DIETARY AND LIFESTYLE DETERMINANTS ASSOCIATED WITH THE RISK OF COLORECTAL CANCER

Laura Barrubés Piñol

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Dietary and lifestyle determinants associated with the risk of colorectal cancer

DOCTORAL THESIS

Supervised by Dr. Nancy Babio and Prof. Jordi Salas-Salvadó.

Department of Biochemistry and Biotechnology
Human Nutrition Unit.

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I STATE that the present study, entitled "***Dietary and lifestyle determinants associated with the risk of colorectal cancer***", presented by Ms. Laura Barrubés Piñol for the award of the degree of Doctor, has been carried out under my supervision at the Department of Biochemistry and Biotechnology of this university and it is currently up for an international distinction.

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"A little goes a long way"

Adriene Mishler

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Abstract

ENGLISH

Worldwide, colorectal cancer (CRC) is the third most incident cancer and the second in terms of mortality for both sexes combined. Besides an ageing population and the acquisition of westernized dietary habits of high-income countries, other modifiable risk factors such as obesity, physical inactivity and smoking increase the risk of CRC development, which brings to light that CRC is largely a preventable disease. Moreover, some dietary patterns such as the Mediterranean diet and the consumption of characteristic foods of this pattern, such as dairy products, have been consistently related to decreased risk of CRC development. However, prospective scientific evidence in this field focusing on elderly populations is scarce.

The general objective of this thesis was to evaluate dietary and lifestyle determinants of CRC incidence. Thus, the potential associations between dairy product consumption with the risk of CRC within the frame of the PREvención con DIeta MEDiterránea (PREDIMED) cohort were investigated. On the other hand, in order to support our results regarding dairy product intake and CRC incidence, we carried out a systematic review and metanalysis of the available evidence coming from prospective cohort and case-control studies in adults, to examine the associations between the consumption of specific types of dairy products and CRC risk. Furthermore, the associations between the adherence to the 2018 WCRF/AICR (cancer-specific recommendations) and the low-risk lifestyle (LRL) (this index comprises smoking status, alcohol consumption, physical activity, diet and body mass index) scores, and the incidence of CRC in the PREDIMED population were also assessed.

The results of this thesis show that high total dairy product consumption was inversely associated with CRC incidence in elderly Spanish individuals with cardiovascular risk, and especially, of importance was the intake of low-fat milk, which was the main driver behind the inverse association. However, the consumption of other dairy product subtypes (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) was not significantly associated with CRC risk. In addition, the systematic-review and meta-analysis of observational studies included in the present thesis showed that higher consumption of total dairy products and total milk was consistently inversely related to CRC risk at all sites, cheese consumption was inversely associated with the risk of CRC and proximal colon cancer, and low-fat milk consumption was associated with decreased colon cancer risk in adults. No significant associations were found between CRC incidence and the consumption of low-fat dairy products, whole milk, fermented dairy products and cultured milk. Finally, adhering to emergent lifestyle

scores, such as the 2018 WCRF/AICR and the LRL scores, was substantially associated to a lower CRC risk in the PREDIMED study.

In conclusion, consuming dairy products such as low-fat milk might contribute to decrease CRC risk in elderly individuals with high CVD risk. Moreover, our systematic review and meta-analyses conducted in adults showed inverse associations with CRC for the consumption of total milk and cheese. The associations between different subtypes of dairy products and CRC risk differed by colon cancer location and subsite. Besides, following cancer-specific recommendations and healthier dietary and lifestyle patterns might also contribute to decrease CRC risk in elderly individuals who are at high cardiovascular risk.

CATALAN

Mundialment, el càncer colorectal (CCR) és el tercer càncer més incident i el segon en termes de mortalitat en ambdós sexes combinats. A més d'un envelliment de la població i de l'adquisició d'hàbits dietètics occidentalitzats dels països amb rendes altes, altres factors de risc modificables com l'obesitat, la inactivitat física i el tabaquisme augmenten el risc de desenvolupament de CCR. És per això que, el CCR és en gran part una malaltia que es pot prevenir. D'altra banda, alguns patrons dietètics com la dieta mediterrània i el consum d'aliments característics d'aquest patró, com els productes làctics, han estat relacionats amb la disminució del risc de desenvolupament de CCR. No obstant això, les evidències científiques prospectives en aquest camp que estudiïn poblacions d'edat avançada és escassa.

L'objectiu general d'aquesta tesi és avaluar els determinants dietètics i d'estil de vida de la incidència de CCR. Per tant, es van investigar les possibles associacions entre el consum de productes làctics amb el risc de CCR en el marc de la cohort PREvención con DIeta MEDiterránea (PREDIMED). D'altra banda, amb l'objectiu de corroborar els nostres resultats en relació amb la ingesta de productes làctics i la incidència de CCR, vam dur a terme una revisió sistemàtica i metanàlisi de les evidències disponibles procedents d'estudis de cohort prospectius i de casos-control en adults, amb l'objectiu d'estudiar les associacions entre el consum de diferents subtipus de productes làctics i el risc de CCR. D'altra banda, també es va avaluar la incidència de CCR en la població PREDIMED, associada a l'adherència a l'índex 2018 WCRF/AICR (recomanacions específiques de càncer) i a l'índex d'estil de vida de baix risc (LRL) (aquest índex comprèn l'hàbit tabàquic, la ingesta d'alcohol, l'activitat física, la dieta i l'índex de massa corporal).

Els resultats d'aquesta tesi mostren que, un consum elevat de productes lactis totals es va associar inversament amb la incidència de CCR en persones espanyoles d'edat avançada amb risc cardiovascular, i especialment, la ingesta de llet baixa en greix, va mostrar ser el principal contribuent de l'associació inversa. No obstant això, la ingesta d'altres subtipus de productes làctics (productes làctics sencers i baixos en greix; iogurt total, baix en greix i sencer; formatge; llet total, baixa en greix i sencera; productes làctics concentrats en greix, productes làctics ensucrats i làctics fermentats) no es va associar significativament amb el risc de CCR. A més, la revisió sistemàtica i metanàlisi d'estudis observacionals inclosa en la present tesi, va mostrar que un major consum de productes làctics totals i de llet total es relacionava inversament de forma consistent amb el risc de CCR en totes les localitzacions. El consum de formatge es va associar inversament amb el risc de CCR i de càncer de còlon proximal, i el consum de llet desnatada es va associar amb un risc disminuït de càncer de còlon. No es van trobar associacions significatives entre el risc de CCR i el consum de productes làctics baixos en greix, llet sencera, productes làctics fermentats i llet fermentada. Finalment, l'adherència a índexs emergents d'estil de vida,

com els índexs 2018 WCRF/AICR i LRL, es va associar substancialment amb un menor risc de CCR en l'estudi PREDIMED.

En conclusió, consumir productes làctics, com la llet baixa en greix, podria contribuir a disminuir el risc de CCR en persones d'edat avançada amb risc cardiovascular elevat. D'altra banda, la revisió sistemàtica i metanàlisi realitzada en adults mostra associacions inverses amb el risc de CCR pel consum de llet i de formatge totals. Les associacions entre els diferents subtipus de productes làctics i el risc de CCR va diferir segons la localització del càncer de còlon. A més, seguir recomanacions específiques per la prevenció del càncer i patrons de dieta i estil de vida més saludables també poden contribuir a disminuir el risc de CCR en persones grans amb elevat risc cardiovascular.

SPANISH

Mundialmente, el cáncer colorrectal (CCR) es el tercer cáncer más incidente y el segundo en términos de mortalidad en ambos sexos combinados. Además del envejecimiento de la población y de la adquisición de hábitos dietéticos occidentalizados de los países con ingresos altos, otros factores de riesgo modificables como la obesidad, la inactividad física y el tabaquismo aumentan el riesgo de desarrollo de CCR, lo que hace que este cáncer sea en gran medida una enfermedad prevenible. Además, algunos patrones dietéticos como la dieta mediterránea y el consumo de alimentos característicos de este patrón, como los productos lácteos, se han relacionado consistentemente con la disminución del riesgo de CCR. Sin embargo, las evidencias científicas prospectivas en este campo, centradas en poblaciones de edad avanzada es escasa.

El objetivo general de esta tesis es evaluar los determinantes dietéticos y de estilo de vida de la incidencia de CCR. Por tanto, se investigaron las posibles asociaciones entre el consumo de productos lácteos con el riesgo de CCR en el marco de la cohorte PREvención con DIeta MEDiterránea (PREDIMED). Por otro lado, con el fin de corroborar nuestros resultados en relación con la ingesta de productos lácteos y la incidencia del CCR, llevamos a cabo una revisión sistemática y metanálisis de las evidencias disponibles procedentes de estudios de cohorte prospectivos y de casos y controles en adultos, para examinar las asociaciones entre el consumo de diferentes subtipos de productos lácteos y el riesgo de CCR. Además, también se evaluaron las asociaciones entre la adherencia al índice 2018 WCRF/AICR (recomendaciones específicas para el cáncer) y al índice de estilo de vida de bajo riesgo (LRL) (este índice comprende el hábito tabáquico, el consumo de alcohol, la actividad física, la dieta y el índice de masa corporal) y la incidencia de CCR en la población PREDIMED.

Los resultados de esta tesis muestran que el consumo elevado de productos lácteos totales se asoció inversamente con la incidencia de CCR en personas españolas de edad avanzada con riesgo de enfermedad cardiovascular y, especialmente, la ingesta de leche baja en grasa fue el principal contribuyente a la asociación inversa. Sin embargo, la ingesta de otros subtipos de productos lácteos (productos lácteos enteros y bajos en grasa; yogur total, bajo en grasa y entero; queso; leche total, baja en grasa y entera; productos lácteos concentrados en grasa, productos lácteos azucarados y productos lácteos fermentados) no se asoció significativamente con el riesgo de CCR. Además, la revisión sistemática y metanálisis de los estudios observacionales incluidos en la presente tesis mostró que un mayor consumo de productos lácteos totales y de leche total estaba relacionado inversamente, de forma consistente, con el riesgo de CCR en todas las localizaciones. El consumo de queso se asoció inversamente con el riesgo de cáncer de colon y de colon proximal, y el consumo de leche baja en grasa se asoció con una disminución del riesgo de cáncer de colon en adultos. No se encontraron asociaciones significativas entre el CCR y el consumo de productos lácteos bajos en grasa, leche entera, productos lácteos fermentados o

leche fermentada. Por último, la adherencia a índices emergentes de estilo de vida, como los índices 2018 WCRF/AICR y LRL, se asoció sustancialmente a un menor riesgo de CCR en el estudio PREDIMED.

En conclusión, el consumo de productos lácteos como la leche baja en grasa podría ayudar a reducir el riesgo de CCR en personas de edad avanzada con alto riesgo cardiovascular. Por otro lado, la revisión sistemática y metanálisis llevada a cabo en adultos, mostró asociaciones inversas con el riesgo de CCR para el consumo total de leche y queso. Las asociaciones entre los diferentes subtipos de productos lácteos y el riesgo de CCR difirieron según la localización del cáncer de colon. Además, el seguimiento de recomendaciones específicas para la prevención del cáncer y seguir patrones de estilo de vida más saludables también puede contribuir a disminuir el riesgo de CCR en personas mayores con riesgo cardiovascular.

Abbreviations

5-FU	5-fluorouracil
AECOSAN	*Agencia Española de Consumo, Seguridad Alimentaria y Nutrición*
APC	Adenomatous polyposis coli
BMI	Body mass index
BRAF	B-Raf proto-oncogene
CI	Confidence Interval
CIMP	CpG island methylation phenotype
CRC	Colorectal cancer
CT	Computed tomography
CUP	Continuous Update Project
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DII	Dietary inflammatory index
EPIC	European Prospective Investigation into Cancer and Nutrition
EVOO	Extra virgin olive oil
FAP	Familial adenomatous polyposis
FFQ	Food frequency questionnaire
FINUT	Iberoamerican Nutrition Foundation
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HNPCC	Hereditary nonpolyposis CRC
HR	Hazard Ratio
IARC	International Agency for Research on Cancer
IGF1	Insulin-like growth factor 1
IGFBP	Insulin-like growth factor binding protein
IQR	Interquartile range
IR	Insulin resistance
LDL	Low-density lipoprotein
LRL	Low-risk lifestyle
LTPA	Leisure-time physical activity
MedDiet	Mediterranean diet
MET	Metabolic equivalents of task
MLH-1	MutL Homolog 1
MRI	Magnetic resonance imaging
NAOS	*Nutrición, Actividad Física y Prevención de la Obesidad*

NOS	Newcastle-Ottawa Scale
NSAID	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PA	Physical activity
PET	Positron Emission Tomography
RR	Relative risk
SD	Standard deviation
SEER	Surveillance, Epidemiology, and the End Results
SENC	*Sociedad Española de Nutrición Comunitaria*
SSB	Sugar sweetened beverage
T2D	Type 2 diabetes
VAT	Visceral adipose tissue
WC	Waist circumference
WCRF/AICR	World Cancer Research Fund/American Institute for Cancer Research
WHO	World Health Organization

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I. Introduction

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I. INTRODUCTION

1. COLORECTAL CANCER

1.1. Definition

The term cancer defines a wide range of malignant tumors that might influence almost all organs and tissues of the body. It is principally a consequence of genetic mutations within a cell, which result in the proliferation of abnormal cells [1].

Colorectal cancer (CRC), often referred to as bowel cancer, is a type of lower gastrointestinal cancer that includes malignant tumors of the colon and rectum (colorectum) [23].

1.2. Anatomical subsites

Although CRC develops in a single organ, this type of cancer is a highly heterogeneous disease across anatomic location of the primary tumor [4]. The colorectum is anatomically divided into three segments: proximal colon (bowel segment from the cecum to the proximal two thirds of the transverse colon), distal colon (distal third of the transverse colon to the upper anal canal) and rectum. Because these three segments of the large intestine have different embryological origin, disparity in the incidence, pathogenesis, oncological pathways and outcome exists between the tumors developed [5–8]. In addition, variations in the gut microbiota of the colon and host characteristics may also influence on this heterogeneity across the tumor locations [9,10].

On the other hand, CRC risk factors differ by subsite in the large bowel suggesting that tumors in different anatomical locations might have distinct etiologies [8,11–13]. Recently, in the European Prospective Investigation into Cancer and Nutrition (EPIC) study (n=521,330 men and women; 14.9 years of follow-up), current smoking was associated with increased risk of proximal colon and rectal cancer, but not with distal colon cancer [12].

According to demographical factors, variable distribution of subsite specific CRC has been also described [8]. Proximal colon cancer is more prevalent in women [12], older individuals [14,15], and white and black individuals [168]. Distal colon cancer is more prevalent in men [17] and younger individuals [15], and rectal cancer in early-onset CRC (<50 years of age) [18] and Asian individuals [19,20].

1.3. Incidence and mortality

Globally, cancer causes one in eight deaths [21] and many countries have recorded a greater number of deaths from cancer than from cardiovascular disease (CVD) annually [22]. By 2030, the

global cancer burden is estimated to increase to 21.7 million new cases and 13 million deaths mainly owing to an ageing population [21].

In 2018, the International Agency for Research on Cancer (IARC) estimated approximately 18.1 million new cases and 9.6 million cancer deaths globally. CRC accounted for over 1.8 million new cases and 881,000 deaths. Worldwide, CRC is the third most incident cancer (10.2% of the total cases) and the second in terms of mortality (9.2%) for both sexes combined. By sex, CRC is the second most commonly diagnosed cancer in females (**Figure 1**) and the third among males (**Figure 2**) [23].

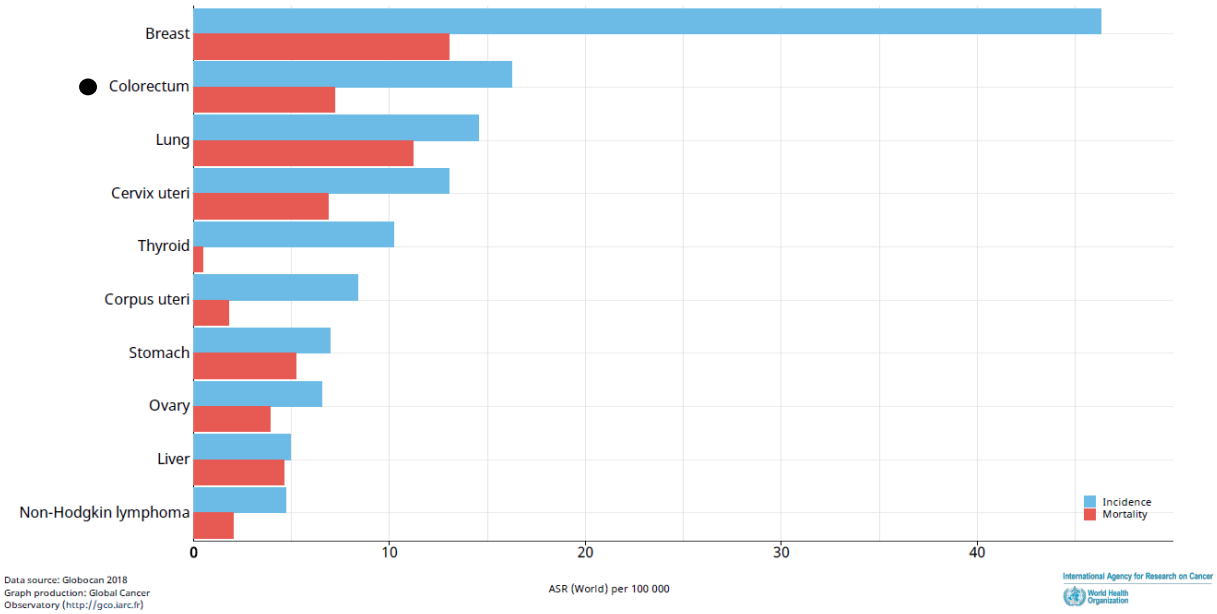

Figure 1. Estimated age-standardized incidence and mortality rates (worldwide) in 2018, females, all ages (per 100,000 inhabitants). Source: GLOBOCAN 2018.

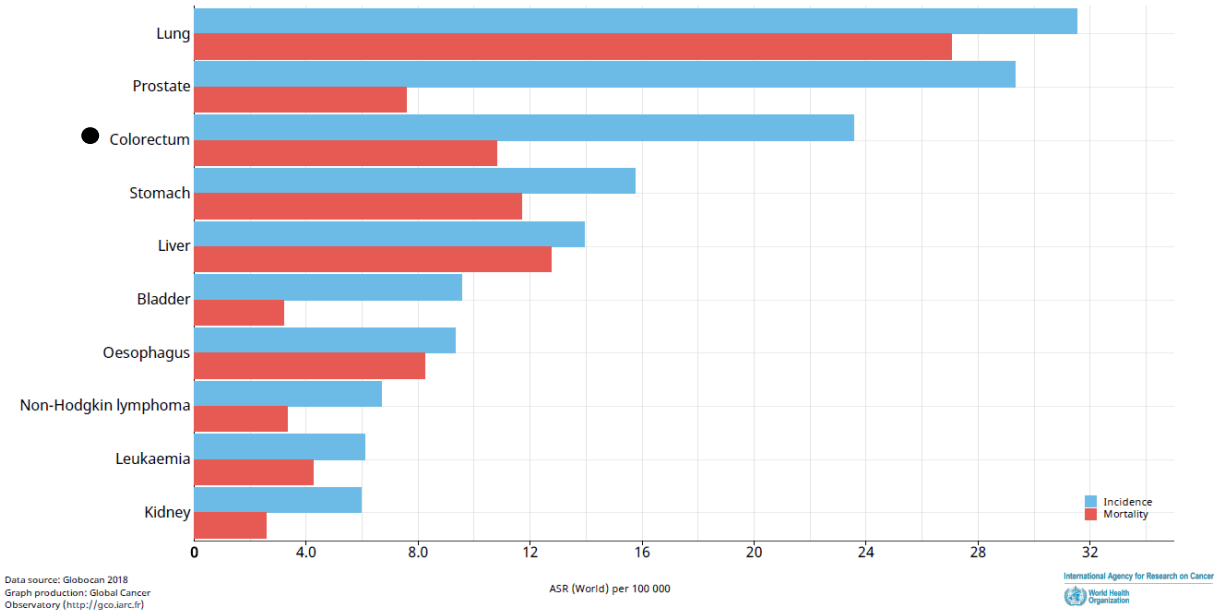

Figure 2. Estimated age-standardized incidence and mortality rates (worldwide) in 2018, males, all ages (per 100,000 inhabitants). Source: GLOBOCAN 2018.

Geographical trends

CRC incidence rates strongly vary around the globe being approximately 3-fold higher in economically developed countries than in transitioning countries [23]. For colon cancer, the highest incidence rates occur in some parts of Europe (Hungary, Slovenia, Slovakia, the Netherlands and Norway), Australia/New Zealand, North America, Eastern Asia (Japan, Republic of North Korea, and Singapore in women) and in Uruguay. Even though rectal cancer incidence rates have similar regional distribution as colon cancer, the highest incidences are found in the Republic of Korea among males, and in Macedonia among females. In the meantime, most regions of Africa and Southern Asia have the lowest incidence figures for both cancers [23].

However, increasing incidence rates do not always necessarily translate into increasing mortality statistics. In 2017, Arnold and collaborators [24] identified three CRC incidence and mortality tendencies connected with development levels. These global temporal patterns were: a) increasing incidence and mortality (many low- and middle-income countries comprising several Eastern European countries and in populations in Latin America and Asia); b) increasing incidence and decreasing mortality (several European countries, Canada and Singapore); and c) decreasing incidence and mortality (highly developed countries such as Australia, Iceland, New Zealand and Japan).

Taking all these into account, because CRC incidence rates have been linked with economic transition and Western lifestyles, this disease could be considered as a marker of socioeconomic development [24].

1.4. Physiopathology

Cancer appears as a consequence of mutations in somatic cells affecting critical genes involved in the regulation of cell proliferation and survival [25]. This is a multi-step process characterized by the acquisition of different biological capabilities (i.e. hallmarks of cancer). Furthermore, tumors contain stromal cells that contribute to the development and expression of certain hallmark capabilities [26].

More than 90% of CRCs are adenocarcinoma, which is a malignant neoplasm developed from glandular epithelial cells from the inner lining of the colon and rectum. Other rare types of CRCs include squamous cell carcinoma, adenosquamous carcinoma, spindle cell carcinoma and undifferentiated carcinoma [8,27].

Natural history of colorectal cancer

The natural history of CRC comprises four main stages (**Figure 3**) which are initiation, promotion, progression and metastasis [28]. Initiation is characterized by irreversible genetic damages that predispose affected cells to neoplastic transformation. Subsequently, the initiated cells proliferate inducing abnormal growth (neoplasm) during the promotion phase. In the progression stage, further genetic and epigenetic alterations are undergone conferring selective growth advantage to cells. In this stage, benign tumor cells transform into malignant cancer cells and obtain metastatic potential. Metastasis occurs because of dissemination of cancer cells from the primary organ to other organs and tissues through the bloodstream or the lymphatic system. The most common metastatic site is the liver, followed by the lung and bone.

The duration of each phase has wide ranges taking a long time since adenomas transform into cancer over 10-20 years. Of note, for hereditary CRC, progression through some of the stages can be faster [29,30].

Pathways of colorectal carcinogenesis

CRC is usually characterized by the proliferation of normal glandular epithelial cells of the colon and rectum into benign adenomatous polyps. The cell origin for most CRCs is currently assumed to be a stem cell or stem-cell-like cell (placed in the base of the colonic crypts) which are the product of progressive accumulation of genetic and epigenetic alterations that inactivate tumor-suppressor genes and activate oncogenes. Additionally cancer stem cells have been also proposed to be the seeds of metastases [31,32].

The polyp develops into an advance adenoma (clearly premalignant), afterwards into an invasive adenocarcinoma, and eventually metastatic cancer [3,33] (**Figure 3**). It is worth mentioning that, although all adenomas have the potential to become cancerous, less than 10% are estimated to progress to invasive cancer [34].

The aforementioned classic tumor progression model based on the adenoma-carcinoma sequence explains the majority of CRCs, and was first described by Fearon and Vogelstein in 1990 [35]. However, subsequent works have shown that CRC can arise through alternative carcinogenic pathways (**Figure 3**): a) the adenoma-carcinoma sequence [35] (85-90% of sporadic CRCs); b) the serrated pathway [36,37] (10-15% of sporadic CRCs); and c) the inflammatory pathway (<2% of all CRCs) [38].

