American Journal of Epidemiology
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Vol. 156, No. 2
Printed in U.S.A.
DOI: 10.1093/aje/kwf022

Association of Dairy Products, Lactose, and Calcium with the Risk of Ovarian Cancer

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Received for publication October 12, 2001; accepted for publication March 14, 2002.

Epidemiologic findings have been inconsistent regarding the association of dietary fat, dairy products, and lactose with risk of ovarian cancer. The authors conducted a case-control study in Hawaii and Los Angeles, California, to examine several dietary hypotheses regarding the etiology of ovarian cancer in a population with a broad range of dietary intakes. A total of 558 patients with ovarian cancer diagnosed in 1993–1999 and 607 controls were interviewed regarding their diet. Consumption of all dairy products, all types of milk, and low-fat milk, but not consumption of whole milk, was significantly inversely related to the odds of ovarian cancer. Similar inverse gradients in the odds ratios were obtained for intakes of lactose and calcium, although these nutrients were highly correlated ($r = 0.77$). The odds ratio for ovarian cancer was 0.46 (95% confidence interval: 0.27, 0.76) among women in the highest quartile of dietary calcium intake versus the lowest (p for trend = 0.0006). The significant dietary association was limited to dairy sources of calcium (p for trend = 0.003), although a nonsignificant inverse gradient in risk was also found in relation to calcium supplement intake. These results suggest that intake of low-fat milk, calcium, or lactose may reduce the risk of ovarian cancer. *Am J Epidemiol* 2002;156:148–57.

calcium; case-control studies; dairy products; diet; lactose; ovarian neoplasms

Abbreviations: CI, confidence interval; GALT, galactose-1-phosphate uridyltransferase; OR, odds ratio.

Data compiled by the National Cancer Institute have indicated that rates of ovarian cancer in the United States are approximately 60 percent greater among Caucasian women than among Asian women (1, 2). Aside from differences in reproductive factors, dietary differences might account for some of the ethnic variation in ovarian cancer rates. In several case-control studies, investigators have reported a positive association of dietary fat with risk of ovarian cancer (3–7), although others have failed to reproduce this result (8–10). In accordance with the findings on animal fat, a positive relation between ovarian cancer and consumption of dairy products has been shown in some studies (3, 5, 7, 11–13) but not in others (8, 14–17). Although some investigators have reported associations between ovarian cancer and intakes of specific types or components of dairy food—such as butter (3, 11), whole milk (3, 5, 7), skim milk (12), yogurt (7, 13), cottage cheese (13), and ice cream (7)—inverse associations with intakes of all milk (14), skim/low-fat milk (3, 5, 7, 16), and cheese (17) have also been found.

While results from past dietary studies are provocative, they indicate a need for a more careful examination of the influence of fat and dairy food consumption on risk of ovarian cancer. Only a few studies (12, 18) have attempted to separate an association between ovarian cancer and fat from an association between ovarian cancer and lactose or other components of dairy food. Furthermore, other dietary correlates of dairy product intake, such as intakes of calcium and vitamin D, have been examined by only a few investigators (12). The objective of this analysis was to examine the hypothesis that intake of dairy products and related compounds is positively associated with the odds of epithelial ovarian cancer.

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MATERIALS AND METHODS

We initiated a case-control study of ovarian cancer in Hawaii and Los Angeles, California, to explore several dietary hypotheses regarding the etiology of epithelial ovarian cancer. Eligibility criteria for participation included 1) residency in Hawaii or Los Angeles County for at least 1 year prior to diagnosis (cases) or interview (controls); 2) age ≥18 years; 3) Caucasian, Asian (Japanese, Chinese, Filipino, Korean), or other (including Pacific Islander or Hispanic) ancestry; and 4) no prior history of ovarian cancer.

Eligible patients included all women with histologically confirmed malignant epithelial carcinoma of the ovary diagnosed in 1993–1999 whose cases were reported to one of two population-based cancer registries, the Hawaii Tumor Registry and the Los Angeles County Cancer Surveillance Program at the University of Southern California (19). Each of these registries is subject to annual quality-control audits by the National Cancer Institute, and case ascertainment is thought to be more than 99 percent complete (19). Interview information was obtained from 603 (62 percent) of the 972 ovarian cancer patients eligible for participation in the study. Reasons for nonparticipation included physician refusal (n = 69), patient refusal (n = 222), and inability to locate the patient (n = 78). Response rates among eligible cases did not differ substantially by study location (65 percent in Hawaii, 61 percent in Los Angeles) or ethnic group (63 percent among Asian Americans, 65 percent among Pacific Islanders, 60 percent among Caucasians). Thirty-nine cases were excluded because of equivocal histologic classification, and six additional cases were excluded because their dietary information was considered unreliable (defined as having an energy intake more than three standard deviations from the mean based on the control lognormal distribution). Of the 558 ovarian cancer patients included in this analysis, 220 were from Hawaii and 338 were from Los Angeles.

