in the reference group.

***Canadian National Breast Screening Study, the Netherlands Cohort Study, Swedish Mammography Cohort are excluded from the total calcium and vitamin D analyses because they did not have supplement use data available for these nutrients.

††† New York State Cohort, Nurses' Health Study (part a) were not included in the category ≥500 g/d of dietary vitamin D because this study had no cases in that category.

‡‡‡ Adventist Health Study, Canadian National Breast Screening Study, the Netherlands Cohort Study, New York University Women's Health Study are excluded from the dietary and total (dietary and supplemental) vitamin D analyses because they did not assess vitamin D intake; Swedish Mammography Cohort is excluded from the total (dietary and supplemental) vitamin D analyses because they did not have supplement use data available.

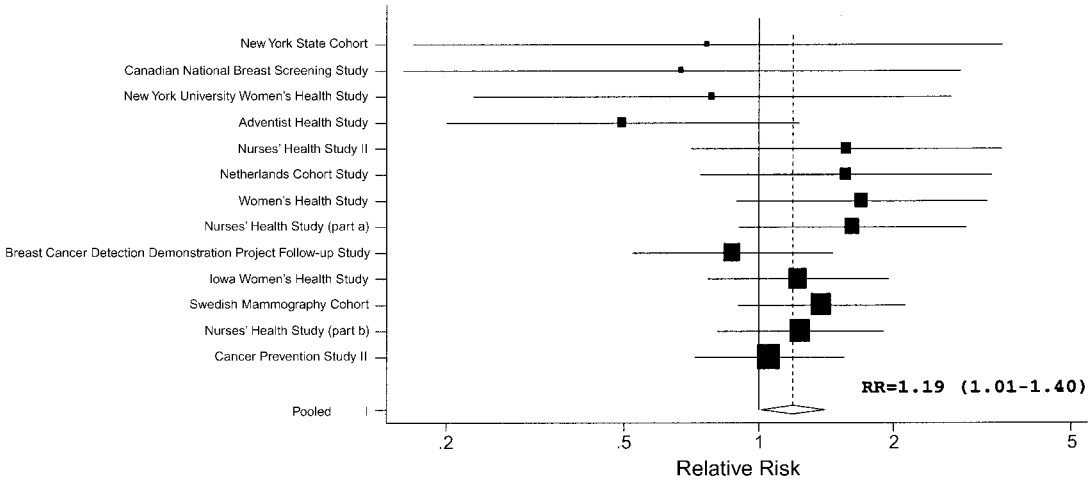

Figure 1. Multivariate adjusted RRs and 95% CI for ovarian cancer according to lactose intake (≥30 compared with <10 g/d) by study. Multivariate RRs were adjusted for age at menarche (<13, 13, >13 years), menopausal status at baseline (premenopausal, postmenopausal, dubious), oral contraceptive use (ever, never), hormone replacement therapy use among postmenopausal women (never, past, current), parity (0, 1, 2, >2), BMI (<23, 23 to <25, 25 to <30, ≥30 kg/m^2), smoking status (never, past, current), physical activity (low, medium, high), and energy intake (continuously), modeled identically across studies. *Black squares and horizontal lines,* study-specific RRs and 95% CIs for ≥30 g/d lactose intake compared with <10 g/d. The area of the black squares is proportional to the inverse of the sum of the between-studies variance and the study-specific variance, which is related to the sample size, the total number of cases, and the range of variation in intake. *Diamond,* pooled multivariate RR and the 95% CI. *Vertical dashed line,* pooled multivariate RR.