Relative to genetic abnormalities produced in colorectal carcinogenesis, the adenoma-carcinoma sequence is mainly associated with the development of chromosomal instability (CIN)-positive subtype, which encompasses alteration in the chromosome number [8].

In the serrated pathway, B-Raf proto-oncogene (*BRAF*) mutation occurs as a critical early event inducing uncontrolled cell proliferation that contributes to the formation of hyperplastic polyp. Furthermore, CpG island methylation phenotype (CIMP) leads to epigenetic silencing of a considerable number of tumor-suppressing genes, including MutL Homolog 1 (*MLH1*), fostering progressions to sessile serrated adenoma and eventually cancer [8,36,37].

Unlike the other pathways, in the inflammatory pathway, dysplasia takes place in the background of chronic mucosal inflammation, frequently present in flat mucosa with multifocality [39]. In comparison to the general population, patients with inflammatory bowel disease, mainly ulcerative colitis, have 2.4-fold higher CRC risk [8,40]. In this pathway, *p53* mutations are an initial event and adenomatous polyposis coli (*APC*) mutations occur late in the carcinogenic process and are much less frequent [38].

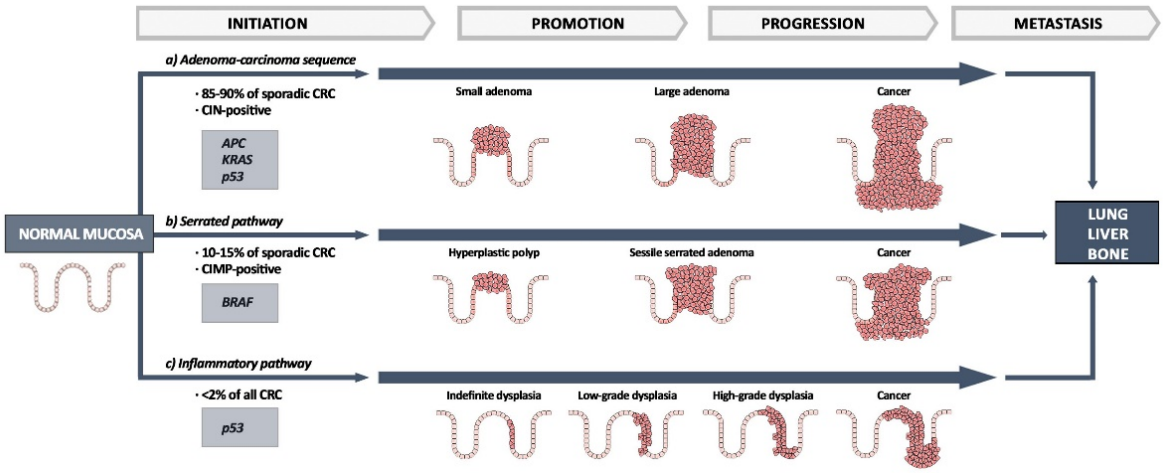

Figure 3. Pathways of colorectal carcinogenesis. Adapted from: Keum, et al. Nat Rev Gastroenterol Hepatol. 2019;16(12):713-732 [8].

2. RISK FACTORS FOR COLORECTAL CANCER

The etiology of CRC is multifactorial. Not only have genetic factors substantial effects on CRC development, but also lifestyle and environmental risk factors play a fundamental role on colorectal carcinogenesis [41]. This section comprises an extended review of both non-modifiable and modifiable risk factors which have been associated with the risk of developing CRC.

2.1. Non-modifiable risk factors

2.1.1. Sex

Concerning sex differences, men present higher incidence and mortality age-adjusted rates of CRC (1.4 and 1.5-fold difference, respectively) than women, at all anatomical subsites. This could be, in part, due to a combination of multiple factors. In comparison to females, males might exhibit greater vulnerability to environmental factors than by genetic factors, as well as increased exposure to such risk factors (e.g. cigarette smoking) [8,42]. Moreover, women might have better awareness and screening for CRC in comparison to men [16,43]. Also, it has been suggested that women might benefit from the potential protective effect of endogenous and exogenous hormones [8,44–46], albeit the existing research on this field remains inconclusive [43,46,47].

2.1.2. Age

Since CRC is an age-related disease, the risk of developing CRC increases with age. Worldwide, rates of CRC incidence and death increase quickly after 50 years old, with approximately 90% of

cases and deaths occurring after this age [8,48]. Nonetheless, although CRC is primarily diagnosed in elderly people, its incidence in younger individuals (<50 years old) has been increasing over the past decade, especially rectal cancer and left-sided colon cancer. In addition, this population have shown to develop advance-stage disease at diagnosis than those above 50 years of age [49–53].

2.1.3. Race/ethnicity

CRC burden varies considerably across race and ethnicity. Current statistics in the United States [53] have described the highest incidence and mortality rates in black individuals, followed closely by American Indians and Alaska Natives, and the lowest in Asian Americans/Pacific Islanders. These dissimilarities could reflect differences in socioeconomic status [54], prevalence of lifestyle factors associated with CRC risk [55], CRC screening [56] and treatment, as well as genetic factors [8,57,58].

2.1.4. Genetic risk factors

Most of the CRCs (c.a. 60-65%) appear sporadically through acquired somatic genetic and epigenetic aberrations, whereas the remaining 35-40% of cases are an inherited form of the disease [8]. The hereditary components of CRC are: a) family history of CRC (25%) [59,60]; b) hereditary cancer syndromes (5%) such as hereditary nonpolyposis CRC (HNPCC) also known as Lynch syndrome (2-4%) -though the two terms describe different, although overlapping diseases [61]- , or familial adenomatous polyposis (FAP) (<1%) [62,63]; c) common known but CRC low-penetrance genetic variations (<1%); and d) other inherited aberrations still remaining to be known.

In connection with family history, the degree and number of relatives affected with CRC, or their age at diagnosis affect the risk of developing CRC in those individuals with positive family history of the disease [60,64,65].

The most common form of hereditary CRC is Lynch syndrome which is characterized by a dominant pattern of heredity carrying germline genetic mutations in any of the DNA mismatch repair genes (*MLH1, MSH2, MSH6* and *PMS2*) [66]. Those individuals with the disease present about a 20% chance to develop CRC by age 50 years as well as higher risk of developing more than one type of cancer [67,68].

The second most common hereditary CRC syndrome is FAP. In the same way as Lynch syndrome, FAP is an autosomal dominant disease, albeit caused by germline mutations in the *APC* gene. FAP is characterized by the appearance of hundreds to thousands of pre-cancerous colorectal polyps throughout the large bowel and has a very early onset. It is noteworthy that, nearly 100% of patients with FAP develop CRC by after 40 years [68,69].

It should be pointed out that, CRC associated with heritably components is not completely hereditary because environmental factors also contribute to carcinogenesis [8,70].

2.1.5. Other non-modifiable risk factors

Scientific literature has described other high-risk factors increasing CRC risk [3,68]. Among these conditions are inflammatory bowel disease [40,71–73], abdominal radiation [74–76], cystic fibrosis [77], cholecystectomy [78,79], androgen deprivation therapy in men [80] and *Streptococcus bovis* Bacteremia [81,82].

2.2. Modifiable risk factors

Compelling evidence have confirmed the central role of modifiable risk factors in the development of CRC [70,83]. In the *Diet, nutrition, physical activity and colorectal cancer* report by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) [84], which is one of the many parts that make up the Continuous Update Project (CUP) Third Expert Report [85]; it was stated that there is strong evidence that being physically active decreases the risk of colon cancer, and that whole grains, foods containing dietary fiber, dairy products and calcium supplements are protective factors of this type of cancer. On the other hand, there is strong evidence that the consumption of red and processed meat, the intake of two or more alcoholic drinks per day, being overweight and obese and being tall increases the risk to develop CRC (**Figure 4**). Besides an ageing population and westernized dietary habits of high-income countries, other risk factors such as obesity, physical inactivity and smoking increase the risk of CRC development [86]. In the section that follows, a more complete description of the modifiable risk factors associated with CRC is detailed.

DIET, NUTRITION, PHYSICAL ACTIVITY AND COLORECTAL CANCER			
		DECREASES RISK	**INCREASES RISK**
STRONG EVIDENCE	**Convincing**	Physical activity	Processed meat Alcoholic drinks Body fatness Adult attained height
	Probable	Wholegrains Food containing dietary fiber Dairy products Calcium supplements	Red meat
LIMITED EVIDENCE	**Limited-suggestive**	Foods containing vitamin C Fish Vitamin D Multivitamin supplements	Low intakes of non-starchy vegetables Low intakes of fruits Foods containing heme iron
	Limited-no conclusion	Cereals (grains) and their products; potatoes; animal fat; poultry; shellfish and other seafood; fatty acid composition; cholesterol; dietary n-3 fatty acid from fish; legumes; garlic; non-dairy sources of calcium; foods containing added sugars; sugar (sucrose); coffee; tea; caffeine; carbohydrate; total fat; starch; glycemic load; glycemic index; folate; vitamin A; vitamin B6; vitamin E; selenium; fat; methionine; beta-carotene; alpha-carotene; lycopene; retinol; energy intake; meal frequency; dietary pattern	
STRONG EVIDENCE	**Substantial effect on risk unlikely**	-	

Figure 4. Summary of the evidence on diet, nutrition, physical activity and body fatness related to colorectal cancer risk according to the WCRF/AICR 2018. Adapted from: WCRF/AICR. CUP Expert Report 2018 [85].
Abbreviations: WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research; CUP, Continuous Update Project.

2.2.1. Body fatness

Incidence of obesity-related cancers [87–96] rises in parallel with the dramatic increase in the prevalence of overweight and obesity in many parts of the world [97]. Epidemiological studies support that excess adiposity measured by body mass index (BMI), waist circumference (WC) and waist-to-hip ratio is an established risk factor for CRC, and that this association is stronger for colon cancer than rectal cancer [97,98].

In a systematic review and meta-analysis of prospective observational studies [98], associations between BMI and CRC risk (risk ratio [95% CI] for 5 kg/m^2 increase in BMI) were significantly stronger in men (1.24 [1.21-1.28]; 1.09 [1.06-1.12]) than in women (1.09 [1.05-1.14]; 1.02 [0.99-1.04], for both colon and rectal cancer, respectively.

Along the same lines, a prospective cohort study within the frame of the Nurses' Health Study and Health Professionals Follow-up Study (23-24 years of follow-up) suggested that obesity is associated with less CRC risk in women than in men [99]. This could be explained because in comparison to women, men present higher susceptibility towards visceral obesity, which is associated with increased CRC risk than gluteofemoral adipose tissue distribution [100]. Moreover,

as previously described in this section, endogenous estrogens confer CRC risk protection. Thus, despite the excess adiposity of women in later life, its cancer-promoting effect through insulin and insulin-like growth factor 1 (IGF1) could be counterbalanced by the anticancer effect of estrogens [8].

It is noteworthy that, even though BMI (which reflects overall body fatness) and WC (which represents visceral adiposity) are measures of adiposity consistently associated with CRC risk, WC might be a stronger risk factor for CRC than BMI [99,101,102]. It has been suggested that visceral adipose tissue (VAT) may play an underlying role in linking excess adiposity to colorectal carcinogenesis. VAT secrets more proinflammatory adipokines [103] and is heavily infiltrated with immune cells such as macrophages [104], hence contributing to the development of low-grade chronic systemic inflammation and related insulin resistance (IR) [105,106]. This inflammatory state in the tumor microenvironment may promote tumor growth and progression [8].

In view of the above and considering that an imbalance between food intake and energy expenditure leads to an excessive accumulation of adipose tissue, the patterns of altered levels of adipokine among obese subjects may be considered as predictive of CRC risk. Therefore, measures to prevent obesity could be protective against both chronic diseases and cancer [107].

2.2.2. Insulin resistance and diabetes

High energy intake in Western diets together with physical inactivity has been related to increased prevalence of obesity. As commented in the previous section, obese people develop IR and subsequent hyperinsulinemia. This metabolic condition leads to reduced synthesis of insulin-like growth factor binding protein (IGFBP) 1 in the liver, and probably also decreases its synthesis locally in other tissues. In addition, increased fasting insulin levels have been also related with reduced levels of IGFBP2 in the blood. This results in augmented amount of free IGF1 which alongside insulin has been proposed to promote colorectal carcinogenesis. The insulin-IGF1 signaling pathway, through activation of insulin and IGF-1 receptors, has been suggested to promote colorectal carcinogenesis by increasing cell proliferation and reducing apoptosis of the intestinal mucosa [8,107–109].

Regarding type 2 diabetes (T2D), this metabolic condition is associated with IR, and in most cases with compensatory hyperinsulinemia. Increasing evidence suggest that those individuals with T2D have an increased risk of CRC than non-diabetic people [110,111]. In a systematic review and meta-analysis of cohort studies in China, it was reported that individuals with T2D may have 27% higher risk of CRC than non-diabetic individuals (summary relative risk (RR) [95% confidence interval (CI)] = 1.27 [1.21-1.34], *P* value= 0.002, I^2= 48.4%) [110]. Similarly, another meta-analysis of cohort studies found a statistically significant positive correlation between T2D and

CRC risk (summary RRs [95% CI] = 1.21 [1.02-1.42]) albeit with significant heterogeneity between studies (I^2= 96%) [111].

Therefore, though the relationship between IR and CRC risk has been shown to be consistent, further longitudinal studies evaluating CRC risk associated with T2D are warranted. Since the literature on this topic is inconclusive, it is of great importance to continue to investigate the role of T2D in CRC preventive behaviors [112], as well as to elucidate CRC subsite and gender differences in this association.

2.2.3. Physical activity

According to the latest evidence published by the WCRF/AICR [84], physical activity (PA) of all types (occupational, household, transport and recreational) convincingly decreases the risk of colon cancer (**Figure 4**) although no conclusion was drawn for rectal cancer.

Of note, CRC cancer and, especially colon cancer, is one of few cancers together with breast cancer for which lack of PA has been recognized as a risk factor. In 2018, an umbrella review (19 reviews, 26 meta-analyses and 541 original studies) analyzing the associations between PA and several cancer sites reported that recreational PA was associated with a 21% reduction in the risk of colon cancer (RR [95% CI] = 0.79 [0.71-0.86]) with strong grade of evidence. [113].

Even though the optimal intensity and dose of PA to prevent CRC has not been yet defined. Both the World Health Organization (WHO) and the American Cancer Society advise adults to engage in at least 150 min. of moderate-intensity aerobic PA (3-5.9 metabolic equivalents of task (MET)) or at least 75 min. of vigorous-intensity PA (≥6 METs), or an equivalent combination of the two throughout the week (of note, 2 min. of moderate intensity activity = 1 min. of vigorous intensity activity) [114–116].

2.2.4. Dietary patterns

Because foods and nutrients are not consumed in isolation, it has been suggested that dietary patterns might thus be more predictive of disease risk and mortality than foods or nutrients independently. Hence, nutritional epidemiology has shifted its focus from individual nutrients or specific foods to overall dietary patterns. On that basis, a dietary pattern could decrease or increase CRC risk by the combined effect of its components [8,117]. Moreover, some dietary indexes such as the dietary inflammatory index (DII®) have gained much attention since they offer a tool for measuring the inflammatory potential and quality of individuals' diets [118].

Generally, the 'healthy' dietary patterns, such as the prudent or Mediterranean dietary pattern, mainly characterized by high consumption of fruits and vegetables, wholegrains, nuts and legumes, virgin olive oil, fish and other seafood, moderate intake of dairy products and red wine,

and low in meat, processed meat and sugar drinks, appears to be protective against colorectal adenoma and cancer incidence. On the other hand, the 'unhealthy' dietary patterns, such as the Western dietary pattern, which are based on high consumption of red and processed meat, sugar-sweetened beverages (SSBs), refined grains, desserts and potatoes have been associated with higher risk of CRC [118–121]. Notwithstanding, even though the most convincing evidences show a potential role of overall diet in certain cancers, evidence is not conclusive and may be driven or mediated by lifestyle factors [119].

In their last report, the WCRF/AICR judged that evidence for the associations between dietary patterns and CRC is limited and no conclusion was drawn [84] (**Figure 4**). However, subsequent meta-analytical evidence support that *a priori* dietary patterns such as the Dietary Approaches to Stop Hypertension (DASH) diet [122] might be associated with decreased CRC risk (RR [95% CI] = 0.80 [0.74-0.85]) whereas another dietary pattern characterized by a combination of pro-inflammatory foods might increase the risk of CRC (RR [95% CI] = 1.43 [1.25-1.63]) [123].

In light of this, the identification of potential associations of the overall whole diet with CRC development might provide valuable understandings for the definition of dietary guidelines as a way to prevent CRC [118]. However, since there are few studies evaluating the associations between dietary patterns and CRC and they show inconclusive results, further prospective research on this field is needed.

2.2.5. Foods

Concerning individual foods, in the CUP Expert Report 2018 [84] it was concluded that convincing evidence has been achieved that consumption of whole grains, foods containing dietary fiber and dairy products decreases CRC risk, whilst consumption of red and processed meat and alcoholic drinks intake is associated with an increased risk of developing CRC. Findings for other dietary components comprising cereals and their products, potatoes, shellfish and other seafood, poultry, legumes, foods containing added sugars, among other foodstuffs, are still controversial and no conclusion was drawn (**Figure 4**).

Red and processed meat

In 2018, the CUP Panel judged that consumption of red meat is probably a cause of CRC (**Figure 4**) [84]. Red meat consumption can influence CRC risk through different potential carcinogenic compounds. On the one hand, heme iron which is present at high levels in red meat has exhibited to promote colorectal carcinogenesis by inducing formation of endogenous carcinogenic N-nitroso compound [124–126]. On the other hand, heterocyclic amines and polycyclic aromatic hydrocarbons formed when meats are cooked at high temperatures have been shown to increase CRC risk in experimental studies [127–129].

Concerning processed meat, there is stronger evidence to consider that its consumption is a convincing cause of CRC. Similar to red meat, processed meat is rich in heme iron and protein which can promote tumorigenesis via the same mechanism such as those described above [127]. In addition, processed meat is characterized by higher fat content than red meat, which may stimulate CRC through production of secondary bile acids, although human studies supporting this hypothesis are weak. Also, processed exogenous N-nitroso compounds from processed meat, are thought to increase CRC risk [8,125,126,129].

In 2018, a meta-analysis of prospective studies by Schwingshackl and co-workers [130] found that each 100 g/day increase in red meat consumption was associated with a 12% higher risk of CRC (RR [95% CI] = 1.12 [1.06-1.19]; n=21), whereas a 50 g/d increment in processed meat intake was related with 17% augmented CRC risk (RR [95% CI] = 1.17 [1.10-1.23]; n=16). In the same line, in a later systematic review and meta-analyses of 29 prospective cohort studies evaluating the relationship between CRC incidence and processed meat consumption, the association for CRC (Hazard Ratio $(HR)_{50\ g/d}$ [95% CI] = 1.15 [1.06-1.24]) and for colon cancer risk ($HR_{50\ g/d}$ [95% CI] = 1.25 [1.15-1.37]) was similar. However, processed meat intake was not significantly related with rectal cancer risk when comparing high versus low intake in either women or men (HR [95% CI] = 1.21 [0.98-1.49]) [131].

Foods containing dietary fiber

In the last CUP report, it was concluded that the consumption of foods containing dietary fiber probably protects against CRC [84] (**Figure 4**).

There are some physical mechanisms and prebiotic effects that may explain the anticarcinogenic role of dietary fiber against colorectal carcinogenesis [132]. Dietary fiber is fermented within the bowel, forming short-chain fatty acids such as butyrate, which has been shown to have anti-proliferative effects in experimental studies. Other mechanisms by which greater dietary fiber intake may lower CRC risk comprise the reduction of the intestinal transit time and increased fecal bulk, which could reduce the duration of exposure for potential fecal mutagens to interact with the intestinal epithelium, and a reduction of secondary bile acid production [133,134]. High-fiber diets may also reduce IR, which is a risk factor for CRC and other types of cancer [135].

Recently, a meta-analysis including 11 prospective cohort studies [136] demonstrated that individuals with the smallest intake of dietary fiber have a 21% and 14% higher risk of distal colon cancer (RR [95% CI] = 0.79 [0.71-0.87]) and proximal colon cancer (RR [95% CI] = 0.86 [0.78-0.95]), respectively, in comparison to those with the highest intake. In the same line, another meta-analysis of cohort and case-control studies by Gianfredi [137] found a 26% reduction in colon cancer risk (95% CI = 0.67-0.82) after comparing highest versus the lowest dietary fiber intake, although moderate statistical heterogeneity was detected. For rectal cancer, current meta-

analytical evidence [132] suggests a 22% risk reduction of CRC linked to dietary fiber intake (RR [95% CI] = 0.77 [0.66-0.89]) after evaluating a total of 2,876,136 subjects. However, this result should be taken cautiously since there was moderate heterogeneity between the included studies (I^2= 59.11%).

Taken together, evidences and strong mechanistic plausibility suggest that dietary fiber intake might play a protective role against CRC. Nonetheless, epidemiological evidence has shown controversial results mainly due to heterogeneity between study designs, fiber sources, among others. Additionally, most studies report data on overall CRC, which represents a difficulty to evaluate the associations with dietary fiber intake for colon and rectum separately. Therefore, further prospective studies should be undertaken in this area in order to overcome these challenges.

Alcoholic drinks

Ethanol in alcoholic drinks is a convincing cause of CRC based on evidence for intakes above 30 g/day, which is equivalent about two drinks a day (**Figure 4**). Also, there is robust evidence for mechanisms operating in humans [84]. This association is stronger in men than in women probably due to hormone-related variations in alcohol metabolism and higher alcoholic drink intakes and under-reporting of alcohol consumption in men [68,138,139]. Concerning levels of alcohol consumption, it has been suggested that there is a J-shaped association between alcohol consumption and CRC risk [140]. In comparison to non-/occasional drinking, light/moderate drinking (up to 2 drinks/day) was related with a 8% decreased CRC, heavy drinking (2-3 drinks/day) was not significantly associated with the risk of developing CRC, and very heavy drinking (>3 drinks/day) was associated with 25% significant increased CRC risk [140].

Ethanol reaches colonocytes probably through the systemic circulation and probably diffuses into lumen, which is metabolized by microbial alcohol dehydrogenase into acetaldehyde. This last metabolite can cause injury to the intestinal mucosa and regenerative cellular proliferation. On the other hand, intracellular acetaldehyde may foster colorectal carcinogenesis by causing DNA damage and destroying intracellular folate [8,141–143].

2.2.6. Other modifiable risk factors

In addition to diet, nutrition and PA, outlined above, other recognized risk factors comprising smoking and some medications can affect the risk of developing CRC [144]. Smoking 40 cigarettes/day (2 packs) increased CRC risk about 40% and virtually doubled the risk of CRC mortality [145]. Smoking may affect differentially by anatomic subsites predisposing more towards proximal colon and rectal cancer [12,68]. Furthermore, it has been shown that long-term use (≥5 years) of at least 75 mg. daily of aspirin can lower incidence and mortality due to CRC [146].

Nonetheless, since non-steroidal anti-inflammatory drugs (NSAIDs) are associated with greater risk of gastrointestinal bleeding and heart attack, its consumption for preventing CRC is not recommended in the general population [12]. Also, hormone therapy in postmenopausal women has been shown to decrease the risk of CRC [147].

3. A FOCUS ON DAIRY PRODUCT CONSUMPTION AND HEALTHY LIFESTYLE PATTERNS AS DETERMINANTS OF CRC INCIDENCE IN ELDERLY INDIVIDUALS AT HIGH CARDIOVASCULAR RISK

Based on the evidence reported above, the present doctoral thesis focuses specifically on the association between healthy lifestyle patterns in general, and dairy product consumption in particular, and their relationship with CRC risk. Hence, a more detailed literature review on these topics are given in the following section.

3.1. Dairy products

3.1.1. Definition of dairy products

In the Spanish Food Code [148], the definition of dairy products and their different subtypes comprises those foods derived from milk, not altered or adulterated, without colostrum and hygienically extracted from milking healthy and well-fed domestic mammal females. Moreover, dairy product subtypes (cream, butter, cheeses and melted cheeses, fermented dairy, dairy serums, casein and curd) are those products obtained from milk through appropriate technological treatments.

