

Dairy products and colorectal cancer risk: a systematic review and meta-analysis of cohort studies

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Received 10 February 2011; revised 24 March 2011; accepted 29 March 2011

Background: Previous studies of the association between intake of dairy products and colorectal cancer risk have indicated an inverse association with milk, however, the evidence for cheese or other dairy products is inconsistent.

Methods: We conducted a systematic review and meta-analysis to clarify the shape of the dose–response relationship between dairy products and colorectal cancer risk. We searched the PubMed database for prospective studies published up to May 2010. Summary relative risks (RRs) were estimated using a random effects model.

Results: Nineteen cohort studies were included. The summary RR was 0.83 (95% CI [confidence interval]: 0.78–0.88, $I^2 = 25%$) per 400 g/day of total dairy products, 0.91 (95% CI: 0.85–0.94, $I^2 = 0%$) per 200 g/day of milk intake and 0.96 (95% CI: 0.83–1.12, $I^2 = 28%$) per 50 g/day of cheese. Inverse associations were observed in both men and women but were restricted to colon cancer. There was evidence of a nonlinear association between milk and total dairy products and colorectal cancer risk, $P < 0.001$, and the inverse associations appeared to be the strongest at the higher range of intake.

Conclusion: This meta-analysis shows that milk and total dairy products, but not cheese or other dairy products, are associated with a reduction in colorectal cancer risk.

Key words: colorectal cancer, dairy products, diet, meta-analysis

Introduction

Colorectal cancer is the third most common type of cancer worldwide with ~1.2 million new cases diagnosed in 2008 accounting for 9.7% of all incident cancers [1]. Ecological, secular trend and migration studies have provided strong evidence that environmental factors including lifestyle are likely to be the main determinants of colorectal cancer risk [2–4]. Dietary factors are known to be important risk factors for colorectal cancer, but to date, only intakes of alcohol (among men) and red and processed meat are considered to be convincing dietary causes of colorectal cancer [5].

Dairy products have been hypothesized to protect against colorectal cancer risk due to their high calcium content, which may bind proinflammatory secondary bile acids and ionized fatty acids and may reduce cell proliferation and promote cell differentiation [6, 7]. However, some dairy products, such as certain cheeses and creams, also have a high-fat content that potentially could increase colorectal cancer risk by increasing bile acid levels in the colon [8]. Epidemiological studies of dairy products and colorectal cancer risk have provided mixed results [9–24]. Some cohort studies have reported inverse associations between intake of total dairy products, milk and/or yogurt and colorectal cancer risk [14, 16, 23, 24],

however, other studies found no association [9–13, 15, 17–22]. In the second report from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) published in 2007 ‘*Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective*’, it was stated that milk intake probably protects against colorectal cancer, but there was limited suggestive evidence that intake of cheese increases risk [5]. Because there also was evidence that high calcium and dairy intake increases prostate cancer risk, no recommendation was provided with regard to intakes of dairy products. For future recommendations to be made with regard to dairy product intake, it will be important to clarify the shape of the dose–response relationship and whether there are any gender-specific differences in the risk. In addition, further exploration of possible confounding by other lifestyle factors is needed to firmly establish the potential preventive role of dairy products in colorectal cancer etiology. A number of additional studies have been published since the second WCRF/AICR report [25–30] and here we update the evidence up to May 2010 with a specific aim to address whether the association differs by gender and if there is a nonlinear association between intake of dairy products and colorectal cancer risk.

Methods

Search strategy

We updated the systematic literature review published in 2007 [5] by searching the PubMed database up to May 2010 for cohort studies of dairy

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product intake and colorectal cancer risk. We followed a predefined protocol for the review (http://www.dietandcancerreport.org/downloads/SLR_Manual.pdf), which includes details of the search terms used. We also searched the reference lists of all the studies that were included in our analysis as well as those listed in the published systematic reviews and meta-analyses [31, 32]. We followed standard criteria for conducting and reporting meta-analyses [33].

study selection

We included prospective cohort, case-cohort and nested case-control studies of total dairy products or specific types of dairy products and colorectal cancer incidence. To be included in the analyses, estimates of the relative risk (RR) (such as hazard ratio or risk ratio) with the 95% confidence intervals (CIs) had to be available in the publication. For the dose-response analysis, a quantitative measure of intake had to be provided. When there were several publications from the same study, we selected the publication with the largest number of cases. If all the required information was not provided in the paper, we used the publication that presented the results with sufficient information to be incorporated into the dose-response analyses. Thirty-five potentially relevant full-text publications [9–30, 34–46] were identified. We excluded seven publications of colorectal cancer mortality [36, 37, 40, 42–45], one publication reporting on childhood dairy intake that only had information on intake by household level [46], two publications that did not provide risk estimates [38] or CIs [39] and one duplicate publication [41]. For the dose-response analysis, we further excluded one publication because no quantities of the intake were provided [14], and four others because only the highest versus the lowest level of intake was reported [11, 28, 34, 35].

data extraction

The following data were extracted from each study: The first author's last name, publication year, country where the study was conducted, the study name, follow-up period, sample size, gender, age, number of cases, dietary assessment method (type, number of food items and whether it had been validated), type of dairy product (total dairy, milk, cheese etc.), quantity of intake, RRs and 95% CIs for dairy product intake and variables adjusted for in the analysis. The search and data extraction of articles published up to June 2006 was conducted by several reviewers at Wageningen University during the systematic literature review for the WCRF/AICR report (http://www.dietandcancerreport.org/downloads/SLR/Colon_and_Rectum_SLR.pdf). The search from June 2006 to May 2010 was conducted by two of the authors (DSMC and RL). Data was extracted into a database by three authors (DSMC, RL and DA).

statistical methods

Random effects models were used to calculate summary RRs and 95% CIs for the highest versus the lowest level of dairy product intake and for the dose-response analysis [47]. The natural logarithm of the RR from each study was weighted by the inverse of its variance and pooled across studies. A two-tailed $P < 0.05$ was considered statistically significant. When results were reported separately for men and women, but not combined, we combined the two results first using a fixed-effects model to obtain an overall estimate for both the sexes combined, before pooling with other studies.