In multivariate-adjusted continuous models, no association with dietary calcium and total calcium (includes intake from supplements) intake was observed with risk of ovarian cancer (Table 4). Higher intakes of lactose were associated with a nonstatistically significant higher risk of ovarian cancer (pooled multivariate RR for 10 g/d increment of lactose, 1.04; 95% CI, 0.99-1.08). Higher intake of dietary vitamin D was also associated with a higher risk of ovarian cancer (pooled multivariate RR for 100 IU/d increment of vitamin D, 1.06; 95% CI, 1.00-1.12), although, again, the association was not present for dietary and supplement vitamin D intake (Table 4). When conducting calcium and lactose continuous multivariate analyses with measurement error correction, we found that the associations between calcium (pooled multivariate RR for 350 mg/d increment of calcium, 1.09; 95% CI, 0.91-1.29) and lactose (pooled multivariate RR for 10 g/d increment of lactose, 1.09; 95% CI, 0.96-1.25) and ovarian cancer risk were similar to the results presented. Of the cases with histology information collected (94% of cases), ~13% were endometrioid, 7% were mucinous, and 48% of cases were serous. Only 5% of cases with histologic information were clear cell, whereas similar or even smaller percentages represented Brenner or transitional tumors, poorly differentiated tumors, carcinosarcomas, and mixed histology, so we were unable to analyze these groups. Generally, when examining serous, mucinous, endometrioid ovarian cancers separately, the results were similar to the overall findings (Table 4). A slightly higher risk of serous ovarian cancer was observed for higher intakes of low-fat milk and ice cream, whereas a positive association between total (dietary and supplemental) vitamin D intake and endometrioid ovarian cancer was seen. There was no statistically significant difference in the common effect between endometrioid, mucinous, and serous ovarian cancers for dairy nutrients and foods.

Similar estimates to the overall findings were observed when participants were stratified by age at diagnosis, parity, oral contraceptive use, hormone replacement therapy use, baseline menopausal status, and median fat intake (data not shown). Results were similar when using the crude nutrient estimate of dietary calcium, lactose, and vitamin D compared with the energy-adjusted nutrient models presented (data not shown). In addition, cases that occurred close in time to the completion of the food frequency questionnaires may represent individuals who altered their diet due to factors, such as prediagnostic disease symptoms. To assess this, sensitivity analyses, excluding cases diagnosed during the first year and second year of follow-up, were conducted to determine if the estimates were affected by including cases with an early diagnosis. Estimates from both models were comparable with the overall estimates (data not shown). Additionally, results were similar when we limited analyses to the first 6 years of follow-up compared with ≥6 years of follow-up (data not shown).

Discussion

Higher intakes of milk and lactose are hypothesized to increase the risk of ovarian cancer. However, in this pooled analysis of 12 cohort studies that prospectively assessed the association between diet and ovarian cancer risk, no statistically significant associations were observed for milk or calcium intake. A weak, marginally significant positive association was observed for lactose and ovarian cancer risk, although lactose was highly correlated with milk and calcium intake within this pooled analysis (median r across studies >0.83 and 0.90, respectively). For the lactose analysis, we were able to analyze the amount of lactose found in the equivalent of three or more servings of milk (750 g) per day due to the contribution of lactose from other food sources. If lactose is truly a causal factor, the accurate assessment of lactose intake per se would reduce measurement error compared with the use of milk consumption as a surrogate of lactose intake because the latter ignores other dietary sources. Also, we cannot exclude the possibility that other correlated factors in dairy products, such as hormones, could be causal factors for ovarian cancer. For example, high milk consumption increases blood levels of insulin-like growth factor-I (69, 70), which has been associated with ovarian cancer (71, 72).

Similar to our results, some (17, 20, 25, 28), but not all (15, 21, 22, 24, 27), case-control studies of milk intake have reported no association with ovarian cancer risk. In contrast to our results showing a positive association between lactose intake and risk of ovarian cancer, many case-control studies

examining lactose intake and ovarian cancer risk have found no association (8, 20, 22, 25, 29, 31, 32) or an inverse association (21, 27, 30). However, two case-control studies have found higher risk of ovarian cancer with lactose absorption (22) and metabolism (18).

Some (32, 36), although not all (21), case-control studies have shown a lower risk of ovarian cancer with higher intakes of dietary vitamin D. In our analysis, a nonsignificant higher risk of ovarian cancer was associated with higher intakes of dietary vitamin D, but not with higher total (dietary and supplemental) vitamin D intake. To better understand this inconsistency, we also examined other nondairy sources of dietary vitamin D (73-75), such as fish and cereal, and saw no association between intakes of these foods and ovarian cancer risk (data not shown). Because neither of these other food sources of vitamin D nor supplemental vitamin D was related to ovarian cancer, vitamin D is unlikely to be a causal factor.

