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Research Article

Prediagnostic Intake of Dairy Products and Dietary Calcium and Colorectal Cancer Survival—Results from the EPIC Cohort Study

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Abstract

Background: We investigated whether prediagnostic reported intake of dairy products and dietary calcium is associated with colorectal cancer survival.

Methods: Data from 3,859 subjects with colorectal cancer (42.1% male; mean age at diagnosis, 64.2 ± 8.1 years) in the European Investigation into Cancer and Nutrition cohort were analyzed. Intake of dairy products and dietary calcium was assessed at baseline (1992–2000) using validated, country-specific dietary questionnaires. Multivariable Cox regression models were used to calculate HR and corresponding 95% confidence intervals (CI) for colorectal cancer–specific death (n = 1,028) and all-cause death (n = 1,525) for different quartiles of intake.

Results: The consumption of total dairy products was not statistically significantly associated with risk of colorectal cancer–specific death (adjusted HR Q4 vs. Q1, 1.17; 95% CI, 0.97–1.43) nor that of all-cause death (Q4 vs. Q1, 1.16; 95% CI, 0.98–1.36). Multivariable-adjusted HRs for colorectal cancer–specific death (Q4 vs. Q1) were 1.21 (95% CI, 0.99–1.48) for milk, 1.09 (95% CI, 0.88–1.34) for yoghurt, and 0.93 (95% CI, 0.76–1.14) for cheese. The intake of dietary calcium was not associated with the risk of colorectal cancer–specific death (adjusted HR Q4 vs. Q1, 1.01; 95% CI, 0.81–1.26) nor that of all-cause death (Q4 vs. Q1, 1.01; 95% CI, 0.84–1.21).

Conclusions: The prediagnostic reported intake of dairy products and dietary calcium is not associated with disease-specific or all-cause risk of death in patients diagnosed with colorectal cancer.

Impact: The impact of diet on cancer survival is largely unknown. This study shows that despite its inverse association with colorectal cancer risk, the prediagnostic intake of dairy and dietary calcium does not affect colorectal cancer survival. *Cancer Epidemiol Biomarkers Prev; 23(9); 1813–23. ©2014 AACR.*

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Introduction

Worldwide, colorectal cancer is the third most commonly diagnosed cancer in men and second in women and accounts for an estimated total deaths of 608,000 per year (1). A great number of studies have shown that colorectal cancer development depends, to a large extent, on diet and lifestyle factors (2). However, the impact of diet on colorectal cancer survival is largely unknown. Studies are scarce, often small and retrospective, and have not resulted in definitive conclusions, as was also concluded in three recent systematic reviews including the second World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) expert report (2–4).

With respect to colorectal cancer survival, dairy products are of potential interest as the consumption of dairy products has been reported to be associated with a decreased risk for developing colorectal cancer and especially colon cancer (5, 6). The reported inverse associations between the consumption of dairy products and colorectal cancer have mainly been attributed to calcium (6–12). Studies have shown that calcium can induce apoptosis (9), prevent colonic K-*ras* mutations (13), inhibit heme-induced promotion of colon carcinogenesis (14), and has an antiproliferative effect on colonic epithelium cells directly (15) and indirectly by binding toxic bile and fatty acids, rendering them inert (16, 17). In addition, results from intervention trials suggest that calcium supplementation reduces colorectal adenoma recurrence risk (18), and may modulate potential biomarkers of risk for colorectal neoplasms such as oxidative DNA damage (19, 20). In contrast, however, milk consumption is also associated with increased levels of insulin-like growth factor-I (IGF-I; ref. 21), and a high ratio of IGF-I and IGF-binding protein-3 has been reported to be associated with an increased colon cancer risk (22, 23). In addition, IGF-I has been found to stimulate proliferation of colon cancer cell lines (24, 25) and to induce VEGF (26), an angiogenic factor that stimulates tumor growth.

Except for a small French study (27), no studies have reported on the prediagnostic intakes of dairy products and calcium and survival after colorectal cancer diagnosis. We therefore investigated whether prediagnostic intake of dairy products (total, milk, yoghurt, and cheese) and dietary calcium (total, dairy, and nondairy) is associated with colorectal cancer–specific and all-cause death in a large cohort of patients with colorectal cancer that were included in the European Investigation into Cancer and Nutrition (EPIC) cohort.

Materials and Methods

Study population

The EPIC study is a multicenter population-based cohort study to investigate the relation between diet, nutritional and metabolic characteristics, lifestyle factors, and subsequent cancer incidence and cause-specific mortality. Between 1992 and 2000, 521,448 participants (70% women and mostly ages between 25 and 70 years at inclusion) were included in 23 centers from 10 European countries, i.e., Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and United Kingdom. Detailed information about the rationale of the study, the selection of the study population, data collection, and follow-up procedures was reported previously (28, 29). The study was approved by the International Agency for Research on Cancer ethical review committee and by the local committees at the participating centers.