For the dose-response analysis, we used the method described by Greenland and Longnecker [48] to compute study-specific slopes (linear trends) and 95% CIs from the natural logs of the RRs and CIs across categories of dairy product intake. The method requires that the distribution of cases and person-years or noncases and the RRs with the variance estimates for at least three quantitative exposure categories are known. We estimated the distribution of cases and person-years in

studies that did not report these, but reported the total number of cases/person-years, if dairy intake was analyzed by quantiles (and could be approximated), e.g., the total number of person-years was divided by 5 when data were analyzed by quintiles in order to derive the number of person-years in each quintile. If this information was missing and the results were reported by functional categories (e.g. <1 , 1–3, 4–6, and ≥ 7 servings per week), we used variance-weighted least squares regression to estimate the slopes. The median or mean level of dairy product intake in each category of intake was assigned to the corresponding RR for each study. For studies that reported dairy product intake by ranges of intake, we estimated the midpoint in each category by calculating the average of the lower and upper bound. When the highest or the lowest category was open-ended, it was assumed that the open-ended interval length had the same length as the adjacent interval. If the intakes were reported in densities (i.e. g per 1000 kcal), we recalculated the reported intakes to absolute intakes using the mean or median energy intake reported in the publication [27, 29]. When studies reported the intake in servings and times per day or week, we converted the intakes to grams of intake per day using standard units of 244 g (or 244 ml) for milk, 43 g for cheese (two slices) and 177 g for total dairy products based on serving sizes reported in the 'United States Department of Agriculture Food and Nutrient Database for Dietary Studies' [49]. For one study that reported cheese intake in slices per week and per day, we used 21.5 g as a unit for each slice [26]. The dose-response results in the forest plots are presented for a 400, 200 and 50 g/day increment for total dairy, total milk and cheese, respectively. We examined a potential nonlinear dose-response relationship between total dairy and total milk intakes and colorectal cancer by using fractional polynomial models [50]. We determined the best-fitting second order fractional polynomial regression model, defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity [51].

Heterogeneity between the studies was assessed by I^2 , which is the amount of total variation that is explained by the between-study variation and the Q test [52]. Subgroup and meta-regression analyses by study characteristics were conducted to investigate potential sources of heterogeneity. Publication bias was assessed with funnel plots, Egger's test [53] and with Begg's test [54] with the results considered to indicate potential publication bias when $P < 0.10$. We conducted sensitivity analyses excluding one study at a time to explore whether the results were robust.

Stata version 10.1 software (StataCorp, College Station, TX) was used for the statistical analyses.

results

Nineteen cohort studies (24 publications) [9–30, 34, 35] could be included in the analysis of the highest versus the lowest dairy product intake and colorectal cancer risk and 17 of these studies (18 publications) [9, 10, 12, 13, 15–20, 22–27, 29, 30] were included in the dose-response analysis (Supplemental Table S1, available at *Annals of Oncology* online; Figure 1). Eight of the studies were from Europe, nine from the United States and two from Asia. All studies provided adjusted risk estimates. A summary of the study characteristics of the included studies is provided in the Supplemental Table S1 (available at *Annals of Oncology* online).

total dairy products

high versus low analysis. Twelve cohort studies [14, 16–19, 22, 23, 25–29] investigated the association between high versus low total dairy product intake and colorectal cancer risk and

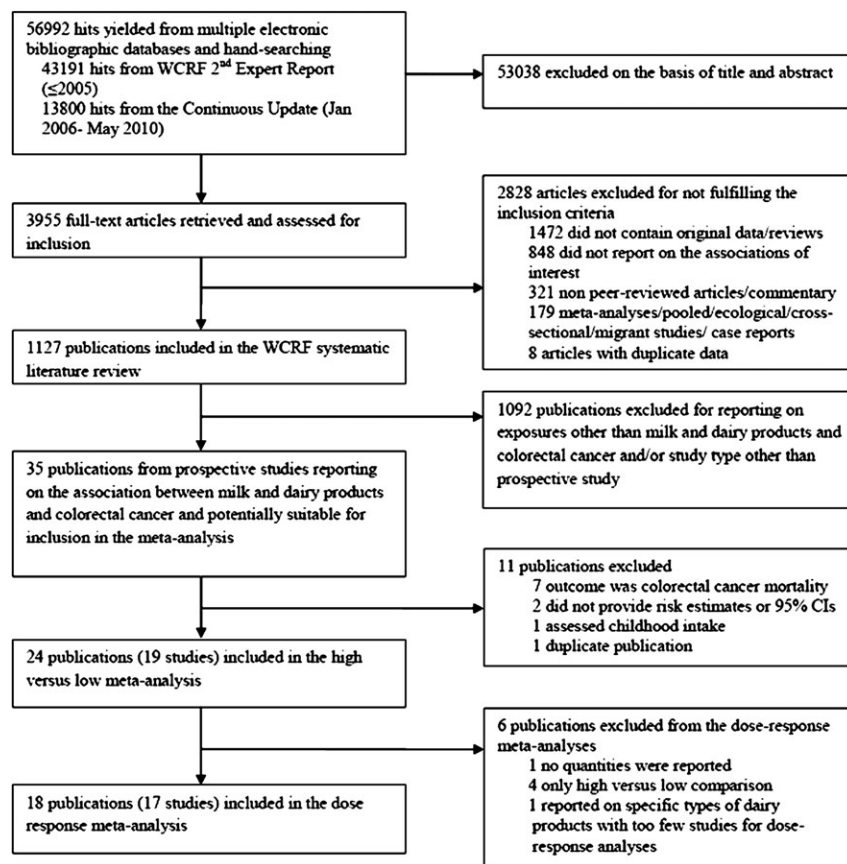


Figure 1. Flow-chart of study selection. CI, confidence interval; WCRF, World Cancer Research Fund.

included 11 579 cases among 1 170 942 participants. The summary RR for all studies was 0.81 (95% CI: 0.74–0.90), with moderate heterogeneity, $I^2 = 42\%$ and $P_{\text{heterogeneity}} = 0.06$ (Figure 2A). The association was in the direction of decreased risk for colon cancer [9, 17–19, 26], summary RR = 0.72 (95% CI: 0.51–1.02, $I^2 = 50\%$, $P_{\text{heterogeneity}} = 0.09$, $n = 5$), but not statistically significant, while no association was observed for rectal cancer [17–19, 26, 34], summary RR = 0.96 (95% CI: 0.65–1.41, $I^2 = 44\%$, $P_{\text{heterogeneity}} = 0.13$, $n = 5$) (results not shown).

dose–response analysis. Ten cohort studies [16–19, 22, 23, 25–27, 29] were included in the dose–response analysis of total dairy product intake and colorectal cancer risk. The summary RR per 400 g increase per day (g/day) was 0.83 (95% CI: 0.78–0.88) with little evidence of heterogeneity, $I^2 = 25\%$ and $P_{\text{heterogeneity}} = 0.22$ (Figure 2B). There was a significant inverse association for colon cancer (RR = 0.84, 95% CI: 0.72–0.97) but not for rectal cancer (Table 1). The summary RR for colorectal cancer ranged from 0.80 (95% CI: 0.77–0.84) when the Swedish Mammography Cohort study was excluded to 0.85 (95% CI: 0.81–0.89) when the Cohort of Swedish Men was excluded. There was no indication of publication bias with Egger’s test ($P = 0.58$) or with Begg’s test ($P = 0.79$). There was statistical evidence of a nonlinear association between total dairy product intake and colorectal cancer risk, P for nonlinearity < 0.001 , though the nonlinearity was observed at intakes below ~ 100 g/day, for which there was no evidence of decreased colorectal

cancer risk. The association appeared broadly linear above this range of intake (Figure 3A).

