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Colorectal cancer and non-fermented milk, solid cheese, and fermented milk consumption: A systematic review and meta-analysis of prospective studies

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ABSTRACT

Colorectal cancer is the second most prevalent cancer worldwide. A systematic review and meta-analysis of prospective studies was conducted to examine the association between intake of different types of dairy foods during adulthood and the development of colorectal

cancer, specifically comparing non-fermented milk, solid cheese, and fermented milk. Seven databases were systematically searched and 15 cohort studies selected for inclusion, involving over 900,000 subjects and over 5200 colorectal cancer cases. Meta-analysis resulted in an overall relative risk of colon cancer of 0.74 (95% confidence interval 0.60-0.91) in men consuming non-fermented milk (highest intake category averaging 525 grams/day). No association was found between consumption of non-fermented milk and rectal cancer in men or non-fermented milk and colon or rectal cancer in women. No protective association was found between consumption of solid cheese or fermented milk and colorectal cancer. Reasons for the differences in the impact of non-fermented milk, solid cheese, and fermented milk in the colon are discussed. This meta-analysis supports the inverse association between non-fermented milk consumption and risk of colon cancer in men, and provides an evidence base to assist in the formulation of dietary guidelines involving dairy foods.

Key words: cheese; colorectal neoplasms; dairy products; meta-analysis; milk; yogurt

INTRODUCTION

In 2002, colorectal cancer (CRC) was the third most commonly diagnosed and the second most prevalent cancer in the world. It is slightly more common in men than women (ratio of 1.2:1) (Parkin et al., 2005). Colon cancer is twice as common as rectal cancer (Parkin et al., 2005). CRC exhibits a very high variability in incidence, from 73-85 cases per 100,000 in developed countries such as Australia, New Zealand, the United States, western Europe, and Japan, to 6-20 cases per 100,000 in Africa, Central America, and western Asia (Parkin et al.,

2005). This variability points to the importance of environmental factors in the etiology of CRC, one of the strongest of which is diet (Cummings and Bingham, 1998).

Epidemiological studies suggest that dairy foods are one important dietary factor protective against CRC (Cho et al., 2004; Huncharek et al., 2009), and contain several potentially active components, including calcium, vitamin D, conjugated linoleic acid, and sphingolipids (Norat and Riboli, 2003). However, dairy foods also come in very different forms (non-fermented versus fermented milks versus solid cheese). Non-fermented milk is a fluid food widely consumed by many populations at levels varying from 180 kg/person/year in Finland to 50 kg/person/year in China and Japan (Haug et al., 2007). This nutrient-rich food is a good source of fats, protein, amino acids and many micronutrients. It also contains immunoglobulins, hormones, growth factors, cytokines and enzymes that may affect cancer growth (Haug et al., 2007). Solid cheese is an aged food, formed when the casein in milk is coagulated and the whey liquid is removed (Haug et al., 2007). The whey protein, which is lost in the cheese making process, is known to have benefit in cancer prevention, particularly due to its high content of sulfur-containing amino acids which can form precursors for the cellular antioxidant, glutathione (Parodi, 2007). In addition, removing the whey when cheese is made also removes approximately 94% of the lactose (Miller et al., 1999). Yogurt, the most common fermented milk product, is traditionally formed by fermenting fluid milk with bacteria of the *Lactobacillus, Streptococcus,* and *Bifidobacterium* genera (Bourlioux and Pochart, 1988; World Health Organization and Food and Agricultural Organization of the United Nations, 2006). Fermented milk, like non-fermented milk, provides a calcium-rich source of high quality protein. In addition, the bacteria present in fermented milk supply the enzyme β-galactosidase, which

hydrolyses lactose. Removal of lactose allows fermented milk to be more readily tolerated than non-fermented milk by people with lactose maldigestion (Miller et al., 1999). The presence of live bacteria in some fermented milks can also increase the absorption of some micronutrients (Fabian et al., 2008; Rosado et al., 2005), improve aspects of immune function (Meyer et al., 2007; Meyer et al., 2006), and protect against pathogenic enteric bacteria which may affect cancer risk (Adolfsson et al., 2004). Due to these differences among non-fermented milk, solid cheese, and fermented milk, it is possible that these dairy foods do not confer equivalent protection against CRC.

Although previous reviews have examined the relationship between dairy food consumption and CRC risk, an updated examination is now warranted to make this distinction between different kinds of dairy foods. The systematic review of Huncharek (2009) (Huncharek et al., 2009) examined associations between intake of dairy products and CRC risk, but combined both CRC mortality and incidence. It also included three published studies from the same cohort, potentially biasing results. Marques-Vidal et al (Marques-Vidal et al., 2006) examined associations between foods and risk of CRC incidence and mortality, but did not perform a meta-analysis in their review. Moreover, although the American Institute for Cancer Research (AICR) recently updated their 2007 report on relationships between total dairy food intake or non-fermented milk intake and CRC, colon cancer, and rectal cancer (World Cancer Research Fund / American Institute for Cancer Research., 2010), they did not separately examine relationships between CRC and solid cheese or fermented milk intake. One pooled analysis has examined the influence of non-fermented milk, solid cheese, and fermented milk separately (Cho et al., 2004), but since this 2004 analysis, additional data from several large cohorts (Kesse et al.,

2005; Larsson et al., 2006; Lee et al., 2009; Park et al., 2007; Sanjoaquin et al., 2004) have become available.

The purpose of this systematic review and meta-analysis was therefore to examine the association between intake of different types of dairy foods during adulthood and the development of CRC. A comparison has been made between the effects of non-fermented fluid milk, solid cheeses, and fermented milks (including both fluid or semi-solid fermented dairy foods) in men and women, examining colon cancer and rectal cancer separately whenever possible. The American Heart Association and guidelines in the United States, Canada, and Australia all recommend including 2-3 servings of non-fat or low fat dairy products per day (American Heart Association, 2010; Health Canada, 2007; Kellett et al., 1998; U.S. Department of Health and Human Services and US Department of Agriculture, 2005).

METHODS

Search methods and inclusion criteria

This systematic review was initiated as part of the wider Australian Dietary Guidelines systematic literature review commissioned by the Australian National Health and Medical Research Council (NHMRC) to examine the influence of dairy products on a variety of different health outcomes. The initial search criteria were approved by the Dietary Guidelines Working Committee of the NHMRC. Overall, seven databases (Cinahl, Medline, PreMedline, PsycInfo, Cochrane/Database of Abstracts of Reviews of Effects, ScienceDirect, and Educational

Resources Information Center) were searched in April 2009 with the following limits: publication date of January 2002 to April 2009, written in the English language, and undertaken in human subjects. While the original search included keywords relating to all outcomes for the principal project, keywords relating only to dairy and CRC for each database searched are listed in Table 1. As also shown in the table, an additional search of the PubMed database was conducted in November 2010 to identify more recent studies. No attempt was made to recover unpublished studies.

