High-fat dairy food and conjugated linoleic acid intakes in relation to colorectal cancer incidence in the Swedish Mammography Cohort[1–3]

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ABSTRACT

Background: High-fat dairy foods contain many potentially anticarcinogenic factors, including conjugated linoleic acid (CLA). However, few epidemiologic studies have specifically evaluated high-fat dairy food consumption, and none have evaluated CLA intake, in relation to colorectal cancer risk.

Objective: The aim of this study was to prospectively examine the associations of long-term high-fat dairy food consumption and CLA intake and the incidence of colorectal cancer.

Design: Our study population consisted of 60 708 women aged 40–76 y who participated in the Swedish Mammography Cohort. The women's consumption of high-fat dairy foods was assessed at baseline, which was from 1987 to 1990, and again in 1997.

Results: We ascertained 798 incident cases of colorectal cancer during an average 14.8 y of follow-up. After adjustment for age and other potential confounders, the women who consumed ≥4 servings of high-fat dairy foods/d (including whole milk, full-fat cultured milk, cheese, cream, sour cream, and butter) had a multivariate rate ratio of colorectal cancer of 0.59 (95% CI: 0.44, 0.79; *P* for trend = 0.002) when compared with the women who consumed <1 serving/d. Each increment of 2 servings of high-fat dairy foods/d corresponded to a 13% reduction in the risk of colorectal cancer (multivariate rate ratio: 0.87; 95% CI: 0.78, 0.96). For CLA, the multivariate rate ratio of colorectal cancer in a comparison of the 2 extreme quartiles of intake was 0.71 (95% CI: 0.55, 0.91; *P* for trend = 0.004).

Conclusion: These prospective data suggest that high intakes of high-fat dairy foods and CLA may reduce the risk of colorectal cancer. *Am J Clin Nutr* 2005;82:894–900.

KEY WORDS Colorectal cancer, cohort studies, conjugated linoleic acid, dairy foods, epidemiology

INTRODUCTION

Dairy foods are a rich source of many potentially anticarcinogenic factors that may play a role in the prevention of colorectal cancer. Indeed, a high consumption of milk and total dairy foods has been associated with a lowered risk of colorectal cancer in several prospective cohort studies (1, 2). Of all the components of dairy foods, calcium has attracted the most attention. Findings from the Pooling Project of Prospective Studies of Diet and Cancer (1), which was based on 10 cohort studies, showed that an inverse association between total milk consumption and the risk of colorectal cancer was attenuated but remained significant after controls for calcium, which suggests that other milk components may confer additional protection. Dairy foods, particularly high-fat dairy foods, are the principal source of not only calcium but also conjugated linoleic acid (CLA) (3), which is a potent anticarcinogen in animal models (4–7). However, to our knowledge, no study has examined the role of CLA in the development of colorectal cancer in humans. Furthermore, epidemiologic studies that specifically investigated the association between high-fat dairy food consumption and the risk of colorectal cancer are sparse and the results are inconsistent (8–11). Although one case-control study (10) observed a nonsignificant inverse association between the consumption of high-fat dairy foods and the risk of colon cancer, the results of 2 other case-control studies (9, 11) and one cohort study of mortality from colon cancer (8) were largely null. In those study populations, however, the consumption of high-fat dairy foods may have been too low to provide a protective effect against colorectal cancer.

The consumption of high-fat dairy foods is relatively high in the Swedish population. We decided, therefore, to prospectively examine the association between long-term consumption of high-fat dairy foods (measured at 2 time points) and the incidence of colorectal cancer, overall and by subsite, in a population-based cohort of Swedish women. We also evaluated whether CLA intake is associated with colorectal cancer risk.

SUBJECTS AND METHODS

The Swedish Mammography Cohort

The Swedish Mammography Cohort was established between 1987 and 1990, when all women who were aged 40–76 y and who resided in the Uppsala and Västmanland counties of central Sweden received a mailed questionnaire, which contained questions on diet, weight, height, and educational level (12). Of the 90 303 eligible women, 66 651 (74%) completed the questionnaire. Exposure data were updated in 1997. The Ethics Committees of the

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Uppsala University Hospital and the Karolinska Institutet (Stockholm, Sweden) approved the study.

