

Intake of dairy products and risk of colorectal neoplasia

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Prospective cohort studies suggest that higher intakes of dairy products, in particular milk, are associated with a decreased risk of colorectal cancer (CRC). In Western populations, dairy products are major contributors to dietary Ca, which may have chemopreventive effects in the colon. The pooling of data from prospective studies suggests a significant protective effect of Ca on CRC risk. Randomised controlled trials with Ca supplements have been conducted with both colorectal adenoma and CRC as endpoints. Results suggest that Ca supplementation at a level of 1000–2000 mg/d reduces adenoma recurrence in individuals with a previous adenoma but has no effect on CRC incidence. There is evidence that the risk reduction from dairy foods may not be solely due to their high Ca content. Dairy products contain other potential chemopreventive components such as vitamin D, butyric acid, conjugated linoleic acid, sphingolipids, and probiotic bacteria in fermented products such as yoghurt. The present review will focus on the epidemiological evidence (and in particular prospective cohort studies) investigating the relationship between dairy product consumption and risk of CRC. An outline of the proposed mechanisms responsible for the protective effect of both Ca and other potential chemopreventive components in dairy products will also be presented.

Dairy products: Colorectal cancer: Adenoma: Calcium: Vitamin D

Introduction

In the UK, colorectal cancer (CRC) affects about 35 000 individuals each year⁽¹⁾. It is the second most common cancer in women (after breast cancer) and the third most common cancer in men (after prostate and lung cancer)⁽¹⁾. About 16 000 individuals each year die from CRC, making it the second most common cause of death from cancer⁽¹⁾. Worldwide, CRC is the third most common cancer after breast and lung cancer, with the highest rates in areas such as Australia, New Zealand and Western Europe and the lowest rates in regions such as Africa and Asia⁽²⁾. Immigrants rapidly acquire the incidence rates of the host country, suggesting that environmental factors play a crucial role in CRC development⁽³⁾.

CRC is an age-related disease, with half of all cases occurring in individuals aged over 60 years⁽¹⁾. The disease is believed to arise from benign tumours called adenomatous polyps (adenomas). Although incidence of adenoma is difficult to predict, necropsy studies show a prevalence of about 35 % in European populations⁽⁴⁾. About 1–10 % of adenomas go on to develop into invasive cancer⁽⁵⁾. Genetic predisposition plays a role in about 15 % of CRC⁽⁶⁾ but most cases are sporadic. It has been estimated that about 70 % of CRC can be prevented by changes in diet and lifestyle⁽⁷⁾.

Factors known to increase risk include age, obesity, physical inactivity, and tobacco and alcohol use⁽⁸⁾. Generally populations with 'Westernised' diets high in red meat and fat and low in fruit, vegetables and dietary fibre are at higher risk⁽⁸⁾. These populations also tend to have a higher proportion of overweight individuals and lower levels of physical activity⁽⁸⁾.

Of the many dietary factors that have been investigated for a potential link with CRC risk, none are more diverse in terms of composition, factors that could potentially influence cancer risk and multiple mechanisms through which these factors could act than dairy products. For example, whole milk and many types of cheese have a relatively high fat content, which may increase the risk of colorectal adenoma and cancer^(9,10). However, dairy products also have high Ca and vitamin D contents, which have been linked to a reduced risk of CRC^(11,12).

Dairy products are important components of the human diet. In the UK they contribute 10 % of the average daily energy intake in the diet of adults⁽¹³⁾ and also contribute significantly to the average daily intakes of vitamins such as riboflavin (33 %), vitamin B₁₂ (36 %) and vitamin D (3 %), and minerals such as Ca (43 %), P (24 %) and Mg (11 %)⁽¹⁴⁾. The present review will focus on the current epidemiological evidence investigating the relationship between

Abbreviations: CLA, conjugated linoleic acid; CRC, colorectal cancer; RR, relative risk.

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dairy product consumption and risk of CRC. An outline of the proposed mechanisms responsible for the observed relationship will also be presented.

Epidemiological studies of dairy products and colorectal cancer risk

A large number of prospective cohort and case-control studies have investigated the link between dairy foods and CRC risk. One of the problems with assessing the evidence is the considerable variation in how consumption data were collected, with some studies reporting overall dairy product consumption, while others report categories such as milk, butter, cheese and fermented milk products. Generally, results from case-control studies are heterogeneous and do not provide evidence of an association between total intake of dairy products and CRC risk⁽¹⁵⁾. Because of the abundance of prospective studies that have investigated the relationship between dairy intake and risk of CRC and because results from case-control studies have been reviewed in detail elsewhere⁽¹⁵⁾, the present review will focus mainly on prospective studies. The prospective studies^(12,16-39) that have assessed the relationship between dairy foods and CRC risk are summarised in Table 1. Data from these studies point to an inverse association, although generally the relationships are statistically non-significant. However, two recent studies, the Cohort of Swedish Men⁽³⁸⁾ and the US Multiethnic Cohort Study⁽¹²⁾, have shown significant reduction in risk (54 and 20 %, respectively) with the highest intake of total dairy products.

Milk is the dairy product that shows the most consistent relationship with CRC risk. Of the cohort studies to date that have investigated this relationship, most showed non-significant decreased risks of CRC with increasing milk intake^(12,17,19,22,23,27,29,30,33,34,38). Most studies have considered all types of milk together, but where these have been separated there are differences between low-fat *v.* whole milk. In the US study on an Adventist population, consumption of skimmed milk, but not whole milk, had a protective effect (relative risk (RR) 0.78 for skimmed milk *v.* RR 1.04 for whole milk)⁽²⁷⁾. A few case-control studies (reviewed by Norat & Riboli⁽¹⁵⁾) have shown similar trends although none of the relationships were statistically significant. In a recent case-control study, whole milk consumption was positively associated with cancer of the rectum (OR 1.22; 95 % CI 1.03, 1.44) while skimmed milk consumption was inversely associated with cancers of the colon (OR 0.84; 95 % CI 0.73, 0.97) and rectum (OR 0.76; 95 % CI 0.64, 0.91)⁽⁴⁰⁾. However, further studies are required to determine any effect of milk fat on CRC risk.

