Dairy product consumption and risk of colorectal cancer in an older Mediterranean population at high cardiovascular risk.

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Abbreviations: CRC, colorectal cancer; MedDiet, Mediterranean diet; CVD, cardiovascular disease; BMI, body mass index; EVOO, extra virgin olive oil; FFQ, food frequency questionnaire; IQR, interquartile range; MET: metabolic equivalent; EPIC, European Prospective Investigation into Cancer and Nutrition; PKC: protein kinase C; CLA: conjugated linoleic acid.

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Novelty and Impact: An inverse association between consumption of dairy product and the risk of colorectal cancer (CRC) has been reported. Little is known regarding subtypes of dairy product or its fat content and CRC risk. We assessed these associations in older individuals at high cardiovascular disease risk. We found that a high consumption of total dairy products and low-fat milk was inversely associated with CRC incidence. However, there are no reasons to advice against whole-fat dairy products.

ABSTRACT

Prospective studies have reported an inverse association between the consumption of total dairy products and milk and the risk of colorectal cancer (CRC). Nonetheless, there is little and inconsistent evidence regarding subtypes of dairy product and CRC risk. We assessed the associations between the consumption of total dairy products, their different subtypes and CRC risk in older Mediterranean individuals at high cardiovascular risk. We analyzed data from 7216 men and women (55-80 years) without CRC at baseline from the PREvención con DIeta MEDiterránea study. Individuals were recruited between 2003 and 2009, and followed-up until December 2012. At baseline and yearly thereafter, consumption of total and specific dairy products was assessed using a validated 137-item food-frequency questionnaire. Cox proportional hazards ratios (HRs) of CRC incidence were estimated for tertiles of mean consumption of dairy products during the follow-up. During a median [inter-quartile range] follow-up of 6.0 [4.4-7.3] years, we documented 101 incident CRC cases. In the multivariable-adjusted models, HRs and 95% confidence intervals (CIs) of CRC for the comparison of extreme tertiles of total dairy product and low-fat milk consumption were 0.55 (95% CI: 0.31-0.99; P-trend= 0.037) and 0.54 (95% CI: 0.32-0.92; P-trend=0.022), respectively. No significant associations with other dairy products (whole-fat and low-fat dairy products; total, low-fat and whole-fat yogurt; cheese; total, low-fat and whole-fat milk; concentrated full-fat dairy products, sugar-enriched dairy products and fermented dairy products) were found. A high consumption of total dairy products and low-fat milk was significantly associated with a reduced CRC risk.

INTRODUCTION

Cancer accounts for one in eight deaths worldwide and affects approximately one in four women and one in three men during their life. In the last 30 years, cancer rates have doubled and it is predicted that it will almost triple by 2030 [1,2].

Colorectal cancer (CRC) is one of the most prevalent human cancers [3]. In 2012, 1.36 million new CRC cases were diagnosed, about 55% of which were in developed countries [4], probably due to the strong relationship between CRC and a Westernized lifestyle [5].

Unhealthy environmental factors such as smoking, physical inactivity, overweight or obesity, as well as adherence to an unhealthful diet characterized by a high consumption of red meat, processed meat and alcohol, and a low intake of dietary fiber, have been related to an increased risk of CRC [6–8].

Adherence to a healthy diet has been reported to be essential for the primary prevention of CRC since dietary factors are estimated to contribute to nearly 50% of cases [9,10]. The traditional Mediterranean dietary pattern, which is characterized by an abundance of plant foods, olive oil and fish, a low consumption of red meat and processed meat, and a moderate consumption of dairy products (principally cheese and yogurt) has been associated with a lower incidence of CRC [11].

Although evidence on the association between CRC and such food groups as processed meat and alcoholic drinks is robust enough to support the argument that there is a convincing relationship, the evidence on the association between the consumption of dairy foods and CRC development is less strong [12]. In addition, these evidences are mainly based on total dairy, milk, cheese and dietary calcium intake, without bearing in mind their fat and sugar content [8,12]. Also, most of the studies evaluating these associations have been performed in apparently healthy populations.

Case-control studies have shown inconsistent results concerning the relationship between dairy product consumption and CRC [14–18]. Furthermore, several prospective cohort studies have found that the consumption of dairy products, especially milk, was associated with a lower CRC risk [19–23]. In addition, the most recent systematic reviews and meta-analyses of prospective studies [24,25] including updated high-quality studies with a large number of cases also found an inverse association between consumption of total dairy products or total milk and CRC risk.

Nonetheless, because most of the studies are based on total dairy products and total milk intake, there is a lack of evidence on the association between specific subtypes of dairy products with regard to their fat and sugar content, and the incidence of CRC. On this basis, we hypothesized that the consumption of different subtypes of dairy products, considering their sugar and fat content, might be differently associated to the risk of CRC. Therefore, we assessed how the consumption of total dairy products and specific dairy product subtypes is associated with the risk of CRC incidence within the frame of the PREDIMED cohort of older individuals at high cardiovascular risk.