Dietary assessment

At baseline (1987–1990), diet was assessed with the use of a 67-item food-frequency questionnaire (FFQ). An expanded FFQ that included 96 items was used to update the information about diet in 1997. In these questionnaires, the participants were asked how often, on average, they had consumed each food or beverage over the past year; 8 predefined frequency categories were available. We also inquired about the types of fat and oil used for food preparation and at meals, and we inquired about the number of sandwiches consumed daily that contained fat and the usual fat layer on these sandwiches (thick, thin, very thin, or no fat). The FFQs included open-ended questions for some commonly consumed foods, such as milk, yogurt, and cheese. Nutrient intakes were calculated as the frequency of consumption multiplied by the nutrient content of age-specific (<53, 53–65, ≥66 y) portion sizes, with the use of composition values from the Swedish Food Administration Database (13). CLA intake was estimated according to published data on the concentrations of CLA found in the total fat of various foods (14, 15). We adjusted all nutrient values for total energy intake using the residual method (16). Total high-fat dairy food consumption was computed by adding the daily servings of whole milk (3% fat), full-fat (3% fat) cultured milk (mainly sour milk), cheese (mainly hard cheese, 28% fat), cream (40% fat), full-fat sour cream (34% fat), reduced-fat sour cream (17% fat), and butter (80% fat). Information on cream and sour cream consumption was first obtained in the 1997 FFQ. Total low-fat dairy food consumption was computed by adding the daily servings of low-fat milk (0.5% fat), medium-fat milk (1.5% fat), and low-fat cultured milk (0.5% fat).

In a study of the validity of the FFQ that was conducted in 129 women who were randomly chosen from the cohort, Spearman correlation coefficients (r) between the mean intake, which was assessed from four 1-wk diet records, and the FFQ ranged from 0.33 (for whole milk) to 0.64 (for low-fat milk) for dairy foods ($\bar{x} = 0.50$). As estimated from the FFQ, the intake of pentadecanoic acid (15:0), which is a marker for dairy fat intake, also correlated with both the pentadecanoic acid intake that was estimated from diet records ($r = 0.63$) and the percentage of this fatty acid in adipose tissue ($r = 0.40$) (17).

Population for the analysis

Of the 66 651 women enrolled in the cohort, we excluded those with an erroneous national registration number, those with missing dates on the questionnaire, those with a cancer diagnosis (except nonmelanoma skin cancer), those who reported implausible intakes for total energy (ie, 3 SDs from the $\log_e$-transformed mean energy intake in the study population), and those with missing responses to all high-fat dairy foods. This left 60 708 women for the analysis.

Ascertainment of cases and follow-up

Passive follow-up of the participants was conducted by linkages to the Swedish Cancer, Total Population, and Death Registers through 30 June 2004. The Swedish Cancer Registry has been documented to be close to 100% complete (18). Tumors located from the cecum through the splenic flexure were considered to be proximal colon cancers, and tumors in the descending and sigmoid colon were defined as distal colon cancers. Rectal cancers included tumors in the rectosigmoid junction and the rectum.

Statistical analysis

Person-time of follow-up for each woman was accumulated from the date of entry into the cohort until the date of a colorectal cancer diagnosis, death from any cause, date of moving away from the study area, or 30 June 2004, whichever came first. We grouped women into categories according to their dairy food consumption. For each category, we calculated the incidence rate of colorectal cancer by dividing the number of cases by the number of person-years of follow-up and computed the rate ratios for each of the upper categories by dividing the rates in these categories by the rate in the lowest category.