In the present doctoral thesis, the Spanish Food Code definition of dairy products was followed in Chapters 1 and 2. However, because Chapter 3 is based on a meta-analysis comprising other papers investigating the associations between dairy product consumption and CRC risk, the dairy product category considered in each paper was used.

3.1.2. Nutritional composition of dairy products

Dairy products contain a unique nutrient package that contribute significantly to meet the nutritional requirements for protein, calcium, magnesium, phosphorus, potassium, zinc, selenium, vitamin A, riboflavin, vitamin B12 and pantothenic acid. Additionally, since dairy products have a high-water content, this food group has relatively low energy density. Furthermore, milk and other dairy products are one of the best sources of dietary calcium since they offer a high calcium bioavailability as well as a high calcium content. It is proposed that this

nutritional composition is difficult to meet in diets that eliminate dairy product consumption for any reason (for instance, vegan diets). It is also noteworthy that many beneficial effects of dairy products on health outcomes are likely to be linked with the interaction between these nutrients rather than to the action of each nutrient separately [149–152].

3.1.3. Dietary recommendations and dairy products

In most dietary guidelines from different countries, the consumption of dairy products is encouraged, especially of milk, yogurt and cheese. However, these guidelines do not give specific recommendations on the type and amount of dairy product consumption [153–155].

In Spain, different Scientific Societies and Foundations have published several dietary guidelines mainly based on the traditional Mediterranean diet (MedDiet). The *Fundación Dieta Mediterránea* recommends the consumption of 2 servings per day of low-fat fermented dairy products, specially yogurt and cheese from sheep and goat, as they are considered typical foods in the Mediterranean countries [156]. For their part, the *Iberoamerican Nutrition Foundation* (FINUT) [157] and the *Agencia Española de Consumo, Seguridad Alimentaria y Nutrición* (AECOSAN) recommend a daily consumption of dairy products such as milk, yogurt and cheese. The AECOSAN recommendation is based on the food pyramid from the Spanish Strategy *Nutrición, Actividad Física y Prevención de la Obesidad* (NAOS), the objective of which is to prevent obesity [158]. Lastly, the *Sociedad Española de Nutrición Comunitaria* (SENC) recommends the consumption of 2 to 3 servings of low-fat dairy products (cheese, yogurt and brick milk) daily [159].

With regard to dairy fat content, most current dietary guidelines advocate the consumption of fat-free or low-fat dairy products in the context of a healthy diet to prevent chronic diseases [153,155,160,161]. However, the scientific rationale behind this recommendation is still under debate [152,162]. Prospective cohort evidence has shown no association between the consumption of full-fat dairy products and either the risk of CRC [163,164] or a significant reduction in the risk [165]. Thus, further research on the association between the consumption of milk foods and the risk of CRC should be of considerable interest in terms of public health.

3.1.4. Dairy products consumption and colorectal cancer risk

As mentioned before, adherence to a healthy dietary pattern has shown to be essential for the primary prevention of CRC. According to this, a study which is part of the Global Burden of Diseases, Injuries, and Risk Factors Study [166] analyzing data from 195 countries concluded that certain dietary risk factors account for a larger burden of CRC than smoking or alcohol intake globally.

In 2018, the WCRF CUP [144] reviewed the very latest accumulated evidence from around the world from cohort studies and randomized controlled trials on diet, nutrition, adiposity, and PA and their

relationship with CRC. Despite the consumption of specific foods such as processed meat increases the risk of CRC with convincing evidence, further research is needed in order to increase evidence for other food groups such as dairy products.

The traditional Mediterranean dietary pattern, which has been previously mentioned, is characterized by a moderate intake of dairy products (principally cheese and yogurt). MedDiet adherence has been related to a reduction in the risk of CRC [167]. According to the WCRF/AICR, the evidence suggesting a protective role of dairy products (total dairy, milk, cheese and dietary calcium intake) consumption against CRC was judged as probable (strong evidence) [144] (**Figure 4**).

Case-control studies investigating the link between dairy product consumption and CRC risk has shown inconsistent results [168,169,178,170–177]. However, prospective cohort studies have consistently reported lower risk of CRC associated with higher consumptions of dairy products, especially milk [165,179–186]. In the same line, the most current systematic reviews and meta-analyses of prospective studies comprising updated high-quality works with many cases have reported that total dairy product or milk consumption is inversely associated with CRC risk [130,187].

In 2017, Vieira and collaborators carried out a systematic-review and meta-analysis of prospective studies [187] in order to update the evidence of the WCRF/AICR CUP. In the dose-response meta-analysis of this work, a significant inverse relationship between the consumption of total dairy products and milk and the risk of CRC incidence was found. For each 400 g/day increase in the intake of dairy products, CRC risk decreased by 13% (RR [95% CI] = 0.87 [0.83-0.90]; I^2=18%; n=10) whilst no association was observed with rectal cancer. For milk consumption, an increase of 200 g/day was associated with a decreased risk of CRC (RR [95% CI] = 0.94 [0.92-0.96]; I^2=0%; n=9), colon cancer (RR [95% CI] = 0.93 [0.90-0.96]; I^2=30%; n=9) and rectal cancer (RR [95% CI] = 0.94 [0.91-0.97]; I^2=0%; n=7). The inverse associations found in the case of milk intake with CRC and colon cancer were significant in men, but not in women, whereas for rectal cancer, the inverse association was significant only in women. The consumption of 50 g/day of cheese was not significantly associated with the risk of developing CRC (RR [95% CI] = 0.94 [0.87-1.02]; I^2=10%; n=7) or colon cancer (RR [95% CI] = 0.91 [0.80-1.03]; I^2=19%; n=6), and the association for rectal cancer was marginally significant (RR [95% CI] = 0.95 [0.90-1.00]; I^2=0%; n=4).

Schwingshackl and co-workers [130] led a systematic search for prospective studies evaluating the association between 12 food groups, including dairy products, and CRC risk. These authors observed an inverse association (RR [95% CI] = 0.83 [0.76-0.89]; I^2=61%; n=18) after comparing the highest versus the lowest intake category of dairy (overall intake range: 0-1,710 g/day). For each additional daily 200 g intake of dairy products, a 7% decrease in CRC risk was

observed (RR [95% CI] = 0.93 [0.91-0.94]; I^2=0%; n=15). In secondary analyses, both low and high-fat dairy product intakes were inversely associated with CRC risk.

3.2. Healthy lifestyle patterns

As discussed above, both diet quality and other environmental factors have been shown to have an important role in the development of chronic diseases. According to this, several *a priori* defined food groups and general index-based dietary patterns have been related with lower CRC risk, supporting the hypothesis that high overall diet quality might decrease the risk of CRC [188–190].

Considering that not only diet quality influences the risk of developing CRC, but also other environmental factors different from diet as well, healthy lifestyle indices have emerged to gain new insight into the development of CRC. Lifestyle scores generated a priori according to current scientific knowledge allow us to examine the potential combined effect of the individual score components on the incidence of different diseases. Previous work on CRC nutritional epidemiology has been mainly focused on the WCRF/AICR score [191]. However, very little is known about other lifestyle indices and their association with this cancer.

3.2.1. World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) score

In 2018, the WCRF/AICR launched the *Diet, Nutrition, Physical Activity, and Cancer: A Global Perspective, the WCRF/AICR Third Expert Report* [85]. This report comprises 10 cancer prevention recommendations, which represent a package of healthy lifestyle behaviors comprising following a healthy diet, maintaining a healthy body weight, and engaging in regular PA.

Following the latest cancer-specific recommendations from the WCRF/AICR, the 2018 WCRF/AICR score was developed with the purpose of establishing a simple, standardized scoring system for researches to quantify adherence to the recommendations and to assess its impact on cancer risk as well as with other health-related outcomes [192].

WCRF/AICR score and CRC risk

Some prospective cohort [191,193–198] and case-control [199–201] studies have investigated the associations between CRC risk and adherence to cancer-specific nutritional recommendations based on the WCRF/AICR score with inconsistent results. In addition, there was no unified method to assess the adherence to the former recommendations. Thus, each study developed their own scoring system which makes comparisons between studies difficult [192]. On the other hand, limited longitudinal studies [198,201] have been conducted to assess associations based on the updated 2018 WCRF/AICR recommendations.

In a systematic literature review and meta-analysis published in 2020 [202], including 38 articles (17 prospective, 8 case-control and 13 cross-sectional), the association between adherence to the 2007 WCRF/AICR score and health outcomes has been investigated. It was found that each 1-point increment in the score was significantly associated with a 14% decrease in CRC risk (RR [95% CI] = 0.86 [0.82-0.89]; n=10). Importantly, the authors concluded that primary prevention of CRC should emphasize modification of modifiable lifestyle factors, and that future studies examining the updated 2018 WCRF/AICR guidelines will further clarify such associations [202].

In 2020, Shams-White and co-workers published a commentary in *the Cancer Epidemiology, Biomarkers & Prevention* journal strongly encouraging researchers to use the standardized score to improve comparability across populations and countries. Also, the authors suggested that articles based on this score should provide detailed descriptions of the methodology in order to promote transparency and reproducibility [192].

3.2.2. Low-risk lifestyle score

The low-risk lifestyle (LRL) score is another lifestyle score including five modifiable lifestyle factors (smoking status, alcohol consumption, PA, diet and BMI). In the context of the Nurses' Health Study and the Health Professionals Follow-up Study, a consistent significant inverse association between the LRL score and all-cause mortality, including cancer and CVD mortality, and with CVD incidence was reported [203].

This prospective analysis by Li included 11,527 participants with T2D diagnosed during follow-up who were free of CVD and cancer at the time of diabetes diagnosis (follow-up period of 13.3 years). The multivariate-adjusted HRs for those participants having ≥3 low-risk lifestyle factors compared with none were (HR [95% CI] = 0.48 [0.40-0.59]) for total CVD incidence, (HR [95% CI] = 0.53 [0.42-0.66]) for incidence of coronary heart disease, (HR [95% CI] = 0.33 [0.21-0.51]) for stroke incidence, and (HR [95% CI] = 0.32 [0.22-0.47]) for CVD mortality (all p-trend<0.001) [203].

Recently, this index has been also related with an increased healthy life expectancy free of T2D, CVD and cancer [204]. However, information regarding this score with cancer incidence is lacking [203,205].

4. COLORECTAL CANCER CLINICAL FEATURES AND DIAGNOSIS

4.1. Presenting symptoms

CRC is principally an asymptomatic disease until it reaches and advance stage. That is why, screening is so important. Patients with this cancer can present a wide range of signs and symptoms such as occult or obvious rectal bleeding, changes in bowel habits, anemia or abdominal pain which vary according the anatomic location of the tumor [12,86,206].

Cancers rising in the cecum and ascending colon might become quite large without resulting in any obstructive symptoms or noticeable alterations in bowel habits because stool is rather liquid as it passes through the ileocecal valve into the right colon. Lesions on the right colon usually cause ulcerations leading to insidious blood loss without a change in the appearance of the stools. Consequently, common symptoms in these patients are fatigue, palpitations or even angina pectoris. Moreover, they can present hypochromic, microcytic anemia due to iron deficiency. Tumors arising in the transverse and descending colon tend to impede the passage of stool which is more formed. Thus, the symptoms when tumors arise in this area are abdominal cramping, occasional obstruction and even perforation. When tumors arise in the rectosigmoid are frequently associated with hematochezia, tenesmus and narrowing of the caliber of stool whilst anemia is an infrequent finding [12,86,206].

4.2. Diagnosis

- **Endoscopy:** Colonoscopy is the method of choice to diagnose CRC. In order to ensure detection, lesions (tumors or polyps) require careful and complete inspection of the mucosa as well as an optimal preparation of the bowel [86,207,208].
- **Imaging:** Imaging techniques are used as a complementary tool for diagnosis although these methods are mostly employed for locoregional and distant staging. For instance, computed tomography (CT) colonography is used after incomplete or inadequate colonoscopy. For rectal cancer, locoregional staging is normally done by magnetic resonance imaging (MRI). Other technics such as Positron Emission Tomography (PET)-CT imaging are also being used although its exact role for staging and assessment of disease burden in advanced stages is still discussed [86,209–211].
- **Laboratory:** On the other hand, all guidelines recommend not only obtaining a complete blood count but also checking carcinoembryonic antigen concentrations at the time of diagnosis. Elevated carcinoembryonic antigen levels at baseline is related with worse prognosis. This laboratory tool also might indicate residual disease when concentrations of this antigen do not normalize in the postoperative phase [86,212].

- **Pathology:** In order to determine pathological staging and subsequent management, histology is still the basis. In addition to the classic TNM (T: depth of tumor penetration, N: presence of lymph node involvement, and M: presence or absence of distant metastases) staging, histological subtyping, grading and histological assessment of lymphatic, perineural, and venous invasion, the value of a large number of tumor-based markers is increasingly being recognized [86,211,213–215].

5. TREATMENT

- **Endoscopic treatment:** Some early CRCs are amenable to local treatment only. Therefore, immediately following the diagnosis, malignant polyps might be resected endoscopically. Of note, endoscopic resection is a feasible option for many large polyps and T1 cancers [86].
- **Surgical treatment:** Surgery is the cornerstone of curative intent treatment when a malignant lesion is detected in the large bowel. Moreover, quality of CRC resection is crucial and can be assessed with objective parameters. Before surgical treatment, an evaluation for the presence of metastatic disease should be undertaken. In the case of rectal cancer, surgery is more complicated due to the accessibility and intricate anatomy of the pelvis [386].
- **Radiotherapy for rectal cancers:** Preoperative radiation therapy to the pelvis is recommended for patients with rectal cancer because it lessens the risk of local recurrence [216]. The absolute risk decrease that is achieved with this treatment option depends on the tumor stage and quality of the surgery [386].
- **Local treatments for metastatic disease:** Due to technical innovations, there is an increasing number of local therapies, such as resection of liver metastases [217], to treat stage IV CRCs which aim to control and possible cure at long-term disease. Even though randomized trials have not demonstrated the worth of eradicating restricted metastatic tumors, this option is generally accepted. It should be noted that, local treatment of lung metastases is more controversial and peritoneal metastases have long been considered as an untreatable condition [86].
- **Systemic treatment:** Systemic therapy for patients with CRC has become more effective being 5-fluorouracil (5-FU) the backbone of treatment for CRC. 5-FU is normally administered intravenously but can be also given orally in the form of capecitabine with apparently similar efficacy. In patients with advanced CRC, concomitant administration of other drugs such as folinic acid has been shown to improve 5-FU efficacy. In addition, monoclonal antibodies are also effective in these patients. For rectal cancer, preoperative or postoperative combined

therapy (5-FU or capecitabine plus radiotherapy) decreases the risk of recurrence and increments the probability of cure in patients with stage II and III tumors [3].

6. PROGNOSIS

The prognosis (prediction of disease outcome) for individuals having CRC is related to the extent to which cancer has spread at the time of diagnosis which is described as its stage. The two most common cancer-staging systems are the TNM system and the Surveillance, Epidemiology, and the End Results (SEER) summary staging system. The TNM system is used in clinical settings whereas the SEER summary staging system is employed for descriptive and statistical analyses of tumor registry data (**Table 1**)[32].

Table 1. Summary of the stages of CRC according the TNM system and the SEER summary staging system [32]

		Staging	Characteristics
Cancer staging system	TNM	*In situ*	Cancers that have not yet begun to invade the wall of the colon or rectum (preinvasive lesions).
		Local	Cancers that have grown into the wall of the colon or rectum but have not extended through the wall to invade nearby tissues.
		Regional	Cancers that have spread through the wall of the colon or rectum and have invaded nearby tissue, or that have spread to nearby lymph nodes.
		Distant	Cancers that have spread to other parts of the body such as the liver or lung.
	SEER	*Stage I* (T1-2N0M0)	- Superficial lesions that do not involve regional lymph nodes and do not penetrate through the submucosa (T1) or the muscularis (T2). - 5-year survival >95% for T1 and >90% for T2.
		Stage II (T3-4N0M0)	- Tumors that penetrate through the muscularis (T3) but have not spread to lymph nodes. - 5-year survival: 70-85%
		Stage III (TXN1-2M0)	- Regional lymph node involvement (N1: 1-3 lymph node metastases, N2: ≥4 lymph node metastases). - 5-year survival is 50-70% for N1 and 25-60% for N2.
		Stage IV (TXNXM1)	- Metastatic spread to distant sites such as liver, lung or bone. - 5-year survival <5%

Abbreviations: SEER, Surveillance, Epidemiology, and the End Results.

Most recurrences of CRC occur during the first 4 years after surgical resection of large-bowel cancer. Thus, 5-year survival is a reliable indicator of cure. The likelihood of 5-year survival in patients with CRC is stage-related. The number of involved lymph nodes might more precisely judge prognosis. Other predictors of poorer outcomes immediately after total surgical CRC resection comprise: a) tumor penetration through the bowel wall; b) poorly differentiated histology; c) perforation and/or tumor adherence to adjacent organs; d) venous invasion; e) preoperative elevation of carcinoembryonic antigen titer (>5 ng/ml); f) specific chromosomal

deletion (in example, mutation in the *BRAF* gene); and g) right-sided location of the primary tumor. However, despite the growing number of scientific literature evaluating a multitude of prognostic factors, pathologic stage of diagnosis remains the best predictor of long-term prognosis [32].

7. PREVENTION

7.1. Primary prevention

In accordance with the abovementioned evidence, accumulating literature suggests that smoking cessation, following a healthy diet, maintaining a healthy weight and engaging in regular PA can prevent CRC. Additionally, the intake of some medications such as aspirin and other NSAIDs has been related to less risk of developing CRC [146,218]. However, because of potential harms (e.g., gastrointestinal bleeding) its intake is not recommended to the general population for preventing CRC. Probably, there is a role for aspirin and NSAIDs intake as primary prevention in those individuals presenting defined hereditary predisposition such as Lynch syndrome and polyposis [69,86]. In addition, hormone replacement therapy in women is also associated with reduced risk for CRC [219].

On the other hand, regular use of multivitamin [220,221], calcium [222] and vitamin D [223] supplements has been associated with reduced risk of CRC. However, despite biological plausible mechanisms working in humans, the WCRF/AICR judged that evidence for a decrease in CRC risk was limited for multivitamin and vitamin D supplement intake, whilst evidence for calcium supplements intake was concluded to be probable [84].

7.2. Secondary prevention

Screening can reduce CRC risk and mortality because allows removal of precancerous lesions or early detection and treatment of CRC [224]. Such screening programs are particularly important for individuals with a family history of the disease in first-degree relatives. There are some screening strategies for CRC available: digital rectal examination, stool testing (occult blood, fecal DNA), imaging (contrast barium enema, virtual colonography), and endoscopy (flexible sigmoidoscopy and colonoscopy) [3]. Of note, there is high degree of heterogeneity in CRC screening among countries and professional organizations [8]. In Spain, after introduction of screening programs, CRC mortality rates became plateaued, although CRC incidence rates continued to increase [248].

7.3. Tertiary prevention

After treatment for CRC, several factors have been related to improved outcomes and decreased risk of CRC-related death. These factors are largely the same as the factors for primary prevention

such as following a healthy lifestyle and regular use of aspirin and other NSAIDs. Because most studies on this field are observational, further randomized trials are needed in order to establish recommendations [24].

Taking all the above into account, possibly, scoring systems based on individual risk calculation models including genetic and environmental factors along with family history of CRC might be useful to develop individualized CRC prevention strategies [86,225].

II. Rationale

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II. RATIONALE

As stated in the previous section, CRC is a central health problem since it is the second most common cause of cancer death in both sexes worldwide. On the one hand, CRC is linked with reduced life quality and expectancy. On the other hand, as a chronic disease, CRC have significant economic healthcare costs. It should be emphasized that, the global burden of CRC is expected to continue increasing, not only due to the growth of the aging population, but also because of the adoption of westernized dietary and lifestyle patterns. Thus, it is of great importance to address this issue in order to increase scientific evidence on CRC prevention that serves as the basis for directing effective public health strategies.

There is a large body of consistent evidence highlighting the importance of the impact of some foods, such as red and processed meats and alcohol intake, on the risk of CRC incidence. However, evidences on CRC incidence associated with the consumption of other foods such as dairy products, which are widely consumed in the Mediterranean countries, are less strong. Importantly, most of the literature on this topic does not consider different dairy subtypes bearing in mind their content in fat and sugar, but rather different dairy subtypes with different nutritional characteristics are considered within the same category. Furthermore, most of dietary guidelines recommend avoiding the consumption of whole-fat dairy products and promote low-fat dairy product consumption without enough evidences. Therefore, this field needs to be deeply investigated to develop dietary recommendations based on consistent scientific evidences.

On the other hand, it has been shown that individual nutrients, foods, drinks or specific components of foods seem increasingly less likely to be important individual factors in causing or protecting against CRC. Instead, research is increasingly focusing in dietary or lifestyle patterns from a holistic point of view. Although there is an increasing number of studies investigating the associations between following specific dietary patterns and the risk of CRC, evidence on CRC risk associated with adherence to healthy lifestyle patterns is scarce. In recent years, there has been growing interest in evaluating the risk of cancer associated with the adherence to the WCRF/AICR score, which is mostly composed of dietary components. Nonetheless, research considering the latest recommendations by the WCRF/AICR is lacking.

Additionally, a critical area on nutritional cancer epidemiology is the impact of diet and other modifiable lifestyle components throughout the life course on cancer risk. Most of the evidences presented in the Introduction section are focused on healthy adult populations. However, there is still a need for epidemiological evidence to prevent CRC in aging individuals, which are at increased risk of CRC.

Therefore, considering the previously gaps of knowledge, the findings of the present doctoral thesis shed new light on the potential role of modifiable dietary and lifestyle determinants of incidence of CRC in a population at high CVD risk within the frame of the PREDIMED trial.

III. Hypotheses and objectives

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III. HYPOTHESES AND OBJECTIVES

- **Hypothesis 1:** Consumption of different subtypes of dairy products, considering their sugar and fat content might be differently associated with the risk of CRC in the PREDIMED study.

  - **Objective 1.1**

To evaluate potential associations between total dairy products consumption and specific dairy product subtypes with the risk of CRC incidence within the frame of the PREDIMED cohort of older Spanish individuals at high CVD risk.

- **Hypothesis 2:** High adhesion to *a priori* lifestyle scores (the WCRF/AICR and the LRL scores) might decrease the risk of developing CRC in the PREDIMED study.

  - **Objective 2.1**

To evaluate the associations between the adherence to the 2018 WCRF/AICR and LRL scores and the incidence of CRC in elderly Spanish individuals at high CVD risk.

  - **Objective 2.2**

To investigate the associated CRC risk for every individual component of each lifestyle score in elderly Spanish individuals at high CVD risk.

- **Hypothesis 3:** The consumption of dairy products and the risk of developing CRC might be associated in different ways depending on the type of dairy product and CRC subsite and location.

  - **Objective 3.1**

To meta-analyze the available evidence coming from prospective cohorts and case-control studies in adults to examine the association between the consumption of specific types of dairy products and CRC incidence.

  - **Objective 3.2**

To investigate whether the associations between the consumption of dairy products and CRC risk depend on the CRC subsite (colon or rectal) and colon cancer location (proximal or distal colon).

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IV. Material and methods

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IV. MATERIAL AND METHODS

This doctoral thesis is composed of 3 articles published in international journals with high scientific impact. The first two chapters of the thesis are prospective observational studies conducted in the context of the PREDIMED clinical trial. The last chapter of the thesis is based on a systematic review and meta-analysis of prospective and case-control studies.

1. PREDIMED (PREvención con DIeta MEDiterránea) study

The PREDIMED study is a multicenter, parallel-group, controlled trial conducted in Spain designed to evaluate the effect of a traditional MedDiet on the primary prevention of CVD (conducted between 2003 and 2011). The project was approved by the "Comité Ético de Investigación Clínica Hospital Clínic" from Barcelona (Project identification register: 2002-1244; date of approval: 16 July 2002). Later, the Institutional Review Boards of each recruitment center approved the protocol (available at NEJM.org) and all participants provided informed consent before starting the study. The trial is registered (http://www.controlled-trials.com/ ISRCTN35739639). The main results of the study were published in *The New England Journal of Medicine* in 2018 [226].

