

REVIEW

Dairy products and colorectal cancer. A review of possible mechanisms and epidemiological evidence

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Objectives: This review provides an overview of the principal hypotheses and epidemiological evidence of the possible links between colorectal cancer and intake of milk and/or dairy products.

Methods: The first section outlines the main hypotheses about the possible effect of calcium, vitamin D, fats and other milk components. The possible role of acid lactic bacteria in fermented products is also discussed. The second section is a summary of the published epidemiological evidence. The results on milk, cheese and yoghurt are summarized using a meta-analytical approach. The results of studies on calcium and vitamin D are briefly described.

Results: Case–control studies are heterogeneous and, on average, do not provide evidence of association between total intake of total dairy products, milk, cheese or yoghurt and colorectal cancer risk. The average result from cohort studies support the hypothesis of a protective effect of total dairy products (odds ratio (OR): 0.62; 95% confidence interval (CI): 0.52–0.74; *P* heterogeneity test: 0.93) and for milk (OR: 0.80; 95% CI: 0.68–0.95; *P* heterogeneity: 0.77). No association was found between cheese (OR: 1.10; 95% CI: 0.88–1.36; *P* heterogeneity: 0.55) or yoghurt (OR: 1.03; 95% CI: 0.83–1.28; *P* heterogeneity: 0.69) in cohort studies.

Conclusions: Cohort studies consistently found a protective effect of total dairy products and milk intake, but the evidence is not supported by case–control studies. No relationship was found with cheese or yoghurt intake. As the number of cohort studies is still limited, their results need to be confirmed by other prospective studies.

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Introduction

Milk and other dairy products are important components of human diet. They contribute about 4% of total energy worldwide and in some geographical regions, such as North America, Australia and Europe, milk and other dairy products provide about 10% of total energy intake (data extracted from Food Balance Sheets, FAO Statistical databases, 1995–1999, <http://apps.fao.org>). Cow's milk is the most frequently consumed, although there is considerable

geographical variation with goat, sheep, camel and water buffalo milk.

Milk and dairy products have the peculiarity of having components that could hypothetically increase the risk of some diseases and other components that could decrease it. Milk has been suggested as a risk factor of atherosclerosis and coronary heart disease because it is a source of cholesterol and saturated fatty acids. Beneficial effects, however, have been attributed to other components of milk, like conjugated linoleic acid, which may have hypolipidaemic and antioxidative and thus antiatherosclerotic properties, calcium, which may protect from hypertension, and folic acid, vitamin B₆ (pyridoxine) and B₁₂ (cyanocobalamin), which contribute to lower homocysteine levels.

Laboratory and epidemiological studies suggest that the intake of dairy products could be associated with cancer risk (World Cancer Research Fund, 1997). Several studies have suggested that dairy consumption may be related to colorectal cancer risk. The main hypothesis underlying a possible protective effect of dairy products relates to their calcium

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content and to a lesser extent vitamin D, conjugated linoleic acid, sphingolipids, butyric acid and fermentation products. On the other hand, milk fats and particularly saturated fats might increase cancer risk.

The purpose of this review is to provide an overview of the principal hypotheses and epidemiological evidence of the possible links between milk and dairy products intake, and colorectal cancer. The first section outlines the main biological hypotheses about the possible association of dairy products and colorectal cancer risk. The second section is a summary of the published epidemiological studies. The results on milk, cheese and yoghurt are summarized using a meta-analytical approach. The results of studies on calcium and vitamin D are briefly described as they have been the object of other reviews recently published (Bergsma-Kadijk *et al*, 1996; Martinez & Willett, 1998).

Principal hypotheses linking dairy products intake and colorectal cancer

Calcium

Among various micronutrients, calcium has attracted significant interest as a potential chemopreventive agent. It has been proposed that ionized calcium (Newmark *et al*, 1984) or calcium phosphate (van der Meer *et al*, 1991) might reduce colon cancer by binding secondary bile acids and free fatty acids, primarily deoxycholic and lithocolic acids, thereby reducing their effective toxic dose to the colonic epithelial cells and preventing their stimulatory effects on proliferation of the intestinal mucosa (Lapre *et al*, 1993; Govers *et al*, 1996). Calcium has been shown to reduce the colonic content of diacylglycerol formed by bacteria which may activate cellular transduction pathways and has been postulated to increase proliferation in the colonic epithelium (Holt *et al*, 1996).

Another hypothesis derived from studies on human epithelial cells *in vitro* (Lipkin & Newmark, 1985; Lipkin, 1991) invokes an intracellular action of calcium, which could inhibit the proliferation of epithelial cells of the colon by inducing their differentiation (Lipkin & Newmark, 1995). It has been shown that administration of calcium to rodents reduces the incidence and multiplicity of chemically induced tumours (Appleton *et al*, 1987; Sitrin *et al*, 1991). Calcium also reduces the number of guanine-to-adenine mutations in the *K-ras* gene in colorectal neoplasms of the rat (Llor *et al*, 1991). Calcium may increase the rate of apoptosis occurring in colonic epithelial cells which, itself, could normalize a possible discrepancy between the proliferation/apoptosis ratio in preneoplastic mucosa (Chang *et al*, 1997).

Vitamin D

The foods naturally richest in vitamin D are fatty fish and fish oil. In most Western populations, however, intake of fatty fish and fish oil is low. Multivitamin supplements and

enriched foods, particularly dairy products, can constitute a significant source of vitamin D (Chen *et al*, 1993; Holick, 1994).

Many tissues contain vitamin D receptors, including the colon. More differentiated colon cancer cells show higher levels of vitamin D receptors than less differentiated cell lines (Shabahang *et al*, 1993).

In 1980, Garland and collaborators proposed that vitamin D is protective against colon cancer. This hypothesis was based upon the geographical distribution of colon cancer deaths in the United States. In a subsequent study, Garland and coworkers found a significant reduction of the risk of developing colon cancer in subjects with higher levels of serum 25-hydroxyvitamin D (Garland *et al*, 1989).

Experimental studies suggest that vitamin D may inhibit cell proliferation (Shabahang *et al*, 1994; Cross *et al*, 1992; Wallach *et al*, 1966; Taniyama *et al*, 2000). The cell growth inhibitory properties of the vitamin appear to be related to the concentrations of vitamin D receptors on the cell surface rather than vitamin D concentrations. The inhibition might also be due to the effect of vitamin D on calcium absorption.

Fats

Dairy products could act as a dietary source of total and saturated fats. The major part (97–98%) of milk lipids is triglycerides or esters of fatty acids. The remainder comprises phospholipids (0.22–1%), sterols, free fatty acids and variable quantities of liposoluble vitamins (A, D, E and K). Around two-thirds of the fatty acids in milk are saturated. Polyunsaturated fatty acids make up less than 4% of milk fat.

The main hypothesis supporting a possible effect of fat on colon cancer risk is based on the intraluminal effect of products of fat digestion. It has been postulated that dietary fat may promote colon cancer by increasing bile acid and fatty acid excretion in the colonic lumen. The microbial flora hydrolyses bile acids to form secondary bile acids. Free fatty acids and ionized secondary bile acids may damage colonic epithelial cells and thus induce a compensatory hyperproliferation of crypt cells (van der Meer *et al*, 1991).

A more recent hypothesis is based on the circulatory effects of fat on increasing insulin concentrations. Evidence from animal studies suggested that insulin is an important growth factor of colonic epithelial cells and a mitogen of tumour cell growth *in vitro* (McKeown-Eyssen, 1994; Giovannucci, 1995). Some epidemiological studies have provided support for the theory that chronic hyperinsulinaemia consequent to insulin resistance increases colon cancer risk (Bird *et al*, 1996; Hu *et al*, 1999; Kaaks *et al*, 2000; Kono *et al*, 1998; Schoen *et al*, 1999; Will *et al*, 1998; Yamada *et al*, 1998).

Epidemiologic studies do not generally support the hypothesis that the total fat content of the diet increases colon cancer risk. However, it is possible that some subtype of fat could be related to colorectal carcinogenesis (Giovannucci & Goldin 1997).

Besides the postulated 'negative' effect of fat, other lipidic components of dairy products could be beneficial, such as butyric acid and conjugated linoleic acid (CLA). Butyric acid may inhibit proliferation and induce differentiation in a wide range of tumour cell lines *in vitro* (McBain *et al*, 1997; Parodi, 1999; Velazquez *et al*, 1996). Dietary butyric acid occurs exclusively in the lipid fraction of milk and its derivatives. Butyrate can likewise result from fermentation of dietary fibre by the microflora of the colon that has not been digested by intestinal enzymes. Some experimental studies have indicated a protective effect of butyric acid against colon cancer (Hague & Paraskeva, 1995; Hague *et al*, 1995; Aukema *et al*, 1997; Marchetti *et al*, 1997). Dietary butyric acids are rapidly absorbed by the intestine and are largely metabolized in the liver, and thus never reach the colon (Parodi, 1997). Consequently, it is unlikely that butyric acid from milk is involved in colon carcinogenesis in any way similar to that of butyrate produced by the colonic microflora from fibre fermentation.

Milk lipids constitute the principal dietary source of dietary CLA (Lin *et al*, 1995). Studies of cell lines have shown that CLA inhibits the proliferation of colorectal, breast and skin tumour cells (Parodi, 1997), mammary tumorigenesis in rats (Ip & Scimeca, 1997) and decreases the number of aberrant crypt foci in rats on 2-amino-3-methylimidazo [4,5-f] quinoline-induced colon carcinogenesis (Liew *et al*, 1995). CLA could have a cancer-protective effect by modifying the fluidity of cell membranes, reducing the synthesis of prostaglandins and/or stimulating the immune response (Parodi, 1997). Ip *et al* (1994) calculated that the anticancer properties of CLA in a rat mammary model of breast cancer are expressed at concentrations close to human consumption levels (0.1–1%). However, there is no consistent evidence of the postulated beneficial effects of these milk components in humans.

Lactic acid bacteria

The possible protective role on health of fermented dairy products such as yoghurt was originally proposed at the beginning of the last century. Metchnikoff in 1908 postulated that *Lactobacillus bulgaricus*, one of the various microbial species (*Lactobacillus bulgaricus*, *Streptococcus thermophilus*, *Lactobacillus acidophilus*, *Bifidobacterium bifidus*, etc.) that can be used in the preparation of fermented products, suppresses toxins produced by putrefactive bacteria in human intestines (cited by Meydani & Ha, 2000). Some strains of *Bifidobacteria* and *Lactobacilli* are known to bind the apical surface of colonic epithelial cells in culture without injuring them, which could explain their protective action in gastrointestinal diseases (Ouweland *et al*, 1999). By protecting the surface epithelium, *Bifidobacteria* may thus facilitate repair and reduce irritation and epithelial permeability to electrolytes (Bruce *et al*, 2000).

Skim milk fermented with *Bifidobacterium* sp. may act against the development of aberrant crypt foci (ACF) in the

colon of rats (Abdelali *et al*, 1995; Kulkarni & Reddy, 1994). Studies *in vitro* have shown that lactic acid bacteria have a capacity to absorb mutagens from cooked foods (Zhang & Ohta, 1993). This finding is consistent with an experimental study in humans in which it was observed that ingestion of *L. acidophilus* significantly reduced the excretion of mutagens following consumption of meat heavily browned or burnt by cooking at high-temperature (Lidbeck *et al*, 1992).

It has been suggested that yoghurt and other fermented products may have immunostimulatory properties related to their bacterial components. Oral administration to mice of milk containing *L. bulgaricus* or *L. casei* has been shown to activate the lymphocytes and macrophages (Perdigon *et al*, 1999). Addition of yoghurt to cultures of human blood lymphocytes stimulated by a mutagen leads to increased production of gamma-interferon, a cytokine with anti-proliferative properties that is able to activate natural killer (NK) cells (De Simone *et al*, 1987). The mechanism of intestinal colonisation by lactic acid bacteria has not yet been established, and it is likely that their consumption would have to be very frequent in order to have a significant effect on the intestine.

