ORIGINAL INVESTIGATION

Dairy Food, Calcium, and Risk of Cancer in the NIH-AARP Diet and Health Study

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Background: Dairy food and calcium intakes have been hypothesized to play roles that differ among individual cancer sites, but the evidence has been limited and inconsistent. Moreover, their effect on cancer in total is unclear.

Methods: Dairy food and calcium intakes in relation to total cancer as well as cancer at individual sites were examined in the National Institutes of Health (NIH)-AARP (formerly known as the American Association of Retired Persons) Diet and Health Study. Intakes of dairy food and calcium from foods and supplements were assessed with a food frequency questionnaire. Incident cancer cases were identified through linkage with state cancer registries. A Cox proportional hazard model was used to estimate relative risks and 2-sided 95% confidence intervals (CIs).

Results: During an average of 7 years of follow-up, we identified 36 965 and 16 605 cancer cases in men and women, respectively. Calcium intake was not related to total cancer in men but was nonlinearly associated with total cancer in women: the risk decreased up to approximately 1300 mg/d, above which no further risk reduction was observed. In both men and women, dairy food and calcium intakes were inversely associated with cancers of the digestive system (multivariate relative risk for the highest quintile of total calcium vs the lowest, 0.84; 95% CI, 0.77-0.92 in men, and 0.77; 95% CI, 0.69-0.91 in women). Decreased risk was particularly pronounced with colorectal cancer. Supplemental calcium intake was also inversely associated with colorectal cancer risk.

Conclusion: Our study suggests that calcium intake is associated with a lower risk of total cancer and cancers of the digestive system, especially colorectal cancer.

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Because of the benefit of calcium on bone health,[1] dietary guidance has emphasized intakes of both calcium and dairy food. For example, the Institute of Medicine recommends 1200 mg/d of calcium for adults aged 50 years and older,[1] and the 2005 dietary guidelines for Americans[2] recommend 3 cups per day of fat-free or low-fat dairy food.

The role of dairy food and calcium intakes in cancer, however, has engendered considerable controversy owing to observations from epidemiologic studies of protective, null, and even positive associations for different organ sites.[3-7] Dairy food and calcium intakes have been consistently inversely associated with colorectal cancer,[3] whereas few studies have suggested possible inverse associations with lung and breast cancer.[4,5] On the other hand, positive associations have been reported for prostate and ovarian cancer.[6,7]

Because of limited evidence on the relationship of dairy food and calcium intakes to cancers at individual sites, especially cancers with a relatively low incidence, it has been difficult to assess the overall effect of dairy food and calcium intakes on total cancer. Therefore, in a large cohort of men and women, we examined whether intakes of dairy food and calcium were associated with risk of total cancer as well as cancer at multiple individual sites.

METHODS

STUDY POPULATION

The National Institutes of Health (NIH)-AARP (formerly known as the American Association of Retired Persons) Diet and Health Study, a collaboration between the NIH and AARP, mailed a questionnaire to AARP members aged 50 to 71 years who resided in 1 of 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia, and Detroit, Michigan) in 1995 and 1996.[8] Among 567 169 participants who returned questionnaires, we excluded individuals who (1) provided duplicate questionnaires (n=179); (2) requested to be withdrawn (n=6); (3) had moved out of the study area or died before baseline (n=582); (4) indicated that they were proxies for the intended respondents (n=15 760); (5) had any

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prevalent cancer except nonmelanoma skin cancer at baseline (n=51 193); and (6) had reported end-stage renal disease at baseline (n=997). Also, we excluded individuals who reported extreme intakes (greater than twice the interquartile ranges above the 75th percentile or below the 25th percentile of sex-specific log-transformed intake) of total energy (n=4417) and calcium from foods (n=1225). After these exclusions, the analytic cohort consisted of 293 907 men and 198 903 women. For analyses of ovarian and endometrial cancer, we excluded women who reported, respectively, a history of oophorectomy (n=43 536) and hysterectomy (n=81 025) at baseline. The study was approved by the National Cancer Institute Special Studies Institutional Review Board.

DIETARY AND RISK FACTOR ASSESSMENT

At baseline in 1995 and 1996, dietary intake was assessed with a self-administered 124-item food frequency questionnaire (FFQ), an earlier grid-based version of the Diet History Questionnaire developed at the National Cancer Institute.[9] Participants were asked to report their usual frequency of intake and portion size over the last 12 months using 10 predefined frequency categories ranging from "never" to "6+ times per day" for beverages and from "never" to "2+ times per day" for solid foods as well as 3 categories of portion size. The food items, portion sizes, and nutrient database were constructed using the US Department of Agriculture's 1994-1996 Continuing Survey of Food Intakes by Individuals.[10,11] The FFQ also asked about frequency and types of multivitamins and frequency and dosage of individual calcium supplements, including calcium-containing antacids (eg, Tums). Calcium intake was estimated from foods only (dietary calcium) and from foods and supplements combined (total calcium). Dietary calcium intake was adjusted for total energy intake using the residual method.[12]

Dairy food and its serving sizes were defined by the Pyramid Servings Database corresponding to the 1994-1996 Continuing Survey of Food Intakes by Individuals, which used a recipe file to disaggregate food mixtures into their component ingredients and assigned them to food groups. One serving of dairy food was defined according to standard portion sizes developed by the US Department of Agriculture, such as 1 cup of milk or yogurt, 1.5 oz of natural cheese, or 2 oz of processed cheese.[13] We did not consider butter a dairy food because it has not generally been included in the dairy food category in previous studies and was not a major contributor to calcium intake. The FFQ used in the study was calibrated against 2 nonconsecutive 24-hour dietary recalls in 1953 AARP participants.[14] The energy-adjusted correlation coefficient of dietary calcium intake between a FFQ and the reference method was 0.63 in men and 0.64 in women.

In the baseline questionnaire, we also asked about demographic characteristics, current body weight and height, medical history, family history of cancer, and lifestyle factors, including frequency of vigorous physical activity that lasted at least 20 minutes, smoking status, time since quitting smoking, and smoking dose. In a subsequent questionnaire mailed in 1996 and 1997, we asked for a detailed medical history, including medication use and prostate cancer screening using a prostate-specific antigen (PSA) test.

CANCER ASCERTAINMENT

During follow-up from 1995 to 2003, cancer cases were identified through probabilistic linkage with a cancer registry database from the original 8 states and 3 additional states (Arizona, Nevada, and Texas). We expanded the cancer ascertainment areas to follow up participants who moved to those states. The cancer registries are certified by the North American Association of Central Cancer Registries as being at least 90% complete within 2 years of cancer occurrence. Our case ascertainment method has been described in a previous study, which demonstrated that approximately 90% of cancers were identified through the registries.[15] Vital status was ascertained through annual linkage of the cohort to the Social Security Administration Death Master File in the United States, follow-up searches of the National Death Index Plus for participants who matched to the Social Security Administration Death Master File, cancer registry linkage, questionnaire responses, and responses to other mailings.

Incident cancer cases were invasive and consisted only of the first malignant neoplasm diagnosed during the follow-up period if multiple cancers had been diagnosed in the same participant. We defined cancers using the Surveillance Epidemiology and End Results site recode and the *International Classification of Diseases for Oncology, Third Edition,*[16] code: head and neck (C000-C009, C019-C119, C129-C140, C142-C148, C300-C301, C310-C329, C339-C349, C381-C384, C388, C390, C398, and C399), esophageal (C150-C159), stomach (C160-C169), colorectal (C180-C189, C199, C209, and C260), liver (C220 and C221), pancreatic (C250-C259), lung (C340-C349), breast (C500-C509), ovarian (C569), endometrial (C540-C549 and C559), prostate (C619), bladder (C670-C679), kidney (C649 and C659), thyroid (C739), and brain (C710-C719) cancer. Non-Hodgkin lymphoma (NHL), leukemia, and myeloma were also defined by the Surveillance Epidemiology and End Results Program. Total cancer included those cancers listed above, skin cancer (excluding basal and squamous cell cancer), other miscellaneous cancers, and unspecified cancers. We also grouped cancers by anatomical area: head and neck, digestive system (C150-C189, C199, C209-C212, C218, C220-C221, C239-C260, C268-C269, C480-C482, and C488); respiratory system, excluding larynx (C300-C301, C310-C319, C339-C349, C381-C384, C388, C390, C398, and C399); reproductive system (men: C600-C609, C619-C639; women: C510-C519, C529-C549, C559, and C569-C589); urinary system (C649, C659, and C669-C689); brain and other nervous systems (C700-C729); endocrine system (C739-C759, and C379); and others.

