See corresponding editorial on page 1388 and article on pages 1447 and 1458.

Postdiagnostic dairy products intake and colorectal cancer survival in US males and females

Xing Liu,[1,2] Wanshui Yang,[3,4] Kana Wu,[1] Shuji Ogino,[1,5,6,7] Weibing Wang,[2] Na He,[2] Andrew T Chan,[3,7,8,9] Zuo-Feng Zhang,[10,11] Jeffrey A Meyerhardt,[12] Edward Giovannucci,[1,3,10] and Xuehong Zhang[1,3]

[1]Department of Nutrition, T. H. Chan School of Public Health, Harvard University, Boston, MA, USA; [2]Department of Epidemiology, School of Public Health, Fudan University, Shanghai, P.R. China; [3]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [4]Department of Nutrition, School of Public Health, Anhui Medical University, Hefei, Anhui, P.R. China; [5]Department of Oncologic Pathology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA; [6]Program in MPE Molecular Pathological Epidemiology, Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [7]Broad Institute of MIT and Harvard, Cambridge, MA, USA; [8]Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; [9]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; [10]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, CA, USA; [11]Jonsson Comprehensive Cancer Center, UCLA, Los Angeles, CA, USA; and [12]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

ABSTRACT

Background: To evaluate the association between postdiagnostic dairy intake and survival among patients with colorectal cancer (CRC).

Methods: This study analyzed data from the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). Postdiagnostic dairy intake and other dietary and lifestyle factors were obtained from validated questionnaires. Individual dairy items including milk, cheese, yogurt, and so on were reported, and total, high-fat, and low-fat dairy intakes were derived.

Results: A total of 1753 eligible CRC cases were identified until 2012, from which 703 deaths were documented after a median follow-up time of 8.2 y, and 242 were due to CRC. Overall, when comparing those who consumed 21+ servings/wk with <7 servings/wk, postdiagnostic total dairy intake did not show significant associations with CRC-specific mortality (HR: 1.35; 95% CI: 0.85, 2.13) or overall mortality (HR: 1.28; 95% CI: 0.98, 1.67). However, high-fat dairy, including whole milk and cream cheese, was positively associated with overall mortality (HR: 1.33; 95% CI: 1.08, 1.65) but not significantly with CRC-specific mortality (HR: 1.31; 95% CI: 0.91, 1.90) when comparing those who consumed 10.5+ servings/wk with <3.5 servings/wk. For the same comparison, low-fat dairy, including skim or nonfat milk and cottage cheese, was inversely associated with overall mortality (HR: 0.74; 95% CI: 0.59, 0.92) but not CRC-specific mortality (HR: 0.91; 95% CI: 0.63, 1.29).

Conclusions: Total dairy products intake did not show significant association with CRC-specific or overall mortality. However, high intake of high-fat dairy products was associated with increased mortality, whereas low-fat dairy was associated with lower risk of overall mortality. *Am J Clin Nutr* 2021;113:1636–1646.

The Nurses' Health Study and Health Professionals Follow-up Study were supported by the National Cancer Institute at the NIH (grants UM1 CA186107, P50 CA127003, P01 CA87969, and U01 CA167552). This work was supported by the NIH (grant numbers R01 CA137178 to A.T.C., K24 DK098311 to A.T.C., K07 CA188126 to X.Z., and R21 CA238651 to X.Z.). A.T.C. is a Stuart and Suzanne Steele MGH Research Scholar. X.Z. is also supported by the American Cancer Society Research Scholar Grant (RSG NEC-130476), Dana-Farber Harvard Cancer Center (DF/HCC) GI SPORE Developmental Research Project Award (P50CA127003), and DF/HCC Cancer Center Support Grant (CCSG, P30CA006516-55). The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH. The funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Edward Giovannucci and Xuehong Zhang are co-senior authors.

Supplemental Tables 1–8 and Supplemental Figure 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Address correspondence to XZ (e-mail: xuehong.zhang@channing.harvard.edu).

Abbreviations used: AHEI, Alternative Healthy Eating Index; CRC, colorectal cancer; EPIC, European Investigation into Cancer and Nutrition cohort; HPFS, Health Professionals Follow-up Study; IWH, Iowa Women's Health Study; NDI, National Death Index; NHS, Nurses' Health Study.

Received August 3, 2020. Accepted for publication February 16, 2021.

First published online April 19, 2021; doi: https://doi.org/10.1093/ajcn/nqab059.

Keywords: dairy, high-fat dairy, low-fat dairy, colorectal cancer, survival

Background

Colorectal cancer (CRC) is ranked third in incidence and second in mortality among cancers worldwide in 2020, with more than 1.9 million new cases diagnosed annually (1). The high incidence is partially due to unhealthy dietary patterns and lifestyle factors and obesity, whereas mortality was improved in more developed countries by early detection of CRC and precursor lesions from screening and treatment in time (2, 3). As the number of people with CRC is growing, many are seeking advice for effective dietary and lifestyle modifications, which requires a better understanding of the relevant factors (4).

Dairy products are among the most commonly consumed food in Western countries, including the United States (5, 6). They provide important nutrients, including protein; calcium; potassium; phosphorus; vitamins A, D, and B-12; riboflavin; and niacin. However, the high content of saturated fat may have some deleterious health consequences (7). Previous studies have examined the associations of nutrients from dairy products, including calcium and vitamin D, with CRC survival. For example, higher calcium intake was associated with lower mortality after CRC diagnosis (8, 9). Although no clear association has been found between vitamin D intakes and CRC survival (9), plasma 25(OH) vitamin D concentration was inversely associated with CRC mortality (10, 11). Recent randomized controlled clinical trials reported benefits from high-dose vitamin D intake for survival among patients with advanced CRC (12) and suggestively with digestive cancer survival (13). Three prospective studies have examined the associations between dairy food intake and CRC-specific survival and overall survival. Null associations have been reported for total dairy intake (HR: 0.73–1.17), yogurt (HR: 1.08–1.09), and cheese (HR: 0.87–0.93), whereas null or positive associations have been reported for milk (HR: 0.72–1.21) (9, 14, 15). Two of the studies used baseline dietary information before cancer diagnosis, and limited dairy items were examined. Dairy products are diverse, and the nutrient compositions vary, which may have different effects. One systematic review indicated an inverse association between total dairy products intake and CRC incidence, but the associations varied across types of dairy products (16). Thus, we examined both total intake of dairy products and individual dairy items after CRC diagnosis in relation to survival of patients with CRC.

We used 2 large cohorts that had comprehensive data collected on dietary and lifestyle factors and sufficient CRC cases to investigate postdiagnostic intake of dairy products and CRC-specific survival and overall survival in the US population.

Methods

Study cohorts

Participants were from the Nurses' Health Study (NHS) established in 1976 with 121,700 female registered nurses aged 30–55 y at baseline and the Health Professionals Follow-up Study (HPFS) established in 1986 with 51,529 male dentists, veterinarians, pharmacists, optometrists, osteopath physicians, and podiatrists aged 40–75 y. A questionnaire collecting detailed information on demographic characteristics, lifestyle factors, and medical history was returned by participants at baseline and biennially during follow-up in both cohorts. The response rates were >90% for both cohorts throughout the years.

Study participants

During follow-up, the incident CRC cases were identified by report from returned biennial questionnaires. Patients were then asked for written permission to access their medical records, including pathologic reports. For those participants who did not respond, the state cancer registries and the National Death Index (NDI) were searched to identify CRC diagnosis or CRC-related death (17). For CRC-related deaths identified from the NDI, we requested the permission for medical records review from next-of-kin of the participants. CRC was defined as a primary tumor with International Classification of Diseases, Ninth Revision codes of 153 (malignant neoplasm of colon) and 154 (malignant neoplasm of rectum and rectosigmoid junction). The obtained medical and pathologic records were reviewed carefully to confirm CRC diagnoses. Tumor-related information, including anatomic location, stage, differentiation, and histologic type, was extracted by study physicians with no idea of potential exposure data.