To represent long-term diet, we applied a cumulative average method (19) using dietary data from the baseline and 1997 questionnaires. In this analysis, colorectal cancer incidence from 1987 through 1997 was related to the dietary intake that was assessed by the baseline questionnaire, and incidence from 1998 through June 2004 was related to the average intake that was reported at baseline and in 1997.

We estimated rate ratios (RRs) with 95% CIs using Cox proportional hazards modeling (20) stratified by age (in mo) at recruitment and the year of entry into the cohort. All multivariate models had controls for age, body mass index, education, and intakes of total energy, folate, vitamin B-6, cereal fiber, and red meat. Using data from the 1997 questionnaire, we conducted additional analyses that were adjusted for smoking, physical activity, family history of colorectal cancer, and use of multivitamins, aspirin, oral contraceptives, and postmenopausal hormones. We also examined whether associations with high-fat dairy foods could be attributed to calcium and vitamin D by adding these nutrients to the multivariate model. Tests for trend were performed by assigning the median consumption of high-fat dairy foods for categories treated as a continuous variable. We also used restricted cubic spline Cox proportional hazards regression models with 4 knots (21) to flexibly model the association between high-fat dairy food consumption and the risk of colorectal cancer. Differences in the results in colorectal cancer subsites (proximal colon, distal colon, and rectum) were tested with the Wald test (22). All analyses were conducted with SAS version 9.1 (SAS Institute Inc, Cary, NC). All P values are 2-sided.

We performed secondary analyses to examine the association of CLA intake with colorectal cancer risk using baseline diet data (values for CLA were not available for the 1997 questionnaire). In addition to the variables that were included in the multivariate analyses of high-fat dairy food consumption, all multivariate analyses of CLA intake were also adjusted for calcium and vitamin D intakes.

RESULTS

During a mean 14.8 y of follow-up, 798 incident cases of colorectal cancer were diagnosed in the 60 708 eligible women. Of these cancers, 543 were located in the colon (246 proximal, 170 distal, and 127 unknown subsite) and 249 in the rectum; 6 cases of both colon and rectal cancer were diagnosed. The baseline characteristics of the study population according to their consumption of high-fat dairy foods are shown in **Table 1**. At baseline, cheese was the largest source of high-fat dairy foods

TABLE 1
Baseline characteristics of the study population according to frequency of total high-fat dairy food consumption[1]

Characteristic	High-fat dairy food consumption (servings/d)[2]					*P* for trend
	<1.0 (n = 8103)	1.0 to <2.0 (n = 17 538)	2.0 to <3.0 (n = 15 304)	3.0 to <4.0 (n = 9078)	≥4.0 (n = 10 685)	
Age at baseline (y)	53.8 ± 9.6[3]	53.9 ± 9.7	53.8 ± 9.7	53.4 ± 9.8	53.1 ± 9.7	< 0.001
BMI (kg/m^2)	25.4 ± 4.1	25.0 ± 3.9	24.6 ± 3.8	24.4 ± 3.7	24.1 ± 3.8	< 0.001
Postsecondary education (%)	11.4	12.1	13.4	13.4	13.3	< 0.001
Dietary intake[4]						
Conjugated linoleic acid (mg/d)	50.9 ± 28.1	89.5 ± 33.2	127.8 ± 48.0	141.6 ± 52.6	177.1 ± 66.5	< 0.001
Folate (μg/d)	253 ± 70	246 ± 56	236 ± 53	230 ± 48	220 ± 47	< 0.001
Vitamin B-6 (mg/d)	1.9 ± 0.4	1.9 ± 0.3	1.8 ± 0.3	1.8 ± 0.3	1.7 ± 0.3	< 0.001
Vitamin D (μg/d)	4.7 ± 1.6	4.5 ± 1.3	4.2 ± 1.2	4.1 ± 1.3	4.0 ± 1.3	< 0.001
Calcium (mg/d)	865 ± 307	952 ± 260	1021 ± 265	991 ± 253	1021 ± 248	< 0.001
Cereal fiber (g/d)	15.4 ± 6.5	14.9 ± 5.3	14.1 ± 5.0	13.8 ± 4.7	13.1 ± 4.6	< 0.001
Red meat consumption (g/d)	71.2 ± 42.3	73.4 ± 37.5	74.8 ± 39.8	77.1 ± 39.8	79.1 ± 45.2	< 0.001