Hypotheses related to other milk components: proteins, folate, growth factors

Lactoferrin, a glycoprotein that participates in the transport and storage of iron, has a bacteriostatic effect by binding the iron that is necessary for microbial development. Lactoferrin may have other protective functions, by activating NK cells and stimulating lymphokine-activated killer (LAK) cells (Shau *et al*, 1992; Sekine *et al*, 1997). Human lactoferrin may inhibit the development of solid tumours of the colon and of metastases from a melanoma cell line in mice (Bezault *et al*, 1994; Yoo *et al*, 1997) and may reduce significantly the incidence and number of adenocarcinomas of the large intestine in rats (Sekine *et al*, 1997). The protective activity of lactoferrin against chemically induced rat tumours is consistent with results obtained using preparations of proteins from whey and other dairy products (Abdelali *et al*, 1995). Thus, even if lactoferrin should be confirmed to be a milk component with cancer-chemopreventive properties, the effect of lactoferrin would probably be limited for most dairy products because of its low natural concentration (0.02% in cows' milk) and its destruction by heat treatments used for milk conservation (Sekine *et al*, 1997). The lack of clinical and epidemiological data in humans precludes any firm conclusion on a specific effect of milk proteins in carcinogenesis.

There is some evidence that folate is associated with a reduced risk of colorectal neoplasia. Foliates represent an important B vitamin, participating in one-carbon transfer reactions required in many metabolic pathways, especially purine and pyrimidine biosynthesis (DNA and RNA) and amino acid interconversions. One of the postulated mechanisms is that folate, central to methyl-group metabolism, may

influence both methylation of DNA and the available nucleotide pool for DNA replication and repair (Freudenheim *et al*, 1991; Giovannucci *et al*, 1993).

Folate concentrations in cow's milk are in the range of 5–10 µg per 100 g. Fermented milk contains slightly higher amounts of folate, sometimes double, depending on the starter culture used. Most cheese varieties contain between 10 and 40 µg of folate per 100 g. Ripened soft cheese may contain up to 100 µg per 100 g (Forssen *et al*, 2000). The bioavailability of milk folates has not been fully determined under conditions of actual consumption, including the consequences of interactions between various food constituents. There is no evidence of the effect of milk folates on colorectal cancer risk.

Insulin-like growth factors (IGFs), IGF-I and IGF-II, present in mammalian milk, play an important role during gastrointestinal tract development. *In vitro* studies and animal experiments have shown that plasma IGF-1 may have direct effects on colorectal carcinogenesis, by stimulating cell proliferation, and by inhibiting apoptosis (Singh & Rubin, 1993). Research on growth-factor digestion in human adults is very limited, but it has been shown in animal experiments that IGF-II is stable in the gastro-intestinal tract in adult rats while IGF-I is less stable in the intestine of adult than in suckling rats (Philipps *et al*, 2000).

Epidemiological evidence on the association between dairy products and colorectal cancer risk

Most of the evidence in nutritional epidemiology comes from observational studies, such as case–control and cohort studies. Randomized controlled trials are less frequent, firstly because they are only justified when there is enough evidence of a possible benefit, and secondly because of the difficulties in randomizing subjects to different diets. Some intervention studies of calcium supplementation have been reported, but there are no trials on milk and/or dairy products and colorectal cancer.

At least 30 case–control or cohort studies have investigated the relationship between colorectal cancer and dairy products (Tables 1 and 2). The evidence for the four types of dairy products that were most often investigated (total dairy products, milk, cheese and yoghurt) is summarized in a meta-analysis. The measure of effect used is the weighted average relative risk/odds ratio (OR) of the highest category of consumption vs the lowest, as reported in the studies. The inverse of the variance of the ORs was used as weight and 95% confidence intervals (95% CI) were computed. Tests of heterogeneity were performed and random effect models used when there was evidence of heterogeneity (DerSimonian & Laird, 1986).

Total dairy products

Some studies evaluated the intake of all types of dairy products as a food group. The ORs for the highest category

of consumption vs the lowest are summarized in Figure 1. Out of 11 case–control studies, three found a significant risk increase (Benito *et al*, 1990; Iscovich *et al*, 1992; Steinmetz & Potter, 1993) and three other studies a significantly decreased risk (Shannon *et al*, 1996; Kampman *et al*, 2000; Murata *et al*, 1999). The diversity of dairy products may to some extent explain the inconsistencies of these results. Case–control studies have heterogeneous results (P heterogeneity < 0.0000) and, on average, do not provide evidence of association between total intake of dairy products and colorectal cancer risk (OR: 1.07; 95% CI: 0.84–1.34). One cohort study in male smokers in Finland (Pietinen *et al*, 1999) found a significant protective effect, while three cohort studies (Bostick *et al*, 1994; Kato *et al*, 1997; Hsing *et al*, 1998) found no significant protective association. The average result from cohort studies supports the hypothesis of a protective effect (OR: 0.62; 95% CI: 0.52–0.74). The assumption of homogeneity is not rejected (P heterogeneity: 0.93) for cohort studies, in contrast to what was found for case-control studies.

Milk

Two case–control studies found a significant risk increase associated to milk consumption. In one of them, conducted in Belgium, the risk increase was associated with milk consumption higher than 1775 g per week (Tuyns *et al*, 1988). The other study, conducted in the USA, evaluated the risk of different cancers in relation to milk consumption. This study found a significantly increased risk in subjects that consumed whole milk daily compared to non-consumers (Mettlin *et al*, 1990). The daily consumption of 2% fat-milk or skim milk was not associated with colon cancer but 2% fat-milk was found to be significantly protective for rectal cancer. Four case-control studies reported significant protective effects (Kune *et al*, 1987; Macquart-Moulin *et al*, 1986; La Vecchia *et al*, 1988), but not consistently for both sexes or both colon and rectum. The average estimate from case–control studies is OR: 0.98 (95% CI: 0.82–1.05; (Figure 2). As for dairy products, case–control studies were heterogeneous (P heterogeneity < 0.00).

The prospective studies published to date found reduced relative risks of colorectal cancer associated with higher levels of milk consumption. The cohort from Finland in male smokers (Pietinen *et al*, 1999) and the prospective study on an Adventist population (Singh & Fraser, 1998) found a significant protection. Only the Adventist study found a non-significant relative risk higher than 1 in women (Phillips & Snowdon, 1985). On average, cohort studies are supportive of a protective effect of milk consumption (OR: 0.80; 95% CI: 0.68–0.95; P heterogeneity: 0.77).

Cheese

No association between cheese consumption and colorectal cancer risk was found on average by case-control and cohort

Table 1 Dairy products and colorectal cancer: case-control studies

Authors, place	Design	Type of dairy products and partition/OR (95% CI)					
Miller <i>et al</i> (1983), Canada	348 colon (171 men and 177 women) 194 rectum (114 men and 80 women) 542 hospital and 535 population controls. Adjusted by age, sex, saturated fat, other foods	Homogenized, 2% and skim milk, buttermilk, dried milk, yoghurt (g/day)					
		Men	Colon	Rectal	Women	Colon	Rectal
		< 153	1	1	< 138	1	1
		153–361	1.2	1	138–326	1.4	1.2
		> 361	1.2	1.1	> 326	1.3	1.2
		Cream, milk desserts, ice cream, ice milk and sherbert (g/day)					
Men	Colon	Rectal	Women	Colon	Rectal		
0	1	1	0	1	1		
< 24.8	1.2	1.5	< 16	1.4	1.2		
≥ 24.8	1.2	1.7	≥ 16	1.3	1.8		
Manousos <i>et al</i> (1983), Greece	Colorectal: 100; controls: 100 hospital-based	Milk and milk products: no heterogeneity between case and control distributions by tertile of intake					
Pickle <i>et al</i> (1984), USA	Colon 58; rectum 28; controls 176; hospital-based. mean age: 74. Rural area. Adjusted by age, sex, ethnic group, others	Milk, cheese, yoghurt, butter, ice cream, pudding, custard, cream. More than 27 servings/week vs less				Colon: 0.74 Rectum: 0.92	
Tajima & Tominaga (1985), Japan	Colon 42; rectum 51; controls 186; hospital based. Age 40–74. Adjusted by sex, age	Milk (10 y ago) 1–6 times/week vs less					
		Cheese		Colon	Rectum	Yogurt	
		Less than once per week		1	1	Less than once per week	
		1–3 times/week		1.81	1.35	1–3 times/week	
≥ 4 times per week		1.36	1.20	≥ 4 times per week			
Macquart-Moulin <i>et al</i> (1986), France	Colorectal 399; control 399; hospital-based. Adjusted by age, sex, total energy, weight	Milk median intake g/day		Quartiles	Cheese mean intake g/day		Quartiles
		Men: 112.4		1	Men: 67		1
		Women: 164.3		0.82	Women: 51.4		1.04
				0.64			1.09
Kune <i>et al</i> (1987), Australia	Colon 392; rectum 323; controls 727; population-based. Adjusted by age, sex, other dietary variables	Milk drinks (ml/week)					
		Men	1		Women	1	
		< 670	0.61		< 570	0.78	
		< 1200	0.65		< 976	0.83	
		< 1735	0.63		< 1440	0.51	
		< 2650	1.50		< 2080	0.59	
Cheese, yogurt, ice cream, custard and cream (ml/week) Men < 855 vs < 184; Women < 860 vs < 210: no association							
Vlajinac <i>et al</i> (1987), Belgrade	Colon 81; controls 162; hospital and neighbourhood-based. Age 24–85	Cheese, more than 8 times/month vs less			Hospital controls	Neighbours	
		Cream, more than 3 times/month vs less			1.23	0.92	
					1.70	2.00	
La Vecchia <i>et al</i> (1988), Italy	Colon 339; rectum 236; controls 778; hospital-based. Age < 75. Adjusted by age, sex, education, area, other foods	Milk	Colon	Rectal	Cheese	Colon	Rectal
		Low	1	1	Low	1	1
		Intermediate	1.34	1.09	Intermediate	1.19	1.32
		High	1.15	0.87	High	1.02	1.31
Young & Wolf (1988), USA	Colon 353; controls 618; population-based. White Americans. Age 35–89. Adjusted by age, sex	Highest vs lowest quartile		Age < 18	Age 18–35	Age > 35	
		Milk		0.84 (0.60–1.17)	0.62 (0.45–0.86)	0.71 (0.55–0.92)	
		Cultured milk		0.89 (0.53–1.48)	1.18 (0.54–1.83)	1.04 (0.71–1.51)	
Tuyns <i>et al</i> (1988), Belgium	Colon 453; rectum 365; controls 3669, population-based. Adjusted by age, sex, province	Milk (g/week)	Colon	Rectum			
		< 375	1	1			
		< 900	1.32	1.26			
		< 1775	1.72**	1.27			
		≥ 1775	1.77**	1.71**			