By June 1, 2012, for the NHS and January 31, 2012, for the HPFS, a total of 3924 CRC cases were identified. We set these cutoffs to allow time to assess mortality after diagnosis. Exclusion criteria included the following: participants died before 1980 for NHS or 1986 for HPFS, cancer diagnoses before 1980 for NHS or 1986 for HPFS, cancer diagnosed after the end of this study period, participants died before cancer diagnosis, CRC cases at stage IV, missing data on dietary report, missing data on dairy intake, and dairy information assessed <6 mo or >4 y after CRC diagnosis (**Supplemental Figure 1**). The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T. H. Chan School of Public Health, as well as those of participating registries as required.

Assessment of outcome

Death and cause of death were identified by reviewing the NDI and the postal office or the next-of-kin in response to the follow-up questionnaires. Death information was reviewed by cohort investigators, and the primary cause of death was determined.

Assessment of dairy product consumption

A 116-item FFQ for food intake was administered to participants from the NHS in 1984 and was expanded to a 131-item FFQ in 1986 to collect updated diet information every 4 y thereafter. A similar FFQ was used for HPFS participants every 4 y since 1986.

In FFQs, participants were asked how often, on average, they consumed a standard serving of each dairy product item in the previous year. The frequency was described in 9 categories, ranging from "never or less than once per month" to "6 or more times per day." The dairy product items and their standard serving sizes included "skim or low-fat milk" (8-oz glass, 1 oz = 25.57 mL), "whole milk" (8-oz glass, 1 oz = 25.57 mL), "cottage or ricotta cheese" (1/2 cup), "cream cheese" (1 oz, 25.57 mL), "other cheese (including American, cheddar)" (1 slice or 1 oz, 25.57 mL), "yogurt" (4–6 oz, 1 oz = 25.57 mL), "cream" (1 tablespoon), "ice cream" (1 cup), "sherbet" (1 cup), and "butter" (spread). Consistent with previous studies from the same cohorts (18, 19), consumption of total dairy products was calculated as the sum of intakes of each individual item. Moreover, intake of "skim or low-fat milk" and "whole milk" was summed up to "milk." "Cottage or ricotta cheese," "cream cheese," and "other cheese" were summed up to "total cheese." We also calculated total consumption of low-fat dairy products, including "sherbet," "skim or low-fat milk," "yogurt," and "cottage or ricotta cheese," and total consumption of high-fat dairy products, including "whole milk," "cream," "ice cream," "cream cheese," "other cheese," and "butter." The evaluation of the validity and precision of the FFQ has been described in detail in previous publications (20–23). Briefly, the correlation coefficients of intakes based on four 1-wk dietary records from 1 y with the FFQ for each dairy product item ranged from 0.57 for other cheese to 0.97 for yogurt (21). To facilitate future comparisons across studies from different populations, absolute categories of dairy intake were used instead of relative cutoffs such as quintiles in this analysis.

Assessment of covariates

Information on BMI (in kg/m^2), physical activity (metabolic equivalents from recreational and leisure-time activities, METs h/wk), current cigarette smoking status, pack-year of smoking, alcohol intake (g/d), regular aspirin use (≥2 tablet/wk), family history of CRC, and postmenopausal hormone use (only for nurses) were obtained from the biennial questionnaires for participants from both cohorts. Other dietary factors, including red meat and processed meat intake, and dietary components including fiber, fat, folate, calcium, vitamin D, total energy intake (kcal/d), Alternative Healthy Eating Index (AHEI), and so on were collected or derived from the FFQ every 4 y.

Statistical analysis

Person-years to event was calculated for each participant from the date of FFQ return for postdiagnostic assessment to death or the end of this observation (June 1, 2012, for the NHS and January 31, 2012, for the HPFS), whichever came first. Because active treatment right after diagnosis might affect diet, postdiagnostic intake was defined as dietary intake from the first FFQ collected at least 6 mo and no more than 4 y after diagnosis, as consistent with previous studies from the same cohorts (8). Cox proportional hazard regression models were used to estimate HRs and 95% CIs for death comparing different levels of dairy product intake. Cox regressions were stratified by age, tumor stage, and study cohort, and were adjusted for tumor differentiation, tumor subsite, year of diagnosis, time between CRC diagnosis and measurement of dairy food intake assessment, and prediagnostic total dairy intake. The covariates further included in the models were postdiagnostic BMI, physical activity, pack-year of smoking, alcohol drinking, total energy intake, family history of CRC, and postmenopausal hormone use (only for females). Data were analyzed all together first because there was no statistically heterogeneity by sex (*P*-heterogeneity = 0.99 for total dairy intake and overall survival), and then stratified analyses were conducted by sex and other important covariates.

We excluded participants if they missed information on all items regarding dairy intake. For dairy categories, they were the sum of individual items in that category. If a participant missed information on 1 item, the category variable was still calculated from all other items available in that category. Previous studies in our cohorts had shown that most missing individual items in the FFQs were from individuals not consuming that item (24). The proportions of participants missing information on dairy items ranged from 0 for yogurt to 0.6% for cream cheese. For those who missed information for covariates on 1 round of follow-up, the data from the previous round were carried forward. The proportions of missing for covariates ranged from 0% to 6.6%, except that the proportion of missing for cancer stage was 13%. For those who missed information on covariates, a missing category was assigned and entered into the regression analyses.

In sensitivity analyses, more covariates were added to the model, including postdiagnostic AHEI, intake of vitamin D, folate, total fat, ω-3 fatty acids, ω-6 fatty acids, fiber, red meat, and multivitamin. Although the AHEI includes dairy foods as one of the components, it serves here as an index for overall dietary quality (25). Sensitivity analysis was also conducted by excluding those patients with unknown stage for cancer diagnosis, including stage IV patients, and excluding those who died within 3 mo of FFQ return.

SAS 9.4 software was used for all analyses (SAS Institute).

Results

A total of 1753 CRC cases, including 1074 from the NHS and 679 from the HPFS, were included in this study. The median follow-up time was 8.2 y from the date of returning the FFQ after diagnosis of CRC to the end of the observation. During follow-up, 703 deaths occurred (391 from the NHS and 312 from the HPFS), including 242 deaths due to CRC (159 from the NHS and 83 from the HPFS). The median intake of postdiagnostic total dairy was 13.5 servings/wk (IQR: 8.5, 22.5 servings/wk) for females and 11.6 servings/wk (IQR: 7.5, 19.0 servings/wk) for males. The level of postdiagnostic total dairy product intake was categorized and analyzed in 4 groups (<7, 7 to <14, 14 to <21, 21+ servings/wk), and participants with higher total dairy intake tended to have higher BMI, had a lower AHEI, and were less likely to smoke, drink alcohol, or use aspirin (**Table 1**). Similar patterns were observed for male and female participants (**Supplemental Table 1**).