Data collection

Diet over the previous 12 months was assessed at inclusion by validated country-specific questionnaires (30). Consumption of dairy products and individual categories of dairy products, including milk, yoghurt, and cheese, was calculated in grams per day (g/day). Yoghurt included natural and flavored products, and fermented milk in Denmark, Norway, and Sweden. Cheese included fresh, fermented, and matured cheese products. Other categories of dairy products, such as ice cream, cream deserts, milk-based puddings, and milk beverages, were not analyzed individually due to incomplete measurements across centers and relatively low consumption. Dietary intake of calcium (total, dairy, and nondairy in milligrams per day) was calculated using the standardized EPIC Nutrient Data Base (31). There were no data available on the use of calcium supplements and thus were not included with calcium intake. Nondietary data on demographic characteristics, lifestyle habits, risk factors, and presence of chronic diseases were collected through questionnaires at study enrollment. Anthropometric measurements were taken at recruitment by trained health professionals in most centers, except for part of the Oxford cohort, the Norwegian cohort, and approximately two thirds of the French cohort, among whom weight and height were self-reported.

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Colorectal cancer ascertainment and selection

Identification of cancer cases was done through linkage with regional cancer registries (Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom; complete up to December 2006) or via a combination of methods, including linkage with health insurance and pathology registries and active follow-up (France, Germany, Greece, and Naples; complete up to June 2010). Tumors included those in the colon (C18.0–C18.7), rectum (C19 and C20), and overlapping/unspecified localization (C18.8 and C18.9) according to the second edition of the International Classification of Diseases for Oncology (ICD-O; ref. 32).

Information on tumor stage differed between centers. A harmonization procedure was performed to assign a broad category for tumor stage (I–IV and unknown) using available information on the tumor–node–metastasis (TNM) classification ($n = 1{,}787$), Dukes classification ($n = 442$), and/or classification provided by the centers (i.e., localized, metastatic regional, metastatic distant, metastatic; $n = 994$) as previously described (33). Differentiation grade of the tumor was categorized as well, moderately, poorly, or unknown differentiation. There was no information available on tumor stage for cases from Malmø and Oxford ($n = 636$) and on differentiation grade for cases from Aarhus, Cambridge, Copenhagen, Malmø, Oxford, and Umea ($n = 1{,}815$).

After excluding cases diagnosed with colorectal cancer after the dates of complete follow-up (see "Vital status follow-up"; $n = 426$), with *in situ* or a metastatic tumor ($n = 172$), nonadenocarcinoma or unknown morphology ($n = 144$), missing date of death or diagnosis ($n = 21$), unknown cause of death ($n = 8$) or cases in which cancer diagnosis was obtained from a death certificate or autopsy report ($n = 6$), cases who withdrew consent ($n = 3$) or emigrated to another region ($n = 3$) or country ($n = 6$), and cases with no information on intake of dairy products ($n = 65$), a total number of 3,859 cases who developed a first primary adenocarcinoma (2,423 colon and 1,436 rectum) remained for the analyses of this study.

Vital status follow-up

Information on vital status and movement of participants (98.5% complete) was obtained through record linkage with the municipal and national mortality registries in all countries except France, Germany, and Greece, where data were collected through a combination of methods, including health insurance records, cancer and pathology registries, and active follow-up of study subjects and their next-of-kin. The date of colorectal cancer diagnosis was used as the start of follow-up for this study. The date of censoring was defined as the last date at which follow-up data were judged to be complete, the last date of contact, or date of death. Censoring dates for complete follow-up were between June 2005 and June 2009 in Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom, and between December 2007 and December 2009 in France, Germany, and Greece.

Cause-specific mortality was coded according to the 10th revision of the International Classification of Diseases, Injuries and Causes of Death (ICD-10). Up to six qualifiers of the cause of death were reviewed, and colorectal cancer–specific death was assigned based on the underlying cause of death.