Population controls were matched to cases according to specific ethnicity (e.g., Japanese), age (year of birth ±5 years), and study location. Controls were required to report whether or not they had undergone oophorectomy and, if so, whether one or both ovaries had been removed. Eligible controls had to have at least one intact ovary. In Hawaii, the control pool consisted of lists of female Oahu residents who were interviewed by the Health Surveillance Program of the Hawaii Department of Health (20). Potential controls were randomly selected from the pool so that the ethnic and 5-year age distribution would match that of the case group at a 1:1 ratio. In Los Angeles, over 95 percent of the controls were selected on the basis of a neighborhood walk procedure (21). A total of 907 women meeting these eligibility criteria were contacted to participate in the study. Complete demographic and nutrient information was obtained for 609 (67 percent) of these women. We excluded two control women from the analysis because their dietary data were considered unreliable. Of the 607 controls included in this analysis, 283 were from Hawaii and 324 were from Los Angeles.

The majority of the subjects (>95 percent) were interviewed in their homes by trained interviewers. All interviews were administered according to a standard protocol, regardless of the location of the interview, and took 1½–2½ hours to complete. A structured interviewer-administered questionnaire was developed for this investigation. The questionnaire gathered information on diet, including use of nutritional supplements, reproductive and gynecologic history, use of contraceptives and exogenous hormones, medical history, and other lifestyle practices.

The diet questionnaire was modeled after the one used in a multiethnic cohort study of over 215,000 men and women living in California and Hawaii that included the ethnic groups of interest in this study (22). The 256 food items or categories identified for inclusion in the questionnaire were representative of the eating patterns of the ethnic groups in the study and were selected from 3-day measured food records completed by a population-based sample of adults. The dietary reference period was the year before diagnosis for cases and the year before the interview for controls. If there had been a recent change in diet (within 3 years), the dietary reference period was the period before that change. For each food or beverage item, the respondent indicated the usual frequency with which the item was consumed per day, week, or month, with yearly frequencies being recorded for particular seasonal items. Photographs indicating the three most representative serving sizes were used to assist subjects in estimating amounts consumed. Both combination and multiple servings could be selected. Dairy items assessed included milk (whole, low-fat, nonfat, lactose-free, *Lactobacillus acidophilus*-containing), milk-based drinks, yogurt (regular, low-fat, nonfat), cheese (hard, soft), cottage cheese, ice cream, ice milk, and frozen yogurt. Intakes of alcoholic beverages and dietary supplements (nine categories) were also assessed.

The quantity of each food item consumed on a daily basis was calculated as the product of frequency and serving size. The nutrient content of foods was determined from a customized food composition database (22). The food composition data were compiled largely from US Department of Agriculture Handbook no. 8 (23, 24), with supplementation by laboratory analyses of foods, and other commercial publications (25–27). In addition to values for energy and macronutrients, the database includes values for over 90 other nutrients, including lactose, calcium, and vitamin D. Total nutrient intake was calculated as the sum of the nutrients derived from foods and supplements.

In this article, we focus on the relation of macronutrients, dairy products, and related compounds to risk of epithelial ovarian cancer. A preliminary examination of the data included comparisons of cases and controls with respect to several demographic characteristics and risk factors of interest. We used analysis of covariance to compare log-transformed mean intakes of nutrients and foods between cases and controls while adjusting for age, ethnicity, location, and energy intake (28). We calculated partial Pearson correlations (r) for continuous dietary and nondietary variables, adjusting for age, ethnicity, location, and energy intake, to evaluate collinearity.

We evaluated risks associated with different levels of the exposure variables by unconditional logistic regression modeling case/control status (29). We computed odds ratios and 95 percent confidence intervals by exponentiating the coefficients (and confidence intervals) for the binary indi-

cator variables representing the quartile levels of nutrient or food intake. The quartile cutpoints were based on the distribution in the combined population of cases and controls. Adjustment factors included age as a continuous variable, ethnicity as an indicator variable (Caucasian, Asian, other), study location (Hawaii, Los Angeles), education (continuous variable), oral contraceptive use (ever vs. never), parity (ever vs. never), tubal ligation (yes vs. no), and log-transformed energy intake (in dietary analyses). We also considered other potential risk factors as adjustment variables, such as menopausal status and family history, but these did not materially alter the fit of the models. We employed various methods of calorie adjustment, including the standard and residual methods (30). Odds ratios were generally similar for each of the three methods, so we have presented results from the standard method in which calories were introduced as a model covariate. We performed a test for linear trend in the logit of risk by comparing twice the difference in log likelihoods for models with and without a trend variable assigned the median value for each quartile. Similarly, the likelihood ratio test was used to evaluate the effect of interaction between variables on the risk of ovarian cancer. This test compared a no-interaction model containing main-effect terms with a fully parameterized model containing all possible interaction terms for the variables of interest.