milk

high versus low analysis. Ten cohort studies [10, 11, 17, 19, 20, 22, 23, 26, 27, 30] were included in the analysis of high versus low milk intake and colorectal cancer risk, including a total of 5011 cases among 655 483 participants. The summary RR was 0.83 (95% CI: 0.74–0.93) for colorectal cancer, with low heterogeneity, $I^2 = 14\%$ and $P_{\text{heterogeneity}} = 0.31$ (Figure 4A). The summary RR was 0.82 (95% CI: 0.72–0.94, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.54$, $n = 7$) for colon cancer [13, 17, 19, 26, 30, 35] and 0.79 (95% CI: 0.60–1.06, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.79$, $n = 4$) for rectal cancer [17, 19, 26, 30] (results not shown).

dose–response analysis. Nine cohort studies [10, 17, 19, 20, 22, 23, 26, 27, 30] were included in the dose–response analysis for colorectal cancer. The summary RR for a 200 g/day increase in the intake was 0.90 (95% CI: 0.85–0.94), with no evidence of heterogeneity, $I^2 = 0\%$ and $P_{\text{heterogeneity}} = 0.62$ (Figure 4B). The inverse association was statistically significant only for colon cancer (summary RR = 0.88, 95% CI: 0.79–0.97, $I^2 = 44\%$, $P_{\text{heterogeneity}} = 0.11$) (Table 1). In a sensitivity analysis, the summary RR for colorectal cancer ranged from 0.87 (95% CI: 0.83–0.92) when excluding the Cancer Prevention Study II Nutrition Cohort to 0.91 (95% CI: 0.86–0.96) when excluding the Cohort of Swedish men. There was no indication of publication bias with Egger’s test ($P = 0.86$) or with Begg’s test

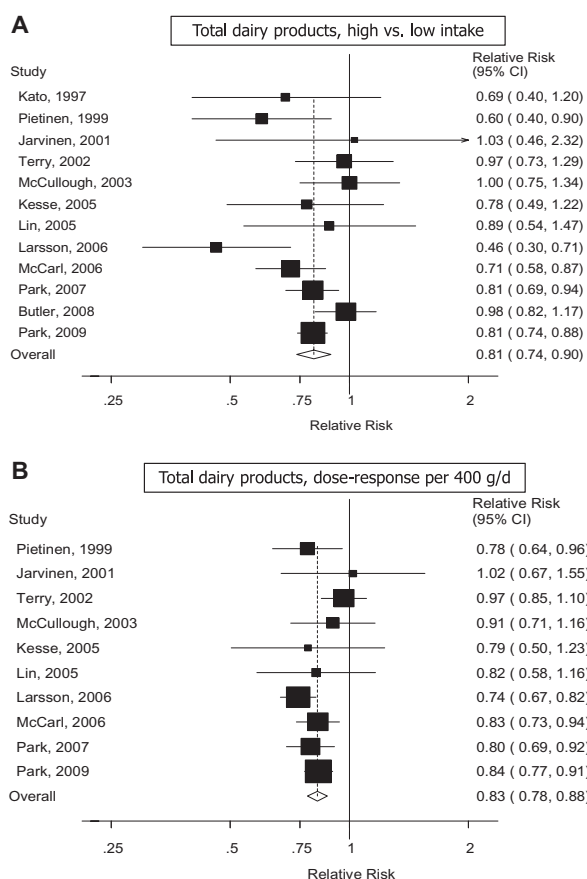


Figure 2. Total dairy products and colorectal cancer. CI, confidence interval.

($P = 0.84$). There was evidence of a nonlinear association between milk intake and colorectal cancer risk, P for nonlinearity < 0.001 , with no substantial association below ~ 200 g/day and with the greatest reduction over the higher levels of intake (a 20%–30% reduction in risk at levels between 500 and 800 g/day) (Figure 3B).

cheese

high versus low analysis. Seven cohort studies [10, 17, 20, 22–24, 26] were included in the analysis of cheese intake and colorectal cancer risk and included 1635 cases among 177 551 participants. The summary RR was 0.94 (95% CI: 0.75–1.18) and there was moderate heterogeneity, $I^2 = 39\%$ and $P_{\text{heterogeneity}} = 0.14$ (Figure 5A). The summary RR was 1.04 (95% CI: 0.69–1.55, $I^2 = 58\%$, $P_{\text{heterogeneity}} = 0.05$, $n = 5$) for colon cancer [12, 15, 17, 24, 26] and 0.88 (95% CI: 0.59–1.30, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.84$, $n = 3$) for rectal cancer [17, 24, 26] (results not shown).

dose-response analysis. Seven cohort studies [10, 17, 20, 22–24, 26] were included in the dose-response analysis for colorectal cancer. The summary RR per 50 g/day was 0.96 (95% CI: 0.83–1.12), with no indication of heterogeneity, $I^2 = 28\%$ and $P_{\text{heterogeneity}} = 0.22$ (Figure 5B). There was no significant association between cheese intake and either colon or rectal cancer (Table 1).

other dairy products

Other specific types of dairy products including high-fat dairy products [9, 21, 24], low-fat dairy products [18, 21], cottage cheese [15, 17, 23, 26], fermented dairy products [10, 12, 16, 18, 22], fermented milk [17, 24, 26, 35], yogurt [22, 23] and butter [17, 24] were not significantly associated with risk (Table 2). Studies of ice-cream [12], nonfermented dairy products [18], low-fat milk [15] and non-fat milk [15] also found no significant association.

subgroup, sensitivity and meta-regression analyses. In subgroup analyses of total dairy and milk intake and colorectal cancer, there were inverse associations in most, but not all strata of the study characteristics (Table 1). In the meta-regression analyses, none of the variables investigated significantly explained the heterogeneity observed in the data (which anyway was low or moderate in most of the analyses), although for cheese, there was borderline significant heterogeneity between studies that adjusted and did not adjust for red meat intake ($P_{\text{heterogeneity}} = 0.07$), with a significant inverse association among studies that adjusted for red meat but a nonsignificant positive association among studies that did not adjust for red meat.

In a sensitivity analysis, we explored whether exclusion of studies from the dose-response meta-analyses affected our results. When we repeated the high versus low intake analyses with the same studies as in the dose-response analysis, the summary RR for total dairy products was 0.79 (95% CI: 0.71–0.88, $I^2 = 37\%$, $P_{\text{heterogeneity}} = 0.11$) and for milk was 0.83 (95% CI: 0.73–0.94, $I^2 = 23\%$, $P_{\text{heterogeneity}} = 0.24$). We further repeated the high versus low analyses including studies that reported on total dairy products [40], total milk [36, 42, 43] and cheese [36, 42, 43] in relation to colorectal cancer mortality. However, the results were similar, summary RR = 0.81 (95% CI: 0.73–0.89, $I^2 = 40\%$, $P_{\text{heterogeneity}} = 0.07$) for total dairy products, summary RR = 0.84 (95% CI: 0.75–0.95, $I^2 = 24\%$, $P_{\text{heterogeneity}} = 0.20$) for total milk and summary RR = 1.02 (95% CI: 0.84–1.23, $I^2 = 34\%$, $P_{\text{heterogeneity}} = 0.15$) for cheese.

discussion

In this meta-analysis, high intakes of milk and total dairy products were associated with a statistically significant reduction in colorectal cancer risk as compared with low intake. There were significant inverse associations both among men and women for colorectal cancer, but when stratified by cancer site the inverse associations were only present for colon cancer. There was evidence of a nonlinear association for both total dairy and milk, with the strongest reduction in risk at the higher level of intake, but for total dairy the nonlinearity may have been an artifact related to a small group of nonconsumers. Intake of cheese or other specific dairy products was not significantly associated with colorectal cancer risk, although the number of studies was small.