[1] All values (except age) were standardized to the age distribution of the study population.
[2] High-fat dairy foods include whole milk, full-fat cultured milk, cheese, cream, full-fat sour cream, reduced-fat sour cream, and butter.
[3] $\bar{x}$ ± SD (all such values).
[4] All nutrients and dietary fiber were energy-adjusted (to 1700 kcal/d) with the residual method (16).

consumed and constituted 49% of the total servings; butter, whole milk, and full-fat cultured yogurt constituted 26%, 13%, and 12%, respectively. Compared with women who consumed low amounts of high-fat dairy food, the women who had higher consumption were younger, leaner, and more likely to have a postsecondary education; they also had higher intakes of red meat and calcium but lower intakes of folate, vitamin B-6, vitamin D, and cereal fiber.

Total high-fat dairy food consumption was significantly and inversely associated with the risk of colorectal cancer (**Table 2**). Compared with the women who consumed <1 serving of high-fat dairy foods/d, the women who consumed ≥4 servings/d had a multivariate RR of 0.59 (95% CI: 0.44, 0.79). Additional adjustments for alcohol consumption, family history of colorectal cancer, smoking, physical activity, and the use of multivitamin supplements, aspirin, oral contraceptives, and postmenopausal hormones did not signficantly change the results. Also, these findings remained after addition of calcium and vitamin D intakes to the multivariate model (RR: 0.58; 95% CI: 0.42, 0.79). After exclusion of cancer cases that occurred during the first 3 y of follow-up, the multivariate RR of colorectal cancer was 0.57 (95% CI: 0.40, 0.81). Results of analyses that used only the baseline diet were similar to those obtained with the use of the average cumulative diet (multivariate RR: 0.64; 95% CI: 0.48, 0.85). The reduction in the risk of cancer that was associated with high consumption of high-fat dairy foods was most pronounced for the incidence of cancer of the distal colon (Table 2). A test for the difference in associations by cancer site was statistically significant (P for heterogeneity = 0.04 in a comparison of the highest categories).

TABLE 2
Rate ratios (RRs) of colorectal cancer by long-term high-fat dairy food consumption

	High-fat dairy food consumption (servings/d)					*P* for trend
	<1.0	1.0 to <2.0	2.0 to <3.0	3.0 to <4.0	≥4.0	
Colorectal cancer						
No. of cases	110	212	211	132	133	
Age-adjusted RR (95% CI)	1.0	0.79 (0.62, 0.99)	0.80 (0.63, 1.01)	0.78 (0.60, 1.01)	0.67 (0.52, 0.86)	0.02
Multivariate RR (95% CI)[1]	1.0	0.75 (0.60, 0.96)	0.74 (0.58, 0.95)	0.68 (0.52, 0.90)	0.59 (0.44, 0.79)	0.002
Proximal colon cancer						
No. of cases	33	70	62	33	48	
Age-adjusted RR (95% CI)	1.0	0.85 (0.56, 1.30)	0.77 (0.50, 1.18)	0.60 (0.37, 0.99)	0.80 (0.51, 1.26)	0.23
Multivariate RR (95% CI)[1]	1.0	0.87 (0.57, 1.33)	0.78 (0.50, 1.22)	0.62 (0.37, 1.05)	0.84 (0.50, 1.42)	0.40
Distal colon cancer						
No. of cases	26	49	50	29	16	
Age-adjusted RR (95% CI)	1.0	0.75 (0.46, 1.22)	0.77 (0.47, 1.25)	0.68 (0.40, 1.18)	0.32 (0.17, 0.61)	0.001
Multivariate RR (95% CI)[1]	1.0	0.71 (0.43, 1.16)	0.70 (0.42, 1.16)	0.60 (0.33, 1.07)	0.28 (0.14, 0.56)	0.0008
Rectal cancer						
No. of cases	37	54	63	49	46	
Age-adjusted RR (95% CI)	1.0	0.60 (0.39, 0.92)	0.74 (0.49, 1.12)	0.89 (0.57, 1.37)	0.72 (0.47, 1.13)	0.91
Multivariate RR (95% CI)[1]	1.0	0.57 (0.37, 0.88)	0.68 (0.44, 1.04)	0.79 (0.50, 1.26)	0.62 (0.37, 1.02)	0.64