MATERIALS AND METHODS

The present analysis was performed as an observational prospective cohort study by using data from the PREDIMED (PREvención con DIeta MEDiterránea) study. The PREDIMED study (PREDIMED website: http://www.predimed.es) is a parallel-group, multicenter and controlled trial designed to assess the effect of a traditional Mediterranean Diet (MedDiet) on the primary prevention of cardiovascular disease (CVD) (registered at http://www.controlled-trials.com as ISRCTN35739639) [26]. The design of the PREDIMED trial and the results with respect to the primary endpoint have been reported elsewhere [27]. The study was conducted in accordance with the Declaration of Helsinki. All participants provided informed consent and the protocol was approved by the institutional review boards of each recruitment center. Although for the main outcome of CVD, the trial was completed after a median follow-up of 4.8 years in June 2011, the endpoint for the present analysis was based on an extended follow-up until December 2012.

Participants

Between 2003 and 2009, a total of 7447 individuals were recruited to the PREDIMED trial. Participants were men (aged 55-80 years) and women (aged 60-80 years) with no previously documented CVD at baseline but who were at high risk because they had either type 2 diabetes mellitus or at least three of the following cardiovascular risk factors: current smoking, hypertension, hypercholesterolemia, low high-density lipoprotein cholesterol, overweight/obesity or family history of premature coronary heart disease. Exclusion criteria were the presence of any severe chronic illness, alcohol or drug abuse, a BMI≥40 kg/m^2 and allergy or intolerance to olive oil or nuts.

Individuals were allocated to one of the three intervention groups: MedDiet supplemented with nuts, MedDiet supplemented with extra virgin olive oil (EVOO), or advice to reduce all sources of fat (control group).

For this analysis, we further excluded those participants who had implausible daily energy intake values (<500 or >3500 kcal/day for women or <800 or >4000 kcal/day for men) and those who did not complete the baseline Food Frequency Questionnaire (FFQ).

Ascertainment of incident and fatal colorectal cancer

CRC was a prespecified secondary outcome in the original study protocol. Cases were defined as the first invasive CRC (*International Classification of Diseases for Oncology* topographical codes C18.0-C20.9). Availability of the results from a cytological or histological examination was considered to be confirmation. Nonetheless, incident CRC cases were also accepted when information about pathological anatomy was not available. Cases were identified from a variety of sources: review of all the medical records of each participant by a panel of physicians and researchers (who were blinded to the intervention), at both primary healthcare and hospital level, and the National Death Index. The Endpoint Adjudication Committee, whose members were blinded to the intervention, determined the cause of death, confirmed major events and updated the endpoints of the PREDIMED study on a yearly basis.

Assessment of covariates

In a face-to-face interview with participants at baseline and yearly during the follow-up, trained dietitians completed: (a) a questionnaire about lifestyle variables, medical history, and medication use; (b) a 14-item validated questionnaire designed to assess adherence to the traditional MedDiet in all the intervention groups and a separate 9-item screening questionnaire used to evaluate adherence to the control diet; (c) a validated semi-quantitative FFQ which included 137 food items and frequencies of consumption of food items reported on an incremental scale with 9 levels (never or almost never; 1-3 servings/month; 1, 2-4 and 5-6 servings/weeks; and 1, 2-3, 4-6 and >6 servings/day); and (d) the validated Spanish version of the Minnesota Leisure-Time Physical Activity questionnaire [28]. The FFQ was previously validated in a Spanish population at high CVD risk [29]. We used Spanish food composition tables to estimate energy and nutrient intake [28]. Energy restriction and physical activity were not encouraged in any group during the intervention.

Additionally, trained personnel took anthropometric measurements (weight, height and waist-circumference). To measure weight and height, calibrated scales and a wall mounted stadiometer were used, respectively, with participants wearing light clothing and with no shoes. Waist circumference was measured midway between the lowest rib and the iliac crest using an anthropometric tape. Blood pressure was measured with a validated oscillometer (Omron HEM705CP, Hoofddorp, the Netherlands) in triplicate with a 5-min interval between each measurement.

Assessment of dairy consumption

In the FFQ validation study, the intra-class correlation coefficient between consumption of total dairy products from the FFQ and repeated 24-h food records was 0.84 [29]. The responses to individual dairy items of the FFQ were converted to average daily consumption (g/day) and categorized as total dairy products (including all types of milk, yogurt and cheese, custard, whipped cream, butter and ice-cream), low-fat dairy products (semi-skimmed/skimmed milk and skimmed yogurt) and whole-fat dairy products (whole-fat milk, whole-fat yogurt and cheese). Dairy food consumption was also categorized by subtypes into the intake of milk (total, low-fat and whole-fat milk), yogurt (total, low-fat and whole-fat yogurt), cheese (Petit suisse, ricotta, cottage, spreadable and semi-cured/cured cheeses), concentrated full-fat dairy (butter, whipped cream and all types of cheeses), sugar-enriched dairy products (condensed milk, milkshakes, ice cream and custard) and fermented dairy foods (all types of yogurt and cheese). Consumption of dairy products at baseline and in yearly follow-up assessments was adjusted for total energy intake using the residual method.