The results from this meta-analysis are consistent with two previous meta-analyses of case-control and cohort studies [31, 32] and a pooled analysis of ten cohort studies [55], which found inverse associations between intake of dairy products and milk and colorectal cancer risk. However, in contrast to the two previous meta-analyses on the subject that only conducted analyses of the highest versus the lowest intake [31, 32], we

Table 1. Subgroup analyses of milk and dairy product intakes and colorectal cancer, dose–response analysis

	Dairy products					Milk					Cheese					
	<i>n</i>	RR (95% CI)	<i>I</i> ² (%)	<i>P</i> _h ^a	<i>P</i> _h ^b	<i>n</i>	RR (95% CI)	<i>I</i> ² (%)	<i>P</i> _h ^a	<i>P</i> _h ^b	<i>n</i>	RR (95% CI)	<i>I</i> ² (%)	<i>P</i> _h ^a	<i>P</i> _h ^b	
All studies	10	0.83 (0.78–0.88)	24.6	0.22		9	0.90 (0.85–0.94)	0	0.62		7	0.96 (0.83–1.12)	27.8	0.22		
Duration of follow-up																
<10 years follow-up	4	0.90 (0.80–0.98)	8.1	0.35	0.10	6	0.88 (0.84–0.94)	0	0.50	0.30	3	0.96 (0.79–1.16)	33.2	0.22	0.95	
≥10 years follow-up	6	0.80 (0.76–0.85)	0	0.53		3	0.96 (0.84–1.11)	0	0.73		4	1.01 (0.75–1.37)	43.5	0.15		
Sex																
Men	5	0.81 (0.75–0.88)	30.2	0.22	0.56	3	0.86 (0.81–0.93)	0	0.40	0.32	3	0.93 (0.75–1.14)	31.2	0.23	0.68	
Women	7	0.84 (0.76–0.93)	35.3	0.16		5	0.81 (0.59–1.11)	0	0.40		1	0.85 (0.71–1.02)				
Men ^c	3	0.86 (0.79–0.94)	0	0.70	0.22	2	0.89 (0.82–0.98)	0	0.70	0.47	0					
Women ^c	3	0.79 (0.67–0.92)	28.9	0.25		2	0.97 (0.83–1.12)	42.2	0.19		0					
Subsite																
Colon	5	0.84 (0.72–0.97)	35.4	0.19	0.30	6	0.88 (0.79–0.97)	44.1	0.11	0.72	5	0.84 (0.68–1.04)	8.5	0.36	0.64	
Rectum	4	1.00 (0.77–1.28)	68.9	0.02		4	0.90 (0.79–1.02)	0	0.53		3	0.90 (0.70–1.15)	0	0.93		
Colon ^d	4	0.83 (0.69–0.99)	51.5	0.10	0.32	4	0.81 (0.74–0.90)	0	0.99	0.30	3	0.81 (0.64–1.02)	13.4	0.32	0.54	
Rectum ^d	4	1.00 (0.77–1.28)	68.9	0.02		4	0.90 (0.79–1.02)	0	0.53		3	0.90 (0.70–1.15)	0	0.93		
Geographic location																
Europe	5	0.84 (0.72–0.97)	63.7	0.03	1.00	5	0.86 (0.79–0.93)	0	0.58	0.34	6	0.96 (0.82–1.12)	35.8	0.17	0.60	
America	5	0.83 (0.78–0.88)	0	0.93		3	0.92 (0.87–0.99)	0	0.62		1	1.16 (0.63–2.13)				
Asia	0					1	0.81 (0.59–1.11)				0					
Number of cases																
<500	5	0.77 (0.70–0.83)	0	0.67	0.56	7	0.87 (0.80–0.94)	0	0.55	0.49	6	1.01 (0.86–1.18)	19.4	0.29	0.24	
500 to <1500	3	0.90 (0.81–0.99)	25.3	0.26		1	0.94 (0.83–1.05)				1	0.79 (0.62–1.02)				
≥1500	2	0.83 (0.77–0.89)	0.0	0.58		1	0.91 (0.83–0.99)				0					
Adjustment for confounders																
Alcohol	Yes	6	0.83 (0.75–0.91)	50.6	0.07	0.79	4	0.87 (0.77–1.00)	26.2	0.25	0.27	4	0.96 (0.83–1.11)	11.9	0.33	0.83
	No	4	0.84 (0.77–0.91)	0	0.63		5	0.91 (0.86–0.97)	0	0.95		3	1.04 (0.66–1.64)	57.6	0.09	
Smoking	Yes	7	0.81 (0.76–0.85)	0	0.49	0.15	6	0.89 (0.84–0.94)	0	0.47	0.60	5	0.99 (0.83–1.18)	24.3	0.26	0.58
	No	3	0.89 (0.79–1.00)	30.5	0.24		3	0.93 (0.80–1.08)	0	0.50		2	0.93 (0.62–1.41)	60.2	0.11	
Body mass index, weight, WHR	Yes	9	0.83 (0.78–0.89)	32.9	0.16	0.99	7	0.89 (0.85–0.94)	0	0.50	0.97	6	0.94 (0.80–1.10)	28.6	0.22	0.44
	No	1	0.83 (0.73–0.94)				2	0.90 (0.72–1.13)	0	0.36		1	1.13 (0.80–1.61)			
Physical activity	Yes	7	0.80 (0.76–0.85)	0	0.65	0.09	5	0.89 (0.83–0.96)	23.8	0.26	0.76	3	0.93 (0.79–1.09)	10.9	0.33	0.78
	No	3	0.91 (0.80–1.02)	33.9	0.22		4	0.91 (0.81–1.03)	0	0.84		4	1.04 (0.77–1.40)	49.6	0.11	
Red processed meat	Yes	4	0.84 (0.74–0.94)	69.4	0.02	0.93	2	0.89 (0.71–1.12)	64.4	0.09	0.27	3	0.85 (0.74–0.97)	0	0.51	0.07
	No	6	0.83 (0.76–0.89)	0	0.83		7	0.91 (0.86–0.97)	0	0.92		4	1.12 (0.93–1.36)	0	0.66	
Fruit, vegetables	Yes	3	0.81 (0.73–0.89)	50.8	0.13	0.41	2	0.87 (0.76–1.00)	65.5	0.09	0.48	1	0.85 (0.71–1.02)			0.35
	No	7	0.86 (0.80–0.92)	2.9	0.40		7	0.91 (0.85–0.97)	0	0.85		6	1.02 (0.85–1.22)	23.4	0.26	
Folate	Yes	3	0.89 (0.80–0.99)	44.6	0.17	0.10	1	0.94 (0.83–1.05)			0.45	1	0.79 (0.61–1.02)			0.24
	No	7	0.79 (0.74–0.84)	0	0.74		8	0.89 (0.84–0.94)	0	0.60		6	1.01 (0.86–1.18)	19.4	0.29	
Energy intake	Yes	9	0.83 (0.78–0.89)	32.9	0.16	0.99	8	0.89 (0.85–0.94)	0	0.57	0.51	6	0.94 (0.80–1.10)	28.6	0.22	0.44
	No	1	0.83 (0.73–0.94)				1	1.00 (0.72–1.39)				1	1.13 (0.80–1.61)			

n denotes the number of studies. WHR, waist-to-hip ratio.