The primary outcome of the PREDIMED trial was to evaluate the effects of two MedDiets on a composite endpoint of cardiovascular death, myocardial infarction and stroke in comparison with a low-fat control diet. Secondary outcomes were death from any cause, incidence of heart failure, diabetes mellitus, dementia or other neurodegenerative disorders and major cancers (colorectal, breast, lung, stomach and prostate). With the aim to better understand how dietary changes may modify the risk of clinical events, intermediate outcomes comprising changes in blood pressure, weight gain, fasting blood glucose, blood lipids and markers of inflammation were also assessed [227].

Enrollment of participants began on June 25, 2003, and the last participant was recruited on June 30, 2009. Eleven centers from 9 cities in Spain participated in the recruitment process: Sevilla, Málaga, Reus-Tarragona, Barcelona, Islas Baleares, Pamplona, País Vasco, Valencia and Gran Canarias. After a median follow-up of 4.8 years, the trial was stopped because of a prespecified interim analysis. The database closeout took place on September 2011 and included primary end-points events occurring through December 1, 2010. In order to explore other hypotheses subsequent follow-up continued as an observational multi-purpose cohort, and to carry out nested case-control analyses for studies of biomarkers and gene-nutrient interactions [227].

Inclusion criteria

Participants were eligible to participate in the PREDIMED study if they were community-dwelling adults aged 55 to 80 years in men, and 60 to 80 years in women, free at CVD at enrollment (ischemic heart disease including angina pectoris or heart attack; stroke and peripheral arteriopathy), but who were at high CVD risk because they had either T2D or at least three of the following major risk factors:

- Current smoking (>1 cigarette/day during the last month).
- Hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or antihypertensive medication).
- High low-density lipoprotein (LDL) cholesterol levels (≥160 mg/dl or lipid-lowering therapy).
- Low high-density lipoprotein (HDL) cholesterol levels (≤40 mg/dl in men or ≤50 mg/dl in women).
- Overweight or obesity (BMI ≥25 kg/m^2).
- Family history of premature coronary heart disease.

Exclusion criteria

Participants were excluded if they met one of the ensuing criteria:

- Previous history of CVD: coronary heart disease (angina, myocardial infarction, coronary revascularization procedures or existence of abnormal Q waves in the electrocardiogram, stroke (ischemic or hemorrhagic, including transient ischemic attacks) and peripheral artery disease.
- Presence of medical conditions that could impair the ability of the person to participate in the study or to attend visits.
- Life expectancy less than one year.
- Immunodeficiency or human immunodeficiency virus (HIV)-positive status.
- Illegal drug use or chronic alcoholism or total daily consumption of 50 g of alcohol.
- BMI ≥40 kg/m^2.
- Difficulties or major inconvenience to change dietary habits.
- Impossibility to follow a MedDiet due to religious reasons or presence of disorders that affect chewing or swallowing.
- Low predicted likelihood to change dietary habits according to Prochaska and Diclemente transtheoretical model.
- Food allergy with hypersensitivity to any of the components in olive oil or nuts.
- Participation in any drug trial or use of any investigational drug within the last year.

- Institutionalized patients for chronic care, those who lacked autonomy, were unable to walk, lacked a stable address or were unable to attend visits in the Primary Care Health Centers every three months.
- Illiteracy.
- Patients with an acute infection or inflammation were allowed to participate in the study after three months from the resolution of their condition.

1.1. Randomization and intervention

A total of 7,447 participants were randomly allocated to three intervention groups in a 1:1:1 ratio: MedDiet enriched with extra virgin olive oil (EVOO) (MedDiet+EVOO), MedDiet enriched with mixed nuts (MedDiet+nuts), or low-fat control group. The two groups assigned to the MedDiets received intensive education to follow the MedDiet supplemented with either EVOO (1 l/wk.) or nuts (15 g walnuts, 7.5 g hazelnuts and 7.5 g almonds daily) at no cost. Those participants in the control group were given advice to follow a low-fat diet. PREDIMED dietitians were the responsible for all the dietary interventions and they received specific training sessions before and during the trial to ensure good implementation of the intervention. The main aim was to promote adherence to the Mediterranean dietary pattern in both MedDiet groups. During the trial, no calorie restriction was advised, nor was PA promoted.

All the participants in the PREDIMED study attended to a face-to-face visit in their primary care centers at baseline, 6 months and yearly during the follow-up. In these visits, different questionnaires were administered, and anthropometric and biochemical measurements were collected.

1.2. Study population for the analyses in the PREDIMED trial

In Chapters 1 and 2 of the present dissertation inclusion and exclusion criteria were the same as in the PREDIMED trial. Moreover, from the 7,447 participants, those individuals with energy intake values outside de pre-specified limits (<500 or >3500 kcal/day for women or <800 or >4000 kcal/day for men) (n=153), and those with no baseline food frequency questionnaire (FFQ) (n=78) were excluded. Thus, the final sample for the analyses included 7,216 individuals.

1.3. Ascertainment of colorectal cancer cases

For the present doctoral thesis, new CRC events were defined as the first invasive CRC according to the International Classification of Diseases for Oncology topographical codes C18.0–C20.9. The results of the histological examination were considered confirmatory in most events (n=67). Events were identified from the following sources: a review of all the medical records by a panel of physicians and researchers blinded to the intervention, at both primary healthcare and hospital level, and the national death index. The Endpoint Adjudication Committee, whose members were

also blinded to the intervention, determined the cause of death, confirmed major events, and updated the endpoints of the PREDIMED study on a yearly basis.

1.4. Ascertainment of dairy product consumption

On a yearly basis, a validated semi-quantitative 137-food items [228] was administered by trained dietitians in order to assess dietary intake during the previous year. Participants were asked to report their frequency of consumption of food items comprising dairy products, 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). Nutrient and energy consumption were estimated from the FFQ responses using Spanish Food composition tables [229,230].

In the FFQ validation study, the intraclass correlation coefficient between consumption of total dairy products from the FFQ and repeated 24-hour food records was 0.84 [228]. 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).

1.5. Assessment of lifestyle and clinical variables

Trained personnel took anthropometric measurements (weight, height, and WC). All anthropometric variables were measured annually.

- Weight and height were measured using calibrated scales and a wall-mounted stadiometer, respectively, with participants wearing light clothing and no shoes.
- WC was measured midway between the lowest rib and the iliac crest using an anthropometric tape.
- BMI was calculated by dividing the weight (kg) by the square of the height (m^2).
- Blood pressure was measured with a validated oscillometer (Omron HEM705CP, Hoofddorp, The Netherlands) in triplicate with a 5-min interval between each measurement.
- PA: the validated Spanish version of the Minnesota leisure-time PA (LTPA) questionnaire [231,232] was used to assess the amount and intensity of LTPA. The questionnaire consisted

of 67 activities divided into 9 sections. The participants were asked to complete the form, reporting the number of days and min./day they had performed the activities during the previous week and year. PA was quantified in METs per minute per day (METs min/day). This unit was calculated by multiplying the METs assigned to each activity and their mean duration in min. per day. LTPA was classified as light (intensity<4 METs), moderate (intensity= 4–5.5 METs), and vigorous (intensity≥6 METs). This questionnaire was completed during a baseline visit and annually thereafter.

- Smoking status or education level, medical history, and medication use were asked using a general questionnaire about lifestyle variables that was completed and recorded at baseline and yearly thereafter.

1.6. World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) score operationalization

To evaluate the associations between the accomplishment of the last cancer prevention recommendations [85] and the risk of developing CRC in the PREDIMED study, a 7-point score based on the last WCRF/AICR was constructed. The individual score components are shown in **Figure 5**. More detailed information on the score construction is given in Chapter 2 (see the Results section).

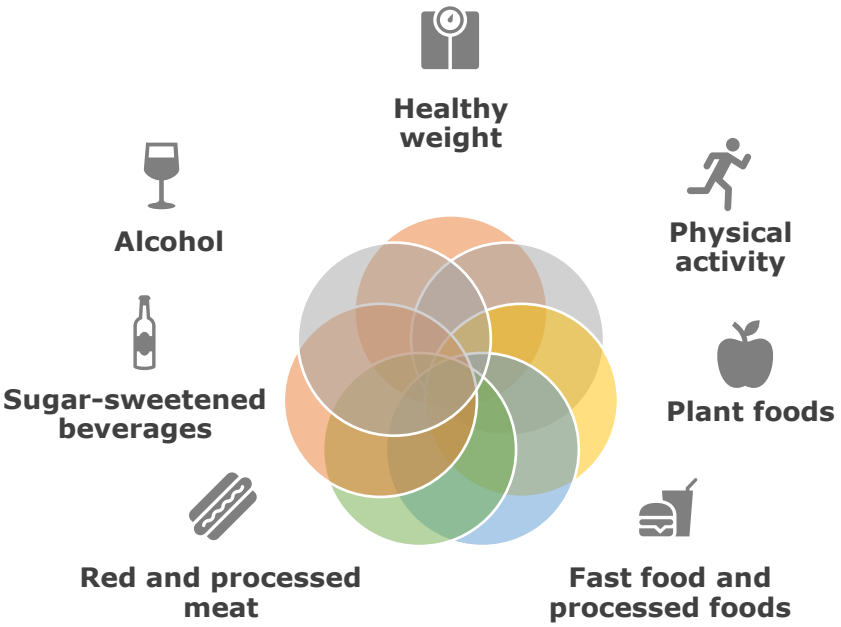

Figure 5. Individual components of the 2018 WCRF/AICR score.

The cut-off points for each score component were based on the 2018 WCRF/AICR recommendations when available or previously published literature otherwise. For each of the recommendations, we assigned 1 point when the recommendation was met, 0.5 points when it was partially met, and 0 points when it was not met. For those components with sub-recommendations, the considered component score was the average of the sub-recommendation scores. The mean score for each component was between 0.36 (red and processed meat consumption) and 0.70 (SSB intake) points. The final index was the sum of all the components and ranged from 0 to 7. Higher scores indicated better adherence to cancer prevention recommendations.

1.7. Low-risk lifestyle score operationalization

The LRL score was constructed in terms of adherence to five LRL-related factors proposed by Li and colleagues [203]. Detailed information on the score operationalization can be obtained in Chapter 2 (see the Results section). The individual score components are shown in **Figure 6**. For each risk factor, 1 point was given if the participant met the criterion for low risk, or 0 points otherwise. The mean score for each component was between 0.07 (healthy body weight) and 0.62 (never smoking) points. The final score was the sum of all components (score range from 0 to 5), with higher scores indicating a healthier lifestyle.

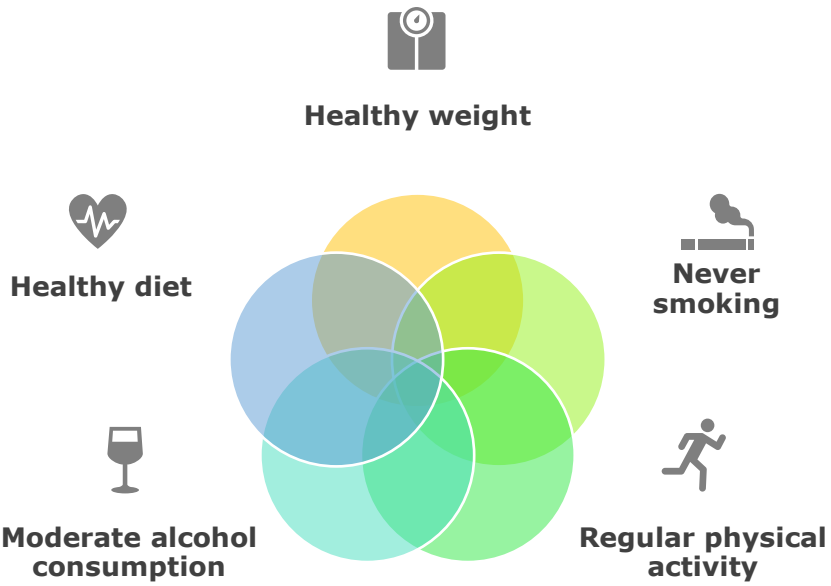

Figure 6. Individual components of the Low-Risk Lifestyle score.

1.8. Statistical analyses of the observational PREDIMED cohort studies:

The analyses based on the PREDIMED study were conducted using data as if it was an observational prospective cohort study from a clinical trial.

The baseline characteristics of the participants were expressed as means and standard deviation (SD) or medians and interquartile ranges [IQR] for continuous variables, and percentage (%) and number (n) for categorical variables. Chi-square (for categorical data), one-factor ANOVA test and t-Student tests (both for continuous data) were used to assess differences in the baseline characteristics of the participants.

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.

To evaluate the risk of developing CRC associated with different exposures, multivariable Cox proportional regression models were used. The results were the HRs and their 95% CIs for the comparison between the highest versus the lowest quantiles for each exposure (consumption of dairy products in Chapter 1, and adherence to lifestyle recommendations in Chapter 2) in categorical analyses, and for each 1-point increment in the exposure variables in the continuous analyses. The linear trend was calculated by assigning the median value of each category and then using it as a continuous variable.

All models were adjusted for potential confounders including intervention group, sex, age, LTPA, BMI, smoking status, family history of cancer, education level, history of diabetes, use of aspirin as well as other variables that could statistically significantly modify the associations.

Analyses were performed using the STATA (14.0, StataCorp LP, Lakeway Drive, TX. USA) and R (v. 3.5.1) software (GNU General Public License, Boston, MA, USA). All P-values were two-sided, and a P-value <0.05 was considered statistically significant.

2. DESIGN OF THE SYSTEMATIC-REVIEW AND META-ANALYSIS

The systematic review and meta-analysis (Chapter 3) was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [233]. The results were presented following the "Meta-Analysis of Observational Studies in Epidemiology" [234] and the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement" guidelines [235]. The protocol for the systematic review and meta-analysis is available in PROSPERO (www.crd.york.ac.uk; identifier: CRD42017057490).

2.1. Study selection for the systematic-review and meta-analysis

In Chapter 3 of the present thesis, identification and selection of relevant publications for the systematic review and meta-analysis was conducted. It was systematically searched for published case-control and prospective cohort studies investigating the associations between the consumption of total dairy products and their subtypes and the risk of developing CRC.

- All studies that met the following criteria (**inclusion criteria**) were considered for inclusion in the meta-analysis:

  - Those conducted in humans (>18 years old).
  - Those written in English, Spanish or French.
  - Those in which the outcome of interest was CRC, colon or rectal cancer.
  - Those that provided estimates of the odds ratio (OR) or RR (such as the HR or risk ratio) with the corresponding 95% CIs or gave enough data for these values to be calculated.
  - Those in which the estimates were adjusted for age.
  - Those that evaluated the consumption of dairy products using validated food questionnaires.
  - Those that assessed the consumption of any subtype or total dairy product (cow, goat, or sheep milk; skim, low-fat, or full-fat milk; total, low-fat, or full-fat yogurt; cheese; and full-fat dairy, sweetened dairy, or other dairy products) as the exposure variable.

- For the **dose-response analysis** we required the following criteria to be met:

  - A quantitative measure of intake had to be provided.
  - When there were several publications from the same study, we selected the publication with the largest number of cases.
  - If all the information required was not provided in the paper, we used the publication that provided enough information for a dose-response analysis to be conducted.

- The following types of publications were excluded **(exclusion criteria)**:

  - Non-original papers (reviews, commentaries, editorials, or letters).
  - Ecologic assessments and correlation studies.
  - Cross-sectional studies.
  - Meta-analysis studies.
  - Non-peer-reviewed articles.
  - Off-topic studies.

- Studies on CRC mortality.
- Studies lacking specific CRC data.
- Animal and mechanistic studies.
- Studies conducted in children, adolescents, or pregnant women.
- Supplements to the main manuscript.
- Duplicate publications.
- Low methodologic quality studies: Newcastle-Ottawa Scale (NOS) for cohort or case-control studies scored less than 6 points.

Of the 780 reports remaining after duplicates removed, 29 studies were included in the meta-analysis: 15 prospective cohort studies and 14 case-control studies evaluating the associations between consumption of dairy product and CRC risk.

2.2. Statistical analysis of the systematic review and meta-analysis:

To calculate the summary risk estimates and 95% CIs for the highest compared with the lowest categories of consumption of dairy products and dairy product subtypes, we conducted both random (≥5 study comparisons) and fixed (<5 study comparisons) effects analyses. We natural log–transformed and pooled the RRs/HRs (cohort studies) and ORs (case-control studies) using the generic inverse variance method. When the highest level of consumption was considered as the reference category, we recalculated the estimate (RR and 95% CI) of the highest category.

When the results of the studies were stratified by subgroups, such as sex, they were treated as separate studies. We carried out prespecified stratified analyses for the study design (prospective cohort and case-control studies) and outcome (CRC, colon cancer, proximal or distal colon cancer, and rectal cancer).

We performed linear and nonlinear dose-response analyses with data from the cohort studies. We carried out generalized least-squares trend estimation modeling and spline curve modeling (MKspline STATA command). This method requires at least 3 quantitative exposure levels or quantiles.

Analyses were performed with Review Manager version 5.3 (The Nordic Cochrane Center) and STATA (14.0, StataCorp LP, Lakeway Drive, TX. USA) software. A 2-tailed P-value<0.05 was considered statistically significant. The heterogeneity among studies was assessed with the use of Cochran's *Q* statistic and quantified with the I^2 statistic (P<0.10 was considered significant, and I^2≥50% was interpreted as substantial heterogeneity).

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Table 2. List of the three original publications included in the present doctoral thesis: reference, impact factor, category and journal rank [1].

Reference	Impact factor	Category	Journal Rank
Chapter 1			
Barrubés L, Babio N, Mena-Sánchez G, Toledo E, Ramírez-Sabio JB, Estruch R, Ros E, Fitó M, Arós F, Fiol M, Santos-Lozano JM, Serra-Majem L, Pintó X, Martínez-González MÁ, Sorlí JV, Basora J, Salas-Salvadó J; PREvención con DIeta MEDiterránea Study Investigators. Dairy product consumption and risk of colorectal cancer in an older mediterranean population at high cardiovascular risk. Int J Cancer. 2018;143(6):1356-1366. doi: 10.1002/ijc.31540.	4.982	Oncology	51/230 (Q1)
Chapter 2			
Barrubés L, Babio N, Hernández-Alonso P, Toledo E, Ramírez Sabio JB, Estruch R, Ros E, Fitó M, Alonso-Gómez AM, Fiol M, Lapetra J, Serra-Majem L, Pintó X, Ruiz-Canela M, Corella D, Castañer O, Macías-González M, Salas-Salvadó J. Association between the 2018 WCRF/AICR and the Low-Risk Lifestyle Scores with Colorectal Cancer Risk in the Predimed Study. J Clin Med. 2020;9(4). pii: E1215. doi: 10.3390/jcm9041215.	5.688	Medicine, General & Internal	15/160 (D1)
Chapter 3			
Barrubés L, Babio N, Becerra-Tomás N, Rosique-Esteban N, Salas-Salvadó J. Association Between Dairy Product consumption and Colorectal Cancer Risk in Adults: A Systematic Review and Meta-Analysis of Epidemiologic Studies. Adv Nutr. 2019;10(suppl_2):S190-S211. doi: 10.1093/advances/nmy114.	7.240	Nutrition & Dietetics	3/87 (D1)

[1] Accessed date: May 5, 2020 (Journal Citation Reports of the ISI web of Knowledge Thompson Reuters).

Abbreviations: D, decile; Q, quartile.

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Chapter 1

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

Barrubés L, Babio N, Mena-Sánchez G, Toledo E, Ramírez-Sabio JB, Estruch R, Ros E, Fitó M, Arós F, Fiol M, Santos-Lozano JM, Serra-Majem L, Pintó X, Martínez-González MÁ, Sorlí JV, Basora J, Salas-Salvadó J; PREvención con DIeta MEDiterránea Study Investigators.

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Cancer Epidemiology

Dairy Product Consumption and Risk of Colorectal Cancer in an Older Mediterranean Population at High Cardiovascular Risk

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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 7,216 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 [interquartile 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.

Key words: colorectal cancer, mediterranean diet, dairy products, milk, PREDIMED study

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

Additional Supporting Information may be found in the online version of this article.

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What's new?

Relative to other aspects of the Mediterranean diet, such as the intake of alcohol and processed meats, little is known about the relationship between the consumption of dairy products or their fat content and colorectal cancer (CRC) risk. Here, potential relationships were assessed among older Mediterranean individuals at high risk of cardiovascular disease. The data suggest that CRC incidence is inversely related to high total dairy product consumption. Of particular importance was the intake of low-fat milk, which was the primary driver behind the inverse association. Other dairy products were not significantly associated with CRC risk.

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 as 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.[12,13] 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 7,447 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 $\geq$ 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 >3,500 kcal/day for women or <800 or >4,000 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: (*i*) a questionnaire about lifestyle variables, medical history and medication use; (*ii*) 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; (*iii*) 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); (*iv*) 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 intraclass correlation coefficient between consumption of total dairy products from the FFQ and repeated 24-hr 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. 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 $\pm$ SD or medians and interquartile ranges [IQR] for continuous variables, and percentages (%) and number (*n*) for categorical variables. χ^2 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 to estimate the associations between dietary calcium intake from different food sources and CRC risk (Supporting Information, 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 fit. 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: (*i*) 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 (*ii*) 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] To assess a possible association between the intake of calcium supplements and the risk of CRC, (*iii*) we repeated the models after adjusting for the intake of mineral supplements (yes/no) containing calcium (Supporting Information, Tables 3 and 4), and (iv) we also repeated the analyses after excluding those individuals taking calcium supplements (Supporting Information, Tables 5 and 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) 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 7,216 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 (Supporting Information, 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 Tables 2 and 3. Additionally, HRs for CRC incidence associated with the intake of dietary calcium from different food sources across energy-adjusted tertiles are shown in Supporting Information, 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 nonsignificant 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

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* = 2,406	T2 (266.52–445.10), *n* = 2,405	T3 (≥445.26), INTRO *n* = 2,405	*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 (1,030)	63.0 (1,514)	66.6 (1,601)	<0.001
Education level, % (*n*)				<0.001
Primary, secondary or high school	90.7 (2,182)	93.8 (2,254)	94.1 (2,264)	
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 (1,177)	48.6 (1,169)	50.0 (1,202)	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 (1,058)	48.9 (1,176)	53.8 (1,293)	<0.001
Hypertension, % (*n*)	83.7 (2,013)	83.4 (2,006)	81.1 (1,951)	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)	2,321.7 ± 561.5	2,059.1 ± 502.9	2,327.6 ± 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 cutoffs 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 χ^2 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*)	41/14,063	36/14,086	20/14,091	
Rate per 1,000 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*)	32/14,140	29/14,061	36/14,038	
Rate per 1,000 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*)	40/14,053	36/14,075	21/14,112	
Rate per 1,000 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 cutoffs 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.

of dietary calcium intake from all food sources, dairy sources and total milk showed a nonsignificant inverse association with CRC incidence compared to the reference tertile (model 2) (Supporting Information, 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 nonsignificant 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 (Supporting Information, 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

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*)	36/14,119	34/14,068	27/14,053	
Rate per 1,000 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*)	37/14,070	30/14,116	30/14,054	
Rate per 1,000 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*)	33/14,153	35/14,046	29/14,041	
Rate per 1,000 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*)	32/14,163	29/14,037	36/14,040	
Rate per 1,000 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*)	40/14,057	33/14,088	24/14,095	
Rate per 1,000 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*)	46/14,035	29/14,087	22/14,117	
Rate per 1,000 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*)	31/14,154	31/14,056	35/14,029	
Rate per 1,000 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

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 (Continued)

	Tertiles of specific dairy product consumption (g/day)[1]			
	T1	T2	T3	*P*-trend
Concentrated full-fat dairy products [P25–P75]; g/day[9]	11 [6–16]	26 [23–30]	45 [38–55]	
Cases/ person-year (*n*)	33/14,165	30/14,039	34/14,035	
Rate per 1,000 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*)	30/14,177	38/14,087	29/13,976	
Rate per 1,000 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[10]	36 [20–52]	97 [81–115]	166 [147–221]	
Cases/ person-year (*n*)	39/14,111	30/14,097	28/14,031	
Rate per 1,000 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 cutoffs 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.

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, this 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 nonsignificant. Although we observed a nonsignificant inverse association between total yogurt intake and CRC risk, Pala *et al.*[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 antitumor 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 precancer 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, 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 expand 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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The other authors declare that they have no conflicts of interest.