Authors, place	Design	Type of dairy products and partition/OR (95% CI)							
Lee et al (1989), Singapore	Colorectal 203, controls 426 hospital-based. Colon: 77 men; 55 women. Rectum: 44 men; 27 women. Chinese origin. Adjusted by age, sex, dialect, education	Total milk (g/day)		Colorectal	Colon	Rectum			
		Men	Women	1	1	1			
		< 16	0						
		< 76	< 43.8	0.84 (0.54–1.29)	0.89 (0.54–1.46)	0.71 (0.34–1.44)			
		> 76	> 43.8	0.92 (0.60–1.34)	0.81 (0.49–1.33)	1.12 (0.59–2.10)			
Peters et al (1989), USA	147 colorectal cancer; 147 neighborhood-based controls. White men, age < 45. Adjusted by race, sex, age, place of residence	Milk (times/week)		Colorectal	Rectum (n=41)				
				1	1				
		≤ 1							
		2–4		1.6 (0.8–3.3)	2.1 (0.6–7.4)				
		≥ 5		1.0 (0.6–1.8)	2.1 (0.8–5.4)				
Mettlin et al (1990), USA	504 colon and 312 rectum; 1300 control; hospital-based. Adjusted by sex, age, smoking history, education, residence	Milk preference		Colon	Rectum	Milk fat index	Colon	Rectum	
		No milk		1	1	Low	1	1	
		Low fat milk		0.9 (0.6–1.2)	0.9 (0.6–1.3)	2	1 (0.7–4)		0.8 (0.5–1.2)
		Mixture		1.3 (0.9–1.9)	1.2 (0.8–1.9)	3	1.4 (1.0–1.9)		1.4 (1.0–2.0)
		Whole milk only		1.6 (1.0–2.3)	1.8 (1.1–2.8)	High	1.2 (0.8–1.6)		0.9 (0.6–1.3)
				Whole milk		2% Milk		Skim milk	
		None		Colon	Rectum	Colon	Rectum	Colon	Rectum
		< Daily		1	1	1	1	1	1
		Daily		1.4 (1.1–1.9)	1.4 (1.0–1.9)	0.9 (0.7–1.3)	0.9 (0.6–1.2)	0.9 (0.6–1.4)	1.0 (0.6–1.6)
				1.8 (1.3–2.4)	2.0 (1.4–2.8)	0.8 (0.6–1.0)	0.6 (0.4–0.8)	1.0 (0.7–1.4)	0.8 (0.5–1.3)
Negri et al (1990), Northern Italy	Colon 558; rectum 352; controls 1032; Hospital-based. Age range 26–74. Adjusted by age, sex, education, area of residence, selected foods	Highest vs lowest quintiles			Colon	Rectum			
					1	1			
					1.1 (0.7–1.5)	0.8 (0.6–1.3)			
					1.4 (1.0–2.0)	1.1 (0.8–1.7)			
					1.2 (0.9–1.7)	1.2 (0.8–1.8)			
					1.1 (0.8–1.6)	1.2 (0.8–1.9)			
Benito et al (1990), Spain	Colon 144; men 72; women 72; rectum 130; men 74; women 56; population controls 295. Age < 80. Adjusted by age, sex, weight, physical activity, other foods, education, occupation	Milk, yoghurt, cheese, cottage chese, custard, cream, ice cream							
		Times/month		Colorectal	Colon	Rectum			
		< 34		1	1	1			
		< 49		1.26	0.83	1.58			
		< 71		1.39*	0.98				
Hu et al (1991), China	Colon 111; rectal 225; controls 336; hospital-based	Milk consumption prior to 1966 and prior to 1985			No association with colon nor with . rectal cancer in men and women				
Bidoli et al (1992), Italy	Colon 123; rectum 125; controls 699; hospital-based. Mean age: controls 56.4 y (colon 57 y; rectum 62 y). Adjusted by age, sex, social status	Milk		Colon	Rectum	Cheese	Colon	Rectum	
		Low		1	1	Low	1	1	
		Intermediate		0.9	0.9	Intermediate	0.8	1.5	
		High		1.0	1.0	High	1.4	1.6	
Peters et al (1992), USA	White men and women! 746 colon cancer (327 women, 419 men); 746 hospital- based controls. Adjusted by age, sex, social class, alcohol, calcium, weight, physical activity, family history, others	Milk (units in serving/month)			Both sexes 1.04 (0.98–1.10)				
		Yoghurt (units in serving/month)			Men 1.00; women 0.95**				
					Both sexes 0.83 (0.70–0.98)**				
					Men 0.80**; Women 0.83**				
Iscovich et al (1992), Argentina	Colon 110; controls 220; population-based. Adjusted by age, sex, residence, other foods	Milk, yoghurt, cheese, butter and cream.		1	Whole milk, whole milk		1		
		Cut-off points times/y		0.68 (0.32–1.46)	yoghurt, milk jam		0.74 (0.36–1.53)		
		290–485–719		1.23 (0.59–2.56)	Cut-off points times/y		0.59 (0.27–1.29)		
				2.09 (1.01–4.33)	11–187–341		1.56 (0.78–3.12)		
		Cheese Cut-off points times/y		1	Skim milk, low-fat yoghurt				
		71–138–278	0.56 (0.26–0.24)	21 times/y vs less: 0.88 (0.50–1.52)					
			0.88 (0.41–1.89)						
			1.93 (0.93–4.02)**						

Authors, place	Design	Type of dairy products and partition/OR (95% CI)				
Steinmetz & Potter (1993), Australia	Colon; men: 121 cases; 241 controls, women: 99 cases; 197 controls, population-based. Adjusted by age, sex, occupation, Quetelet index, alcohol intake. Adjusted by age, sex	Dairy foods, servings/week				
		Men		Women		
		≤ 4.4	1	≤ 4.7	1	
	4.5–8.6	0.58 (0.29–1.16)	4.8–8.2	1.34 (0.66–2.70)		
	8.7–13.5	1.32 (0.70–2.51)	8.3–13.8	1.69 (0.84–3.39)		
	≥ 13.6	1.14 (0.58–2.24)	≥ 13.9	2.69 (1.16–6.22)		
Centonze et al (1994), Italy	Colorectal 119; controls 121; population-based. Rural area. Median age 67. Adjusted by age, sex, smoking, education, changes in diet	Dairy products (g/day)		Milk (g/day)		
		≤ 130	1	≤ 6	1	
		131–262	0.94 (0.50–1.77)	7–172	0.87 (0.50–1.52)	
		≥ 263	0.60 (0.30–1.18)	≥ 173	0.62 (0.23–1.62)	
		Cheese (g/day)		Milk products (g/day)		
		≤ 55	1	≤ 31	1	
56–104	1.02 (0.53–1.94)	32–69	0.81 (0.44–1.51)			
≥ 105	0.71 (0.37–1.37)	≥ 69	0.91 (0.46–1.79)			
Fresh curd cheese: 5 g/day or more vs less: 1.09 (0.62–1.94)						
Kampman et al (1994a), Netherlands	232; 259; men 130; 136; women 102; 123; population-based. Age < 75. Adjusted by age, sex, total energy, alcohol intake, family history, others Adjusted by age, sex	Dairy products (g/day)				
		< 270	1			
		270–404		0.88 (0.52–1.51)		
		405–588		0.77 (0.44–1.34)		
		> 588		1.27 (0.75–2.17)		
Kotake et al (1995), Japan	187 colon and 176 rectal cancer; 213 screening and 150 hospital-based controls. Adjusted by age, sex	Milk (times/week)		Colon: 0.8 (0.37–1.62)		
		Daily vs < 1–2		Rectum: 0.9 (0.43–1.86)		
Boutron et al (1996), France	Colorectal; 109 men, 69 women; 309 population-based controls. Dietary history adjusted by age, sex, caloric intake	Milk (g/day)		Cheese (g/day)		
		Men	Women	Men	Women	
		< 14.2	< 20	1	< 34	< 17.6
		< 62.7	< 76.3	1.7 (0.9–3.2)	< 52.6	< 40
		< 147.9	< 157.8	0.8 (0.4–1.6)	< 71.5	< 59.4
		< 459.4	< 262.6	1.2 (0.6–2.2)	< 95.8	< 84.3
Yoghurt men < 26.3 g/day vs more: 1.0 (0.7–1.7)				women < 69.8 g/day vs more: 1.0 (0.6–1.6).		
Full-fat milk; men 1.8, P=0.03; women 1.0, P=0.95						
Shannon et al (1996), USA	Colon; men 238 cases; controls: 224; women 186 cases; controls: 190. Population-based. Age: 30–62. Adjusted by age, sex, total energy	Total dairy servings/day				
		Men		Women		
		0–1.2	1	0–1.3	1	
		> 1.2–2.14	1.82 (1.05–3.16)	> 1.3–1.8	0.31 (0.16–0.58)	
		> 2.14–3.32	1.57 (0.89–2.76)	> 1.8–2.8	0.71 (0.40–1.28)	
		> 3.32	0.92 (0.49–1.71)	> 2.8	0.40 (0.21–0.79)	
		Yoghurt servings/week		Women	Men	
		0	1			
		> 0–1		1.01 (0.62–1.63)	0.98 (0.60–1.61)	
		> 1		0.65 (0.37–1.16)	1.27 (0.69–2.36)	
		High-fat dairy, servings/day				
		Women		Men		
		0–0.21	1	0–0.42	1	
		> 0.21–0.57	0.67 (0.36–1.24)	> 0.42–0.78	0.64 (0.36–1.14)	
> 0.57–1.14	0.76 (0.40–1.45)	> 0.78–1.46	1.06 (0.63–1.80)			
> 1.14	0.78 (0.39–1.55)	> 1.46	0.73 (0.41–1.30)			
Low-fat dairy, servings/day						
Women		Men				
0–0.30	1	0–0.14	1			
< 0.30–0.94	0.70 (0.40–1.23)	< 0.14–0.65	1.27 (0.75–2.17)			
< 0.94–1.51	0.60 (0.33–1.06)	< 0.65–1.42	1.35 (0.79–2.31)			
> 1.51	0.61 (0.34–1.09)	> 1.42	1.0 (0.58–1.71)			
			2.0			

Authors, place	Design	Type of dairy products and partition/OR (95% CI)							
Slattery et al (1997), USA	Colon cases: 1993; population-based controls: 2410 men: 1097 cases, 1298 controls; women: 894 cases, 1120 controls. CARDIA diet-history questionnaire adjusted by age, sex, area of residence, tumor site, BMI, physical activity, total energy intake	Number of items of dairy products		Men	Women				
		< 3		1	1				
		3–4		0.9 (0.7–1.1)	1.1 (0.8–1.4)				
		4.1–5		1.0 (0.8–1.2)	0.9 (0.7–1.2)				
		5.1–6		1.0 (0.8–1.3)	1.1 (0.8–1.5)				
> 6		0.9 (0.7–1.2)	1.2 (0.9–1.6)						
Franceschi et al (1997), Italy	Colon 1225; rectum 728; controls 4154; population-based Age: 19–74. Adjusted by age, sex, education, total energy, physical activity, others	Milk	servings/week	Cheese	servings/week				
		0	1	< 2.4	1				
		< 3.5	1.03 (0.86–1.23)	< 3.5	1.15 (0.97–1.37)				
		< 7	1.01 (0.86–1.18)	< 4.7	0.99 (0.83–1.18)				
		< 10.3	0.94 (0.77–1.13)	< 6.2	0.91 (0.76–1.09)				
Milk: OR for increase of one serving per day; colon: 0.96 (0.89–1.03); rectum: 0.92 (0.84–1.01); colorectal: 0.95 (0.89–1.01)		Cheese: OR for increase of one serving per day; colon: 0.96 (0.80–1.15); rectum: 0.99 (0.79–1.25); colorectal: 0.97 (0.83–1.13)							
Murata et al (1999), Japan	Colon 265; rectum 164; controls 794; hospital-based. Adjusted by age, sex, tobacco, eating attitude, other foods	Dairy products		Colon: 0.98 (0.86–1.12) Rectum: 0.83 (0.71–0.97)*					
		Eating frequency (frequent vs infrequent)							
Levi et al (1999), Switzerland	Colon 119; rectal 104; control 491; hospital-based. Mean age: 63. Adjusted by age, sex, BMI, smoking, total energy intake alcohol, physical activity Cheese. Increase of one serving per day	Milk, servings/week		Cheese servings/week					
		< 4		< 3.75					
		1		1					
		< 12		1.04 (0.67–1.64)					
		≥ 12		1.66 (1.07–2.59)					
Colorectal: 1.09 (0.98–1.22) Colon: 1.10 (0.99–1.22) Rectum: 1.07 (0.94–1.21)									
Boutron-Ruault et al (1999), France	Right colon 43; left colon 63; rectum 65; controls 309; Population-based. Age 30–79. Dietary history. Adjusted by age, sex, caloric intake	Quartiles, reference:	Milk	Cottage cheese and yogurt	Cheese				
		lowest	1	1	1				
			1.4 (0.8–2.4)	1.0 (0.6–1.8)	1.2 (0.7–2.0)				
			1.0 (0.5–1.7)	1.3 (0.8–2.3)	1.2 (0.7–2.1)				
	1.0 (0.6–1.8)	1.1 (0.6–1.9)	0.9 (0.5–1.5)						
Kampman et al (2000), USA	Colon 1993; men 1095; women 1114; controls 2410; population-based. Adjusted for age, sex, BMI, family history, total energy intake, physical activity, dietary fibre, others	Total dairy servings/day				Cheese servings/day			
		Men	1	Women	1	Men	1	Women	1
		0.7	1.0 (0.7–1.2)	0.5	0.7 (0.5–0.9)	0.08	0.9 (0.7–1.2)	0.08	0.8 (0.6–1.1)
		1.4	1.1 (0.8–1.4)	1.1	0.7 (0.5–0.9)	0.18	1.1 (0.8–1.4)	0.17	0.9 (0.6–1.2)
		2.2	0.9 (0.7–1.2)	1.8	0.7 (0.5–0.9)	0.31	0.9 (0.7–1.2)	0.29	1.0 (0.7–1.3)
		3.5	0.8 (0.6–1.1)	2.7	0.7 (0.5–0.9)	0.52	0.9 (0.7–1.2)	0.51	0.8 (0.7–1.1)
		Low-fat dairy, servings/day				High-fat dairy, servings/day			
		Men	1	Women	1	Men	1	Women	1
		0.04	0.8 (0.6–1.0)	0.09	1.0 (0.7–1.3)	0.15	1.0 (0.8–1.3)	0.11	0.9 (0.6–1.1)
		0.44	0.9 (0.7–1.2)	0.46	0.8 (0.6–1.1)	0.38	1.2 (0.9–1.5)	0.25	1.1 (0.8–1.5)
		1.15	0.8 (0.6–1.0)	1.08	0.8 (0.6–1.1)	0.72	0.9 (0.7–1.2)	0.47	1.1 (0.8–1.5)
		2.26	0.8 (0.6–1.0)	2.06	0.7 (0.5–1.0)	1.35		0.89	1.2
		Dietary calcium, mg/day				Dietary vitamin D, mg/day			
Men	1	Women	1	Men	1	Women	1		
681	1.1 (0.8–1.5)	546	0.8 (0.6–1.1)	3.6	1.4 (1.1–1.8)	2.6	0.9 (0.9–1.3)		
941	1.1 (0.8–1.5)	762	0.8 (0.6–1.0)	5.8	1.1 (0.8–1.4)	4.2	1.1 (0.8–1.4)		
1261	0.9 (0.6–1.1)	998	0.8 (0.6–1.1)	7.9	1.1 (0.8–1.5)	5.9	1.0 (0.7–1.3)		
1701	0.7 (0.5–0.9)	1330	0.6 (0.4–0.9)	11.2	1.1 (0.7–1.7)	8.6	1.1 (0.7–1.7)		
Yoghurt > 0; men: 1.0 (0.8–1.2), women: 1.1 (0.9–1.3)									