The pooling of data from prospective studies has revealed significant relationships between milk intake and CRC risk. Norat & Riboli⁽¹⁵⁾ analysed data from eleven cohorts and showed a RR of 0.80 (95 % CI 0.68, 0.95) for the highest *v.* the lowest milk intake. Similarly, Cho *et al.*⁽¹¹⁾ analysed data from ten cohorts from five countries, including 534 536 individuals, of whom 4992 were diagnosed with CRC at follow-up. A significant protective effect of milk was found; individuals that consumed more than a glass of milk per d (≥ 250 g) had a 15 % reduced risk of developing CRC (RR 0.85; 95 % CI 0.78, 0.94) compared with those that

consumed < 70 g/d. Each 500 g/d increase in milk intake reduced the risk of CRC by 12 % (RR 0.88; 95 % CI 0.82, 0.95). The inverse association was consistent across studies and sex. The main strength of this meta-analysis is the pooling of individual level prospective data. All included studies used validated diet assessment methods, minimising the possibility of an incorrect recording of the actual intake of dairy products. However, although Cho *et al.*⁽¹¹⁾ adjusted the multivariable RR for energy, alcohol, red meat and dietary folate intakes, they did not adjust for other dietary variables related to CRC risk, such as dietary fibre and fruit and vegetable intakes; therefore it is possible that some residual confounding remains.

Data for other dairy products generally do not support a protective effect against CRC. In the meta-analysis by Cho *et al.*⁽¹¹⁾ dairy foods such as cottage or ricotta cheese, butter, cream and ice cream (which were measured in at least five out of the ten studies) also showed inverse associations with CRC risk, although results were not statistically significant. Data on fermented milk products such as yoghurt suggest no relationship with CRC risk^(22,23,30,38). For cheese intake, RR range from 0.68 to 1.35 and in most studies the RR was greater than 1.0, although none of these relationships were statistically significant^(17,22,23,27,30,34,38). Some studies^(27,38) have attempted to separate hard cheese from soft cheeses such as ricotta and cottage cheese, with the latter appearing to have a protective effect; however, the relationships were not significant and it is difficult to draw any reasonable conclusions from such few studies. A recent meta-analysis on three cohort studies^(23,27,37) conducted for the second expert report on diet and the prevention of cancer⁽⁸⁾ showed a RR of 1.14 (95 % CI 0.82, 1.58) per serving of cheese per d, with low heterogeneity, although it is not clear which kind of cheese was included in the analysis. The Panel concluded that there is some (albeit limited) evidence that cheese is a cause of CRC⁽⁸⁾. Cheese is high in saturated fats, which have been shown to increase insulin production and expression of insulin on colonic cells⁽⁴¹⁾. Saturated fats may also induce the expression of some inflammatory mediators associated with the cancer process⁽⁴²⁾. However, it is difficult to reconcile this with data on the protective effects of dietary Ca, which is abundant in cheese⁽⁴³⁾.

Although there are inconsistencies between studies, most of the evidence points to a decreased risk of CRC with increasing intake of Ca, both dietary and total (including supplements)^(12,24,28,31,32,35,36). Several meta-analyses have quantified the relationship between Ca intake and CRC risk^(8,11,44). An early meta-analysis of eight cohort and sixteen case-control studies showed that the highest category of Ca intake was associated with a 14 % decrease in risk of CRC, although there was considerable heterogeneity between studies, which made reaching a conclusion difficult⁽⁴⁴⁾. In the meta-analysis by Cho *et al.*⁽¹¹⁾ individuals consuming the highest category of dietary Ca had a significantly lower risk of developing CRC (RR 0.86; 95 % CI 0.78, 0.95). A meta-analysis on ten cohort studies conducted for the second expert report on diet and the prevention of cancer⁽⁸⁾ showed a RR of 0.98 (95 % CI 0.95, 1.00) per 200 mg/d, with low heterogeneity. Both meta-analyses suggested a threshold effect of Ca intake; no further protection was observed at intakes > 1000 mg/d.

Table 1. Prospective studies of dairy and/or dietary calcium and vitamin D intake and risk of colorectal cancer (CRC)