^a*P* for heterogeneity within each subgroup.

^b*P* for heterogeneity between subgroups with meta-regression analysis.

^cSubgroup analyses restricted to studies that reported results both for men and women.

^dSubgroup analyses restricted to studies that reported results both for colon and rectum.

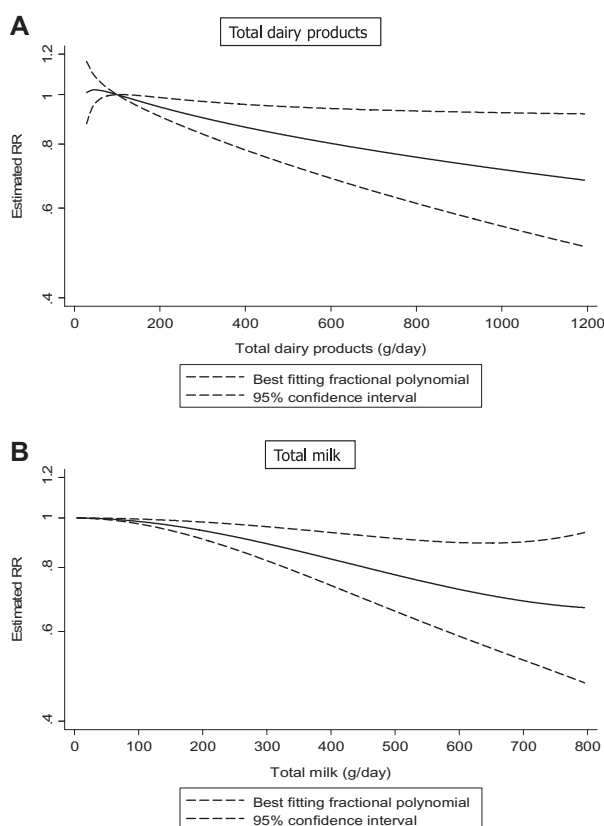


Figure 3. Total dairy products and total milk and colorectal cancer, nonlinear dose–response. RR, relative risk.

further quantified the association between milk and dairy product intakes and colorectal cancer risk by conducting linear and nonlinear dose–response analyses, and in addition, we also conducted detailed subgroup analyses to identify potential sources of heterogeneity. In the most recent report from the WCRF/AICR, it was stated that milk intake probably protects against colorectal cancer risk, while there was limited suggestive evidence that cheese increases risk. No judgment was provided for total dairy product intake, but our results suggest a protective effect. However, the result for total dairy product intake may largely be driven by an effect of milk intake, as milk accounts for a large part of total dairy intakes in most populations. The difference between our results and the results from the report, with regard to cheese intake, may partly be due to two additional studies having been published after the report was completed [24, 26], which found inverse associations, thus driving the overall result toward the null. These additional studies may also have adjusted for more dietary confounders than several older studies. The inverse associations with milk and total dairy products were restricted to colon cancer, in contrast to the results from the pooled analysis where an inverse association with milk intake was also observed for rectal cancer [55]. However, fewer studies were included in our rectal cancer analysis compared with the pooled analysis, thus we may have had limited statistical power in this subgroup analysis.

Our meta-analysis may have several limitations that need to be addressed. Because of the observational nature of the data, it is possible that the observed inverse association between

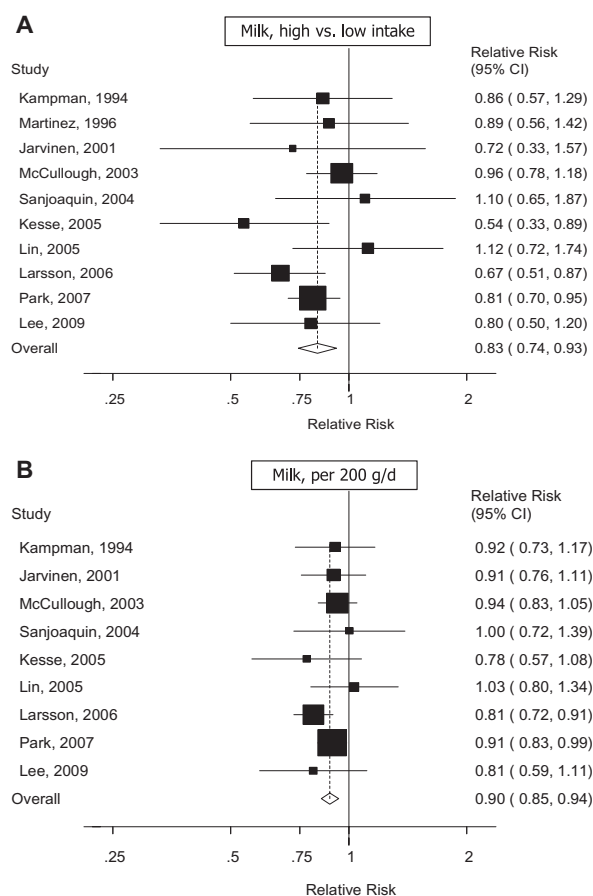


Figure 4. Milk and colorectal cancer. CI, confidence interval.

milk and total dairy product intakes and colorectal cancer risk could be due to unmeasured or residual confounding. Higher intake of milk and dairy products may be associated with other health behaviors including higher levels of physical activity, lower prevalence of smoking and overweight/obesity and lower intakes of alcohol and red and processed meat [27, 29], although it is also possible that different types of dairy products may be differentially associated with some of these confounders [24]. However, many of the studies adjusted for known confounding factors such as age, body mass index, smoking, alcohol, red and processed meat and energy intake. In addition, the results were generally similar in the subgroup analyses when we stratified the results according to adjustment for confounding factors or other study characteristics, with no heterogeneity between subgroups for total dairy products and milk. Only in the analysis of cheese was there some indication of heterogeneity between studies with and without adjustment for red meat with an inverse association in studies that adjusted for red meat, while studies without adjustment for red meat showed a nonsignificant positive association, suggesting potential confounding. Nevertheless, because of the few studies in these subgroups any future studies could clarify this finding.