* $p < 0.05$ ** $p < 0.01$ y: years

Table 2 Dairy products and colorectal cancer: cohort studies

Authors, place	Design	Type of dairy products and partition/OR (95% CI)					
Phillips & Snowdon (1985), Seventh-day Adventist, USA	Colorectal cancer mortality cohort: 25 493 subjects. Age > 35. Cases: colon 147; rectum 35. Recruitment: 1960. Follow-up 20 y FFQ(21). Adjusted by age, sex	Milk (glasses/day)		Colon		Colorectal	Rectal
			Men	Women	Both sexes	Both sexes	
		< 1	1	1	1	1	
		1–2	0.9 (0.5–1.6)	1.6 (1.0–2.7)	1.4 (1.0–1.9)	1.3 (0.6–2.8)	
		≥ 3	0.5 (0.2–1.1)	1.1 (0.5–2.2)	0.9 (0.6–1.5)	0.8 (0.3–2.4)	
		Cheese (days/week)		Colon		Colorectal	Rectal
		Men	Women	Both sexes	Both sexes		
		< 1	1	1	1		
		1–2	1.0 (0.4–2.0)	0.8 (0.5–1.3)	0.8 (0.5–1.1)	0.5 (0.2–1.3)	
		≥ 3	1.9 (1.0–3.6)	0.8 (0.5–1.4)	1.1 (0.8–1.6)	1.0 (0.5–2.2)	
Ursin et al (1990), Norway	Cohort: 15 914 subjects; cases: 92 colon (53 men), 63 rectum (35 men); recruitment: 1964; follow-up: 11.5 y. Adjusted by sex, age, place of residence (plus cigarette smoking in men strata)	Milk (glasses/day)		Both sexes: Colon 0.85; rectum 0.85		Men: Colon 0.75; rectum 1.09	
		≥ 2 vs < 1					
Thun et al (1992), Cancer Prevention Study, USA	Colon cancer mortality Cohort: 1 185 124 subjects; mean age: 57 y. Deaths: 2757. Recruitment: 1982. Follow-up: 2 y	Butter, cheese, whole milk, ice cream and eggs. Quintiles (reference: lowest)		Men	Women		
				1	1		
				0.92	1.03		
				1.04	0.87		
				0.90	0.87		
				1.05	0.96		
Kampman et al (1994b), Netherlands	Cohort: women 58 279; Men 62 573. Age 55–69. Case-cohort colon cancer cases: men 157; women 155. Recruitment: 1986–1990. Follow-up: 3.3 y. Adjusted by age, sex, family history, total calories, fat, dietary fiber, BMI, others	Milk g/day		Buttermilk and yoghurt, g/day			
		Nonusers		Nonusers			
		1		1			
		< 120	0.81 (0.59–1.09)	< 30	0.83 (0.56–1.21)		
		120–240	0.90 (0.67–1.22)	30–90	1.10 (0.77–1.56)		
		> 240	0.86 (0.57–1.29)	90–180	0.93 (0.66–1.31)		
				≥ 180	0.89 (0.60–1.33)		
		Hard cheese, g/day		Total dietary calcium, mg/day			
		Nonusers		Nonusers			
		1		1			
		< 15	0.67 (0.47–0.97)	768	0.84 (0.58–1.22)		
		15–30	0.94 (0.65–1.37)	893	0.96 (0.67–1.39)		
		≥ 30	0.88 (0.59–1.33)	1032	0.93 (0.64–1.36)		
				1288	0.90 (0.64–1.34)		
Calcium (mg/day) from unfermented dairy		Calcium (mg/day) from fermented products					
1		1					
45	0.78 (0.54–1.11)	64	1.01 (0.69–1.48)				
150	0.69 (0.48–1.01)	181	1.29 (0.89–1.88)				
238	0.79 (0.55–1.14)	287	1.18 (0.80–1.72)				
345	0.71 (0.48–1.05)	394	1.14 (0.77–1.68)				
540		634					
Bostick et al (1994), Iowa Women Health's Study, USA	Colon: 212; cohort: 35 216; women (167 447 person/y). Age: 55–69; recruitment: 1986. Follow-up: 4 y. Adjusted by age, sex, total energy intake, height, parity, low-fat meat intake, vitamin E intake, others	Dietary calcium, mg/day		Dietary vitamin D, U/day			
		< 496		< 127			
		1		1			
		496–662	0.90 (0.58–1.38)	127–190	0.90 (0.59–1.35)		
		663–845	0.96 (0.62–1.50)	191–268	0.81 (0.52–1.26)		
		846–1186	1.09 (0.69–1.70)	269–373	0.93 (0.60–1.43)		
		> 1186	0.95 (0.57–1.61)	> 373	0.98 (0.61–1.58)		
		Total dairy, servings/week		Fat-containing dairies, servings/week			
		1		1			
		< 8	1.03 (0.73–1.46)	< 4	0.76 (0.50–1.14)		
8–12	0.83 (0.51–1.37)	4–6	0.79 (0.53–1.18)				
13–18	0.98 (0.61–1.60)	7–9	0.84 (0.54–1.25)				
19–25	0.72 (0.38–1.36)	10–14	0.78 (0.45–1.36)				
> 25		> 14					
Kearney et al (1996), Health Professionals Follow-up Study, USA	Cohort: 47 935 men; age 40–75; Cases: colon 203; recruitment: 1986; end-point: 1992. Adjusted by age, total calories, family history, previous polyp, screening, smoking,	Milk (glass)		Ice cream			
		< 1/month		< 1/month			
		1		1			
		1–4/month	1.08 (0.68–1.71)	1–4 month	0.91 (0.64–1.56)		
		2–4/week	0.85 (0.56–1.29)	2–7/week	0.91 (0.56–1.46)		
5–7/week	0.72 (0.45–1.15)	> 1/day	0.93 (0.42–2.04)				

Authors, place	Design	Type of dairy products and partition/OR (95% CI)			
		> 1/day	0.87 (0.52–1.44)		
	alcohol, aspirin, physical activity, BMI, red meat, saturated fat, dietary fibre	Hard cheese (1 oz serving)	Fermented (median intake)		
		< 1/month	1	< 1/month	
		1–4 month	1.27 (0.69–2.32)	1–4 month	0.70 (0.45–1.09)
		2–7/week	1.34 (0.71–2.49)	2–4/week	0.81 (0.51–1.26)
		> 1/day	1.35 (0.67–2.75)	5–7/week	0.96 (0.62–1.48)
				> 1/day	1.09 (0.70–1.72)
		Cottage cheese	Vitamin D dairy products, IU/day		Calcium from dairy products, mg/day
		< 2/month	1	< 22	1
		< 2/week	1.11 (0.75–1.65)	22–57	0.89 (0.59–1.34)
		≥ 2/week	0.74 (0.49–1.11)	58–104	0.76 (0.49–1.16)
				105–153	0.72 (0.46–1.14)
				≥ 154	0.75 (0.47–1.22)
					< 137
					137–255
					256–374
					375–619
					≥ 620
					0.65 (0.41–0.99)
					0.68 (0.44–1.03)
					0.71 (0.45–1.10)
					0.68 (0.42–1.09)
Martinez et al (1996), The Nurses Health Cohort Study, USA	Cohort: 89 448 women; cases: colon 396; rectum 105; age: 34–59; recruitment: 1980. Follow-up: 12 y. Questionnaires item nos: 61, 121, 136. Adjusted by age, BMI, physical activity, family history, aspirin, smoking, red meat intake, alcohol	Dietary calcium 1980–1986 average intake	Dietary vitamin D, IU/day		
		< 500	1	< 85	1
		500–600	1.05	85–120	1.34
		601–650	1.28	121–150	0.94
		651–750	1.19	151–190	1.29
		751–850	1.22	191–230	1.17
		851–1000	0.75	231–280	1.08
		> 1000	0.74 (0.36–1.50)	> 280	0.72 (0.34–1.54)
		RR per 800 mg	Colon: 0.74 (0.38–1.38) Rectum: 0.74 (0.38–1.38)	RR per 250 IU	Colon: 0.90 (0.58–1.35) Rectal: 0.47 (0.18–1.22)
				Total vitamin D	IU/day
				< 120	1
				120–170	1.17
				171–220	0.83
				221–280	0.88
				281–380	0.84
				381–550	0.97
				> 550	0.42 (0.19–0.91)
				RR per 500 IU	Colon: 0.90 (0.58–1.35) Rectum: 0.47 (0.18–1.22)
Kato et al (1997), New York University Women's Health Study, USA	Cohort: 15 785 women (105 044 person-y); recruitment: 1985–1991. Age: 34–65. Adjusted by age, total caloric intake, education, others		Dairy products Quartiles of intake (reference: lowest)		1 1.08 (0.65–1.80) 0.52 (0.28–0.95) 0.69 (0.40–1.20) (significant trend)
Hsing et al (1998), Lutheran Brotherhood Cohort, USA	Colorectal: cancer mortality in white men; Cohort: 28 6731 person-y; cases: colon 120; rectum 25; recruitment: 1966; follow-up: 20 y. Adjusted by age, smoking status, alcohol intake, total calories	Dairy products times/month	Colon	Colorectal	
		< 26	1	1	
		26–50	0.8 (0.5–1.3)	0.8 (0.5–1.2)	
		51–85	0.7 (0.4–1.1)	0.7 (0.4–1.3)	
		> 85	0.6 (0.3–1.3)	0.6 (0.3–1.2)	
Singh & Fraser (1998), Adventist Health Study, USA	Cohort: 32 051 subjects; age > 25; cases: colorectal 157 (135 colon 22 recto- sigmoidal junction); recruitment: 1976–1982.	Non fat milk	Low fat milk		
		Never	1	Never	
		> 0 to < 1/week	0.80 (0.48–1.33)	> 0 to < 1/week	0.80 (0.49–1.30)
		≥ 1/week	0.78 (0.48–1.28)	≥ 1/week	0.97 (0.66–1.42)
	Adjusted by BMI, physical activity, parental history of colon cancer, tobacco, alcohol	Whole milk	Cheese*		
		Never	1	< 2/month	
		> 0 to < 1/week	1.33 (0.88–1.99)	< 2/week	1.27 (0.86–1.87)
		≥ 1/week	1.04 (0.69–1.59)	≥ 2/week	1.31 (0.84–2.03)
Zheng et al (1998), Iowa Women's Health Study, USA	Rectal: 144; subjects: 34 702 women at risk. Follow-up: 9 y. Adjusted by age, smoking, hormone replacement therapy, total energy intake	Calcium, mg/day	Vitamin D, IU/day		
		< 800.9	1	< 224.1	
		800.9–127.8	0.90 (0.61–1.33)	224.1–475.5	
		> 127.8	0.59 (0.37–0.94)	> 475.5	
				0.71 (0.47–1.08)	
				0.76 (0.50–1.16)	