Statistical analyses

The primary endpoint of this study was colorectal cancer–specific death and the secondary endpoint was death from any cause. Quartiles for prediagnostic intake of dairy products (total, milk, yoghurt, and cheese) and dietary calcium (total, dairy, and nondairy) were computed. EPIC-wide cutoff points were as follows: total dairy, 150, 276, and 452 g/day; milk, 24, 148, and 293 g/day; yoghurt, 2, 25, and 89 g/day; cheese, 15, 26, and 49 g/day; total dietary calcium, 699, 921, and 1,201 mg/day; dairy calcium, 327, 525, and 775 mg/day; nondairy calcium 299, 372, and 471 mg/day. Age-adjusted and multivariable Cox regression models were used to calculate HR and corresponding 95% confidence intervals (CI) for colorectal cancer–specific and all-cause death for different levels of consumption and by using the first quartile as a reference. All models were stratified by center and adjusted for age at colorectal cancer diagnosis (continuous per one year increase). Age at colorectal cancer diagnosis and age at death or censoring were used as the underlying time variables. Two multivariable-adjusted models were tested: one adjusted for age at colorectal cancer diagnosis, sex, prediagnostic body mass index (BMI; continuous), smoking status (never, former, current, unknown), and energy intake (continuous), and one model additionally adjusted for tumor subsite (colon or rectum), disease stage (I, II, III, IV, unknown, unavailable for center), and differentiation grade (well, moderately, poorly, unknown, unavailable for center). Other potential confounding factors that were considered but not included in the models due to a less than 10% change of the risk estimates of outcomes of interest were year of diagnosis, physical activity, level of education, menopausal status, ever hormone replacement therapy, number of cigarettes per day, and intake of alcohol, fibers, and red- and processed meat. Country-specific quartiles for the consumption of dairy products (total, milk, yoghurt, and cheese) were used in sensitivity analyses.

Cox regression models were used to compute the risk estimates on a continuous scale for the intake of total dairy products (per 100 g/day), milk (per 100 g/day), yoghurt (per 50 g/day), cheese (per 25 g/day) and intake of dietary calcium (total, dairy, and nondairy per 200 mg/day).

Potential effect modification was tested by adding multiplicative interaction terms to the models and using likelihood ratio tests for interaction. For these analyses, we used the interaction terms of quartiles of consumption for total dairy and dietary calcium with categorical variables for tumor stage (I + II + III, IV), tumor subsite (colon and rectum), time between study inclusion and colorectal cancer diagnosis (<3, 3–6, 6–9, >9 years), sex, age at

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colorectal cancer diagnosis (<60, 60–69, ≥70), smoking status (never, former, current), and BMI (<25, 25–30, >30 kg/m^2). Stratified analyses were conducted to explore potential differences according to disease stage (I + II + III, IV) and tumor subsite (colon and rectum).

The effect of unavailable information on disease stage for Malmø and Oxford and unknown disease stage for other centers was investigated using multiple approaches: (i) using a separate "missing" category for unavailable disease stage for Malmø and Oxford and one for unknown disease stage for other centers (primary analysis), (ii) combining unavailable disease stage for Malmø and Oxford and unknown disease stage for other centers in one "missing" category, (iii) analysis excluding colorectal cancer cases from Malmø and Oxford, and (iv) imputation of missing values for disease stage in Malmø and Oxford with SAS PROC MI procedure, under the missing at random assumption, based on sex, age at colorectal cancer diagnosis, year of diagnosis, vital status, tumor subsite, and period between colorectal cancer diagnosis and death or censoring.

All statistical analyses were conducted with SAS 9.2 (SAS Institute Inc.). Two-sided *P* values of <0.05 were considered statistically significant.

Results

Patient characteristics

Of the 3,859 colorectal cancer cases that were included in this study, a total of 1,525 subjects died (1,028 colorectal cancer–specific deaths). Mean age at colorectal cancer diagnosis was 64.2 ± 8.1 years, and 42.1% of the subjects were male. Mean time from colorectal cancer diagnosis to end of follow-up was 4.1 ± 3.3 years and to death was 2.2 ± 2.2 years. The median prediagnostic consumption of dairy products was 276 g/day and ranged between 166 g/day in Germany and 374 g/day in the Netherlands (Table 1). Median consumption of milk was 148 g/day, of yoghurt was 25 g/day, and of cheese was 26 g/day. The median intake of dietary calcium was 921 mg/day and ranged between 599 mg/day in Norway and 1,026 mg/day in the United Kingdom. The percentages of nonconsumers for dairy products, milk, yoghurt, and cheese were 0.1%, 9.2%, 23.2%, and 3.5%, respectively. High consumption of dairy products was positively associated with age at colorectal cancer diagnosis and female sex and inversely associated with current smoking status and more advanced disease stage. Further patient characteristics are shown in Table 2.