Statistical analysis

For each participant, we calculated the follow-up time as the interval between the date of randomization and the date of CRC diagnosis, death from any cause or the date of the last contact visit, whichever came first. In order to better represent the long-term intake of dairy products and to minimize within-person variation, the average energy-adjusted dairy product consumption, based on data from all the FFQs during the follow-up period was considered for the analysis. Participants were categorized into tertiles of average total dairy products and subtypes of dairy product consumption during the follow-up.

The baseline characteristics of the participants are expressed as means±SD or medians and interquartile ranges [IQR] for continuous variables, and percentages (%) and number (n) for categorical variables. Chi-square and one-factor ANOVA tests were used to assess differences in the baseline characteristics of the study population.

Multivariable Cox proportional regression models were used to evaluate the association between total dairy products and subtypes of dairy product consumption during the follow-up and the subsequent risk of developing CCR. Additional multivariable Cox proportional regression models were carried out in order to estimate the associations between dietary calcium intake from different food sources and CRC risk (Supplemental table 2). Hazard ratios (HRs) and their 95% CIs were calculated using the lowest tertile of intake as the reference category. The assumption of proportional hazards was tested by analyzing the scaled Schoenfeld residuals.

Three different Cox regression models were fitted. The crude model was a univariate model. Model 1 was adjusted for the following potential confounders: intervention group (control, nut or olive oil supplemented MedDiets), sex (men/women), age (years), leisure time physical activity as metabolic equivalents (METs per min/d), BMI (kg/m^2), smoking status (former, current or never), family history of cancer (yes/no), education level (primary, secondary or high school/university, graduate), history of diabetes (yes/no) and use of aspirin (yes/no) at baseline. Model 2 was additionally adjusted for the energy-adjusted tertiles of average consumption during follow-up of vegetables, fruits, legumes, cereals, fish, meat, olive oil and nuts (all in grams per day) and alcohol (grams per day and quadratic term).

Statistical interaction between tertiles of total dairy products and dairy product subtypes and potential confounders such as sex, diabetes status and BMI was evaluated by including interaction terms in the models.

To test the robustness of our findings, we performed different sensitivity analyses: (a) we repeated the models after excluding the incident CRC cases diagnosed within the first 2 years of follow-up to evaluate possible reverse causation, and (b) we replaced missing values of dietary variables (total dairy products, low-fat milk, vegetables, fruits, legumes, cereals, meat, fish, nuts, olive oil, alcohol and energy intake) during the follow-up by the carry-forward method [30]. In order to assess a possible association between the intake of calcium supplements and the risk of CRC, (c) we repeated the models after adjusting for the intake of mineral supplements (yes/no) containing calcium (Supplemental tables 3, 4), and (d) we also repeated the analyses after excluding those individuals taking calcium supplements (Supplemental tables 5, 6) at baseline.

We performed a secondary analysis to evaluate the potential calcium mediating role on the association between the consumption of dairy products and CRC risk. Therefore, in those exposure variables showing a significant association with CRC incidence, we additionally estimated the associations after adding the total dietary calcium intake as a covariate in the fully-adjusted model. Linear trend tests were conducted by assigning the median value of each tertile of dairy product consumption and then using it as a continuous variable. All P-values are two-tailed and $P<0.05$ was considered statistically significant. Analyses were performed using the STATA (14.0, StataCorp LP, Tx. USA) software.

RESULTS

During a median [IQR] follow-up of 6.0 [4.4-7.3] years we documented 101 incident cases of CRC. After excluding individuals with energy intake values outside the pre-specified limits (n=153) and those with no baseline FFQ (n=78), we finally included in our analysis 97 incident CRC cases from the 7216 study participants. The most common incident cancer location among participants who developed CRC was colon (79.4%) followed by rectum (20.6%).

Baseline characteristics of participants according to tertiles of average total dairy product consumption are shown in Table 1. The mean age of the participants was 67.0 years old, 57% of whom were women. When compared with individuals in the reference tertile of average total dairy product consumption, those individuals in the top tertile were more likely to be older, be women, have a higher BMI and suffer from diabetes. Furthermore, these individuals had a lower level of education and leisure time physical activity and were less likely to smoke.

The median cumulative average total dairy product consumption during the follow-up in the whole study population was 350 g/day. The largest contributors to total dairy product consumption were low-fat dairy products (72.6%). In particular, low-fat milk and low-fat yogurt accounted for 57.4% and 11.4% of total dairy product consumption, respectively. Sugar-enriched dairy products were the dairy products that were least consumed (1.4% of total dairy consumption). During follow-up, the median cumulative average consumption was 65 g/day for total yogurt, 25 g/day for cheese, 220 g/day for total milk, 26 g/day for concentrated-full fat dairy products, 5 g/d for sugar-enriched dairy products and 97 g/day for fermented dairy products (Supplemental table 1).

Compared to individuals in the lowest tertile of dairy product consumption, those in the top tertile consumed higher amounts of fruits and legumes and lower amounts of meat, fish, cereals, nuts, olive oil and alcohol (P<0.05).