Abstracts recovered from both searches were reviewed to determine if the entire article should be retrieved. All studies that investigated the effect of milk or dairy consumption on all types of cancer in adult men or women were retrieved. Studies focusing on subjects with acute or chronic medical conditions or studies on elite athletes were excluded. Studies examining cow, goat, or sheep milk, skim, low fat, or full fat milk, yogurt, cheese, and custard were included, while other foods were excluded as in our previous study (Ralston et al., 2011). Only retrieved publications dealing with CRC are discussed in the present analysis. All retrieved publications on CRC were reviewed to determine their level of evidence, with only those at level I or II considered here, and coded indicating inclusion or exclusion as in our previous study (Ralston et al., 2011). Level I evidence was defined as a systematic review of studies of level II evidence, while level II evidence comprised well-designed randomized controlled trials or prospective cohort studies with > 1000 subjects and with a follow-up period of > 5 years (National Health and Medical Research Council, 1999).

Retrieved studies that provided level I or II evidence were read carefully and information was extracted by two investigators with backgrounds in nutrition/dietetics. The initial data

extraction template was provided by NHMRC, but this was modified and optimized for the current study. Extracted data included: author affiliation and financial support, study design and location, sample size and number of incident cases, characteristics of the study population and its exposure (intake of dairy foods), outcomes measured and length of follow-up. Internal validity was addressed by assessing the comparisons made between groups, the presence of any measurement bias, and the proportion of participants who were available for follow-up. The overall quality of each study was then assessed by the same two investigators as *negative*, *neutral* or *positive* through reference to a set of standard questions. The initial quality criteria were extracted from the American Dietetic Association Evidence Analysis Manual (Scientific Affairs and Research of American Dietetic Association, 2008), but modified for greater applicability for cohort studies. To distinguish between *neutral* and *negative* quality, the method of handling participants that were not followed up, statistical analysis, funding source, and introduction of other biases were considered. To be of *positive* quality, in addition to these five factors, a study required: subject selection with minimal bias, adequately described dependent and independent variables and comparisons, clearly defined outcomes, and reliable measurements. Control of potential confounders (age, sex, smoking status, socioeconomic status, physical activity, body mass index (BMI), energy intake and other diet components, alcohol consumption, ethnicity, supplement use, family history of CRC, non-steroidal anti-inflammatory drugs (NSAID) use, and hormone replacement therapy (HRT) in women) was also noted following advice from the World Cancer Research Fund systematic review specification manual (Butrum et al., 2007), but studies that failed to control for these potential confounders

were still included in the meta-analysis. All extracted data and quality ratings were reviewed and discussed by all co-authors.

Reference lists of retrieved systematic reviews were also examined to identify additional studies not retrieved by the database searches. Individual cohort studies from these published systematic reviews were included in the current review if they met inclusion criteria (as above). Data extraction and quality assessment was performed on these studies as for our other retrieved studies. Throughout, studies examining cancer mortality rather than incidence were excluded.

Statistical methods

A meta-analysis was performed to examine the association between CRC and intake of non-fermented milks, solid cheeses, and fermented milks (which include both fluid and semi-solid fermented dairy foods). When sufficient data were available, summary statistics for gender and colorectal subsite (colon cancer versus rectal cancer) were calculated separately. If a study analyzed hard cheeses and soft cheeses (e.g. cottage or ricotta cheese) separately, only the analysis for hard cheese was included in the present meta-analysis. One study reported individual relative risks (RR) for non-fat, low fat, and whole milk but not total milk; here the RR for only whole milk was included, as this was the primary milk consumed at the time and location of the cohort study (Economic Research Service, 2009). Studies were excluded from the meta-analysis if they examined only calcium or vitamin D intake rather than dairy food intake, or if they examined total dairy food intake rather than specific types of dairy foods.

When reported, the RRs of developing colon cancer, rectal cancer, and CRC in men and women were extracted for each individual study, comparing the lowest versus the highest category of dairy food intake. Study weights and summary statistics for overall RRs were generated with Review Manager Version 5.0.21 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) using the generic inverse variance method and the random effects model as outlined in our previous study (Ralston et al., 2011). Meta-analysis could only be conducted on those categories including at least two primary studies. One study (Ursin et al., 1990) did not report a confidence interval (CI) or standard error, but for the meta-analysis this was estimated using the reported observed and expected number of cases in the cohort. RR with 95% CI and P values are reported. Heterogeneity between studies within subgroups was examined first qualitatively, then quantitatively by using the I^2 statistic, with I^2 values of < 25, < 50 and < 75% used to define low, moderate and high heterogeneity, respectively (Higgins and Thompson, 2003).

The average consumption of the highest category of intake (g/day) of non-fermented milk, solid cheese, and fermented milk was calculated from the individual studies. If an individual study reported intake in number of servings, the United States standard serving sizes (U.S. Department of Health and Human Services and US Department of Agriculture, 2005) for milk, cheese, and yogurt were used to convert servings to grams.

RESULTS

Figure 1 depicts the strategy used for selecting studies included in the final review and reasons for exclusion. From the initial search conducted in April 2009, five studies were retrieved with the outcome of CRC, including two systematic reviews (Cho et al., 2004; Huncharek et al., 2009) and three cohort studies (Khan et al., 2004; Lee et al., 2009; Sellers et al., 2008)). An additional search of PubMed in November 2010 resulted in 288 citations: 18 had already been identified in the original search, 179 met exclusion criteria (as above), while 91 appeared relevant. Of these 91 studies, 19 studies met inclusion criteria for the present review: three systematic reviews (Alvarez-Leon et al., 2006; Marques-Vidal et al., 2006; Szilagyi et al., 2006) and 16 cohort studies (Gaard et al., 1996; Järvinen et al., 2001; Kato et al., 1997; Kearney et al., 1996; Kesse et al., 2005; Kojima et al., 2004; Larsson et al., 2006; Larsson et al., 2005; Lin et al., 2005; Martínez et al., 1996; McCullough et al., 2003; Park et al., 2007; Park et al., 2009; Pietinen et al., 1999; Terry et al., 2002; van der Pols et al., 2007). No randomized controlled trials were found by either search. With the addition of one systematic review (World Cancer Research Fund / American Institute for Cancer Research., 2010) recovered via hand searching, collating all searches resulted in six systematic reviews and 19 cohort studies. Examination of studies appearing in the six systematic reviews revealed ten additional cohort studies that met inclusion criteria. Upon further review, fourteen of the included cohort studies were excluded from our meta-analysis (see Figure 1 for reasons). In total, 15 cohort studies (Gaard et al., 1996; Järvinen et al., 2001; Kearney et al., 1996; Kesse et al., 2005; Khan et al., 2004; Larsson et al., 2006; Lee et al., 2009; Lin et al., 2005; Martínez et al., 1996; McCullough et al., 2003; Park et al., 2007; Pietinen et al., 1999; Sanjoaquin et al., 2004; Singh and Fraser, 1998; Terry et al.,

2002; Ursin et al., 1990) were included in our meta-analyses. A list of all excluded studies and reason for exclusion can be provided upon request by the authors.