Dairy products and survival

Main results for the prediagnostic consumption of total dairy, milk, yoghurt, and cheese are presented in Table 3. The consumption of total dairy products was neither statistically significantly associated with colorectal cancer–specific (multivariable-adjusted HR for Q4 vs. Q1, 1.17; 95% CI, 0.96–1.43; *P* trend, 0.06) nor all-cause death (multivariable-adjusted HR for Q4 vs. Q1, 1.16; 95% CI, 0.98–1.36; *P* trend, 0.05) in patients with colorectal cancer. Also on a continuous scale per 100 g/day increase, we found no statistically significant associations for the consumption of dairy products and risk of death. For the individual products of milk, yoghurt, and cheese, no statistically significant associations were observed with colorectal cancer–specific and all-cause death, with the exception of an increased risk in the upper quartile of milk consumption and all-cause death (multivariable-adjusted HR for Q4 vs. Q1, 1.21; 95% CI, 1.03–1.43; *P* trend, 0.09). Multivariable-adjusted HRs for colorectal cancer–specific death in the highest quartiles compared with the lowest quartiles of consumption were 1.21 (95% CI, 0.99–1.48; *P* trend, 0.05) for milk, 1.09 (95% CI, 0.88–1.34; *P* trend, 0.59) for yoghurt, and 0.93 (95% CI, 0.76–1.14; *P* trend, 0.48) for cheese. Of note, compared with the null results of the age-adjusted models and multivariable models not adjusted

Table 1. Number of cases and median intake of dairy products and dietary calcium per EPIC center in 3,859 colorectal cancer cases

		Median intake per day				
Country	Cases	Total dairy (g/day)	Milk (g/day)	Yoghurt (g/day)	Cheese (g/day)	Dietary calcium (mg/day)
Denmark	719	286	168	21	24	974
France	310	243	84	70	52	978
Germany	401	166	25	28	29	789
Greece	80	208	83	40	62	947
Italy	387	197	106	4	54	933
Netherlands	374	374	202	46	30	1,018
Norway	173	198	111	25	24	599
Spain	319	230	188	0	14	803
Sweden	542	353	195	67	24	918
United Kingdom	554	370	293	18	15	1,026
Total	3,859	276	148	25	26	921

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Table 2. Baseline characteristics of 3,859 colorectal cancer cases according to intake of dairy products

Intake of dairy products	Q1 <150 g/day	Q2 150–276 g/day	Q3 276–452 g/day	Q4 >452 g/day	*P* value
Number of cases	964	967	963	965	—
Follow-up, mean ± SD (years)					
Baseline to diagnosis	6.4 ± 3.4	6.5 ± 3.5	6.3 ± 3.3	6.5 ± 3.4	0.38
Diagnosis to end of follow-up	4.0 ± 3.2	4.2 ± 3.4	4.2 ± 3.3	3.8 ± 3.2	0.01
Diagnosis to death	2.3 ± 2.2	2.2 ± 2.2	2.4 ± 2.2	2.1 ± 2.1	0.35
Male, %	49.4	37.8	40.0	41.4	<0.0001
Age at diagnosis, mean (years)	63.1	63.1	64.8	65.7	<0.0001
BMI, mean (kg/m^2)	26.5	26.3	26.6	26.2	0.11
Energy intake, median (kcal/day)	1,924	1,934	2,047	2,202	<0.0001
Milk intake, median (g/day)	9	113	218	440	<0.0001
Yoghurt intake, median (g/day)	3	25	48	63	<0.0001
Cheese intake, median (g/day)	24	27	27	26	<0.0001
Calcium intake, median (mg/day)	615	791	998	1,334	<0.0001
Smoking status, %					
Never	25.8	43.3	43.3	42.8	<0.01
Former	33.8	31.4	33.7	34.9	
Current	27.9	23.5	22.0	20.8	
Unknown	2.0	1.8	1.0	1.5	
Tumor subsite, %					
Colon	61.9	63.1	65.1	61.0	0.28
Rectum	38.1	36.9	34.9	39.0	
Disease stage[a]					
I	21.1	21.2	22.3	22.7	<0.0001
II	21.1	21.5	21.0	21.4	
III	33.3	32.8	33.7	34.7	
IV	14.6	12.8	11.8	9.8	
Unknown	9.9	11.7	11.2	11.4	
Differentiation grade[b]					
Well differentiated	12.6	15.5	13.7	13.0	<0.0001
Moderately differentiated	54.3	53.0	55.7	60.8	
Poorly differentiated	15.6	14.6	14.3	14.5	
Unknown	17.5	16.9	16.3	11.7	

[a]No information available about disease stage for subjects from Malmø and Oxford.
[b]No information available about tumor differentiation grade for subjects from Aarhus, Cambridge, Copenhagen, Malmø, Oxford, and Umea.

for disease characteristics, increasing intakes of total dairy and of milk were associated with increasing risk of death in the multivariable models adjusted for disease characteristics. This was largely due to the adjustment for disease stage.