[1] Adjusted for age (in mo), body mass index (in kg/m^2; <23, 23–24.9, 25– 29.9, and ≥30), education (less than high school, high school graduate, or more than high school), total energy intake (continuous), and quintiles of intakes of folate, vitamin B-6, cereal fiber, and red meat.

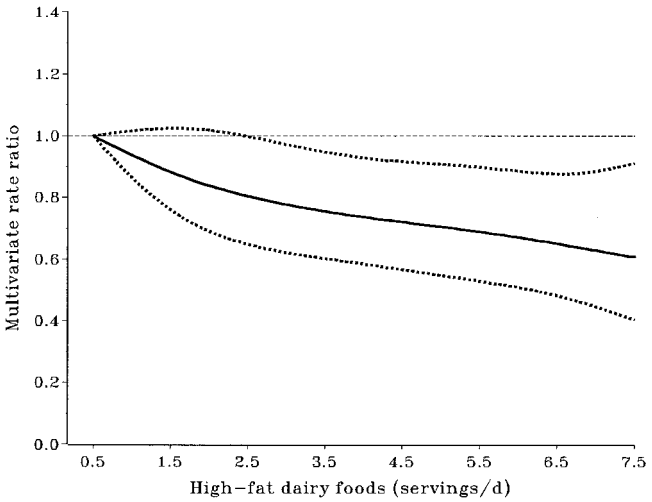

FIGURE 1. Multivariate rate ratios of colorectal cancer by long-term high-fat dairy food consumption. Data were fitted with the use of a restricted cubic spline Cox proportional hazards model. Multivariate rate ratios were adjusted for age (in mo), body mass index (in kg/m^2; <23, 23–24.9, 25–29.9, and ≥ 30), education (less than high school, high school graduate, or more than high school), total energy intake (continuous), and quintiles of intakes of folate, vitamin B-6, cereal fiber, and red meat. The dotted lines represent 95% CIs.

A spline regression analysis showed a dose-response relation between high-fat dairy food consumption and the risk of colorectal cancer (**Figure 1**). The multivariate RR for a daily increase in consumption of 2 servings of high-fat dairy foods was 0.87 (95% CI: 0.78, 0.96) for colorectal cancer and 0.66 (95% CI: 0.52, 0.84) for distal colon cancer.

We next examined the association between the individual high-fat dairy food items and the risk of colorectal cancer (**Table 3**). The lowest risk of colorectal cancer was observed for high consumption of cheese. In a multivariate model, we observed a 35% (95% CI: 4%, 56%) reduction in the risk of colorectal cancer in the women who consumed ≥3 servings of cheese/d compared with the women who consumed <1 serving/d. High consumption of butter and full-fat cultured milk also showed significant inverse associations with the risk of colorectal cancer. We observed no association between low-fat dairy food consumption and the risk of colorectal cancer. Compared with the lowest category of consumption (never or seldom), the multivariate RRs for increasing categories of total low-fat dairy food consumption (<1.0, 1.0 to <2.0, 2.0 to <3.0, and ≥3.0 servings/d) were 1.09, 1.09, 1.03, and 1.06, respectively (95% CI: 0.72, 1.54).

CLA intake was significantly and inversely related to colorectal cancer risk (**Table 4**). The multivariate RR for women in the highest quartile of CLA intake compared with those in the lowest quartile was 0.71 (95% CI: 0.56, 0.91). Similar to the observation for high-fat dairy foods, this reduction in risk was largely due to a strong association with cancer of the distal colon.