A summary of the 15 studies included in the meta-analysis is shown in Table 2. These studies include 919,680 subjects (34% men, 62% women, 5% persons of undefined gender) from six countries with over 5200 cases of CRC, colon cancer, or rectal cancer (4963 cases of undefined CRC, 1458 cases of colon cancer, 728 cases of rectal cancer). Length of follow-up ranged from five to 24 years. While individual studies varied in their reporting of dairy food intake, the highest category of reported intake among the included studies ranged from > 35 to > 976 g non-fermented milk/day, > 8 to > 70 g solid cheese/day, and > 110 to > 350 g fermented milk/day. The lowest category of intake ranged from 0 to < 407, < 2.5 to < 30, and 0 to < 32 g/day for non-fermented milk, solid cheese, and fermented milk, respectively. As standard serving sizes vary among countries, Table 3 compares standard serving sizes of milk, cheese, and yogurt for the United States, Canada, Australia, and the United Kingdom (in this review, equivalent to non-fermented milk, solid cheese, and fermented milk, respectively).

The results of meta-analyses of the published data examining non-fermented milk, solid cheese, and fermented milk consumption and development of CRC, colon cancer, and rectal cancer are shown in Figures 2 and 3. Unlike solid cheese or fermented milk where no association was evident, the consumption of non-fermented milk was found to have a significant inverse association with risk of CRC. Meta-analysis of 14 published studies (Gaard et al., 1996; Järvinen et al., 2001; Kearney et al., 1996; Kesse et al., 2005; Larsson et al., 2006; Lee et al., 2009; Lin et al., 2005; Martínez et al., 1996; McCullough et al., 2003; Park et al., 2007; Sanjoaquin et al., 2004; Singh and Fraser, 1998; Terry et al., 2002; Ursin et al., 1990), including

17 measures of RR, resulted in an overall RR of 0.85 (95% CI 0.77-0.93) in men and women in the highest category of intake (average: 439 g non-fermented milk/day). When gender and colorectal subsite were analyzed separately, the association remained significant in a meta-analysis of the four studies (Gaard et al., 1996; Larsson et al., 2006; McCullough et al., 2003; Ursin et al., 1990) examining men (highest category of intake averaging 525 g non-fermented milk/day) and risk of colon cancer (RR 0.74, 95% CI 0.60-0.91), suggesting it was this group and subsite that was the source of statistical significance in the first analysis. No association was found between non-fermented milk consumption and risk of rectal cancer in men, or risk of colon cancer or rectal cancer in women (see Figure 2). Little statistical heterogeneity (I^2=0%) was observed in the non-fermented milk analyses, apart from analysis of CRC in women where "moderate" heterogeneity (I^2=42%) was observed (Higgins and Thompson, 2003).

In men and women combined, the RRs of CRC for consumption of solid cheese (Järvinen et al., 2001; Kearney et al., 1996; Kesse et al., 2005; Larsson et al., 2006; Lin et al., 2005; Sanjoaquin et al., 2004; Singh and Fraser, 1998) and fermented milk (Järvinen et al., 2001; Kearney et al., 1996; Kesse et al., 2005; Larsson et al., 2006; Lin et al., 2005; Pietinen et al., 1999; Terry et al., 2002) were 1.11 (95% CI: 0.90-1.36) and 1.01 (95% CI: 0.89-1.15), respectively, indicating no association (Figure 3). The highest categories of intake averaged 39 g solid cheese/day and 187 g fermented milk/day. There remained no associations when men and women were analyzed separately. Once again, little statistical heterogeneity was observed for these analyses performed (I^2 ranging from 0 to16%), with the exception of solid cheese consumption and risk of CRC in men, where the I^2 statistic indicated "moderate" heterogeneity (I^2=43%) (Higgins and Thompson, 2003). As there were too few studies to allow separate

analyses of both gender and colorectal subsite, further analyses for consumption of solid cheese and fermented milk and risk of colon cancer and rectal cancer were performed combining both genders. As these results were found too statistically heterogeneous to be meaningful, they have not been reported (I^2: 49-77%).

Among the included primary studies, the majority (11 of 15) were of *positive* quality, while three studies were ranked *neutral* and one study was ranked *negative*. The specific shortcomings of the *neutral* studies were: adjustment for age only and not other potential confounders (Gaard et al., 1996); report of a RR for milk intake, but insufficient methodological detail (the main focus was calcium and vitamin D rather than milk) (Martínez et al., 1996); and study design inadequate to examine dairy intake or CRC incidence (Ursin et al., 1990). The one study of *negative* quality introduced bias through study recruitment (Sanjoaquin et al., 2004). Participants were vegetarians recruited through a vegetarian society plus non-vegetarians recruited through friends and relatives of the vegetarian group. Additionally, the FFQ was validated only for dietary fiber and not for other nutrients or food groups.

DISCUSSION

In this analysis of 15 studies and over 900,000 subjects, consumption of non-fermented milk was associated with a 15% reduced risk of colon cancer in men. It is noteworthy that dairy consumption recommendations in the US, Canada, Australia, and the UK (Table 3) support this level of non-fermented milk intake. No association was found between risk of CRC, colon cancer, or rectal cancer and consumption of solid cheese or fermented milk.

When data were analyzed separately by gender and colorectal subsite, no association was found between non-fermented milk intake and risk of rectal cancer in men, although it should be noted that only three risk estimates were available to examine this. In addition, non-fermented milk intake was not associated with risk of CRC, colon cancer, or rectal cancer in women. Although it is unknown why an association between non-fermented milk and colon cancer risk exists among men but not among women, it could be related to the higher incidence of CRC (and one can assume a higher incidence of colon cancer) in men compared to women (Parkin et al., 2005). Others have suggested that gender differences affecting health behaviors that influence cancer development, gender differences in CRC pathogenesis, or differences in dietary measurement error between men and women may explain these data (Miller et al., 2010).