STATISTICAL ANALYSIS

We estimated relative risks (RRs) and 2-sided 95% confidence intervals (CIs) with the Cox proportional hazards model[17] using the SAS PROC PHREG procedure.[18] We calculated person-years of follow-up time from the date of the baseline questionnaire until the date of cancer diagnosis, death, move out of the registry areas, or end of follow-up (December 31, 2003), whichever occurred first. We confirmed that the proportional hazards assumption was met for the main exposures and covariates by including interaction terms with time and using the Wald χ^2 procedure to test whether all coefficients equaled 0. For dairy food analyses, we used a nutrient density model, in which daily intake was expressed as number of pyramid servings per 1000 kcal of total energy intake. The RRs were estimated according to sex-specific quintiles of dairy food and dietary and total calcium intakes. Supplemental calcium intake was categorized into 4 groups (0, >0-<400, 400-<1000, and ≥1000 mg/d). We performed a test for linear trend across quintiles and categories of intake using the median value in each quintile or category.

In multivariate models, we adjusted for potential risk factors pertinent to individual cancers and listed covariates for site-specific cancers in table footnotes. Potential risk factors examined were race/ethnicity; education; marital status; body mass index; family history of cancer; vigorous physical activity; smoking status; time since quitting smoking; smoking dose; personal history of hypertension and diabetes; antacid use; consumption

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Table 1. Selected Characteristics of Study Participants by Categories of Dairy Food and Total Calcium Intakes

	Dairy Foods				Total Calcium[a]			
	Men		Women		Men		Women	
Variable	Quintile 1	Quintile 5	Quintile 1	Quintile 5	Quintile 1	Quintile 5	Quintile 1	Quintile 5
Dairy food,[b] servings per 1000 kcal	0.2	1.4	0.2	1.6	0.3	1.4	0.3	1.2
Dietary calcium,[b] mg/d	496	1325	428	1157	491	1239	451	925
Supplemental calcium,[b] mg/d	141	149	356	388	20	398	29	1037
White, non-Hispanic, %	87	94	82	93	90	94	84	94
College and postcollege, %	40	45	27	32	39	48	23	37
Married, %	83	84	45	41	84	84	45	45
BMI[b]	27.1	27.3	26.8	26.7	27.3	27.1	27.5	25.8
Family history of any cancer, %	46	47	50	51	47	47	50	52
Current smokers, %	13	10	19	12	15	8	21	9
>20 Cigarettes per day among ever smokers,%	50	47	31	28	50	48	32	31
Quit smoking ≥10 y ago among former smokers, %	70	72	57	63	69	73	55	66
Physical activity ≥5 times/wk, %	21	22	15	18	17	25	11	22
Personal history of diabetes, %	8	13	7	9	7	12	7	5
Personal history of hypertension, %	42	40	41	40	39	36	41	33
Antacid use, %	22	33	19	27	30	32	25	34
Current MHT use, %	NA	NA	41	45	NA	NA	35	54
Multivitamin use, %	49	54	54	64	26	71	30	79
Alcohol consumption, g/d[b]	31	9	9	4	32	10	9	5
Fruits and vegetables, servings per 1000 kcal[b]	3.7	3.4	4.7	4.1	3.1	3.8	3.9	4.8
Red meat, g/1000 kcal[b]	41	32	32	24	45	30	37	23
Whole grains, servings per 1000 kcal[b]	0.6	0.7	0.6	0.7	0.5	0.8	0.6	0.7
Total fat, % of energy[b]	30	29	31	27	31	28	33	27
Total folate, μg/d[b]	606	672	573	629	455	794	415	751
Total energy, kcal/d[b]	2065	1959	1542	1545	2044	2035	1594	1538

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MHT, menopausal hormone therapy; NA, not applicable.

[a] From diet and supplements combined.

[b] Mean value.

of alcohol and total beverages; intake of fruits and vegetables, red meat, whole grains, tomatoes, total fat, protein, folate, α-linoleic acid, selenium, and total energy; PSA test in men; menopausal hormone therapy and duration; parity; oral contraceptive use; age at menopause; and history of oophorectomy and hysterectomy in women. Dietary and supplemental calcium intakes were mutually adjusted in the multivariate models.

We assigned missing responses in most of the covariates (missingness <4%) to their respective reference group after checking that cancer risk in individuals with such missing values did not statistically significantly differ from that of individuals in the reference group using a Wald statistic. However, we created an indicator variable for missing responses for smoking, antacid use, personal history of hypertension, and PSA test because individuals with missing responses in those variables showed a significantly different risk of cancer than their respective reference group. In sensitivity analyses, we analyzed the data using an indicator variable for missing responses in each covariate,[19,20] excluding participants with missing responses in any covariate.[21] We found that the results from these methods were similar to those of the main analyses.

We examined whether the associations for dairy food and calcium intakes differed by sex by including a cross-product term of sex and intake of dairy food or calcium, and no significant interaction was observed. We also tested whether dairy food and total calcium intakes were log-linearly associated with risk of total cancer by comparing a nonparametric regression curve obtained using restricted cubic splines with the linear model.[22] We used the likelihood ratio test and visual inspection of the restricted cubic splines. We identified the number and location of the knots through a stepwise selection process.

RESULTS

During 3 383 377 person-years of follow-up, we identified 36 965 cancer cases in men and 16 605 cancer cases in women. The 10th to 90th percentiles of dietary and total calcium and dairy food intakes were 478 to 1247 mg/d, 526 to 1530 mg/d, and 0.3 to 2.9 servings per day, respectively, in men and 409 to 1101 mg/d, 494 to 1881 mg/d, and 0.3 to 2.7 servings per day, respectively, in women. Dairy food intake was positively correlated with dietary calcium intake (r=0.83 in men and 0.82 in women) and total calcium intake (r=0.68 in men and 0.47 in women), and dietary calcium intake was also positively correlated with total calcium intake (r=0.83 in men and 0.60 in women). The prevalence of calcium-containing multivitamin use was 49% in men and 57% in women, and the prevalence of individual calcium supplement use (≥4 times/wk) was 14% in men and 41% in women.

Compared with participants in the lowest quintile of dairy food or total calcium intake, participants in the highest quintile were more likely to be white, non-Hispanic; college educated; physically active; and current menopausal hormone therapy users if female, but they were less

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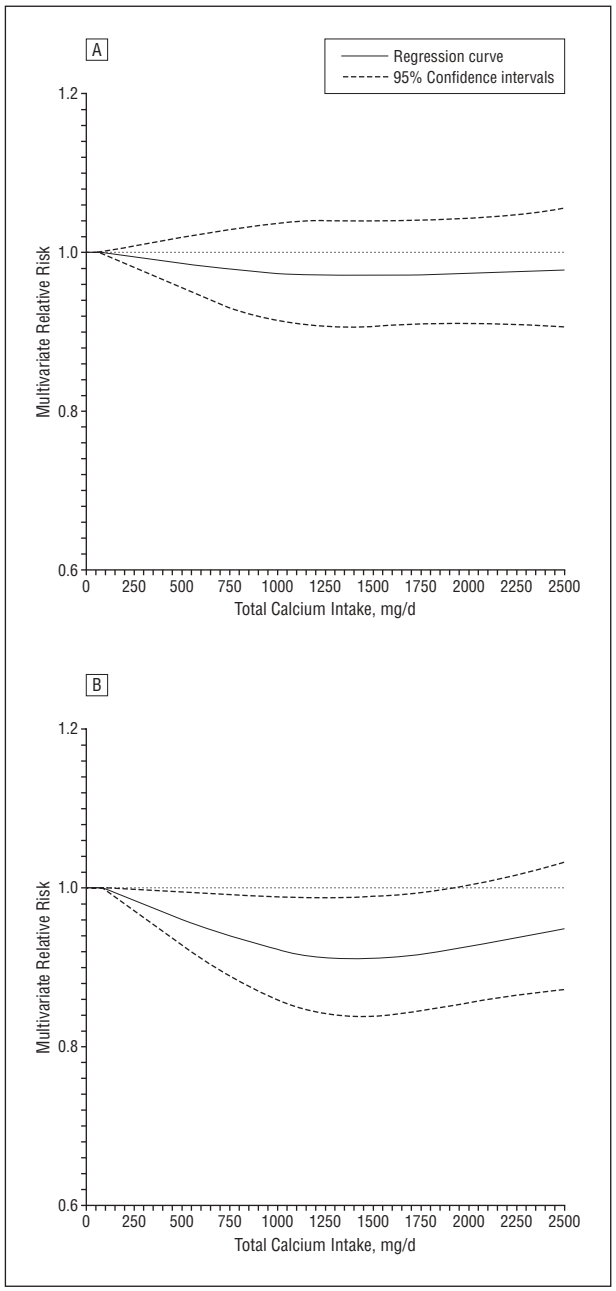

