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Colorectal Cancer Risk and Dietary Intake of Calcium, Vitamin D, and Dairy Products: A Meta-Analysis of 26,335 Cases From 60 Observational Studies

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Colorectal Cancer Risk and Dietary Intake of Calcium, Vitamin D, and Dairy Products: A Meta-Analysis of 26,335 Cases From 60 Observational Studies

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In vivo and in vitro studies suggest that dairy products, calcium, and dietary vitamin D inhibits the development of colorectal cancer (CRC). A meta-analysis was performed to evaluate this relationship in observational studies. Data from 60 epidemiological studies enrolling 26,335 CRC cases were pooled using a general variance-based meta-analytic method. Summary relative risk (RR) estimates and 95% confidence intervals (CIs) were calculated for the highest vs. the lowest intake categories. Sensitivity analyses tested the robustness of these summary effect measures and the statistical heterogeneity. The summary RR for high milk and dairy product intake, respectively, on colon cancer risk was 0.78 (95% CI = 0.67–0.92) and 0.84 (95% CI = 0.75–0.95). Milk intake was unrelated to rectal cancer risk. High calcium intake had a greater protective effect against tumors of the distal colon and rectal cancer vs. proximal colon. The risk reduction associated with calcium was similar for dietary and supplemental sources. Vitamin D was associated with a nonsignificant 6% reduction in CRC risk. Higher consumption of milk/dairy products reduces the risk of colon cancer, and high calcium intake reduces the risk of CRC. Low vitamin D intake in the study populations may limit the ability to detect a protective effect if one exists.

INTRODUCTION

Colorectal cancer is the third most common malignancy and the second leading cause of cancer related death in the United States, with over 153,000 incident cases expected in 2007 (1,2). International incidence rates vary, and migration studies have documented increasing rates among groups moving from low incidence to high incidence areas (3,4). This finding suggests a role for an environmental factor or factors, such as diet, in colorectal carcinogenesis (5,6). In fact, Doll and Peto (7) estimated that 90% of deaths secondary to large-bowel cancer could be attributable to diet.

Data derived from in vitro, in vivo, and some observational studies have suggested that high dietary intake of calcium and vitamin D may reduce the risk of colorectal neoplasms by a variety of mechanisms including the binding of secondary bile acids and free fatty acids in the colon, thereby reducing epithelial cell exposure to their toxic effects, inhibiting proliferation of the intestinal mucosa, and by inhibiting the proliferation of epithelial cells by inducing their differentiation via the intracellular action of calcium (8,9). Vitamin D may protect against colorectal neoplasia by reducing epithelial cell proliferation and inducing differentiation in target tissue, with experimental findings supporting such a mechanism (10). Additional work suggests that low-fat dairy foods reduce proliferation of colonic epithelial cells and normalize differentiation, thereby supporting a role in reducing colorectal carcinogenesis (11).

The true relationship between these dietary components and colorectal cancer risk remains unclear because human epidemiological studies are inconsistent (12). In addition, two prior pooled analyses (13,14) did not resolve these inconsistencies,

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with the older report showing no association between calcium and colorectal cancer risk, whereas the more recent analysis of cohort studies by Cho et al. (14) showed a significant but modest 14% reduction in risk associated with the highest intakes of dietary calcium. Interestingly, these reports pooled different databases, with neither study including data from all available published observational studies.

Identification of dietary factors important in the etiology of colorectal cancer could provide opportunities for the development of effective disease prevention strategies. We therefore conducted a comprehensive meta-analysis pooling all available published observational data examining the relationship between calcium, vitamin D, and dairy product intake and colorectal cancer risk.

METHODS

The methods used in the design of this study have been previously described (15–16). A protocol was developed outlining a meta-analysis designed to examine the risk of colorectal cancer associated with dietary intake of dairy products, calcium, and vitamin D. Eligibility criteria for study inclusion were determined prospectively, as were the specific data elements to be extracted from each published report. The study protocol also included details of the planned statistical analysis.

A data extraction form was designed for recording relevant information, with two researchers performing data extraction. Differences were resolved by consensus. Other data collected but not included in the eligibility criteria were number of patients and location for each study; dietary assessment methods; length of follow-up and cohort description; type of statistical adjustments, if any, to the individual study odds ratios (ORs) or relative risks (RRs); as well as source of controls for case-control studies.

Literature Search

Literature retrieval was performed by previously described methods (16). A MEDLARS search was conducted of English language literature published between January 1966 and February 2007 as well as review of CancerLit and the CD-ROM version of Current Contents. The Cochrane database was also searched from January 1966 to February 2003. Search terms were *dairy products,* [*calcium, dietary*], *dietary fats, vitamin D,* and *colon/rectal neoplasms.* If a series of articles was published, all data were retrieved from the most recent article. Hand searches of bibliographies of published reports, review articles, and textbooks were also performed.

Initial citations (in the form of abstracts) from this literature search were screened by a physician investigator to exclude those that did not meet protocol-specified inclusion criteria. Rejected formats included animal studies, in vitro studies, review articles, letters to the editor, abstracts, and non-peer-reviewed articles. Eligibility criteria included published observational studies enrolling patients with histologically proven adenocarcinoma of colon/rectum in adult patients (i.e., age 18 yr or older); availability of data on exposures of interest including dairy products, dietary calcium, and/or vitamin D intake; availability of ORs or RRs with 95% confidence intervals (CIs) for each report or availability of raw data to calculate these parameters; and availability of data on outcome of interest including incident colorectal cancer or death from colorectal cancer.

Statistical Analysis

Data analysis was performed according to meta-analytic procedures described by Greenland (15). For each included study, ORs were derived reflecting the risk of developing colon or rectal cancer associated with dietary intake of dairy products, calcium, and/or vitamin D followed by calculation of the natural logarithm of the estimated RR for each data set as well as calculation of an estimate of the variance. When both crude and adjusted RRs were provided, the most fully adjusted value was used. The 95% CI from each study was employed to calculate the variance the study's measure of effect. ORs/RRs for the highest vs. lowest intake categories were used. If these measures were missing, they were calculated using standard methods (16). Whenever possible, adjusted outcome measures were used for statistical pooling. If several outcomes were presented in a report, the estimate adjusted for the largest number of confounders was used.

A weight for each included report was calculated as 1/variance followed by a summation of the weights. The product of the study weight and the natural logarithm of the estimated RR was calculated and summed. Finally, a summary RR and 95% CI were calculated. A statistical test for homogeneity was performed (Q). This procedure tests the hypothesis that the effect sizes are equal in all of the included studies (16). If Q exceeds the upper tail critical value of chi-square ($P < 0.10$) at k–1 *df,* the observed variance in study effect sizes is greater than expected by chance if all studies shared a common population effect size. If the studies are not homogeneous, they are not measuring an effect of the same size, and calculation of a pooled estimate of effect may be of questionable validity. Explanations for the observed heterogeneity must be sought. Sensitivity analyses and/or further stratified analyses are then performed based on the magnitude of Q.

The potential for publication bias was not examined. Publication bias occurs because published studies may not be representative of all studies that have ever been done. The funnel plot method and other statistical tools have been constructed in an attempt to address this issue. Unfortunately, these methods lack firm statistical theoretical support and are not generally recommended for medical applications (17).

RESULTS

The initial electronic literature search yielded 1,112 citations in the form of abstracts. Initial screening reduced the total to 205 citations, which were subsequently entered onto an

"initial accept log." Full papers were obtained for all 205 and further screened for eligibility. Seventy-seven of these did not meet inclusion criteria, leaving 128 for final review.

Careful review of the remaining 128 revealed that 67 did not meet specified inclusion criteria for various reasons including lack of data on the outcome of interest, ecological/cross-sectional study design or biochemical study with no relevant dietary information, and lack of data to calculated 95% CIs for specified outcomes, among others. These citations were entered onto a reject log along with reasons for exclusion. This left 60 observational studies that constitute the database for the pooled analysis (18–77). All reports were entered onto an accept list and are summarized in Tables 1 and 2.

Twenty-six cohort and 34 case-control studies enrolling 26,335 colorectal cancer cases were available for analysis. Follow-up among cohort studies ranged from 3.3 to 24 yr (Refs. 24 and 23, respectively). Of the cohort studies, only Phillips and Snowdon (35) used colorectal cancer death as the endpoint of interest. Among 34 case-control studies, 10 used hospital-derived controls (45,49–52,59–61,63,65). White et al. (75) was the only analysis to examine calcium intake from supplements alone.