To assess whether the observed inverse relation between high-fat dairy food consumption and colorectal cancer could be attributed to CLA, we simultaneously entered baseline intakes of high-fat dairy foods and CLA ($r = 0.70$) in a multivariate model. The inverse association between high-fat dairy food consumption and the risk of colorectal cancer was somewhat attenuated (RR for the highest compared with the lowest category: 0.75; 95% CI: 0.49, 1.14). In this model, the multivariate RR in a comparison of the 2 extreme quartiles of CLA intake was 0.81 (95% CI: 0.57, 1.15).

DISCUSSION

We observed a significant inverse association between long-term consumption of high-fat dairy foods and the risk of colorectal cancer, particularly of cancer of the distal colon, in this large population-based cohort of women who had repeated diet assessments. For each daily increment of 2 servings of high-fat dairy foods, the risk of colorectal cancer decreased by 13% and the risk of distal colon cancer decreased by 34%. The reduction

TABLE 3
Multivariate rate ratios (RRs) of colorectal cancer by long-term high-fat dairy food consumption[1]

	Colorectal cancer			Proximal colon cancer			Distal colon cancer			Rectal cancer		
	Cases (no.)	RR (95% CI)	*P* for trend	Cases (no.)	RR (95% CI)	*P* for trend	Cases (no.)	RR (95% CI)	*P* for trend	Cases (no.)	RR (95% CI)	*P* for trend
Whole milk			0.49			0.10			0.15			0.99
Never or seldom	528	1.0		140	1.0		129	1.0		171	1.0	
<1 serving/d	90	1.03 (0.82, 1.30)		39	1.65 (1.14, 2.39)		11	0.49 (0.26, 0.93)		22	0.81 (0.52, 1.29)	
≥1 serving/d	180	1.08 (0.90, 1.29)		67	1.58 (1.15, 2.16)		30	0.72 (0.47, 1.10)		56	0.99 (0.72, 1.37)	
Full-fat cultured milk			0.05			0.27			0.13			0.57
Never or seldom	335	1.0		109	1.0		72	1.0		99	1.0	
<1 serving/d	314	0.87 (0.74, 1.03)		90	0.77 (0.57, 1.03)		72	0.96 (0.68, 1.35)		103	0.98 (0.74, 1.32)	
≥1 serving/d	149	0.81 (0.66, 1.00)		48	0.80 (0.56, 1.15)		26	0.71 (0.44, 1.13)		47	0.91 (0.62, 1.31)	
Cheese			0.04			0.44			0.03			0.74
<1 serving/d	205	1.0		67	1.0		46	1.0		63	1.0	
1 to <3 servings/d	558	0.98 (0.82, 1.16)		167	0.97 (0.72, 1.31)		121	0.93 (0.65, 1.33)		172	0.95 (0.70, 1.29)	
≥3 servings/d	35	0.65 (0.44, 0.96)		12	0.76 (0.39, 1.50)		3	0.24 (0.07, 0.82)		14	0.89 (0.46, 1.71)	
Butter			0.03			0.76			0.06			0.14
Never or seldom	537	1.0		157	1.0		119	1.0		169	1.0	
<15 g/d	158	0.88 (0.73, 1.04)		52	0.91 (0.65, 1.26)		33	0.85 (0.57, 1.28)		48	0.91 (0.65, 1.28)	
≥15 g/d	103	0.80 (0.64, 1.00)		37	1.10 (0.75, 1.61)		18	0.63 (0.37, 1.08)		32	0.75 (0.50, 1.11)	

[1] Multivariate RRs were adjusted for age (in mo), body mass index (in kg/m^2; <23, 23–24.9, 25–29.9, and ≥30), education (less than high school, high school graduate, or more than high school), total energy intake (continuous), and quintiles of intakes of folate, vitamin B-6, cereal fiber, and red meat.