The association of a reduced risk of colon cancer with consumption of non-fermented milk but not with consumption of solid cheese or fermented milk has a number of possible explanations. The first relates to the total level of consumption, as the highest category of non-fermented milk consumption in the cohorts (mean: 439 g/day – about 2 servings) was higher than that for solid cheese (mean: 39 g/day – about 1 serving) and fermented milk (mean: 187 g/day – about 1 serving). These intakes correspond to 514 mg calcium, 280 mg calcium, and 346 mg calcium/day, respectively, indicating a much higher calcium intake through consumption of non-fermented milk (Food Standards Australia New Zealand, 2006). Calcium may protect the colon by binding bile acids and free fatty acids, reducing proliferation of cancer cells (Cho et al., 2004; Huncharek et al., 2009; Norat and Riboli, 2003). Therefore, the lower calcium intake in subjects consuming solid cheese and fermented milk may in part explain the lack of association seen in these first two groups. Longitudinal studies investigating effects of higher consumption of solid

cheese and fermented milks are needed to determine if a protective association exists with CRC, colon cancer, or rectal cancer. Moreover, as probiotic bacteria remain in the intestine for only a short time (Corthésy et al., 2007), examination of regular versus irregular consumption of fermented milk is also important for such future studies.

Another explanation to be considered is the amount of lactose consumed through the different forms of dairy foods. Although their data were heterogeneous, Szilagyi et al. (Szilagyi et al., 2006) found that dairy foods protected against CRC in a population with adequate levels of the lactase enzyme and high dairy intake (RR: 0.80 (95% CI 0.73-0.88)) as well as in a population with inadequate levels of the lactase enzyme and consequent low dairy intake (RR: 0.84 (95% CI 0.73-0.97)), suggestive of an additional protective mechanism. In people with insufficient lactase, lactose from non-fermented milk remains undigested in the small intestine, passing through to the colon where it can act as a prebiotic, promoting the growth of cancer-protective colonic microflora (Szilagyi et al., 2006). Lactase is found at high levels in infants but declines throughout life, leaving only 10-25% of the enzyme present by early childhood and 5-10% by adulthood (Harrington and Mayberry, 2008). Consequently, it is estimated that 75% of people worldwide are affected by some level of lactose maldigestion (Gaskin and Ilich, 2009), creating a large population potentially receiving undigested lactose in the colon. Lactose is lost in cheese production (Miller et al., 1999): one serving of non-fermented milk contains 11-15 g of lactose, while one serving of cheddar cheese (40 g) contains at most only 0.1 g of lactose (Table 3) (Food Standards Australia New Zealand, 2006). In fermented milk, the presence of β-galactosidase hydrolyses lactose during storage and during digestion, substantially reducing the amount that reaches the colon even in people with lactase insufficiency (Miller et al., 1999).

While neither solid cheese nor fermented milk consumption results in lactose reaching the colon, consumption of non-fermented milk delivers sufficient lactose to the colon to support appreciable prebiotic activity. This may in part explain why only non-fermented milk had protective effects against colon cancer in the current meta-analysis. Additional prospective studies controlling the amount of lactose in dairy foods are required to examine this hypothesis.

The current analysis updates and complements findings of four previously published meta-analyses or pooled statistics. The updated AICR review (World Cancer Research Fund / American Institute for Cancer Research., 2010) reported that non-fermented milk intake protected against CRC in men alone as well as in men and women combined. Significance was lost when analyses were confined to colon cancer or rectal cancer alone. The current meta-analysis excludes one (Kampman et al., 1994) of the seven studies included in the AICR analysis due to its short duration (3.3 years).

As in the current review, the Huncharek meta-analysis indicated that a 'high' milk intake compared to a 'low' milk intake reduced the risk of colon cancer in men and women combined, but had no effect on rectal cancer. Association of CRC with consumption of either solid cheese or fermented milk was not reported, nor was the effect of gender analyzed separately. The current meta-analysis excludes ten of the 20 studies included in the Huncharek analysis: five that examined total dairy food consumption rather than intake of specific dairy foods (Bostick et al., 1993; Kato et al., 1997; Lin et al., 2004 ; Wu et al., 2002 ; Zheng et al., 1998), three with an outcome of mortality (Hsing et al., 1998; Kojima et al., 2004; Phillips and Snowdon, 1985), one that used a duplicate cohort (Larsson et al., 2005), and one of short duration (Kampman et al., 1994). The current meta-analysis, moreover, includes four additional cohort studies (Lee et al.,

2009; Lin et al., 2005; Park et al., 2007; Sanjoaquin et al., 2004) and over 310,000 additional subjects.

Marques-Vidal et al. (Marques-Vidal et al., 2006) reported that two studies found an inverse association between milk consumption and CRC or colon cancer risk, while nine studies found no relationship. Based on qualitative assessment only, the authors concluded that milk consumption does not significantly affect CRC or colon cancer risk. The current meta-analysis excludes seven of the 12 studies in their review: six were the same studies as those excluded from the Huncharek review (above), and one additional that examined total dairy food intake only (Sellers et al., 2008). It is interesting that different conclusions were drawn from the Marques-Vidal review and both the Huncharek and the current meta-analysis. This suggests the importance of assigning a greater weight to primary studies with less variability, as is done in meta-analysis.

While the pooling method used by Cho et al. (Cho et al., 2004) has several benefits, it is not verifiable because the individual data are not published. Moderate non-fermented milk consumption (> 250 g milk/day) was inversely related to risk of CRC (adjusted RR: 0.85 (95% CI 0.78-0.94)). There was also a significant inverse association with daily consumption of > 25 g ricotta or cottage cheese, but no association with consumption of yogurt (equivalent to fermented milk in the present review) or solid cheeses. The current meta-analysis confirms these pooled results, but here we add nine cohorts and report verifiable data from published studies.

The strength of any high quality systematic review lies in the thorough, meticulous, and objective process undertaken during its preparation, to reduce sources of bias (Lichtenstein et al., 2008). In addition, meta-analyses are able to increase the statistical power of cohort studies that

may not have been large enough to find statistically significant events. This particular systematic review has several strong points: a very comprehensive search strategy approved by NHMRC Dietary Guidelines Working Committee and unbiased methods for study selection based on pre-set inclusion/exclusion criteria. Moreover small study bias has been avoided by including only large cohort studies (> 1000 subjects) of long duration, while biased evaluation was prevented through use of a consistent set of predetermined questions to assess study quality (Stroup et al., 2000). Heterogeneity was assessed both qualitatively and quantitatively, and in all except three analyses was sufficiently low to allow calculation of a summary statistic. Finally, only cancer incidence, not mortality, was accepted as an outcome.