Study	Location	Endpoint	Cohort size/number of cases	Follow-up (years)	Dairy products evaluated*	RR†	95% CI
Phillips (1975) ⁽¹⁶⁾	USA	CRC mortality	35460 (number of CRC cases not given)	8	Milk (<one serving per d v. >one serving per d)	0.3	
Phillips & Snowdon (1985) ⁽¹⁷⁾	USA	CRC mortality	25493/182 Seventh-Day Adventists	20	Milk (<one v. ≥three glasses per d) Cheese (<1 v. ≥3 d/week)	0.9 1.1	0.6, 1.5 0.8, 1.6
Garland <i>et al.</i> (1985) ⁽¹⁸⁾	USA	CRC incidence	1954/100	19	Combined index of dietary Ca and vitamin D (lowest v. highest)	Lowest 38.9/1000 population Highest 14.3/1000 population	
Ursin <i>et al.</i> (1990) ⁽¹⁹⁾	Norway	CRC incidence	15914/155	11.5	Milk (≥two glasses v. <one glass per d)	0.85	
Thun <i>et al.</i> (1992) ⁽²⁰⁾	USA	CRC mortality	1185124/2757	2	Butter, cheese, whole milk, ice cream and eggs (lowest v. highest quintile of intake)	1.05 (men) 0.96 (women)	
Bostick <i>et al.</i> (1993) ⁽²¹⁾	USA	Colon cancer incidence	35215/212 Women's Health Study	4	Total dairy (<eight v. >twenty-five servings per week) Fat-containing dairy products (<four v. >fourteen servings per week)	0.72 0.78	0.38, 1.36 0.45, 1.36
Kampman <i>et al.</i> (1994) ⁽²²⁾	Holland	CRC incidence	120852/312	3.3	Dietary Ca (<496 v. >1186 mg/d)	0.95	0.57, 1.61
					Dietary vitamin D (<127 v. >373 IU/d)‡	0.98	0.61, 1.58
					Milk (non-users v. >240 g/d)	0.86	0.57, 1.29
					Buttermilk and yoghurt (non-users v. ≥180 g/d)	0.89	0.60, 1.33
					Hard cheese (non-users v. ≥30 g/d)	0.88	0.59, 1.33
					Total dietary Ca (596 v. 1288 mg/d)	0.90	0.64, 1.34
					Ca from unfermented products (45 v. 540 mg/d)	0.71	0.48, 1.05
Kearney <i>et al.</i> (1996) ⁽²³⁾	USA	Colon cancer incidence	47935/203 Health Professionals Follow-Up Study	6	Ca from fermented products (64 v. 634 mg/d)	1.14	0.77, 1.68
					Milk (<one 8 oz glass per month v. five to seven 8 oz glasses per week)	0.72	0.45, 1.15
					Ice cream (4 ounce serving: <one per month v. >one per d)	0.93	0.42, 2.04
					Hard cheese (1 ounce serving: <one per month v. >one per d)	1.35	0.67, 2.75
					Fermented dairy products (median intake <one per month v. >one per d)	1.09	0.70, 1.72
					Ca dairy products (<137 v. ≥620 mg/d)	0.68	0.42, 1.09
					Vitamin D dairy products (<22 v. ≥154 IU/d)§	0.75	0.47, 1.22
Martinez <i>et al.</i> (1996) ⁽²⁴⁾	USA	CRC incidence	89448/501 Nurses' Health Study	12	Dietary Ca (<500 v. >1000 mg/d)	0.74	0.36, 1.50
					Dietary vitamin D (<85 v. >280 IU/d)	0.72	0.34, 1.54
					Total vitamin D (<120 v. >550 IU/d)¶	0.42	0.19, 0.91
Kato <i>et al.</i> (1997) ⁽²⁵⁾	USA	CRC incidence	15785/100 New York University Women's Health Study	7.1	Dairy products, quartiles of intake (lowest v. highest)	0.69 (<i>P</i> = 0.04 for trend)	0.40, 1.20
Hsing <i>et al.</i> (1998) ⁽²⁶⁾	USA	CRC mortality	286731/145 Lutheran Brotherhood Cohort	20	Dairy products (times per month: <26 v. >85)	0.6	0.3, 1.2
Singh & Fraser (1998) ⁽²⁷⁾	USA	CRC incidence	32051/157 Adventist Health Study	6	Whole milk (never v. ≥one serving per week)	1.04	0.69, 1.59
					Low-fat milk (never v. ≥one serving per week)	0.97	0.66, 1.42
					Non-fat milk (never v. ≥one serving per week)	0.78	0.48, 1.28
					Non-cottage cheese (never v. ≥one serving per week)	1.31	0.84, 2.03
Zheng <i>et al.</i> (1998) ⁽²⁸⁾	USA	Rectal cancer incidence	34702/144 Iowa Women's Health Study	9	Cottage cheese (never v. ≥one serving per week)	0.74	0.49, 1.11
					Ca (<801 v. >1279 mg/d)	0.59	0.37, 0.94
					Vitamin D (<224 v. >476 IU/d)**	0.76	0.50, 1.16
Pietinen <i>et al.</i> (1999) ⁽²⁹⁾	Finland	CRC incidence	27111/185 ATBC Prevention Study (male smokers)	8	Milk products (318 v. 1089 g/d)	0.6	0.4, 0.9
					Soured milk products (0 v. 350 g/d)	1.1	0.7, 1.3