RESULTS

The ovarian cancer patients included in the study population were generally of European or Asian ancestry. The ethnic category "other" included largely Native Hawaiian women and English-speaking, non-Caucasian Hispanic women (table 1). The average age of cases and controls was 54.8 years. Cases were not as well educated as controls (mean years of education: cases, 13.0 years; controls, 13.4 years), and they tended to have lower family incomes (mean annual income: cases, $54,389; controls, $60,711). Seventy-nine percent of cases and 76 percent of controls had ever been pregnant, and pregnancy reduced the risk of ovarian cancer by 41 percent (95 percent confidence interval (CI): 0.4, 0.8) (data not shown). An inverse gradient in risk (p for trend < 0.0001) was associated with an increasing number of pregnancies. Oral contraceptives were used by 43 percent of cases and 56 percent of controls (odds ratio (OR) = 0.6, 95 percent CI: 0.4, 0.8), with an inverse dose-response relation between risk and increasing years of use (p for trend < 0.0001). Other significant risk factors included history of tubal ligation and family history of breast or ovarian cancer.

We found no significant difference between cases and controls in crude or covariate-adjusted mean intakes of any of the major macronutrients, including fat, carbohydrate, and protein (data not shown). Adjusted mean energy intake was 1,997 kcal/day for cases and 1,960 kcal/day for controls. Age-standardized average daily energy consumption among controls differed substantially between Native Hawaiian (2,335 kcal), Caucasian (2,082 kcal), and Japanese (1,885 kcal) women. Daily intake of dairy products was lower among cases (mean = 146.7 g) than among controls (mean = 179.9 g) after adjustment for covariates (data not shown). This difference in mean values was significant (p = 0.0008).

When examined across quartiles of intake, macronutrients remained unrelated to ovarian cancer risk (table 2). Likewise, no association was found for protein and fat derived from meat, dairy, or vegetable sources or for percentage of calories derived from fat, protein, or carbohydrate (data not shown). Energy adjustment had little influence on the odds ratios.

Consumption of all dairy products, all types of milk, and low-fat milk was significantly inversely related to risk of ovarian cancer (table 3, model 1), but consumption of whole milk was not. Women with the highest intake of butter (>75th percentile) were at significantly reduced risk of ovarian cancer compared with women with the lowest intake (≤25th percentile), but the trend in the odds ratios was not significant. No relations were found between ovarian cancer risk and intakes of yogurt, cheese, and ice cream. Associations were generally homogeneous within each ethnic group. Odds ratios associated with the top three quartiles of all dairy food consumption compared with the lowest quartile were 0.7 (95 percent CI: 0.4, 1.2), 0.6 (95 percent CI: 0.3, 1.1), and 0.7 (95 percent CI: 0.4, 1.2), respectively, for Caucasians (p for trend = 0.21); 1.0 (95 percent CI: 0.6, 1.6), 0.6 (95 percent CI: 0.4, 1.1), and 0.5 (95 percent CI: 0.3, 1.0), respectively, for Asians (p for trend = 0.03); and 0.8 (95 percent CI: 0.3, 2.1), 0.5 (95 percent CI: 0.2, 1.3), and 0.4 (95 percent CI: 0.2, 1.3), respectively, for persons of "other" ethnicity (p for trend = 0.09).

The age-, race-, and location-adjusted correlations between intakes of dairy products and lactose (r = 0.96) and intakes of dairy products and calcium (r = 0.83) underscore the difficulty of identifying independent relations between these dietary exposures and ovarian cancer risk. In table 3, we report odds ratios for ovarian cancer associated with the consumption of dairy products after adjustment for calcium intake (model 2) or lactose intake (model 3). Adjustment for either calcium or lactose tended to attenuate the odds ratios so that the trend in risk associated with dairy product intake was no longer statistically significant.

Intakes of lactose and calcium but not intakes of vitamin D or other sugars (data not shown) were significantly inversely associated with the risk of ovarian cancer after adjustment for energy intake and other confounders (table 4). The strong correlation (r = 0.77) between intakes of lactose and calcium suggested overlapping food sources for these nutrients. The trend associated with calcium intake remained significant (p for trend = 0.02) after adjustment for lactose intake, but the relation of lactose to ovarian cancer risk was substantially attenuated by adjustment for calcium (p for trend = 0.68) (data not shown). The odds ratios associated with the top three quartiles of calcium consumption as compared with the lowest quartile were 0.4 (95 percent CI: 0.3, 1.1), 0.3 (95 percent CI: 0.2, 0.6), and 0.5 (95 percent CI: 0.3, 1.2), respectively, among Caucasian women (p for trend = 0.09) and 0.8 (95 percent CI: 0.5, 1.4), 0.5 (95 percent CI: 0.3, 1.0), and 0.4 (95 percent CI: 0.2, 1.0), respectively, among Asian women (p for trend = 0.02).