Figure 1. Nonparametric regression curve for the association between total calcium intake and risk of all cancers for men (A) and women (B). Both models were adjusted for race/ethnicity, education, marital status, body mass index, family history of cancer, vigorous physical activity, smoking status, time since quitting smoking, smoking dose, antacid use, personal history of diabetes and hypertension, alcohol consumption, and intakes of fat, red meat, fruits and vegetables, whole grains, protein, beverages, folate, tomatoes, α-linolenic acid, selenium, and total energy. The model for men was also adjusted for prostate-specific antigen test, and the model for women was also adjusted for age at menopause, parity, oral contraceptive use, menopausal hormone therapy use, and duration of menopausal hormone therapy use.

likely to smoke cigarettes and to drink alcohol (**Table 1**). Women in the highest quintile of total calcium intake had a lower body mass index than those in the lowest quintile.

Total calcium intake was not associated with risk of total cancer incidence in men, but it was nonlinearly associated with the risk of total cancer incidence in women (*P* for nonlinearity, .05, **Figure 1**). In nonparametric regression analyses, the RRs for total cancer incidence in women decreased up to approximately 1300 mg/d of total calcium intake, and no further risk reduction was observed above 1300 mg/d. The association between total calcium intake and risk of total cancer did not differ by cancer stages or cancer grades (data not shown). In a secondary analysis excluding nonaggressive prostate cancer that contributed to a large proportion of total cancer cases, we observed a weak inverse association between total calcium intake and total cancer incidence in men. With the lowest quintile of total calcium intake as reference, the multivariate RRs for total cancer incidence in the second through the highest quintile were 1.00, 0.98, 0.99, and 0.96 (95% CI, 0.92-1.02; *P* for trend, .16) in men.

Dairy food and dietary and supplemental calcium intakes were not related to total cancer incidence in men, whereas dietary calcium, but not dairy food or supplemental calcium, intake was inversely related to total cancer incidence in women (**Table 2** and **Table 3**). When cancers diagnosed during the first 2 years of follow-up were excluded, the association with total cancer became slightly stronger for dietary calcium intake in men (multivariate RR in the highest quintile vs the lowest quintile [$RR_{Q5\ vs\ Q1}$] = 0.96; 95% CI, 0.92-1.00; *P* for trend, .05 [n = 27 720 cases]) and for dairy food intake in women (multivariate $RR_{Q5\ vs\ Q1}$ = 0.93; 95% CI, 0.88-0.99; *P* for trend, .01 [n = 12 395 cases]).

Death from total cancer and death from cardiovascular disease in relation to dairy food and calcium intakes were examined. Dairy food and dietary, supplemental, and total calcium intakes were not associated with total cancer mortality in both men (n = 8787 deaths) and women (n = 4479 deaths): the multivariate $RR_{Q5\ vs\ Q1}$ for dairy food and total calcium intakes was 1.05 (95% CI, 0.97-1.14) and 1.02 (95% CI, 0.94-1.11), respectively, in men and 0.93 (95% CI, 0.84-1.04) and 0.97 (95% CI, 0.87-1.08), respectively, in women.

Total calcium intake was related to a 16% lower risk of cancers of the digestive system in men (multivariate $RR_{Q5\ vs\ Q1}$ = 0.84; 95% CI, 0.77-0.92) and a 23% lower risk in women (multivariate $RR_{Q5\ vs\ Q1}$ = 0.77; 95% CI, 0.69-0.91, **Figure 2**). Similar inverse association with cancers of the digestive system was observed for dairy food intake in both men and women (data not shown). Total calcium and dairy food intakes were not associated with cancer in any other anatomical systems.

For specific cancers in men, dairy food intake was inversely associated with cancers of the head and neck, esophagus, stomach, colorectum, and bladder, whereas it was positively associated with prostate cancer (Table 2). Dietary and supplemental calcium intakes were also significantly inversely associated with colorectal cancer. Total calcium intake was significantly related to a lower risk of colorectal cancer and showed a weak inverse association with kidney cancer. On the other hand, total calcium intake was not related to prostate cancer.

In women, intake of dairy food was significantly inversely associated with colorectal cancer and showed a weak inverse association with stomach cancer (Table 3). Dietary, supplemental, and total calcium intakes were also inversely related to colorectal cancer. Supplemental cal-

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Table 2. Multivariate RRs[a] and 95% CIs of Cancer for Categories of Dairy Food and Dietary, Supplemental, and Total Calcium Intakes in Men