HRs of incident CRC across energy-adjusted tertiles of average total and specific dairy product consumption are shown in Table 2 and Table 3. Additionally, HRs for CRC incidence associated with the intake of dietary calcium from different food sources across energy-adjusted tertiles are shown in Supplemental Table 2. In the fully-adjusted model (model 2), participants in the upper tertile of total dairy product consumption exhibited 45% lower risk of developing CRC than those in the reference tertile [HR: 0.55; 95% CI: 0.31-0.99; P-trend=0.037]. Neither whole-fat nor low-fat dairy product consumption showed significant associations with CRC incidence. Nonetheless, low-fat dairy foods exhibited a non-significant inverse association with the development of CRC [HR: 0.62; 95% CI: 0.36-1.07; P-trend=0.072] after adjusting for confounders (Table 2). After separately analyzing specific subgroups of dairy products, those individuals in the top tertile of low-fat milk consumption exhibited a lower risk of CRC incidence in comparison to those participants in the reference tertile [HR: 0.54; 95% CI: 0.32-0.92; P-trend=0.022]. We did not find significant differences in the risk of developing CRC with the other subtypes of dairy products (Table 3).

We detected a significant inverse association between the higher intake of calcium from low-fat milk and the risk of CRC [HR: 0.53; 95% CI: 0.31-0.91; P-trend=0.105] after comparing with the lowest intake (model 2). The top tertile of dietary calcium intake from all food sources, dairy sources and total milk showed a non-significant inverse association with CRC incidence compared to the reference tertile (model 2) (Supplemental Table 2).

In a secondary analysis, we evaluated the associations between total dairy products and low-fat milk consumption, and the incidence of CRC after additional adjustment for total dietary calcium intake in the fully-adjusted model. After comparing participants in the top tertile with those in the reference tertile, the associations were attenuated and became non-significant for the consumption of both low-fat milk [HR: 0.61; 95% CI: 0.31-1.17; P-trend=0.110] and total dairy products [HR: 0.59; 95% CI: 0.23-1.49; P-trend=0.275].

After CRC cases diagnosed within the first 2 years of follow-up had been excluded, the inverse associations between total dairy products [HR: 0.50; 95% CI: 0.25-1.00; P-trend=0.042] and low-fat dairy milk intake [HR: 0.53; 95% CI: 0.29-0.97; P-trend=0.041], and the risk of CRC incidence were still significant.

In the sensitivity analysis of yearly updated dietary exposures, the HR for the comparison between individuals in the upper tertile with the participants in the first tertile was [HR: 0.59; 95% CI: 0.35-1.02; P-trend=0.064] for total dairy products and [HR: 0.63; 95% CI: 0.38-1.06; P-trend=0.090] for low-fat milk intake in the fully adjusted model. We found no statistical interaction between total dairy and dairy product subtypes, and sex, age or diabetes.

After considering the intake of calcium supplements as a covariate in the Cox regression models, as well as when we excluded those participants taking calcium supplements in the baseline moment

(Supplemental tables 3-6), the inverse associations between total dairy products and low-fat milk consumption with the incidence of CRC remained.

DISCUSSION

In this large prospective cohort study, we found suggestive evidence that high consumption of total dairy products and low-fat milk is associated with lower CRC incidence. The main contributor to total dairy product consumption was milk, so the inverse association between dairy food consumption and CRC risk might be largely driven by milk intake, particularly low-fat milk. We did not find any significant association between the consumption of other specific types of dairy product and the risk of CRC. These results suggest a potential benefit of dairy foods for the prevention of CRC in older individuals. Some systematic reviews and meta-analysis of cohort studies have assessed the associations of the consumption of total dairy products, milk and solid cheese [24,25,31,32] and CRC risk. Our results are in line with the last published systematic review and meta-analysis of prospective studies which updated the evidence of the WCRF-AICR Continuous Update Project in relation to the association of food groups and beverages with CRC risk [24]. In this meta-analysis, a significant inverse association between the consumption of total dairy products or milk, and CRC incidence was reported. With regard to total dairy product consumption and CRC risk, the aforementioned meta-analysis reported similar associations in men and women. Of note, the relationship between milk consumption and CRC risk was significant only in men. No association was found between cheese and CRC. Neither were any differences found in the associations with cancer location or sex, probably because of the limited number of incident cases. However, although an inverse association between dairy product consumption and CRC risk is suggested based on prospective cohort studies conducted in healthy populations, there is insufficient evidence assessing this association in older Mediterranean individuals at high cardiovascular risk. Therefore, the present study expands these associations to other populations.

Few prospective studies have assessed the associations between types of dairy product by fat content and the risk of CRC [19,33]. In the European Prospective Investigation into Cancer and Nutrition (EPIC)[19], a study conducted in 477,122 men and women followed for a mean of 11 years, the higher consumption of different subtypes of milk was inversely associated with CRC incidence. In our study, a significant reduction of CRC risk was not observed in the case of whole-fat milk consumption, possibly due to the low consumption of this subtype of milk in our population (a median 1.7% of the total milk intake), or because the fat content in whole-fat milk might mitigate the potential benefits of the other bioactive components [34]. In the last decades, most dietary worldwide guidelines have advocated the consumption of low-fat dairy products instead of full-fat counterparts, being this the main reason for the low consumption of whole-fat milk in our study.