Table 1. Continued

Study	Location	Endpoint	Cohort size/number of cases	Follow-up (years)	Dairy products evaluated*	RR†	95% CI	
Jarvinen <i>et al.</i> (2001) ⁽³⁰⁾	Finland	CRC incidence	9959/72	24	Milk (men < 511 v. > 1131 g/d; women < 302 v. > 700 g/d)	0.72	0.33, 1.57	
					Total dairy (men < 693 v. > 1271 g/d; women < 480 v. > 868 g/d)	1.03	0.36, 2.32	
					Fermented milk (men < 1 v. > 160 g/d; women < 1 v. > 206 g/d)	1.28	0.68, 2.40	
					Cheese (men < 3 v. > 18 g/d; women < 2 v. > 18 g/d)	1.65	0.84, 3.23	
Terry <i>et al.</i> (2002) ⁽³¹⁾	Sweden	CRC incidence	61463/572	11.3	Butter (men < 36 v. > 67 g/d; women < 23 v. > 47 g/d)	1.37	0.62, 3.03	
					Dietary Ca (486 v. 914 mg/d)	0.72	0.56, 0.93	
Wu <i>et al.</i> (2002) ⁽³²⁾	USA	CRC incidence	47344/399 (Men)	10	Dietary vitamin D (113 v. 367 IU/d)††	0.98	0.78, 1.56	
			Health Professionals Follow-Up Study		16	Total Ca intake (≤ 500 v. > 1250 mg/d)	Distal colon cancer	0.65 (pooled)
McCullough <i>et al.</i> (2003) ⁽³³⁾	USA	CRC incidence	121749/683	4		Cancer Prevention Study II Nutrition Cohort (men and women)	0.58 (men)	0.32, 1.05
					Total dairy (< two servings per week v. ≥ two servings per d)	1.00	0.41, 1.27	
					Milk (< two servings per week v. ≥ two servings per d)	0.96	0.72, 1.81	
					Dietary Ca (< 504 v. > 988 mg/d)	0.92	0.45, 1.87	
Sanjoaquin <i>et al.</i> (2004) ⁽³⁴⁾	UK	CRC incidence	10998/95	17	Dietary vitamin D (< 90 v. > 240 IU/d)††	0.73 (women)	0.75, 2.16	
					Total dairy (< two servings per week v. ≥ two servings per d)	1.10	0.75, 1.34	
					Milk (< 0.5 v. > 0.5 pints per d)	1.10	0.65, 1.87	
					Cheese (< five v. ≥ ten times per week)	0.98	0.48, 2.03	
Flood <i>et al.</i> (2005) ⁽³⁵⁾	USA	CRC incidence	45354/482	8.5	Dietary Ca (412 v. 831 mg/d)	0.74 (P = 0.05 for trend)	0.56, 0.98	
Kesse <i>et al.</i> (2005) ⁽³⁶⁾	France	CRC incidence	67312/172	7	Total Ca (< 766 v. > 1202 mg/d)	0.72	0.47, 1.10	
					Dairy Ca (< 359 v. > 736 mg/d)	0.86	0.56, 1.32	
Lin <i>et al.</i> (2005) ⁽³⁷⁾	USA	CRC incidence	36976/223	10	Vitamin D (< 1.72 v. > 3.23 μg/d)	0.89	0.58, 1.36	
			French E3N-EPIC Prospective Study		Dietary Ca (< 480 v. > 1083 mg/d)	0.90	0.53, 1.54	
Larsson <i>et al.</i> (2006) ⁽³⁸⁾	Sweden	CRC incidence	45306/449	6.7	Women's Health Study	Dietary vitamin D (< 125 v. ≥ 333 IU/d)§§	0.96	0.60, 1.55
					Cohort of Swedish Men	Total dairy products (< two servings per week v. ≥ seven servings per d)	0.46	0.30, 0.71
					Milk (< two glasses per week v. ≥ 1.5 glasses per d)	0.67	0.51, 0.87	
					Cultured milk (none v. ≥ one serving per d)	1.07	0.86, 1.34	
Shin <i>et al.</i> (2006) ⁽³⁹⁾	China	CRC incidence	73314/283	5.7	Cream/soured cream (< 0.5 servings per week v. ≥ two servings per week)	0.84	0.65, 1.09	
					Hard cheese (< four slices per week v. ≥ three slices per d)	0.79	0.56, 1.12	
					Cottage/cream cheese (none v. ≥ one serving per month)	0.68	0.40, 1.16	
					Total Ca intake (< 956 v. ≥ 1445 mg/d)	0.68	0.51, 0.91	
Shin <i>et al.</i> (2006) ⁽³⁹⁾	China	CRC incidence	73314/283	5.7	Dietary Ca (1st v. 5th quintile of intake)	0.9	0.6, 1.4	
					Shanghai Women's Health Study	0.6 (after excluding first 2 follow-up years)	0.3, 1.1	

Dairy intake and colorectal cancer

Table 1. Continued

Study	Location	Endpoint	Cohort size/number of cases	Follow-up (years)	Dairy products evaluated*	RRT†	95% CI
Park <i>et al.</i> (2007) ⁽¹²⁾	USA	CRC incidence	191011/2110	7-3	Total dairy products (g/1000 kcal per d)	0.80 (men) 0.81 (women)	0.64, 0.99
			Multietnic Cohort Study (men and women)		Milk (<11 v. ≥ 122 g/1000 kcal per d)	0.78 (men) 0.85 (women)	0.65, 1.00 0.63, 0.96
					Dietary Ca (<260 v. ≥ 333 mg/1000 kcal per d)	0.70 (men) 0.64 (women)	0.68, 1.06 0.52, 0.93
					Dietary vitamin D (<31 v. ≥ 96 IU/1000 kcal per d)‡	0.91 (men) 0.78 (women)	0.50, 0.83 0.73, 1.13 0.63, 0.96

RR, relative risk; EPIC, European Prospective Investigation into Cancer and Nutrition.
 *1 ounce serving = 28.35 g serving; 4 ounce serving = 113.4 g serving; 8 oz glass, 237 ml; 1000 kcal = 4184 kJ.
 † Adjusted RR for the highest dietary intake compared with the lowest dietary intake.
 ‡ < 127 v. > 373 IU/d (<3.2 v. > 9.3 µg/d).
 § < 22 v. ≥ 154 IU/d (0.6 v. ≥ 3.9 µg/d).
 || < 85 v. > 280 IU/d (<2.1 v. > 7.0 µg/d).
 ¶ < 120 v. > 550 IU/d (<3.0 v. > 13.8 µg/d).
 ** < 224 v. > 476 IU/d (<5.6 v. > 11.9 µg/d).
 †† 113 v. 367 IU/d (<2.8 v. > 9.2 µg/d).
 ††† < 90 v. > 240 IU/d (<2.3 v. > 6.0 µg/d).
 §§ < 125 v. ≥ 333 IU/d (<3.1 v. > 8.3 µg/d).
 ||| < 31 v. ≥ 96 IU (<0.8 v. > 2.4 µg).