Variable	Categories, Multivariate RR (95% CI)[b]					*P* Value for Trend
	1	2	3	4	5	
All cancers[c] (N=36 965[d])						
Dairy foods	1 [Reference]	1.02 (0.98-1.05)	1.02 (0.99-1.06)	1.04 (1.01-1.08)	1.03 (0.99-1.07)	.19
Dietary calcium	1 [Reference]	1.00 (0.96-1.03)	0.99 (0.96-1.03)	1.01 (0.97-1.05)	1.00 (0.96-1.05)	.76
Supplemental calcium	1 [Reference]	0.97 (0.94-1.00)	0.97 (0.93-1.01)	0.96 (0.90-1.03)	NA	.18
Total calcium	1 [Reference]	0.99 (0.96-1.03)	0.99 (0.96-1.03)	0.95 (0.96-1.03)	0.99 (0.95-1.03)	.74
Head and neck cancer[e] (n=1038)						
Dairy foods	1 [Reference]	0.98 (0.82-1.18)	0.89 (0.74-1.08)	0.87 (0.72-1.06)	0.84 (0.69-1.02)	.05
Dietary calcium	1 [Reference]	0.93 (0.78-1.12)	0.84 (0.69-1.02)	0.92 (0.76-1.12)	0.78 (0.64-0.96)	.03
Supplemental calcium	1 [Reference]	1.21 (1.06-1.38)	1.22 (0.98-1.52)	1.18 (0.81-1.73)	NA	.07
Total calcium	1 [Reference]	1.00 (0.83-1.20)	0.90 (0.74-1.10)	0.99 (0.82-1.21)	0.99 (0.81-1.21)	.99
Esophageal cancer[f] (n=468)						
Dairy foods	1 [Reference]	1.11 (0.85-1.46)	1.07 (0.82-1.41)	0.75 (0.55-1.02)	0.70 (0.51-0.96)	.002
Dietary calcium	1 [Reference]	0.91 (0.70-1.19)	0.72 (0.54-0.97)	0.75 (0.56-1.00)	0.66 (0.49-0.90)	.01
Supplemental calcium	1 [Reference]	0.94 (0.77-1.15)	1.21 (0.89-1.63)	1.32 (0.80-2.17)	NA	.14
Total calcium	1 [Reference]	0.98 (0.74-1.29)	0.84 (0.63-1.13)	0.89 (0.67-1.19)	0.84 (0.62-1.13)	.23
Stomach cancer[g] (n=512)						
Dairy foods	1 [Reference]	1.03 (0.80-1.34)	0.95 (0.73-1.24)	0.72 (0.54-0.96)	0.80 (0.61-1.06)	.03
Dietary calcium	1 [Reference]	1.13 (0.87-1.47)	0.95 (0.72-1.25)	0.93 (0.70-1.24)	0.87 (0.65-1.16)	.15
Supplemental calcium	1 [Reference]	1.12 (0.92-1.35)	0.99 (0.72-1.36)	1.51 (0.95-2.39)	NA	.17
Total calcium	1 [Reference]	1.07 (0.81-1.41)	1.13 (0.86-1.48)	1.04 (0.79-1.38)	0.96 (0.72-1.29)	.58
Colorectal cancer[h] (n=3463)						
Dairy foods	1 [Reference]	0.91 (0.82-1.01)	0.83 (0.75-0.93)	0.89 (0.80-0.99)	0.85 (0.76-0.94)	.01
Dietary calcium	1 [Reference]	0.86 (0.77-0.95)	0.83 (0.74-0.92)	0.85 (0.76-0.95)	0.84 (0.75-0.94)	.03
Supplemental calcium	1 [Reference]	0.96 (0.88-1.05)	0.91 (0.79-1.04)	0.74 (0.58-0.94)	NA	.01
Total calcium	1 [Reference]	0.89 (0.80-0.98)	0.83 (0.75-0.93)	0.87 (0.78-0.97)	0.79 (0.70-0.89)	.001
Liver cancer[i] (n=311)						
Dairy foods	1 [Reference]	1.02 (0.72-1.45)	1.05 (0.74-1.50)	1.07 (0.75-1.52)	1.04 (0.72-1.48)	.84
Dietary calcium	1 [Reference]	0.84 (0.59-1.19)	0.97 (0.69-1.38)	0.87 (0.61-1.26)	0.99 (0.69-1.42)	.86
Supplemental calcium	1 [Reference]	0.92 (0.72-1.17)	0.78 (0.50-1.20)	1.03 (0.53-2.03)	NA	.54
Total calcium	1 [Reference]	0.75 (0.52-1.08)	1.20 (0.87-1.67)	0.83 (0.58-1.20)	0.88 (0.61-1.27)	.61
Pancreatic cancer[j] (n=717)						
Dairy foods	1 [Reference]	0.96 (0.76-1.20)	1.01 (0.80-1.27)	1.00 (0.79-1.26)	0.82 (0.64-1.05)	.13
Dietary calcium	1 [Reference]	0.94 (0.75-1.18)	1.04 (0.83-1.31)	0.92 (0.72-1.16)	0.82 (0.64-1.06)	.11
Supplemental calcium	1 [Reference]	0.95 (0.81-1.11)	0.90 (0.69-1.19)	1.17 (0.77-1.77)	NA	.90
Total calcium	1 [Reference]	0.93 (0.74-1.16)	0.90 (0.72-1.14)	0.98 (0.78-1.23)	0.87 (0.68-1.11)	.39
Lung cancer[j] (n=4287)						
Dairy foods	1 [Reference]	1.04 (0.94-1.14)	1.01 (0.92-1.11)	1.04 (0.95-1.15)	1.05 (0.95-1.16)	.36
Dietary calcium	1 [Reference]	0.97 (0.89-1.07)	1.02 (0.93-1.13)	1.04 (0.95-1.15)	1.00 (0.91-1.11)	.68
Supplemental calcium	1 [Reference]	0.97 (0.91-1.03)	1.03 (0.92-1.15)	1.04 (0.86-1.27)	NA	.64
Total calcium	1 [Reference]	1.05 (0.96-1.15)	1.03 (0.94-1.13)	1.03 (0.94-1.13)	1.03 (0.93-1.13)	.76
Prostate cancer[k] (n=17 189)						
Dairy foods	1 [Reference]	1.02 (0.97-1.07)	1.05 (1.00-1.10)	1.06 (1.01-1.12)	1.06 (1.01-1.12)	.01
Dietary calcium	1 [Reference]	1.01 (0.96-1.06)	1.00 (0.95-1.05)	1.03 (0.98-1.08)	1.04 (0.98-1.09)	.14
Supplemental calcium	1 [Reference]	0.99 (0.95-1.02)	0.97 (0.92-1.03)	0.96 (0.88-1.05)	NA	.21
Total calcium	1 [Reference]	0.99 (0.95-1.04)	1.01 (0.96-1.06)	1.00 (0.95-1.05)	1.03 (0.98-1.08)	.21

(continued)

cium intake was also inversely associated with liver cancer, while total calcium intake was related to an increased risk of NHL. Dairy food, dietary, supplemental, and total calcium intakes were not related to breast, ovarian, or endometrial cancer.

When we examined the associations among men and women combined, we found that the results for esophageal, stomach, liver, pancreatic, and brain cancer were similar to those for men alone. We also observed that total calcium intake was now significantly inversely associated with kidney cancer (multivariate $RR_{Q5\ vs\ Q1}$=0.77; 95% CI, 0.63-0.94; *P* for trend, .01).

COMMENT

In this large prospective cohort study, we found that total calcium intake was nonlinearly associated with total cancer incidence in women: the risk decreased up to approximately 1300 mg/d, after which no further risk reduction was observed. The associations with dairy food and calcium intakes differed among individual cancer sites. Dairy food and calcium intakes were inversely associated with cancers of the digestive system in both men and women, especially with colorectal cancer. Supplemen-

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Table 2. Multivariate RRs[a] and 95% CIs of Cancer for Categories of Dairy Food and Dietary, Supplemental, and Total Calcium Intakes in Men (continued)

Variable	Categories, Multivariate RR (95% CI)[b]					*P* Value for Trend
	1	2	3	4	5	
Bladder cancer[l] (n=1417)						
Dairy foods	1 [Reference]	1.02 (0.86-1.19)	0.94 (0.80-1.11)	0.85 (0.72-1.01)	0.86 (0.72-1.02)	.03
Dietary calcium	1 [Reference]	1.14 (0.97-1.34)	0.99 (0.84-1.17)	0.90 (0.75-1.07)	0.94 (0.78-1.12)	.10
Supplemental calcium	1 [Reference]	0.90 (0.80-1.01)	0.99 (0.83-1.20)	0.84 (0.59-1.18)	NA	.34
Total calcium	1 [Reference]	0.96 (0.82-1.13)	0.82 (0.69-0.97)	0.87 (0.73-1.03)	0.87 (0.73-1.03)	.11
Kidney cancer[m] (n=991)						
Dairy foods	1 [Reference]	1.06 (0.86-1.30)	1.09 (0.89-1.34)	1.12 (0.91-1.38)	1.08 (0.87-1.35)	.54
Dietary calcium	1 [Reference]	0.93 (0.76-1.14)	0.93 (0.75-1.14)	0.97 (0.78-1.20)	0.98 (0.78-1.24)	.86
Supplemental calcium	1 [Reference]	0.89 (0.77-1.02)	0.86 (0.68-1.09)	0.90 (0.61-1.34)	NA	.22
Total calcium	1 [Reference]	0.90 (0.74-1.10)	0.93 (0.76-1.14)	0.94 (0.76-1.15)	0.80 (0.64-1.01)	.10
Thyroid cancer[i] (n=170)						
Dairy foods	1 [Reference]	1.02 (0.60-1.72)	1.48 (0.91-2.42)	1.59 (0.98-2.57)	0.78 (0.45-1.37)	.41
Dietary calcium	1 [Reference]	1.53 (0.90-2.62)	1.67 (0.98-2.84)	1.71 (1.00-2.91)	1.19 (0.67-2.12)	.98
Supplemental calcium	1 [Reference]	0.85 (0.61-1.17)	0.92 (0.54-1.57)	0.70 (0.26-1.91)	NA	.44
Total calcium	1 [Reference]	0.95 (0.58-1.56)	1.07 (0.66-1.74)	1.15 (0.71-1.87)	0.79 (0.46-1.34)	.43
Brain cancer[i] (n=390)						
Dairy foods	1 [Reference]	0.82 (0.59-1.14)	0.89 (0.64-1.22)	1.01 (0.74-1.37)	0.83 (0.60-1.14)	.52
Dietary calcium	1 [Reference]	0.81 (0.58-1.13)	1.02 (0.74-1.39)	0.77 (0.55-1.08)	0.91 (0.65-1.26)	.65
Supplemental calcium	1 [Reference]	1.18 (0.95-1.46)	1.31 (0.94-1.83)	1.11 (0.62-1.99)	NA	.25
Total calcium	1 [Reference]	0.79 (0.57-1.10)	0.82 (0.59-1.13)	0.91 (0.66-1.25)	0.89 (0.65-1.23)	.98
Non-Hodgkin lymphoma[i] (n=1267)						
Dairy foods	1 [Reference]	0.92 (0.76-1.10)	1.09 (0.91-1.30)	1.06 (0.89-1.27)	1.02 (0.85-1.22)	.56
Dietary calcium	1 [Reference]	0.97 (0.81-1.17)	1.01 (0.84-1.21)	1.11 (0.93-1.33)	1.00 (0.83-1.20)	.76
Supplemental calcium	1 [Reference]	0.84 (0.74-0.95)	0.87 (0.71-1.07)	0.99 (0.72-1.36)	NA	.33
Total calcium	1 [Reference]	1.03 (0.86-1.24)	1.15 (0.96-1.38)	0.95 (0.79-1.14)	1.02 (0.85-1.23)	.77
Leukemia[i] (n=757)						
Dairy foods	1 [Reference]	1.16 (0.92-1.46)	0.93 (0.73-1.19)	1.16 (0.92-1.47)	1.11 (0.88-1.41)	.41
Dietary calcium	1 [Reference]	0.90 (0.72-1.13)	0.82 (0.65-1.04)	0.95 (0.76-1.19)	0.87 (0.69-1.11)	.49
Supplemental calcium	1 [Reference]	1.17 (1.01-1.36)	0.96 (0.73-1.25)	0.93 (0.59-1.47)	NA	.78
Total calcium	1 [Reference]	0.93 (0.74-1.17)	0.95 (0.75-1.19)	0.96 (0.76-1.21)	0.88 (0.69-1.21)	.38
Myeloma[i] (n=369)						
Dairy foods	1 [Reference]	1.06 (0.75-1.49)	1.38 (1.00-1.92)	1.15 (0.81-1.61)	1.14 (0.81-1.61)	.63
Dietary calcium	1 [Reference]	1.08 (0.77-1.51)	1.07 (0.76-1.50)	1.27 (0.91-1.77)	1.05 (0.74-1.50)	.71
Supplemental calcium	1 [Reference]	0.92 (0.74-1.14)	0.69 (0.46-1.04)	0.60 (0.28-1.27)	NA	.04
Total calcium	1 [Reference]	1.03 (0.74-1.43)	1.07 (0.77-1.48)	0.91 (0.65-1.28)	0.92 (0.65-1.30)	.42