Milk drinking was the most common source of calcium among both Caucasian women (22 percent of daily intake) and Asian women (20 percent) (data not shown). Dairy foods were ranked in the top 10 sources of calcium among Cauca-

TABLE 1. Odds ratios* for the association between selected nondietary variables and risk of ovarian cancer, Hawaii and Los Angeles, California, 1993–1999

Variable	Cases (n = 558)		Controls (n = 607)		Odds ratio	95% confidence interval	p for trend†
	No.	%	No.	%			
Age (years)‡							
<45	130	23.3	149	24.6			
45-54	160	28.7	171	28.2			
55-64	117	21.0	98	16.1			
≥65	151	27.1	189	31.1			
Ethnicity‡							
Caucasian	258	46.2	266	43.8			
Asian	206	37.2	254	41.8			
Other	94	16.6	87	14.3			
Education (years)							
<13	189	33.9	163	26.9	1§		
13–14	194	34.8	214	35.2	0.75	0.55, 1.02	
15	113	20.2	150	24.7	0.63	0.41, 0.96	
≥16	62	11.1	80	13.2	0.59	0.41, 0.83	0.002
No. of full-term pregnancies							
0	159	28.5	107	17.6	1§		
1	77	13.8	90	14.8	0.60	0.41, 0.89	
2	139	24.9	179	29.5	0.60	0.42, 0.84	
≥3	183	32.8	231	38.1	0.53	0.37, 0.75	0.002
Oral contraceptive use (years)							
0	320	57.3	269	44.3	1§		
<1.9	93	16.7	99	16.3	0.74	0.51, 1.08	
1.9–5.39	82	14.7	110	18.1	0.61	0.42, 0.88	
≥5.4	63	11.3	129	21.3	0.36	0.24, 0.54	<0.0001
History of tubal ligation							
No	490	87.8	487	80.2	1§		
Yes	68	12.2	120	19.8	0.70	0.50, 0.99	
Menopausal status¶							
Premenopausal	172	31.5	231	39.4	1§		
Postmenopausal	374	68.5	355	60.6	2.22	1.52, 3.24	
Perineal use of talc powder							
Never	456	81.7	513	84.5	1§		
Ever	102	18.3	94	15.5	1.21	0.88, 1.67	
Family history of ovarian or breast cancer							
No	473	84.8	548	90.3	1§		
Yes	85	15.2	59	9.7	1.69	1.17, 2.43	

* Data were adjusted by unconditional multiple logistic regression for age, ethnicity, study center, education, use of oral contraceptives, parity, and tubal ligation (where appropriate).

† Based on a likelihood ratio test comparing models with and without a trend variable that was assigned median values for the categories.

‡ Cases and controls were frequency-matched according to age and ethnicity.

§ Reference category.

¶ Menopausal status was unknown for 12 cases and 21 controls.

sian women. In addition to dairy food, among Asian women the top 10 sources of calcium included tofu (accounting for 4 percent of daily calcium intake), oranges (3 percent), and broccoli (2 percent). A slightly greater amount of calcium in the diet was from dairy food sources (42 percent among cases, 40 percent among controls) than from nondairy food sources (38 percent among cases, 35 percent among controls), with a lesser percentage of calcium being obtained

TABLE 2. Odds ratios* for the association between quartiles† of dietary macronutrient intake and ovarian cancer risk, Hawaii and Los Angeles, California, 1993–1999

Nutrient	Q2‡ vs. Q1§		Q3 vs. Q1		Q4 vs. Q1		*p* for trend¶
	OR‡	95% CI‡	OR	95% CI	OR	95% CI	
Energy	1.09	0.78, 1.53	0.90	0.64, 1.27	1.21	0.85, 1.72	0.44
Protein	1.47	0.99, 2.17	1.01	0.63, 1.63	1.21	0.64, 2.27	0.81
Total fat	1.07	0.73, 1.56	0.77	0.48, 1.22	0.88	0.47, 1.63	0.50
Saturated fat	0.95	0.65, 1.38	0.76	0.48, 1.20	0.84	0.46, 1.51	0.44
Carbohydrate	1.20	0.81, 1.77	1.15	0.72, 1.83	1.21	0.65, 2.25	0.58
Starch	1.08	0.74, 1.57	1.13	0.74, 1.73	1.01	0.59, 1.73	0.89
Fiber	0.95	0.66, 1.36	0.97	0.65, 1.45	1.01	0.63, 1.63	0.95
Alcohol	1.17	0.83, 1.65	0.88	0.62, 1.25	0.84	0.58, 1.20	0.18

* Data were adjusted by unconditional multiple logistic regression for age, ethnicity, study center, education, use of oral contraceptives, parity, tubal ligation, and energy intake (except in the energy model).

† The quartile cutpoints for daily nutrient intake were as follows: energy, 1,526, 1,999, and 2,658 kcal; protein, 55.5, 75.5, and 102.5 g; total fat, 49.5, 72.4, and 107.3 g; saturated fat, 14.1, 20.8, and 32.1 g; carbohydrate, 193, 258, and 342 g; starch, 81.3, 115.3, and 160.3 g; dietary fiber, 15.3, 21.6, and 29.4 g; alcohol, 0.001, 0.008, and 2.85 g.

‡ Q, quartile; OR, odds ratio; CI, confidence interval.

§ Reference category.

¶ Based on a likelihood ratio test comparing models with and without a trend variable that was assigned median values for the categories.

from supplements (19 percent among cases, 24 percent among controls). Twenty-eight percent of cases and 33 percent of controls used calcium supplements.