Postdiagnostic intake of total dairy products did not show significant associations with CRC-specific mortality (HR: 1.35; 95% CI: 0.85, 2.13; 21+ compared with <7 servings/wk) and overall mortality (HR: 1.28; 95% CI: 0.98, 1.67; 21+ compared with <7 servings/wk) in multivariable models (**Table 2**). Higher intake of high-fat dairy showed positive association with overall mortality (HR: 1.33; 95% CI: 1.08, 1.65; 10.5+ compared with <3.5 servings/wk) but not CRC-specific mortality (HR: 1.31; 95% CI: 0.91, 1.90; 10.5+ compared with <3.5 servings/wk). Higher intake of low-fat dairy showed an inverse association

TABLE 1 Characteristics of patients with colorectal cancer according to postdiagnostic weekly dairy intake in the Nurses' Health Study and Health Professionals Follow-up Study cohorts[1]

	Postdiagnostic dairy intake, servings/wk											
	Total dairy				Low-fat dairy				High-fat dairy			
Characteristic	<7 (n = 324)	7 to <14 (n = 614)	14 to <21 (n = 359)	21+ (n = 456)	<3.5 (n = 509)	3.5 to <7 (n = 328)	7 to <10.5 (n = 423)	10.5+ (n = 493)	<3.5 (n = 686)	3.5 to <7 (n = 405)	7 to <10.5 (n = 284)	10.5+ (n = 378)
Age, y	67.7	68.4	68.2	67.9	67.9	68.1	68.4	68.2	68.4	68.6	66.8	68.0
White, %	95.8	97.7	98.3	98.3	97.9	96.6	97.1	98.6	96.9	97.9	97.5	99.0
BMI, kg/m^2	25.6	26.3	26.4	26.6	26.0	26.5	26.5	26.2	25.8	26.3	26.7	26.7
Physical activity, METs[2] h/wk	17.6	21.9	19.1	17.8	16.7	20.9	20.4	20.3	20.9	18.5	20.8	16.7
Current smoking, %	11.6	11.1	7.6	9.2	15.5	9.5	8.6	5.9	7.6	9.5	12.8	12.9
Pack-years of smoking	17.0	16.4	15.8	16.8	20.1	15.3	15.5	14.5	14.9	16.7	17.4	18.8
Alcohol, g/d	8.8	8.4	7.9	5.9	9.2	8.3	7.4	5.9	7.2	8.7	8.0	7.3
Regular aspirin use (2 or more tablets/wk), %	38.2	34.6	33.4	32.7	35.2	34.4	34.1	34.2	37.0	35.9	32.2	30.9
Family history of colorectal cancer, %	16.8	21.8	22.5	21.3	18.7	20.0	20.7	24.3	19.1	21.4	26.5	19.3
Alternate Healthy Eating Index	52.3	51.2	51.8	49.2	48.7	51.5	51.9	52.4	53.9	50.7	48.8	47.9
Prediagnosis total dairy intake, servings/wk	8.2	12.5	16.3	23.9	11.9	12.9	15.3	21.0	12.4	14.9	15.8	21.6
Postdiagnosis total dairy intake, servings/wk												
Total	3.8	10.1	17.0	30.5	10.0	11.4	14.8	25.2	10.3	13.3	16.7	27.1
Low fat	2.0	5.8	9.4	16.0	1.2	4.9	8.2	18.7	9.1	8.4	8.4	7.5
High fat	1.9	4.3	7.6	14.5	8.8	6.5	6.6	6.6	1.2	4.9	8.3	19.6
Milk	1.0	3.8	6.4	11.9	1.5	3.0	5.8	12.5	5.6	5.7	6.0	6.6
Skim or low-fat milk	0.8	3.3	5.7	10.6	0.4	2.6	5.3	11.9	5.4	5.2	5.1	5.0
Whole milk	0.1	0.3	0.4	0.9	1.0	0.3	0.2	0.2	0.0	0.1	0.5	1.5
Yogurt	0.2	0.7	1.1	1.6	0.2	0.7	0.8	1.9	0.9	0.8	1.0	0.9
Total cheese	1.5	2.9	4.3	5.9	2.9	3.4	3.5	4.9	2.3	3.7	4.3	5.8
Cottage or ricotta cheese	0.3	0.6	0.9	1.3	0.3	0.6	0.7	1.4	0.7	0.7	0.8	0.8
Cream cheese	0.2	0.4	0.6	0.7	0.4	0.4	0.3	0.6	0.2	0.4	0.6	0.8
Other cheese (American, cheddar)	1.0	1.9	2.8	4.0	2.1	2.3	2.5	3.0	1.4	2.6	2.9	4.1
Cream	0.2	0.4	1.0	2.6	1.1	0.9	1.2	1.0	0.1	0.5	1.1	3.3
Regular ice cream	0.4	0.8	1.3	1.5	1.2	1.1	0.9	1.0	0.3	1.0	1.5	2.0
Sherbet, frozen yogurt, or nonfat ice cream	0.3	0.6	0.9	1.2	0.2	0.5	0.6	1.6	1.0	0.9	0.6	0.4
Butter	0.3	0.9	2.1	5.8	3.1	2.0	2.0	2.2	0.2	0.9	2.1	8.0
Processed meat, servings/wk	4.6	5.2	5.8	5.9	6.1	5.3	5.1	5.0	4.0	5.9	6.0	6.8
Red meat, servings/wk	1.5	1.8	1.9	2.1	2.3	1.9	1.7	1.6	1.2	2.0	2.1	2.6
Total fiber, g/d	23.2	21.7	21.1	19.5	20.4	21.7	21.6	21.7	24.0	20.3	19.8	18.4
Total fat, g/d	58.2	59.2	60.0	60.0	64.8	60.3	57.8	54.7	53.2	61.4	61.9	66.4
Total ω-3 fat, mg/d	32.8	30.1	28.1	24.9	28.3	31.1	29.1	27.5	33.2	27.3	27.3	23.9
Total folate intake, μg/d	688	675	661	643	632	666	669	698	726	645	646	605
Total vitamin D, IU/d	473	510	530	591	455	494	527	624	564	501	534	492
Total calcium intake, mg/d	664	837	910	1093	681	812	886	1148	900	865	900	874
Calcium supplement intake, mg/d	388	344	325	326	343	356	323	355	368	344	359	296
Tumor subsite, %												
Proximal colon	39.5	37.9	41.4	44.7	37.7	42.3	40.0	43.1	41.7	36.4	42.9	42.3
Distal colon	28.5	34.6	30.0	29.4	32.5	33.0	29.7	29.9	30.9	31.0	29.6	32.5
Rectum	26.6	21.0	21.5	21.3	24.0	18.0	23.2	22.2	21.5	25.3	21.3	20.3
Unspecified	5.3	6.5	7.1	4.6	5.9	6.7	7.2	4.7	5.9	7.4	6.2	4.9

(*Continued*)

TABLE 1 (*Continued*)

Characteristic	Postdiagnostic dairy intake, servings/wk: Total dairy <7 (n = 324)	7 to <14 (n = 614)	14 to <21 (n = 359)	21+ (n = 456)	Low-fat dairy <3.5 (n = 509)	3.5 to <7 (n = 328)	7 to <10.5 (n = 423)	10.5+ (n = 493)	High-fat dairy <3.5 (n = 686)	3.5 to <7 (n = 405)	7 to <10.5 (n = 284)	10.5+ (n = 378)
Tumor grade, %												
Grade 1 well differentiated	14.7	14.4	16.6	15.0	15.9	16.4	12.6	15.5	16.8	14.0	10.7	16.1
Grade 2 moderately differentiated	59.7	60.2	50.1	54.1	58.6	56.5	57.9	52.9	55.1	58.8	57.3	54.8
Grade 3 poorly differentiated	11.2	10.4	16.4	15.2	10.5	11.2	13.6	16.1	13.9	10.5	15.1	13.2
Unspecified	14.4	15.0	16.9	15.6	15.0	15.9	15.8	15.6	14.3	16.6	16.9	15.9
Tumor stage, %												
Stage I	32.3	33.5	34.3	34.7	33.2	32.5	34.0	34.8	34.7	31.8	32.3	35.1
Stage II	28.8	31.5	25.8	28.7	29.9	29.2	30.2	26.9	29.2	27.6	29.7	28.8
Stage III	25.2	23.4	23.6	24.8	22.2	25.8	22.4	26.5	24.0	26.9	24.7	21.6
Unspecified	13.6	11.6	16.3	11.8	14.7	12.6	13.4	11.8	12.1	13.6	13.3	14.5

[1]Values are means for continuous variables; percentages are calculated for categorical variables and are standardized to the age distribution of the study population. Values of polytomous variables may not sum to 100% due to rounding.