References

1. Siegel R, Ward E, Brawley O, et al. Cancer statistics, 2011: the impact of eliminating socio-economic and racial disparities on premature cancer deaths. *CA Cancer J Clin* 2011;61: 212–36.
2. Bray F, Jemal A, Grey N, et al. Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. *Lancet Oncol* 2012;13:790–801.
3. Ferlay J, Shin H-R, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893–917.
4. Ferlay J, Soerjomataram II, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015;136:E359–86.
5. Arnold M, Sierra MS, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017;66:683–91.
6. Center MM, Jemal A, Ward E. International trends in colorectal cancer incidence rates. *Cancer Epidemiol Biomarkers Prev* 2009;18:1688–94.
7. Center MM, Jemal A, Smith RA, et al. Worldwide variations in colorectal cancer. *CA Cancer J Clin* 2009;59:366–78.
8. American Cancer Society. Colorectal cancer facts & figures 2017–2019. Atlanta: American Cancer Society, 2017.
9. Kune GA, Bannerman S, Watson LF. Attributable risk for diet, alcohol, and family history in the Melbourne Colorectal Cancer Study. *Nutr Cancer* 1992;18:231–5.
10. Shike M. Diet and lifestyle in the prevention of colorectal cancer: an overview. *Am J Med* 1999; 106:11S–5S. discussion 50S–51S.
11. Trichopoulou A, Lagiou P, Kuper H, et al. Cancer and Mediterranean dietary traditions. *Cancer Epidemiol Biomarkers Prev* 2000;9:869–73.

12. World Cancer Research Fund/American Institute for Cancer Research. Diet, nutrition, physical activity and colorectal cancer. 2017
13. Research WCRF/AI for C, Pekmezi D, Demark-Wahnefried W. Updated evidence in support of diet and exercise interventions in cancer survivors. *Acta Oncol (Madr).* 2011;50:167–78.
14. Abu Mweis SS, Tayyem RF, Shehadah I, et al. Food groups and the risk of colorectal cancer. *Eur J Cancer Prev* 2015;24:313–20.
15. Green CJ, de Dauwe P, Boyle T, et al. Tea, coffee, and milk consumption and colorectal cancer risk. *J Epidemiol* 2014;24:146–53.
16. Cox B, Sneyd MJ. School milk and risk of colorectal cancer: a national case-control study. *Am J Epidemiol* 2011;173:394–403.
17. Sun Z, Wang PP, Roebothan B, et al. Calcium and vitamin D and risk of colorectal cancer: results from a large population-based case-control study in Newfoundland and Labrador and Ontario. *Can J Public Health* 2011;102:382–9.
18. Azzeh FS, Alshammari EM, Alazzeh AY, et al. Healthy dietary patterns decrease the risk of colorectal cancer in the Mecca Region, Saudi Arabia: a case-control study. *BMC Public Health* 2017;17:607
19. Murphy N, Norat T, Ferrari P, et al. Consumption of dairy products and colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). *PLoS One* 2013;8:e72715.
20. Larsson SC, Bergkvist L, Rutegård J, et al. Calcium and dairy food intakes are inversely associated with colorectal cancer risk in the Cohort of Swedish Men. *Am J Clin Nutr* 2006;83:667–73.
21. Thompson FE, Potischman N, Subar AF, et al. Adolescent and mid-life diet: risk of colorectal cancer in the NIH-AARP Diet and Health Study 1 – 3. *Am J Clin Nutr* 2011;94:1607–19.
22. Lee S-A, Shu XO, Yang G, et al. Animal origin foods and colorectal cancer risk: a report from the Shanghai Women's Health Study. *Nutr Cancer* 2009;61:194–205.
23. Tantamango-Bartley Y, Knutsen SF, Jaceldo-Siegl K, et al. Independent associations of dairy and calcium intakes with colorectal cancers in the Adventist Health Study-2 cohort. *Public Health Nutr* 2017;20:2577–86.
24. Vieira AR, Abar L, Chan D, et al. Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. *Ann Oncol* 2017;128:1788–802.
25. Schwingshackl L, Schwedhelm C, Hoffmann G, Knüppel S, Preterre AL, Iqbal K, Bechthold A,D, Henauw S, Michels N, Devleesschauwer B, Boeing H, Schlesinger S. Food groups and risk of colorectal cancer. *Int J Cancer.* 2017.
26. Martínez-González MÁ, Corella D, Salas-Salvadó J, et al. Cohort profile: design and methods of the PREDIMED study. *Int J Epidemiol* 2012;41:377–85.
27. Estruch R, Martínez-González MA, Corella D, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Ann Intern Med* 2006;145:1–11.
28. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368:1279–90.
29. Fernández-Ballart JD, Piñol JL, Zazpe I, et al. Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. *Br J Nutr* 2010;103:1808–16.
30. Saha C, Jones MP. Bias in the last observation carried forward method under informative dropout. *J Stat Plan Inference* 2009;139:246–55.
31. Aune D, Lau R, Chan DSM, et al. Dairy products and colorectal cancer risk: A systematic review and meta-analysis of cohort studies. *Ann Oncol* 2012;23:37–45.
32. Ralston RA, Truby H, Palermo CE, et al. Colorectal cancer and nonfermented milk, solid cheese, and fermented milk consumption: a systematic review and meta-analysis of prospective studies. *Crit Rev Food Sci Nutr* 2014;54:1167–79.
33. Larsson SC, Bergkvist L, Wolk A. High-fat dairy food and conjugated linoleic acid intakes in relation to colorectal cancer incidence in the Swedish Mammography Cohort. *Am J Clin Nutr* 2005;82:894–900.
34. Vargas AJ, Thompson PA. Diet and nutrient factors in colorectal cancer risk. *Nutr Clin Pract* 2012;27:613–23.
35. Pala V, Sieri S, Berrino F, et al. Yogurt consumption and risk of colorectal cancer in the Italian European prospective investigation into cancer and nutrition cohort. *Int J Cancer* 2011;129:2712–9.
36. Fardet A, Dupont D, Rioux L-E, et al. Influence of food structure on dairy protein, lipid and calcium bioavailability: a narrative review of evidence. *Crit Rev Food Sci Nutr* 2018;2:1–24.
37. Guéguen L, Pointillart A. The bioavailability of dietary calcium. *J Am Coll Nutr* 2000;19:119S–36S.
38. Lamprecht SA, Lipkin M. Cellular mechanisms of calcium and vitamin D in the inhibition of colorectal carcinogenesis. *Ann N Y Acad Sci* 2001;952:73–87.
39. Pufulete M. Intake of dairy products and risk of colorectal neoplasia. *Nutr Res Rev* 2008;21:56–67.
40. Parodi PW. Cows' milk fat components as potential anticarcinogenic agents. *J Nutr* 1997;127:1055–60.
41. Bassaganya-Riera J, Hontecillas R, Horne WT, et al. Conjugated linoleic acid modulates immune responses in patients with mild to moderately active Crohn's disease. *Clin Nutr* 2012;31:721–7.
42. Bassaganya-Riera J, Hontecillas R, Beitz DC. Colonic anti-inflammatory mechanisms of conjugated linoleic acid. *Clin Nutr* 2002;21:451–9.
43. Kritchevsky D. Antimutagenic and some other effects of conjugated linoleic acid. *Br J Nutr* 2000;83:459–65.
44. Williams L, Williams EA, Coxhead JM, et al. Anti-cancer effects of butyrate: use of micro-array technology to investigate mechanisms. *Proc Nutr Soc.* 2003;62:107–15.
45. Tsilidis KK, Kasimis JC, Lopez DS, et al. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. *BMJ* 2015;350:g7607.
46. Aune D, Norat T, Romundstad P, et al. Dairy products and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies. *Am J Clin Nutr* 2013;98:1066–83.

Supplemental Table 1. Energy adjusted dairy product consumption during follow-up in the study population

	Mean±SD; g/day	Median [P25, P75]; g/day
Total dairy products[1]	375.3±186.4	350 [247-499]
Whole-fat dairy products[2]	59.0±112.2	21 [1-65]
Low-fat dairy products[3]	279.2±197.5	254 [136-409]
Total yogurt[4]	81.4±75.3	65 [22-122]
Low-fat yogurt[5]	60.2±71.5	40 [3-96]
Whole-fat yogurt[6]	21.2±42.6	6 [0-25]
Cheese[7]	28.2±20.1	25 [15-37]
Total milk[8]	256.8±161.4	220 [163-364]
Low-fat milk[9]	219.0±171.8	201 [90-329]
Whole-fat milk[10]	37.8±96.8	6 [0-21]
Concentrated full-fat dairy products[11]	29.0±20.5	26 [16-38]
Sugar-enriched dairy products[12]	8.9±20.4	5 [1-10]
Fermented dairy products[13]	109.6±79.5	97 [52-147]

Abbreviations: SD, standard deviation; P, percentile.
[1]Includes all dairy products: all types of milk, yogurt and cheeses, custard, whipped cream, butter and ice-cream.
[2]Includes whole-fat milk and whole-fat yogurt.
[3]Includes semi-skimmed/skimmed milk and low-fat yogurt.
[4]Includes all types of yogurt: low-fat and whole-fat yogurt.
[5]Includes low-fat yogurt.
[6] Includes whole-fat yogurt.
[7] Includes all types of cheese: petit Suisse, ricotta, cottage, spreadable and semi-cured/cured cheeses.
[8] Includes all types of milk: semi-skimmed/skimmed milk and whole-fat milk.
[9] Includes semi-skimmed and skimmed milk.
[10] Includes whole-fat milk.
[11] Includes butter, whipped cream and all types of cheese.
[12] Includes condensed milk, milkshakes, ice cream and custard.
[13] Includes all fermented dairy products: all types of yogurt and cheeses.

Supplemental Table 2. Hazard ratios (95% CI) of colorectal cancer incidence across energy-adjusted tertiles of average calcium consumption in elderly individuals at high cardiovascular risk.

	Tertiles of calcium consumption (mg/day)[1]			
	T1	T2	T3	P- trend
Calcium from all food sources, median [P25-P75]; g/day[2]	738[632-810]	992[931-1061]	1337[1232-1487]	
Cases/ person-year (n)	45/14116	27/14103	25/14020	
Rate per 1000 person-years	3.19	1.91	1.78	
Crude model	1.00 ref	0.60 (0.37-0.97)	0.56 (0.34-0.91)	0.021
Multivariate model 1	1.00 ref	0.63 (0.39-1.04)	0.65 (0.39-1.09)	0.121
Multivariate model 2	1.00 ref	0.60 (0.36-1.00)	0.60 (0.34-1.05)	0.091
Calcium from dairy sources, median [P25-P75]; g/day[3]	330[234-398]	573[512-642]	916[823-1067]	
Cases/ person-year (n)	41/14066	32/14110	24/14064	
Rate per 1000 person-years	2.91	2.27	1.71	
Crude model	1.00 ref	0.78 (0.49-1.23)	0.59 (0.35-0.97)	0.042
Multivariate model 1	1.00 ref	0.81 (0.50-1.32)	0.66 (0.39-1.12)	0.141
Multivariate model 2	1.00 ref	0.78 (0.47-1.29)	0.61 (0.34-1.08)	0.105
Calcium from low-fat milk, median [P25-P75]; g/day[4]	3[-10-17]	260[247-268]	647[292-661]	
Cases/ person-year (n)	46/14035	29/14086	22/14119	
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	0.69 (0.44-1.10)	0.55 (0.33-0.93)	0.025
Multivariate model 2	1.00 ref	0.68 (0.42-1.08)	0.53 (0.31-0.91)	0.105
Calcium from total milk, median [P25-P75]; g/day[5]	111[18-206]	274[257-290]	638[592-669]	
Cases/ person-year (n)	40/14061	33/14075	24/14103	
Rate per 1000 person-years	2.84	2.34	1.70	
Crude model	1.00 ref	0.82 (0.52-1.31)	0.60 (0.36-0.99)	0.062
Multivariate model 1	1.00 ref	0.88 (0.56-1.40)	0.67 (0.39-1.13)	0.157
Multivariate model 2	1.00 ref	0.83 (0.52-1.33)	0.62 (0.35-1.10)	0.105

Abbreviations: P, percentile; T, tertile.

Cox regression model 1 adjusted by intervention group, sex, age (years), leisure time physical activity (MET-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, history of diabetes (yes/no) and use of aspirin treatment at baseline.

Cox regression model 2 additionally adjusted by average consumption during the follow-up of vegetables (g/d), fruit (g/d), legumes (g/d), cereals (g/d), fish (g/d), meat (g/d), alcohol (g/d), olive oil (g/d) and nuts (g/d). All models were stratified by recruitment center.

[1]Tertile cut-offs are based on energy-adjusted average calcium consumption during the follow-up.

[2] Includes dietary calcium from all food sources.

[3] Includes calcium from all dairy sources: all types of milk, yogurt and cheeses, custard, whipped cream, butter and ice-cream.

[4] Includes calcium from low-fat milk: semi-skimmed and skimmed milk.

[5] Includes calcium from all types of milk: semi-skimmed/skimmed milk and whole-fat milk.

Supplemental table 3. 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 after additional adjustment for intake of calcium supplements

	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 (0.33-1.01)	0.043
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 (0.64-1.66)	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)	0.077
Multivariate model 2	1.00 ref	0.97 (0.62-1.52)	0.62 (0.36-1.07)	0.071

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), use of aspirin treatment (yes/no) and use of calcium supplements (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.

Supplemental table 4. 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 after additional adjustment for intake of calcium supplements

	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)	0.799
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)	0.991
Multivariate model 2	1.00 ref	0.97 (0.59-1.61)	1.06 (0.65-1.73)	0.910
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	1.12 (0.69-1.86)	0.88 (0.53-1.47)	0.418
Multivariate model 2	1.00 ref	1.07 (0.65-1.79)	0.86 (0.51-1.46)	0.418
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)	0.379
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)	0.148
Multivariate model 2	1.00 ref	0.83 (0.52-1.33)	0.63 (0.36-1.10)	0.134
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 (0.66-1.84)	1.10 (0.66-1.83)	0.773
Multivariate model 2	1.00 ref	1.07 (0.65-1.78)	1.06 (0.64-1.75)	0.891
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)	0.639
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	0.88 (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), use of aspirin (yes/no) and use of calcium supplement (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.

Supplemental table 5. 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 after excluding those individuals taking calcium supplements at baseline (n= 6719)

	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]	562 [499-639]	
Cases/ person-year (n)	40/13349	35/13209	17/12951	
Rate per 1000 person-years	3.00	2.65	1.31	
Crude model	1.00 ref	0.88 (0.56-1.39)	0.44 (0.25-0.77)	0.004
Multivariate model 1	1.00 ref	1.04 (0.65-1.68)	0.53 (0.29-0.97)	0.031
Multivariate model 2	1.00 ref	1.01 (0.61-1.66)	0.50 (0.27-0.94)	0.025
Whole-fat dairy products, median [P25-P75]; g/day[3]	0 [0-1]	21 [13-28]	115 [66-215]	
Cases/ person-year (n)	31/13285	25/13095	36/13129	
Rate per 1000 person-years	2.33	1.91	2.74	
Crude model	1.00 ref	0.82 (0.48-1.39)	1.18 (0.73-1.90)	0.406
Multivariate model 1	1.00 ref	0.85 (0.49-1.47)	1.07 (0.66-1.74)	0.744
Multivariate model 2	1.00 ref	0.83 (0.48-1.44)	1.07 (0.65-1.75)	0.740
Low-fat dairy products, median [P25-P75]; g/day[4]	67 [5-136]	254 [214-299]	495 [409-562]	
Cases/ person-year (n)	39/13250	35/13281	18/12977	
Rate per 1000 person-years	2.94	2.64	1.39	
Crude model	1.00 ref	0.89 (0.57-1.41)	0.47 (0.27-0.82)	0.009
Multivariate model 1	1.00 ref	0.99 (0.62-1.58)	0.58 (0.32-1.04)	0.061
Multivariate model 2	1.00 ref	0.99 (0.62-1.57)	0.57 (0.32-1.02)	0.054

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.

Supplemental table 6. 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 after excluding those individuals taking calcium supplements at baseline (n= 6719)

	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]	64 [54-85]	128 [122-184]	
Cases/ person-year (n)	34/13457	33/13081	25/12970	
Rate per 1000 person-years	2.53	2.52	1.93	
Crude model	1.00 ref	1.00 (0.62-1.61)	0.76 (0.45-1.28)	0.292
Multivariate model 1	1.00 ref	1.18 (0.72-1.95)	0.91 (0.54-1.53)	0.703
Multivariate model 2	1.00 ref	1.21 (0.73-2.02)	0.93 (0.53-1.62)	0.784
Low-fat yogurt, median [P25, P75]; g/day[3]	1 [0-4]	40 [24-54]	122 [96-150]	
Cases/ person-year (n)	36/13322	29/13235	27/12951	
Rate per 1000 person-years	2.70	2.19	2.08	
Crude model	1.00 ref	0.81 (0.50-1.32)	0.77 (0.47-1.27)	0.285
Multivariate model 1	1.00 ref	0.94 (0.57-1.56)	0.95 (0.57-1.58)	0.749
Multivariate model 2	1.00 ref	0.98 (0.59-1.63)	0.98 (0.58-1.65)	0.821
Whole-fat yogurt, median [P25-P75]; g/day[4]	0	6 [4-9]	45 [25-78]	
Cases/ person-year (n)	32/13324	31/13151	29/13034	
Rate per 1000 person-years	2.40	2.36	2.23	
Crude model	1.00 ref	0.98 (0.60-1.61)	0.93 (0.56-1.53)	0.739
Multivariate model 1	1.00 ref	1.06 (0.63-1.78)	0.91 (0.54-1.53)	0.580
Multivariate model 2	1.00 ref	1.02 (0.60-1.73)	0.91 (0.54-1.56)	0.630
Cheese, median [P25-P75]; g/day[5]	15 [6-27]	23 [15-32]	36 [26-46]	
Cases/ person-year (n)	31/13437	27/13090	34/12981	
Rate per 1000 person-years	2.31	2.06	2.62	
Crude model	1.00 ref	0.89 (0.53-1.49)	1.13 (0.70-1.84)	0.612
Multivariate model 1	1.00 ref	0.92 (0.54-1.59)	1.18 (0.71-1.96)	0.479
Multivariate model 2	1.00 ref	0.93 (0.54-1.60)	1.19 (0.70-2.02)	0.471
Total milk, median [P25-P75]; g/day[6]	0	6 [3-10]	60 [21-180]	
Cases/ person-year (n)	29/13327	29/12989	34/13192	

Rate per 1000 person-years	2.18	2.23	2.58	
Crude model	1.00 ref	0.82 (0.51-1.31)	0.55 (0.32-0.93)	0.040
Multivariate model 1	1.00 ref	0.90 (0.56-1.44)	0.63 (0.36-1.09)	0.126
Multivariate model 2	1.00 ref	0.85 (0.52-1.37)	0.60 (0.33-1.08)	0.121
Low-fat milk, median [P25-P75]; g/day[7]	15 [0-91]	201 [188-211]	406 [329-497]	
Cases/ person-year (n)	46/13187	27/13289	19/13032	
Rate per 1000 person-years	3.49	2.03	1.46	
Crude model	1.00 ref	0.58 (0.36-0.94)	0.42 (0.25-0.71)	0.001
Multivariate model 1	1.00 ref	0.66 (0.41-1.06)	0.50 (0.29-0.87)	0.016
Multivariate model 2	1.00 ref	0.64 (0.40-1.04)	0.49 (0.28-0.86)	0.014
Whole-fat milk, median [P25-P75]; g/day[8]	0	6 [3-10]	60 [21-180]	
Cases/ person-year (n)	29/13327	29/12989	34/13192	
Rate per 1000 person-years	2.18	2.23	2.58	
Crude model	1.00 ref	1.02 (0.61-1.71)	1.18 (0.72-1.94)	0.497
Multivariate model 1	1.00 ref	1.17 (0.69-2.00)	1.18 (0.70-1.99)	0.664
Multivariate model 2	1.00 ref	1.14 (0.68-1.93)	1.16 (0.69-1.95)	0.695
Concentrated full-fat dairy products [P25-P75]; g/day[9]	11 [6-16]	26 [23-30]	45 [38-55]	
Cases/ person-year (n)	32/13453	28/13064	32/12992	
Rate per 1000 person-years	2.38	2.14	2.46	
Crude model	1.00 ref	0.90 (0.54-1.49)	1.03 (0.63-1.69)	0.783
Multivariate model 1	1.00 ref	0.94 (0.55-1.61)	1.07 (0.64-1.78)	0.724
Multivariate model 2	1.00 ref	0.94 (0.55-1.61)	1.07 (0.62-1.84)	0.736
Sugar enriched dairy products [P25-P75]; g/day[10]	0 [0-1]	5 [3-6]	14 [10-25]	
Cases/ person-year (n)	28/13369	36/13092	28/13048	
Rate per 1000 person-years	2.09	2.75	2.15	
Crude model	1.00 ref	1.31 (0.80-2.15)	1.03 (0.61-1.73)	0.988
Multivariate model 1	1.00 ref	1.58 (0.95-2.63)	1.08 (0.61-1.91)	0.960
Multivariate model 2	1.00 ref	1.54 (0.92-2.58)	1.06 (0.59-1.91)	0.999
Fermented dairy products [P25-P75]; g/day[11]	36 [20-51]	97 [81-115]	166 [147-220]	
Cases/ person-year (n)	37/13510	29/13099	26/12899	

Rate per 1000 person-years	2.74	2.21	2.02	
Crude model	1.00 ref	0.81 (0.50-1.31)	0.74 (0.45-1.21)	0.218
Multivariate model 1	1.00 ref	0.93 (0.56-1.54)	0.88 (0.52-1.48)	0.600
Multivariate model 2	1.00 ref	0.93 (0.56-1.56)	0.89 (0.51-1.56)	0.649

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.

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UNIVERSITAT ROVIRA I VIRGILI
DIETARY AND LIFESTYLE DETERMINANTS ASSOCIATED WITH THE RISK OF COLORECTAL CANCER
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Chapter 2

Association between the 2018 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) and the low-risk lifestyle scores with colorectal cancer risk in elderly individuals at high cardiovascular risk.

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Article

Association between the 2018 WCRF/AICR and the Low-Risk Lifestyle Scores with Colorectal Cancer Risk in the Predimed Study

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Abstract: Limited longitudinal studies have been conducted to evaluate colorectal cancer (CRC) incidence based on the updated 2018 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations or other global lifestyle indices, and none in aged populations at high cardiovascular risk. We aimed to assess the association between CRC incidence and adherence to two emerging lifestyles indices (2018 WCRF/AICR score and another low-risk lifestyle (LRL) score comprising smoking status, alcohol consumption, physical activity, diet, and body

mass index) in the Spanish PREvencion con DIeta MEDiterranea (PREDIMED) cohort. We studied 7216 elderly men and women at high cardiovascular risk. The 2018 WCRF/AICR and LRL scores were calculated. Multivariable Cox proportional regression models were fitted to estimate the HRs (hazard ratios) and 95% confidence intervals (CIs) for incident CRC events. During a median interquartile range (IQR) follow-up of 6.0 (4.4–7.3) years, 97 CRC events were considered. A significant linear association was observed between each 1-point increment in the WCRF/AICR score (score range from 0 to 7) and CRC risk (HR (95% CI) = 0.79 (0.63–0.99)). Similarly, each 1-point increment in the LRL score (score range from 0 to 5) was associated with a 22% reduction in CRC risk (0.78 (0.64–0.96)). Adhering to emergent lifestyle scores might substantially reduce CRC incidence in elderly individuals. Further longitudinal studies, which take different lifestyle indexes into account, are warranted in the future.

Keywords: WCRF/AICR score; low-risk lifestyle index; colorectal cancer; PREDIMED; lifestyle patterns

1. Introduction

Worldwide, colorectal cancer (CRC) is an important public health problem since it is the second most commonly occurring cancer in women and the third in men. CRC is also the second most common cause of cancer death in both sexes globally. In 2018, there were over 1.8 million new CRC cases, and the global burden is expected to increase further due to the growth of the aging population and the adoption of westernized behaviors and lifestyles [1].

There is convincing evidence that some dietary components (i.e., processed meat and alcohol intake) and body fatness are modifiable risk factors, contributing to the development of CRC, whereas physical activity decreases the risk [2].