Dietary calcium intake and survival

Main results for the prediagnostic intake of total dietary calcium and calcium intake from dairy and nondairy products are presented in Table 4. The intake of dietary calcium was neither associated with colorectal cancer–specific (multivariable-adjusted HR for Q4 vs. Q1, 1.01; 95% CI, 0.81–1.26; *P* trend, 0.95) nor with all-cause death (multivariable-adjusted HR for Q4 vs. Q1, 1.01; 95% CI, 0.84–1.21; *P* trend, 0.84). We did not find any association with colorectal cancer–specific and all-cause death either when the analyses were performed on a continuous scale per 200 mg/day increase of calcium, or when calcium intake was stratified by dairy and nondairy sources.

Effect modification by factors associated with colorectal cancer survival and stratified analyses for disease stage and tumor subsite

None of the examined factors known to be associated with colorectal cancer survival showed statistically significant interaction with the intake of dairy products and colorectal cancer–specific survival: time between study inclusion and colorectal cancer diagnosis, $P = 0.99$; age at colorectal cancer diagnosis, $P = 0.97$; sex, $P = 0.66$; BMI, $P = 0.99$; smoking, $P = 0.56$; disease stage, $P = 0.31$; and

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Table 3. Age-adjusted and multivariable-adjusted HRs for colorectal cancer–specific and all-cause death according to the intake of dairy products

			Colorectal cancer–specific death				All-cause death			
Dairy products	Daily intake (g/day)	Cases	Colorectal cancer–specific deaths	Age adjusted HR (95% CI)	Multivariable[a] HR (95% CI)	Multivariable[a,b] HR (95% CI)	Total deaths	Age adjusted HR (95% CI)	Multivariable[a] HR (95% CI)	Multivariable[a,b] HR (95% CI)
Total										
Quartile 1	<150	964	245	ref.	ref.	ref.	369	ref.	ref.	ref.
Quartile 2	150–275	967	239	0.94 (0.78–1.13)	0.94 (0.78–1.13)	0.96 (0.80–1.16)	359	0.93 (0.80–1.09)	0.95 (0.81–1.10)	0.98 (0.84–1.14)
Quartile 3	276–452	963	255	0.89 (0.74–1.08)	0.90 (0.75–1.09)	0.97 (0.80–1.18)	387	0.90 (0.78–1.05)	0.93 (0.79–1.08)	0.99 (0.84–1.16)
Quartile 4	>452	965	289	1.02 (0.85–1.23)	1.05 (0.86–1.27)	1.17 (0.96–1.43)	410	0.99 (0.85–1.15)	1.02 (0.87–1.20)	1.16 (0.98–1.36)
P trend				0.68	0.49	0.06		0.95	0.62	0.05
Per 100 g/day				1.00 (0.97–1.03)	1.00 (0.98–1.03)	1.02 (0.99–1.05)		1.00 (0.98–1.02)	1.00 (0.98–1.02)	1.02 (0.99–1.04)
Milk										
Quartile 1	<24	965	220	ref.	ref.	ref.	351	ref.	ref.	ref.
Quartile 2	24–147	970	256	1.01 (0.84–1.22)	1.01 (0.84–1.22)	1.03 (0.85–1.25)	373	1.02 (0.88–1.19)	1.03 (0.88–1.20)	1.05 (0.90–1.23)
Quartile 3	148–293	993	264	0.91 (0.75–1.11)	0.91 (0.75–1.11)	0.99 (0.81–1.20)	394	0.97 (0.83–1.13)	0.97 (0.83–1.14)	1.04 (0.89–1.22)
Quartile 4	>293	931	288	1.07 (0.88–1.29)	1.08 (0.89–1.32)	1.21 (0.99–1.48)	407	1.07 (0.91–1.25)	1.09 (0.93–1.28)	1.21 (1.03–1.43)
P trend				0.48	0.40	0.05		0.45	0.32	0.09
Per 100 g/day				1.01 (0.98–1.04)	1.01 (0.98–1.04)	1.02 (0.99–1.05)		1.01 (0.98–1.03)	1.01 (0.98–1.03)	1.02 (0.99–1.05)
Yoghurt										
Quartile 1	<2	936	245	ref.	ref.	ref.	380	ref.	ref.	ref.
Quartile 2	2–24	993	262	0.96 (0.78–1.18)	0.95 (0.78–1.17)	1.06 (0.86–1.31)	374	0.91 (0.77–1.07)	0.91 (0.77–1.08)	1.01 (0.85–1.20)
Quartile 3	25–89	965	273	1.06 (0.88–1.28)	1.06 (0.87–1.29)	1.15 (0.94–1.40)	400	1.03 (0.89–1.21)	1.06 (0.91–1.24)	1.13 (0.96–1.33)
Quartile 4	>89	965	248	0.98 (0.80–1.19)	1.00 (0.81–1.22)	1.09 (0.88–1.34)	371	0.94 (0.80–1.10)	0.98 (0.83–1.15)	1.08 (0.92–1.28)
P trend				0.96	0.83	0.59		0.82	0.74	0.34
Per 50 g/day				0.99 (0.95–1.03)	0.99 (0.96–1.03)	1.01 (0.97–1.04)		0.98 (0.95–1.01)	0.99 (0.96–1.02)	1.01 (0.98–1.04)
Cheese										
Quartile 1	<15	943	270	ref.	ref.	ref.	416	ref.	ref.	ref.
Quartile 2	15–25	985	277	0.93 (0.78–1.10)	0.93 (0.78–1.11)	0.97 (0.81–1.16)	401	0.84 (0.73–0.97)	0.85 (0.74–0.98)	0.90 (0.78–1.04)
Quartile 3	26–49	966	236	0.91 (0.75–1.10)	0.92 (0.76–1.12)	0.93 (0.77–1.14)	358	0.87 (0.75–1.01)	0.88 (0.75–1.03)	0.92 (0.79–1.08)
Quartile 4	>49	965	245	0.89 (0.73–1.08)	0.91 (0.74–1.12)	0.93 (0.76–1.14)	350	0.83 (0.71–0.98)	0.85 (0.72–1.00)	0.87 (0.74–1.04)
P trend				0.30	0.44	0.48		0.07	0.12	0.19
Per 25 g/day				0.97 (0.92–1.01)	0.97 (0.91–1.04)	0.98 (0.92–1.05)		0.97 (0.92–1.01)	0.97 (0.92–1.02)	0.98 (0.93–1.03)