In our cohort, associations between types of dairy product other than milk, such as cheese or yogurt, and the incidence of CRC were not detected which is in agreement with meta-analytical evidence [31,32]. Few prospective studies have found an inverse association between cheese consumption and CRC. In the EPIC study [19], cheese and yogurt consumption was inversely associated with CRC in the categorical models, although in the linear model the association was non-significant. Although we observed a non-significant inverse association between total yogurt intake and CRC risk, Pala and collaborators [35] reported a significant decrease in the risk of CRC associated with high yogurt consumption. Differences in the populations studied, the dietary assessment tools and the types of yogurt may explain this discrepancy. Furthermore, both the bio-accessibility and bioavailability of the nutrients contained in dairy products may be different depending on the nature of their food matrix [36]. For example, the higher lactose content in milk compared with fermented dairy products such as cheese or yogurt might decrease the bioavailability of calcium [37]. For this reason, but also because of the lower consumption of fermented dairy products in comparison to milk, we suggest that perhaps we were not able to detect significant associations between the consumption of these subtypes of dairy products and CRC risk.

The main biological and widely studied mechanism explaining the potential benefits of dairy products on CRC is their calcium content. According to the last WCRF/AICR report [12], dietary calcium is considered to be a nutrient that is probably associated with CRC. After adjustment for dietary calcium intake, we found that the associations between total dairy product and low-fat milk consumption with CRC risk were attenuated. Although we did not observe a consistent inverse association after analyzing the HRs for CRC incidence associated with dietary calcium intake, we could consider calcium as a potential mediator of this association.

Calcium has been shown to exert its potential anti-tumor action through two mechanisms. On the one hand, dietary calcium can bind secondary bile acids and free fatty acids. These are potential inducers of damage and proliferation effects on colonic mucosa. On the other hand, calcium can inhibit cell proliferation and promote differentiation and cell apoptosis in normal and transformed colonic cells by activating calcium-sensing receptors in intestinal epithelial cells, and consequently initiating a cascade of intracellular events which activate protein kinase C (PKC) and stimulate the release of intracellular stored calcium. PKC activation and its downstream cascade events may redirect the colon pre-cancer cell at early stages of the neoplastic process into the differentiation pathway [38,39]. Other micronutrients and bioactive constituents of dairy products, such as conjugated linoleic acid (CLA) and butyric acid might also exert a protective effect against CRC. CLA, naturally present in dairy products, might protect against CRC by inhibiting cell proliferation, modifying the fluidity of cell membranes, decreasing the production of inflammatory mediators like prostaglandins and stimulating the immune response [40–43]. The butyric acid contained in milk and milk products might play a role in colorectal neoplasia by inducing apoptosis, cell cycle arrest and differentiation. However, these beneficial effects are more likely to be due to the fermentation of dietary fiber in the colon by the microbiota because butyric acid in foods is rapidly absorbed in the small intestine and metabolized in the liver [39,44].

Among the strengths of our study are its large-scale prospective design, the ascertainment and confirmation of cancer cases by an independent Event Adjudication Committee, the use of a validated FFQ for measuring food consumption and the ability to control for several potential confounders. Furthermore, in order to minimize errors in diet measurement caused by within-person variation and dietary changes, we have taken advantage of the repeated measurements of intake, and calculated the cumulative average for dietary variables.

Limitations should also be considered. First, it may be difficult to generalize our results to other populations because we studied an older Mediterranean population at high cardiovascular risk. However, the inverse association between dairy consumption and CRC has been recognized in young individuals from different populations. Therefore, our results expands the findings to the previously reported literature on this association. Because dairy product consumption has been associated to a decreased risk of obesity and diabetes, both conditions highly prevalent in older populations, we cannot discard that these inverse associations may be mediated by these metabolic conditions [45,46]. Second, although we used a validated FFQ to assess dietary variables, potential measurement errors are unavoidable. Third, because this is a prospective observational study based on a randomized clinical trial, we cannot rule out a restriction on the consumption of dairy products due to the dietary intervention, especially in the control group, which may have an impact on the outcomes. Likewise, the number of incident CRC cases was quite limited. Consequently, we were not able to assess differences in risk neither by tumor subsite nor sex.

In summary, a high consumption of total dairy products and low-fat milk was strongly associated with a reduced risk of CRC in older Mediterranean individuals at high cardiovascular risk. Because of the evidence on the benefits that low-fat milk can have on the risk of CRC, and the lack of evidence on an increased CRC risk derived from whole-fat dairy consumption, there are no reasons to advice against whole-fat dairy products. Thus, the recommendation to drink milk might be reasonable. Further prospective studies and clinical trials on secondary prevention are warranted to clarify the associations between dairy foods and CRC risk.

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CONFLICT OF INTEREST DISCLOSURE

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Prof Jordi Salas-Salvadó declares that he is a member of Danone S.A.'s Advisory Board, a member of the Danone Institute Spain, and that he received payments from Danone S.A. for the purposes of scientific and technical consulting, but not for the preparation of this study.
The other authors declare that they have no conflicts of interest.