TABLE 4
Rate ratios (RRs) of colorectal cancer by quartiles of conjugated linoleic acid intake

	Conjugated linoleic acid intake (mg/d)				
	<73.4	73.4–106.8	106.9–149.2	≥149.3	*P* for trend
Colorectal cancer					
No. of cases	224	219	184	171	
Age-adjusted RR (95% CI)	1.0	0.97 (0.80, 1.17)	0.86 (0.70, 1.05)	0.82 (0.66, 1.00)	0.03
Multivariate RR (95% CI)[1]	1.0	0.95 (0.78, 1.16)	0.80 (0.64, 1.00)	0.71 (0.55, 0.91)	0.004
Proximal colon cancer					
No. of cases	64	68	51	63	
Age-adjusted RR (95% CI)	1.0	1.05 (0.74, 1.48)	0.83 (0.57, 1.21)	1.03 (0.72, 1.48)	0.97
Multivariate RR (95% CI)[1]	1.0	1.01 (0.70, 1.47)	0.75 (0.50, 1.14)	0.82 (0.53, 1.28)	0.29
Distal colon cancer					
No. of cases	52	54	34	30	
Age-adjusted RR (95% CI)	1.0	1.08 (0.73, 1.59)	0.70 (0.45, 1.08)	0.61 (0.38, 0.96)	0.01
Multivariate RR (95% CI)[1]	1.0	1.03 (0.68, 1.56)	0.66 (0.41, 1.08)	0.53 (0.31, 0.92)	0.01
Rectal cancer					
No. of cases	64	68	72	45	
Age-adjusted RR (95% CI)	1.0	1.07 (0.75, 1.51)	1.19 (0.84, 1.68)	0.75 (0.51, 1.11)	0.20
Multivariate RR (95% CI)[1]	1.0	1.08 (0.76, 1.53)	1.20 (0.84, 1.72)	0.75 (0.49, 1.13)	0.22

[1] Adjusted for age (in mo), body mass index (in kg/m^2; <23, 23–24.9, 25–29.9, and ≥30), education (less than high school, high school graduate, or more than high school), total energy intake (continuous), and quintiles of intakes of folate, vitamin B-6, vitamin D, calcium, cereal fiber, and red meat.

in colorectal cancer risk associated with high consumption of high-fat dairy foods was not explained by other potential risk factors for colorectal cancer and persisted after control for calcium and vitamin D intakes.

Components in high-fat dairy foods that might reduce the risk of colorectal cancer include CLA, sphingomyelin, and ether lipids (23). Although these components have been shown to inhibit colorectal carcinogenesis in animal models (4–7, 23–26), to our knowledge no published epidemiologic data exist on the relation between these compounds and the risk of colorectal cancer in humans. CLA is a collective term for a group of positional and geometric isomers of linoleic acid that have various biological effects. Although *cis*-9, *trans*-11-CLA is the predominant isomer (80–90%) in dairy foods, it is found in equal proportions with the *trans*-10, *cis*-12-CLA isomer in commercial preparations of CLA (27). Recent studies that used specific CLA forms indicate that the 2 isomers can have different effects on metabolism and cell functions and can act through different cell signaling pathways (27). A small number of studies have also raised the concern that supplementation with the *trans*-10, *cis*-12-CLA isomer might have adverse effects on insulin sensitivity, on biomarkers of oxidative stress and inflammation, and on the blood lipid profile in humans (28–30).

In the present study, we examined whether the observed inverse association between high-fat dairy food consumption and the risk of colorectal cancer could be explained by CLA. The inverse relation remained but was no longer significant after control for CLA intake, which indicated that the observed protective effect of high-fat dairy foods may only be partly attributable to CLA intake. Hence, other components in high-fat dairy foods, possibly sphingomyelin and ether lipids, may contribute to additional protection from colorectal cancer.