Calcium

Seventeen cohort studies provided data on calcium intake and colorectal cancer risk (total/dietary intake) (18–21,24–27,29,31,33,34,36,37,39,40,42), with almost all individual study estimates of effect less than 1, i.e., consistent with an inverse relationship between dietary calcium intake and risk of colorectal cancer. For this initial analysis and all subsequent ones, data on rectal cancer were pooled separately due to the fact that the epidemiology of tumors at these sites differ (78), suggesting possible differences in etiology.

Pooling relevant cohort studies using colorectal or colon cancer as the outcome of interest gave a summary RR of 0.77 (95% CI = 0.71–0.81). Q was not statistically significant (P = 0.21), indicating that pooling of studies was appropriate. The results based on pooling the 10 studies using colon cancer alone were similar [RR = 0.76 (95% CI = 0.69–0.84); (Q = 12.64, P = 0.70)]. Calcium intake was similarly analyzed for the 17 case-control studies of colon/colorectal cancer (46,49,50,53,55–60,63–65,67–69,73). Dietary/total calcium intake also showed an inverse relationship with colorectal cancer risk, i.e., a RR of 0.77 (CI = 0.72–0.82). The case-control data were statistically heterogeneous ($P < 0.001$), and sources of heterogeneity were sought.

Contrasting the relevant cohort vs. case-control studies, Tables 1 and 2 indicated that although the majority of cohort analyses examining dietary/total calcium intake used cohorts from the United States (11 of 17), only 6 of 17 case-control studies were conducted in the United States or North America. Differences in dietary habits, race, composition of dairy products, and other demographic differences between populations could contribute to the variability in these case-control reports (79). The case-control data were therefore stratified by geographic location. Pooling North American studies (United States and Canada) (53,55,64,67,69,73), there was no statistical heterogeneity (P value for Q = 0.13). The resultant RRs for total/dietary calcium intake and colorectal cancer risk from North American case-control studies was consistent with the cohort findings, i.e., RR of 0.55 (95% CI = 0.48–0.63), a statistically significant result. This indicates a 45% reduction in colorectal cancer risk with high vs. low intake of dietary/total calcium. Data for the remaining reports from various other locations showed continued heterogeneity (P value for Q = 0.002).

Among the 13 case-control studies using colon cancer as the endpoint of interest (49,50,53,55,56,58,59,64,65,67,68,69,73), the individual study ORs range from 0.4 (69) to 1.81 (56) (Table 2). Although the RRs from this meta-analysis gave a value similar to that seen for the pooled cohort data using colon/colorectal cancer as the endpoint, i.e., 0.77 (95% CI = 0.71–0.84), Q showed substantial heterogeneity ($P < 0.001$). Sensitivity analyses evaluating the effects of country of origin or source of controls did not suggest either factor as accounting for the heterogeneity. Although Ref. 69 accounted for over one-third of the observed statistical heterogeneity, Q remained statistically significant even if the data were pooled without including these data (P = 0.003). No clear source of heterogeneity was otherwise identified.

Using rectal cancer as the outcome of interest, the cohort studies examining dietary/total calcium intake (19,29,33,34,37,40,43) also showed an approximately 30% reduction in colorectal cancer risk [RRs = 0.72 (95% CI = 0.60–0.86)] without statistical heterogeneity (P = 0.92). For the 10 case-control studies with relevant data (49,50,52,58,59,64,65,68,72,76), the individual study ORs for rectal cancer risk associated with dietary/total calcium intake were largely less than 1 (i.e., an inverse relationship) and consistent with the above noted findings from cohort studies. The pooled RRs for case-control reports showed an inverse effect, i.e., RR = 0.89 (95% CI = 0.81–0.97), although analysis for Q showed substantial statistical heterogeneity (P = 0.001). The small number of studies available for analysis complicates a search for the source or sources of heterogeneity. Four of the case-control reports were from the United States (52,64,72,76), whereas the others originated in a wide variety of countries, e.g., Singapore, Uruguay, etc. The data presented by Whittemore et al. (76) contributed almost a third of the heterogeneity (data not shown). Although this report was from the United States, the subjects analyzed were all of Chinese ancestry. This could contribute to the observed heterogeneity, whereas several of the other reports showing substantial heterogeneity were hospital-based vs. population-based analyses (e.g., 49,52). Dropping Whittemore et al. (76) from the analysis and pooling only those studies using population derived controls (58,64,69,72) eliminated all observed heterogeneity with Q = 1.87, P = 0.60. The RR associated with the pooled population based case-control reports

TABLE 1
Characteristics of 26 cohort studies included in meta-analysis examining dietary calcium/dairy intake and colon cancer risk[a]

Lead Author/ Reference/Year	Cohort Description	Sex M/F Cases	Length of Follow-Up (yr)	No. Cases and Endpoint	Dietary Assessment	Dairy/Calcium Type	RR (95% CI)	Adjustments to RR
Bostick (18) 1993	US Iowa Women's Health Study cohort, 35,216 women, 55–69 yr	212F	5	212 CC	FFQ validated	Total Ca Dietary Ca Suppl. Ca Total Vit D Dietary Vit D Suppl. Vit D Total Dairy	0.68(0.41–1.11) 0.95(0.57–1.61) 0.66(0.43–1.02) 0.73(0.45–1.18) 0.98(0.61–1.58) 0.67(0.40–1.13) 0.72(0.45–1.36)	Age, energy, ht, parity, low-fat meat intake, total Vit E + age
Flood (19) 2005	US-Breast Cancer Detection and Demonstration Project cohort, 45,354 women	482F	8.5	482 CR 74 R 284 CC 112 DC 172 PC	FFQ validated	Dietary Ca Total Ca Suppl. Ca Dietary Ca Total Ca Dietary Ca Total Ca Dietary Ca Total Ca Dietary Ca Total Ca	0.74(0.56–0.98) CR 0.74(0.55–0.99) CR 0.76(0.56–0.98) CR 0.87(0.43–1.77) R 0.93(0.43–2.01) R 0.62(0.43–0.90) CC 0.69(0.48–0.99) CC 0.66(0.37–1.16) DC 0.71(0.40–1.26) DC 0.60(0.38–0.97) PC 0.68(0.42–1.08) PC	Age
Gaard (20) 1996	Norwegian National Health Screening Service cohort, 50,535 subjects	83M/60F	11.4	143 CC	FFQ validated	Total Ca (men) Total Ca (women) Milk (men) Milk (women)	0.57(0.29–1.13) 1.20(0.60–2.39) 0.72(0.25–2.07) 1.24(0.35–4.40)	Age, energy, ht, BMI, smoking
Garland (21) 1985	US-Western Electric Hawthorne Works cohort, 1,954 men	49M	19.0	49 CR	FFQ validated a	Dietary C Vitamin D	0.32(0.13–0.79) 0.54(0.31–1.0)	Age, smoking, BMI
Hsing (22) 1998	US-Lutheran Brotherhood Insurance Society cohort, 17,633 white males	125M	20	25 R 120 CC	FFQ validated	Dairy products[b]	0.6(0.3–1.3) CC 0.6(0.3–1.2) CR	Age, smoking, alcohol, total calories
Jarvinen (23) 2001	Finland Social Insurance Inst. Mobile Clinic cohort, 9,959 men and women	36M/36F	24	34R 38CC	FFQ validated	Milk products[c]	1.03(0.46–2.32) CR 0.37(0.12–1.39) CC 2.52(0.80–7.90) R	Age, BMI, occupation, smoking, energy, geographical area
						Milk (whole, low-fat, skim)	0.72(0.33–1.57) CR 0.46(0.14–1.46) CC 1.13(0.39–3.31) R	
						Fermented milk (buttermilk, cultured whole, yogurt)	1.28(0.68–2.40) CR 0.79(0.34–1.79) CC 2.67(0.91–7.80) R	
						Cheese	1.65(0.84–3.23) CR 2.42(0.91–6.43) CC 1.12(0.43–2.91) R	