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Table 1. Baseline characteristics of individuals at high cardiovascular risk across energy-adjusted tertiles of cumulative average total dairy product consumption during follow-up[1]

	Total dairy products consumption (g/day)[2]			
	T1 (≤ 266.43) n=2406	T2 (266.52-445.10) n=2405	T3 (≥ 445.26) n=2405	P-value[3]
Total dairy products, g/day	166.9±78.1	338.6±45.7	634.8±140.3	<0.001
Age, years	66.3±6.4	67.3±6.2	67.6±6.0	<0.001
Women, % (n)	42.8 (1030)	63.0 (1514)	66.6 (1601)	<0.001
Education level, % (n)				<0.001
Primary, secondary or high school	90.7 (2182)	93.8 (2254)	94.1 (2264)	
University/graduate	9.3 (224)	6.3 (151)	5.9 (141)	
Age at diagnosis of cancer, years	73.5±5.3	69.6±7.2	71.5±5.4	0.022
Family history of cancer, % (n)	48.9 (1177)	48.6 (1169)	50.0 (1202)	0.608
Cancer location				0.229
Colon, % (n)	72.5 (29)	80.0 (28)	90.9 (20)	
Rectum, % (n)	27.5 (11)	20.0 (7)	9.1 (2)	
Diabetes, % (n)	44.0 (1058)	48.9 (1176)	53.8 (1293)	<0.001
Hypertension, % (n)	83.7 (2013)	83.4 (2006)	81.1 (1951)	0.037
Waist circumference, cm				
Women	98.1±10.7	98.8±10.6	98.3±10.6	0.274
Men	103.7±9.1	102.9±9.3	102.9±9.4	0.075
BMI, kg/m^2	29.8±3.7	30.0±3.9	30.1±4.0	0.012
Leisure time physical activity, METs min/day	244.3±246.9	218.5±221.6	230.3±246.6	0.001
Former smokers, % (n)	31.9 (768)	23.0 (552)	18.9 (454)	<0.001
Current smokers, % (n)	19.0 (457)	10.4 (251)	12.3 (298)	<0.001
Current medication use, % (n)				
Use of aspirin	20.8 (500)	22.2 (534)	24.1 (579)	0.099
Use of hormone replacement therapy (only women)	2.33 (24)	2.64 (40)	3.19 (51)	0.035
Intervention groups, % (n)				0.183
MedDiet+EVOO	33.4 (803)	33.9 (814)	35.6 (857)	
MedDiet+nuts	34.3 (824)	31.9 (768)	31.9 (768)	
Control low-fat diet	32.4 (779)	34.2 (823)	32.4 (780)	

Energy intake (kcal/day)	2321.7±561.5	2059.1±502.9	2327.6±522.3	<0.001
MedDiet adherence (score 1-14)	8.7±1.9	8.6±1.9	8.7±1.9	0.025
Food consumption, g/day[4]				
Vegetables	330.1±148.8	336.4±133.4	335.7±150.6	0.258
Fruits	359.2±203.0	375.4±183.3	370.6±200.0	0.013
Legumes	20.4±14.5	19.8±10.6	21.6±14.3	<0.001
Meat	137.2±56.0	132.8±49.0	123.2±51.8	<0.001
Fish	102.2±49.2	100.7±47.9	94.8±49.2	<0.001
Cereals	242.2±88.3	225.9±74.3	207.4±80.83	<0.001
Nuts	10.7±13.9	10.5±12.2	9.2±13.2	<0.001
Olive oil	40.1±16.7	39.6±15.9	37.4±17.4	<0.001
Alcohol	12.4±16.9	7.9±10.8	4.7±9.7	<0.001

Abbreviations: T, tertile; BMI, body mass index; MET, metabolic equivalent task; MedDiet, Mediterranean diet; EVOO, extra virgin olive oil.
[1]Data are expressed as means (standard deviation) or medians [IQR, interquartile range] for continuous variables and percentage and number (n) for categorical variables.
[2]Tertile cut-offs are based on energy-adjusted cumulative average of total dairy product consumption during the follow-up.
[3]P values for differences between tertiles were calculated by chi-square or ANOVA tests for categorical and continuous variables, respectively.
[4]All dietary variables were adjusted for energy using the residual method.

Table 2. Hazard ratios (95% confidence intervals) of colorectal cancer incidence across energy-adjusted tertiles of cumulative average consumption of total dairy, whole-fat dairy and low-fat dairy products in elderly individuals at high cardiovascular risk