There are also several limitations of this review. The initial database search only located studies published from 2002, assuming that recent systematic reviews would provide an adequate search of earlier literature, as studies included in previously published systematic reviews were also included in the present meta-analysis. Only studies published in English were included, which may have excluded a small number of relevant studies, although it has been previously estimated that this is likely to cause no more than a 2% overestimation of the effect (Moher et al., 1999). As suggested by Moher et al. (Moher et al., 1999), publication bias is possible because unpublished studies were not sought. In addition, the highest category of non-fermented milk, solid cheese, and fermented milk intake for each component study was compared to the bottom category of intake, combining different intake levels into the meta-analysis. Therefore, it was not possible to determine the lowest intake of non-fermented milk associated with a protective effect. Inherent in any meta-analysis of prospective studies, diversity of study populations and designs and biases in the original publications is possible. Finally, as mentioned above, there

were not always enough data points to sufficiently analyze gender and colorectal subsite separately. These limitations must be considered when interpreting the summary statistic.

Conclusion

This meta-analysis of over 900,000 subjects and over 5,000 cases of CRC supports the inverse association between consumption of non-fermented milk and risk of colon cancer in men. With the average daily intake in the primary studies of approximately two servings of non-fermented fluid milk, this relationship can serve as part of the evidence base for development of future dietary guidelines involving non-fermented milk, and supports the current recommendations in the US, Canada, Australia, and the UK that adults should consume 2-3 servings of dairy foods per day. While no association was seen with consumption of solid cheese or fermented milk, this could be a result of lower intake levels or varied content of biologically active compounds provided by these foods. Longitudinal studies both investigating higher daily consumption and controlling for the amount of lactose present in the dairy food are needed before conclusive dietary recommendations for solid cheeses and fermented dairy foods can be made.

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and helped with manuscript revision. CP determined studies for exclusion and inclusion, extracted data from included studies, and contributed to manuscript revision. KW oversaw and advised the entire study, designed the review process, chose studies to be retrieved, and contributed to manuscript preparation and revision. All authors approved the final manuscript. None of the authors have a conflict of interest to disclose. This work was undertaken as part of a systematic literature review to update the Dietary Guidelines for Australians by the Dietitians Association of Australia under contract to the National Health and Medical Research Council, Australia.

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FIGURE LEGENDS

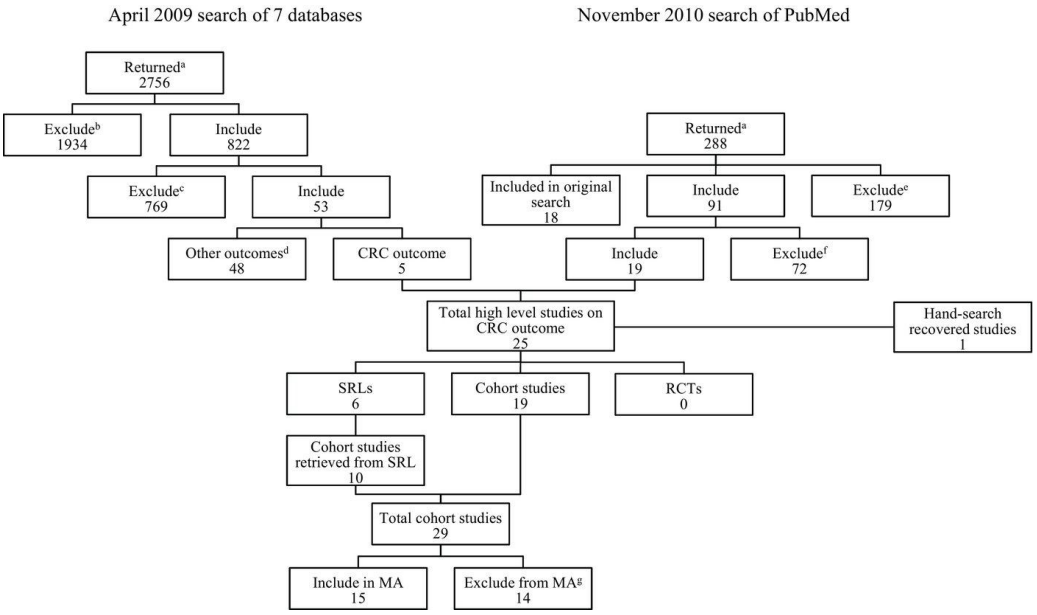

Figure 1. Flow diagram depicting selection of studies to be included in final review examining the association between consumption of non-fermented milk, solid cheese, and fermented milk and incidence of colorectal cancer, colon cancer, and rectal cancer. CRC = colorectal cancer;

MA = meta-analysis; RCT = randomized controlled trial; SRL = systematic review of the literature.

[a] Total of studies retrieved from database search and studies retrieved from search of reference lists;

[b] Reasons for exclusion: not a relevant outcome or intervention (n=980), not a relevant population (n=445), duplicate study (n=362), not a study (n=147);

[c] Reasons for exclusion: not a relevant outcome or intervention (n=492), studies below level I and II evidence (n=143), not a study (n=89), not a relevant population (n=24), duplicate study (n=21);

[d] Other outcomes included bone health, hip fracture, heart disease, stroke, hypertension, type 2 diabetes, metabolic syndrome, obesity, social equity, mental health, dental health, other types of cancers, and CRC mortality;

[e] Reasons for exclusion: not an outcome or intervention of interest (n=137), not a population (n=33), not a study (n=7), not in English language (n=2);

[f] Reasons for exclusion: low level of evidence (n=69), short study duration (n=2), not an outcome or intervention of interest (n=1);

[g] Reasons for exclusion: reported total dairy consumption only (n=6), outcome of mortality (n=5), consumption not quantified (n=1), intake data from childhood (n=1), duplicate cohort (n=1).