						Butter	1.37(0.62–3.03) CR 0.90(0.30–2.67) CC 2.30(0.71–7.50) R	
						Vitamin D	1.74(0.82–3.68) CR 1.18(0.40–3.45) CC 2.54(0.89–7.27) R	
Kampman (24) 1994	Netherlands-The Netherlands Cohort Study 120,852 Dutch men and women	NG	3.3	215 CC 111 R	FFQ validated	Fermented milk unfermented milk[d] hard cheese Dietary Ca Nondairy Ca Fermented dairy product Ca Unfermented dairy product Ca	0.89(0.60–1.33) CR 0.86(0.57–1.29 CR 0.88(0.59–1.33) CR 0.92(0.64–1.34) CR 1.77(1.08–2.90) CR 1.14(0.77–1.68) CR 0.71(0.48–1.05) CR	Age, sex, family Hx, BMI, energy, chole-cystectomy, fat, fiber
Kato (25) 1997	US-The New York University Women's Health Study, 15,785 women	100F	7.1	84 CC 18 R	FFQ validated	Total Ca Dairy product Ca Dairy products	0.71(0.39–1.28) CR 0.65(0.38–1.11) CR 0.69(0.40–1.20) CR	Age, calorie intake, education, place of enrollment
Kearney (26) 1996	US-Health Professions Follow-up Study, 51,529 males, 40–75 yr old	203M	6.0	203 CC	FFQ validated	Total Ca Dietary Ca Dairy product Ca Nondairy product Ca Total Vit D Dietary Vit D Supplementary Vit D Dairy product Vit D Nondairy product Vit D Milk (whole, skim, low-fat) Ice cream Hard cheese Fermented dairy products	0.75(0.48–1.15) 0.81(0.52–1.28) 0.68(0.42–1.09) 0.86(0.50–1.48) 0.66(0.42–1.05) 0.88(0.54–1.42) 0.48(0.22–1.02) 0.75(0.47–1.22) 0.66(0.42–1.04) 0.87(0.52–1.44) 0.93(0.42–2.04) 1.35(0.67–2.75) 1.09(0.70–1.72)	Age, BMI, family Hx, physical activity, Previous polyp, screening, energy, Saturated fat, fiber, red meat, aspirin, alcohol, smoking
Keese (27) 2005	France- The E3N-EPIC Prospective Study, 100,000 women, aged 40–65 yr	172F	6.9	172 CR	FFQ validated	Total Ca Dairy product Ca Total Vit D Total dairy Milk Yogurt Cottage cheese Cheese	0.72(0.47–1.10) 0.86(0.56–1.32) 0.89(0.58–1.36) 0.78(0.49–1.22) 0.54(0.33–0.89) 0.82(0.54–1.25) 0.71(0.46–1.08) 0.97(0.61–1.54)	Education, smoking, family Hx, BMI, physical activity, energy intake, alcohol intake
Kojima (28) 2004	Japan- Japan Collaborative Cohort Study	254M/203F	9.9	284 CR 173 R	FFQ validated	Milk (men) (women) Yogurt (men)(women)	1.22(0.74–2.02) CC 1.05(0.64–1.71) R 1.16(0.71–1.90) CC 1.64(0.70–3.82) R 0.80(0.42–1.51) CC 0.46(0.21–1.02) R 0.97(0.61–1.56) CC	Age, family Hx, BMI, alcohol intake, smoking, Walking time/day, education, region of

(Continued on next page)

TABLE 1
Characteristics of 26 cohort studies included in meta-analysis examining dietary calcium/dairy intake and colon cancer risk[a] *(Continued)*

Lead Author/ Reference/Year	Cohort Description	Sex M/F Cases	Length of Follow-Up (yr)	No. Cases and Endpoint	Dietary Assessment	Dairy/Calcium Type	RR (95% CI)	Adjustments to RR
							1.51(0.60–3.80) R	enrollment
						Cheese (men) (women)	1.17(0.68–2.01) CC	
							1.19(0.70–2.02) R	
							1.01(0.61–1.69) CC	
							2.52(1.11–5.72) R	
						Butter (men)	0.88(0.53–1.46) CC	
							1.18(0.66–2.09) R	
						(women)	1.07(0.67–1.72) CC	
							1.29(0.54–3.08) R	
Larsson (29) 2006	Sweden- Cohort of Swedish Men 45,306 men aged 45–79 yr	449M	6.7	449 CR-total 276 CC 124 PC 131 DC 173 R 21 unspeci-fied	FFQ validated	Total calcium	0.68(0.51–0.91) CR	Age, education, family Hx, BMI, exercise, Hx diabetes, smoking, aspirin use, vitamin use, total energy, saturated fat intake,
							0.72(0.50–1.04) CC	
							0.58(0.33–1.00) PC	
							0.83(0.49–1.40) DC	
							0.61(0.38–0.98) R	
						Total dairy	0.46(0.30–0.71) CR	Vitamin D intake, alcohol, fruit, red meat, and vegetable intake
							0.44(0.25–0.76) CC	
							0.37(0.16–0.88) PC	
							0.43(0.20–0.93) DC	
							0.48(0.23–0.99) R	
						Milk (whole, low fat, medium fat)	0.67(0.51–0.87) CR	
							0.65(0.46–0.91) CC	
							0.76(0.45–1.30) PC	
							0.53(0.33–0.87) DC	
							0.69(0.45–1.06) R	
						Cultured milk	1.07(0.86–1.34) CR	
							1.17(0.88–1.56) CC	
							1.10(0.72–1.69) PC	
							1.26(0.84–1.91) DC	
							0.94(0.66–1.33) R	
						Cream/cream cheese	0.84(0.65–1.09) CR	
							0.72(0.52–1.01) CC	
							0.70(0.42–1.17) PC	
							0.72(0.45–1.14) DC	
							1.12(0.74–1.70) R	
						Hard cheese	0.79(0.56–1.12) CR	
							0.78(0.51–1.21) CC	
							0.76(0.40–1.43) PC	
							0.87(0.45–1.70) DC	
							0.80(0.45–1.41) R	

						Cottage/cream cheese	0.68(0.40–1.16) CR 0.88(0.48–1.59) CC 0.98(0.42–2.29) PC 0.93(0.40–2.17) DC 0.36(0.11–1.15) R	
Larsson (30) 2005	Sweden- Swedish mammography cohort, 60,708 women, aged 40–76 yr	798F	14.8	543 CC 246 PC 170 DC 127 un-known 249 R	FFQ validated	Dairy (high-fat)[e]	0.59(0.44–0.79) CR 0.84(0.50–1.42) PC 0.28(0.14–0.56) DC 0.62(0.37–1.02) R	Age, education, family Hx, BMI, smoking, total energy, cereal fiber, folate,
						Milk (whole)	1.08(0.90–1.29) CR 1.58(1.15–2.16) PC 0.72(0.47–1.10) DC 0.99(0.72–1.37) R	Vitamin B6, contraceptives hormones
						Milk (full-fat cultured)	0.81(0.66–1.00) CR 0.80(0.56–1.15) PC 0.71(0.44–1.13) DC 0.91(0.62–1.31) R	
						Cheese	0.65(0.44–0.96) CR 0.76(0.39–1.50) PC 0.24(0.07–0.82) DC 0.89(0.46–1.71) R	
						Butter	0.80(0.64–1.00) CR 1.10(0.75–1.61) PC 0.63(0.37–1.08) DC 0.75(0.50–1.11) R	
Lin (31) 2004	US- Women's Health Study, 37,547 women, aged ≥ 45yrs	223F	8.7	202 CR 83 PC 75 DC 41 R 4 unkown	FFQ validated	Dairy (high-fat) Dairy (low-fat)	0.98(0.65–1.56) CR 1.02(0.65–1.59) CR	Age, random treatment assignment, BMI, family Hx, Hx of polyps, physical activity, smoking, alcohol intake, hormone Tx, energy intake
Lin (32) 2005		US-Women's Health Study, 36,976 women	10	223 CR 174 CC 46 R	FFQ validated	Total calcium Dietary calcium Calcium suppl. Total vitamin D Dietary vitamin D Vitamin D suppl. Dairy products Milk Milk-fermented	1.20(0.79–1.85) CR 0.90(0.53–1.54) CR 1.30(0.90–1.87) CR 1.34(0.84–2.13) CR 0.96(0.60–1.55) CR 1.36(0.95–1.95) CR 0.89(0.54–1.47) CR 1.12(0.72–1.74) CR 1.11(0.69–1.77) CR	Age, BMI, family history, Hx polyps, physical activity, smoking, red meat intake, alcohol intake, total energy, saturated fat intake, multivitamin use, menopausal status, hormone therapy use

(Continued on next page)

TABLE 1
Characteristics of 26 cohort studies included in meta-analysis examining dietary calcium/dairy intake and colon cancer risk[a] *(Continued)*