Authors, place	Design	Type of dairy products and partition/OR (95% CI)				
Pietinen et al (1999), ATBC Prevention Study, Finland	Cohort: 27 111 male smokers; age: 50–69; cases: 185; recruitment: 1988; follow-up: 8 y. Adjusted by age, tobacco years, BMI, alcohol, education, physical activity, others	Milk products (median g/day)	318	1	Sour milk products (median g/day)	0
			6565	0.7 (0.5–1.1)	33	1.3 (0.9–1.9)
			864	0.8 (0.5–1.2)	168	1.1 (0.7–1.6)
			1089	0.6 (0.4–0.9)	350	1.1 (0.7–1.3)

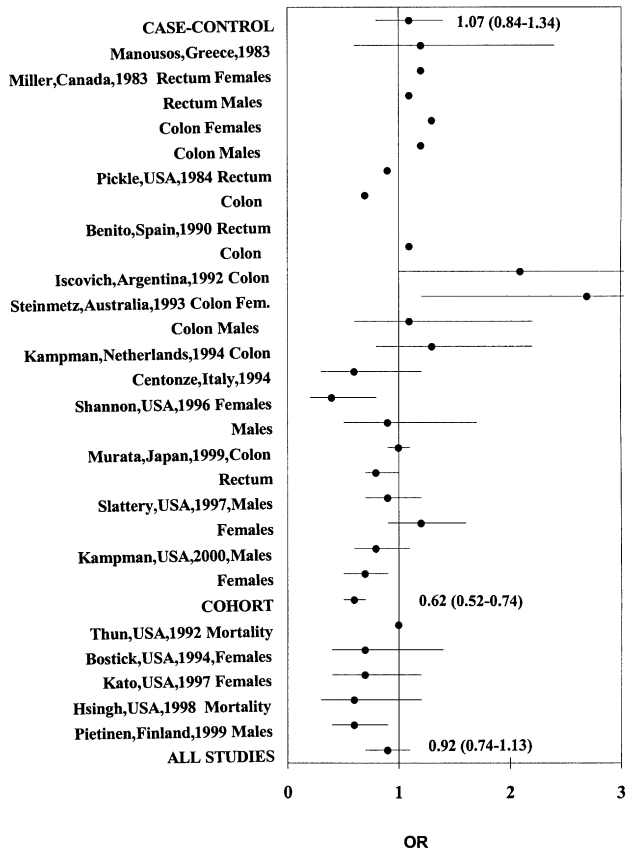


Figure 1 Odds ratios of colorectal cancer for 'high' vs 'low' dairy product consumption in case-control and cohort studies.

studies (Figure 3). The average estimate for case-control studies is OR 1.07 (95% CI: 0.87–1.32; *P* heterogeneity: 0.02) and OR 1.10 (95% CI: 0.88–1.36) for cohort studies. Homogeneity is not rejected for cohort studies (*P* heterogeneity: 0.55).

Yoghurt

The number of studies that have investigated the effect of yoghurt intake in colorectal cancer is limited (Figure 4). So far, case-control and cohort studies are not supportive of the hypothesis of a protective effect. Homogeneity is not rejected for case-control studies (*P* heterogeneity: 0.69), nor for cohort studies (*P*: 0.69). The average estimates are OR

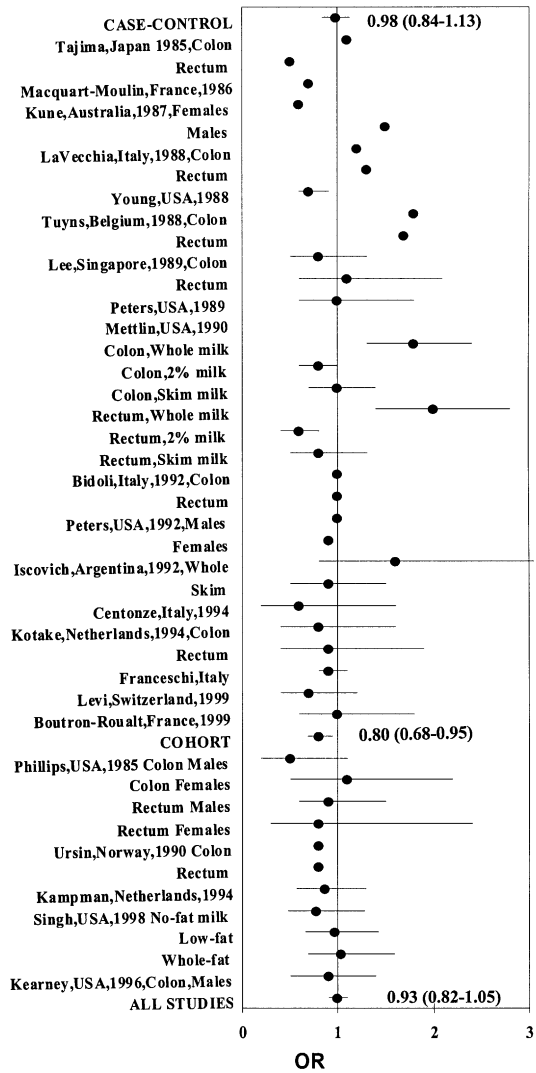


Figure 2 Odds ratios of colorectal cancer for 'high' vs 'low' for milk consumption in case-control and cohort studies.

0.93 (95% CI: 0.84–1.03) for case-control and OR 1.03 (95% CI: 0.83–1.28) for cohort studies.

Fat from milk and dairy products

Some epidemiological studies have investigated low-fat dairy products separately from high-fat dairy products. One case-

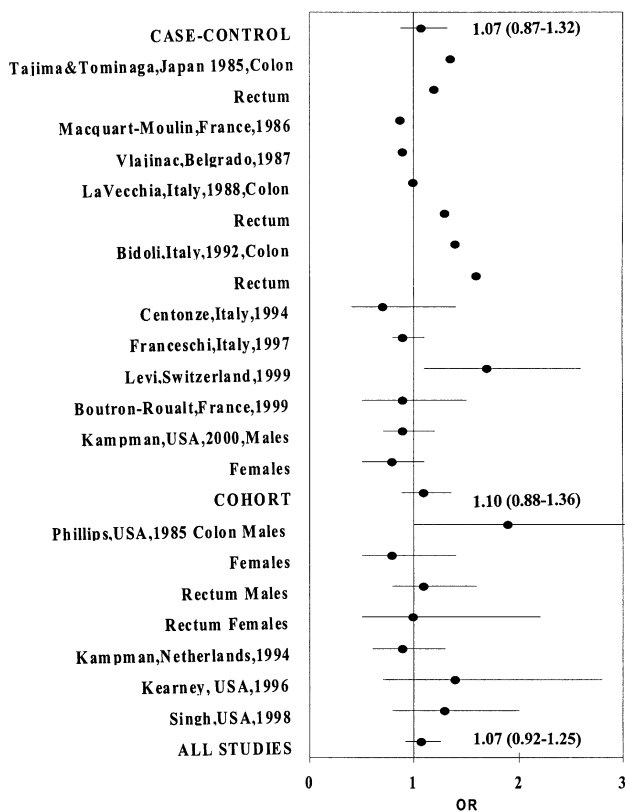


Figure 3 Odds ratios of colorectal cancer for 'high' vs 'low' cheese consumption in case-control and cohort studies.

control study (Miller *et al*, 1983) did not find significant associations between low-fat and high-fat dairy products and colorectal cancer risk with the exception of a significant risk increase in rectal cancer in women associated with an intake higher than 16 g per day of cream, milk desserts, ice cream, ice milk and sherbert cheese. Two other case-control studies (Iscovich *et al*, 1992; Shannon *et al*, 1996) reported higher odds ratios for high-fat than for low-fat dairy intake, but the association was not statistically significant. An American hospital-based case-control study on patterns of milk consumption and risk of different cancers found a significant increased risk in subjects that consumed whole milk daily compared to non-consumers (Mettlin *et al*, 1990). In this study, the daily consumption of 2% milk or skim milk was not associated with colorectal cancer. The data were not adjusted for total caloric intake. A prospective study on an Adventist population (Singh & Fraser, 1998) found a relative risk of 1.04 (95% CI: 0.69–1.59) for consumption of whole milk more often than once a week compared with no consumption. The relative risk for the same levels of consumption of non-fat milk was 0.78 (95% CI: 0.48–1.28). These results are suggestive of a risk increase associated with intake of high-fat dairy products. Nevertheless, these results could hardly be interpreted as an evidence of the fat hypothesis, first because of the sparse number of studies and secondly,

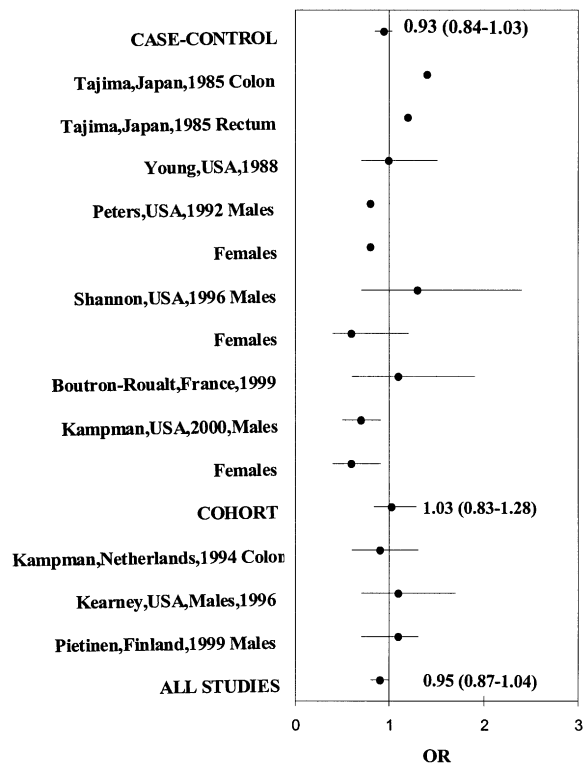


Figure 4 Odds ratios of colorectal cancer for 'high' vs 'low' yoghurt consumption in case-control and cohort studies.

because no association was found when investigating other dairy products richer in fat, such as cheese.

Calcium

A recent meta-analysis (Bergsma-Kadijk *et al*, 1996) and a review of the epidemiological evidence from published case-control and cohort studies (Martinez & Willett, 1998) concluded that calcium intake was not associated with a substantially lower risk of colorectal cancer or polyps. Studies published after these two reviews support the hypothesis that high levels of calcium may reduce the risk of colorectal cancer. A cohort study in Finland observed a significant 40% reduction in risk of colon cancer at high levels of calcium intake (Pietinen *et al*, 1999) as did a large multi-centre case-control study from the USA (Kampman *et al*, 2000) and a case-control study conducted in Wisconsin (Marcus & Newcomb, 1998). A prospective study among Iowa women also suggested an inverse association between calcium and colon cancer, but limited to the subjects without a history of colorectal cancer among first-degree relatives (Sellers *et al*, 1998).

Two major different end points have been used in clinical trials as intermediate biomarkers of risk of colorectal neoplasia: the recurrence of adenomatous polyps, a last intermediate biomarker of risk, and colorectal epithelial cell

proliferation, an earlier biomarker. The results of five small uncontrolled clinical trials (Lipkin & Newmark, 1985; Buset *et al*, 1986; Lipkin *et al*, 1989; Rozen *et al*, 1989; O'Sullivan *et al*, 1993), nine small randomized placebo-controlled trials (Gregoire *et al*, 1989; Stern *et al*, 1990; Barsoum *et al*, 1992; Wargovich *et al*, 1992; Thomas *et al*, 1993; Bostick *et al*, 1993; Cats *et al*, 1995; Weisgerber *et al*, 1996; Bostick *et al*, 1997) and three full-scale randomized placebo-controlled trials (Armitage *et al*, 1995; Baron *et al*, 1995; Bostick *et al*, 1995) suggested that it is unlikely that calcium supplementation can substantially lower colorectal epithelial cell proliferation rates, but it may normalize the distribution of proliferating cells within colon crypts, as reviewed by Bostick, (1997). This is still consistent with the hypothesis that a higher consumption of calcium may reduce the risk of colorectal cancer.