The evidence for Ca suggests that the protective effect of milk or total dairy may be due in part to its Ca content, since dietary Ca can be considered a marker of dairy intake in populations that consume high amounts of milk and dairy products⁽⁴⁵⁾. Most of the published cohort studies are from dairy-consuming countries such as the USA, Holland, Finland and Sweden, so it is reasonable to assume that a large proportion of dietary Ca comes from dairy products. Recent data from the ongoing Cohort of Swedish Men trial⁽³⁸⁾, a high-quality study established in 1997 to study lifestyle–disease interactions, also reported a decrease in risk of CRC (RR 0.68; 95 % CI 0.51, 0.91) in subjects with the highest Ca intake. This study also confirmed previous findings that milk was the individual dairy food with the strongest influence on risk but the analysis provided some evidence that the risk reduction from dairy foods may not be solely due to their high Ca content⁽³⁸⁾. First, Ca and total dairy consumption had different effects on risk when the various parts of the colon were considered; for example, Ca reduced the risk for the rectum while total dairy intake reduced the risk for the proximal colon, distal colon and rectum⁽³⁸⁾. Second, even though Ca intake was closely associated with total dairy or milk intake, when the analysis was controlled for Ca intake, the influence of milk or dairy intake on risk was diminished but not eliminated⁽³⁸⁾. These findings suggest that other milk-associated factors may be partially responsible for the protective effects and these will be reviewed under the section on mechanisms.

Epidemiological studies of calcium and dairy products and adenoma risk

Most case–control studies on colorectal adenoma risk have investigated intake of dietary and supplemental Ca rather than individual dairy products^(46–51). OR for these studies range from 0.50–0.97 and most do not reach statistical significance^(47–49,51) although some do show a protective effect of Ca^(46,50). In some studies the protective effect of Ca was present in men but not in women⁽⁴⁷⁾. In other studies the protective effects was mainly due to Ca supplement use; for example, Peters *et al.*⁽⁵⁰⁾ found a decrease in adenoma risk for subjects taking 1200 mg Ca/d compared with non-users (OR 0.74; 95 % CI 0.58, 0.95), after adjustment for vitamin supplement intake as well as other confounders associated with supplement use. Similarly, high Ca (>900 mg/d) and lower fat intakes (<34 % of energy intake) were also reported to protect against colorectal adenomas in a US population, an effect that was not observed with high Ca and higher fat intakes (≥ 34 % of energy intake)⁽⁵¹⁾.

Prospective studies^(36,52–56) that have investigated Ca intakes in relation to adenoma risk are listed in Table 2. Martinez *et al.*⁽⁵⁴⁾ showed that intake above 1068 mg/d v. intake below 698 mg/d was associated with a significant reduction in adenoma recurrence among 1304 male and female participants in the Wheat Bran Fiber trial of adenoma recurrence (OR 0.56; 95 %CI 0.39, 0.80; P trend = 0.007) and dietary Ca was found to be more protective than supplemental Ca. Kampman *et al.*⁽⁵²⁾ used data from the Health Professionals Follow-Up Study and the Nurses’ Health Study and showed no relationship between a high total Ca intake or dietary Ca intake and risk of adenoma.

Table 2. Prospective studies of dairy and/or calcium and vitamin D intake and risk of colorectal adenoma

Study	Location	Endpoint	Cohort >size/number of cases	Follow-up (years)	Dairy products evaluated*	RR†	95% CI
Kampman <i>et al.</i> (1994) ⁽⁵²⁾	USA	Adenoma incidence	9159/331 (Men) Health Professionals Follow-Up Study	4	Whole milk (one 8 ounce glass: almost never v. > one per d)	0.94	0.38, 2.34
					Skimmed milk (one 8 ounce glass: almost never v. > one per d)	1.02	0.70, 1.49
					Fermented dairy products (4 v. 111 g/d)	1.10	0.75, 1.62
					Hard cheese (1 ounce serving: <three per month v. > one per d)	1.45	1.02, 2.05
					Total Ca intake (mg/d 547 v. 1649)	1.13	0.76, 1.66
			8585/350 (Women) Nurses' Health Study	8	Dietary vitamin D (118 v. 954 IU/d)‡	1.29	0.87, 1.93
					Whole milk (one 8 ounce glass: almost never v. > one per d)	1.46	0.82, 2.57
					Skimmed milk (one 8 ounce glass: almost never v. > one per d)	0.87	0.50, 1.50
					Fermented dairy products (10 v. 134 g/d)	0.87	0.62, 1.23
					Hard cheese (1 ounce serving: <three per month v. > one per d)	0.91	0.45, 1.83
Hyman <i>et al.</i> (1998) ⁽⁵³⁾	USA	Adenoma recurrence	709/260 Antioxidant Polyp Prevention Study	1–4	Total Ca intake (388 v. 1232 mg/d)	1.17	0.81, 1.69
					Dietary vitamin D (500 v. 909 IU/d; 1980–88)§	0.68	0.41, 1.13
Martinez <i>et al.</i> (2002) ⁽⁵⁴⁾	USA	Adenoma recurrence	1304/365 Wheat Bran Fiber Trial	3	Dietary Ca (610 v. 1044 mg/d)	0.72	0.43, 1.22
					Total Ca intake (698 v. 1068 mg/d)	0.56 (<i>P</i> = 0.007 for trend)	0.39, 0.80
Kesse <i>et al.</i> (2005) ⁽³⁶⁾	France	Adenoma incidence	4804/516 French E3N-EPIC Prospective Study	7	Vitamin D (<1.14 v. >8.7 µg/d)	0.78	0.54, 1.13
					Total Ca (<786 v. >1226 mg/d)	0.80 (<i>P</i> = 0.04 for trend)	0.62, 1.03
Hartman <i>et al.</i> (2005) ⁽⁵⁵⁾	USA	Adenoma recurrence	1905/754 Polyp Prevention Trial	4	Dairy Ca (<371 v. >755 mg/d)	0.86 (<i>P</i> = 0.04 for trend)	0.67, 1.11
					Vitamin D (<1.73 v. >3.26 µg/d)	1.15	0.88, 1.49
					Total Ca (<666 v. >1226 mg/d)	0.91	0.67, 1.23
Oh <i>et al.</i> (2007) ⁽⁵⁶⁾	USA	Distal adenoma incidence	48115/2747 Nurses' Health Study	22	Dietary Ca (<635 v. >1048 mg/d)	0.86	0.62, 1.18
					Dietary vitamin D (<2.75 v. >5.95 µg/d)	0.93	0.69, 1.25
					Total vitamin D (<3.35 v. >11.7 µg/d)	0.84 (<i>P</i> = 0.03 for trend)	0.62, 1.13
					Total Ca intake (510 v. 946 mg/d)	0.88 (<i>P</i> = 0.06 for trend)	0.74, 1.04
					Total vitamin D intake (107 v. 587 IU/d)	0.79 (<i>P</i> = 0.07 for trend)	0.63, 0.99