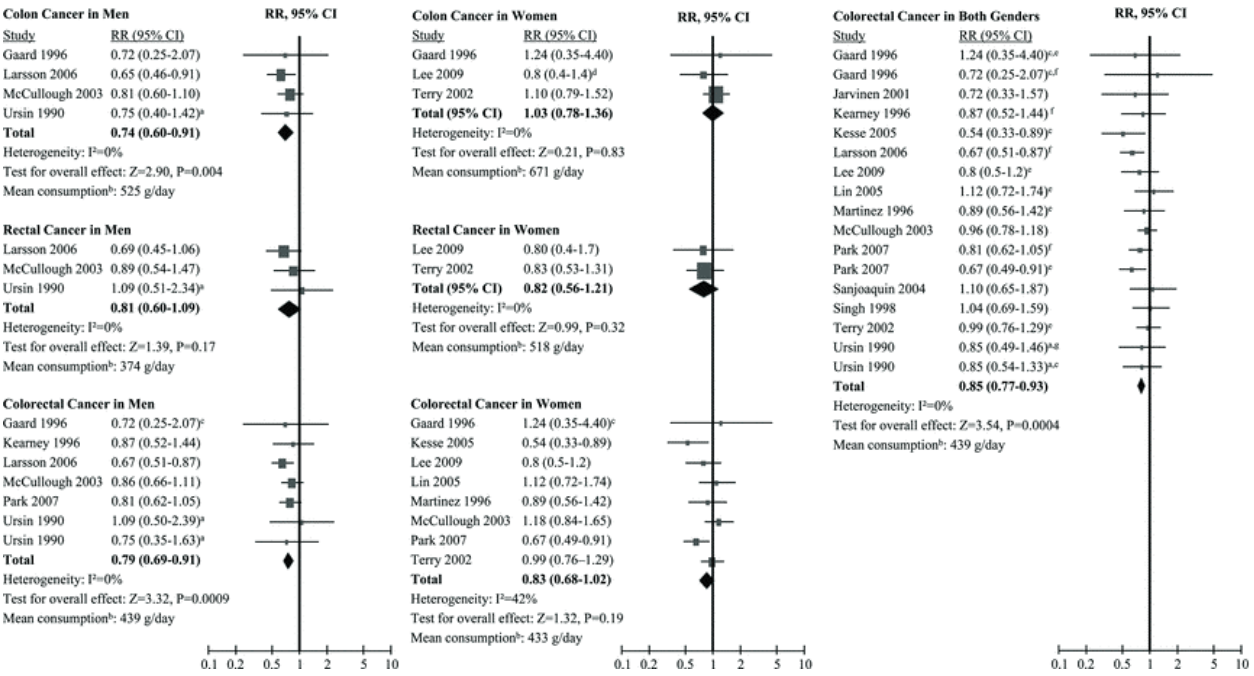

Figure 2. Forest plot of prospective studies examining the association between consumption of non-fermented milk and risk of colon cancer, rectal cancer, and colorectal cancer in men and women separately, using the generic inverse variance method and random effects model. CI = confidence interval; RR = relative risk.

[a] Study did not report a CI or standard error; for meta-analysis, this was estimated using the reported observed and expected number of cases in the cohort;

[b] Mean consumption indicates the average of the individual studies' highest category of consumption. If an individual study reported intake in number of servings, the US standard serving size (U.S. Department of Health and Human Services and US Department of Agriculture, 2005) for milk was used to convert servings to grams;

[c] RR reported for colon cancer only;

[d] Study reported a CI that was asymmetrical around the mean; therefore the widest CI was used to calculate the summary statistic;

[e] RR reported in females only;

[f] RR reported in males only;

[g] RR reported for rectal cancer only.

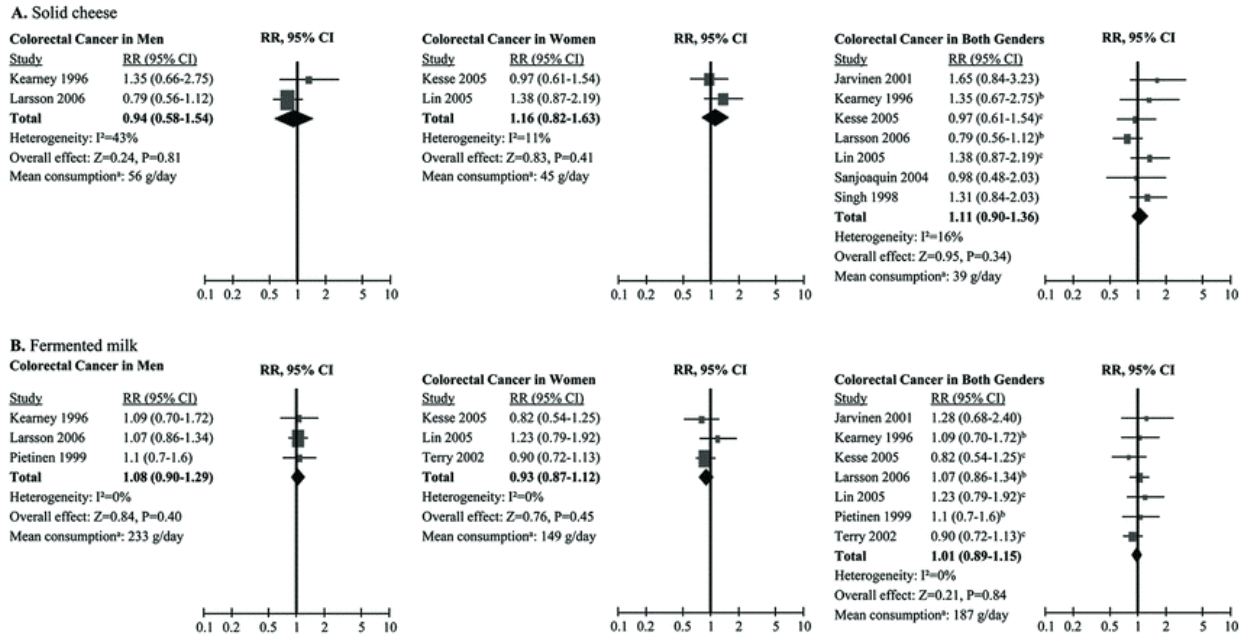

Figure 3. Forest plot of prospective studies examining the association between consumption of solid cheese and fermented milk and risk of colorectal cancer in men and women separately, using the generic inverse variance method and random effects model. CI = confidence interval; RR = relative risk.

[a] Mean consumption indicates the average of the individual studies' highest category of consumption. If an individual study reported intake in number of servings, the US standard

serving sizes (U.S. Department of Health and Human Services and US Department of Agriculture, 2005) for cheese and yogurt were used to convert servings to grams;

[b] RR reported in males only;

[c] RR reported in females only.

TABLES

Table 1. Databases and search terms used for this systematic review on the effects of non-fermented milk, solid cheese, and fermented milk consumption on protection against colorectal cancer, colon cancer, and rectal cancer.