More recent studies have not provided on average evidence of a beneficial effect of calcium supplementation on epithelial cell proliferation. In a double-blind, placebo-controlled randomized trial involving supplementation of fibre and calcium intake in 93 patients with resected colorectal adenomas, neither the wheat bran fibre nor the calcium carbonate supplements significantly reduced cellular proliferation rates in rectal mucosal biopsies (Alberts *et al*, 1997). A randomized trial of calcium and antioxidant vitamins on 77 patients operated on for colorectal cancer showed that calcium and vitamin supplementation does not reduce cell kinetics of the colon (Cascinu *et al*, 2000). Only a small, 1 y trial of calcium supplementation found a significant suppression of rectal epithelial cell proliferation levels in the intervention group (Rozen *et al*, 2001).

Recent trials on recurrent adenomas are suggestive of a beneficial effect of calcium supplementation, though modest. A double-blind 3 y intervention with calcium and antioxidants in 116 polyp-bearing patients showed a beneficial effect on adenoma recurrence, although not on adenoma growth (Hofstad *et al*, 1998). The Calcium Polyp Prevention Study, a large clinical controlled trial, showed that calcium carbonate supplementation was associated with a significant, though moderate, reduction in the risk of recurrent adenomas (Baron *et al*, 1999). In the European Cancer Prevention Intervention Study, a placebo-controlled trial on the prevention of adenoma recurrence in 655 patients, calcium supplementation was associated with a modest but not significant reduction in the risk of adenoma recurrence (Bonithon-Kopp *et al*, 2000).

Vitamin D

Whereas the relation between calcium and colon or colorectal cancer has been studied in numerous epidemiological studies, the role of vitamin D has only been addressed in a smaller number of epidemiological studies. The available results for vitamin D suggest protective rather than harmful effects of vitamin D on colon cancer risk, as reviewed by Martinez and Willett (1998). Only one of the three case-control studies identified in the review reported a significant

protective effect of dietary vitamin D against colorectal cancer risk. Three other studies not included in the review reported discordant results: a French case-control study (Boutron *et al*, 1996) that did not find association between vitamin D intake (nor calcium) and colorectal cancer risk; a Swedish study (Pritchard *et al*, 1996) that reported a protective effect of dietary vitamin D, more pronounced for cancer of the rectum (no association with calcium); and a large case-control study (Kampman *et al*, 2000) that found an inverse significant association of dietary calcium and calcium supplement use with colon cancer, but no significant association with dietary vitamin D, supplements or sunshine exposure. Four of the five prospective studies included in the review have reported an inverse association for dietary vitamin D and colon cancer, but this was only significant in the Western Electric study (Garland *et al*, 1985). This was a small prospective study with only 49 colorectal cancer cases identified after 19 y of follow-up. The same author reported a protective effect of serum 25-hydroxyvitamin D on colon cancer from a nested case-control study, but only 34 cases of colon cancer were included (Garland *et al*, 1989).

The significant risk reduction among high vitamin D consumers has not been confirmed by any of the prospective studies. As most studies that observed an inverse association with vitamin D intake are prospective studies in which exposure is assessed many years before diagnosis, it is possible that vitamin D has a protective effect only on early stages of tumour development (Kampman *et al*, 2000).

One of the hypotheses currently under discussion relating cancer and vitamin D is its potentially protective effect against prostate cancer (Miller *et al*, 1995; Giovannucci, 1998). This hypothesis is based on the possible role of vitamin D as a moderator of cell proliferation and differentiation, and on a range of epidemiological, clinical and biological observations on risk factors traditionally associated with prostate cancer (black race, geographic origin in terms of a north/south gradient, and advanced age), which have a common associated feature of a low level of endogenous 1, 25-(OH)₂ vitamin D. Calcium could play an indirect role in the development of prostate cancer, through a reduction in plasma levels of the active form of vitamin D (1, 25-(OH)₂ vitamin D), in contrast to the potentially protective effect of calcium against colon cancer that was discussed in the previous section.

Conclusions

The main conclusions which can be reached based on our review and meta-analysis are that there is some epidemiological evidence that the consumption of total dairy products and in particular milk, may be associated to a modest reduction in colorectal cancer risk. This evidence is limited to cohort studies, while case-control studies provided heterogeneous results. We found no evidence of either reduction or increase of colorectal cancer risk specifically associated with consumption of cheese or yoghurt.

However, our conclusions should be taken with caution. The reviewed epidemiological studies and the meta-analytical procedure used to obtain a summary estimate of the association have some limitations, such as the large variability in the type and composition of the dairy products consumed in different study populations, which for practical purposes were condensed in three or four food groups, the intrinsic methodological limitations of the dietary measurement obtained through usual questionnaires and, last but not least, publication bias, which may distort the representativeness of available results.

For future research, it will be essential to conduct further epidemiological studies on specific types of dairy products and to study the mechanisms of action of each of their components in experimental carcinogenesis models, as well as their possible interactions. The possibility of using specific biological markers of consumption of milk lipids, such as pentadecanoic (C15) and heptadecanoic (C17) acids (Wolk *et al*, 1998) opens some perspectives for clinical and epidemiological research into the specific roles of fatty acids from dairy products in carcinogenesis. The measurement of other biological markers such as plasma levels of 1,25-(OH)₂ vitamin D and 25-(OH) vitamin D and calcium in human studies in addition to classical analyses of the main food groups may allow better estimation of individual exposures, and testing of hypotheses on the specific roles of milk and its components in cancer etiology, which until now have been developed mainly within the context of experimental studies.

References

- Abdelali H, Cassand P, Soussotte V, Daubeze M, Bouley C & Narbonne JF (1995): Effect of dairy products on initiation of precursor lesions of colon cancer in rats *Nutr. Cancer* **24**, 121–132.
- Alberts DS, Einspahr J, Ritenbaugh C, Aickin M, Rees-McGee S, Atwood J, Emerson S, Mason-Liddil N, Bettinger L, Patel J, Bellapravalu S, Ramanujam PS, Phelps J & Clark L (1997): The effect of wheat bran fiber and calcium supplementation on rectal mucosal proliferation rates in patients with resected adenomatous colorectal polyps. *Cancer Epidemiol. Biomarkers Prev.* **6**, 161–169.
- Appleton GV, Davies PW, Bristol JB & Williamson RC (1987): Inhibition of intestinal carcinogenesis by dietary supplementation with calcium. *Br. J. Surg.* **74**, 523–525.
- Armitage NC, Rooney PS, Gifford KA, Clarke PA & Hardcastle JD (1995): The effect of calcium supplements on rectal mucosal proliferation. *Br. J. Cancer* **71**, 186–190.
- Aukema HM, Davidson LA, Pence BC, Jiang YH, Lupton JR & Chapkin RS (1997): Butyrate alters activity of specific CAMP-receptor proteins in a transgenic mouse colonic cell line. *J. Nutr.* **127**, 18–24.
- Baron JA, Tosteson TD, Wargovich MJ, Sandler R, Mandel J, Bond J, Haile R, Summers R, van Stolk R & Rothstein R (1995): Calcium supplementation and rectal mucosal proliferation: a randomized controlled trial. *J. Natl Cancer Inst.* **87**, 1303–1307.
- Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS, Rothstein R, Summers RW, Snover DC, Beck GJ, Bond JH & Greenberg ER (1999): Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *New Engl. J. Med.* **340**, 101–107.
- Barsoum GH, Thompson H, Neoptolemos JP & Keighley MR (1992): Dietary calcium does not reduce experimental colorectal carcinogenesis after small bowel resection despite reducing cellular proliferation. *Gut* **33**, 1515–1520.
- Benito E, Obrador A, Stiggelbout A, Bosch FX, Mulet M, Munoz N & Kaldor JA (1990): Population-based case-control study of colorectal cancer in Majorca. I. Dietary factors. *Int. J. Cancer* **45**, 69–76.
- Bergsma-Kadijk JA, van't Veer P, Kampman E & Burema J (1996): Calcium does not protect against colorectal neoplasia. *Epidemiology* **7**, 590–597.
- Bezault J, Bhimani R, Wiprovnick J & Furmanski P (1994): Human lactoferrin inhibits growth of solid tumors and development of experimental metastases in mice. *Cancer Res.* **54**, 2310–2312.
- Bidoli E, Franceschi S, Talamini R, Barra S & La Vecchia C (1992): Food consumption and cancer of the colon and rectum in North-Eastern Italy. *Int. J. Cancer* **50**, 223–229.
- Bird CL, Ingles SA, Frankl HD, Lee ER, Longnecker MP & Haile RW (1996): Serum lipids and adenomas of the left colon and rectum. *Cancer Epidemiol. Biomarkers Prev.* **5**, 607–612.
- Bonithon-Kopp C, Kronborg O, Giacosa A, Rath U & Faivre J (2000): Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. European Cancer Prevention Organisation Study Group. *Lancet* **356**, 1300–1306.
- Bostick RM (1997): Human studies of calcium supplementation and colorectal epithelial cell proliferation. *Cancer Epidemiol. Biomarkers Prev.* **6**, 971–980.
- Bostick RM, Potter JD, Fosdick L, Grambsch P, Lampe JW, Wood JR, Louis TA, Ganz R & Grandits G (1993): Calcium and colorectal epithelial cell proliferation: a preliminary randomized, double-blinded, placebo-controlled clinical trial. *J. Natl Cancer Inst.* **85**, 132–141.
- Bostick RM, Potter JD, Kushi LH, Sellers TA, Steinmetz KA, McKenzie DR, Gapstur SM & Folsom AR (1994): Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). *Cancer Causes Control* **5**, 38–52.
- Bostick RM, Fosdick L, Wood JR, Grambsch P, Grandits GA, Lillemoe TJ, Louis TA & Potter JD (1995): Calcium and colorectal epithelial cell proliferation in sporadic adenoma patients: a randomized, double-blinded, placebo-controlled clinical trial. *J. Natl Cancer Inst.* **87**, 1307–1315.
- Bostick RM, Boldt M, Darif M, Wood JR, Overn P & Potter JD (1997): Calcium and colorectal epithelial cell proliferation in ulcerative colitis. *Cancer Epidemiol. Biomarkers Prev.* **6**, 1021–1027.
- Boutron-McC, Faivre J, Marteau P, Couillaud C, Senesse P & Quipourt V (1996): Calcium, phosphorus, vitamin D, dairy products and colorectal carcinogenesis: a French case-control study. *Br. J. Cancer* **74**, 145–151.
- Boutron-Ruault MC, Senesse P, Faivre J, Chatelain N, Belghiti C & Meance S (1999): Foods as risk factors for colorectal cancer: a case-control study in Burgundy (France). *Eur. J. Cancer Prev.* **8**, 229–235.
- Bruce WR, Giacca A & Medline A (2000): Possible mechanisms relating diet and risk of colon cancer. *Cancer Epidemiol. Biomarkers Prev.* **9**, 1271–1279.
- Buset M, Lipkin M, Winawer S, Swaroop S & Friedman E (1986): Inhibition of human colonic epithelial cell proliferation in vivo and in vitro by calcium. *Cancer Res.* **46**, 5426–5430.
- Cascinu S, Ligi M, Del Ferro E, Foglietti G, Ciocolini P, Staccioli MP, Carnevali A, Luigi Rocchi MB, Alessandrini P, Giordani P, Catalano V, Polizzi V, Agostinelli R, Mureto P & Catalano G (2000): Effects of calcium and vitamin supplementation on colon cell proliferation in colorectal cancer. *Cancer Invest.* **18**, 411–416.
- Cats A, Kleibeuker JH, van der Meer R, Kuipers F, Sluiter WJ, Hardonk MJ, Oremus ET, Mulder NH & de Vries EG (1995): Randomized, double-blinded, placebo-controlled intervention study with supplemental calcium in families with hereditary nonpolyposis colorectal cancer. *J. Natl Cancer Inst.* **87**, 598–603.
- Centonze S, Boeing H, Leoci C, Guerra V & Misciagna G (1994): Dietary habits and colorectal cancer in a low-risk area. Results from a population-based case-control study in Southern Italy. *Nutr. Cancer* **21**, 233–246.