Dairy intake and colorectal cancer

RR, relative risk; EPIC, European Prospective Investigation into Cancer and Nutrition.
 * 1 US fluid ounce = 29.57 ml; 8 US fluid ounces = 237 ml; 1 ounce serving = 28.35 g serving.
 † Adjusted RR for the highest dietary intake compared with the lowest dietary intake.
 ‡ 118 v. 954 IU/d (<3.0 v. >23.9 µg/d).
 § 500 v. 909 IU/d (<12.5 v. >22.7 µg/d).
 || 107 v. 587 IU/d (<2.7 v. >14.7 µg/d).

Kesse *et al.* ⁽³⁶⁾ found a trend of decreasing risk of adenoma with increasing Ca intake, although the RR for the highest *v.* the lowest quartiles of intake was not significant. An analysis of the baseline data on dietary intake and supplement use from the Polyp Prevention Trial showed that there was no association between Ca or dietary vitamin D intake and adenoma recurrence ⁽⁵⁵⁾, although there were inverse associations between Ca and vitamin D supplementation with both single and multiple adenoma recurrence. Oh *et al.* ⁽⁵⁶⁾ using data from the Nurses' Health Study showed that higher intakes of total Ca were associated with a reduced risk of distal colorectal adenoma.

Relatively few studies have reported dairy intakes (as opposed to Ca) in relation to colorectal adenoma risk. A case-control study in a Japanese population has reported a protective effect on colorectal adenomas of high dairy intakes in conjunction with other healthy dietary patterns ⁽⁵⁷⁾. Data from the Health Professionals Follow-Up Study and the Nurses' Health Study showed that fermented dairy products and cheese were not associated with adenoma risk, even after adjusting for saturated fat intake ⁽⁵²⁾ and baseline data from the Polyp Prevention Trial showed that there was no association between the consumption of low- or high-fat dairy products and adenoma recurrence ⁽⁵⁵⁾. An early systematic review of eleven case-control and two cohort studies did not find an association between dairy intake and colorectal adenoma risk ⁽⁵⁸⁾.

Vitamin D and colorectal cancer risk

Animal studies have shown that dietary Ca and vitamin D status act synergistically to modify CRC risk ⁽⁵⁹⁾. Vitamin D is an important component of dairy foods, and Ca and vitamin D are metabolically related since the absorption of Ca in the gut relies on adequate levels of vitamin D. Several prospective studies that have assessed total vitamin D intake and CRC or colorectal adenoma risk have reported non-significant inverse associations (see Tables 1 and 2), although in some studies total vitamin D intake was unrelated to risk ^(37,52). A few studies have reported a dose-response effect ^(18,33,55). However, these findings need to be interpreted with caution since dietary sources do not account for total vitamin D status; UV radiation induces vitamin D₃ production in the skin, making sun exposure an important source of the vitamin ⁽⁶⁰⁾.

Intervention trials provide some evidence of benefit of high vitamin D intake on adenoma recurrence, although these studies have generally investigated Ca and vitamin D in combination. Hartman *et al.* ⁽⁵⁵⁾ found a reduced risk of adenoma and a significant trend in individuals from the Polyp Prevention Trial. Similarly Oh *et al.* ⁽⁵⁶⁾ also found a reduced risk of distal adenoma in women from the Nurses' Health Study, with $P = 0.07$ for trend. Of further interest are studies of genetic variations in the vitamin D receptor, such as the vitamin D receptor *FokI* polymorphism, which have been related to the risk of CRC ^(61,62). These studies offer independent evidence (free from the effects of confounding associated with the measurement of dietary intakes) that vitamin D is important for human CRC. There is some evidence of interaction between vitamin D receptor polymorphisms and the consumption of dairy products ⁽⁶³⁾,

Ca ^(50,61,64) and vitamin D ⁽⁶⁵⁾ and the risk of colorectal adenoma or cancer in some, though not all ⁽⁶⁶⁾, studies. These important interactions between Ca and vitamin D highlight a limitation in the epidemiological studies that have investigated the dairy-CRC link; most have failed to take into account vitamin D status of the individuals taking part in the studies because of the difficulties in trying to estimate the contribution to vitamin D by sunlight ⁽⁶⁰⁾.

Evidence from calcium supplementation trials

Several prospective studies have shown that Ca supplements decrease the risk of CRC ^(21,22,32,33,37). In the pooled analysis of ten cohort studies by Cho *et al.* ⁽¹¹⁾, the reduction in risk was greater when Ca from supplements was included in the analysis (RR 0.78 (95 % CI 0.69, 0.88) *v.* RR 0.86 (95 % CI 0.78, 0.95) for Ca from food sources). Three prospective studies showed a decreased risk of adenoma recurrence with Ca supplements ⁽⁵³⁻⁵⁵⁾. A meta-analysis ⁽⁸⁾ on the studies by Martinez *et al.* ⁽⁵⁴⁾ and Hartman *et al.* ⁽⁵⁵⁾ gave a summary effect estimate of 0.91 (95 % CI 0.85, 0.98) per 200 mg Ca/d.