[a]Stratified by center and adjusted for age at colorectal cancer diagnosis (continuously per one year increase), sex, prediagnostic BMI (continuous), smoking status (never, former, current, unknown), and energy intake (continuous).

[b]Additionally adjusted for tumor subsite (colon and rectum), disease stage (I, II, III, IV, unknown, unavailable for center), and differentiation grade (well, moderately, poorly, unknown, unavailable for center).

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Table 4. Age-adjusted and multivariable-adjusted HRs for colorectal cancer–specific and all-cause death according to the intake of dietary calcium

			Colorectal cancer–specific death				All-cause death			
Dietary calcium	Daily intake (mg/day)	Cases	Colorectal cancer–specific deaths	Age adjusted HR (95% CI)	Multivariable[a] HR (95% CI)	Multivariable[a,b] HR (95% CI)	Total deaths	Age adjusted HR (95% CI)	Multivariable[a] HR (95% CI)	Multivariable[a,b] HR (95% CI)
Total										
Quartile 1	<699	963	249	ref.	ref.	ref.	378	ref.	ref.	ref.
Quartile 2	699–920	966	255	1.03 (0.86–1.23)	1.04 (0.86–1.25)	1.06 (0.88–1.29)	368	0.98 (0.85–1.14)	1.00 (0.86–1.16)	1.01 (0.86–1.18)
Quartile 3	921–1,200	966	264	1.03 (0.85–1.23)	1.05 (0.86–1.27)	1.08 (0.89–1.32)	400	1.03 (0.89–1.19)	1.05 (0.90–1.23)	1.10 (0.93–1.29)
Quartile 4	>1,200	964	260	0.94 (0.78–1.13)	0.97 (0.78–1.20)	1.01 (0.81–1.26)	379	0.94 (0.80–1.09)	0.96 (0.80–1.15)	1.01 (0.84–1.21)
P trend				0.41	0.69	0.95		0.48	0.72	0.84
Per 200 mg/day				0.99 (0.96–1.02)	0.99 (0.95–1.03)	1.01 (0.97–1.05)		0.99 (0.97–1.02)	1.00 (0.97–1.03)	1.02 (0.98–1.05)
From dairy										
Quartile 1	<327	966	249	ref.	ref.	ref.	387	ref.	ref.	ref.
Quartile 2	327–524	963	246	0.93 (0.78–1.12)	0.94 (0.78–1.13)	0.94 (0.78–1.13)	361	0.87 (0.75–1.01)	0.88 (0.76–1.02)	0.89 (0.76–1.03)
Quartile 3	525–774	964	275	1.06 (0.89–1.27)	1.09 (0.90–1.31)	1.16 (0.96–1.40)	399	1.00 (0.86–1.15)	1.03 (0.88–1.19)	1.10 (0.94–1.28)
Quartile 4	>774	962	256	0.91 (0.76–1.10)	0.94 (0.77–1.15)	1.02 (0.83–1.25)	376	0.91 (0.78–1.05)	0.94 (0.80–1.10)	1.02 (0.87–1.21)
P trend				0.53	0.79	0.54		0.49	0.82	0.35
Per 200 mg/day				0.99 (0.95–1.02)	0.99 (0.95–1.03)	1.01 (0.98–1.06)		0.99 (0.96–1.02)	0.99 (0.96–1.03)	1.02 (0.98–1.05)
From nondairy										
Quartile 1	<299	959	277	ref.	ref.	ref.	394	ref.	ref.	ref.
Quartile 2	299–371	964	260	0.98 (0.81–1.18)	1.01 (0.83–1.22)	0.93 (0.77–1.13)	384	1.03 (0.89–1.20)	1.07 (0.91–1.25)	0.97 (0.83–1.14)
Quartile 3	372–470	971	227	0.84 (0.69–1.02)	0.87 (0.70–1.08)	0.84 (0.67–1.05)	354	0.89 (0.76–1.04)	0.92 (0.77–1.10)	0.88 (0.74–1.05)
Quartile 4	>470	961	262	0.97 (0.79–1.19)	1.03 (0.79–1.34)	0.96 (0.74–1.26)	391	1.04 (0.88–1.23)	1.10 (0.88–1.36)	1.01 (0.82–1.26)
P trend				0.66	0.92	0.83		0.84	0.54	0.90
Per 200 mg/day				0.98 (0.89–1.09)	1.03 (0.89–1.19)	0.98 (0.84–1.14)		1.01 (0.93–1.10)	1.06 (0.94–1.19)	1.01 (0.89–1.14)