Lead Author/ Reference/Year	Cohort Description	Sex M/F Cases	Length of Follow-Up (yr)	No. Cases and Endpoint	Dietary Assessment	Dairy/Calcium Type	RR (95% CI)	Adjustments to RR
[g]Martinez (33) 1996	US-Women's Health Study, 89,448 females, 30–55 yr old at enrollment, 1976	501F	12	501 CR 396 CC 105 R	FFQ validated	Dietary Ca Dietary Vit D Total Vit D Dairy product Ca Dairy product Vit D Milk (all types) Dietary Ca Dietary Vit D Total Vit D	0.74(0.53–1.05) CR 0.77(0.54–1.09) CR 0.67(0.47–0.95) CR 0.92(0.69–1.21) CR 0.85(0.64–1.12) CR 0.90(0.56–1.42) CR 0.98(0.52–1.75) CC 0.72(0.15–2.61) R 1.19(0.72–1.96) CC 0.51(0.15–1.35) R 0.90(0.58–1.35) CC 0.47(0.18–1.22) R	Age, BMI, physical activity, family Hx, aspirin use, smoking, red meat intake, alcohol use
McCullough (34) 2003	US- Cancer Prevention Study II Nutrition Cohort, 60,866 men, 66,883 women	421M/262F	5	683 CR	FFQ validated	Dairy[f] (both sexes) (men) (women) Milk (both sexes) (men) (women) Dietary Ca (both sexes) (men) (women) Supplemental Ca (both sexes) (men) (women) Total Ca (both sexes) (men) (women) Total Vit D (both sexes) (men) (women) Dietary Vit D (both sexes) (men) (women) Dairy products Milk	1.00(0.75–1.34) CR 0.96(0.67–1.38) CR 1.11(0.68–1.83) CR 0.96(0.78–1.18) CR 0.86(0.66–1.11) CR 1.18(0.84–1.65) CR 0.92(0.72–1.47) CR 0.82(0.60–1.13) CR 1.08(0.72–1.63) CR 0.69(0.49–0.96) CR 0.60(0.33–1.10) CR 0.73(0.49–1.10) CR 0.87(0.67–1.12) CR 0.82(0.58–1.16) CR 0.94(0.63–1.39) CR 0.80(0.62–1.02) CR 0.71(0.51–0.98) CR 1.00(0.68–1.47) CR 0.92(0.71–1.18) CR 0.83(0.60–1.15) CR 1.08(0.72–1.62) CR 0.84(0.54–1.29) CC 0.49(0.24–1.03) PC 1.18(0.55–2.57) DC 1.22(0.64–2.33) R 0.81(0.60–1.10) CC 0.68(0.42–1.09) PC 0.92(0.54–1.58) DC 0.89(0.54–1.47) R	

						Dietary Ca	0.83(0.57–1.23) CC 0.81(0.45–1.47) PC 0.91(0.41–2.00) DC 0.79(0.45–1.40) R	
						Total Ca	0.74(0.49–1.12) CC 0.57(0.28–1.13) PC 1.00(0.47–2.13) DC 1.01(0.53–1.93) R	
						Dietary Vit D	0.72(0.49–1.05) CC 0.64(0.36–1.13) PC 0.74(0.33–1.63) DC 1.11(0.58–2.15) R	
						Total Vit D	0.58(0.39–0.86) CC 0.72(0.39–1.31) PC 0.50(0.24–1.04) DC 1.01(0.54–1.88) R	
Phillips (35) 1985	US- Seventh Day Adventist cohort, 25,493 subjects 30 yr and older	285M and F	21	285 CR/deaths	FFQ validated	Milk (both sexes) (males) (females) Cheese (both sexes) (males) (females)	0.7(0.8–1.6) CR 1.2(0.6–2.7) R 0.5(0.2–1.1) CC 1.1(0.5–2.2) CC 1.1(0.8–1.6) CR 1.0(0.5–2.2) R 1.9(1.0–3.6) CC 0.8(0.5–1.45) CC	Age, sex
Pietinen (36) 1999	Finland- Alpha Tocopherol Beta-Carotene Cancer Prevention Study, 27,111 men aged 50–69 yr	185M	8	185 CR	FFQ validated	Total Ca Vitamin D Milk products Sour milk products	0.6(0.4–0.9) CR 1.0(0.7–1.5) CR 0.6(0.4–0.9) CR 1.1(0.7–1.3) CR	Age, smoking, BMI, alcohol, education, phyical activity, Ca intake
Shin (37) 2006	US- Shanghai Women's Health Study, 73,314 women, aged 40–70 yr	283F	5.7	165 CC 118 R	FFQ validated	Total Ca	0.6(0.3–1.0) CR 0.6(0.3–1.1) CC 0.6(0.2–1.4) R	Age, menopause education, smoking, alcohol, family Hx, calorie intake, vitamin supplement use
Singh (38) 1998	US- Advent Health Study 32,051 white men, mean age 53 yr	157 (65M/92F)	6	156CR	FFQ validated	Milk (whole) (non-fat) (low-fat) Cheese Cottage cheese	1.04(0.69–1.59) CR 0.78(0.48–1.28) CR 0.97(0.66–1.42) CR 1.31(0.84–2.03) CR 0.74(0.49–1.11) CR	Age, sex, BMI, physical activity, family Hx, smoking, alcohol, and aspirin use
Stemmerman (39) 1990	US/Hawaii/Japanese Japan-Hawaii Cancer Study, 8,006 men	277M	22	277CR 189CC 88R	FFQ validated	Total calcium Dairy calcium Nondairy calcium	0.77(0.56–1.11) CR 0.83(0.56–1.11) CR 0.91(0.63–1.25) CR	Age

(Continued on next page)

TABLE 1
Characteristics of 26 cohort studies included in meta-analysis examining dietary calcium/dairy intake and colon cancer risk[a] *(Continued)*

Lead Author/ Reference/Year	Cohort Description	Sex M/F Cases	Length of Follow-Up (yr)	No. Cases and Endpoint	Dietary Assessment	Dairy/Calcium Type	RR (95% CI)	Adjustments to RR
Terry (40) 2002	Sweden- Central Sweden, 61,463 women /mammography cohort	572F	11.3	572 CR 371 CC 191 R 10 both R and CC	FFQ validated	Dietary Ca	0.72(0.56–0.93) CR 0.74(0.54–1.01) CC 0.87(0.55–1.39) PC 0.45(0.26–0.79) DC 0.70(0.45–1.09) R	Age, BMI, education, quartile of red meat, alcohol, energy adjusted fat, folic acid, Vit C, Vit D
						Vitamin D	1.05(0.83–1.33) CR 1.24(0.92–1.66) CC 0.87(0.55–1.37) PC 1.57(0.93–2.68) DC 0.74(0.49–1.10) R	
						Total dairy	0.97(0.73–1.29) CR 1.03(0.72–1.47) CC 1.32(0.77–2.28) PC 0.71(0.38–1.30) DC 1.04(0.64–1.71) R	
						Low-fat dairy	0.94(0.91–1.23) CR 1.01(0.72–1.42) CC 1.00(0.60–1.66) PC 0.84(0.45–1.56) DC 0.79(0.49–1.27) R	
						Fermented dairy (yogurt, cultured milk)	0.90(0.72–1.13) CR 0.76(0.57–1.01) CC 0.67(0.44–1.03) PC 0.80(0.47–1.35) DC 1.28(0.87–1.89) R	
						Nonfermented dairy (milk, cheese)	0.99(0.76–1.29) CR 1.10(0.79–1.52) CC 1.43(0.87–2.37) PC 0.64(0.37–1.10) DC 0.83(0.53–1.31) R	
Ursin (41) 1990	Norway	NG	11.5	92 CC 63 R	FFQ validated	Milk	0.85(0.54–1.33) CC 0.85(0.49–1.19) R	Age, place of residence, sex