Randomised controlled trials have been conducted with both adenoma and CRC as endpoints. For colorectal adenoma, two trials showed a decreased risk of adenoma with Ca supplements. In the Calcium Polyp Prevention Study Group, Baron *et al.* ⁽⁶⁷⁾ showed that supplementation with 1200 mg Ca/d for 4 years in 930 subjects with recently resected adenoma was associated with a 19 % reduction in risk of adenoma recurrence (RR 0.81; 95 % CI 0.67, 0.99). A 5-year follow-up after the end of the intervention showed that subjects in the Ca group still had a significantly lower risk of adenoma than those in the placebo group (31.5 *v.* 43.2 %; adjusted RR 0.63 (95 % CI 0.46, 0.87); $P = 0.005$) ⁽⁶⁸⁾. However, follow-up for a further 5 years did not show any difference between the groups ⁽⁶⁸⁾. Bonithon-Kopp *et al.* ⁽⁶⁹⁾ showed that supplementation with 2000 mg Ca/d for 3 years also reduced adenoma recurrence in 665 subjects, although the effect was not significant (OR 0.66; 95 % CI 0.38, 1.17). The results of both the above trials combined showed a significant reduction in adenoma recurrence with Ca supplementation (OR 0.74; 95 % CI 0.58, 0.95) ⁽⁷⁰⁾. In another 3-year intervention trial where 1600 mg Ca was given in conjunction with β -carotene (15 mg), vitamin C (150 mg), vitamin E (75 mg) and Se (101 μ g) there was no effect on the growth of pre-existing adenomas, although there was a non-significant reduced risk of new adenoma growth in subjects < 60 years of age (mean difference 2.3 mm; 95 % CI 0.26, 4.36) ⁽⁷¹⁾.

A recent intervention trial involving 36 282 postmenopausal women participating in the Women's Health Initiative showed that 1000 mg elemental Ca/d (as calcium carbonate) in conjunction with 10 μ g (400 IU) vitamin D for 7 years had no effect on the incidence of CRC ⁽⁷²⁾. Overall this was a good-quality study, loss to follow-up was minimal (data were available on 97 % of living participants) and adherence to the intervention was relatively good (70 % of women took ≥ 50 % of their study medication through the 6th year). Serum concentrations of vitamin D at baseline and additional use of Ca and vitamin D supplements by a subgroup of participants did not modify the effect of the intervention on the outcome. However, baseline

Ca and vitamin D intakes (1151 mg/d and 9.1 µg (367 IU), respectively) were relatively high in this population. This may explain the lack of effect, particularly since pooled data from prospective studies suggest no further effect on CRC risk of Ca beyond this level of intake⁽¹¹⁾; this is in contrast to intervention trials with adenoma recurrence as an endpoint, in which intakes > 1000 mg/d reduced the risk of colorectal adenoma⁽⁷⁰⁾. Another explanation for the lack of effect could be the duration of the intervention and the short follow-up period; CRC takes 10–20 years to develop so a follow-up period longer than 7 years may be necessary to detect any beneficial effects of Ca supplements on CRC risk.

Potential chemopreventive agents in dairy foods

Although Ca has been the main component in dairy products to be investigated for its protective role in CRC, dairy products contain many potential chemopreventive components such as vitamin D, butyric acid, conjugated linoleic acid (CLA), sphingolipids, and probiotic bacteria in fermented products such as yoghurt⁽¹⁵⁾. The following section will present a brief review of the proposed mechanisms and evidence for them.

Ca may provide protection against CRC through two mechanisms. In the colon, Ca sequesters secondary bile acids such as deoxycholic acid (a by-product of fat metabolism)⁽⁷³⁾ and phospholipids, both of which promote colorectal tumours in animal models, possibly by increasing bacterial production of diacylglycerol. Diacylglycerol is the second messenger for protein kinase C, a key enzyme involved in signal transduction, which stimulates cell proliferation⁽⁷⁴⁾. Ca has also been suggested to act directly on the colonic epithelium to inhibit the proliferation of epithelial cells by inducing differentiation and increasing apoptosis⁽⁷⁵⁾, both of which are important processes for eliminating cancerous cells in the colon. Ca has been shown to decrease cell proliferation when added in high concentrations to human colonic epithelial cells cultured *in vitro*⁽⁷⁶⁾.

Early studies in human subjects suggested a reduction in colonic epithelial cell proliferation with increasing Ca intake^(76–78), although these studies had small sample sizes. Subsequent studies showed that Ca supplementation did not reduce epithelial cell proliferation in the rectal mucosa of subjects with adenoma^(79–81), ulcerative colitis⁽⁸²⁾ or hereditary non-polyposis CRC⁽⁸³⁾, although Holt *et al.*⁽⁸⁴⁾ showed that increasing Ca intake from dairy products in seventy individuals with previously resected colonic adenomas changed colonic biomarkers of cancer risk (proliferative activity of colonic epithelial cells and markers of normal cellular differentiation) towards normal. One study has shown that supplementation of the diet with Ca tablets or low-fat dairy foods lowered colonic epithelial cell proliferation⁽⁸⁵⁾. Generally, however, the weight of the evidence suggests that Ca supplements do not lower epithelial cell proliferation rates.