Studies in animals have shown that dietary CLA significantly reduces carcinogen-induced mutagenesis in the distal colon but not in the proximal colon (31, 32). In agreement with these experimental findings, we observed that the reduction in cancer risk with high intakes of high-fat dairy foods and CLA was most pronounced for the incidence of distal colon cancer. Multiple lines of evidence indicate that proximal and distal colon cancers may have different causes (33, 34), and it has been postulated that exogenous factors, such as diet, are more related to tumors in the distal colon (33).

Of the high-fat dairy foods that were assessed in this analysis, the strongest inverse association was observed for cheese, which is the single largest contributor of dairy fat in the cohort. Findings of previous studies on the relation between cheese consumption and colorectal cancer risk have mostly been null. In a meta-analysis of 10 case-control and 4 cohort studies, the overall RR of colorectal cancer was 1.07 (95% CI: 0.92, 1.25) when the top and bottom categories of cheese consumption were compared (2). The Pooling Project of Prospective Studies of Diet and Cancer (1) also observed no association between cheese consumption and colorectal cancer risk. A possible explanation for the null results in previous studies might be that the consumption of cheese in the populations studied was too low for a protective effect. The findings of the present study suggest that ≥3 servings of cheese/d (≈60 g/d or more) are needed for a reduction in the risk of colorectal cancer. The mean cheese consumption in the Swedish Mammography Cohort is about twice that of most of the other cohort studies in the Pooling Project (1); the cutoff value for the highest category of cheese consumption in the Pooling Project was 25 g/d (1).

Our study has several important strengths, which include its large size, the large number of colorectal cancer cases, and its population-based and prospective design. The completeness of follow-up of the study population minimized the likelihood that our findings were affected by bias because of differential follow-up of exposed compared with unexposed women. Because information about dietary intake was collected before the colorectal cancer diagnosis, any error in the measurement of high-fat dairy food consumption would have attenuated rather than exaggerated a true association. We had repeated measures of dietary intake and were able to examine both baseline and cumulative updated diet values. Cumulative updating of diet

intakes can reduce random within-person measurement error and can better reflect long-term dietary intake.

As in any observational study, we cannot rule out the possibility that some unmeasured factor or residual confounding factor accounted for the observed associations. In the present study, higher consumption of high-fat dairy foods was associated with lower intakes of folate, vitamin B-6, and cereal fiber and with higher red meat consumption. The confounding effects of these variables would tend to bias the results toward a positive, not an inverse, association. Indeed, findings from multivariate analyses that were adjusted for these dietary factors showed associations that were somewhat stronger than those in the age-adjusted analyses.

Besides CLA, high-fat dairy foods are a source of saturated fat. Although ecologic studies have implicated high intake of saturated fat as a risk factor for coronary heart disease (35), most large prospective cohort studies have not found significant positive associations between intakes of saturated fat (36–38) or high-fat dairy foods (39) and the risk of coronary heart disease. However, more research on the relation between CLA and high-fat dairy foods and the risk of colorectal cancer and other health outcomes is needed to evaluate the potential risks and benefits of increasing intakes of high-fat dairy foods.

In conclusion, our findings from a large population-based cohort of women with repeated diet assessments suggest that high consumption of high-fat dairy foods may lower the risk of colorectal cancer, particularly of cancer of the distal colon. The observed inverse association might, in part, be related to CLA intake, but other potentially anticarcinogenic components in high-fat dairy foods cannot be excluded. Our observational study cannot prove a cause-effect relation, and it is premature to recommend increased consumption of high-fat dairy foods. Because of the potential public health implications of these findings, more studies of the relation between the risk of colorectal cancer and CLA and high-fat dairy food intakes are warranted. Additional work is also needed to elucidate the mechanisms underlying the ability of dietary fat to protect against colorectal cancer.

SCL and AW contributed to the study concept and design. LB and AW contributed to the data collection and interpretation of the results. SCL contributed to the data analyses, writing of the manuscript, and interpretation of the results. All authors reviewed the final manuscript. None of the authors had any financial or personal conflicts of interest.

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