Initial Search in April 2009, searching publication dates January 2002 to April 2009		
Database	Search Terms	Limits
Cinahl	Neoplasms and milk, cheese, or custard	Systematic review, review, English language
Medline	Neoplasm and milk (includes cow's milk), goats milk, sheep milk, cheese, yoghurt, low fat milk, skim milk, full fat milk, or custard	Systematic review, meta-analysis, review, English language, humans
PreMedline	Cancer and goats milk, sheep milk, yoghurt, cheese, custard, full fat milk, skim milk, reduced fat milk, full cream milk, or low fat milk	None
PsycInfo	Neoplasms and cheese, yoghurt, custard, skim milk, reduced fat milk, low fat milk, full cream milk, full fat milk, sheep milk, cows milk, or goats milk	Systematic review, literature review, meta-analysis
Cochrane/Database of Abstracts of Reviews of Effects (DARE)	Cows milk, goats milk, sheep milk, skim milk, full fat milk, full cream milk, milk, reduced fat milk, low fat milk, yoghurt, cheese, or custard	None
ScienceDirect	Cancer or neoplasm and milk, skim milk, cows milk, goats milk, sheep milk, full cream milk, reduced fat milk, low fat milk, yoghurt, cheese, or custard	Systematic review, review, meta-analysis
Educational Resources Information Center (ERIC)	Cancer and cows milk, sheep milk, goats milk, skim milk, low fat milk, reduced fat milk, full cream milk, cheese, yoghurt, or custard	None

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Additional Search in July 2009, searching publication dates January 1990 to July 2009		
Database	Search Terms	
PubMed	Milk, custard, yoghurt, cheese, dairy, colon, colorectal, rectal, or rectum and neoplasm, cancer, carcinoma, or tumour	Humans

Table 2. Characteristics of cohort studies included in meta-analysis.

Non-fermented milk								
Published study	Study cohort and characteristics (age in years)	Length of follow up (years)	Intake range	Size of cohort	Number of cases	Outcome	RR (95% CI)	Quality rating
Gaard et al. 1996[a]	Norway, age >20	11.4	≥4 glasses vs <1 glass/d	24 897 25 638	83 60	Colon cancer in men Colon cancer in women	0.72 (0.25-2.07) 1.24 (0.35-4.40)	0
Jarvinen et al. 2001[b]	Finland, age >15	24	men: >1131g vs <511g/d women:>700g vs <302g/d	9959	38 34 72	Colon cancer in both sexes Rectal cancer in both sexes CRC in both sexes	0.46 (0.14–1.46) 1.13 (0.39–3.31) 0.72 (0.33–1.57)	P
Kearney et al. 1996[c]	US: Health Professionals Follow-Up Study, age 40-75	6.0	>237mL/d vs <237mL/mo	47 935	203	CRC in men	0.87 (0.52–1.44)	P
Kesse et al. 2005[d]	France: E3N-EPIC Cohort Study, age 40-65	6.9	>210g vs <79.72g/d	100 000	172	CRC in women	0.54 (0.33–0.89)	P
Larsson et al. 2006[e]	Sweden: Cohort of Swedish Men, age 45-79	6.7	≥1.5 glasses/d vs <2 glasses/wk	45 306	276 173 449	Colon cancer in men Rectal cancer in men CRC in men	0.65 (0.46-0.91) 0.69 (0.45-1.06) 0.67 (0.51–0.87)	P
Lee et al. 2009[f]	China: Shanghai Women's Health Study, age 40-70	7.4	>200g vs 0g/d	73 224	236 158 394	Colon cancer in women Rectal cancer in women CRC in women	0.8 (0.4-1.3) 0.8 (0.4-0.7) 0.8 (0.5-1.2)	P
Lin et al. 2005[g]	US: Women's Healthy Study, age ≥45	10	>1 serving vs <0.1 serving/d	36 976	223	CRC in women	1.12 (0.72-1.74)	P
Martinez et al 1996[h]	US: Nurse's Health Study, age 30-55	12	≥2 servings/d vs <1 serving/mo	89 448	501	CRC in women	0.89 (0.56-1.42)	0
McCullough et al. 2003[i]	US: Cancer Prevention Study II Nutrition Cohort, age 50-74	5	≥1.1 servings/d vs none	127 749	302 109 421 262 683	Colon cancer in men Rectal cancer in men CRC in men CRC in women CRC in both sexes	0.81 (0.60–1.10) 0.89 (0.54–1.47) 0.86 (0.66–1.11) 1.18 (0.84–1.65) 0.96 (0.78–1.18)	P

Park et al. 2007[j]	US: Multiethnic Cohort Study, age 45-75	5-8	≥122g vs <11g/1000kcal	105 108 85 903	536 745	CRC in women CRC in men	0.67 (0.49-0.91) 0.81 (0.62-1.05)	P
Sanjoaquin et al. 2004[k]	UK: Oxford Vegetarian Study, 42% vegetarian, age 16-89	17	>0.5 pint vs <0.5pint/d	10 998	93	CRC in both sexes	1.10 (0.65-1.87)	N
Singh et al. 1998[l]	US: Adventist Health Study, age >25	22	≥1 serving/wk vs none	32 051	135	CRC in both sexes	1.04 (0.69–1.59)	P
Terry et al. 2002[m]	Sweden: Swedish Mammography Cohort, age 39-70	11.3	24-46 servings vs 0-8 servings/wk	61 463	371 191 572	Colon cancer in women Rectal cancer in women CRC in women	1.10 (0.79–1.52) 0.83 (0.53–1.31) 0.99 (0.76–1.29)	P
Ursin et al. 1990[n]	Norway: 83% male, age 35-74	11.5	≥2 glasses vs <1 glass/d	15 914	53 35 92 63	Colon cancer in men Rectal cancer in men Colon cancer in both sexes Rectal cancer in both sexes	0.75 (0.40-1.42) 1.09 (0.51-2.34) 0.85 (0.54–1.33) 0.85 (0.49-1.46)	0
Solid cheese								
Jarvinen et al. 2001[b]	Finland: age >15	24	men: >18g vs <3g/d women:>18g vs <2g/d	9959	38 34 72	Colon cancer in both sexes Rectal cancer in both sexes CRC in both sexes	2.42 (0.91–6.43) 1.12 (0.43–2.91) 1.65 (0.84–3.23)	P
Kearney et al. 1996[c]	US: Health Professionals Follow-Up Study, age 40-75	6.0	>28.35g/d vs <28.35g/mo	47 935	203	CRC in men	1.35 (0.67–2.75)	P
Kesse et al. 2005[d]	France: E3N-EPIC Cohort Study, age 40-65	6.9	>70.13g vs <26.67g/d	100 000	172	CRC in women	0.97 (0.61–1.54)	P
Larsson et al. 2006[e]	Sweden: Cohort of Swedish Men, age 45-79	6.7	≥3 slices/d vs <4 slices/wk	45 306	276 173 449	Colon cancer in men Rectal cancer in men CRC in men	0.78 (0.51–1.21) 0.80 (0.45–1.41) 0.79 (0.56–1.12)	P
Lin et al. 2005[g]	US: Women's Healthy Study, age ≥45	10	≥0.7 serving vs <0.1 serving/d	36 976	223	CRC in women	1.38 (0.87-2.19)	P
Sanjoaquin et al. 2004[k]	UK: Oxford Vegetarian Study, 42% vegetarian, age 16-89	17	>10 servings vs <5 servings/wk	10 998	92	CRC in both sexes	0.98 (0.48-2.03)	N
Singh et al. 1998[l]	US: Adventist Health Study, age >25	22	≥2 servings/wk vs 0-2 servings/mo	32 051	142	CRC in both sexes	1.31 (0.84–2.03)	P
Fermented milk								
Jarvinen et al. 2001[b]	Finland: age >15	24	men: >160g vs <1g/d women:>206g vs <1g/d	9959	38 34 72	Colon cancer in both sexes Rectal cancer in both sexes CRC in both sexes	0.79 (0.34–1.79) 2.67 (0.91–7.80) 1.28 (0.68–2.40)	P
Kearney et al. 1996[c]	US: Health Professionals Follow-Up Study, age 40-75	6.0	110g vs 5g/d	47 935	203	CRC in men	1.09 (0.70–1.72)	P