[2]METs, metabolic equivalents from recreational and leisure-time activities.

with overall mortality (HR: 0.74; 95% CI: 0.59, 0.92; 10.5+ compared with <3.5 servings/wk) but not CRC-specific mortality (HR: 0.91; 95% CI: 0.63, 1.29; 10.5+ compared with <3.5 servings/wk). Associations between individual items of dairy product with survival were also shown in Table 2. The overall results were similar for males and females, although the associations slightly varied across sexes for different dairy items (**Supplemental Tables 2** and **3**).

In stratified analyses, total dairy intake of 21+ servings/wk compared with <7 servings/wk was positively associated with CRC-specific mortality among those aged <65 y (HR: 2.42; 95% CI: 1.23, 4.78; P-interaction < 0.01) and among those females who never used postmenopausal hormone (HR: 3.05; 95% CI: 1.45, 6.41; P-interaction = 0.07). It was also positively associated with overall mortality among those females who never used postmenopausal hormone (HR: 1.76; 95% CI: 1.12, 2.77; P-interaction = 0.03) (**Table 3**). Stratified analyses were also performed for high-fat (**Supplemental Table 4**) and low-fat dairy (**Supplemental Table 5**).

Prediagnostic dairy product intake was not significantly associated with survival among patients with CRC (**Supplemental Table 6**).

In sensitivity analyses, first, more covariates were added to the model, including postdiagnostic AHEI and intake of vitamin D, folate, total fat, ω-3 fatty acids, ω-6 fatty acids, fiber, red meat, and multivitamins. There was no significant change in the observed associations. Second, when those who died within 3 mo of FFQ return were excluded from the analyses, no obvious change for the conclusions was noted. Third, instead of adjusting for prediagnostic total dairy intake in models, prediagnostic high-fat dairy was adjusted for in examining the association between postdiagnostic high-fat dairy and CRC survival, and prediagnostic low-fat dairy was adjusted for in examining postdiagnostic low-fat intake; this change did not affect the results. Fourth, when postdiagnostic high-fat dairy and low-fat dairy were included in 1 regression model simultaneously, with or without adjusting for prediagnostic total dairy, the associations remained similar (**Supplemental Table 7**). Fifth, we defined intake of less than 7 servings/week as low level of high-fat or low-fat dairy intake, analyzed the association for high-fat dairy among those low-level intakers of low-fat dairy, and vice versa. We found that the positive associations between high-fat dairy and mortality remained, while the associations for low-fat dairy attenuated (**Supplemental Table 8**). Sixth, after excluding those patients with unknown stage for cancer diagnosis, including stage IV patients, or excluding those who died within 3 mo of FFQ return, the direction and magnitude of the associations remained similar (data not shown).

Discussion

After following up 1753 US participants with nonmetastatic CRC, this study suggested that higher intake of high-fat dairy was associated with ∼33% increase in overall mortality, whereas higher intake of low-fat dairy was associated with ∼26% risk reduction in overall mortality.

Dairy products have been associated with reduced risk of several cancers, including CRC (26, 27). One meta-analysis based on 19 cohort studies reported reduction in CRC risk among those who had a higher intake of total dairy products,

TABLE 2 Postdiagnostic dairy intake and colorectal cancer–specific and overall survival in the NHS and HPFS cohorts[1]

Dairy items (servings/wk)	No. of subjects	No. of CRC deaths	CRC-specific survival, HR (95% CI)		No. of overall deaths	Overall survival, HR (95% CI)	
			Model 1[2]	Model 2[3]		Model 1[2]	Model 2[3]
Total dairy							
<7	324	44	Reference	Reference	134	Reference	Reference
7 to <14	614	75	0.91 (0.60, 1.36)	0.96 (0.62, 1.47)	237	0.96 (0.76, 1.21)	0.92 (0.73, 1.17)
14 to <21	359	48	1.02 (0.64, 1.62)	1.01 (0.61, 1.68)	141	0.97 (0.74, 1.27)	0.93 (0.70, 1.23)
21+	456	75	1.35 (0.85, 2.13)	1.38 (0.84, 2.28)	191	1.28 (0.98, 1.67)	1.19 (0.90, 1.59)
P-trend			0.65	0.80		0.16	0.35
High-fat dairy							
<3.5	686	80	Reference	Reference	273	Reference	Reference
3.5 to <7	405	67	1.36 (0.97, 1.90)	1.39 (0.98, 1.96)	159	1.02 (0.83, 1.25)	1.00 (0.81, 1.23)
7 to <10.5	284	37	0.99 (0.66, 1.49)	0.99 (0.65, 1.51)	106	0.97 (0.77, 1.23)	0.94 (0.74, 1.20)
10.5+	378	58	1.31 (0.91, 1.90)	1.30 (0.88, 1.92)	165	1.33 (1.08, 1.65)	1.23 (0.99, 1.54)
P-trend			0.27	0.36		<0.01	0.01
Low-fat dairy							
<3.5	509	79	Reference	Reference	235	Reference	Reference
3.5 to <7	328	42	0.85 (0.57, 1.25)	0.91 (0.61, 1.36)	130	0.79 (0.63, 0.99)	0.89 (0.71, 1.13)
7 to <10.5	423	47	0.66 (0.45, 0.97)	0.74 (0.50, 1.09)	155	0.69 (0.56, 0.85)	0.76 (0.61, 0.94)
10.5+	493	74	0.91 (0.63, 1.29)	0.95 (0.65, 1.38)	183	0.74 (0.59, 0.92)	0.78 (0.62, 0.98)
P-trend			0.52	0.47		0.07	0.11
Milk							
<3.5	855	116	Reference	Reference	356	Reference	Reference
3.5 to <7	183	22	0.86 (0.53, 1.38)	0.89 (0.55, 1.45)	61	0.73 (0.55, 0.97)	0.77 (0.58, 1.03)
7+	715	104	0.94 (0.69, 1.26)	0.95 (0.69, 1.29)	286	0.84 (0.70, 0.99)	0.82 (0.69, 0.98)
P-trend			0.99	0.71		0.54	0.43
Skim or low-fat milk							
0	464	75	Reference	Reference	233	Reference	Reference
>0 to <7	647	77	0.80 (0.57, 1.12)	0.90 (0.63, 1.27)	233	0.72 (0.60, 0.87)	0.82 (0.67, 1.00)
7+	642	90	0.80 (0.57, 1.13)	0.89 (0.62, 1.27)	237	0.66 (0.55, 0.81)	0.73 (0.60, 0.89)
P-trend			0.49	0.40		0.02	0.03
Whole milk							
0	1534	194	Reference	Reference	582	Reference	Reference
>0 to <7	170	38	1.42 (0.98, 2.06)	1.29 (0.88, 1.89)	89	1.48 (1.16, 1.88)	1.45 (1.14, 1.84)
7+	49	10	1.40 (0.71, 2.75)	1.26 (0.63, 2.51)	32	1.73 (1.18, 2.52)	1.36 (0.92, 2.01)
P-trend			0.01	0.03		<0.01	<0.01
Total cheese							
<3.5	899	123	Reference	Reference	366	Reference	Reference
3.5 to <7	614	81	0.88 (0.66, 1.18)	0.88 (0.64, 1.20)	241	0.99 (0.84, 1.18)	0.97 (0.81, 1.16)
7+	239	38	1.22 (0.83, 1.78)	1.23 (0.82, 1.86)	96	1.08 (0.85, 1.38)	1.04 (0.81, 1.34)
P-trend			0.81	0.64		0.39	0.67
Cottage or ricotta cheese							
0	761	110	Reference	Reference	302	Reference	Reference
>0 to <2	758	96	0.69 (0.52, 0.92)	0.76 (0.57, 1.03)	300	0.80 (0.67, 0.95)	0.85 (0.72, 1.02)
2+	234	36	0.73 (0.49, 1.10)	0.83 (0.55, 1.26)	101	0.87 (0.68, 1.11)	0.90 (0.71, 1.16)
P-trend			0.29	0.63		0.40	0.53