	Tertiles of dairy consumption (g/day)[1]			
	T1	T2	T3	P- trend
Total dairy product consumption, median [P25-P75]; g/day[2]	206 [139-247]	350 [315-387]	564 [499-640]	
Cases/ person-year (n)	41/14063	36/14086	20/14091	
Rate per 1000 person-years	2.92	2.56	1.42	
Crude model	1.00 ref	0.88 (0.56-1.37)	0.49 (0.29-0.83)	0.007
Multivariate model 1	1.00 ref	1.00 (0.62-1.59)	0.58 (0.33-1.02)	0.044
Multivariate model 2	1.00 ref	0.96 (0.59-1.56)	0.55 (0.31-0.99)	0.037
Whole-fat dairy products, median [P25-P75]; g/day[3]	0 [0-1]	21 [14-28]	114 [65-217]	
Cases/ person-year (n)	32/14140	29/14061	36/14038	
Rate per 1000 person-years	2.26	2.06	2.56	
Crude model	1.00 ref	0.91 (0.55-1.50)	1.13 (0.70-1.83)	0.589
Multivariate model 1	1.00 ref	0.92 (0.55-1.56)	1.03 (0.64-1.68)	0.940
Multivariate model 2	1.00 ref	0.89 (0.53-1.49)	1.01 (0.62-1.64)	0.982
Low-fat dairy products, median [P25-P75]; g/day[4]	67 [5-136]	254 [214-300]	495 [409-563]	
Cases/ person-year (n)	40/14053	36/14075	21/14112	
Rate per 1000 person-years	2.85	2.56	1.49	
Crude model	1.00 ref	0.90 (0.57-1.41)	0.52 (0.31-0.89)	0.016
Multivariate model 1	1.00 ref	0.98 (0.62-1.54)	0.62 (0.36-1.08)	0.078
Multivariate model 2	1.00 ref	0.97 (0.62-1.52)	0.62 (0.36-1.07)	0.072

Abbreviations: P, percentile; T, tertile.
Cox regression model 1 adjusted for intervention group, sex, age (years), leisure time physical activity (METs in min-day), BMI (kg/m^2), current smoker (yes/no), former smoker (yes/no), never smoker (yes, no), family history of cancer (yes/no), education level (primary or secondary/high school university or graduate), history of diabetes (yes/no) and use of aspirin treatment (yes/no) at baseline.
Cox regression model 2 additionally adjusted for tertiles of cumulative average consumption during the follow-up of vegetables, fruits, legumes, cereals, fish, meat, olive oil and nuts (all in g/day) and alcohol (g/day and quadratic term).
All models were stratified by recruitment center.
[1]Tertile cut-offs are based on energy-adjusted cumulative average total dairy products, whole-fat or low-fat dairy product consumption during the follow-up.
[2] Includes all dairy products: all types of milk, yogurt and cheese, custard, whipped cream, butter and ice-cream.
[3] Includes whole-fat milk and whole-fat yogurt.
[4] Includes semi-skimmed/skimmed milk and low-fat yogurt.

Table 3. Hazard ratios (95% CI) of colorectal cancer incidence across energy-adjusted tertiles of cumulative average consumption of specific dairy products (yogurt, cheese, milk, concentrated full-fat dairy products, sugar-enriched dairy products and fermented dairy products) in elderly individuals at high cardiovascular risk

	Tertiles of specific dairy product consumption (g/day)[1]			
	T1	T2	T3	P- trend
Total yogurt, median [P25-P75]; g/day[2]	8 [1-22]	65 [54-85]	128 [122-186]	
Cases/ person-year (n)	36/14119	34/14068	27/14053	
Rate per 1000 person-years	2.55	2.42	1.92	
Crude model	1.00 ref	0.95 (0.59-1.52)	0.75 (0.46-1.24)	0.249
Multivariate model 1	1.00 ref	1.13 (0.69-1.84)	0.92 (0.56-1.51)	0.705
Multivariate model 2	1.00 ref	1.15 (0.70-1.90)	0.94 (0.56-1.59)	0.800
Low-fat yogurt, median [P25, P75]; g/day[3]	1 [0-4]	40 [24-54]	122 [96-151]	
Cases/ person-year (n)	37/14070	30/14116	30/14054	
Rate per 1000 person-years	2.63	2.13	2.13	
Crude model	1.00 ref	0.81 (0.50-1.31)	0.81 (0.50-1.31)	0.377
Multivariate model 1	1.00 ref	0.94 (0.57-1.54)	1.02 (0.63-1.65)	0.992
Multivariate model 2	1.00 ref	0.97 (0.59-1.61)	1.06 (0.65-1.73)	0.909
Whole-fat yogurt, median [P25-P75]; g/day[4]	0 [0]	6 [4-9]	45 [25-77]	
Cases/ person-year (n)	33/14153	35/14046	29/14041	
Rate per 1000 person-years	2.33	2.49	2.07	
Crude model	1.00 ref	1.07 (0.66-1.72)	0.89 (0.54-1.46)	0.514
Multivariate model 1	1.00 ref	1.13 (0.69-1.86)	0.88 (0.53-1.47)	0.419
Multivariate model 2	1.00 ref	1.07 (0.65-1.79)	0.86 (0.51-1.46)	0.419
Cheese, median [P25-P75]; g/day[5]	11 [6-15]	25 [22-29]	44 [37-54]	
Cases/ person-year (n)	32/14163	29/14037	36/14040	
Rate per 1000 person-years	2.26	2.07	2.56	
Crude model	1.00 ref	0.91 (0.55-1.51)	1.13 (0.70-1.82)	0.603
Multivariate model 1	1.00 ref	0.97 (0.57-1.64)	1.23 (0.75-2.02)	0.368
Multivariate model 2	1.00 ref	0.96 (0.56-1.64)	1.23 (0.74-2.06)	0.378
Total milk, median [P25-P75]; g/day[6]	117 [36-163]	220 [204-242]	449 [364-501]	
Cases/ person-year (n)	40/14057	33/14088	24/14095	