Since foods are not consumed in isolation and have additive or synergistic health-related effects, the current literature focuses on examining diet as a multidimensional exposure [3]. Several a priori defined food groups and general index-based dietary patterns have been associated with lower CRC risk, supporting the hypothesis that high overall diet quality is associated with decreased CRC risk [4,5].

Moreover, since both diet quality and other environmental factors have been shown to play an important role in the development of chronic diseases, healthy lifestyle indices have emerged. Previous work on CRC nutritional epidemiology has mainly focused on the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) score [6]. Nonetheless, very little is known about other lifestyle indices and their association with the risk of this type of cancer [7].

Some prospective cohort studies [6,8–13] and case-control studies [14–16] have evaluated the associations between CRC risk and adherence to cancer-specific nutritional recommendations with inconsistent results. However, limited longitudinal studies [13,16] have been conducted to assess associations based on the updated 2018 WCRF/AICR recommendations.

Another recent score by Li and coworkers [7], in the context of the Nurses' Health Study and the Health Professionals Follow-up Study, composed of five modifiable lifestyle factors (smoking status, alcohol consumption, physical activity, diet, and body mass index (BMI)), has consistently shown significant inverse associations with all-cause mortality, including cancer and cardiovascular disease (CVD) mortality and also with CVD incidence. Recently, this index has been also related to an increased healthy life expectancy (i.e., free of chronic diseases) [17]. However, information regarding this score with cancer incidence is lacking [7,18].

Lifestyle scores-generated a priori, according to current scientific knowledge, allows us to examine the potential combined effect of the individual score components on the incidence of different diseases. To the best of our knowledge, no previous study has evaluated the association between the aforementioned lifestyle score (low-risk lifestyle (LRL) score from now on) and the risk of developing CRC.

In an attempt to know whether using scores based on overall lifestyle patterns may be useful to prevent CRC in aging individuals, we aimed to evaluate the associations between adherence to the 2018 WCRF/AICR and LRL scores with CRC incidence in elderly Spanish individuals at high CVD risk. Our secondary objective was to evaluate the associated CRC risk for every individual component of each score.

2. Materials and Methods

2.1. Study Design

We conducted a prospective, longitudinal, observational cohort study within the frame of the PREDIMED (PREvencion con DIeta MEDiterranea) study. Briefly, the PREDIMED study is a multicenter, parallel-group controlled trial designed to assess the effect of a traditional Mediterranean Diet (MedDiet) on the primary prevention of CVD [19]. The PREDIMED Project was approved by the "Comité Ético de lnvestigación Clínica Hospital Clínic" from Barcelona (Project identification register: 2002–1244; date of approval: 16 July 2002).

The design and results of the PREDIMED trial with respect to the primary endpoint have been reported elsewhere [20]. Before starting the study, all participants provided informed consent. The Institutional Review Boards of each recruitment center approved the protocol. Even though for the main outcome of CVD, the trial was completed after a median follow-up of 4.8 years, we analyzed data based on the extended follow-up until December 2012.

2.2. Participants

A total of 7447 individuals from primary care centers were recruited to the PREDIMED trial between 2003 and 2009. Eligible participants were community-dwelling men (aged 55–80 years) and women (aged 60–80 years) free from CVD at baseline but who were at high risk because they had either type 2 diabetes (T2D) 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, malignant tumors diagnosis in the last five years prior to the recruitment, alcohol or drug abuse, a BMI $\geq$ 40 kg/m^2, and allergy or intolerance to olive oil or nuts. Participants were allocated to one of the three intervention groups: Mediterranean Diet (MedDiet) supplemented with nuts, MedDiet supplemented with extra virgin olive oil, or advice to reduce all sources of fat (control group). Energy restriction and physical activity were not encouraged in any group during the intervention. For this analysis, those participants who had implausible baseline 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) were excluded.

2.3. Ascertainment of Incident and Fatal CRC

New CRC events were defined as the first invasive CRC according to the International Classification of Diseases for Oncology topographical codes C18.0–C20.9. The results of the histological examination were considered confirmatory in most events (n = 67). Events were identified from the following sources: a review of all the medical records by a panel of physicians and researchers blinded to the intervention, at both primary healthcare and hospital level, and the national death index. The Endpoint Adjudication Committee, whose members were also blinded to the intervention, determined the cause of death, confirmed major events, and updated the endpoints of the PREDIMED study on a yearly basis.

2.4. Dietary Assessment

A validated semi-quantitative FFQ [21], which included 137 food items, was used to assess the dietary habits of participants in face-to-face interviews conducted by trained dietitians. The frequency of consumption of food items was asked 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). We used Spanish food composition tables to estimate energy and nutrient intake [22,23].

2.5. Other Lifestyle Variables Assessment

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 no shoes. Waist circumference was measured midway between the lowest rib and the iliac crest using an anthropometric tape. All anthropometric variables were measured annually. BMI was calculated by dividing the weight (kg) by the square of the height (m^2). Blood pressure was measured with a validated oscillometer (Omron HEM705CP, Hoofddorp, The Netherlands) in triplicate with a 5 min interval between each measurement.

The validated Spanish version of the Minnesota leisure-time physical activity (LTPA) questionnaire [24,25] was used to assess the amount and intensity of LTPA. The questionnaire consisted of 67 activities divided into 9 sections. The participants were asked to complete the form, reporting the number of days and minutes/day they had performed the activities during the previous week and year. Physical activity was quantified in the metabolic equivalent of tasks per minute per day (METs min/day). This unit was calculated by multiplying the METs assigned to each activity and their mean duration in minutes per day. LTPA was classified as light (intensity <4 METs), moderate (intensity 4–5.5 METs), and vigorous (intensity ≥6 METs). This questionnaire was completed during a baseline visit and annually thereafter. Moderate and vigorous intensity levels were combined into one category for purposes of analysis. A general questionnaire about lifestyle variables, such as smoking status or education level, medical history, and medication use, was completed and recorded at baseline and yearly thereafter.

2.6. 2018 WCRF/AICR Score Operationalization

We constructed a 7-point score based on the 2018 WCRF/AICR recommendations for cancer prevention [2]. The score components were (1) healthy weight, (2) physical activity, (3) plant foods, (4) fast food and processed foods, (5) red and processed meat, (6) sugar-sweetened beverages, and (7) alcohol. Detailed information on the score construction is shown in Table S1. The cut-off points for each component were based on 2018 WCRF/AICR recommendations when available or previously published literature otherwise. For each of the recommendations, we assigned 1 point when the recommendation was met, 0.5 points when it was partially met, and 0 points when it was not met. For those components with sub-recommendations, the considered component score was the average of the sub-recommendation scores. The mean score for each component was between 0.36 (red and processed meat consumption) and 0.70 (sugar-sweetened drink intake) points. The final index was the sum of all the components and ranged from 0 to 7. Higher scores indicated better adherence to cancer prevention recommendations.

2.7. Low Risk Lifestyle Score Operationalization

The LRL score is a 5-component index that was developed to assess the impact of healthy lifestyle factors on any-cause, cardiovascular, and cancer mortality in the US population [7]. We constructed this score in terms of adherence to the following LRL-related factors: (1) never smoking, (2) healthy weight, (3) regular physical activity, (4) healthy diet, and (5) moderate alcohol consumption. Detailed information on the score operationalization is presented in Table S2. For each risk factor, 1 point was given if the participant met the criterion for low risk or 0 points otherwise. The mean score for each component was between 0.07 (healthy body weight) and 0.62 (never smoking) points. The final

score was the sum of all components (score range from 0 to 5), with higher scores indicating a healthier lifestyle.

2.8. Statistical Analyses

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. The baseline characteristics of the participants were expressed as medians and (IQR) for continuous variables, and percentage (%) and number (*n*) for categorical variables. Chi-square and *t*-Student tests were used to assess differences in the baseline characteristics between CRC incident events and non-events. Continuous variables were normally distributed.

Multivariable time-dependent Cox proportional regression models were used to evaluate the associations between 2018 WCRF/AICR and LRL scores at baseline and the risk of developing CRC. Results were the hazard ratios (HRs) and their 95% confidence intervals (CIs) for the comparison between the highest vs. the lowest quantile for each overall score (quartile (Q) 4 vs. Q1 for 2018 WCRF/AICR score, and tertile (T) 3 vs. T1 for LRL score). Quantiles for each index were calculated considering the distribution of the variable in the analyzed population. The highest vs. the lowest categories for each individual component and their association with CRC risk were also compared. We used robust estimates of the variance to correct for potential intra-cluster correlation.

To calculate the associated CRC risk with both lifestyle scores, three different Cox regression models were used. The crude model was a univariate model. Model 1 was adjusted for age (years, as a continuous variable) and sex. Model 2 comprised model 1 additionally adjusted for the intervention group, family history of cancer (yes/no), education level (primary or secondary/high school university or graduate), history of diabetes (yes/no), baseline energy intake (Kcal/day, as a continuous variable), and treatment with aspirin (yes/no) at baseline. Model 2 for the 2018 WCRF/AICR score was further adjusted for smoking (current (yes/no), former (yes/no), or never (yes/no) smoker). The CRC risk associated with categories of the individual components of the 2018 WCRF/AICR score at baseline was additionally and mutually adjusted (model 3) for the other individual components at baseline: healthy weight (0, 0.25, 0.5, >0.75 point), physical activity (0, 0.5, 1 point), consumption of plant foods (0–0.5, >0.5–0.75, >0.75 point), fast food and processed foods (0, 0.5, 1 point), red and processed meat (0, 0.5, 1 point), sugar-sweetened beverages (0, 0.5, 1 point), and alcohol intake (0, 0.5, 1 point). Model 3 for the LRL components at baseline was model 2 plus the other individual LRL components at baseline: BMI ≥18.5 and <25 kg/m^2 (yes/no), never smoker (yes/no), low-risk alcohol consumption (yes/no), alternate healthy eating index (AHEI)-2010 score ≥P60 (yes/no), and moderate to vigorous physical activity (MVPA) ≥150 minutes/wk (yes/no). All models were stratified by recruitment center. The association with CRC for each 1-point increment in the WCRF/AICR and the LRL scores were also calculated by adding the score variable as continuous in the Cox regression models.

Statistical interactions between quantiles of both WCRF/AICR and LRL scores and potential confounders, such as age (years, as continuous), sex, and diabetes status, were evaluated by including interaction terms in the full-adjusted models. There were no statistical interactions between the WCRF/AICR and LRL scores, age, sex, and diabetes status. Linear trend tests were conducted by assigning the median value of each quantile of scores and individual score components and then using it as a continuous variable. In secondary analyses, we explored the contribution of certain relevant variables to all primary analyses of the scores. Thus, we conducted subgroup analyses by age (<67 or ≥67 y old), sex (men or women), and T2D status (prevalent or non-prevalent).

To test the robustness of our findings, we used a mixed-effects Cox regression model to take into account repeated measures of the covariates and the participants' deviances into the model. We used a robust estimate of the variance to account for intra-cluster correlation within the same families or clinics (as previously reported in [20]) and the repeated measures of the covariates as the fixed effects. However, the variable for the different scores was set at baseline for comparison purposes with our main analysis. All *p*-values were two-sided, and a p-value < 0.05 was considered statistically

significant. Analyses were performed using the STATA (14.0, StataCorp LP, Lakeway Drive, TX. USA) and R (v. 3.5.1) software (GNU General Public License, Boston, MA, USA).

3. Results

During a median (IQR) follow-up of 6.0 (4.4–7.3) years, we documented 101 CRC events. Of the 7447 participants, we excluded those with energy intake values outside the pre-specified limits (n = 153) and those lacking baseline FFQ (n = 78). Finally, 7216 individuals and 97 new CRC events were included in our analysis.

3.1. Baseline Characteristics of the Participants

The general baseline characteristics of the PREDIMED population are shown in Table 1. The median age of the participants was 67 years, 57% of whom were women, and 49% of whom had prevalent T2D. The median (IQR) age at cancer diagnosis was 72.4 (66.8–76.4) years. The median (IQR) 2018 WCRF/AICR score in the whole population was 3.8 (3.3–4.4) points, with no statistically significant differences between events/non-events (p-value = 0.110). The overall median (IQR) for the LRL score was 2 (1–2) points, with CRC events showing statistically significant lower scores than non-events (p-value = 0.021). Among the participants who developed CRC, there were significantly more men than women compared with non-events (58.8% vs. 41.2%, respectively; p-value = 0.001). In addition, those who did not develop CRC were more likely to be never-smokers in comparison to new CRC cases (61.7% vs. 47.4%, respectively; p-value = 0.011).

Table 1. Baseline characteristics of the study population in the PREvención con DIeta MEDiterránea (PREDIMED) study [a].

	Total Study Population n **= 7216**	**Colorectal Cancer Events** n **= 97**	**Non-Events** n **= 7119**	p**-Value** [b]
2018 WCRF/AICR score	3.8 (3.3–4.4)	3.8 (3.2–4.2)	3.8 (3.3–4.4)	0.110
Low-risk lifestyle score	2 (1–2)	1 (1–2)	2 (1–2)	0.021 *
Age, years	67 (62–72)	67 (62–72)	67 (62–72)	0.269
Women, % (n)	57.4 (4145)	41.2 (40)	57.7 (4105)	0.001 *
Education level, % (n)				
Primary, secondary, high school	92.9 (6700)	92.8 (90)	92.9 (6610)	0.980
University/graduate	7.2 (516)	7.2 (7)	7.2 (509)	
Age at diagnosis of cancer, years	72.4 (66.8–76.4)	72.4 (66.8–76.4)	–	–
Family history of cancer, % (n)	49.2 (3548)	41.2 (40)	49.3 (3508)	0.116
Cancer location				
Colon, % (n)	77 (79.4)	77 (79.4)	–	–
Rectum, % (n)	20 (20.6)	20 (20.6)	–	–
Diabetes, % (n)	48.9 (3527)	51.6 (50)	48.8 (3477)	0.597
Hypertension, % (n)	82.7 (5970)	80.4 (78)	82.8 (5892)	0.543
Waist circumference, cm				
Women	99 (91–105)	98.2 (92–107)	99 (91–105)	0.614
Men	103 (97–109)	103 (96–11)	103 (97–109)	0.441
BMI, kg/m^2	29.7 (27.2–32.5)	29.9 (27.6–32.3)	29.7 (27.2–32.5)	0.813
MVPA, min./wk.	42.2 (0–296.5)	52.5 (0–311)	42.1 (0–296.5)	0.982
Smoking status, % (n)				
Never smokers	61.5 (4438)	47.4 (46)	61.7 (4392)	
Former smokers	24.6 (1774)	30.9 (30)	24.5 (1744)	0.011 *
Current smokers	13.9 (1004)	21.7 (21)	13.8 (983)	
Current medication, % (n)				
Aspirin	22.4 (1613)	24.7 (24)	22.3 (1589)	0.758
HRT (only in women)	2.8 (115)	5 (2)	2.8 (113)	0.234
Intervention groups, % (n)				
MedDiet + EVOO	34.3 (2474)	39.2 (38)	34.2 (2436)	
MedDiet + nuts	32.7 (2360)	34.0 (33)	32.7 (2327)	0.390
Control low–fat diet	33.0 (2382)	26.8 (26)	33.1 (2356)	
Energy intake (kcal/day)	2184.4 (1842.9–2579.7)	2183.4 (1942–2669.3)	2184.5 (1841.6–2578.2)	0.263
AHEI–2010 score	64.4 (58.8–70.2)	62.6 (57.4–69.1)	64.4 (58.9–70.2)	0.210

Table 1. *Cont.*

	Total Study Population *n* = 7216	Colorectal Cancer Events *n* = 97	Non-Events *n* = 7119	*p*-Value [b]
Food consumption, g/day				
Vegetables	313.7 (235–408.7)	289.2 (221.2–367)	314 (235–409.3)	0.164
Fruits	333.1 (227.2–475)	324.5 (222.4–459.2)	333.3 (227.6–475)	0.454
Legumes	17.1 (12.6–25.1)	17.1 (16–25.1)	17.1 (12.6–25.1)	0.778
Red and processed meat	68.1 (42.6–100)	68.3 (45.7–111.7)	68.1 (42.4–100)	0.073
Fast food and processed foods	72.4 (45.7–109.2)	77.2 (51–108.6)	72.4 (45.7–109.2)	0.746
Sugar-sweetened beverages	13.3 (0–85.7)	13.3 (0–99.1)	13.3 (0–85.7)	0.388
Alcohol	1.5 (0–10.4)	4.3 (0–12.2)	1.5 (0–10.4)	0.093

[a] Data are expressed as medians (IQR, interquartile range) for continuous variables and percentage and number (*n*) for categorical variables. [b] *p*-values for comparison between colorectal cancer cases and non-cases were calculated by chi-square or *t*-Student tests for categorical and continuous variables, respectively. All statistical tests were two-sided. * *p*-value <0.05. Abbreviations: AHEI, alternate healthy eating index; BMI, body mass index; EVOO, extra virgin olive oil; HRT, hormone replacement therapy; MedDiet, Mediterranean diet; min/wk., min/week; MVPA, moderate-to-vigorous physical activity; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

3.2. World Cancer Research Fund/American Institute for Cancer Research and Low Risk Lifestyle Scores and Risk of Colorectal Cancer

Table 2 shows the associations (HRs and 95% CIs) for CRC incidence with the overall 2018 WCRF/AICR and LRL scores at baseline. Statistically significant linear associations were observed between a 1-point increment in the WCRF/AICR score and CRC risk in all statistical models (HR $_{\text{model 2}}$ (95% CI) = 0.79 (0.63–0.99); *p* for trend = 0.045). Similarly, each 1-point increment in the LRL score was associated with a 22% lower CRC risk (HR $_{\text{model 2}}$ (95% CI) = 0.78 (0.64–0.96); *p* for trend = 0.017).

Table 2. HRs and 95% CIs between the 2018 WCRF/AICR and the low-risk lifestyle scores and colorectal cancer risk at baseline in the PREDIMED study (*n* = 7216).

	2018 WCRF/AICR Score		Low-Risk Lifestyle Score	
	Continuous Analysis (1-Point Increment), HR (95% CI)	*p* for Trend	Continuous Analysis (1-Point Increment), HR (95% CI)	*p* for Trend
Events/non-events (*n*)	97/7216	-	97/7216	-
Crude model	0.79 (0.63–0.98) *	0.033 *	0.77 (0.62–0.95) *	0.016 *
Model 1	0.78 (0.62–0.98) *	0.034 *	0.78 (0.64–0.96) *	0.019 *
Model 2	0.79 (0.63–0.99) *	0.045 *	0.78 (0.64–0.96) *	0.017 *

Model 1 adjusted for age (years - continuous) and sex. Model 2 was model 1 plus intervention group (MedDiet + EVOO, MedDiet + nuts, low-fat control), family history of cancer (yes/no), education level (primary or secondary/high school, university or graduate), history of diabetes (yes/no), baseline energy intake (Kcal/day, continuous), and treatment with aspirin (yes/no) at baseline. Model 2 for the 2018 WCRF/AICR score was further adjusted for a current smoker (yes/no), former smoker (yes/no), never smoker (yes/no). All models were stratified by recruitment center. * *p*-value < 0.05. Abbreviations: CI, confidence interval; EVOO, extra virgin olive oil; HR, hazard ratio; MedDiet, Mediterranean Diet; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

Along the same lines, when we analyzed the associations between CRC incidence and categories of adherence to each overall score (Figure 1), high adherence to WCRF/AICR recommendations was inversely associated with CRC risk (HR Q4 vs. Q1 (95% CI) = 0.52 (0.27–0.99); *p* for trend = 0.130) compared to the reference category. For adherence to the LRL score, the reduction in CRC risk remained statistically significant (HR T3 vs. T1 (95% CI) = 0.48 (0.26–0.86); *p* for trend = 0.007) when analyzed as categorical. A sensitivity analysis using mixed-effects Cox regression models mirrored our results for the WCRF/AICR (HR Q4 vs. Q1 (95% CI) = 0.57 (0.32–0.82)) and LRL scores (HR T3 vs. T1 (95% CI) = 0.44 (0.20–0.68)). Baseline characteristics of the participants and the number of CRC cases according to quantiles of each score are shown in the Supplementary Materials (Tables S3 and S4).

For each 1-point increment in the number of components of the LRL score, there was a statistically significant 23% lower risk of CRC (HR $_{\text{model 2}}$ (95% CI) = 0.77 (0.62–0.95); *p* for trend = 0.016) (Table S5).

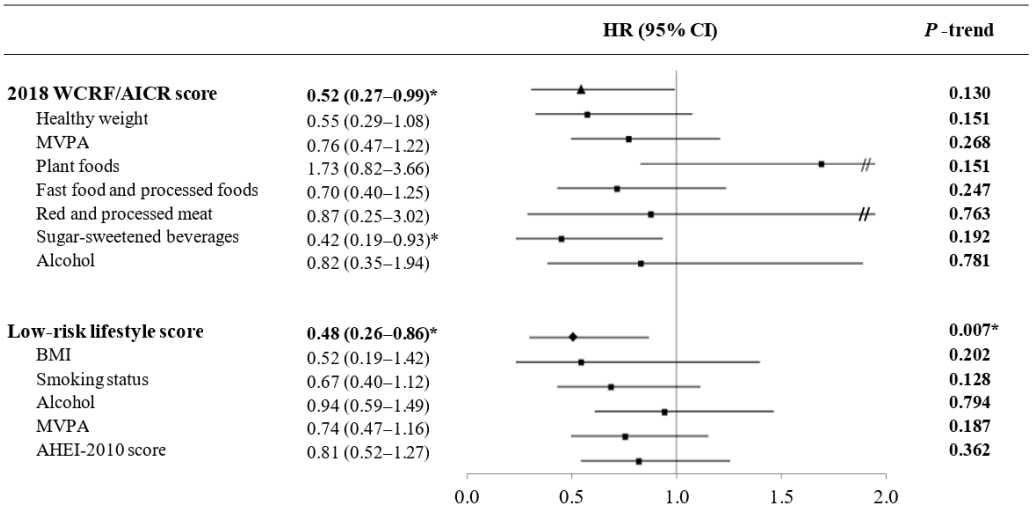

Figure 1. Colorectal cancer risk associated with 2018 WCRF/AICR and low-risk lifestyle scores and the individual components of each index in the PREvención con DIeta MEDiterránea (PREDIMED) cohort (n = 7216). Multivariable Cox proportional regression models were used. Results were the HRs (95% CIs) for the comparison between the highest vs. the lowest quantile for each overall score (2018 WCRF/AICR score: Quartile (Q) 4 vs. Q1; low-risk lifestyle score: Tertile (T) 3 vs. T1) and the comparison for the highest vs. the lowest category for each individual component of the score (see Tables 3 and 4). * p-value < 0.05. p for trend stands for linear trend. Abbreviations: AHEI, alternate healthy eating index; BMI, body mass index; CI, confidence interval; HR, hazard ratio; MVPA, moderate-to-vigorous physical activity; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research. The triangle represents the HR for the WCRF/AICR score; the square represents the HRs for the individual components of each score, and the diamond represents the HR for the LRL score; Double slash appears when CI > 2.

3.3. Individual Components of the Scores and Risk of CRC

Table 3 shows the mutually adjusted HRs and 95% CIs for CRC risk associated with categories of individual components of the WCRF/AICR score at baseline. In model 3, those individuals with the maximum score (1 point) for the sugar-sweetened beverages component exhibited a significantly lower risk of developing CRC (HR (95% CI) = 0.42 (0.19–0.93); p for trend = 0.192) than those with the lowest score (0 points). Non-statistically significant associations with CRC risk were observed for the other score components (healthy body weight, physical activity and consumption of plant foods, fast food and processed foods, red and processed meat, and alcohol intake).

Table 4 shows the HRs and 95% CIs for CRC risk associated with different categories of individual LRL components at baseline. In the crude model, participants who had never smoked presented a statistically significant linear decreased risk of developing CRC (HR (95% CI) = 0.55 (0.36–0.83); p for trend = 0.004) in comparison to current and former smokers. Nonetheless, when the model was further adjusted for confounding variables, the association was attenuated and became non-significant (HR (95% CI) = 0.67 (0.40–1.12); p for trend = 0.128). Non-significant inverse associations between the other LRL recommendations (BMI, alcohol intake, physical activity, and diet) and CRC risk were observed.