(*Continued*)

TABLE 2 (*Continued*)

Dairy items (servings/wk)	No. of subjects	No. of CRC deaths	CRC-specific survival, HR (95% CI)		No. of overall deaths	Overall survival, HR (95% CI)	
			Model 1[2]	Model 2[3]		Model 1[2]	Model 2[3]
Cream cheese							
0	1033	146	Reference	Reference	419	Reference	Reference
>0 to <2	598	75	0.78 (0.58, 1.04)	0.81 (0.60, 1.10)	228	0.91 (0.77, 1.08)	0.96 (0.80, 1.14)
2+	112	13	0.77 (0.43, 1.37)	0.71 (0.39, 1.29)	47	0.98 (0.72, 1.34)	0.91 (0.66, 1.26)
P-trend			0.12	0.12		0.78	0.87
Other cheese (American, cheddar, etc.)							
<3.5	1468	193	Reference	Reference	590	Reference	Reference
3.5 to <7	156	21	1.06 (0.67, 1.68)	1.07 (0.66, 1.73)	61	1.07 (0.81, 1.40)	1.11 (0.83, 1.47)
7+	119	20	1.69 (1.05, 2.73)	1.64 (0.99, 2.73)	43	1.09 (0.79, 1.50)	0.93 (0.66, 1.31)
P-trend			0.43	0.43		0.44	0.87
Cream							
0	1113	138	Reference	Reference	455	Reference	Reference
>0 to <2	419	65	1.02 (0.75, 1.40)	1.06 (0.76, 1.47)	161	0.91 (0.75, 1.11)	0.95 (0.78, 1.16)
2+	211	31	1.14 (0.76, 1.71)	1.18 (0.78, 1.80)	78	0.90 (0.70, 1.16)	0.97 (0.75, 1.26)
P-trend			0.52	0.53		0.26	0.35
Regular ice cream							
0	662	77	Reference	Reference	255	Reference	Reference
>0 to <2	753	105	1.04 (0.76, 1.40)	1.08 (0.79, 1.48)	291	0.85 (0.71, 1.01)	0.93 (0.78, 1.12)
2+	338	60	1.39 (0.97, 1.98)	1.51 (1.04, 2.20)	157	1.19 (0.96, 1.46)	1.24 (1.00, 1.54)
P-trend			<0.01	<0.01		<0.01	<0.01
Sherbet, frozen yogurt, or nonfat ice cream							
0	984	135	Reference	Reference	410	Reference	Reference
>0 to <2	530	69	0.83 (0.62, 1.13)	0.90 (0.66, 1.23)	193	0.79 (0.66, 0.94)	0.84 (0.70, 1.01)
2+	229	30	0.99 (0.66, 1.50)	1.06 (0.69, 1.62)	91	0.87 (0.68, 1.10)	0.91 (0.72, 1.17)
P-trend			0.80	0.72		0.46	0.46
Yogurt							
0	1025	144	Reference	Reference	439	Reference	Reference
>0 to <2	432	61	0.93 (0.69, 1.27)	0.99 (0.72, 1.36)	161	0.91 (0.76, 1.10)	1.01 (0.83, 1.22)
2+	296	37	1.00 (0.69, 1.47)	0.99 (0.67, 1.46)	103	1.06 (0.85, 1.33)	1.10 (0.87, 1.38)
P-trend			0.89	0.84		0.96	0.89
Butter							
0	966	137	Reference	Reference	387	Reference	Reference
>0 to <7	567	68	0.91 (0.68, 1.23)	0.97 (0.71, 1.32)	216	1.09 (0.92, 1.30)	1.10 (0.92, 1.31)
7+	220	37	1.26 (0.85, 1.85)	1.28 (0.86, 1.92)	100	1.48 (1.17, 1.87)	1.44 (1.13, 1.83)
P-trend			0.73	0.95		<0.01	0.01

[1]Postdiagnostic intake at least 6 mo (to avoid potential influence of active treatment) but no more than 4 y after diagnosis of colorectal cancer. CRC, colorectal cancer.

[2]Cox model stratified by age at diagnosis (<55, 55–59, 60–64, 65–69, 70–74, and ≥75 y), cancer stage (I, II, III, and unspecified), and study [Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)], with additional adjustments for tumor grade of differentiation (well differentiated, moderately differentiated, poorly differentiated, and unspecified), tumor subsite (proximal colon, distal colon, rectum, and unspecified), year of diagnosis (continuous), time between CRC diagnosis and measurement of dairy food intake assessment (continuous), and prediagnostic intake of total dairy (in quartiles).

[3]Model 1 + postdiagnostic BMI (<23, 23–24.9, 25–27.4, 27.5–29.9, ≥30 kg/m^2), postdiagnostic physical activity (<3, 3–8.9, 9–11.9, 12–17.9, ≥18 metabolic equivalents, h/wk), postdiagnostic regular use of aspirin (yes or no), postdiagnostic smoking (0, 1–9, 10–19, 20–39, ≥40 pack-years), postdiagnostic alcohol consumption (<5, 5–14.9, ≥15 g/d), postdiagnostic intake of total energy (in quartiles), and family history of colorectal cancer (yes or no).

TABLE 3 Stratified analyses of postdiagnostic total dairy intake with survival among patients with colorectal cancer[1]