- Chang WC, Chapkin RS & Lupton JR (1997): Predictive value of proliferation, differentiation and apoptosis as intermediate markers for colon tumorigenesis. *Carcinogenesis* **18**, 721–730.
- Chen TC, Shao A, Heath H III & Holick MF (1993): An update on the vitamin D content of fortified milk from the United States and Canada. *New Engl. J. Med.* **329**, 1507.
- Cross HS, Pavelka M, Slavik J & Peterlik M (1992): Growth control of human colon cancer cells by vitamin D and calcium in vitro. *J. Natl Cancer Inst.* **84**, 1355–1357.
- DerSimonian R & Laird N (1986): Meta-analysis in clinical trials. *Control Clin. Trials* **7**, 177–188.
- De Simone C, Vesely R, Negri R, Bianchi Salvadori B, Zanzoglu S, Cilli A & Lucci L (1987): Enhancement of immune response of Murine Peyer's patches by a diet supplemented with yoghurt. *Immunopharmac. Immunotoxicol.* **9**, 87–100.
- Forsen KM, Jagerstad MI, Wigertz K & Witthoft CM (2000): Folate and dairy products: a critical update. *J. Am. Coll. Nutr.* **19**(2 Suppl), 100S–110S.
- Franceschi S, Favero A, La Vecchia C, Negri E, Conti E, Montella M, Giacosa A, Nanni O & Decarli A (1997): Food groups and risk of colorectal cancer in Italy. *Int. J. Cancer* **72**, 56–61.
- Freudenheim JL, Graham S, Marshall JR, Haughey BP, Cholewinski S & Wilkinson G (1991): Folate intake and carcinogenesis of the colon and rectum. *Int. J. Epidemiol.* **20**, 368–374.
- Garland C, Shekelle RB, Barrett-Connor E, Criqui MH, Rossof AH & Paul O (1985): Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. *Lancet* **1**, 307–309.
- Garland CF, Comstock GW, Garland FC, Helsing KJ, Shaw EK & Gorham ED (1989): Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. *Lancet* **2**, 1176–1178.
- Giovannucci E (1995): Insulin and colon cancer. *Cancer Causes Control* **6**, 164–179.
- Giovannucci E (1998): Dietary influences of 1,25(OH)₂ vitamin D in relation to prostate cancer: a hypothesis. *Cancer Causes Control* **9**, 567–582.
- Giovannucci E & Goldin B (1997): The role of fat, fatty acids, and total energy intake in the etiology of human colon cancer. *Am. J. Clin. Nutr.* **66** (6 Suppl), 1564S–1571S.
- Giovannucci E, Stampfer MJ, Colditz GA, Rimm EB, Trichopoulos D, Rosner BA, Speizer FE & Willett WC (1993): Folate, methionine, and alcohol intake and risk of colorectal adenoma. *J. Natl Cancer Inst.* **85**, 875–884.
- Govers MJ, Termont DS, Lapre JA, Kleibeuker JH, Vonk RJ & van der Meer R (1996): Calcium in milk products precipitates intestinal fatty acids and secondary bile acids and thus inhibits colonic cytotoxicity in humans. *Cancer Res.* **56**, 3270–3275.
- Gregoire RC, Stern HS, Yeung KS, Stadler J, Langley S, Furrer R & Bruce WR (1989): Effect of calcium supplementation on mucosal cell proliferation in high risk patients for colon cancer. *Gut* **30**, 376–382.
- Hague A & Paraskeva C (1995): The short-chain fatty acid butyrate induces apoptosis in colorectal tumour cell lines. *Eur. J. Cancer Prev.* **4**, 359–364.
- Hague A, Elder DJ, Hicks DJ & Paraskeva C (1995): Apoptosis in colorectal tumour cells: induction by the short chain fatty acids butyrate, propionate and acetate and by the bile salt deoxycholate. *Int. J. Cancer* **60**, 400–406.
- Hofstad B, Vatn MH, Andersen SN, Owen RW, Larsen S & Osnes M (1998): The relationship between faecal bile acid profile with or without supplementation with calcium and antioxidants on recurrence and growth of colorectal polyps. *Eur. J. Cancer Prev.* **7**, 287–294.
- Holick MF (1994): Vitamin D—new horizons for the 21st century. McCollum award lecture. *Am. J. Clin. Nutr.* **60**, 619–630.
- Holt PR, Moss SF, Whelan R, Guss J, Gilman J & Lipkin M (1996): Fecal and rectal mucosal diacylglycerol concentrations and epithelial proliferative kinetics. *Cancer Epidemiol. Biomarkers Prev.* **5**, 937–940.
- Hsing AW, McLaughlin JK, Chow WH, Schuman LM, Co Chien HT, Gridley G, Bjelke E, Wacholder S & Blot WJ (1998): Risk factors for colorectal cancer in a prospective study among U.S. white men. *Int. J. Cancer* **77**, 549–553.
- Hu FB, Manson JE, Liu S, Hunter D, Colditz GA, Michels KB, Speizer FE & Giovannucci E (1999): Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women. *J. Natl Cancer Inst.* **91**, 542–547.
- Hu JF, Liu YY, Yu YK, Zhao TZ, Liu SD & Wang QQ (1991): Diet and cancer of the colon and rectum: a case-control study in China. *Int. J. Epidemiol.* **20**, 362–367.
- Ip C & Scimeca JA (1997): Conjugated linoleic acid and linoleic acid are distinctive modulators of mammary carcinogenesis. *Nutr. Cancer* **27**, 131–135.
- Ip C, Scimeca JA & Thompson HJ (1994): Conjugated linoleic acid. A powerful anticarcinogen from animal fat sources. *Cancer* **74**(3 Suppl), 1050–1054.
- Iscovich JM, L'Abbe KA, Castelletto R, Calzona A, Bernedo A, Chopita NA, Jmelnitzsky AC & Kaldor J (1992): Colon cancer in Argentina. I: risk from intake of dietary items. *Int. J. Cancer* **51**, 851–857.
- Kaaks R, Toniolo P, Akhmedkhanov A, Lukanova A, Biessy C, Dechaud H, Rinaldi S, Zeleniuch-Jacquotte A, Shore RE & Riboli E (2000): serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. *J. Natl Cancer Inst.* **92**, 1592–1600.
- Kampman E, van 't Verr P, Hiddink GJ, Aken-Schneijder P, Kok FJ & Hermus RJ (1994a): Fermented dairy products, dietary calcium and colon cancer: a case-control study in The Netherlands. *Int. J. Cancer* **59**, 170–176.
- Kampman E, Goldbohm RA, van den Brandt PA & van 't Veer P (1994b): Fermented dairy products, calcium, and colorectal cancer in The Netherlands cohort study. *Cancer Res.* **54**, 3186–3190.
- Kampman E, Slattery ML, Caan B & Potter JD (2000): Calcium, vitamin D, sunshine exposure, dairy products and colon cancer risk (United States). *Cancer Causes Control* **11**, 459–466.
- Kato I, Akhmedkhanov A, Koenig K, Toniolo PG, Shore RE & Riboli E (1997): Prospective study of diet and female colorectal cancer: the New York University women's health study. *Nutr. Cancer* **28**, 276–281.
- Kearney J, Giovannucci E, Rimm EB, Ascherio A, Stampfer MJ, Colditz GA, Wing A, Kampman E & Willett WC (1996): Calcium, vitamin D, and dairy foods and the occurrence of colon cancer in men. *Am. J. Epidemiol.* **143**, 907–917.
- Kono S, Honjo S, Todoroki I, Nishiwaki M, Hamada H, Nishikawa H, Koga H, Ogawa S & Nakagawa K (1998): Glucose intolerance and adenomas of the sigmoid colon in Japanese men (Japan). *Cancer Causes Control* **9**, 441–446.
- Kotake K, Koyama Y, Nasu J, Fukutomi T & Yamaguchi N (1995): Relation of family history of cancer and environmental factors to the risk of colorectal cancer: a case-control study. *Jpn. J. Clin. Oncol.* **25**, 195–202.
- Kulkarni N & Reddy BS (1994): Inhibitory effect of bifidobacterium longum cultures on the azoxymethane-induced aberrant crypt foci formation and fecal bacterial beta-glucuronidase. *Proc. Soc. Exp. Biol. Med.* **207**, 278–283.
- Kune S, Kune GA & Watson LF (1987): Case-control study of dietary etiological factors: the Melbourne colorectal cancer study. *Nutr. Cancer* **9**, 21–42.
- La Vecchia C, Negri E, Decarli A, D'Avanzo B, Gallotti L, Gentile A & Franceschi SA (1988): Case-control study of diet and colorectal cancer in Northern Italy. *Int. J. Cancer* **41**, 492–498.
- Lapre JA, De Vries HT, Koeman JH & van der Meer R (1993): The antiproliferative effect of dietary calcium on colonic epithelium is mediated by luminal surfactants and dependent on the type of dietary fat. *Cancer Res.* **53**, 784–789.
- Lee HP, Gourley L, Duffy SW, Esteve J, Lee J & Day NE (1989): Colorectal cancer and diet in an Asian population—a case-control study among Singapore Chinese. *Int. J. Cancer* **43**, 1007–1016.
- Levi F, Pasche C, La Vecchia C, Lucchini F & Franceschi S (1999): Food groups and colorectal cancer risk. *Br. J. Cancer* **79**, 1283–1287.