A significant inverse association between ovarian cancer risk and calcium derived from dairy sources was found (table 4). We also found a nonsignificant inverse gradient in risk for calcium supplement intake but no relation of nondairy calcium intake to risk. When we limited the calcium analysis to the subset of women who did not report use of calcium supplements (403 cases, 409 controls), odds ratios associated with the top three quartiles of calcium consumption compared with the lowest were 0.7 (95 percent CI: 0.5, 1.1), 0.4 (95 percent CI: 0.2, 0.7), and 0.3 (95 percent CI: 0.2, 0.6), respectively ($p = 0.0002$).

We modeled the joint association of lactose and dietary calcium intakes (excluding supplements) with risk of ovarian cancer by creating dummy indicator variables consisting of combinations of lactose intake (≤8.5 g/day vs. >8.5 g/day) and calcium intake (≤779 mg/day vs. >779 mg/day), using women with a low intake of both nutrients as the reference category (table 5). Women with high intakes of both calcium and lactose were at significantly decreased risk of ovarian cancer compared with women with low intakes of these nutrients. The inverse association of calcium intake with ovarian cancer risk was modified by lactose intake: Calcium was beneficial among women with a low lactose intake (OR = 0.35/1 = 0.35) but not among women with a high lactose intake (OR = 0.57/0.51 = 1.12). The relation of lactose intake to ovarian cancer was also strongly modified by amount of calcium consumed on a daily basis: Lactose intake was inversely associated with risk among women with a low calcium intake (OR = 0.51/1 = 0.51) but not among women with a calcium intake above the median level (OR = 0.57/0.35 = 1.63). The effect of the interaction between calcium and lactose consumption on the odds ratios for disease was significant ($p = 0.0001$).

We also modeled the two-way interaction of dietary calcium or lactose intake (greater than median vs. median or less) and oral contraceptive use (never vs. ever), parity (never vs. ever), and menopausal status (premenopausal vs. postmenopausal) with risk of ovarian cancer (table 6). We found no significant effect of an interaction between these factors on disease risk. Women who had used oral contraceptives and who had high calcium intakes were at particularly low risk of ovarian cancer (OR = 0.34, 95 percent CI: 0.23, 0.52) in comparison with women who had never used oral contraceptives and who had nutrient intakes below the median. Calcium and lactose intakes were inversely related to ovarian cancer regardless of oral contraceptive use, parity, or menopausal status.

DISCUSSION

It has been a more than decade since Cramer et al. (13) hypothesized that galactose, a component sugar of lactose, was positively associated with ovarian cancer through increases in gonadotropin levels. Hypogonadism or ovarian failure in association with gonadotropin stimulation has been found in galactosemic women who are deficient in the enzyme galactose-1-phosphate uridyltransferase (GALT) (31). In an analysis of a case-control study of 235 cases and 239 controls conducted in the Boston, Massachusetts, area between 1983 and 1987, Cramer et al. initially reported that GALT activity was significantly lower among cases (13). A significant positive trend in risk associated with the ratio of lactose intake to GALT activity was also found. However, in

TABLE 3. Odds ratios for the association between quartiles* of dairy product intake and ovarian cancer risk, Hawaii and Los Angeles, California, 1993–1999

Dairy product and model†	Q2‡ vs. Q1§		Q3 vs. Q1		Q4 vs. Q1		*p* for trend¶
	OR‡	95% CI‡	OR	95% CI	OR	95% CI	
All dairy products							
Model 1	0.76	0.54, 1.08	0.60	0.42, 0.86	0.59	0.41, 0.87	0.003
Model 2	0.90	0.61, 1.32	0.79	0.50, 1.25	0.90	0.50, 1.61	0.52
Model 3	0.77	0.49, 1.20	0.61	0.34, 1.09	0.60	0.28, 1.30	0.14
All types of milk							
Model 1	0.92	0.65, 1.29	0.85	0.60, 1.20	0.64	0.45, 0.91	0.009
Model 2	1.01	0.71, 1.44	1.06	0.71, 1.58	0.93	0.57, 1.50	0.66
Model 3	1.01	0.68, 1.49	1.01	0.61, 1.67	0.83	0.43, 1.59	0.36
Whole milk							
Model 1	1.07	0.76, 1.52	1.09	0.76, 1.58	1.06	0.72, 1.54	0.80
Model 2	1.10	0.77, 1.56	1.15	0.80, 1.67	1.16	0.79, 1.71	0.44
Model 3	1.12	0.79, 1.59	1.17	0.81, 1.70	1.23	0.83, 1.83	0.31
Low-fat milk							
Model 1	0.87	0.62, 1.22	0.83	0.59, 1.17	0.59	0.41, 0.83	0.002
Model 2	0.90	0.64, 1.27	0.93	0.65, 1.33	0.74	0.49, 1.13	0.18
Model 3	0.89	0.63, 1.26	0.88	0.60, 1.28	0.65	0.41, 1.04	0.07
Yogurt							
Model 1	0.83	0.60, 1.16	1.05	0.74, 1.47	1.01	0.72, 1.43	0.68
Model 2	0.92	0.66, 1.29	1.20	0.84, 1.70	1.29	0.89, 1.87	0.11
Model 3	0.89	0.64, 1.25	1.15	0.81, 1.63	1.20	0.83, 1.73	0.22
Cheese							
Model 1	0.98	0.68, 1.40	1.20	0.81, 1.78	0.89	0.57, 1.39	0.88
Model 2	1.05	0.73, 1.51	1.37	0.91, 2.04	1.13	0.71, 1.80	0.40
Model 3	1.03	0.72, 1.47	1.26	0.85, 1.88	0.97	0.62, 1.51	0.86
Ice cream							
Model 1	0.99	0.73, 1.35	0.87	0.61, 1.26	1.14	0.81, 1.61	0.63
Model 2	0.99	0.72, 1.34	0.89	0.62, 1.28	1.14	0.81, 1.61	0.61
Model 3	1.01	0.74, 1.37	0.94	0.65, 1.35	1.24	0.87, 1.75	0.33
Butter							
Model 1	0.80	0.57, 1.13	0.82	0.58, 1.17	0.68	0.48, 0.98	0.09
Model 2	0.82	0.58, 1.15	0.82	0.57, 1.17	0.67	0.47, 0.96	0.06
Model 3	0.84	0.59, 1.18	0.86	0.60, 1.22	0.70	0.49, 1.00	0.08