	CRC-specific survival			Overall survival		
	Servings/wk, HR (95% CI)			Servings/wk, HR (95% CI)		
Characteristic	7 to <14	14 to <21	21+	7 to <14	14 to <21	21+
Study						
HPFS	1.02 (0.60, 1.73)	0.77 (0.39, 1.52)	0.91 (0.47, 1.77)	0.99 (0.75, 1.32)	0.99 (0.70, 1.41)	1.32 (0.95, 1.85)
NHS	0.91 (0.57, 1.44)	1.17 (0.70, 1.97)	1.58 (0.97, 2.57)	0.85 (0.65, 1.12)	0.94 (0.69, 1.28)	1.10 (0.82, 1.48)
Age, y						
<65	0.91 (0.45, 1.83)	1.36 (0.65, 2.86)	2.42 (1.23, 4.78)	0.87 (0.57, 1.35)	0.93 (0.57, 1.52)	1.48 (0.96, 2.29)
65+	0.99 (0.59, 1.67)	0.85 (0.47, 1.55)	0.89 (0.49, 1.63)	0.94 (0.71, 1.25)	0.93 (0.67, 1.27)	1.06 (0.77, 1.47)
Smoking						
Never	2.01 (0.21, 19.6)	1.89 (0.17, 21.4)	2.69 (0.27, 26.6)	1.07 (0.43, 2.69)	0.90 (0.32, 2.54)	0.83 (0.29, 2.42)
Ever	0.98 (0.64, 1.50)	0.96 (0.59, 1.57)	1.42 (0.88, 2.30)	1.04 (0.81, 1.33)	0.99 (0.74, 1.31)	1.35 (1.02, 1.80)
Alcohol consumption, g/d						
<10	0.96 (0.58, 1.59)	1.13 (0.64, 2.00)	1.40 (0.81, 2.42)	0.97 (0.73, 1.29)	0.93 (0.68, 1.29)	1.19 (0.87, 1.63)
10+	0.84 (0.36, 1.95)	0.78 (0.27, 2.19)	1.46 (0.60, 3.56)	0.88 (0.57, 1.38)	1.09 (0.64, 1.84)	1.37 (0.83, 2.27)
AHEI						
<50	0.86 (0.52, 1.43)	1.07 (0.59, 1.92)	0.99 (0.56, 1.74)	0.87 (0.66, 1.15)	0.92 (0.66, 1.28)	1.03 (0.75, 1.41)
50+	1.08 (0.64, 1.81)	1.03 (0.55, 1.90)	1.83 (1.02, 3.25)	0.93 (0.68, 1.26)	0.92 (0.65, 1.31)	1.27 (0.89, 1.80)
BMI, kg/m^2						
<25	1.23 (0.67, 2.27)	1.20 (0.60, 2.37)	1.94 (1.00, 3.75)	0.98 (0.69, 1.39)	0.95 (0.64, 1.42)	1.28 (0.87, 1.89)
25+	0.69 (0.38, 1.22)	0.68 (0.34, 1.36)	0.92 (0.49, 1.71)	0.89 (0.63, 1.24)	0.90 (0.61, 1.31)	1.04 (0.73, 1.50)
Physical activity (METs, h/wk)						
<9	1.41 (0.77, 2.56)	1.53 (0.78, 3.03)	1.98 (1.03, 3.81)	1.09 (0.78, 1.51)	1.11 (0.76, 1.63)	1.37 (0.95, 1.98)
9+	0.57 (0.30, 1.09)	0.78 (0.38, 1.58)	0.98 (0.50, 1.92)	0.74 (0.52, 1.06)	0.79 (0.53, 1.18)	1.06 (0.72, 1.57)
Regular aspirin use						
No	0.90 (0.54, 1.49)	0.98 (0.56, 1.74)	1.30 (0.76, 2.24)	0.91 (0.68, 1.23)	0.88 (0.63, 1.24)	1.06 (0.77, 1.47)
Yes	1.09 (0.54, 2.18)	1.05 (0.46, 2.40)	1.56 (0.73, 3.34)	0.93 (0.63, 1.37)	1.01 (0.65, 1.57)	1.50 (0.99, 2.27)
Family history of CRC						
No	0.89 (0.56, 1.41)	1.11 (0.66, 1.85)	1.43 (0.86, 2.37)	0.86 (0.66, 1.11)	0.96 (0.71, 1.30)	1.15 (0.86, 1.55)
Yes	1.19 (0.46, 3.09)	0.62 (0.19, 2.02)	1.12 (0.40, 3.12)	1.29 (0.75, 2.25)	0.89 (0.48, 1.65)	1.45 (0.81, 2.60)
Cancer subsite						
Colon	1.10 (0.65, 1.86)	1.28 (0.71, 2.32)	1.60 (0.90, 2.83)	0.98 (0.74, 1.29)	0.95 (0.68, 1.32)	1.20 (0.87, 1.64)
Rectum	0.77 (0.37, 1.60)	0.68 (0.29, 1.63)	1.06 (0.50, 2.25)	0.71 (0.44, 1.15)	0.64 (0.38, 1.08)	0.86 (0.52, 1.40)
Cancer stage						
Stage I/II	0.74 (0.45, 1.24)	0.52 (0.26, 1.05)	1.03 (0.57, 1.86)	0.89 (0.68, 1.16)	0.75 (0.54, 1.04)	1.04 (0.75, 1.43)
Stage III	2.09 (1.22, 3.56)	3.07 (1.65, 5.74)	3.26 (1.83, 5.83)	1.27 (0. 90, 1.79)	1.37 (0.90, 2.09)	1.48 (1.02, 2.16)
Postmenopausal hormone use						
Never	1.23 (0.60, 2.52)	1.69 (0.77, 3.71)	3.05 (1.45, 6.41)	1.04 (0.69, 1.57)	1.20 (0.75, 1.90)	1.76 (1.12, 2.77)
Ever	1.17 (0.48, 2.87)	1.07 (0.40, 2.90)	1.41 (0.54, 3.65)	0.85 (0.49, 1.45)	0.82 (0.45, 1.50)	0.82 (0.46, 1.45)
Years since CRC diagnosis						
<5	1.41 (0.72, 2.77)	1.10 (0.55, 2.22)	1.11 (0.57, 2.14)	1.12 (0.69, 1.81)	0.90 (0.53, 1.52)	0.95 (0.58, 1.54)
5+	0.85 (0.45, 1.59)	1.04 (0.51, 2.09)	1.77 (0.93, 3.39)	0.92 (0.69, 1.22)	0.98 (0.71, 1.36)	1.22 (0.89, 1.69)

[1]Postdiagnostic intake at least 6 mo (to avoid potential influence of active treatment) but no more than 4 y after diagnosis of CRC. Cox model stratified by age at diagnosis (<55, 55–59, 60–64, 65–69, 70–74, and 75+ years), cancer stage (I, II, III, and unspecified), and study (NHS and HPFS), with additional adjustments for tumor grade of differentiation (well differentiated, moderately differentiated, poorly differentiated, and unspecified), tumor subsite (proximal colon, distal colon, rectum, and unspecified), year of diagnosis (continuous), time between CRC diagnosis and measurement of dairy food intake assessment (continuous), prediagnostic intake of total dairy (in quartiles), postdiagnostic BMI (<23, 23–24.9, 25–27.4, 27.5–29.9, 30+ kg/m^2), postdiagnostic physical activity (<3, 3–8.9, 9–11.9, 12–17.9, 18+ METs, h/wk), postdiagnostic regular use of aspirin (yes or no), postdiagnostic smoking (0, 1–9, 10–19, 20–39, 40+ pack-years), and postdiagnostic alcohol consumption (<5, 5–14.9, 15+ g/d), except when the factor is the variable for stratification. For CRC-specific survival, the *P* values for interaction were 0.05 for cohort, <0.01 for age, 0.98 for smoking, 0.37 for alcohol, 0.12 for AHEI, 0.37 for BMI, 0.36 for physical activity, 0.67 for regular aspirin use, 0.20 for family history of CRC, 0.69 for cancer subsite, 0.64 for cancer stage, 0.07 for postmenopausal hormone use, and 0.21 for years since CRC diagnosis. For overall survival, the *P* values for interaction were 0.99 for cohort, 0.05 for age, 0.16 for smoking, 0.30 for alcohol, 0.53 for AHEI, 0.48 for BMI, 0.98 for physical activity, 0.41 for regular aspirin use, 0.48 for family history of CRC, 0.46 for cancer subsite, 0.67 for cancer stage, 0.03 for postmenopausal hormone use, and 0.16 for years since CRC diagnosis. AHEI, Alternative Healthy Eating Index; CRC, colorectal cancer; HPFS, Health Professionals Follow-up Study; METs, metabolic equivalents; NHS, Nurses' Health Study.

milk, or cheese (16). However, the literature on the association between dairy intake and CRC survival is limited. The American Cancer Society Cancer Prevention Study-II Nutrition Cohort study examined both pre- and postdiagnostic intake and reported inverse associations of postdiagnostic total dairy (HR: 0.75; 95% CI: 0.56, 1.01) and milk (HR: 0.72; 95% CI: 0.55, 0.94) with all-cause mortality and no association between prediagnostic dairy intake and survival (9). In contrast, the European Investigation into Cancer and Nutrition cohort (EPIC) and the Iowa Women's Health Study (IWH) examined only the prediagnostic intake.

EPIC reported an overall null association between prediagnostic total dairy intake and survival among patients with CRC, a marginal association between milk (HR: 1.21; 95% CI: 0.99, 1.48, Quartile 4 compared with Quartile 1) and CRC-specific mortality, and no association between yogurt or cheese and survival (14). IWH reported associations of prediagnostic whole milk (HR: 1.20; 95% CI: 1.13, 1.27) and low or nonfat milk (HR: 0.91; 95% CI: 0.86, 0.96) with all-cause mortality (15). We observed similar results in most of the associations, different in a few. Moreover, it was concordant that the association of prediagnostic dairy intake with survival was weaker than that of postdiagnosis intake.