Abbreviations: CI, confidence interval; NA, not applicable; RR, relative risk.

[a] Adjusted for race/ethnicity (white, non-Hispanic; black, non-Hispanic; and others); education (less than high school, high school graduate, some college, and college graduate/postgraduate); marital status (married, not married); body mass index (continuous); family history of cancer (yes, no); vigorous physical activity (never/rarely; ≤3 times/mo; and 1-2, 3-4, and ≥5 times/wk); alcohol consumption (0, <5, 5-<15, 15-<30, and ≥30 g/d); intakes of red meat (quintiles) and total energy (continuous); and additional variables listed in each footnote below.

[b] Dairy food and dietary and total calcium intakes were categorized according to quintiles of the distribution. The medians for category 1 through 5 were 0.2, 0.4, 0.6, 0.8, and 1.4 servings per 1000 kcal/d for dairy food; 478, 616, 739, 899, and 1247 mg/d for dietary calcium; and 526, 498, 857, 1073, and 1530 mg/d for total calcium. Supplemental calcium intake was categorized into 4 groups (0, >0-<400, 400-<1000, and ≥1000 mg/d). Dietary and supplemental calcium intakes were mutually adjusted in the multivariate models.

[c] Adjusted for variables listed in footnote a plus smoking status (never, former, and current); time since quitting smoking (never, stopped ≥10 years ago, stopped 5-9 years ago, stopped 1-4 years ago, stopped <1 year ago, and currently smoking); smoking dose (0, 1-10, 11-20, 21-30, 31-40, 41-50, 51-60, >60 cigarettes per day); antacid use (yes, no); personal history of diabetes (yes, no) and hypertension (yes, no), prostate-specific antigen test (yes, no); and intakes of fat (quintiles), fruits and vegetables (quintiles), whole grains (quintiles), protein (quintiles), total beverages (quintiles), folate (quintiles), tomatoes (quintiles), α-linolenic acid (quintiles), and selenium (quintiles).

[d] Number of cases.

[e] Adjusted for variables listed in footnote a plus smoking status, time since quitting smoking, smoking dose, and intake of fruits and vegetables.

[f] Adjusted for variables listed in footnote a plus smoking status, time since quitting smoking, smoking dose, antacid use, and intake of fruits and vegetables.

[g] Adjusted for variables listed in footnote a plus smoking (never, ≤20 cigarettes per day in the past, >20 cigarettes per day in the past, currently ≤20 cigarettes per day, and currently >20 cigarettes per day), and antacid use.

[h] Adjusted for variables listed in footnote a plus smoking, and intakes of fruits and vegetables, whole grains, and folate.

[i] Adjusted for variables listed in footnote a plus smoking.

[j] Adjusted for variables listed in footnote a plus smoking status, time since quitting smoking, and smoking dose.

[k] Adjusted for variables listed in footnote a plus smoking, personal history of diabetes, prostate-specific antigen test, and intakes of tomatoes, α-linolenic acid, and selenium.

[l] Adjusted for variables listed in footnote a plus smoking status, time since quitting smoking, smoking dose, and intakes of fruits and vegetables and total beverages.

[m] Adjusted for variables listed in footnote a plus smoking, personal history of diabetes and hypertension, and intake of protein.

tal calcium intake was also inversely associated with colorectal cancer. Calcium intake was not related to breast or prostate cancer.

Dairy food and calcium intakes have been hypothesized to play roles that differ among individual cancer sites. Dairy food, which is relatively high in potentially

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Table 3. Multivariate RRs[a] and 95% CIs of Cancer for Categories of Dairy Food and Dietary, Supplemental, and Total Calcium Intakes in Women