Animal studies have shown that dietary Ca and vitamin D status act synergistically to modify CRC risk⁽⁵⁹⁾. Vitamin D may regulate the production of growth factors and cytokines, which are important for normal cell function, and also influence apoptosis and differentiation⁽⁵⁹⁾. These effects act in unison and may inhibit uncontrolled cell

growth. Studies in cell lines⁽⁸⁶⁾ and animals⁽⁸⁷⁾ have shown growth inhibition of tumour cells following administration of vitamin D. In animal studies, adequate vitamin D supply has been shown to prevent the hyperproliferation and adenoma formation induced by stress diet (high fat, low Ca, high phosphate and low vitamin D) or carcinogen treatment (azoxymethane or 1,2-dimethylhydrazine). Human studies have shown that administration of vitamin D (in combination with Ca) resulted in decreased proliferative indices and other markers of tumour growth in rectal mucosa of individuals with adenoma⁽⁸⁸⁾. Increased levels of the circulating form of vitamin D (25-hydroxyvitamin D₃) in the serum were significantly correlated with several independent indices of cell proliferation⁽⁸⁹⁾. It is possible that vitamin D may be important in determining the effect of Ca on cell proliferation, and failure to account for vitamin D status may be partly responsible for the discrepancies between Ca supplementation studies with cell proliferation as an endpoint.

Apart from Ca and vitamin D, other potential chemopreventive agents in dairy products have received more limited attention. Dietary butyric acid, found in the lipid fraction of milk and milk products, has been suggested to play a role in colorectal neoplasia. Butyric acid has been shown to inhibit proliferation and induce differentiation in tumour cell lines⁽⁹⁰⁾ and animal studies⁽⁹¹⁾. However, it is more likely that these effects are a result of butyric acid production in the colon as a result of fermentation of dietary fibre by colonic microflora⁽⁹²⁾, since dietary butyric acid is rapidly absorbed in the small bowel and metabolised in the liver and therefore never reaches the colon⁽⁹³⁾.

More convincing evidence exists for CLA⁽⁹⁴⁾, a naturally occurring fatty acid present in dairy and beef products. CLA is derived from linoleic acid, a PUFA that is converted to CLA by bacteria in the rumen of ruminant animals⁽⁹⁵⁾. Studies in cell lines have shown that CLA inhibits the growth of a variety of tumour cells^(95–97). Dietary CLA has also been shown to reduce colon cancer incidence in animals administered a colorectal carcinogen⁽⁹⁸⁾. In a human epidemiological study in which CLA intakes were estimated, high CLA intakes were associated with a reduced risk of CRC; the RR associated with the highest vs the lowest quartile of intake was 0.71 (95% CI 0.55, 0.91; *P* for trend = 0.004)⁽⁹⁹⁾. CLA may protect against cancer by inhibiting cell proliferation, modifying the fluidity of cell membranes, decreasing the production of prostaglandins (inflammatory mediators) and also stimulating the immune response⁽⁹³⁾.

Bacteria in fermented dairy products such as yoghurt may also have benefits for colonic health. Some strains of *Bifidobacteria* have been shown to reduce the formation of precursor lesions for CRC (for example, aberrant crypt foci)^(100,101). Studies on cell lines have shown that lactic acid bacteria can bind carcinogens present in cooked foods to their cell-wall skeletons⁽¹⁰²⁾ and animal studies have shown the prevention of heterocyclic amine-induced DNA damage in the colon and liver of rats by different lactobacillus strains⁽¹⁰³⁾. A study in human subjects has shown that the consumption of *Lactobacillus acidophilus* significantly reduced the excretion of carcinogens that had been ingested from heavily browned or burnt meat cooked at

high temperature⁽¹⁰⁴⁾. Bacteria in yoghurt and other fermented dairy products may also be capable of stimulating the immune system; mice fed milk containing *L. bulgaricus* or *L. casei* had increased production of immune cells such as lymphocytes and macrophages⁽¹⁰⁵⁾. However, other studies have shown more ambivalent results; administration of lactic acid bacteria to carcinogen-treated rats had no effect on tumour growth⁽¹⁰⁶⁾ and some strains of lactic acid bacteria induced DNA damage and increased the effects of reactive oxygen species-generating chemicals in human colonic cells *in vitro*⁽¹⁰⁷⁾.

Other components of milk that may have beneficial properties include sphingolipids such as sphingomyelin, which is a potent inhibitor of cell growth and also induces differentiation and apoptosis⁽¹⁰⁸⁾. Dietary sphingomyelin fed in amounts that can be found in dairy products has been shown to inhibit aberrant crypt foci formation and decrease the proportion of malignant tumours in mice⁽¹⁰⁹⁾. Another category of sphingolipids known as glycosphingolipids were also shown to inhibit the formation of aberrant crypts by up to 60% in mice treated with a colorectal carcinogen⁽¹¹⁰⁾. Other compounds that may have beneficial effects include lactoferrin⁽¹¹¹⁾ and the milk protein casein⁽¹¹²⁾, although the evidence for these is limited.

Conclusions

Generally, individual studies looking at dairy intake in relation to CRC risk have reported non-significant inverse associations, although the pooling of data from these studies shows a significant protective effect. Ca has been the main component in dairy products to be investigated. However, it is currently difficult to translate the evidence into effective public health recommendations, since the Ca dose at which protection is maximised differs between studies from less than 1000 mg/d⁽³³⁾ to 1400 mg/d⁽³⁸⁾. This issue needs to be resolved, particularly as there are concerns that high dietary Ca intake may be a risk factor for advanced prostate cancer^(40,113). Apart from Ca, components such as vitamin D, dairy proteins, sphingolipids, CLA and probiotic bacteria in fermented dairy foods may also have beneficial effects, although most of the evidence for these comes from animal studies that have yet to be replicated in human subjects. The evidence for a protective role in CRC is strongest for milk, although the effect is evident from pooled data rather than individual cohort studies, which are generally non-significant. The limited evidence that hard cheese may increase CRC risk despite its high Ca content highlights the difficulties associated with trying to determine risk posed by a complex food group where an interplay of protective and harmful factors coexist.

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