High-fat dairy intake was found to be positively and low-fat dairy inversely associated with CRC-specific and overall mortality in this study. Individual items from the high-fat category (whole milk, American or cheddar cheese, ice cream, and butter) showed a positive association, whereas those from the low-fat category (skim or low-fat milk, cottage or ricotta cheese, and sherbet, frozen yogurt, or nonfat ice cream) showed an inverse association. The aforementioned associations remained essentially unchanged after adjustment for or stratification by important lifestyle factors or confounders, including BMI (28, 29), physical activity (30, 31), alcohol (32) or tobacco use (33, 34), total energy intake (35), or AHEI (36). Obesity and Western dietary pattern are both risk factors of CRC (28, 37), and underlying mechanisms include insulin resistance, low-grade inflammation, changes in gut microbiota, and fat-derived hormonal imbalance (38, 39). Although important nutrients from dairy such as calcium and vitamin D had been observed to be inversely associated with CRC mortality (8, 9, 40), the potential beneficial effect may be reduced by fat or fat-related components. It has been observed that the fasting LDL cholesterol was higher after intake of butter than cheese, and postprandial glucose was higher after cheese than milk, indicating a different effect of fat from different types of dairy products (41). However, it is still controversial whether postdiagnostic fat intake is detrimental to CRC survival, given that generally, neither total nor subtypes of dietary fat were associated with mortality (42). Furthermore, although scientific evidence supports some benefits of dairy products in human health (27, 43–45), dairy products were found to be associated with risk of ovarian cancer (46) and prostate cancer (47), suggesting a cautious recommendation of dairy intake.

Although overall there was no significant association found between total dairy intake and CRC-specific mortality, in subgroup analyses, positive associations were detected among those who were younger, had a lower BMI, had a higher AHEI score, were less physically active, were at cancer stage III, and were females who reported never using postmenopausal hormone. Previous studies observed that sociodemographic characteristics, behaviors, and cancer stage, subtype, and site may modify the associations between exposure and CRC survival (8, 48). It is of further research interest both in populations and in the laboratory to explore whether and why the associations between dairy products and CRC survival vary across certain populations.

The strengths of this study include a large sample size of CRC survivors across the United States, with detailed data on dairy products and important covariates collected. This study also has several limitations. The measurements of dairy product intake and covariates were collected through self-reported questionnaires and thus were inevitably prone to measurement errors, although the FFQs had been validated with reasonable correlations. Second, the participants were primarily white people working as health professionals, and they may differ from the general population with regard to socioeconomic status and lifestyles, including dietary patterns and other behavioral factors, which limits the generalizability of the conclusions. Third, information on treatment after CRC diagnosis was limited. We dealt with this problem by stratification by cancer stage and year of diagnosis, since the treatments for CRC would be under standard protocol based on stage at each time period. Fourth, as an observational study, the association observed between dairy intake and mortality might have been influenced by residual confounding. The socioeconomic status was not fully collected and controlled for study participants. Of note, low-fat dairy tended to be associated with healthful behaviors and high-fat dairy with less healthful behaviors, and we controlled for various behavioral and lifestyle factors available, including smoking, alcohol drinking, and physical activity; adjustment for these multiple factors did not alter the results appreciably. Moreover, we further included marital status, highest degree earned, and husband's degree in analyses for NHS, as well as included marital status in analyses for HPFS and the pooled analyses. The results from regression analyses did not change significantly. Also, as a study conducted among healthy health care workers nested within 2 cohorts instead of specifically among patients with CRC in a clinical setting, complications of CRC were not collected or analyzed as covariates. However, we partly dealt with the potential impact from complications on dairy intake by considering a time lag: dairy information assessed within 6 mo of CRC diagnosis was excluded to avoid short-term disturbance from diagnosis, treatment, or complications.

In conclusion, an overall null association was observed between postdiagnostic dairy product intake and CRC survival. However, higher intake of high-fat dairy, including whole milk and American or cheddar cheese, showed a potential effect on increased mortality, whereas low-fat dairy, including skim or nonfat milk and cottage or ricotta cheese, showed a potential protective effect. Further study is needed, and a moderate intake of high-fat dairy after CRC diagnosis is suggested.

We thank the participants and staff of the NHS and the HPFS for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, and WY. The authors assume full responsibility for analyses and interpretation of these data.

The authors' contributions were as follows—XZ: designed research; XL, WY, KW, SO, EG, and XZ: conducted research; XL and WY: analyzed data; XL: wrote the first draft of the paper; SO, WW, NH, ATC, Z-FZ, JAM, EG, and XZ: revised the draft or provided comments or suggestions; XZ: had primary responsibility for final content; and all authors: read and approved the final manuscript.

Author disclosure: The authors report no conflicts of interest.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending approval from each participating cohort studies.