Our analyses were conducted using baseline food frequency questionnaires that generally covered intakes during the year before the beginning of the follow-up period of each study. Thus, a limitation of our analyses is that we could not assess whether there was a change in intake during follow-up. Additionally, because we only measured intake during adulthood, we may not have captured the relevant exposure time for ovarian cancer risk. It may be that dietary factors during a different life period (i.e., adolescence) may be the biologically relevant exposure period (76).

Because diet was measured before diagnosis of ovarian cancer, reporting of dairy foods would not be expected to be systematically biased by disease status in these prospective studies, but general misclassification of dairy food intake was likely nondifferential misclassification, and such misclassification would have attenuated the RR estimates for the relation between intakes of dairy foods and nutrients and risk of ovarian cancer. When conducting calcium and lactose continuous multivariate analyses with measurement error correction, we found that the associations between calcium and lactose and ovarian cancer risk were similar to results presented.

In this study, not all cohorts were included in each dairy food and nutrient analysis because some items were not ascertained on the study food frequency questionnaire. The dietary assessment methods used differed across studies by number of questions and type of questions. For all analyses conducted, there was no between-study heterogeneity present. Thus, even with different questionnaires and populations, the individual studies estimated similar risks of ovarian cancer for each exposure.

Similarly, not all covariates were measured in each study. Within our models, we adjusted for most of the important ovarian cancer risk factors (e.g., age at menarche, oral contraceptive use, and parity) if they were measured in a study; results from age-adjusted and multivariate models were similar, suggesting that residual or unmeasured confounding would be small. A major advantage of pooling compared with

Table 4. Pooled multivariate adjusted RRs and 95% CIs for histologic subtypes of ovarian cancer according to dairy food and nutrient intake, continuous model

	Increment* (/d)	All ovarian cancer			Endometrioid cancer†			Mucinous cancer‡			Serous cancer§			P‖
		Case, *n*	RR (95% CI)¶	P**	Case *n*	RR (95% CI)¶	P**	Case *n*	RR (95% CI)¶	P**	Case *n*	RR (95% CI)¶	P**	
Foods														
Milk	250 g	2,106	1.02 (0.97-1.08)	0.34	255	1.10 (0.95-1.27)	0.50	120	0.97 (0.77-1.22)	0.40	1,015	1.06 (0.94-1.19)	0.01	0.60
Whole milk††	250 g	1,919	0.98 (0.88-1.10)	0.09	240	0.91 (0.65-1.27)	0.29	113	1.19 (0.88-1.61)	0.88	930	0.91 (0.76-1.08)	0.19	0.37
Low-fat milk††	250 g	1,983	1.04 (0.98-1.09)	0.64	249	1.16 (1.00-1.34)	0.81	116	0.93 (0.73-1.20)	0.42	968	1.08 (0.99-1.18)	0.26	0.21
Cheese														
Hard cheese‡‡	25 g	2,027	1.02 (0.93-1.11)	0.17	259	1.11 (0.92-1.35)	0.77	122	1.00 (0.75-1.33)	0.56	982	1.07 (0.97-1.18)	0.69	0.75
Cottage cheese§§	105 g	1,464	0.82 (0.63-1.08)	0.22	182	0.95 (0.50-1.81)	0.64	87	1.59 (0.92-2.57)	0.53	708	0.90 (0.62-1.32)	0.21	0.05
Yogurt‖‖	227 g	1,809	0.91 (0.77-1.07)	0.80	239	0.98 (0.64-1.49)	0.83	119	0.83 (0.42-1.64)	0.71	931	0.93 (0.74-1.18)	0.93	0.95
Ice cream¶¶	66 g	1,753	1.00 (0.84-1.20)	0.49	237	1.13 (0.68-1.87)	0.76	96	0.47 (0.12-1.83)	0.20	869	1.17 (0.94-1.44)	0.85	0.36
Nutrients														
Dietary calcium	350mg	2,132	1.03 (0.97-1.09)	0.32	261	1.08 (0.93-1.25)	0.39	122	0.88 (0.70-1.11)	0.70	1,025	1.08 (0.97-1.21)	0.03	0.50
Total calcium***	350mg	1,414	1.01 (0.99-1.02)	0.41	148	1.08 (0.94-1.24)	0.03	59	1.08 (0.89-1.30)	0.48	682	1.00 (0.93-1.07)	0.29	0.53
Lactose	10 g	2,132	1.04 (0.99-1.08)	0.26	261	1.07 (0.95-1.20)	0.63	122	0.97 (0.81-1.16)	0.66	1,025	1.06 (0.97-1.16)	0.02	0.63
Dietary vitamin D†††	100 IU	1,583	1.06 (1.00-1.12)	0.28	198	1.17 (0.97-1.42)	0.04	81	0.95 (0.73-1.24)	0.22	782	1.04 (0.98-1.12)	0.83	0.84
Total vitamin D‡‡‡	100 IU	1,296	1.02 (0.99-1.04)	0.31	148	1.08 (1.02-1.15)	0.21	59	0.99 (0.85-1.10)	0.25	647	1.02 (0.94-1.09)	0.85	0.17