Kesse et al. 2005[d]	France: E3N-EPIC Cohort Study, age 40-65	6.9	>120.42g vs <32.29g/d	100 000	172	CRC in women	0.82 (0.54–1.25)	P
Larsson et al. 2006[e]	Sweden: Cohort of Swedish Men, age 45-79	6.7	≥1serving/d vs never	45 306	276 173 449	Colon cancer in men Rectal cancer in men CRC in men	1.17 (0.88–1.56) 0.94 (0.66–1.33) 1.07 (0.86–1.34)	P
Lin et al. 2005[g]	US: Women's Healthy Study, age ≥45	10	≥0.5 serving/d vs none	36 976	223	CRC in women	1.23 (0.79-1.92)	P
Pietinen et al. 1999[o]	Finland: Alpha-Tocopherol Beta-Carotene Prevention Study, age 50-69	8	350g vs none	27 111	185	CRC in men	1.1 (0.7-1.3)	P
Terry et al. 2002[m]	Sweden: Swedish Mammography Cohort, age 39-70	11.3	6-20 servings vs 0-0.5 servings/wk	61 463	371 191 572	Colon cancer in women Rectal cancer in women CRC in women	0.76 (0.57–1.01) 1.28 (0.87–1.89) 0.90 (0.72–1.13)	P

RR = relative risk; 0 = neutral quality; CRC = colorectal cancer; P = positive quality; E3N-EPIC = French cohort of the European Prospective Investigation into Cancer and Nutrition; N = negative quality.

[a] Adjusted for age;

[b] Adjusted for age, gender, occupation, smoking, geographical area, BMI, and total energy intake;

[c] Adjusted for age, family history of colon cancer, previous intestinal polyp, screening, smoking, aspirin use, physical activity, BMI, total energy, saturated fat, and dietary fiber intakes, and alcohol and red meat consumption;

[d] Adjusted for education, family history of colon cancer, smoking, physical activity, BMI, total energy intake, and alcohol consumption;

[e] Adjusted for age, education, family history of CRC, history of diabetes, smoking, aspirin use, physical activity, BMI, total energy, saturated fat, and vitamin D intakes, alcohol, fruit, vegetable, and red meat consumption, and multivitamin use;

[f] Adjusted for age, education, income, survey season, non-steroidal anti-inflammatory drug use, total energy and dietary fiber intakes, and tea consumption;

[g] Adjusted for age, randomized treatment assignment, family history of CRC, history of colon polyps, smoking, menopausal status, baseline postmenopausal hormone therapy use, physical activity, BMI, total energy and saturated fat intakes, red meat and alcohol consumption, and multivitamin use;

[h] Adjusted for age, family history of CRC, smoking, aspirin use, physical activity, BMI, and alcohol and red meat consumption;

[i] Adjusted for age, education, family history of CRC, smoking, hormone replacement therapy use, physical activity, BMI, total energy and saturated fat intakes, fruit and vegetable consumption, and long-term multivitamin use;

[j] Adjusted for age, ethnicity, time since cohort entry, family history of CRC, previous intestinal polyp, smoking, hormone replacement therapy use (women), non-steroidal anti-inflammatory drug use, physical activity, BMI, total energy and dietary fiber intakes, and regular multivitamin use;

[k] Adjusted for age, gender, smoking, and alcohol intake;

[l] Adjusted for age, gender, family history of colon cancer, smoking, aspirin use, physical activity, BMI, and alcohol use;

[m] Adjusted for age, education, BMI, total energy, folic acid, and vitamin C intakes, and alcohol and red meat consumption;

[n] Adjusted for age, gender, and region of residence;

[o] Adjusted for age, education, supplement group, smoking, physical activity at work, BMI, and alcohol consumption.

Table 3. Daily amount of milk, cheese, and yogurt recommended by the US, Canada, Australia, and UK.

	United States	Canada	Australia	United Kingdom
Suggested servings of total dairy food/day[a]	3	2	2	3
Milk				
Serving size (g (ml))[b]	244 (240)	258 (250)	258 (250)	203 (200)
Ca^{2+} (mg)/serving[c]	285-344	301-364	301-364	238-286
Lactose (g)/serving[c]	11-14	12-15	12-15	10-12
Total (g (ml))/day	732 (720)	516 (500)	516 (500)	609 (600)
Ca^{2+} (mg)/day	855-1032	602-728	602-728	714-858
Lactose (g)/day	33-42	24-30	24-30	30-36
Cheese				
Serving size (g)[b]	42.5	50	40	30
Ca^{2+} (mg)/serving[c]	197-409	232-482	186-385	139-289
Lactose (g)/serving[c]	0	0	0	0
Total (g)/day	127.5	100	80	90
Ca^{2+} (mg)/day	592-1228	464-963	371-770	418-867
Lactose (g)/day	0-0.1	0-0.1	0-0.1	0-0.1
Yogurt				
Serving size (g (ml))[b]	245 (240)	175 (171)	200 (196)	150 (147)
Ca^{2+} (mg)/serving[c]	269-576	193-411	220-470	165-353
Lactose (g)/serving[c]	7-12	5-9	6-10	4-8
Total (g (ml))/day	735 (720)	350 (342)	400 (392)	450 (441)
Ca^{2+} (mg)/day	807-1728	386-822	440-940	495-1059
Lactose (g)/day	21-36	10-18	12-20	12-24

[a] Based on a typical adult consuming 1600+ kcal/d (US) or aged 19-50y (Canada, Australia, UK);

[b] Recommended serving sizes for the USA, Canada, Australia, and the UK are based on the Dietary Guidelines for Americans (U.S. Department of Health and Human Services and US Department of Agriculture, 2005), Eating Well with Canada's Food Guide (Health Canada, 2007), The Australian Guide to Healthy Eating (Kellett et al., 1998), and the UK Dairy Council (The Dairy Council, 2007), respectively;

[c] Calculated using the NUTTAB 2006 online version (Food Standards Australia New Zealand, 2006).