Although publication bias can be a problem in meta-analyses of published literature, we found no evidence of such bias in this analysis. The few studies that were excluded from the dose–response analysis are not likely to have altered the results,

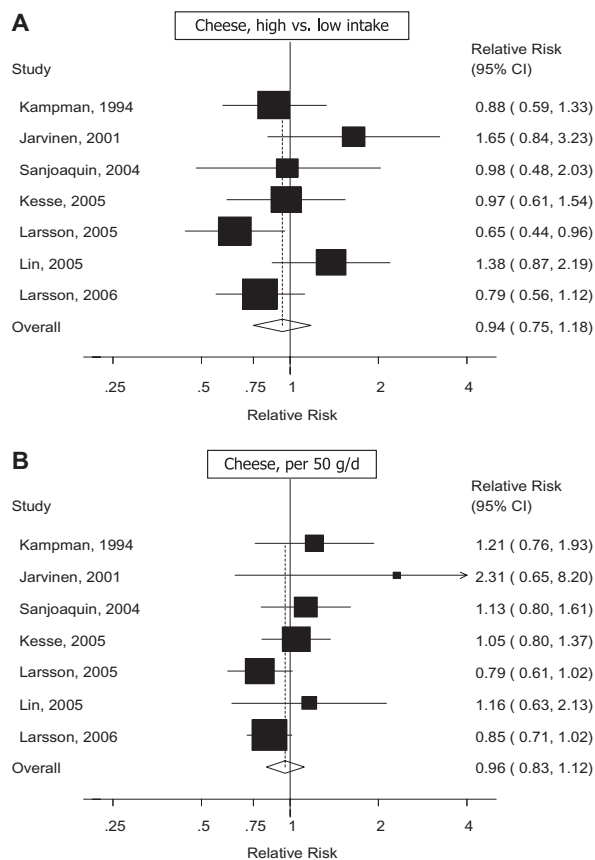


Figure 5. Cheese and colorectal cancer. CI, confidence interval.

Table 2. Other dairy products and colorectal cancer

Type of dairy product	N	RR (95% CI)	I^2	$P_{\text{heterogeneity}}$
High-fat dairy products	3	0.74 (0.53–1.02)	45	0.16
Low-fat dairy products	2	0.97 (0.74–1.28)	0	0.78
Cottage cheese	4	0.82 (0.59–1.14)	43	0.16
Fermented dairy products	5	0.97 (0.83–1.13)	0	0.83
Fermented milk	4	0.93 (0.78–1.11)	33	0.22
Yogurt	2	1.00 (0.67–1.48)	41	0.19
Butter	2	0.91 (0.58–1.43)	39	0.20

because when we repeated the high versus low analyses with the same dataset as in the dose–response analyses, the results were very similar. Because of the few studies that reported on other specific types of dairy products (except milk and cheese), we may have had limited statistical power to detect associations with these items.

Measurement errors in the assessment of dietary intake are known to bias effect the estimates. However, biases are most likely to be toward the null. Dietary changes after baseline may also attenuate associations between dietary intake and cancer risk, however, the only study that had updated dietary information available for the analyses found similar results when using cumulative updated and baseline questionnaires for the analyses [11]. Almost all the studies included in our

meta-analysis used validated food-frequency questionnaires, but none of the studies made any corrections for measurement error in their analyses. Nevertheless, several validation studies have shown that dairy product intake can be assessed relatively well with food-frequency questionnaires and reported correlation coefficients of 0.6–0.8 between intake of dairy foods assessed by food diaries or food records and food-frequency questionnaires [56–58].

Several mechanisms may explain a protective effect of dairy foods upon colorectal cancer risk [24, 31]. Dairy products are one of the main dietary sources of calcium, which has been hypothesized to prevent colon cancer by binding secondary bile acids and ionized fatty acids and thus reduce their proliferative effects in the colonic epithelium [6]. In addition, it has been shown that calcium can influence multiple intracellular pathways leading to differentiation in normal cells and apoptosis in transformed cells [7] and that calcium can reduce the number of mutations in the *K-ras* gene in rat colorectal neoplasms [59]. Several clinical trials have reported reduced cell proliferation in the colon and rectum with intake of calcium and dairy products [60–64] and other trials have found reduced risk of colorectal adenoma recurrence with calcium sup-plementation [65]. In the most recent report from the WCRF/AICR, it was stated that high calcium intake probably protects against colorectal cancer [5]. Some fat components of dairy products including conjugated linoleic acid and butyric acid have been shown to be protective in experimental studies [66, 67], but few studies were available for our analysis of high-fat dairy products [9, 21, 24]. Other possible protective components of dairy products include lactoferrin [68], lactic acid bacteria in fermented dairy products [31] and vitamin D in fortified dairy products [31, 69].

Our meta-analysis has several strengths. Because we based our analyses on prospective studies, we have effectively avoided recall and selection bias. There was little evidence of heterogeneity in the analyses except for the high versus the low analysis of total dairy products. This was probably due to differences in intake levels across studies because when the level of intake was taken into account in the dose–response analysis there was no significant heterogeneity, confirming the importance of conducting dose–response analyses. The studies included a large number of cases and participants, with a total of ~650 000 and 1.2 million participants and 5000 and 11 500 cases in the analyses of milk and total dairy products, respectively. Thus, we had statistical power to detect moderate and weak associations in the colorectal cancer analysis, although fewer studies and cases were included in the stratified analyses of colon and rectal cancer. Our results are comparable with the results of a pooled analysis of 10 cohort studies, which found a 15% reduction in colorectal cancer risk for high versus low intake of milk [55]. However, to our knowledge this is the first meta-analysis to explore a potential nonlinear association between dairy products and colorectal cancer risk.

The interpretation of our results with regard to public health recommendations is, however, complicated by the fact that consumption of milk and dairy products may have both beneficial and adverse effects with regard to other diseases.

There is evidence of a reduced risk of cardiovascular disease and type 2 diabetes [70], no association with total mortality [71], but of an increased risk of prostate cancer [5] and Parkinson's disease [72] with higher dairy intake. Thus, the question of possible threshold effects both with regard to adverse and beneficial effects of dairy products remains. In this analysis, the reduced risk was most pronounced at the higher levels of intake (e.g. equivalent to 2–3 glasses of milk per day), which complicates the interpretation of the findings, at least among men because of the increased prostate cancer risk at such levels of intake [5, 73]. Further studies of dairy intake in relation to other cancers and overall cancer risk and mortality are needed to better assess the risk–benefit of dairy product consumption, both overall and for specific types of dairy products, and whether any gender-specific recommendations are warranted.