Wu (42) 2002	US- Nurse's Health Study and Health Professionals Follow-Up Study cohorts, 87,998 women and 47,344 men	399M/626F	10	1,025 CC 426 PC 411 DC	FFQ validated	Total Ca (males) (females) (males) (females) (males) (females) (both sexes) Dietary Ca (males) (females) Dairy Ca (males) (females) Nondairy Ca (males) (females) Supplemental Ca (males) (females) (both sexes)	0.64(0.43–0.95) CC 0.94(0.66–1.33) CC 0.92(0.45–1.87) PC 1.28(0.75–2.16) PC 0.58(0.32–1.05) DC 0.73(0.41–1.27) DC 1.14(0.72–1.81) PC 0.65(0.43–0.98) DC 0.67(0.46–0.96) CC 0.97(0.68–1.38) CC 0.78(0.53–1.16) CC 0.78(0.50–1.21) CC 1.02(0.73–1.43) CC 1.03(0.70–1.54) CC 0.70(0.43–1.14) DC 0.69(0.48–1.00) DC 0.69(0.51–0.94) DC	
Zheng (43) 1998	US- Iowa Women's Health Study Cohort, 41,836 women aged 55–69 y	144F	9	144 R	FFQ validated	Total Ca Total Vit D	0.59(0.37–0.94) R 0.76(0.50–1.16) R	Age, smoking, pack/yr smoking, use of hormone replacement therapy, total energy intake

[a] Abbreviations are as follows: RR, relative risk; CI, confidence interval; CC, colon cancer; CR, colorectal; DC, distal colon; ht, height; M, male; F, female; NG, not given; PC, proximal colon; R, rectal cancer; Ca, calcium; suppl., supplemental.
[b] Milk and ice cream.
[c] Milk, fermented milk, cheese, cream, ice cream.
[d] Whole milk, low-fat/skim milk.
[e] Whole milk, full-fat cultured milk, cheese, cream, full-fat sour cream, reduced-fat sour cream, and low-fat cultured milk.
[f] Whole milk, low-fat milk, skim milk, cheese, yogurt, ice-cream.
[g] Mortality study.

TABLE 2
Characteristics of 34 case-control studies included in meta-analysis examining dietary calcium/dairy intake and colon cancer risk[a]

Lead Author/ Reference/Year	Location of Study	No. of Cases and Endpoint	Sex, No. (M/F)	No. Controls and Type	Dietary Assessment	Dairy Type	OR (95% CI)[b]	Adjustments to OR
Benito (44) 1990	Majorca	286 CR 156 CC 130 R	151M/135F	581 P	FFQ validated	Dairy	2.00(1.24-3.24)	CR Age, wt, sex
Bidoli (45) 1992	Italy	248 CR 123 CC 125 R	155M/93F	699 H	FFQ nonvalidated	Milk Cheese	1.13(0.72–1.78) CC 1.14(0.72–1.79) R 1.36(0.88–2.11) CC 1.64(1.03–2.63) R	Age, sex, social status
Boutron (46) 1996	France	171 CR	109M/62F	427 P	FFQ validated	Calcium (nondairy) Calcium Dairy calcium Vitamin D Milk (all) Milk (low-fat) Cheese Cottage cheese Yogurt	1.7(0.8–2.3) CR 1.6(0.8–3.0) CR 1.8(0.9–3.4) CR 0.8(0.4–1.6) CR 1.2(0.6–2.2) CR 1.0(0.5–1.9) CR 1.2(0.6–2.2) CR 1.2(0.8–1.9) CR 1.0(0.6–1.6) CR	Age, sex, caloric intake
Centonze (47) 1994	Italy	132 CR total 62 CC 56 R	132MF	132 P	FFQ validated	Dairy products Milk Milk products Cheese Fresh curd cheese	0.46(0.22–1.04) CR 0.62(0.23–1.62) CR 0.91(0.46–1.79) 0.71(0.37–1.37) 1.09(0.46–1.79)	Age, education, smoking, change in diet in past 10 yr, sex
Chiu (48) 2003	China	931 CC	462M/469F	1,552 P	FFQ validated	Dairy (males) (females)	0.9(0.7–1.3) CC 1.0(0.7–1.4) CC	Age, total energy, income, physical activity
De Stefani (49) 1997	Uruguay	282 CR total 153 CC 129 R	282MF	564 H	FFQ validated	Calcium	0.41(0.24–0.69) CR 0.46(0.24–0.89) CC 0.36(0.18–0.72) R	Age, sex, residence, total energy, protein, total fat, folate intake
Ferraroni (50) 1994	Italy	1,326 CR total 828 CC 498 R	711M/615F	2,024 H	FFQ validated	Calcium Vitamin D	0.84(0.65–1.08) CR 0.73(0.54–0.97) CC 1.05(0.75–1.49) R 0.74(0.58–0.95) R 0.75(0.56–1.01) CC 0.73(0.51–1.03)	Age, sex, education family Hx, BMI, total energy, intake
Francheschi (51) 1999	Italy	1,953C R total 1,225 CC 728 R	1125M/828F	4,154 H	FFQ validated	Milk Cheese	0.83(0.68–1.01) CR 0.99(0.82–1.19) CR	Age, center, education, physical activity, total energy intake

Freudenheim (52) 1990	US	422R	277M/145F	422H	FFQ validated	Calcium (males) (females)	1.51(0.94–2.44) R 1.63(0.91–2.91) R	Age, sex, neighborhood
Ghadirian (53) 1997	Canada	402 CC	200M/202F	668 P	FFQ validated	Calcium	0.69(0.47–1.00) CC	Age, sex, family Hx, total energy intake
Iscovich (54) 1992	Aregentina	110 CC	62M/48F	220 P	FFQ validated	Milk (whole) (skim milk) Cheese	1.56(0.78–3.12) 0.88(0.50–1.52) 1.93(0.93–4.02)	Age, sex, place of residence
Kampman (55) 2000	US	1993 CC	1095M/888F	2,410P	FFQ validated	Calcium (dietary) (men) (women) Vitamin D (men) (women) Calcium supplements (men) (women) Vitamin D supplements (men) (women)	0.7(0.5–0.9) 0.6(0.4–0.9) 1.4(1.0–2.2) 1.1(0.7–1.7) 0.8(0.6–1.1) 0.8(0.6–0.9) 0.5(0.2–1.1) 0.6(0.4–1.1)	Age, BMI, family Hx, aspirin/NSAID use, energy intake, physical activity, fiber, Ca
Kampman (56) 1994	Netherlands	232 CC	232MF	259 P	FFQ validated	Milk (whole) (skim/low-fat) Dairy products (fermented) (unfermented) Buttermilk Yogurt Hard cheese Calcium (total) Dietary) (fermented dairy products) (unfermented dairy products) (nondairy products)	0.95(0.54–1.68) 1.15(0.71–1.84) 1.06(0.61–1.82) 1.59(0.89–2.85) 0.94(0.59–1.50) 1.49(0.89–2.49) 1.18(0.69–2.01) 1.81(1.05–3.12) 1.26(0.74–2.16) 1.10(0.63–1.91) 0.69(0.36–1.32)	Age, sex, urbanization, total energy intake, fat intake, fiber, Vit C, alcohol
Kune (57) 1987	Australia	715 CR 392 CC 323 R	388M/327F	727 P	FFQ validated	Milk Calcium (males) (females)	2.37(1.57–3.58) CR 1.07(0.68–1.67) CR 0.56(0.34–0.91) CR	Age, sex
La Vecchia (58) 1997	Italy	1,953 CR 1,225 CC 728 R	1,125M/828F	4,154 P	FFQ validated	Calcium (males) (females) Vitamin D (males) (females)	0.72(0.6–0.9) CR 0.92(0.8–1.0) CC 0.90(0.8–1.1) R 1.06(0.9–1.2) CR 0.71(0.6–0.8) CR 0.77(0.6–0.9) CR 0.81(0.7–0.9) CC 1.03(0.9–1.2) R 1.00(0.9–1.1) CR 0.73(0.6–0.9) CR	Age, center, sex, education, physical activity, total energy intake, fiber intake
Lee (59) 1989	Singapore	203 CR 132 CC 71 R	121M/82F	425 H	FFQ validated	Calcium Total milk	0.83(0.54–1.27) CR 0.88(0.53–1.45) CC 0.75(0.39–1.45) R 0.92(0.60–1.34) CR 0.81(0.49–1.33) CC 1.12(0.59–2.10) R	Age, sex, Chinese dialect group, occupation

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TABLE 2
Characteristics of 34 case-control studies included in meta-analysis examining dietary calcium/dairy intake and colon cancer risk[a] *(Continued)*