[a]Stratified by center and adjusted for age at colorectal cancer diagnosis (continuously per one year increase), sex, prediagnostic BMI (continuous), smoking status (never, former, current, unknown), and energy intake (continuous).

[b]Additionally adjusted for tumor subsite (colon and rectum), disease stage (I, II, III, IV, unknown, unavailable for center), and differentiation grade (well, moderately, poorly, unknown, unavailable for center).

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tumor subsite, $P = 0.90$. In addition, these factors also did not statistically significantly modify the association between dietary calcium intake and colorectal cancer–specific survival: time between study inclusion and colorectal cancer diagnosis, $P = 0.13$; age at colorectal cancer diagnosis, $P = 0.09$; sex, $P = 0.91$; BMI, $P = 0.64$; smoking, $P = 0.32$; disease stage, $P = 0.52$; and tumor subsite, $P = 0.64$. Similar results were found for all-cause death. Except for an increased overall risk of death after rectal cancer in the upper quartile of dairy intake (multivariable-adjusted HR for Q4 vs. Q1, 1.36; 95% CI, 1.03–1.78; P trend, 0.02), nonsignificant risk estimates for colorectal cancer–specific and overall risk of death were found when the analyses for dairy products and dietary calcium intake were stratified by disease stage and tumor subsite (Supplementary Tables S1 and S2).

Sensitivity analyses

Sensitivity analyses with country-specific cutoff points attenuated the risk estimates for the consumption of dairy products and resulted in nonsignificant associations for colorectal cancer–specific (multivariable-adjusted HR for Q4 vs. Q1, 1.07; 95% CI, 0.92–1.25) and overall risk of death (multivariable-adjusted HR for Q4 vs. Q1, 1.09; 95% CI, 0.90–1.32). Similar results were found for country-specific quartiles of milk consumption and colorectal cancer–specific (multivariable-adjusted HR for Q4 vs. Q1, 1.06; 95% CI, 0.89–1.25) and overall risk of death (multivariable-adjusted HR for Q4 vs. Q1, 1.07; 95% CI, 0.90–1.27). To estimate the effect of unavailable information about disease stage, we used multiple approaches. Similar results were found when using a separate "missing" category for unavailable disease stage for Malmø and Oxford and one for unknown disease stage for other centers (primary analysis), as compared with analyses combining unavailable disease stage for Malmø and Oxford and unknown disease stage for other centers in one "missing" category, excluding centers with no information on disease stage (complete case analysis), or when multiple imputation for disease stage was used (data not shown).

Discussion

The results of the present study demonstrate that the prediagnostic consumption of dairy products (total, milk, yoghurt, and cheese) and dietary intake of calcium (total, dairy, and nondairy) are neither associated with colorectal cancer–specific nor with all-cause death in patients with colorectal cancer. In addition, no statistically significant effect modification by factors known to be associated with colorectal cancer survival was found, and stratified analyses by disease stage and tumor subsite showed no statistically significant associations for the intake of dairy products and dietary calcium and the risk of colorectal cancer–specific and all-cause death.