* The quartile cutpoints for daily intake of dairy products were as follows: all dairy products, 93.5, 207.8, and 371.9 g; all milk, 34.4, 117.2, and 262.4 g; whole milk, 4.4, 13.3, and 37.1 g; low-fat milk, 7.9, 59.4, and 196.2 g; yogurt, 0, 11.3, and 42.6 g; cheese, 6.4, 19.0, and 43.6 g; ice cream, 0, 5.7, and 19.1 g; butter, 0.03, 0.18, and 1.41 g.

† Model 1: Data were adjusted by unconditional logistic regression for age, ethnicity, study center, education, use of oral contraceptives, parity, tubal ligation, and energy intake. Model 2: Data were adjusted for all of the factors in model 1 plus dietary calcium intake. Model 3: Data were adjusted for all of the factors in model 1 plus lactose intake.

‡ Q, quartile; OR, odds ratio; CI, confidence interval.

§ Reference category.

¶ Based on a likelihood ratio test comparing models with and without a trend variable that was assigned median values for the categories.

TABLE 4. Odds ratios for the association of quartiles* of lactose, calcium, and vitamin D intake with ovarian cancer risk, Hawaii and Los Angeles, California, 1993–1999

Nutrient and model†	Q2‡ vs. Q1§		Q3 vs. Q1		Q4 vs. Q1		*p* for trend¶
	OR‡	95% CI‡	OR	95% CI	OR	95% CI	
Dietary calcium (model 1)	0.66	0.45, 0.95	0.43	0.28, 0.65	0.46	0.27, 0.76	0.0006
Dairy calcium (model 1)	0.82	0.58, 1.16	0.47	0.32, 0.69	0.55	0.36, 0.84	0.003
Nondairy calcium (model 1)	1.50	1.02, 2.19	1.12	0.72, 1.73	1.25	0.72, 2.17	0.87
Calcium supplements (model 1)	1.02	0.72, 1.43	0.73	0.52, 1.03	0.81	0.56, 1.17	0.14
Lactose (model 1)	0.77	0.55, 1.09	0.67	0.47, 0.95	0.61	0.42, 0.89	0.007
Vitamin D							
Model 1	0.98	0.70, 1.38	0.80	0.56, 1.14	0.84	0.57, 1.23	0.25
Model 2	1.20	0.82, 1.75	1.16	0.73, 1.83	1.49	0.83, 2.64	0.22
Model 3	1.19	0.83, 1.71	1.14	0.75, 1.71	1.49	0.90, 2.47	0.16

* The quartile cutpoints for daily lactose, calcium, and vitamin D intake were as follows: dietary calcium, 528.1, 779.1, and 1,107.9 mg; dairy calcium, 182.9, 368.5, and 631.4 mg; nondairy calcium, 274.8, 376.4, and 517.1 mg; calcium supplements, 0, 181, and 600 g; lactose, 3.77, 8.46, and 15.87 g; vitamin D, 1.50, 2.82, and 4.67 IU.

† Model 1: Data were adjusted by unconditional logistic regression for age, ethnicity, study center, education, use of oral contraceptives, parity, tubal ligation, and energy intake. Model 2: Data were adjusted for all of the factors in model 1 plus lactose intake. Model 3: Data were adjusted for all of the factors in model 1 plus dietary calcium intake.

‡ Q, quartile; OR, odds ratio; CI, confidence interval.

§ Reference category.

¶ Based on a likelihood ratio test comparing models with and without a trend variable that was assigned median values for the categories.