Rate per 1000 person-years	2.85	2.34	1.70	
Crude model	1.00 ref	0.82 (0.52-1.30)	0.60 (0.36-0.99)	0.063
Multivariate model 1	1.00 ref	0.88 (0.56-1.40)	0.66 (0.39-1.12)	0.149
Multivariate model 2	1.00 ref	0.83 (0.52-1.33)	0.63 (0.36-1.10)	0.135
Low-fat milk, median [P25-P75]; g/day[7]	15 [0-90]	201 [188-211]	407 [329-497]	
Cases/ person-year (n)	46/14035	29/14087	22/14117	
Rate per 1000 person-years	3.28	2.06	1.56	
Crude model	1.00 ref	0.63 (0.39-1.00)	0.48 (0.29-0.79)	0.004
Multivariate model 1	1.00 ref	0.70 (0.44-1.11)	0.55 (0.33-0.93)	0.025
Multivariate model 2	1.00 ref	0.68 (0.43-1.09)	0.54 (0.32-0.92)	0.022
Whole-fat milk, median [P25-P75]; g/day[8]	0 [0]	6 [3-10]	60 [21-181]	
Cases/ person-year (n)	31/14154	31/14056	35/14029	
Rate per 1000 person-years	2.19	2.21	2.49	
Crude model	1.00 ref	1.00 (0.61-1.65)	1.14 (0.70-1.84)	0.561
Multivariate model 1	1.00 ref	1.10 (0.66-1.83)	1.10 (0.66-1.83)	0.773
Multivariate model 2	1.00 ref	1.07 (0.65-1.85)	1.06 (0.64-1.75)	0.892
Concentrated full-fat dairy products [P25-P75]; g/day[9]	11 [6-16]	26 [23-30]	45 [38-55]	
Cases/ person-year (n)	33/14165	30/14039	34/14035	
Rate per 1000 person-years	2.33	2.14	2.42	
Crude model	1.00 ref	0.91 (0.56-1.50)	1.04 (0.64-1.67)	0.786
Multivariate model 1	1.00 ref	0.96 (0.57-1.62)	1.12 (0.68-1.83)	0.607
Multivariate model 2	1.00 ref	0.95 (0.56-1.60)	1.11 (0.66-1.86)	0.638
Sugar enriched dairy products [P25-P75]; g/day[10]	0 [0-1]	5 [3-6]	14 [10-25]	
Cases/ person-year (n)	30/14177	38/14087	29/13976	
Rate per 1000 person-years	2.12	2.70	2.07	
Crude model	1.00 ref	1.27 (0.79-2.06)	0.98 (0.59-1.64)	0.895
Multivariate model 1	1.00 ref	1.50 (0.91-2.47)	1.02 (0.59-1.79)	0.927
Multivariate model 2	1.00 ref	1.45 (0.87-2.41)	0.98 (0.55-1.75)	0.810
Fermented dairy products [P25-P75]; g/day[11]	36 [20-52]	97 [81-115]	166 [147-221]	
Cases/ person-year (n)	39/14111	30/14097	28/14031	

Rate per 1000 person-years	2.76	2.13	2.00	
Crude model	1.00 ref	0.77 (0.48-1.24)	0.72 (0.44-1.17)	0.175
Multivariate model 1	1.00 ref	0.89 (0.54-1.46)	0.89 (0.54-1.46)	0.608
Multivariate model 2	1.00 ref	0.89 (0.54-1.48)	0.90 (0.53-1.53)	0.661

Abbreviations: P, percentile; T, tertile.
Cox regression model 1 adjusted for intervention group, sex, age (years), leisure time physical activity (METs in min-day), BMI (kg/m^2), current smoker (yes/no), former smoker (yes/no), never smoker (yes, no), family history of cancer (yes/no), education level (primary or secondary/high school university or graduate), history of diabetes (yes/no) and use of aspirin (yes/no) at baseline.
Cox regression model 2 additionally adjusted for tertiles of cumulative average consumption during the follow-up of vegetables, fruits, legumes, cereals, fish, meat, olive oil and nuts (all in g/day) and alcohol (g/day and quadratic term).
All models were stratified by recruitment center.
[1]Tertile cut-offs are based on energy-adjusted cumulative average total specific dairy product consumption during the follow-up.
[2] Includes all types of yogurt: low-fat and whole-fat yogurt.
[3] Includes low-fat yogurt.
[4] Includes whole-fat yogurt.
[5] Includes all types of cheese: petit Suisse, ricotta, cottage, spreadable and semi-cured/cured cheeses.
[6] Includes all types of milk: semi-skimmed/skimmed milk and whole-fat milk.
[7] Includes semi-skimmed and skimmed-milk.
[8] Includes whole-fat milk.
[9] Includes butter, whipped cream and all types of cheese.
[10] Includes condensed milk, milkshakes, ice cream and custard.
[11] Includes all fermented dairy products: all types of yogurt and cheeses.