Variable	Categories, Multivariate RR (95% CI)[b]					*P* Value for Trend
	1	2	3	4	5	
All cancers[c] (N=16 605[d])						
Dairy foods	1 [Reference]	0.98 (0.94-1.03)	0.95 (0.90-1.00)	0.97 (0.92-1.02)	0.95 (0.90-1.00)	.10
Dietary calcium	1 [Reference]	0.96 (0.91-1.00)	0.95 (0.90-1.00)	0.95 (0.90-1.01)	0.93 (0.87-0.99)	.04
Supplemental calcium	1 [Reference]	0.97 (0.92-1.01)	0.95 (0.91-1.00)	0.96 (0.91-1.02)	NA	.28
Total calcium	1 [Reference]	0.98 (0.93-1.03)	0.94 (0.89-0.99)	0.93 (0.88-0.98)	0.96 (0.91-1.02)	.23
Head and neck cancer[e] (n=325)						
Dairy foods	1 [Reference]	0.75 (0.53-1.05)	0.90 (0.64-1.25)	1.02 (0.73-1.41)	0.89 (0.63-1.27)	.99
Dietary calcium	1 [Reference]	0.92 (0.66-1.28)	1.09 (0.79-1.52)	0.98 (0.69-1.40)	1.03 (0.72-1.47)	.80
Supplemental calcium	1 [Reference]	1.16 (0.88-1.52)	1.22 (0.90-1.66)	1.05 (0.72-1.53)	NA	.75
Total calcium	1 [Reference]	1.33 (0.97-1.83)	0.92 (0.64-1.31)	1.02 (0.71-1.46)	1.30 (0.91-1.86)	.42
Esophageal cancer[f] (n=79)						
Dairy foods	1 [Reference]	0.82 (0.42-1.60)	1.21 (0.65-2.25)	0.85 (0.42-1.72)	0.64 (0.29-1.44)	.31
Dietary calcium	1 [Reference]	0.83 (0.44-1.57)	1.03 (0.55-1.94)	0.68 (0.32-1.42)	0.60 (0.27-1.34)	.18
Supplemental calcium	1 [Reference]	1.31 (0.75-2.28)	1.35 (0.73-2.48)	0.79 (0.35-1.81)	NA	.61
Total calcium	1 [Reference]	1.47 (0.80-2.71)	1.14 (0.59-2.22)	0.56 (0.24-1.31)	0.83 (0.38-1.81)	.18
Stomach cancer[g] (n=143)						
Dairy foods	1 [Reference]	0.61 (0.37-1.01)	0.49 (0.28-0.84)	0.74 (0.46-1.19)	0.58 (0.35-0.97)	.16
Dietary calcium	1 [Reference]	0.95 (0.58-1.56)	0.50 (0.28-0.91)	0.87 (0.52-1.46)	0.84 (0.50-1.41)	.65
Supplemental calcium	1 [Reference]	0.81 (0.53-1.23)	1.15 (0.75-1.76)	0.54 (0.29-1.01)	NA	.20
Total calcium	1 [Reference]	0.90 (0.54-1.50)	1.37 (0.85-2.20)	0.55 (0.30-1.01)	0.71 (0.40-1.25)	.08
Colorectal cancer[h] (n=1635)						
Dairy foods	1 [Reference]	0.84 (0.73-0.98)	0.86 (0.74-0.99)	0.78 (0.67-0.91)	0.72 (0.61-0.84)	<.001
Dietary calcium	1 [Reference]	0.86 (0.74-1.00)	0.81 (0.70-0.95)	0.74 (0.63-0.87)	0.70 (0.59-0.82)	<.001
Supplemental calcium	1 [Reference]	1.02 (0.89-1.17)	0.86 (0.73-1.00)	0.86 (0.72-1.02)	NA	.02
Total calcium	1 [Reference]	0.87 (0.75-1.01)	0.83 (0.71-0.97)	0.71 (0.60-0.84)	0.72 (0.61-0.86)	.001
Liver cancer[i] (n=86)						
Dairy foods	1 [Reference]	0.91 (0.42-1.99)	1.83 (0.93-3.58)	1.35 (0.66-2.77)	1.58 (0.78-3.20)	.17
Dietary calcium	1 [Reference]	0.48 (0.21-1.11)	1.14 (0.58-2.21)	1.32 (0.68-2.55)	1.45 (0.75-2.82)	.05
Supplemental calcium	1 [Reference]	0.50 (0.29-0.86)	0.61 (0.34-1.08)	0.42 (0.19-0.91)	NA	.04
Total calcium	1 [Reference]	1.38 (0.73-2.61)	1.10 (0.55-2.17)	1.05 (0.52-2.13)	0.96 (0.46-2.03)	.60
Pancreatic cancer[j] (n=384)						
Dairy foods	1 [Reference]	1.19 (0.86-1.66)	1.24 (0.89-1.72)	1.34 (0.96-1.85)	1.12 (0.80-1.58)	.64
Dietary calcium	1 [Reference]	1.01 (0.74-1.38)	0.98 (0.71-1.35)	1.05 (0.77-1.45)	0.85 (0.60-1.20)	.36
Supplemental calcium	1 [Reference]	0.89 (0.69-1.15)	1.02 (0.77-1.33)	0.79 (0.57-1.11)	NA	.34
Total calcium	1 [Reference]	1.03 (0.75-1.40)	0.93 (0.67-1.28)	0.97 (0.71-1.34)	0.88 (0.63-1.24)	.40
Lung cancer[j] (n=2457)						
Dairy foods	1 [Reference]	0.91 (0.81-1.03)	0.86 (0.76-0.97)	0.89 (0.79-1.01)	0.92 (0.81-1.04)	.27
Dietary calcium	1 [Reference]	0.88 (0.78-0.99)	0.87 (0.76-0.98)	0.91 (0.80-1.03)	0.93 (0.81-1.05)	.48
Supplemental calcium	1 [Reference]	1.04 (0.94-1.14)	1.03 (0.92-1.16)	1.04 (0.92-1.19)	NA	.58
Total calcium	1 [Reference]	0.96 (0.85-1.08)	0.91 (0.81-1.03)	0.94 (0.83-1.07)	1.00 (0.88-1.14)	.95
Breast cancer[k] (n=5856)						
Dairy foods	1 [Reference]	0.98 (0.90-1.06)	0.97 (0.89-1.05)	0.94 (0.87-1.03)	0.96 (0.88-1.04)	.28
Dietary calcium	1 [Reference]	0.96 (0.89-1.04)	0.95 (0.87-1.03)	0.97 (0.89-1.05)	0.94 (0.86-1.03)	.28
Supplemental calcium	1 [Reference]	0.95 (0.89-1.02)	0.97 (0.90-1.04)	0.98 (0.91-1.06)	NA	.91
Total calcium	1 [Reference]	0.96 (0.88-1.04)	0.95 (0.87-1.03)	0.94 (0.86-1.02)	0.98 (0.90-1.07)	.84
Ovarian cancer[l] (n=515)						
Dairy foods	1 [Reference]	1.04 (0.78-1.38)	0.94 (0.70-1.25)	1.26 (0.96-1.65)	1.03 (0.77-1.37)	.60
Dietary calcium	1 [Reference]	1.04 (0.78-1.39)	1.05 (0.79-1.40)	1.25 (0.94-1.65)	1.02 (0.75-1.37)	.77
Supplemental calcium	1 [Reference]	0.88 (0.70-1.10)	0.99 (0.78-1.26)	0.97 (0.74-1.27)	NA	.85
Total calcium	1 [Reference]	1.04 (0.78-1.38)	0.99 (0.74-1.33)	1.05 (0.79-1.41)	1.14 (0.85-1.52)	.34
Endometrial cancer[m] (n=1171)						
Dairy foods	1 [Reference]	1.19 (0.98-1.45)	1.17 (0.96-1.42)	1.22 (1.01-1.48)	1.17 (0.97-1.42)	.27
Dietary calcium	1 [Reference]	1.09 (0.90-1.32)	1.26 (1.04-1.52)	1.06 (0.87-1.29)	1.20 (0.99-1.46)	.18
Supplemental calcium	1 [Reference]	0.96 (0.83-1.11)	0.92 (0.78-1.08)	0.92 (0.77-1.11)	NA	.35
Total calcium	1 [Reference]	1.11 (0.92-1.33)	1.01 (0.84-1.22)	1.10 (0.91-1.32)	0.99 (0.81-1.20)	.66
Bladder cancer[n] (n=264)						
Dairy foods	1 [Reference]	1.27 (0.86-1.88)	1.24 (0.83-1.85)	1.25 (0.83-1.88)	1.45 (0.97-2.18)	.12
Dietary calcium	1 [Reference]	1.03 (0.70-1.52)	1.08 (0.73-1.60)	1.02 (0.68-1.54)	1.23 (0.82-1.84)	.33
Supplemental calcium	1 [Reference]	1.17 (0.87-1.58)	0.91 (0.63-1.29)	1.03 (0.69-1.53)	NA	.70
Total calcium	1 [Reference]	0.97 (0.67-1.41)	0.94 (0.64-1.37)	0.91 (0.61-1.35)	0.97 (0.65-1.46)	.85

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Table 3. Multivariate RRs[a] and 95% CIs of Cancer for Categories of Dairy Food and Dietary, Supplemental, and Total Calcium Intakes in Women (continued)