*Increment for foods is based on the standard serving size and for nutrients is based on the mean of the SD of the mean intake for each nutrient.

†Endometrioid analyses additionally exclude Adventist Health Study, New York State Cohort, and New York University Women's Health Study due to small case numbers.

‡Mucinous analyses additionally exclude Adventist Health Study, Breast Cancer Detection Demonstration Project Follow-up Study, New York State Cohort, New York University Women's Health Study, Nurses' Health Study II, and Women's Health Study due to small case numbers.

§Serous analyses additionally exclude Adventist Health Study due to small case numbers.

‖P value for the test for the common effect by histologic types of ovarian cancer (endometrioid, mucinous, and serous).

¶Multivariate RRs were adjusted for age at menarche (<13, 13, >13 years), menopausal status at baseline (premenopausal, postmenopausal, dubious), oral contraceptive use (ever, never), hormone replacement therapy use among postmenopausal women (never, past, current), parity (0, 1, 2, >2), BMI (<23, 23-<25, 25-<30, ≥30 kg/m^2), smoking status (never, past, current), physical activity (low, medium, high), and energy intake (continuously), modeled identically across studies.

**P value, test for between-studies heterogeneity.

††New York State Cohort is not included in the low-fat or whole-milk analyses because they did not measure consumption of these items separately.

‡‡New York State Cohort is not included in the hard cheese analyses because they did not measure consumption of this food item.

§§Cancer Prevention Study II Nutrition Cohort, New York State Cohort, and Swedish Mammography Cohort are excluded from the cottage cheese analyses because they did not measure consumption of this food item.

‖‖Adventist Health Study, Breast Cancer Detection Demonstration Project Follow-up Study, and New York State Cohort are excluded from the yogurt analyses because they did not measure consumption of this food item.

¶¶Adventist Health Study, the Netherlands Cohort Study, and New York State Cohort are excluded from the ice cream analyses because they did not measure consumption of this food item.

***Canadian National Breast Screening Study, the Netherlands Cohort Study, and Swedish Mammography Cohort are excluded from the total calcium analyses because they did not have supplement use data available.

†††Adventist Health Study, Canadian National Breast Screening Study, the Netherlands Cohort Study, New York University Women's Health Study are excluded from the dietary and total vitamin D analyses because they did not assess vitamin D intake.

‡‡‡Swedish Mammography Cohort is excluded from the total vitamin D analyses because they did not have supplement use data available.

a literature-based meta-analysis is the ability to characterize and control for covariates uniformly and classify the main exposures similarly. Furthermore, this prospective analysis was less susceptible to recall and selection biases and minimized the possibility of differential misclassification compared with case-control studies. Due to the inclusion of 12 cohort studies in North America and Europe, we had far greater statistical power than any of the individual cohort studies to examine specific histologic subtypes. Because the studies were conducted in a variety of populations with different dietary habits, we could examine associations over a wide range of dietary intakes.

In summary, we found no association between intakes of several specific dairy foods, dietary calcium, total calcium, and dietary and supplemental vitamin D and risk of ovarian cancer in this pooled analysis of 553,217 women. Our analysis suggests that high intakes of lactose, equivalent to three or more glasses (750 g) of milk per day, may weakly raise the risk of ovarian cancer. As this intake is similar to current U.S. dietary recommendations (77), the relation between dairy product consumption and ovarian cancer deserves further examination.

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