In contrast to the large number of studies that investigated the relation between diet and colorectal cancer risk, only very few studies have investigated the role of diet in relation to colorectal cancer survival (3). In a relatively small French case–control study, including 148 patients with colorectal cancer who underwent a resection of the tumor, high energy intake was associated with an improved 5-year survival, but no significant associations for specific foods, including dairy products (RR for third vs. first tertile, 0.63; 95% CI, 0.30–1.33), were found (27). A prospective U.S. study with 1,009 patients with stage III colon cancer showed a reduced survival for patients with a Western dietary pattern compared with those with a prudent dietary pattern (34). Individual foods were not investigated, but a Western diet was characterized by high intakes of meat, fat, grains, and desserts, whereas a prudent diet was characterized by high intakes of fruit, vegetables, poultry, and fish. The same group also found that an increasing dietary glycemic load and total carbohydrate intake were associated with a higher risk of cancer recurrence or death (35). Furthermore, an increasing intake of red and processed meat, a risk factor for colorectal cancer development, has been shown to be associated with a poorer prognosis among patients with nonmetastatic colorectal cancer (36).

A large number of studies, including a recent analysis within the EPIC cohort (5, 6), demonstrate that the consumption of dairy products and dietary calcium is associated with a reduced colorectal cancer and especially reduced colon cancer risk. However, as far as we are aware, few studies have reported on the intake of dairy and dietary calcium in relation to colorectal cancer survival. Calcium is, at least partially, thought to lower colorectal cancer risk by preventing colonic K-*ras* mutations and by its direct antiproliferative effect on colonic epithelium cells (13, 15). We hypothesized that these anticarcinogenic properties of calcium against cancer development may also affect the chance of survival after colorectal cancer diagnosis. The results of the present study show however no association between increasing prediagnostic intake of dairy and calcium and improved colorectal cancer survival. In contrast, a small nonsignificant increased risk of colorectal cancer–specific death and a borderline significant increased risk of all-cause death were observed for the upper quartile of milk consumption in the multivariable-adjusted models, which however attenuated when using country-specific cutoff points. This counterintuitive increased risk of death was largely due to the adjustment for disease stage and may be explained as a chance finding or by the fact that subjects in the upper quartile of dairy intake less frequently had stage IV disease. However, based on this observation, it can be argued that subjects with a high intake of dairy products that do have stage IV colorectal cancer might have biologically and prognostically different tumors.

Thus, our observations indicate that the intake of dairy products and dietary calcium is not associated with improved survival in patients with colorectal cancer. Although these findings may be surprising when considering the strong inverse associations that have been found for especially colon cancer development, it may well be

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that once cancer has developed, the assumed antiproliferative and anticarcinogenic properties of calcium only have a minor or no effect on tumor progression and survival. On the other hand, the consumption of milk has been found to be associated with increased levels of IGFI (21), and increasing IGF-I levels have been hypothesized to promote tumor progression and to alter colorectal cancer survival (37–39) through increased cell proliferation and promotion of angiogenesis (25, 26, 40). Finally, colorectal cancer survival largely depends on important clinical factors such as disease stage, comorbidities, general physical condition, treatment, and lifestyle factors like smoking habits and BMI. If calcium intake, by any means, does influence tumor growth and progression, then the effect might be diminished by more important clinical factors.

The strengths of this study include the prospective design, the large number of colorectal cancer cases, and the detailed information on potential dietary and lifestyle confounders. However, several limitations of this study may have influenced our results and need to be considered before making final conclusions. First, the assessment of usual diet took place before the diagnosis of colorectal cancer and may not reflect the true dietary intake of dairy products and dietary calcium at time of diagnosis and thereafter. However, Norwegian research among colorectal cancer survivors has shown that the consumption of milk does not significantly change after colorectal cancer diagnosis (41). Another limitation of this study is the lack of data on calcium supplements use in the EPIC cohort. This was however assessed in EPIC-Heidelberg, which showed that calcium supplements were used by less than 10% of subjects (42). Furthermore, results of a randomized controlled trial, investigating the risk of cancer death in over 5,000 subjects with previous fractures who were randomized to use calcium supplements, showed no association between calcium supplements use and cancer mortality (43). Nevertheless, the prediagnostic assessment and the lacking data on calcium supplements may have led, in combination with the self-reported design of the questionnaires, to attenuated risk estimates. Another limitation of the present study is the registration of disease stage. Different classification systems across centers were used (i.e., TNM, Dukes, and EPIC classification) which needed to be combined in one overall disease stage. In addition, there was no data available about disease stage and tumor differentiation grade in several centers, but comprehensive sensitivity analyses to estimate the effect of unavailable information showed similar results compared with the primary analysis. Finally, there was no data available on colorectal cancer treatment. Although we do not expect significant differences in treatment and outcomes between centers included in this study, we did perform the analyses stratified by center.

To conclude, in this large cohort of patients with colorectal cancer, we found no evidence for an association between prediagnostically reported intake of dairy products and dietary calcium and risk of colorectal cancer–specific and overall death. We observed no heterogeneity by tumor subsite or disease stage. More observational studies in patients with colorectal cancer are needed to provide better insights into the role of prediagnostic and postdiagnostic diet and lifestyle in relation to disease progression and survival.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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