TABLE 5. Odds ratios* for the joint association of dietary calcium and lactose intakes with ovarian cancer risk, Hawaii and Los Angeles, California, 1993–1999

Lactose intake (g/day)	Dietary calcium intake (excluding supplements)								*p* for interaction†
	≤779 mg/day				>779 mg/day				
	No. of cases	No. of controls	OR‡	95% CI‡	No. of cases	No. of controls	OR	95% CI	
≤8.5	248	220	1§		43	74	0.35	0.21, 0.56	
>8.5	47	68	0.51	0.33, 0.79	220	245	0.57	0.41, 0.79	0.0001

* Data were adjusted by unconditional multiple logistic regression for age, ethnicity, study center, education, use of oral contraceptives, parity, tubal ligation, and energy intake.

† Based on a likelihood ratio test comparing models with and without a trend variable that was assigned median values for the categories.

‡ OR, odds ratio; CI, confidence interval.

§ Reference category.

a subsequent study of 563 ovarian cancer cases and 523 community controls conducted in New Hampshire and Massachusetts between 1992 and 1997, Cramer et al. found no relation between ovarian cancer risk and lactose or dairy product intake or GALT activity (10).

This investigation had several notable dietary findings, including an inverse association of lactose intake with risk of epithelial ovarian cancer. An inverse association with lactose was unexpected, since most studies have shown little or no relation of lactose to ovarian cancer risk (4–8, 10, 12, 15, 18) and we had hypothesized a positive association, if any. Lactose may increase calcium absorption (32) and promote the growth of lactic acid bacteria, which may play a role in the activation or detoxification of heterocyclic aromatic amines (33). A recent investigation found an inverse association between lactose and colon cancer (34). Only one other case-control study, a study of 108 ovarian cancer cases and 108 controls in Washington State, reported a significant inverse relation between dietary lactose intake and ovarian cancer risk (18). Herrinton et al. (18) found an odds ratio of 0.25 (95 percent CI: 0.07, 0.88) among 56 case–population-control pairs and an odds ratio of 0.96 (95 percent CI: 0.55, 1.7) among 52 case–friend-control pairs. Harlow et al. (35) proposed that the greatest benefit of oral contraceptive use should appear among women with the highest lactose intakes, because oral contraceptives lower gonadotropin levels. However, we found no effect of an interaction between lactose intake and oral contraceptive use on the odds ratios.

To our knowledge, this is the first study to suggest an inverse relation between dietary calcium intake and ovarian cancer risk, although intakes of calcium and lactose in our population were highly correlated and difficult to distinguish. An interaction model suggested that the inverse asso-

TABLE 6. Odds ratios* for the joint association of calcium or lactose intake and oral contraceptive use, parity, and menopausal status with ovarian cancer risk, Hawaii and Los Angeles, California, 1993–1999

	Odds of ovarian cancer by dietary calcium or lactose intake								*p* for interaction†
	No. of cases	No. of controls	OR‡	95% CI‡	No. of cases	No. of controls	OR	95% CI	
	Dietary calcium intake ≤779 mg/day				*Dietary calcium intake >779 mg/day*				
Oral contraceptive use									
Never	188	149	1§		132	120	0.60	0.41, 0.88	
Ever	107	139	0.58	0.40, 0.86	131	199	0.34	0.23, 0.52	0.92
Parity									
Never	64	42	1§		54	35	0.68	0.36, 1.27	
Ever	231	246	0.64	0.41, 1.01	209	284	0.37	0.23, 0.61	0.64
Menopausal status¶									
Premenopausal	87	97	1§		85	134	0.54	0.35, 0.83	
Postmenopausal	204	184	2.09	1.34, 3.26	170	171	1.35	0.85, 2.15	0.49
	Lactose intake ≤8.5 mg/day				*Lactose intake >8.5 mg/day*				
Oral contraceptive use									
Never	186	137	1§		134	132	0.62	0.44, 0.88	
Ever	105	157	0.47	0.32, 0.68	133	181	0.43	0.29, 0.63	0.10
Parity									
Never	59	30	1§		59	47	0.52	0.29, 0.96	
Ever	232	264	0.45	0.28, 0.75	208	266	0.36	0.22, 0.61	0.17
Menopausal status¶									
Premenopausal	80	112	1§		92	119	0.93	0.62, 1.40	
Postmenopausal	205	174	2.56	1.66, 3.93	169	181	1.74	1.12, 2.72	0.22

* Data were adjusted by unconditional multiple logistic regression for age, ethnicity, study center, education, use of oral contraceptives, parity, tubal ligation, and energy intake (where appropriate).

† Based on a likelihood ratio test comparing models with and without a trend variable that was assigned median values for the categories.

‡ OR, odds ratio; CI, confidence interval.

§ Reference category.

¶ Menopausal status was unknown for 12 cases and 21 controls.

ciations of calcium and lactose with risk were strongest at low levels of the other dietary component. Indeed, no additional effect of calcium was observed among subjects with a high lactose intake. Dietary calcium has been reported to be inversely related to breast cancer (36) and colon cancer (37) and positively related to prostate cancer (38). Two previous epidemiologic studies examined the potential association of calcium with ovarian cancer (12, 39). In an investigation of 189 ovarian cancer cases and 200 hospital controls in Athens, Greece, Tzonou et al. (39) found no association between calcium intake and ovarian cancer. In the Iowa Women's Health Study, which contained 139 ovarian cancer cases, Kushi et al. (12) reported no association between calcium intake and ovarian cancer risk, although the rate ratios suggested a positive trend rather than an inverse trend.