Lead Author/ Reference/Year	Location of Study	No. of Cases and Endpoint	Sex, No. (M/F)	No. Controls and Type	Dietary Assessment	Dairy Type	OR (95% CI)[b]	Adjustments to OR
Levi (60) 2000	Switzerland	223 CR 119 CC 104 R	142M/81F	491 H	FFQ validated	Calcium Vitamn D	0.96(0.5–1.7) CR 1.46(0.9–2.3) CR	Age, sex, education, smoking, alcohol, BMI, physical activity, energy intake, fiber intake
Levi (61) 1999	Switzerland	223 CR 119 CC 104 R	142M/81F	491 H	FFQ validated	Milk Cheese	0.72(0.45–1.17) CR 1.66(1.07–2.59) CR	Age, sex, education, smoking, alcohol, BMI, physical activity, energy intake
Ma (62) 2001	United States	193 CR	193M	318 P	FFQ validated	Calcium (from dairy) Calcium (milk) Milk (skim)	0.62(0.38–1.02) 0.66(0.40–1.09) CR 0.39(0.17–0.87) CR	CR Age, smoking, BMI, alcohol, vitamin use, aspirin use, exercise, insulin-like growth factor (IGF-1) to IGF binding protein 3 ratio
Macquart-Moulin (63) 1986	France	399 CR 246 CC 153 R	202M/197F	399 H	FFQ validated	Milk (whole + skim) cheese Calcium	0.65(0.44–0.96) CR 0.72(0.49–1.08) CR 0.62(0.42–0.92) CR	
Marcus (64) 1998	United States	348 CC 164 R	512 F	678 P	FFQ validated	Calcium (total) (dietary) (supplements) Vitamin D (total) (dietary) (supplemental)	0.6(0.4–1.0) CC 0.6(0.3–1.1) R 0.8(0.5–1.4) CC fat 0.7(0.3–1.3) R 1.0(0.7–1.6) CC 0.8(0.5–1.6) R 0.7(0.4–1.1) CC 0.8(0.5–1.5) R 0.8(0.5–1.3) CC 0.9(0.4–1.6) R 0.8(0.6–1.1) CC 0.9(0.6–1.4) R	Age, energy intake, dietary fiber, saturated fat, animal
Negri (65) 1990	Italy	910 CR 558 CC 352 R	478M/432F	1,032 H	FFQ nonvalidated	Calcium	1.1(0.8–1.6) CC 1.2(0.8–1.9) R	Age, sex, education, residence, consumption of pasta/rice/meat green vegetables, coffee

						Milk	1.0(0.7–1.3) CC 1.0(0.7–1.3) R	
						Cheese	1.1(0.8–1.4) CC 1.3(1.0–1.8) R	
Olsen (66) 1994	Denmark	49 CR 32 CC 17R	NG	362 P	FFQ validated	Vitamin D	0.81(0.3–2.0) CR	Age, sex, energy intake, BMI
Peters (67) 1992	United States	746 CC	419M/327F	746 P	FFQ validated	Calcium (dietary) (men) (women) Vitamin D (men) (females)	0.42(0.25–0.69) CC 0.49(0.29–0.83) CC 0.46(0.25–0.85) CC 1.08(0.97–1.20) CC 1.10(0.95–1.26) CC 1.08(0.90–1.28) CC	Weight, family Hx, physical activity source of energy
Pritchard (68) 1996	Sweden	569 CR 352 CC 217 R	270M/299F	512 P	FFQ nonvaidated	Calcium (male) (female) Vitamin D (male) (female) Milk products Ice cream Cheese	1.2(0.7–2.1) CC 1.0(0.5–1.9) R 1.6(0.7–3.7) CC 1.0(0.4–2.5) R 1.0(0.5–2.0) CC 0.9(0.4–2.1) R 0.6(0.4–1.0) CC 0.5(0.3–0.9) R 0.9(0.4–1.8) CC 0.9(0.4–1.8) CC 0.8(0.3–1.8) R 0.4(0.2–0.9) CC 0.3(0.1–0.8) R 1.1(0.7–1.6) CR 1.4(0.7–3.1) CR 1.0(0.8–1.4) CR	Age, sex, energy and protein intake
Satia-Abouta (69) 2003	United States	613 CC	321M/292F	996 P	FFQ validated	Calcium (Whites) (Blacks)	0.4(0.3–0.6) CC 0.6(0.3–1.1) CC	Age, sex, BMI, education, smoking, physical activity, family Hx, NSAID use, vitamin/mineral suppl. use, dietary fiber, calcium, fruits/vegetable total energy
Satia-Abouta (70) 2004	United States	613CC	321M/292F	996P	FFQ validated	Daily (Whites) (Blacks)	0.8(0.5–1.2) CC 0.7(0.4–1.2) CC	BMI, smoking, physical activity, family Hx, NSAID use, fat/carbohydrate/dietary fiber/vitamin C vitamin E/calcium/beta carotene/fruit/vegetable intake, energy

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TABLE 2
Characteristics of 34 case-control studies included in meta-analysis examining dietary calcium/dairy intake and colon cancer risk[a] *(Continued)*

Lead Author/ Reference/Year	Location of Study	No. of Cases and Endpoint	Sex, No. (M/F)	No. Controls and Type	Dietary Assessment	Dairy Type	OR (95% CI)[b]	Adjustments to OR
Shannon (71) 1996	United States	424 CC	238M/186F	414 P	FFQ validated	Total dairy (men (women) High-fat dairy (men) (women) Low-fat dairy (men) (women)	0.92(0.49–1.71) CC 0.40(0.21–0.79) CC 0.73(0.41–1.30) CC 0.92(0.47–1.83) CC 1.00(0.58–1.71) CC 0.61(0.34–1.09) CC	Age, total energy intake
Slattery (72) 2004	United States	952 R	559M/393F	1,205 P	FFQ validated	Calcium (men) (women) Vitamin D (men) (women) Dairy products (men) (women) Dairy products (low-fat) (men) (women) Dairy products (high-fat) (men) (women)	1.02(0.66–1.56) R 0.39(0.24–0.64) R 1.08(0.73–1.60) R 0.52(0.32–0.85) R 1.08(0.65–1.80) R 0.64(0.32–1.30) R 0.84(0.60–1.18) R 0.61(0.39–0.94) R 1.10(0.63–1.91) R 1.28(0.60–2.73) R	Age, physical activity, energy fiber, BMI, NSAID use
Slattery (73)1988	United States	231 CC	112M/119F	391 P	FFQ validated	Calcium (males) (females) Dairy products (males) (females)	0.41(0.19–0.88)CC 0.50(0.24–1.06)CC 0.44(0.23–0.84) CC 0.53(0.28–0.99) CC	Age, religion, crude fiber,caloric intake
Steinmetz (74) 1993	Australia	220 CC	220MF	438 P	FFQ validated	Dairy (males) (females)	1.14(0.58–2.24) CC 1.61(0.76–3.40) CC	Occupation alcohol intake BMI
Whte (75) 1997[b]	United States	444 CC	251M/193F	Telephone interview		Calcium (both sexes) (men) (women)	0.78(0.52–1.18) CC 0.88(0.49–1.57) CC 0.71(0.40–1.26) CC	Age, sex (supplements only)
Whittemore (76) 1990[c]	United States Canada	180 R	180MF	1,192 P	Interview	Calcium	0.31(0.16–0.63) R	Age, physical inactivity, saturated fat, crude fiber, beta-carotene
Young (77) 1988	United States	353 CC	159M/194F	618 P	FFQ validated	Milk Milk (cultured)	1.12(0.82–1.54) CC 0.65(0.41–1.01) CC	Age, sex, interaction term age, sex

[a] Abbreviations are as follows: P, population; H, hospital; CR, colorectal cancer; CC, colon cancer; MF, male/female; R, rectal cancer; Hx, history; BMI, body mass index; Ca, calcium; Vit, vitamin; wt, weight; NSAID, nonsteroidal anti-inflammatory drugs.
[b] Study examined calcium from supplements only.
[c] Analyzed Chinese men and women in North America.

was 0.87 (95% CI = 0.86–0.96), a result consistent with the above noted data from the cohort analyses.

Data were also available examining the impact of dietary/total calcium intake on specific colon subsites from 5 cohort studies, i.e., distal and proximal colon (19,29,34,40,42). Three of these reports were from the United States (19,34,42), and the shortest follow-up time was 5 yr (34). Pooled data using distal colon cancer as the outcome showed an inverse relationship between calcium intake and cancer risk, RR = 0.67 (95% CI = 0.53–0.83), with no observed statistical heterogeneity (P = 0.65 for Q). Calcium showed similar effects at the proximal colon, with high vs. low intake associated with a 25% reduction in cancer risk [RR = 0.75 (95% CI = 0.62–0.91)]. This summary RR was statistically significant, with Q consistent with a lack of heterogeneity ($P = 0.43$).