Table 3. Mutually adjusted HRs and 95% CIs for colorectal cancer risk associated with categories of individual components of the 2018 WCRF/AICR score at baseline in the PREDIMED study (*n* = 7216).

	Component Score, HR (95% CI)				
Healthy weight	**0**	**0.25**	**0.5**	**>0.75**	***p* for trend**
Events/non-events (*n*)	22/1381	22/1723	33/2233	20/1782	-
Crude model	1.00	0.77 (0.41–1.45)	0.90 (0.50–1.60)	0.62 (0.33–1.17)	0.220
Model 1	1.00	0.71 (0.37–1.33)	0.85 (0.48–1.54)	0.54 (0.28–1.06)	0.135
Model 2	1.00	0.71 (0.38–1.33)	0.87 (0.48–1.55)	0.54 (0.28–1.05)	0.134
Model 3	1.00	0.71 (0.38–1.35)	0.88 (0.49–1.56)	0.55 (0.29–1.08)	0.151
Physical activity	**0**	**0.5**	**1**	**-**	***p* for trend**
Events/non-events (*n*)	53/3893	11/590	33/2636	-	
Crude model	1.00	1.25 (0.63–2.48)	0.82 (0.51–1.32)	-	0.441
Model 1	1.00	1.25 (0.63–2.48)	0.75 (0.46–1.22)	-	0.254
Model 2	1.00	1.24 (0.62–2.48)	0.76 (0.47–1.22)	-	0.271
Model 3	1.00	1.24 (0.63–2.46)	0.76 (0.47–1.22)	-	0.268
Plant foods	**0-0.5**	**>0.5–0.75**	**>0.75**	**-**	***p* for trend**
Events/non-events (*n*)	14/1345	56/3952	27/1822	-	
Crude model	1.00	1.38 (0.77–2.47)	1.66 (0.82–3.34)	-	0.158
Model 1	1.00	1.34 (0.75–2.40)	1.57 (0.78–3.16)	-	0.210
Model 2	1.00	1.34 (0.75–2.41)	1.60 (0.77–3.32)	-	0.206
Model 3	1.00	1.38 (0.76–2.49)	1.73 (0.82–3.66)	-	0.151
Fast food and processed foods	**0**	**0.5**	**1**	**-**	***p* for trend**
Events/non-events (*n*)	18/1201	39/2766	40/3152	-	-
Crude model	1.00	0.82 (0.46–1.45)	0.72 (0.41–1.26)	-	0.258
Model 1	1.00	0.84 (0.47–1.49)	0.72 (0.41–1.28)	-	0.260
Model 2	1.00	0.85 (0.48–1.49)	0.73 (0.41–1.29)	-	0.278
Model 3	1.00	0.81 (0.47–1.42)	0.70 (0.40–1.25)	-	0.247
Red and processed meat	**0**	**0.5**	**1**	**-**	***p* for trend**
Events/non-events (*n*)	36/2263	58/4577	3/279	-	-
Crude model	1.00	0.89 (0.58–1.36)	0.77 (0.23–2.55)	-	0.531
Model 1	1.00	0.95 (0.60–1.48)	0.87 (0.26–2.94)	-	0.771
Model 2	1.00	0.97 (0.62–1.54)	0.90 (0.26–3.07)	-	0.868
Model 3	1.00	0.94 (0.60–1.48)	0.88 (0.25–3.06)	-	0.771
Sugar-sweetened beverages	**0**	**0.5**	**1**	**-**	***p* for trend**
Events/non-events (*n*)	8/326	48/3675	41/3118	-	-
Crude model	1.00	0.45 (0.21–0.96) *	0.45 (0.21–0.94) *	-	0.298
Model 1	1.00	0.46 (0.22–0.98) *	0.43 (0.20–0.90) *	-	0.174
Model 2	1.00	0.47 (0.21–1.02)	0.43 (0.20–0.94) *	-	0.185
Model 3	1.00	0.45 (0.21–1.00)	0.42 (0.19–0.93) *	-	0.192
Alcohol intake	**0**	**0.5**	**1**	**-**	***p* for trend**
Events/non-events (*n*)	7/389	60/4111	30/2619	-	-
Crude model	1.00	0.86 (0.40–1.86)	0.68 (0.31–1.52)	-	0.221
Model 1	1.00	0.86 (0.40–1.85)	0.85 (0.38–1.89)	-	0.771
Model 2	1.00	0.96 (0.43–2.12)	0.98 (0.42–2.27)	-	0.979
Model 3	1.00	0.82 (0.36–1.87)	0.82 (0.35–1.94)	-	0.781

Model 1 adjusted for age (years - continuous) and sex. Model 2 was further adjusted for the intervention group (MedDiet + EVOO, MedDiet + nuts, low-fat control), 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), baseline energy intake (Kcal/day, continuous), and treatment with aspirin (yes/no) at baseline. Model 3 was model 2 plus the other individual components at baseline: healthy weight (0, 0.25, 0.5, >0.75 point), physical activity (0, 0.5, 1 point), plant foods (0–0.5, >0.5–0.75, >0.75 point), fast food and processed foods (0, 0.5, 1 point), red and processed meat (0, 0.5, 1 point), sugar-sweetened beverages (0, 0.5, 1 point), and alcohol intake (0, 0.5, 1 point). Categories for each score component were established based on the number of subcomponents and the score distribution in the population studied. All models were stratified by recruitment center. * *p*-value < 0.05. Abbreviations: CI, confidence interval; EVOO, extra virgin olive oil; HR, hazard ratio; MedDiet: Mediterranean diet; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

Table 4. Mutually adjusted HRs and 95% CIs for colorectal cancer risk associated with different categories of individual low-risk lifestyle components at baseline in the PREDIMED study (*n* = 7216).

	Component Score, HR (95% CI)		
BMI	**0**	**1**	***p* for trend**
Events/non-events (*n*)	93/6607	4/512	
Crude model	1.00	0.54 (0.20–1.46)	0.222
Model 1	1.00	0.52 (0.19–1.41)	0.200
Model 2	1.00	0.51 (0.19–1.39)	0.190
Model 3	1.00	0.52 (0.19–1.42)	0.202
Smoking status	**0**	**1**	***p* for trend**
Events/non-events (*n*)	51/2727	46/4392	
Crude model	1.00	0.55 (0.36–0.83) *	0.004 *
Model 1	1.00	0.66 (0.40–1.11)	0.119
Model 2	1.00	0.66 (0.39–1.10)	0.113
Model 3	1.00	0.67 (0.40–1.12)	0.128
Alcohol consumption	**0**	**1**	***p* for trend**
Events/non-events (*n*)	65/4992	32/2127	
Crude model	1.00	1.12 (0.73–1.71)	0.594
Model 1	1.00	0.90 (0.58–1.39)	0.626
Model 2	1.00	0.88 (0.56–1.39)	0.594
Model 3	1.00	0.94 (0.59–1.49)	0.794
Physical activity	**0**	**1**	***p* for trend**
Events/non-events (*n*)	64/4483	33/2636	
Crude model	1.00	0.79 (0.51–1.24)	0.303
Model 1	1.00	0.72 (0.45–1.13)	0.155
Model 2	1.00	0.71 (0.45–1.12)	0.146
Model 3	1.00	0.74 (0.47–1.16)	0.187
AHEI-2010 score	**0**	**1**	***p* for trend**
Events/non-events (*n*)	64/4266	33/2853	0.268
Crude model	1.00	0.81 (0.52–1.25)	0.269
Model 1	1.00	0.78 (0.51–1.21)	0.268
Model 2	1.00	0.78 (0.50–1.21)	0.268
Model 3	1.00	0.81 (0.52–1.27)	0.362

Model 1 adjusted for age (years - continuous) and sex. Model 2 was further adjusted for the intervention group (MedDiet + EVOO, MedDiet + nuts, low-fat control), family history of cancer (yes/no), education level (primary or secondary/high school, university or graduate), history of diabetes (yes/no), baseline energy intake (Kcal/day, continuous), and treatment with aspirin (yes/no) at baseline. Model 3 was model 2 plus the other individual low-risk lifestyle components at baseline: BMI ≥18.5 and ≤24.9 kg/m^2 (yes/no), never smoker (yes/no), low-risk alcohol consumption (yes/no), AHEI-2010 score ≥P60 (yes/no), MVPA ≥150 min./wk (yes/no). All models were stratified by recruitment center. * *p*-value <0.05. Abbreviations: AHEI, alternate healthy eating index; BMI, body mass index; CI, confidence interval; EVOO, extra virgin olive oil; HR, hazard ratio; MedDiet: Mediterranean diet; P, percentile.

We also observed statistically significant differences across age, sex, and prevalent T2D status (Table S6). The inverse association between CRC risk and the WCRF/AICR score (HR $_{\text{model 2}}$ (95% CI) = 0.71 (0.50–0.99; *p* for trend = 0.050) and the LRL score (HR $_{\text{model 2}}$ (95% CI) = 0.76 (0.58–0.99; *p* for trend = 0.048) was stronger in those participants above the median age (≥67 years) than in those below. Associations for the LRL score were stronger in women (HR $_{\text{model 2}}$ (95% CI) = 0.69 (0.50–0.95; *p* for trend = 0.023) than in men (HR $_{\text{model 2}}$ (95% CI) = 0.84 (0.65–1.08; *p* for trend = 0.174). However, for the 2018 WCRF/AICR score, there were no significant differences by sex. Those participants presenting T2D at baseline exhibited a stronger association between the WCRF/AICR score and CRC risk (HR $_{\text{model 2}}$ (95% CI) = 0.71 (0.53–0.96; *p* for trend = 0.024) in comparison to non-prevalent T2D individuals (HR $_{\text{model 2}}$ (95% CI) = 0.87 (0.61–1.24; *p* for trend = 0.443). On the contrary, the association between the LRL score and CRC risk was significantly higher in non-prevalent T2D participants (HR $_{\text{model 2}}$ (95%

CI) = 0.71 (0.52-0.95; *p* for trend = 0.021) than in individuals with T2D at baseline (HR $_{\text{model 2}}$ (95% CI) = 0.81 (0.62–1.06; *P* for trend = 0.443).

4. Discussion

This prospective cohort study showed that adherence to the most recent 2018 WCRF/AICR recommendations, as well as accomplishing a cluster of LRL factors, was inversely associated with CRC incidence in elderly Mediterranean individuals at high cardiovascular risk. As far as we are aware, this was the first study to assess the relationship between the recent LRL score [7] and the risk of CRC. On the other hand, this work provided additional support to confirm that new 2018 WCRF/AICR recommendations also apply for aging individuals at high CVD risk.

In agreement with the results obtained, El Kinany and coworkers [16] found that greater adherence to the 2018 WCRF/AICR score decreased overall CRC risk by 42% after comparing 1516 cases with 1516 controls in Morocco. Similarly, a 24-year-follow-up cohort study [13], with 68,977 women from the Nurses' Health Study and 45,442 men from the Health Professionals Follow-up Study, found a statistically significant inverse association between adherence to the updated WCRF/AICR score and the incidence of CRC risk in men. Furthermore, associations in women were weaker. On the other hand, we did not find any statistically significant differences between sexes in our subgroup analyses for the WCRF/AICR score. However, differences in the sample size, number of CRC cases, and score operationalization between both studies might account for this discrepancy.

Our results confirmed the findings of a meta-analysis of seven prospective cohort studies [26], including 361,616 European and US adults (aged > 60, 43% women) and 6507 CRC cases, within the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES) Project. It showed with a low level of heterogeneity that adherence to WCRF/AICR recommendations for cancer prevention was also applicable in the elderly. Nonetheless, our findings added new evidence to suggest that not only might elderly individuals benefit from following these recommendations but also individuals who are at high CVD risk.

Although some longitudinal studies [6,9,14,15,27] on the former 2007 WCRF/AICR recommendations [28] have also observed statistically significant inverse associations with CRC risk, non-significant results have been reported in other studies [10–12,29]. This inconsistency could be due to differences in the study design, different cut-points used, and the number of components for scoring between studies. It should be noted that the 2018 WCRF/AICR report [2] again recommends the intake of at least 30 g/day of fiber and reducing the consumption of processed food high in fat and sugars, but no longer discourages the consumption of energy-dense foods without taking into consideration their nutritional composition [30].

Even though the LRL score was developed in an attempt to assess the impact of an overall healthy lifestyle pattern on all-cause mortality (including cancer and CVD mortality), our results suggested that this score might also be a useful tool for CRC prevention. This is of great potential importance since non-communicable diseases, such as CVD and cancer, are the leading causes of mortality worldwide [31].

In our study, even though the reduction in CRC risk due to greater adherence to the 2018 WCRF/AICR score and the LRL index was similar (48% and 52%, respectively), some differences between the two indexes should be examined. In the WCRF/AICR score, there was no penalty for tobacco use, which could have modified the inverse association observed. On the other hand, the penalty for alcohol intake was stricter in the WCRF/AICR score than in the LRL score. The WCRF/AICR advises not to consume alcohol and focuses on dietary national guidelines in the case of intake, whereas the LRL score accepts a moderate intake as adhering fully to the alcohol recommendation. These different cut-off points for alcohol intake might also have had different roles in the associations found. Furthermore, the WCRF/AICR score gives more weight to nutritional factors, while the LRL score considers the overall diet as a single component using the AHEI-2010 score and, therefore, does not ignore the synergy between nutritional components.

Regarding subgroup analyses, considering that no significant interactions were found with CRC risk, and because confidence intervals strongly overlapped between subgroups, we could not assure a significant interaction between the scores and CRC risk based on age, sex, and diabetes status.

In terms of the WCRF/AICR score, greater adherence to the sugar-sweetened beverages recommendation was strongly and inversely associated with a statistically significant decreased risk of developing CRC of 58%. Because neither the other individual recommendations of the WCRF/AICR score nor the individual components of the LRL score were significantly associated with CRC risk, it seemed that a synergistic effect between components might be suggested. However, most of the non-significant associations between the components of both scores and CRC risk were in the expected direction.

Our results suggested that synergy between the various factors of each score might be one of the main mechanisms. On the other hand, sugar-sweetened beverages consumption had been shown to be independently associated with CRC risk in our analyses. It should be noted that according to the WCRF/AICR, sugar-sweetened beverages intake is mostly linked to weight gain, which increases CRC risk, while no specific components in the drinks are mentioned that may increase the risk of this cancer. However, other potential mechanisms suggested in the literature should be further explored.

High glycemic index and glycemic load from sugar-sweetened beverages might stimulate postprandial glucose and/or insulin response, which is associated with diabetes-related cancer risk [32]. The evidence suggests that insulin stimulates tumor growth by decreasing the production of insulin-like growth factor-binding protein 1 (IGFBP-1) [33], increasing the tissue bioavailability of Insuline-like growth factor (IGF)-I, or inhibiting apoptosis [34]. Furthermore, some in vitro studies have shown that insulin might also stimulate the mitogenesis of cultured normal colorectal epithelial cells and tumor angiogenesis [35,36]. In addition, it has been reported that consumers of sugar drinks may be exposed to 4-methylimidazole (4-MEI), a potential carcinogen formed during the manufacture of the caramel color, added to many widely consumed beverages as a colorant. More studies are needed to investigate how this chemical contributes to the risk of CRC [37].

The findings of the present study have to be interpreted in light of some limitations. Firstly, score components were added, so they contributed equally to the total score. The fact that not all the components of the WCRF/AICR score are associated with the risk of developing CRC might have weakened the associations observed. Since CRC was a secondary outcome in the PREDIMED trial, we did not have enough CRC cases to evaluate CRC subtypes separately (colon and rectum) or by tumor site (left and right colon) with sufficient statistical power. This lack of statistical power might also explain the lack of association found between individual components consistently associated with decreased CRC. Because of insufficient data, three items from the WCRF/AICR score (breastfeeding, cancer prevention supplement use, and following the recommendations after a cancer diagnosis) were omitted. Nonetheless, it is important to mention that the breastfeeding component is not mandatory since it is only applicable to a specific subpopulation. In addition, multivitamin supplement use in our cohort was extremely low. Therefore, this component would have had very little impact on our results. Besides, we also decided to omit supplement vitamin use and the cancer survivors component because of operational redundancy [30]. Additionally, a generalization of our results might be limited because of our specific study population at high cardiovascular risk. Further, although the intervention arm was considered as a potential confounder in our main statistical models, we could not rule out residual confounding due to changes in diet between groups. Finally, the causality of the observed associations could not be established due to the observational nature of our study.

However, our study had several strengths. First, it had a large-scale prospective design, a long follow-up period, and a large sample. Second, a Clinical Event Adjudication Committee confirmed all major events annually. Third, we used a validated FFQ and, although residual confounding control could not be ruled out, we controlled for several potential confounders in our statistical analyses. Fourth, we used data-driven approaches (quantiles and median cut-offs) to operationalize recommendations that did not provide quantitative cut-offs, and a three-level WCRF/AICR score, which gives a more continuous variable and considers partial adherence. Finally, we confirmed the robustness of our results by testing

our primary results with two different approaches—multivariable time-dependent Cox proportional regression models and mixed-effects Cox regression models—and stratified analyses.

To conclude, following the 2018 WCRF/AICR recommendations and healthier behavior patterns, the calculated LRL score could substantially help to reduce the risk of developing CRC in an elderly Mediterranean population at high CVD risk. Although the WCRF/AICR score was specifically designed in the context of cancer prevention, we suggest that using other scores based on healthy lifestyle patterns, such as the LRL index, might also be a useful tool to prevent CRC, especially in elderly individuals. The results of this study need to be replicated in other populations with different dietary and lifestyle patterns. For this purpose, large-prospective cohorts with more events are needed to extend the evidence on lifestyle patterns and CRC risk.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/9/4/1215/s1, Table S1: Third expert report 2018 WCRF/AICR score operationalization in the PREDIMED cohort; Table S2: Low-risk lifestyle score operationalization in the PREDIMED cohort; Table S3: Baseline characteristics of the study population in the PREDIMED study according to quartiles of WCRF/AICR score; Table S4: Baseline characteristics of the study population in the PREDIMED study according to tertiles of low-risk lifestyle score; Table S5: Mutually adjusted HRs and 95% CIs for colorectal cancer risk associated with different categories of a combination of low-risk lifestyle factors at baseline in the PREDIMED study (n = 7216); Table S6: HRs and 95% CIs between the 2018 WCRF/AICR and the low-risk lifestyle scores and colorectal cancer risk at baseline in the PREDIMED study by subgroups (age, sex, and T2D status).

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References

1. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **2018**, *68*, 394–424. [CrossRef]
2. World Cancer Research Fund/American Institute for Cancer Research Diet, Nutrition, Physical Activity and Cancer: A Global Perspective. *Continuous Update Project Expert Report*. 2018. Available online: https://www.wcrf.org/dietandcancer (accessed on 15 February 2020).
3. Kant, A.K. Dietary patterns and health outcomes. *J. Am. Diet. Assoc.* **2004**, *104*, 615–635. [CrossRef] [PubMed]
4. Steck, S.E.; Guinter, M.; Zheng, J.; Thomson, C.A. Index-Based Dietary Patterns and Colorectal Cancer Risk: A Systematic Review. *Adv. Nutr. Int. Rev. J.* **2015**, *6*, 763–773. [CrossRef] [PubMed]

5. Schwingshackl, L.; Bogensberger, B.; Hoffmann, G. Diet Quality as Assessed by the Healthy Eating Index, Alternate Healthy Eating Index, Dietary Approaches to Stop Hypertension Score, and Health Outcomes: An Updated Systematic Review and Meta-Analysis of Cohort Studies. *J. Acad. Nutr. Diet.* **2018**, *118*, 74–100.e11. [CrossRef] [PubMed]
6. Romaguera, D.; Vergnaud, A.-C.; Peeters, P.H.; van Gils, C.H.; Chan, D.S.M.; Ferrari, P.; Romieu, I.; Jenab, M.; Slimani, N.; Clavel-Chapelon, F.; et al. Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. *Am. J. Clin. Nutr.* **2012**, *96*, 150–163. [CrossRef] [PubMed]
7. Li, Y.; Pan, A.; Wang, D.D.; Liu, X.; Dhana, K.; Franco, O.H.; Kaptoge, S.; Di Angelantonio, E.; Stampfer, M.; Willett, W.C.; et al. Impact of Healthy Lifestyle Factors on Life Expectancies in the US Population. *Circulation* **2018**, *138*, 345–355. [CrossRef]
8. Thomson, C.A.; McCullough, M.L.; Wertheim, B.C.; Chlebowski, R.T.; Martinez, M.E.; Stefanick, M.L.; Rohan, T.E.; Manson, J.E.; Tindle, H.A.; Ockene, J.; et al. Nutrition and physical activity cancer prevention guidelines, cancer risk, and mortality in the women's health initiative. *Cancer Prev. Res.* **2014**, *7*, 42–53. [CrossRef]
9. Kabat, G.C.; Matthews, C.E.; Kamensky, V.; Hollenbeck, A.R.; Rohan, T.E. Adherence to cancer prevention guidelines and cancer incidence, cancer mortality, and total mortality: A prospective cohort study. *Am. J. Clin. Nutr.* **2015**, *101*, 558–569. [CrossRef]
10. Makarem, N.; Lin, Y.; Bandera, E.V.; Jacques, P.F.; Parekh, N. Concordance with World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) guidelines for cancer prevention and obesity-related cancer risk in the Framingham Offspring cohort (1991–2008). *Cancer Causes Control* **2015**, *26*, 277–286. [CrossRef]
11. Nomura, S.J.O.; Dash, C.; Rosenberg, L.; Yu, J.; Palmer, J.R.; Adams-Campbell, L.L. Is adherence to diet, physical activity, and body weight cancer prevention recommendations associated with colorectal cancer incidence in African American women? *Cancer Causes Control* **2016**, *27*, 869–879. [CrossRef]
12. Jones, P.; Cade, J.E.; Evans, C.E.L.; Hancock, N.; Greenwood, D.C. Does adherence to the World Cancer Research Fund/American Institute of Cancer Research cancer prevention guidelines reduce risk of colorectal cancer in the UK Women's Cohort Study? *Br. J. Nutr.* **2018**, *119*, 340–348. [CrossRef] [PubMed]
13. Petimar, J.; Smith-Warner, S.A.; Rosner, B.; Chan, A.T.; Giovannucci, E.L.; Tabung, F.K. Adherence to the World Cancer Research Fund/American Institute for Cancer Research 2018 Recommendations for Cancer Prevention and Risk of Colorectal Cancer. *Cancer Epidemiol. Biomark. Prev.* **2019**, *28*, 1469–1479. [CrossRef] [PubMed]
14. Romaguera, D.; Gracia-Lavedan, E.; Molinuevo, A.; de Batlle, J.; Mendez, M.; Moreno, V.; Vidal, C.; Castelló, A.; Pérez-Gómez, B.; Martín, V.; et al. Adherence to nutrition-based cancer prevention guidelines and breast, prostate and colorectal cancer risk in the MCC-Spain case-control study. *Int. J. Cancer* **2017**, *141*, 83–93. [CrossRef] [PubMed]
15. Turati, F.; Bravi, F.; Di Maso, M.; Bosetti, C.; Polesel, J.; Serraino, D.; Dalmartello, M.; Giacosa, A.; Montella, M.; Tavani, A.; et al. Adherence to the World Cancer Research Fund/American Institute for Cancer Research recommendations and colorectal cancer risk. *Eur. J. Cancer* **2017**, *85*, 86–94. [CrossRef] [PubMed]
16. El Kinany, K.; Huybrechts, I.; Kampman, E.; Boudouaya, H.A.; Hatime, Z.; Mint Sidi Deoula, M.; El Asri, A.; Benslimane, A.; Nejjari, C.; Ibrahimi, S.A.; et al. Concordance with the World Cancer Research Fund/American Institute for Cancer Research recommendations for cancer prevention and colorectal cancer risk in Morocco: A large, population-based case–control study. *Int. J. Cancer* **2019**, *145*, 1829–1837. [CrossRef] [PubMed]
17. Li, Y.; Schoufour, J.; Wang, D.D.; Dhana, K.; Pan, A.; Liu, X.; Song, M.; Liu, G.; Shin, H.J.; Sun, Q.; et al. Healthy lifestyle and life expectancy free of cancer, cardiovascular disease, and type 2 diabetes: Prospective cohort study. *BMJ* **2020**, *368*, l6669. [CrossRef]
18. Liu, G.; Li, Y.; Hu, Y.; Zong, G.; Li, S.; Rimm, E.B.; Hu, F.B.; Manson, J.E.; Rexrode, K.M.; Shin, H.J.; et al. Influence of Lifestyle on Incident Cardiovascular Disease and Mortality in Patients With Diabetes Mellitus. *J. Am. Coll. Cardiol.* **2018**, *71*, 2867–2876. [CrossRef]
19. Martínez-González, M.Á.; Corella, D.; Salas-Salvadó, J.; Ros, E.; Covas, M.I.; Fiol, M.; Wärnberg, J.; Arós, F.; Ruíz-Gutiérrez, V.; Lamuela-Raventós, R.M.; et al. Cohort profile: Design and methods of the PREDIMED study. *Int. J. Epidemiol.* **2012**, *41*, 377–385. [CrossRef]