Our finding of a significant inverse gradient in the odds ratios for low-fat milk but not for whole milk or other dairy products is consistent with the findings of several other studies (3, 5, 7, 16) but inconsistent with a hypothesized relation of calcium or lactose to ovarian cancer. Concentrations of these nutrients are relatively unaffected by reductions in the fat content of milk. The observation that only dairy sources of calcium were related to ovarian cancer might be explained by the lower bioavailability of this nutrient from plants, which contain phytates, oxalates, and other compounds that inhibit calcium absorption (32). We found a strong inverse dose-response gradient in the odds ratios associated with calcium intake among nonusers of supplements, precluding the possibility that the calcium association is a result of dietary supplementation among these women. Neither type of fat consumed, amount of dairy fat consumed, nor percentage of calories derived from fat was related to ovarian cancer in this study. Although some epidemiologic investigators have reported an increased risk of ovarian cancer associated with animal fat and meat intake (3, 4, 6, 7, 11, 14), others have found no association (9, 12, 18, 39). Another component of dairy foods, vitamin D, was unrelated to risk in our investigation and in the Iowa Women's Health Study (12), but dietary vitamin D is a poor measure of total vitamin D exposure.

An inverse association between dietary calcium and ovarian cancer risk is biologically plausible. Calcium down-

regulates the production of parathyroid hormone and parathyroid hormone-related protein, both of which reabsorb calcium from bone to regulate hypocalcemia (40, 41). Small-cell carcinoma of the ovary has been associated with hypercalcemia and expression of parathyroid hormone-related protein (42). McCarty (43) hypothesized that parathyroid hormone is a cancer-promoting agent, activating the protein kinase C and phospholipase C signaling pathways, triggering mitosis, and reducing apoptosis. Several laboratory studies have suggested that parathyroid hormone stimulates the production of local levels but not circulating levels of insulin-like growth factors 1 and 2 and transforming growth factor β1 (40, 41). Insulin-like growth factor and its binding protein may alter susceptibility to cancer through complex interactions with hormones and other growth factors (44). However, results from a random population sample showed an association of insulin-like growth factor 1 with parathyroid hormone among men but not among women (45). Furthermore, we found no association in our study between risk and vitamin D intake, which also down-regulates parathyroid hormone and is inversely related to colon and breast cancer (36, 37).

Use of identical methods and standardization of procedures for subject ascertainment, interviewer training, and data collection in Hawaii and Los Angeles were important components of this investigation. We have focused considerable attention on validating our dietary assessment method against food records (46), and we have demonstrated that our dietary data are reproducible (47). Our dietary assessment method has also been tested in a calibration substudy of the multiethnic cohort that compared diet as reported on the questionnaire with three 24-hour dietary recalls (48). It is unlikely that cases would systematically over- or underestimate their consumption of the many foods included in our questionnaire, although we have no means of examining this possibility. Our interviewers were trained in standardized probing methods that minimized between-interviewer variation. We constructed models that examined location-specific effects of the major dietary exposure variables (e.g., dairy foods, fat) on ovarian cancer risk within ethnic groups. These models were compared by the likelihood ratio test against models with ethnicity-specific effects only and were found to be similar, which suggested that the data could be pooled for statistical analysis. Although the validity of our findings may be somewhat limited by the less-than-optimal response rates in this study (62 percent for cases and 67 percent for controls), these response rates compare favorably with those of other studies of diet and ovarian cancer (5–11, 18).

In summary, we found that women who consume higher quantities of calcium and lactose were at significantly decreased risk of epithelial ovarian cancer. This result is unique among dietary studies but is not without plausibility. The findings were tempered by a lack of consistency for nondairy sources of calcium, but the results were homogeneous across ethnic groups and study locations. Although these results are intriguing, we cannot rule out the possibility that both calcium and lactose are surrogates for another, unidentified component of dairy foods.

ACKNOWLEDGMENTS

This investigation was supported in part by US Public Health Service grant RO1-CA-58598. Incident cancer cases in Hawaii were collected by the Hawaii Tumor Registry, which is supported under contract by the Hawaii Department of Health. Incident cancer cases in Los Angeles County were collected by the University of Southern California Cancer Surveillance Program, which is supported under contract by the California Department of Health. Both registries are also part of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program, under contracts NO1-CN–67001 and NO1-CN–25403 from the National Institutes of Health.

The authors thank the physicians, administrators, and cancer registrars at the following institutions for their support of this study: Castle Memorial Hospital, Kaiser Foundation Hospital, Kapiolani Medical Center for Women and Children, Kuakini Medical Center, Queen's Medical Center, Straub Clinic and Hospital, St. Francis Hospital, Tripler Army Hospital, and Wahiawa General Hospital.

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