acknowledgements

We thank the systematic literature review team at the Wageningen University for their contributions to the colorectal cancer database. The views expressed in this review are the opinions of the authors. They may not represent the views of WCRF International/AICR and may differ from those in future updates of the evidence related to food, nutrition, physical activity and cancer risk. All authors had full access to all the data in the study. DA takes responsibility for the integrity of the data and the accuracy of the data analysis. The systematic literature review team at Wageningen University conducted the search, data selection and data extraction up to June 2006. RL and DSMC did the updated literature search. RL, DSMC and DA did the updated data extraction. DA did the updated study selection, the statistical analyses and wrote the first draft of the original manuscript. DCG was expert statistical advisor and contributed toward the statistical analyses. All authors contributed to the revision of the manuscript. EK was principal investigator (PI) of the systematic literature review at Wageningen University and TN is the PI of the Continuous Update Project.

funding

This work was funded by the World Cancer Research Fund (grant number 2007/SP01) as part of the Continuous Update Project.

disclosure

The authors declare no conflicts of interest.

references

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; 127(12): 2893–2917.
2. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer* 1975; 15: 617–631.
3. Kolonel LN. Cancer patterns of four ethnic groups in Hawaii. *J Natl Cancer Inst* 1980; 65: 1127–1139.
4. Kono S. Secular trend of colon cancer incidence and mortality in relation to fat and meat intake in Japan. *Eur J Cancer Prev* 2004; 13: 127–132.
5. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective*. Washington DC: AICR 2007. Ref Type: Generic.
6. Newmark HL, Wargovich MJ, Bruce WR. Colon cancer and dietary fat, phosphate, and calcium: a hypothesis. *J Natl Cancer Inst* 1984; 72: 1323–1325.
7. Lamprecht SA, Lipkin M. Cellular mechanisms of calcium and vitamin D in the inhibition of colorectal carcinogenesis. *Ann N Y Acad Sci* 2001; 952: 73–87.
8. Narisawa T, Reddy BS, Weisburger JH. Effect of bile acids and dietary fat on large bowel carcinogenesis in animal models. *Gastroenterol Jpn* 1978; 13: 206–212.
9. Bostick RM, Potter JD, Sellers TA et al. Relation of calcium, vitamin D, and dairy food intake to incidence of colon cancer among older women. The Iowa Women's Health Study. *Am J Epidemiol* 1993; 137: 1302–1317.
10. Kampman E, Goldbohm RA, van den Brandt PA, van't Veer P. Fermented dairy products, calcium, and colorectal cancer in The Netherlands Cohort Study. *Cancer Res* 1994; 54: 3186–3190.
11. Martinez ME, Giovannucci EL, Colditz GA et al. Calcium, vitamin D, and the occurrence of colorectal cancer among women. *J Natl Cancer Inst* 1996; 88: 1375–1382.
12. Kearney J, Giovannucci E, Rimm EB et al. Calcium, vitamin D, and dairy foods and the occurrence of colon cancer in men. *Am J Epidemiol* 1996; 143: 907–917.
13. Gaard M, Tretli S, Loken EB. Dietary factors and risk of colon cancer: a prospective study of 50,535 young Norwegian men and women. *Eur J Cancer Prev* 1996; 5: 445–454.
14. Kato I, Akhmedkhanov A, Koenig K et al. Prospective study of diet and female colorectal cancer: the New York University Women's Health Study. *Nutr Cancer* 1997; 28: 276–281.
15. Singh PN, Fraser GE. Dietary risk factors for colon cancer in a low-risk population. *Am J Epidemiol* 1998; 148: 761–774.
16. Pietinen P, Malila N, Virtanen M et al. Diet and risk of colorectal cancer in a cohort of Finnish men. *Cancer Causes Control* 1999; 10: 387–396.
17. Jarvinen R, Knekt P, Hakulinen T, Aromaa A. Prospective study on milk products, calcium and cancers of the colon and rectum. *Eur J Clin Nutr* 2001; 55: 1000–1007.
18. Terry P, Baron JA, Bergkvist L et al. Dietary calcium and vitamin D intake and risk of colorectal cancer: a prospective cohort study in women. *Nutr Cancer* 2002; 43: 39–46.
19. McCullough ML, Robertson AS, Rodriguez C et al. Calcium, vitamin D, dairy products, and risk of colorectal cancer in the Cancer Prevention Study II Nutrition Cohort (United States). *Cancer Causes Control* 2003; 14: 1–12.
20. Sanjoaquin MA, Appleby PN, Thorogood M et al. Nutrition, lifestyle and colorectal cancer incidence: a prospective investigation of 10998 vegetarians and non-vegetarians in the United Kingdom. *Br J Cancer* 2004; 90: 118–121.
21. Lin J, Zhang SM, Cook NR et al. Dietary fat and fatty acids and risk of colorectal cancer in women. *Am J Epidemiol* 2004; 160: 1011–1022.
22. Lin J, Zhang SM, Cook NR et al. Intakes of calcium and vitamin D and risk of colorectal cancer in women. *Am J Epidemiol* 2005; 161: 755–764.
23. Kesse E, Boutron-Ruault MC, Norat T et al. Dietary calcium, phosphorus, vitamin D, dairy products and the risk of colorectal adenoma and cancer among French women of the E3N-EPIC prospective study. *Int J Cancer* 2005; 117: 137–144.
24. Larsson SC, Bergkvist L, Wolk A. High-fat dairy food and conjugated linoleic acid intakes in relation to colorectal cancer incidence in the Swedish Mammography Cohort. *Am J Clin Nutr* 2005; 82: 894–900.
25. McCarl M, Harnack L, Limburg PJ et al. Incidence of colorectal cancer in relation to glycemic index and load in a cohort of women. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 892–896.
26. Larsson SC, Bergkvist L, Rutegard J et al. Calcium and dairy food intakes are inversely associated with colorectal cancer risk in the Cohort of Swedish Men. *Am J Clin Nutr* 2006; 83: 667–673.