Milk/Dairy

As detailed in Table 1, 14 cohort studies provided 20 point estimates for the effect of milk on the risk of colon/colorectal cancer (20,23,24,26–31,33–35,38,41). Pooling the homogeneous data (P value for Q = 0.27) showed that those with "high" intakes of milk (all types) vs. low, as defined by individual authors, showed, on average, a 10% reduction in colon/colorectal cancer risk, RR = 0.90 (95% CI = 0.83–0.97). The summary RR derived by pooling only those cohort studies that used colon cancer vs. colorectal cancer as the outcome (20,23,24,26,29,34,35,41) was 0.78 (95% CI = 0.67–0.92). As discussed below, it appears that milk may have a more profound effect on colon cancer risk than rectal cancer, and the inclusion of rectal cases in an outcome variable such as "colorectal" cancer could attenuate the summary measure of effect. It could also contribute to differences in outcome across studies due to differing proportions of rectal cancer cases. Lack of stratification on milk type across reports precluded any further characterization of these data, although it remains possible that different milk types may show differing effects on disease risk. The available cohort studies examining the effects of dairy products on colorectal cancer risk (18,22–25,27,29,31,32,34,36,40) showed similar attenuations of risk, i.e., RR of 0.84 (95% CI = 0.75–0.95).

Data on milk intake and colon/colorectal cancer risk were available from 13 case-control analyses (see Table 2) (45–47,51,54,56,57,59,61–63,65,77). The Q statistic for these pooled reports revealed that the case-control data were largely homogeneous with the exception of Kune et al. (57). This report accounted for over half the calculated value of Q and exclusion of Kune et al. (57) from the statistical pooling eliminated all observed heterogeneity. That is, calculation of a summary RR for the effects of milk on colon/colorectal cancer risk changed from 0.96 (95% CI = 0.86–1.06) to 0.90 (95% CI = 0.81–1.00), with the latter RRs showing no statistical heterogeneity ($P = 0.31$). The analysis by Kune et al. (57) was based on subjects from Australia. The individual study OR for this report was 2.37, i.e., a more than doubling of the risk of colorectal cancer among high-dairy users. This result is not consistent with the findings of the majority of case-control reports examining this endpoint, as seen in Table 2, and the possible reasons for such an outlier are unclear based on available information. The pooled homogeneous data from case-control studies provide results consistent with the findings of the relevant cohort studies.

Milk intake was not associated with rectal cancer risk. Seven cohort studies (23,28,29,30,34,35,41) with homogeneous data ($P = 0.70$) gave a RR of 0.95 with a nonstatistically significant 95% CI of 0.80–1.14. Only 3 case-control studies analyzed the effects of milk on the risk of rectal cancer (i.e., 45,59,65). These reports yielded a RR of 1.01 (95% CI = 0.79–1.28), showing no effect of milk on disease risk at this site. Despite the fact that the data were homogeneous (Q = 0.45, $P = 0.80$), the sparse data limit further interpretation.

Vitamin D

Ten cohort studies, enrolling a total of 2,813 cancer cases, evaluated the effects of dietary vitamin D on colon/colorectal cancer risk (18,21,23,26,27,32,33,34,36,40) (P for Q = 0.13). Pooling these data yielded a summary RR of 0.94 (95% CI = 0.83–1.06). Five of the available cohort analyses used rectal cancer as the outcome of interest (23,33,34,40,43). Statistically pooling this latter set of data indicated a 17% reduction in rectal cancer risk with high vs. low vitamin D intake, i.e., RR = 0.83 (95% CI = 0.70–1.04; P value for Q = 0.66). Table 3 highlights several issues that may attenuate the demonstrated effect of vitamin D in the pooled analysis, i.e., relatively low vitamin D intakes across the included studies. These differences may also contribute to the statistical heterogeneity seen when pooling data from the case-control studies looking at vitamin D intake and risk of colorectal or rectal cancer. The RRs for the pooled case-control studies with rectal cancer as the outcome showed a small reduction in risk; RR = 0.91 (95% CI = 0.82–1.03). As above, low and variable vitamin D intakes across studies of various designs and its impact on interpretability of the existing data have been discussed in detail elsewhere (80). This factor, along with country of origin, could attenuate the pooled RRs and contribute to observed statistical heterogeneity (80,81).

Calcium Supplements

The effects of calcium supplements on colorectal cancer risk were also examined in 5 cohort studies (18,19,32,34,42), with all but one study showing a protective effect (32). All 5 were conducted in the United States. Quantification of supplement intake differed somewhat across reports and was generally crudely defined, e.g., Wu et al. (42) dichotomized supplement intake as less than or equal to 700 mg/day or $\geq$700 mg/day. Refs. 18, 32, and 34 each showed ranges of intake between 0 mg/day and greater than 500 mg/day.

The RR associated with calcium supplement use was 0.76 (95% CI = 0.65–0.89), consistent with a 24% reduction in colorectal cancer risk, with Q demonstrating no statistical

TABLE 3
Baseline calcium/vitamin D intakes and study stratification ranges[a]

Lead Author (Reference)	Average Ca Intake (mg/day)	Ca Stratification Range (mg/day)	Average Vitamin D Intake (IU/day)	Vitamin D Stratification Ranges
		Cohort Studies		
Bostick (18)	1,007	<629 to >1,547	360	<159 to >618
Flood (19)	NG	<412.3 to >830.9	NG	66.3–270.8
Gaard (20)	907 (men)	≤ 758 to ≥1067 (men)		
	637 (women)	≤ 527 to ≥744 (women)		
Garland (21)	NG	102–906 mg/1000 kcal	NG	2–208 IU/1000 kcal
Jarvinen (23)	approx. 1335–1415	<1178.2 to ≥1953.3	Approx. 3.5–3.8	<103.2 to ≥195.6
Kampman (24)	NG	596–1288		
Kato (25)	NG	NG		
Kearney (26)	839	631–1213	NG	<161 to 613
Keese (27)	1,014.2	766.2–1,201.8	104.4	54.8 to >129.2
Larsson (29)	NG	<956 to >1,445		
Lin (32)	882	<614 to >1,357	271	<161 to ≥545
Martinez (33)	NG	<475 to >957	NG	<76 to >245
McCullough (34)	NG	<561 to 1,255	NG	<110 to >525
Pietinen (36)	approx. 1,312	856–1,789	192	103.2–344.8
Shin (37)	485	<291 to >610.8		
Stemmerman (39)	481.5 colon 524.5 rectum 495.1 large bowel (as per author)	NG		
Terry (40)	688	486–914	28.0	116–148
Wu (42)	NG	397–1,655	NG	174–626
Zheng (43)	NG	800.8–1278.7	NG	224.1–475.5
Lead Author	Avg. Ca Intake Among Controls (mg/day)	Control Ca Stratification Range	Avg. Control Vit D Intake (IU/day)	Control Vitamin D Stratification Range
		Case-control Studies		
Boutron (46)	1047 (men)	766.4–1287.0 (men)	NG	100–228 (men)
	1142 (women)	722.6–1214.5 (women)	NG	84–188 (women)
DeStefani (49)	793.5	<554.3 to >951.9		
Ferraroni (50)	NG	468.1–1,029.7	NG	31.6–78.8
Freudenheim (52)	NG	NG	NG	NG
Ghadirian (53)	1,156	NG		
Kampman (55)	1,228 (men)	681–1,701 (men)	304 (men)	144–448 (men)
	979 (women)	546–1,330 (women)	232 (women)	104–344 (women)
Kune (57)	900 (men)	597–1,150 (men)		
	857 (women)	528–1,042 (women)		
LaVecchia (58)	NG	799 to ≥1,495	NG	80.8–171.2
Lee (59)	238-540 (20% points-men)	388 (men)		
	207-483 (20% points-women)	356 (women)		
Levi (60)	NG	423.4–1,144.9	NG	48–108
Ma (62)	NG	0-918		
Macquart-Moulin (63)	846	NG		
Marcus (64)	807.4	<532 to ≥1,396	364.3	<148 to ≥557
Negri (65)	NG	480 to >1,046		
Olsen (66)			120.0	0 to >1,000

(Continued on next page)