- Lidbeck A, Nord CE, Gustafsson JA & Rafter J (1992): Lactobacilli, anticarcinogenic activities and human intestinal microflora. *Eur. J. Cancer Prev.* **1**, 341–353.
- Liew C, Schut HA, Chin SF, Pariza MW & Dashwood RH (1995): Protection of conjugated linoleic acids against 2-amino-3-methylimidazo[4,5-f]quinoline-induced colon carcinogenesis in the F344 rat: a study of inhibitory mechanisms. *Carcinogenesis* **16**, 3037–3043.
- Lin H, Boylston TD, Chang MJ, Lueddecke LO & Shultz TD (1995): Survey of the conjugated linoleic acid contents of dairy products. *J. Dairy Sci.* **78**, 2358–2365.
- Lipkin M (1991): Application of intermediate biomarkers to studies of cancer prevention in the gastrointestinal tract: Introduction and perspective. *Am. J. Clin. Nutr.* **54**(1 Suppl), 188S–192S.
- Lipkin M & Newmark H (1985): Effect of added dietary calcium on colonic epithelial-cell proliferation in subjects at high risk for familial colonic cancer. *New Engl. J. Med.* **313**, 1381–1384.
- Lipkin M & Newmark H (1995): Calcium and the prevention of colon cancer. *J. Cell Biochem. Suppl.* **22**, 65–73.
- Lipkin M, Friedman E, Winawer SJ & Newmark H (1989): Colonic epithelial cell proliferation in responders and nonresponders to supplemental dietary calcium. *Cancer Res.* **49**, 248–254.
- Llor X, Jacoby RF, Teng BB, Davidson NO, Sitrin MD & Brasitus TA (1991): K-Ras mutations in 1,2-dimethylhydrazine-induced colonic tumors: effects of supplemental dietary calcium and vitamin D deficiency. *Cancer Res.* **51**, 4305–4309.
- Macquart-Moulin G, Riboli E, Cornee J, Charnay B, Berthezene P & Day N (1986): Case-control study on colorectal cancer and diet in Marseilles. *Int. J. Cancer* **38**, 183–191.
- Manousos O, Day NE, Trichopoulos D, Gerovassilis F, Tzonou A & Polychronopoulou A (1983): Diet and colorectal cancer: a case-control study in Greece. *Int. J. Cancer* **32**, 1–5.
- Marchetti MC, Migliorati G, Moraca R, Riccardi C, Nicoletti I, Fabiani R, Mastrandrea V & Morozzi G (1997): Possible mechanisms involved in apoptosis of colon tumor cell lines induced by deoxycholic acid, short-chain fatty acids, and their mixtures. *Nutr. Cancer* **28**, 74–80.
- Marcus PM & Newcomb PA (1998): The association of calcium and vitamin D, and colon and rectal cancer in Wisconsin women. *Int. J. Epidemiol.* **27**, 788–793.
- Martinez ME & Willett WC (1998): Calcium, vitamin D, and colorectal cancer: a review of the epidemiologic evidence. *Cancer Epidemiol. Biomarkers Prev.* **7**, 163–168.
- Martinez ME, Giovannucci EL, Colditz GA, Stampfer MJ, Hunter DJ, Speizer FE, Wing A & Willett WC (1996): Calcium, vitamin D, and the occurrence of colorectal cancer among women. *J. Natl. Cancer Inst.* **88**, 1375–1382.
- McBain JA, Eastman A, Nobel CS & Mueller GC (1997): Apoptotic death in adenocarcinoma cell lines induced by butyrate and other histone deacetylase inhibitors. *Biochem. Pharmacol.* **53**, 1357–1368.
- McKeown-Eyssen G (1994): Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? *Cancer Epidemiol. Biomarkers Prev.* **3**, 687–695.
- Mettlin CJ, Schoenfeld ER & Natarajan N (1990): Patterns of milk consumption and risk of cancer. *Nutr. Cancer* **13**, 89–99.
- Meydani SN & Ha WK (2000): Immunologic effects of yogurt. *Am. J. Clin. Nutr.* **71**, 861–872.
- Miller AB, Howe GR, Jain M, Craib KJ & Harrison L (1983): Food items and food groups as risk factors in a case-control study of diet and colo-rectal cancer. *Int. J. Cancer* **32**, 155–161.
- Miller GJ, Stapleton GE, Hedlund TE & Moffat KA (1995): Vitamin D receptor expression, 24-hydroxylase activity, and inhibition of growth by 1 alpha, 25-dihydroxyvitamin D3 in seven human prostatic carcinoma cell lines. *Clin. Cancer Res.* **1**, 997–1003.
- Murata M, Tagawa M, Watanabe S, Kimura H, Takeshita T & Morimoto K (1999): Genotype difference of aldehyde dehydrogenase 2 gene in alcohol drinkers influences the incidence of Japanese colorectal cancer patients. *Jpn. J. Cancer Res.* **90**, 711–719.
- Negri E, La Vecchia C, D'Avanzo B & Franceschi S (1990): Calcium, dairy products, and colorectal cancer. *Nutr. Cancer* **13**, 255–262.
- Newmark HL, Wargovich MJ & Bruce WR (1984): Colon cancer and dietary fat, phosphate, and calcium: a hypothesis. *J. Natl. Cancer Inst.* **72**, 1323–1325.
- O'Sullivan KR, Mathias PM, Beattie S & O'Morain C (1993): Effect of oral calcium supplementation on colonic crypt cell proliferation in patients with adenomatous polyps of the large bowel. *Eur. J. Gastroenterol. Hepatol.* **5**, 85–89.
- Ouwehand AC, Isolauri E, Kirjavainen PV & Salminen SJ (1999): Adhesion of four bifidobacterium strains to human intestinal mucus from subjects in different age groups. *FEMS Microbiol. Lett.* **172**, 61–64.
- Parodi PW (1997): Cows' milk fat components as potential anticarcinogenic agents. *J. Nutr.* **127**, 1055–1060.
- Parodi PW (1999): Conjugated linoleic acid and other anticarcinogenic agents of bovine milk fat. *J. Dairy Sci.* **82**, 1339–1349.
- Perdigon G, Vintini E, Alvarez S, Medina M & Medici M (1999): Study of the possible mechanisms involved in the mucosal immune system activation by lactic acid bacteria. *J. Dairy Sci.* **82**, 1108–1114.
- Peters RK, Garabrant DH, Yu MC & Mack TM (1989): A case-control study of occupational and dietary factors in colorectal cancer in young men by subsite. *Cancer Res.* **49**, 5459–5468.
- Peters RK, Pike MC, Garabrant D & Mack TM (1992): Diet and colon cancer in Los Angeles County, California. *Cancer Causes Control* **3**, 457–473.
- Phillips RL & Snowdon DA (1985): Dietary relationships with fatal colorectal cancer among seventh-day adventists. *J. Natl. Cancer Inst.* **74**, 307–317.
- Philipps AF, Dvorak B, Kling PJ, Grille JG & Koldovsky O (2000): Absorption of milk-borne insulin-like growth factor-I into portal blood of suckling rats. *J. Pediatr. Gastroenterol. Nutr.* **31**, 128–135.
- Pickle LW, Greene MH, Ziegler RG, Toledo A, Hoover R, Lynch HT & Fraumeni JF Jr (1984): Colorectal cancer in rural Nebraska. *Cancer Res.* **44**, 363–369.
- Pietinen P, Malila N, Virtanen M, Hartman TJ, Tangrea JA, Albanes D & Virtamo J (1999): Diet and risk of colorectal cancer in a cohort of Finnish men. *Cancer Causes Control* **10**, 387–396.
- Pritchard RS, Baron JA & Gerhardtsson de Verdier M (1996): Dietary calcium, vitamin D, and the risk of colorectal cancer in Stockholm, Sweden. *Cancer Epidemiol. Biomarkers Prev.* **5**, 897–900.
- Rozen P, Fireman Z, Fine N, Wax Y & Ron E (1989): Oral calcium suppresses increased rectal epithelial proliferation of persons at risk of colorectal cancer. *Gut* **30**, 650–655.
- Rozen P, Lubin F, Papo N, Knaani J, Farbstein H, Farbstein M & Zajick G (2001): Calcium supplements interact significantly with long-term diet while suppressing rectal epithelial proliferation of adenoma patients. *Cancer* **91**, 833–840.
- Schoen RE, Tangen CM, Kuller LH, Burke GL, Cushman M, Tracy RP, Dobs A & Savage PJ (1999): Increased blood glucose and insulin, body size, and incident colorectal cancer. *J. Natl. Cancer Inst.* **91**, 1147–1154.
- Sekine K, Ushida Y, Kuhara T, Iigo M, Baba-Toriyama H, Moore MA, Murakoshi M, Satomi Y, Nishino H, Kakizoe T & Tsuda H (1997): Inhibition of initiation and early stage development of aberrant crypt foci and enhanced natural killer activity in male rats administered bovine lactoferrin concomitantly with azoxymethane. *Cancer Lett.* **121**, 211–216.
- Sellers TA, Bazyk AE, Bostick RM, Kushi LH, Olson JE, Anderson KE, Lazovich D & Folsom AR (1998): 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* **9**, 357–367.
- Shabahang M, Buras RR, Davoodi F, Schumaker LM, Nauta RJ & Evans SR (1993): 1,25-dihydroxyvitamin D3 receptor as a marker of human colon carcinoma cell line differentiation and growth inhibition. *Cancer Res.* **53**, 3712–3718.
- Shabahang M, Buras RR, Davoodi F, Schumaker LM, Nauta RJ, Uskokovic MR, Brenner RV & Evans SR (1994): Growth inhibition of HT-29 human colon cancer cells by analogues of 1,25-dihydroxyvitamin D3. *Cancer Res.* **54**, 4057–4064.

- Shannon J, White E, Shattuck AL & Potter JD (1996): Relationship of food groups and water intake to colon cancer risk. *Cancer Epidemiol. Biomarkers Prev.* **5**, 495–502.
- Shau H, Kim A & Golub SH (1992): Modulation of natural killer and lymphokine-activated killer cell cytotoxicity by lactoferrin. *J. Leukoc. Biol.* **51**, 343–349.
- Singh PN & Fraser GE (1998): Dietary risk factors for colon cancer in a low-risk population. *Am. J. Epidemiol.* **148**, 761–774.
- Singh P & Rubin N (1993): Insulin-like growth factors and binding proteins in colon cancer. *Gastroenterology* **105**, 1218–1237.
- Sitrin MD, Halline AG, Abrahams C & Brasitus TA (1991): Dietary calcium and vitamin D modulate 1,2-dimethylhydrazine-induced colonic carcinogenesis in the rat. *Cancer Res.* **51**, 5608–5613.
- Slattery ML, Berry TD, Potter J & Caan B (1997): Diet diversity, diet composition, and risk of colon cancer (United States). *Cancer Causes Control* **8**, 872–882.
- Steinmetz KA & Potter JD (1993): Food-group consumption and colon cancer in the Adelaide case–control study. II. Meat, poultry, seafood, dairy foods and eggs. *Int. J. Cancer* **53**, 720–727.
- Stern HS, Gregoire RC, Kashtan H, Stadler J & Bruce RW (1990): Long-term effects of dietary calcium on risk markers for colon cancer in patients with familial polyposis. *Surgery* **108**, 528–533.
- Tajima K & Tominaga S (1985): Dietary habits and gastro-intestinal cancers: a comparative case–control study of stomach and large intestinal cancers in Nagoya, Japan. *Jpn. J. Cancer Res.* **76**, 705–716.
- Taniyama T, Wanibuchi H, Salim EI, Yano Y, Otani S, Nishizawa Y, Morii H & Fukushima S (2000): Chemopreventive effect of 24R,25-dihydroxyvitamin D(3) in N, N'-dimethylhydrazine-induced rat colon carcinogenesis. *Carcinogenesis* **21**, 173–178.
- Thomas MG, Thomson JP & Williamson RC (1993): Oral calcium inhibits rectal epithelial proliferation in familial adenomatous polyposis. *Br. J. Surg.* **80**, 499–501.
- Thun MJ, Calle EE, Namboodiri MM, Flanders WD, Coates RJ, Byers T, Boffetta P, Garfinkel L & Heath CW Jr (1992): Risk factors for fatal colon cancer in a large prospective study. *J. Natl Cancer Inst.* **84**, 1491–1500.
- Tuyns AJ, Kaaks R & Haelterman M (1988): Colorectal cancer and the consumption of foods: a case–control study in Belgium. *Nutr. Cancer* **11**, 189–204.
- Ursin G, Bjelke E, Heuch I & Vollset SE (1990): Milk consumption and cancer incidence: a Norwegian prospective study. *Br. J. Cancer* **61**, 456–459.
- van der Meer R, Kleibeuker JH & Lapre JA (1991): calcium phosphate, bile acids and colorectal cancer. *Eur. J. Cancer Prev.* **1**(Suppl 2), 55–62.
- Velazquez OC, Zhou D, Seto RW, Jabbar A, Choi J, Lederer HM & Rombeau JL (1996): In vivo crypt surface hyperproliferation is decreased by butyrate and increased by deoxycholate in normal rat colon: associated *in vivo* effects on C-Fos and C-Jun expression. *J. Parent. Enteral Nutr.* **20**, 243–250.
- Vlajinac H, Adanja B & Jarebinski M (1987): Case–control study of the relationship of diet and colon cancer. *Arch. Geschwulstforsch.* **57**, 493–498.
- Wallach S, Bellavia JV, Schorr J & Gamponia PJ (1966): Effect of vitamin D on tissue distribution and transport of electrolytes, 47-Ca and 28-Mg. *Endocrinology* **79**, 773–782.
- Wargovich MJ, Isbell G, Shabot M, Winn R, Lanza F, Hochman L, Larson E, Lynch P, Roubein L & Levin B (1992): Calcium supplementation decreases rectal epithelial cell proliferation in subjects with sporadic adenoma. *Gastroenterology* **103**, 1994–1995.
- Weisgerber UM, Boeing H, Owen RW, Waldherr R, Raedsch R & Wahrendorf J (1996): Effect of longterm placebo controlled calcium supplementation on sigmoidal cell proliferation in patients with sporadic adenomatous polyps. *Gut* **38**, 396–402.
- Will JC, Galuska DA, Vinicor F & Calle EE (1998): Colorectal cancer: another complication of diabetes mellitus? *Am. J. Epidemiol.* **147**, 816–825.
- Wolk A, Vessby B, Ljung H & Barrefors P (1998): Evaluation of a biological marker of dairy fat intake. *Am. J. Clin. Nutr.* **68**, 291–295.
- World Cancer Research Fund (1997): *Food, nutrition and the prevention of cancer: a global perspective*. Washington, DC: American Institute for Cancer Research.
- Yamada K, Araki S, Tamura M, Sakai I, Takahashi Y, Kashihara H & Kono S (1998): Relation of serum total cholesterol, serum triglycerides and fasting plasma glucose to colorectal carcinoma in situ. *Int. J. Epidemiol.* **27**, 794–798.
- Yoo YC, Watanabe S, Watanabe R, Hata K, Shimazaki K & Azuma I (1997): Bovine lactoferrin and lactoferricin, a peptide derived from bovine lactoferrin, inhibit tumor metastasis in mice. *Jpn. J. Cancer Res.* **88**, 184–190.
- Young TB & Wolf DA (1988): Case–control study of proximal and distal colon cancer and diet in Wisconsin. *Int. J. Cancer* **42**, 167–175.
- Zhang XB & Ohta Y (1993): Antimutagenicity of cell fractions of microorganisms on potent mutagenic pyrolysates. *Mutat. Res.* **298**, 247–253.
- Zheng W, Anderson KE, Kushi LH, Sellers TA, Greenstein J, Hong CP, Cerhan JR, Bostick RM & Folsom AR (1998): 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.* **7**, 221–225.