27. Park SY, Murphy SP, Wilkens LR et al. Calcium and vitamin D intake and risk of colorectal cancer: the Multiethnic Cohort Study. *Am J Epidemiol* 2007; 165: 784–793.
28. Butler LM, Wang R, Koh WP, Yu MC. Prospective study of dietary patterns and colorectal cancer among Singapore Chinese. *Br J Cancer* 2008; 99: 1511–1516.
29. Park Y, Leitzmann MF, Subar AF et al. Dairy food, calcium, and risk of cancer in the NIH-AARP Diet and Health Study. *Arch Intern Med* 2009; 169: 391–401.
30. Lee SA, Shu XO, Yang G et al. Animal origin foods and colorectal cancer risk: a report from the Shanghai Women's Health Study. *Nutr Cancer* 2009; 61: 194–205.
31. Norat T, Riboli E. Dairy products and colorectal cancer. A review of possible mechanisms and epidemiological evidence. *Eur J Clin Nutr* 2003; 57: 1–17.
32. Huncharek M, Muscat J, Kupelnick B. Colorectal cancer risk and dietary intake of calcium, vitamin d, and dairy products: a meta-analysis of 26,335 cases from 60 observational studies. *Nutr Cancer* 2009; 61: 47–69.
33. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339: b2535.
34. Zheng W, Anderson KE, Kushi LH et al. A prospective cohort study of intake of calcium, vitamin D, and other micronutrients in relation to incidence of rectal cancer among postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 1998; 7: 221–225.
35. Wu K, Willett WC, Fuchs CS et al. Calcium intake and risk of colon cancer in women and men. *J Natl Cancer Inst* 2002; 94: 437–446.
36. Phillips RL, Snowdon DA. Dietary relationships with fatal colorectal cancer among Seventh-day Adventists. *J Natl Cancer Inst* 1985; 74: 307–317.
37. Hirayama T. Association between alcohol consumption and cancer of the sigmoid colon: observations from a Japanese cohort study. *Lancet* 1989; 2: 725–727.
38. Heilbrun LK, Nomura A, Hankin JH, Stemmermann GN. Diet and colorectal cancer with special reference to fiber intake. *Int J Cancer* 1989; 44: 1–6.
39. Ursin G, Bjelke E, Heuch I, Volset SE. Milk consumption and cancer incidence: a Norwegian prospective study. *Br J Cancer* 1990; 61: 454–459.
40. Hsing AW, McLaughlin JK, Chow WH et al. Risk factors for colorectal cancer in a prospective study among U.S. white men. *Int J Cancer* 1998; 77: 549–553.
41. Sellers TA, Bazyk AE, Bostick RM et al. Diet and risk of colon cancer in a large prospective study of older women: an analysis stratified on family history (Iowa, United States). *Cancer Causes Control* 1998; 9: 357–367.
42. Khan MM, Goto R, Kobayashi K et al. Dietary habits and cancer mortality among middle aged and older Japanese living in Hokkaido, Japan by cancer site and sex. *Asian Pac J Cancer Prev* 2004; 5: 58–65.
43. Kojima M, Wakai K, Tamakoshi K et al. Diet and colorectal cancer mortality: results from the Japan Collaborative Cohort Study. *Nutr Cancer* 2004; 50: 23–32.
44. Iso H, Kubota Y. Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). *Asian Pac J Cancer Prev* 2007; 8 (Suppl): 35–80.
45. Matsumoto M, Ishikawa S, Nakamura Y et al. Consumption of dairy products and cancer risks. *J Epidemiol* 2007; 17: 38–44.
46. van der Pols JC, Bain C, Gunnell D et al. Childhood dairy intake and adult cancer risk: 65-y follow-up of the Boyd Orr cohort. *Am J Clin Nutr* 2007; 86: 1722–1729.
47. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177–188.
48. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992; 135: 1301–1309.
49. Bodner-Montville J, Ahuja JKC, Ingwersen LA, Haggerty ES, Wilkinson Enns C, Perloff BP. USDA Food and Nutrient Database for Dietary Studies: Released on the web. *J Food Composition Analysis* 2006; 19: S100–S107.
50. Royston P. A strategy for modelling the effect of a continuous covariate in medicine and epidemiology. *Stat Med* 2000; 19: 1831–1847.
51. Bagnardi V, Zambon A, Quatto P, Corrao G. Flexible meta-regression functions for modeling aggregate dose-response data, with an application to alcohol and mortality. *Am J Epidemiol* 2004; 159: 1077–1086.
52. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539–1558.
53. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–634.
54. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50: 1088–1101.
55. Cho E, Smith-Warner SA, Spiegelman D et al. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. *J Natl Cancer Inst* 2004; 96: 1015–1022.
56. Pietinen P, Hartman AM, Haapa E et al. Reproducibility and validity of dietary assessment instruments. I. A self-administered food use questionnaire with a portion size picture booklet. *Am J Epidemiol* 1988; 128: 655–666.
57. Flagg EW, Coates RJ, Calle EE et al. Validation of the American Cancer Society Cancer Prevention Study II Nutrition Survey Cohort Food Frequency Questionnaire. *Epidemiology* 2000; 11: 462–468.
58. Kesse-Guyot E, Castetbon K, Touvier M et al. Relative validity and reproducibility of a Food Frequency Questionnaire designed for French adults. *Ann Nutr Metab* 2010; 57: 153–162.
59. Llor X, Jacoby RF, Teng BB et al. K-ras mutations in 1,2-dimethylhydrazine-induced colonic tumors: effects of supplemental dietary calcium and vitamin D deficiency. *Cancer Res* 1991; 51: 4305–4309.
60. Holt PR, Atillasoy EO, Gilman J et al. Modulation of abnormal colonic epithelial cell proliferation and differentiation by low-fat dairy foods: a randomized controlled trial. *JAMA* 1998; 280: 1074–1079.
61. Holt PR, Wolper C, Moss SF et al. Comparison of calcium supplementation or low-fat dairy foods on epithelial cell proliferation and differentiation. *Nutr Cancer* 2001; 41: 150–155.
62. Karagas MR, Tosteson TD, Greenberg ER et al. Effects of milk and milk products on rectal mucosal cell proliferation in humans. *Cancer Epidemiol Biomarkers Prev* 1998; 7: 757–766.
63. Rozen P, Lubin F, Papo N et al. Calcium supplements interact significantly with long-term diet while suppressing rectal epithelial proliferation of adenoma patients. *Cancer* 2001; 91: 833–840.
64. Ahearn TU, McCullough ML, Flanders WD et al. A randomized clinical trial of the effects of supplemental calcium and vitamin D3 on markers of their metabolism in normal mucosa of colorectal adenoma patients. *Cancer Res* 2011; 71: 413–423.
65. Carroll C, Cooper K, Papaioannou D et al. Supplemental calcium in the chemoprevention of colorectal cancer: a systematic review and meta-analysis. *Clin Ther* 2010; 32: 789–803.
66. Parodi PW. Cows' milk fat components as potential anticarcinogenic agents. *J Nutr* 1997; 127: 1055–1060.
67. Hague A, Paraskeva C. The short-chain fatty acid butyrate induces apoptosis in colorectal tumour cell lines. *Eur J Cancer Prev* 1995; 4: 359–364.
68. Tsuda H, Kozu T, Iinuma G et al. Cancer prevention by bovine lactoferrin: from animal studies to human trial. *Biometals* 2010; 23: 399–409.
69. Touvier M, Chan DS, Lau RN et al. Meta-analyses of vitamin D intake, 25-hydroxyvitamin D status, vitamin D receptor polymorphisms and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev* 2011; 20(5): 1003–1016.
70. Elwood PC, Pickering JE, Givens DI, Gallacher JE. The consumption of milk and dairy foods and the incidence of vascular disease and diabetes: an overview of the evidence. *Lipids* 2010; 45: 925–939.
71. Soedamah-Muthu SS, Ding EL, Al-Delaimy WK et al. Milk and dairy consumption and incidence of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. *Am J Clin Nutr* 2011; 93(1): 158–171.
72. Chen H, O'Reilly E, McCullough ML et al. Consumption of dairy products and risk of Parkinson's disease. *Am J Epidemiol* 2007 165: 998–1006.
73. Qin LQ, Xu JY, Wang PY et al. Milk consumption is a risk factor for prostate cancer in Western countries: evidence from cohort studies. *Asia Pac J Clin Nutr* 2007; 16: 467–476.