TABLE 3
Baseline calcium/vitamin D intakes and study stratification ranges[a] *(Continued)*

Lead Author	Avg. Ca intake Among Controls (mg/day)	Control Ca Stratification Range	Avg. Control Vit D Intake (IU/day)	Control Vitamin D Stratification Range
Peters (67)	1,048.6	NG	319	NG
Pritchard (68)	865	$\leq$ 640to $\geq$1,057	197.2	112 to $\geq$280
Satia-Abouta (69)	941 (Whites) 672 (Blacks)	456–1,691 (Whites) 304–1,143 (Blacks)		
Slattery (72)	1,170 (men)	743–1,543 (men) 628–1,275 (women)	312	168–408 (men) 124–332 (women)
Slattery (73)	1,070 (men) 866 (women)	$\leq$ 641.2 to >1,401.7 (men) $\leq$ 592.5 to >1,141.0 (women)		
White[b] (75)	NG	0 to >100		
Whittemore (76)	586 (men-North America) 514 (women-North America) 532 (men-China) 485 (women-China)	NG		

[a] Abbreviations are as follows: Ca, calcium; IU, international units; NG, not given; Avg., average; vit, vitamin.
[b] Supplements only.

heterogeneity ($P = 0.23$). Because Wu et al. (42) provided data only for the distal colon subsite, a sensitivity analysis was performed. Dropping Wu et al. (42) from the meta-analysis produced little change in the RR, i.e., 0.79 (95% CI = 0.66–0.94). Separate data for the effects of vitamin D on colorectal cancer risk from case-control studies were not available, nor were data available from cohort studies on the risk of rectal cancer and supplemental calcium use.

DISCUSSION

The present meta-analysis of 60 observational studies, with data on over 26,000 patients, provides cogent evidence of an inverse relationship between calcium intake and a reduced risk of colorectal cancer. Statistically homogeneous data from both cohort and case-control studies suggest that high intake of calcium reduces the risk of both colon and rectal cancer by as much as 45%. Interestingly, both dietary and supplemental sources of calcium showed inverse effects, with the latter reducing colorectal cancer risk by 24%.

Some statistical heterogeneity was noted on the initial pooling of the dietary/total calcium intake data in the case-control studies. Unlike the relevant cohort studies in which 6 of the 11 were conducted in American cohorts, only 6 of 17 case-control studies were conducted in the United States or North America (53,55,64,67,69,73). Differences in dietary habits, race, relative composition of foods that make up dairy products, and other demographic differences across populations could contribute to the variability among the case-control reports. Pooling data only from North American studies resulted in a stronger association between calcium intake and colorectal cancer risk, RR = 0.55 (95% CI = 0.480.63) vs. 0.77 (95% CI = 0.72–0.82), for other countries combined, with analysis for Q showing no heterogeneity. This provides at least partial support for the importance of geographical differences in outcomes across studies.

Similarly, the pooled data from case-control studies using rectal cancer as the endpoint showed greater than expected differences in outcome across reports. Sensitivity analyses showed differences between reports using population-derived vs. hospital based control groups, with the former being statistically homogeneous. Hospital-derived data can be problematic for dietary studies because hospitalization itself among controls may be diet related. The distribution of controls diagnoses likely also varies from one hospital-based control set to another. Prior work shows the existence of demographic/socio-economic difference in use across dairy and milk types (e.g., Ref. 82) with, for instance, high calcium intake associated with higher levels of education (83). Such demographic factors could bias hospital derived case-control analyses.

Milk, a major source of calcium for the U.S. population, also showed a protective effect, although the RRs among reports using colorectal cancer as the outcome could be attenuated due to apparent differential effects of milk on disease risk based on anatomic site. That is, no clear association was demonstrated between milk and risk of rectal cancer in either cohort or case-control studies, whereas studies looking exclusively at tumors of the colon showed a statistically significant inverse relationship (i.e., an approximate 22% reduction in risk). Prior work suggested epidemiological/etiologic differences between colon and rectal tumors (84). For instance, proximal and distal colonic sites differ in embryological origin, physiological function, fecal composition, and transit times (84,85). In addition, alcohol and calcium intake appear more important risk factors for

TABLE 4
Summary of meta-analysis findings[a]

Exposure of Interest	Study Design	Outcome	RRs[b] (95% CI)	Statistical Homogeneity (Y/N)
Dietary/total calcium				
	Cohort	Colon	0.76 (0.69–0.84)	Y
	Cohort	CCC	0.77 (0.71–0.81)	Y
	Case-control	Colon	0.77 (0.71–0.84)	N
				No clear source of heterogeneity identified
	Case-control	C/CC	0.77 (0.72–0.82)	N
			0.55 (0.48–0.63)	Y
				Result of sensitivity analysis pooling only data from studies performed in North America vs. other countries
	Cohort	RC	0.72 (0.60–0.86)	Y
	Case-control	RC	0.89 (0.81–0.97)	N
			0.87 (0.86–0.96)	Y
				Result of sensitivity analysis pooling only studies using population-derived controls vs. hospital control and excluding data from Wu et al. (42) due to racial differences
	Cohort	DCC	0.67 (0.53–0.83)	Y
	Cohort	PCC	0.75 (0.62–0.91)	Y
Calcium supplements	Cohort	C/CC	0.76 (0.65–0.89)	Y
Milk	Cohort	C/CC	0.90 (0.83–0.97)	Y
	Case-control	C/CC	0.96 (0.86–1.06)	N
			0.90 (0.81–1.00)	Y
				RRs excluding data from Kune et al. (57) only
	Cohort	CC	0.78 (0.67–0.92)	Y
	Cohort	RC	0.95 (0.80–1.14)	Y
	Case-control	RC	1.01 (0.79–1.28)	Y
Dairy	Cohort	Colorectal	0.84 (0.75–0.95)	Y
	Case-control	Colorectal	0.90 (0.78–1.04)	N
Vitamin D/dietary vitamin D	Cohort	C/CC	0.94 (0.83–1.06)	Y
	Cohort	RC	0.83 (0.70–1.04)	Y
	Case-control	C/CC	0.93 (0.86–0.99)	N
	Case-control	RC	0.91 (0.82–1.03)	Y

[a] Abbreviations are as follows: RR, relative risk; CI, confidence interval; Y, yes; N, no; C/CC; colon/colorectal cancer; RC, rectal cancer; DCC, distal colon cancer; PCC, proximal colon cancer; CC, colon cancer; CR, colorectal cancer.
[b] Summary RR and 95% CI.

distal colon tumors vs. tumors of the proximal colon (85). This is supported by the present meta-analysis in that dietary calcium appeared to have a stronger inverse association with distal colon tumors than more proximal ones, RRs of 0.67 vs. 0.75 (see Table 4).

The present meta-analysis suggests a possible protective effect for dietary vitamin D intake and colorectal cancer risk. These results are consistent with a prior pooled analysis based on 10 cohort studies (14). An important caveat is the baseline vitamin D intake of the study subjects and the stratification ranges

used by individual authors. As detailed in Table 3, numerous reports show that intake of vitamin D in most populations is rather low, with wide variation in stratification categories used across studies. Low intake could limit or attenuate the ability to detect any effect of this nutrient as reflected in the magnitude of the relevant summary RRs. Given the data presented in Table 4 and the in vivo and in vitro information supporting an important role for vitamin D on cell regulation, additional information is needed to clarify this association, particularly in light of recent work suggesting that current dietary intake recommendations for vitamin D may need to be revised upward (86–88).

The present report is, to our knowledge, the largest comprehensive assessment of the influence of calcium, dairy products, and vitamin D on colorectal cancer risk, with over 26,000 cases. The data are remarkably consistent across exposure categories, outcome measures, and study designs, although they are in contrast to the findings of the recent Women's Health Initiative randomized trial (89). Nonetheless, multiple design issues could account for the lack of effect of calcium and vitamin D supplementation seen in this latter report such as high intakes of calcium and vitamin D at baseline and relatively short follow-up, among others (89). Given the known natural history of colorectal tumors, the randomized trial design may be limited in its ability to address the study question.

The comprehensive nature of our literature search; the use of accepted, standard statistical procedures; and detailed analyses of the influence of study design and other modifying variables on the summary estimates of effect provide a firm basis to conclude that calcium and dairy intake show an inverse relationship with the risk of colorectal cancer development. Due to study design limitations, further work is needed to clarify the influence of vitamin D intake on this disease process.

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