References

1. International Agency for Research on Cancer. GLOBOCAN 2020: new global cancer data [Internet]. 2020. [Cited 2021 Jan 6]. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf
2. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut 2017;66:683–91.
3. Smith RA, Andrews KS, Brooks D, Fedewa SA, Manassaram-Baptiste D, Saslow D, Brawley OW, Wender RC. Cancer screening in the United States, 2017: a review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin 2017;67: 100–21.
4. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, Bandera EV, Hamilton KK, Grant B, McCullough M, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012;62:242–74.
5. WHO. Global and regional food consumption patterns and trends [Internet]. WHO [cited 2019 Dec 13]. Available from: https://www.who.int/nutrition/topics/3_foodconsumption/en/index4.html
6. Bentley J. U.S. trends in food availability and a dietary assessment of loss-adjusted food availability, 1970–2014.EIB-166, U.S. Department of Agriculture, Economic Research Service, January 2017. [Cited 2019 Dec 9]. Available from: https://ageconsearch.umn.edu/record/253947
7. Astrup A, Rice Bradley BH, Brenna JT, Delplanque B, Ferry M, Torres-Gonzalez M. Regular-fat dairy and human health: a synopsis of symposia presented in Europe and North America (2014–2015). Nutrients 2016;8:463.
8. Yang W, Ma Y, Smith-Warner S, Song M, Wu K, Wang M, Chan AT, Ogino S, Fuchs CS, Poylin V, et al. Calcium intake and survival after colorectal cancer diagnosis. Clin Cancer Res 2018;25:1980–8.
9. Yang B, McCullough ML, Gapstur SM, Jacobs EJ, Bostick RM, Fedirko V, Flanders WD, Campbell PT. Calcium, vitamin D, dairy products, and mortality among colorectal cancer survivors: the Cancer Prevention Study-II Nutrition Cohort. J Clin Oncol 2014;32: 2335–43.
10. Giovannucci E, Liu Y, Rimm EB, Hollis BW, Fuchs CS, Stampfer MJ, Willett WC. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst 2006;98: 451–9.
11. Ng K, Wolpin BM, Meyerhardt JA, Wu K, Chan AT, Hollis BW, Giovannucci EL, Stampfer MJ, Willett WC, Fuchs CS. Prospective study of predictors of vitamin D status and survival in patients with colorectal cancer. Br J Cancer 2009;101:916–23.
12. Ng K, Nimeiri HS, McCleary NJ, Abrams TA, Yurgelun MB, Cleary JM, Rubinson DA, Schrag D, Miksad R, Bullock AJ, et al. Effect of high-dose vs standard-dose vitamin D3 supplementation on progression-free survival among patients with advanced or metastatic colorectal cancer: the SUNSHINE Randomized Clinical Trial. JAMA 2019;321:1370–9.
13. Urashima M, Ohdaira H, Akutsu T, Okada S, Yoshida M, Kitajima M, Suzuki Y. Effect of vitamin D supplementation on relapse-free survival among patients with digestive tract cancers: the AMATERASU randomized clinical trial. JAMA 2019;321:1361–9.
14. Dik VK, Murphy N, Siersema PD, Fedirko V, Jenab M, Kong SY, Hansen CP, Overvad K, Tjønneland A, Olsen A, et al. Prediagnostic intake of dairy products and dietary calcium and colorectal cancer survival—results from the EPIC cohort study. Cancer Epidemiol Prev Biomark 2014;23:1813–23.
15. Um CY, Prizment A, Hong C-P, Lazovich D, Bostick RM. Associations of calcium and dairy product intakes with all-cause, all-cancer, colorectal cancer and CHD mortality among older women in the Iowa Women's Health Study. Br J Nutr 2019;121:1188–200.
16. Aune D, Lau R, Chan DSM, Vieira R, Greenwood DC, Kampman E, Norat T. Dairy products and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. Ann Oncol 2012;23:37–45.
17. Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, Hennekens CH. Test of the National Death Index. Am J Epidemiol 1984;119:837–9.
18. Chen M, Sun Q, Giovannucci E, Mozaffarian D, Manson JE, Willett WC, Hu FB. Dairy consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. BMC Med 2014;12:215.
19. Ding M, Li J, Qi L, Ellervik C, Zhang X, Manson JE, Stampfer M, Chavarro JE, Rexrode KM, Kraft P, et al. Associations of dairy intake with risk of mortality in women and men: three prospective cohort studies. BMJ 2019;367:l6204.
20. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.
21. Salvini S, Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B, Willett WC. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol 1989;18:858–67.
22. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–26; discussion 1127–36.
23. Feskanich D, Rimm EB, Giovannucci EL, Colditz GA, Stampfer MJ, Litin LB, Willett WC. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc 1993;93:790–6.
24. Michels KB, Willett WC. Self-administered semiquantitative food frequency questionnaires: patterns, predictors, and interpretation of omitted items. Epidemiology 2009;20:295–301.
25. Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, Stampfer MJ, Willett WC. Alternative dietary indices both strongly predict risk of chronic disease. J Nutr 2012;142:1009–18.
26. Abrams DI. Milking the evidence: diet does matter. J Clin Oncol 2014;32:2290–2.
27. Thorning TK, Raben A, Tholstrup T, Soedamah-Muthu SS, Givens I, Astrup A. Milk and dairy products: good or bad for human health? An assessment of the totality of scientific evidence. Food Nutr Res 2016;60:32527.
28. Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. Gut 2013;62:933–47.
29. Caan BJ, Meyerhardt JA, Kroenke CH, Alexeeff S, Xiao J, Weltzien E, Feliciano EC, Castillo AL, Quesenberry CP, Kwan ML, et al. Explaining the obesity paradox: the association between body composition and colorectal cancer survival (C-SCANS study). Cancer Epidemiol Biomark 2017;26:1008–15.
30. Van Blarigan EL, Meyerhardt JA. Role of physical activity and diet after colorectal cancer diagnosis. J Clin Oncol 2015;33:1825–34.
31. Walter V, Jansen L, Knebel P, Chang-Claude J, Hoffmeister M, Brenner H. Physical activity and survival of colorectal cancer patients: population-based study from Germany. Int J Cancer 2017;140: 1985–97.
32. Kim Y, Je Y, Giovannucci EL. Association between alcohol consumption and survival in colorectal cancer: a meta-analysis. Cancer Epidemiol Biomark 2019;28:1891–901.
33. Liang PS, Chen T-Y, Giovannucci E. Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. Int J Cancer 2009;124:2406–15.
34. Yang B, Jacobs EJ, Gapstur SM, Stevens V, Campbell PT. Active smoking and mortality among colorectal cancer survivors: the Cancer Prevention Study II nutrition cohort. J Clin Oncol 2015;33: 885–93.
35. Dray X, Boutron-Ruault M-C, Bertrais S, Sapinho D, Benhamiche-Bouvier A-M, Faivre J. Influence of dietary factors on colorectal cancer survival. Gut 2003;52:868–73.
36. Fung TT, Kashambwa R, Sato K, Chiuve SE, Fuchs CS, Wu K, Giovannucci E, Ogino S, Hu FB, Meyerhardt JA. Post diagnosis diet quality and colorectal cancer survival in women. PLoS One 2014;9:e115377.
37. Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz LB, Hu FB, Mayer RJ, Nelson H, Whittom R, Hantel A, Thomas J, et al. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. JAMA 2007;298:754–64.
38. O'Keefe SJD. Diet, microorganisms and their metabolites, and colon cancer. Nat Rev Gastroenterol Hepatol 2016;13:691–706.
39. Beyaz S, Mana MD, Roper J, Kedrin D, Saadatpour A, Hong S-J, Bauer-Rowe KE, Xifaras ME, Akkad A, Arias E, et al. High-fat diet enhances stemness and tumorigenicity of intestinal progenitors. Nature 2016;531:53–8.
40. Yuan C, Sato K, Hollis BW, Zhang S, Niedzwiecki D, Ou F-S, Chang I-W, O'Neil BH, Innocenti F, Lenz H-J, et al. Plasma 25-hydroxyvitamin D levels and survival in patients with advanced or metastatic colorectal

cancer: findings from CALGB/SWOG 80405 (Alliance). Clin Cancer Res. 2019;25(24):7497–505.
41. Tholstrup T, Høy C-E, Andersen LN, Christensen RDK, Sandström B. Does fat in milk, butter and cheese affect blood lipids and cholesterol differently? J Am Coll Nutr 2004;23:169–76.
42. Van Blarigan EL, Ou F-S, Niedzwiecki D, Zhang S, Fuchs CS, Saltz L, Mayer RJ, Venook A, Ogino S, Song M, et al. Dietary fat intake after colon cancer diagnosis in relation to cancer recurrence and survival: CALGB 89803 (Alliance). Cancer Epidemiol Biomark 2018;27: 1227–30.
43. Soedamah-Muthu SS, Verberne LDM, Ding EL, Engberink MF, Geleijnse JM. Dairy consumption and incidence of hypertension: a dose-response meta-analysis of prospective cohort studies. Hypertens Dallas Tex 2012;60:1131–7.
44. Dong J-Y, Zhang L, He K, Qin L-Q. Dairy consumption and risk of breast cancer: a meta-analysis of prospective cohort studies. Breast Cancer Res Treat 2011;127:23–31.
45. Genkinger JM, Wang M, Li R, Albanes D, Anderson KE, Bernstein L, van den Brandt PA, English DR, Freudenheim JL, Fuchs CS, et al. Dairy products and pancreatic cancer risk: a pooled analysis of 14 cohort studies. Ann Oncol 2014;25:1106–15.
46. Liu J, Tang W, Sang L, Dai X, Wei D, Luo Y, Zhang J. Milk, yogurt, and lactose intake and ovarian cancer risk: a meta-analysis. Nutr Cancer 2015;67:68–72.
47. Aune D, Navarro Rosenblatt DA, Chan DSM, Vieira AR, Vieira R, Greenwood DC, Vatten LJ, Norat T. Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort studies. Am J Clin Nutr 2015;101:87–117.
48. Jayasekara H, English DR, Haydon A, Hodge AM, Lynch BM, Rosty C, Williamson EJ, Clendenning M, Southey MC, Jenkins MA, et al. Associations of alcohol intake, smoking, physical activity and obesity with survival following colorectal cancer diagnosis by stage, anatomic site and tumor molecular subtype. Int J Cancer 2018;142: 238–50.