Variable	Categories, Multivariate RR (95% CI)[b]					*P* Value for Trend
	1	2	3	4	5	
Kidney cancer[o] (n=367)						
Dairy foods	1 [Reference]	1.02 (0.72-1.45)	1.11 (0.78-1.57)	1.06 (0.75-1.51)	1.13 (0.79-1.63)	.49
Dietary calcium	1 [Reference]	0.84 (0.59-1.19)	1.13 (0.81-1.59)	0.77 (0.53-1.12)	1.02 (0.70-1.48)	.87
Supplemental calcium	1 [Reference]	0.93 (0.73-1.20)	0.79 (0.59-1.06)	0.79 (0.57-1.12)	NA	.12
Total calcium	1 [Reference]	0.87 (0.63-1.21)	0.81 (0.58-1.13)	0.73 (0.51-1.03)	0.79 (0.55-1.13)	.21
Thyroid cancer[i] (n=199)						
Dairy foods	1 [Reference]	0.93 (0.59-1.46)	0.91 (0.58-1.44)	0.90 (0.57-1.41)	1.04 (0.67-1.62)	.74
Dietary calcium	1 [Reference]	1.06 (0.69-1.64)	0.73 (0.45-1.18)	0.89 (0.57-1.41)	1.01 (0.64-1.58)	.98
Supplemental calcium	1 [Reference]	1.16 (0.81-1.66)	1.15 (0.78-1.71)	1.07 (0.68-1.68)	NA	.87
Total calcium	1 [Reference]	0.98 (0.63-1.54)	1.07 (0.69-1.67)	0.88 (0.55-1.41)	1.04 (0.65-1.65)	.98
Brain cancer[i] (n=160)						
Dairy foods	1 [Reference]	0.83 (0.53-1.29)	0.45 (0.26-0.77)	0.61 (0.37-0.99)	0.77 (0.49-1.23)	.38
Dietary calcium	1 [Reference]	0.89 (0.56-1.39)	0.56 (0.34-0.94)	0.65 (0.39-1.06)	0.70 (0.43-1.15)	.14
Supplemental calcium	1 [Reference]	1.03 (0.69-1.53)	1.21 (0.80-1.85)	0.84 (0.49-1.41)	NA	.67
Total calcium	1 [Reference]	0.94 (0.59-1.50)	0.70 (0.42-1.16)	0.79 (0.48-1.29)	0.72 (0.43-1.21)	.20
Non-Hodgkin lymphoma[i] (n=660)						
Dairy foods	1 [Reference]	1.41 (1.10-1.80)	1.06 (0.82-1.37)	1.17 (0.91-1.51)	1.00 (0.77-1.30)	.26
Dietary calcium	1 [Reference]	1.41 (1.11-1.81)	1.15 (0.89-1.49)	1.06 (0.81-1.38)	1.13 (0.87-1.47)	.69
Supplemental calcium	1 [Reference]	0.82 (0.67-1.00)	0.95 (0.77-1.18)	1.25 (0.99-1.56)	NA	.01
Total calcium	1 [Reference]	0.96 (0.75-1.23)	0.89 (0.69-1.15)	0.99 (0.77-1.28)	1.24 (0.97-1.59)	.03
Leukemia[i] (n=280)						
Dairy foods	1 [Reference]	1.08 (0.73-1.60)	1.07 (0.72-1.59)	1.39 (0.95-2.02)	1.20 (0.81-1.77)	.26
Dietary calcium	1 [Reference]	1.10 (0.75-1.61)	0.96 (0.64-1.43)	1.35 (0.93-1.96)	1.13 (0.76-1.67)	.41
Supplemental calcium	1 [Reference]	0.81 (0.60-1.09)	0.71 (0.50-1.00)	1.12 (0.79-1.57)	NA	.54
Total calcium	1 [Reference]	0.92 (0.63-1.35)	1.00 (0.68-1.46)	0.92 (0.62-1.36)	1.25 (0.86-1.83)	.17
Myeloma[i] (n=175)						
Dairy foods	1 [Reference]	1.24 (0.76-2.01)	1.33 (0.84-2.15)	1.18 (0.72-1.95)	1.24 (0.75-2.03)	.61
Dietary calcium	1 [Reference]	1.72 (1.03-2.86)	1.71 (1.02-2.87)	1.71 (1.01-2.88)	1.43 (0.83-2.49)	.55
Supplemental calcium	1 [Reference]	0.84 (0.57-1.24)	1.33 (0.91-1.95)	0.64 (0.37-1.11)	NA	.47
Total calcium	1 [Reference]	1.33 (0.79-2.24)	1.54 (0.93-2.57)	1.91 (1.16-3.15)	1.36 (0.79-2.36)	.25

Abbreviations: CI, confidence interval; NA, not applicable; RR, relative risk.

[a] Adjusted for race/ethnicity (white, non-Hispanic; black, non-Hispanic; and others), education (less than high school, high school graduate, some college, and college graduate/postgraduate); marital status (married, not married); body mass index (continuous); family history of cancer (yes, no); vigorous physical activity (never/rarely; ≤3 times/mo; and 1-2, 3-4, and ≥5 times/wk); menopausal hormone therapy use (never, past, and current); alcohol consumption (0, <5, 5-<15, 15-<30, and ≥30 g/d); intakes of red meat (quintiles) and total energy (continuous); and additional variables listed in each footnote below.

[b] Dairy food and dietary and total calcium intakes were categorized according to quintiles of the distribution. The medians for category 1 through 5 were 0.2, 0.4, 0.7, 1.0, and 1.6 servings per 1000 kcal/d for dairy food; 409, 532, 648, 798, and 1101 mg/d for dietary calcium; and 494, 717, 969, 1296, and 1881 mg/d for total calcium. Supplemental calcium intake was categorized into 4 groups (0, >0-<400, 400-<1000, and ≥1000 mg/d). Dietary and supplemental calcium intakes were mutually adjusted in the multivariate models.

[c] Adjusted for variables listed in footnote a plus smoking status (never, former, and current); time since quitting smoking (never, stopped ≥10 years ago, stopped 5-9 years ago, stopped 1-4 years ago, stopped <1 year ago, and currently smoking); smoking dose (0, 1-10, 11-20, 21-30, 31-40, 41-50, 51-60, and >60 cigarettes per day); antacid use (yes, no); age at menopause(<50, 50-54, and ≥55 years old); parity (nulliparous, ≤2 and ≥3 children); oral contraceptive use (never, <5 and ≥5 years); duration of menopausal hormone therapy use (never, <10 and ≥10 years); personal history of diabetes (yes, no) and hypertension (yes, no); oophorectomy (yes, no); hysterectomy (yes, no); and intakes of fat (quintiles), fruits and vegetables (quintiles), whole grains (quintiles), total beverages (quintiles), protein (quintiles), and folate (quintiles).

[d] Number of cases.

[e] Adjusted for variables listed in footnote a plus smoking status, time since quitting smoking, smoking dose, and intake of fruits and vegetables.

[f] Adjusted for variables listed in footnote a plus smoking status, time since quitting smoking, smoking dose, antacid use, and intake of fruits and vegetables.

[g] Adjusted for variables listed in footnote a plus smoking (never, ≤20 cigarettes per day in the past, >20 cigarettes per day in the past, currently ≤20 cigarettes per day, and currently >20 cigarettes per day), and antacid use.

[h] Adjusted for variables listed in footnote a plus smoking and intakes of fruits and vegetables, whole grains, and folate.

[i] Adjusted for variables listed in footnote a plus smoking.

[j] Adjusted for variables listed in footnote a plus smoking status, time since quitting smoking, and smoking dose.

[k] Adjusted for variables listed in footnote a plus smoking, combined age at first birth, number of children, age at menopause, and intake of fat.

[l] Adjusted for variables listed in footnote a plus smoking, parity, oral contraceptive use, and duration of menopausal hormone therapy.

[m] Adjusted for variables listed in footnote a plus smoking, parity, and oral contraceptive use.

[n] Adjusted for variables listed in footnote a plus smoking status, time since quitting smoking, smoking dose, parity, oral contraceptive use, and intakes of fruits and vegetables and total beverages.

[o] Adjusted for variables listed in footnote a plus smoking, parity, oral contraceptive use, personal history of diabetes and hypertension, and intake of protein.

anticarcinogenic nutrients such as calcium, vitamin D, and conjugated linoleic acid, has been postulated to protect against the development of colorectal and breast cancer.[4,23] Calcium has been shown to reduce proliferation, to stimulate differentiation, and to induce apoptosis in cells in the gastrointestinal tract and breast.[24,25] Also, the binding of calcium to bile and fatty acids in the gastrointestinal tract has been hypothesized to reduce damage

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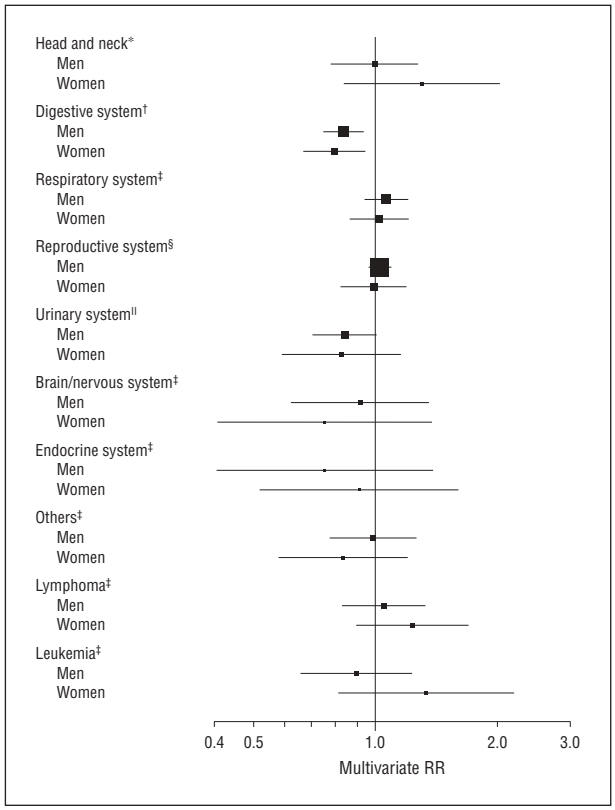

Figure 2. Multivariate relative risks (RRs) and 95% confidence intervals of cancers by anatomical area comparing the highest quintile of total calcium intake with the lowest. The multivariate RR was adjusted for race/ethnicity, education, marital status, body mass index, family history of cancer, vigorous physical activity, alcohol consumption, and intakes of red meat and total energy plus the additional variables that are listed in each footnote. The squares and horizontal lines correspond with the multivariate RR and the 95% confidence intervals. *Adjusted for the variables listed for the multivariate RR plus smoking status, time since quitting smoking, smoking dose, intake of fruits and vegetables, and menopausal hormone therapy (MHT) use in women. †Adjusted for the variables listed for the multivariate RR plus smoking status, time since quitting smoking, smoking dose, MHT use in women, antacid use, and intakes of fruits and vegetables, whole grains, and folate. ‡Adjusted for the variables listed for the multivariate RR plus smoking status, time since quitting smoking, smoking dose, and MHT use in women. §Adjusted for the variables listed for the multivariate RR plus smoking, personal history of diabetes, prostate-specific antigen test, and intakes of tomatoes, α-linolenic acid, and selenium in men as well as for smoking, MHT use, parity, oral contraceptive use, personal history of oophorectomy and hysterectomy, and intake of fat in women. ||Adjusted for variables listed for the multivariate RR plus smoking status, time since quitting smoking, smoking dose, personal history of diabetes and hypertension, parity, MHT and oral contraceptive use in women, as well as for intakes of fruits and vegetables, total beverages, and protein.

to large-bowel mucosa.[24] Nevertheless, high calcium intake has been hypothesized to increase the risk of prostate cancer by suppressing $1,25(OH)_2$ vitamin D, thereby offsetting a potential anticarcinogenic effect of vitamin D.[26] Dairy food has also been found to increase insulin-like growth factor 1, a potent mitogen associated with an increased risk of prostate cancer.[27,28]

We found that total calcium intake was nonlinearly inversely associated with total cancer in women. In contrast, the Women's Health Initiative Study, a randomized clinical trial of daily supplementation of 1000 mg of calcium combined with 400 IU of vitamin D for an average of 7 years, found no effect on total cancer incidence among postmenopausal women (hazard ratio, 0.98; 95% CI, 0.91-1.05 [total cancer cases,1634 in treatment group and 1655 in placebo group]).[29] We note, however, that in the Women's Health Initiative Study, two-thirds of women had at least 800 mg/d of the total calcium at baseline and the total number of cancer cases was small.

Consistent with previous studies,[3,23] we found that intakes of dairy food and calcium were significantly inversely associated with risk of colorectal cancer. In a pooled analysis of 10 cohort studies,[3] a 15% to 20% lower risk of colorectal cancer was observed for total calcium (RR, 0.78; 95% CI, 0.69-0.88 for the highest vs lowest quintile) and milk (RR, 0.85; 95% CI, 0.78-0.94 for <70 g/d vs ≥ 250 g/d). Furthermore, randomized clinical trials have found that calcium supplementation reduced recurrence of colorectal adenomas, which are precursors of colorectal cancer.[30,31]

A limited number of studies, most with case-control designs, have examined dairy food and calcium intakes in relation to head and neck, esophageal, and stomach cancer. Few studies have observed inverse associations of dairy food and calcium intakes with head and neck[32,33] and esophageal cancer[34-36]; other studies have found no associations with cancer in the head and neck,[37] esophagus,[38-42] or stomach.[34,35,42,43] Our study is one of the first large prospective cohort studies to examine dairy food and calcium intakes in relation to these cancers. We found that intakes of dairy food and dietary calcium were inversely associated with cancers of the digestive system in men, while supplemental and total calcium intakes showed suggestive inverse associations in women. Calcium supplement use in men tended to be less prevalent and consistent and therefore more likely to be measured with error, which may explain why the calcium association in men was reflected in dairy food and dietary calcium intakes. In women, the associations for supplemental and total calcium intakes did not achieve statistical significance, but the numbers of cases of these cancers were small. Overall, our findings suggest that calcium intake plays a role in preventing cancers of the digestive system. However, we cannot exclude the possibility of confounding by vitamin D found in dairy food and supplements. Vitamin D, which is tightly related to calcium regulation in the body, has been inversely associated with digestive system cancers in other studies.[44]

In women, supplemental calcium intake was inversely associated with liver cancer, but it was positively related to NHL. Given that the association with liver cancer was observed only in women and that the number of liver cancer cases was small, this finding is likely due to chance. Few studies[45-48] that have investigated the association between dairy food or calcium intake and NHL have suggested that the intake of dairy food was associated with an increased risk of NHL. Further investigation of dairy food and calcium intakes in relation to cancers in liver and NHL is warranted.

The associations between dairy food and calcium intakes and breast cancer have been either null or inverse.[4,49-52] Cohort studies that found dairy food and calcium intakes to be inversely associated with breast cancer suggested that the associations may differ by menopausal status[50,51] or estrogen receptor status of the tumor.[52] Our study, which was conducted mainly among postmeno-

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pausal women, found that dairy food and calcium intakes were not associated with breast cancer. Further studies examining the associations by tumor characteristics of breast cancer and by menopausal status might be informative.

Despite the existence of plausible biologic mechanisms, the effects of dairy food and calcium intakes on prostate cancer are unclear. Epidemiologic studies have found null[53-55] as well as positive[7,56-58] associations for intakes of dairy food and calcium. Among studies that observed a positive association between calcium intake and prostate cancer, a significantly increased risk was generally found only with very high calcium intake (2000 mg/d compared with approximately <750 mg/d) or in advanced prostate cancer.[7,56] However, our study found that calcium, even at a very high intake (≥2000 mg/d vs 500-<750 mg/d), was not associated with prostate cancer.[59]

Our study has some limitations. First, we did not examine whether associations with intakes of dairy food and calcium differed by tumor subtype or tumor aggressiveness of site-specific cancers. It is possible that we missed some associations that may exist only for certain tumor subtypes or aggressive tumors. Second, although we adjusted for all potential risk factors available in our study for site-specific cancers, residual confounding by unknown or unmeasured risk factors may exist for some cancers. Third, in analyses of low-incidence cancers, especially cancers in women with small numbers of cases, we had limited statistical power to examine an association, and some findings may be attributable to chance. Finally, because diet was assessed only once at baseline, it may not reflect long-term usual intake as accurately as repeated measurements of diet during follow-up. Also, we could not examine whether dairy food and calcium intakes during earlier life periods or lifelong cumulative intakes are related to cancer risk.

Nevertheless, our study is one of the first cohort studies to examine dairy food and calcium intakes in relation to total cancer as well as low-incidence cancers. Moreover, our prospective design avoids the recall and selection biases that can affect results from case-control studies. Our study had high statistical power, with more than 53 000 total cancers and at least 100 cases of most individual cancers. Therefore, substantial effects of dairy food and calcium intakes were unlikely to have been missed. A further strength of our study is that we rigorously controlled for all potential risk factors, including both dietary and lifestyle factors for each site-specific cancer. In conclusion, our findings suggest that calcium intake consistent with current recommendations is associated with a lower risk of total cancer in women and cancers of the digestive system, especially colorectal cancer, in both men and women.

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