20. Estruch, R.; Ros, E.; Salas-Salvadó, J.; Covas, M.-I.; Corella, D.; Arós, F.; Gómez-Gracia, E.; Ruiz-Gutiérrez, V.; Fiol, M.; Lapetra, J.; et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N. Engl. J. Med.* **2018**, *378*, e34. [CrossRef]
21. Fernández-Ballart, J.D.; Piñol, J.L.; Zazpe, I.; Corella, D.; Carrasco, P.; Toledo, E.; Perez-Bauer, M.; Martínez-González, M.A.; Salas-Salvadó, J.; Martín-Moreno, J.M. Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. *Br. J. Nutr.* **2010**, *103*, 1808–1816. [CrossRef]
22. Mataix, V.J. *Tabla de Composicion de Alimentos [Food Composition Tables]*, 4th ed.; Universidad de Granada: Granada, Spain, 2003.
23. Moreiras, O.; Cabrera, L.C.A. *Tablas de Composición de Alimentos [Food Composition Tables]*; Ediciones Pirámide: Madrid, Spain, 2005; Volume 9.
24. Elosua, R.; Marrugat, J.; Molina, L.; Pons, S.; Pujol, E. Validation of the minnesota leisure time physical activity questionnaire in Spanish men. The MARATHOM Investigators. *Am. J. Epidemiol.* **1994**, *139*, 1197–1209. [CrossRef] [PubMed]
25. Elosua, R.; Garcia, M.; Aguilar, A.; Molina, L.; Covas, M.I.; Marrugat, J. Validation of the minnesota leisure time physical activity questionnaire in Spanish women. Investigators of the MARATDON Group. *Med. Sci. Sports Exerc.* **2000**, *32*, 1431–1437. [CrossRef]
26. Jankovic, N.; Geelen, A.; Winkels, R.M.; Mwungura, B.; Fedirko, V.; Jenab, M.; Illner, A.K.; Brenner, H.; Ordóñez-Mena, J.M.; Kiefte de Jong, J.C.; et al. Adherence to the WCRF/AICR dietary recommendations for cancer prevention and risk of cancer in elderly from Europe and the United States: A meta-analysis within the CHANCES project. *Cancer Epidemiol. Biomark. Prev.* **2017**, *26*, 136–144. [CrossRef]
27. Hastert, T.A.; White, E. Association between meeting the WCRF/AICR cancer prevention recommendations and colorectal cancer incidence: Results from the VITAL cohort. *Cancer Causes Control* **2016**, *27*, 1347–1359. [CrossRef] [PubMed]
28. *World Cancer Research Fund/American Institute for Cancer Research Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*; AICR: Washington, DC, USA, 2007.
29. Lavalette, C.; Adjibade, M.; Srour, B.; Sellem, L.; Fiolet, T.; Hercberg, S.; Latino-Martel, P.; Fassier, P.; Deschasaux, M.; Kesse-Guyot, E.; et al. Cancer-specific and general nutritional scores and cancer risk: Results from the prospective nutrinet-santé cohort. *Cancer Res.* **2018**, *78*, 4427–4435. [CrossRef] [PubMed]
30. Shams-White, M.M.; Brockton, N.T.; Mitrou, P.; Romaguera, D.; Brown, S.; Bender, A.; Kahle, L.L.; Reedy, J. Operationalizing the 2018 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) cancer prevention recommendations: A standardized scoring system. *Nutrients* **2019**, *11*, 1572. [CrossRef]
31. Geneva: World Health Organization. World Health Organization (WHO) Global Health Observatory. Available online: https://www.who.int/gho/database/en/ (accessed on 15 February 2020).
32. Choi, Y.; Giovannucci, E.; Lee, J.E. Glycaemic index and glycaemic load in relation to risk of diabetes-related cancers: A meta-analysis. *Br. J. Nutr.* **2012**, *108*, 1934–1947. [CrossRef]
33. Suikkari, A.-M.; Koivisto, V.A.; Rutanen, E.-M.; YKI-Järvinen, H.; Karonen, S.-L.; Seppälä, M. Insulin Regulates the Serum Levels of Low Molecular Weight Insulin-Like Growth Factor-Binding Protein*. *J. Clin. Endocrinol. Metab.* **1988**, *66*, 266–272. [CrossRef]
34. Le Roith, D. Insulin-like growth factors. *N. Engl. J. Med.* **1997**, *336*, 633–640. [CrossRef]
35. Bruce, W.R.; Wolever, T.M.S.; Giacca, A. Mechanisms linking diet and colorectal cancer: The possible role of insulin resistance. *Nutr. Cancer* **2000**, *37*, 19–26. [CrossRef]
36. Miele, C.; Rochford, J.J.; Filippa, N.; Giorgetti-Peraldi, S.; Van Obberghen, E. Insulin and insulin-like growth factor-i induce vascular endothelial growth factor mrna expression via different signaling pathways. *J. Biol. Chem.* **2000**, *275*, 21695–21702. [CrossRef] [PubMed]
37. Smith, T.J.S.; Wolfson, J.A.; Jiao, D.; Crupain, M.J.; Rangan, U.; Sapkota, A.; Bleich, S.N.; Nachman, K.E. Caramel color in soft drinks and exposure to 4-methylimidazole: A quantitative risk assessment. *PLoS ONE* **2015**, *10*, e0118138. [CrossRef] [PubMed]

Table S1. Third expert report 2018 WCRF/AICR score operationalization in the PREDIMED cohort

Recommendation		Goals	Operationalization	Scoring
1	Be a healthy weight	Ensure that body weight during childhood and adolescence projects towards the lower end of the healthy adult BMI range	Insufficient data available	-
		Keep your weight as low as you can within the healthy range throughout life	≥18.5 and ≤24.9 Kg/m^2	1
			>24.9 and <30 Kg/m^2	0.5
			<18.5 or ≥30 Kg/m^2	0
		Avoid weight gains (measured as body weight or waist circumference) throughout adulthood[a]	1st tertile of weight change in all the cohort	1
			2nd tertile of weight change in all the cohort	0.5
			3rd tertile of weight change in all the cohort	0
2	Be physically active	Be at least moderately physically active, and follow or exceed national guidelines (about 60 to 75% of heart rate maximum)	≥150 min MVPA/wk.	1
			≥75 and <150 min MVPA/wk.	0.5
			<75 min MVPA/wk.	0
		Limit sedentary habits	Insufficient data available	-
3	Eat a diet rich in wholegrains, vegetables, fruit and beans	Consume a diet that provides at least 30 g/day of fiber from foods	≥30 g/day	1
			≥15 and <30 g/day	0.5
			<15 g/day	0
		Include in most meals foods containing wholegrains, non-starchy vegetables, fruit and pulses (legumes) such as beans and lentils[b]	<1 serv. legumes/wk.	0
			≥1 and <3 serv. legumes/wk.	0.5
			≥3 serv. legumes/wk.	1
		Eat a diet high in all types of plant foods including at least five portions or servings (at least 400 g in total) of a variety of non-starchy vegetables and fruit every day	≥400 g/day	1
			≥200 and <400 g/day	0.5
			<200 g/day	0

	Recommendation	Goals	Operationalization	Scoring
		If you eat starchy roots and tubers as staple foods, eat non-starchy vegetables, fruit and pulses (legumes) regularly too if possible	Insufficient data available	-
4	Limit consumption of 'fast foods' and other processed foods high in fat, starches or sugars	Limit consumption of processed foods high in fat, starches or sugars -including 'fast foods'; many pre-prepared dishes, snacks, bakery foods and desserts; and confectionery (candy)[c]	<1.5 serv./day	1
			≥1.5 and <3 serv./day	0.5
			≥3 serv./day	0
5	Limit consumption of red and processed meat	If you eat red meat, limit consumption to no more than about three portions per week. Three portions are equivalent to about 350 to 500 g cooked weight of red meat. Consume very little, if any, processed meat[d]	RM <450 g/wk. and PM <3 g/day	1
			RM <450 g/wk. and PM ≥3 and <50 g/day	0.5
			RM ≥450 g/wk. and PM ≥50 g/day	0
6	Limit consumption of sugar sweetened drinks	Do not consume sugar-sweetened drinks[d]	0 g/day	1
			>0 g/day and <250 g/day	0.5
			≥250 g/day	0
7	Limit alcohol consumption	For cancer prevention, it is best not to drink alcohol[e]	0 g ethanol/day	1
			>0 to 20 g ethanol/day (women)	0.5
			>0 to 40 g ethanol/day (men)	0.5
			>20 g ethanol/day (women)	0
			>40 g ethanol/day (men)	0
8	Do not use supplements for cancer prevention	High-dose dietary supplements are not recommended for cancer prevention - aim to meet nutritional needs through diet alone	Insufficient data available	-
9	For mothers: breastfeed your baby, if you can	This recommendation aligns with the advice of the WHO, which recommends infants are exclusively breastfed for 6 months, and then up to 2 y of age or beyond alongside appropriate complementary foods	Insufficient data available	-

	Recommendation	Goals	Operationalization	Scoring
10	After cancer diagnosis: follow our Recommendations, if you can	All cancer survivors should receive nutritional care and guidance on physical activity from trained professionals	Insufficient data available	-
		Unless otherwise advised, and if you can, all cancer survivors are advised to follow the Cancer Prevention Recommendations as far as possible after the acute stage of treatment	Insufficient data available	-

[a] Distribution of weight gain in the study population over the follow-up. The mean weight change ± SD (*n*) for the 1st tertile was -5.1 ± 3.7 Kg (2,409 individuals), -0.2 ± 0.7 Kg (2,376 individuals) for the 2nd tertile, and +4.2 ± 3.3 Kg (2,303 individuals) for the 3rd tertile.

[b] The 3rd expert report did not provide cutoffs. Because we have insufficient data available on whole grains consumption, we did not include this food group in the score. Moreover, since fruit and vegetable consumption are considered in another score subcomponent, this item is only composed of legumes consumption (1 serv. = 70 g).

[c] We did not include food groups overlapping with other score components such as processed meats and sugar-sweetened beverages. We included those foods categorized in the 3rd (processed foods) and 4th (ultra-processed foods) groups of the NOVA (a name, not an acronym) classification [1].

[d] The 3rd Expert Report does not provide cut-offs neither for processed meat consumption nor sugar-sweetened beverages intake. Thus, we decided to follow the cutoffs from the previous literature for the comparability of data [2].

[e] The WCRF/AICR recommendations advise not to consume alcoholic drinks. For those individuals consuming alcohol, the recommendations suggest not to exceed the national guidelines. Therefore, we considered the Dietary Guidelines for the Spanish population (SENC, 2016) [3].

Abbreviations: WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research; BMI, Body Mass Index; MVPA, moderate-to-vigorous physical activity; wk., week; serv., servings; RM, red meat; PM, processed meat; WHO, World Health Organization; SD, standard deviation; SENC, 'Sociedad Española de Nutrición Comunitaria'.

Table S2. Low-risk lifestyle score operationalization in the PREDIMED cohort

	Individual lifestyle risk factors	Operationalization	Scoring
1	Smoking status	Never smoking	**1**
2	Alcohol consumption	5 to 15 g/day (women) and 5 to 30 g/day (men)	**1**
3	Physical activity	≥30 min./day MVPA	**1**
4	AHEI-2010	Upper 40% AHEI-2010	**1**
5	BMI	BMI (18.5 to 24.9 kg/m^2)	**1**

Abbreviations: min., minutes; MVPA, moderate-to-vigorous physical activity; AHEI, Alternate Healthy Eating Index; BMI, Body Mass Index.

Table S3. Baseline characteristics of the study population in the PREDIMED study according to quartiles of WCRF/AICR score [a].

	Quartiles of 2018 WCRF/AICR score				
	Q1	**Q2**	**Q3**	**Q4**	***P*-value[b]**
Events/non-events (*n*)	30/1,868	20/1,793	32/1,911	15/1,644	
2018 WCRF/AICR score	2.9 [2.6-3.2]	3.6 [3.4-3.7]	4.2 [4-4.3]	4.9 [4.7-5.2]	<0.001*
Low-risk lifestyle score	1.5 [1-2]	2 [1-2.5]	2 [1.5-2.5]	2.5 [2-3]	<0.001*
Age, years	66 [62-71]	66 [62-71]	67 [63-72]	67 [63-72]	0.787
Women, % (*n*)	55.5 (1,036)	57.3 (1,027)	58.6 (1,119)	58.6 (963)	0.183
Education level, % (*n*)					
Primary, secondary, high school	91.8 (1,715)	92.1 (1,652)	94.3 (1,802)	93.1 (1,531)	0.014*
University/graduate	8.2 (153)	7.9 (141)	5.7 (109)	6.9 (113)	
Age at diagnosis of cancer, years	73 [68.4-78]	69 [64.7-76.1]	72.4 [67.7-76.5]	71.7 [63.2-74.8]	0.957
Family history of cancer, % (*n*)	49.8 (915)	49 (872)	49.6 (938)	50.5 (823)	0.051
Diabetes, % (*n*)	43.3 (809)	46.5 (833)	50.8 (971)	55.6 (914)	<0.001*
Hypertension, % (*n*)	84.6 (1,581)	83.5 (1,497)	82.6 (1,579)	79.9 (1,313)	0.002*
Waist circumference, cm					
Women	100 [94-108]	100 [92-106]	97 [90-104]	96 [89-103]	0.018*
Men	106 [99-112]	104 [98-110]	101 [96-107]	96 [89-103]	0.179
BMI, kg/m^2	30.8 [28.3-33.4]	30.4 [27.7-32.9]	28.9 [26.8-31.6]	28.7 [26.4-31.3]	<0.001*
MVPA, min./wk.	0 [0-37.8]	18.7 [0-182]	98.4 [0-378]	280 [113.7-507.8]	<0.001*
Smoking status, % (*n*)					
Never smokers	57.2 (1,069)	59.7 (1,070)	64.3 (1,229)	65.1 (1,070)	
Former smokers	25.5 (477)	24.3 (436)	24.1 (460)	24.4 (401)	<0.001*
Current smokers	17.2 (322)	16 (287)	11.6 (222)	10.5 (173)	
Current medication, % (*n*)					
Aspirin	22.9 (427)	22.7 (407)	21.3 (406)	22.7 (373)	0.664
HRT (only in women)	3.7 (38)	2.8 (29)	2.9 (32)	1.7 (16)	0.165
Intervention groups, % (*n*)					
MedDiet+EVOO	33.6 (628)	33.7 (604)	32.9 (629)	37.3 (613)	
MedDiet+nuts	32.6 (609)	33 (592)	34.3 (656)	30.6 (503)	0.107
Control low-fat diet	33.8 (631)	33.3 (597)	32.8 (626)	32.1 (528)	
Energy intake (kcal/day)	2,423 [2,043.1-2,834.8]	2,244 [1,868-2,622]	2,116 [1,800-2,453]	1,995.8 [1,705.4-2,321.5]	<0.001*

AHEI-2010 score	60.3 [54.6-65.7]	63.8 [58.6-69.5]	65.3 [60.6-70.7]	68 [62.8-73.1]	<0.001*
Food consumption, g/day					
Vegetables	294.3 [216.5-383.7]	316.2 [238.3-409.3]	313.7 [237.2-404.3]	336.2 [251.8-433.7]	<0.001*
Fruits	321.4 [213.2-458.1]	332.1 [221.9-482.4]	331.4 [230.7-466.9]	359.7 [243.3-499]	<0.001*
Legumes	16.6 [12-25.1]	17.1 [12.6-25.1]	17.1 [12.6-25.1]	17.1 [12.6-25.7]	<0.001*
Red and processed meat	89.1 [55.7-117.7]	69.1 [43.4-101.4]	62.5 [41.3-93]	54 [32.5-78.4]	<0.001*
Fast food and processed foods	102.6 [72.5-146.4]	77.5 [50-113.9]	65.3 [40.1-94.4]	51.8 [31.4-72.7]	<0.001*
Sugar sweetened beverages	41 [13.3-171.4]	26.7 [0-85.7]	0 [0-85.7]	0 [0-13.3]	<0.001*
Alcohol	4.5 [0.7-13.8]	1.93 [0-11]	1.4 [0-10.4]	0 [0-5.1]	<0.001*

[a] Data are expressed as medians [IQR, interquartile range] for continuous variables and percentage and number (n) for categorical variables. [b] *P*-values for comparison between colorectal cancer cases and non-cases were calculated by chi-square or t-Student tests for categorical and continuous variables, respectively. All statistical tests were two-sided. **P*-value <0.05. Abbreviations: AHEI, Alternate Healthy Eating Index; BMI, body mass index; EVOO, extra virgin olive oil; HRT, hormone replacement therapy; MedDiet, Mediterranean Diet; min./wk., minutes/week; MVPA, moderate-to-vigorous physical activity; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

Table S4. Baseline characteristics of the study population in the PREDIMED study according to tertiles of low-risk lifestyle score [a].

	Tertiles of low-risk lifestyle score			
	T1	**T2**	**T3**	***P*-value[b]**
Events/non-events (*n*)	55/3,024	27/2,512	15/1,583	
Low-risk lifestyle score	1 [1-1.5]	2 [2-2.5]	3.5 [3-3.5]	<0.001*
2018 WCRF/AICR score	3.5 [3-4]	3.9 [3.4-4.4]	4.4 [3.8-4.9]	0.790
Age, years	67 [62-72]	67 [62-72]	67 [63-72]	0.154
Women, % (*n*)	54.8 (1,688)	62 (1,574)	55.3 (883)	<0.001*
Education level, % (*n*)				
Primary, secondary, high school	92.5 (2,848)	93.7 (2,380)	92.1 (1,472)	0.087
University/graduate	7.5 (231)	6.3 (159)	7.9 (126)	
Age at diagnosis of cancer, years	72.6 [68-76.3]	68.4 [65.1-75.9]	73.5 [64.5-78]	0.154
Family history of cancer, % (*n*)	50.2 (1,527)	48.2 (1,209)	51.1 (812)	<0.001*
Diabetes, % (*n*)	49.4 (1,520)	48.3 (1,225)	48.9 (782)	0.704
Hypertension, % (*n*)	83.1 (2,558)	83.5 (2,121)	80.8 (1,291)	0.060
Waist circumference, cm				
Women	100 [93-107]	98 [91-106]	95 [87-102]	0.023*
Men	104 [99-111]	102 [97-108]	100 [95-107]	0.158
BMI, kg/m^2	30.3 [27.9-33]	29.7 [27.3-32.5]	28.4 [25.8-31.3]	<0.001*
MVPA, min./wk.	0 [0-74.8]	70.1 [0-342.8]	303.4 [149.5-556]	<0.001*
Smoking status, % (*n*)				
Never smokers	47.9 (1,476)	68.5 (1,738)	76.6 (1,224)	
Former smokers	31.7 (975)	21.1 (535)	16.5 (264)	<0.001*
Current smokers	20.4 (628)	10.5 (266)	6.9 (110)	
Current medication, % (*n*)				
Aspirin	22.5 (694)	22.1 (562)	22.3 (357)	0.709
HRT (only in women)	3.4 (57)	2.4 (38)	2.3 (20)	0.329
Intervention groups, % (*n*)				
MedDiet+EVOO	33.7 (1,037)	35.3 (895)	33.9 (542)	
MedDiet+nuts	30.7 (945)	31.8 (808)	38 (607)	<0.001*
Control low-fat diet	35.6 (1,097)	32.9 (836)	38.1 (449)	
Energy intake (kcal/day)	2,227 [1,854.5-2,653.3]	2,135 [1,811.8-2,514.7]	2,186 [1,875.7-2,530.4]	<0.001*
AHEI-2010 score	60.4 [55.6-63.9]	66.5 [60.7-71.4]	70.8 [67.5-75.1]	<0.001*

Food consumption, g/day				
Vegetables	293.7 [218-380]	318.7 [244.8-419.7]	347.1 [259.8-445]	<0.001*
Fruits	300 [198.3-425]	349.2 [242.6-493.3]	379.5 [268.3-527.9]	<0.057
Legumes	16.6 [12-25.1]	20.6 [16-25.1]	20.6 [16-25.1]	<0.001*
Red and processed meat	75.7 [47.1-106.2]	63.8 [39.9-97.6]	60.5 [38.2-91.6]	<0.001*
Fast food and processed foods	76.4 [48.2-114.8]	71.2 [44.3-106]	68 [44.2-101.8]	<0.001*
Sugar sweetened beverages	26.7 [0-114.3]	13.3 [0-85.7]	0 [0-41.9]	<0.001*
Alcohol	0.7 [0-4.5]	1.5 [0-10.4]	10.2 [1.4-12.5]	<0.001*

[a] Data are expressed as medians [IQR, interquartile range] for continuous variables and percentage and number (n) for categorical variables. [b] *P*-values for comparison between colorectal cancer cases and non-cases were calculated by chi-square or t-Student tests for categorical and continuous variables, respectively. All statistical tests were two-sided. **P*-value <0.05. Abbreviations: AHEI, Alternate Healthy Eating Index; BMI, body mass index; EVOO, extra virgin olive oil; HRT, hormone replacement therapy; MedDiet, Mediterranean Diet; min./wk., minutes/week; MVPA, moderate-to-vigorous physical activity; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

Table S5. Mutually adjusted HRs and 95% CIs for colorectal cancer risk associated with different categories of a combination of low-risk lifestyle factors at baseline in the PREDIMED study (*n*=7,216)

	Number of low-risk factors, HR (95% CI)					*P* for trend
	0 (reference)	**1**	**2**	**>3**	**Continuous analysis (1-point increment)**	
Events/non-events (*n*)	9/601	46/2,423	27/2,512	15/1,583		
Crude model	1.00	1.31 (0.62-2.79)	0.72 (0.32-1.65)	0.61 (0.24-1.52)	0.75 (0.60-0.94)*	0.013*
Model 1	1.00	1.58 (0.75-3.34)	0.87 (0.39-1.96)	0.70 (0.28-1.73)	0.77 (0.62-0.96)*	0.018*
Model 2	1.00	1.59 (0.76-3.34)	0.86 (0.38-1.94)	0.69 (0.28-1.70)	0.77 (0.62-0.95)*	0.016*

Model 1 adjusted for age (years, continuous) and sex.

Model 2 was further adjusted for intervention group (MedDiet + EVOO, MedDiet + nuts, low-fat control), family history of cancer (yes/no), education level (primary or secondary/high school university or graduate), history of diabetes (yes/no), baseline energy intake (Kcal/day, continuous) and treatment with aspirin (yes/no) at baseline.

*p-value <0.05

Abbreviations: HR, Hazard Ratio; CI, confidence interval; MedDiet, Mediterranean Diet; EVOO, extra virgin olive oil.

Table S6. HRs and 95% CIs between the 2018 WCRF/AICR and the low-risk lifestyle scores and colorectal cancer risk at baseline in the PREDIMED study by subgroups (age, sex and T2D status)

	2018 WCRF/AICR score		**Low-risk lifestyle score**	
	Continuous analysis (1-point increment), HR (95% CI)	***P* for trend**	**Continuous analysis (1-point increment), HR (95% CI)**	***P* for trend**
Age< 67 years				
Events/non-events (*n*)	41/3,499	-	41/3,499	-
Crude model	0.89 (0.68-1.17)	0.403	0.78 (0.59-1.05)	0.099
Model 1	0.90 (0.68-1.19)	0.458	0.79 (0.60-1.05)	0.110
Model 2	0.88 (0.67-1.17)	0.382	0.79 (0.60-1.05)	0.109
Age≥ 67 years				
Events/non-events (*n*)	56/3,717	-	56/3,717	-
Crude model	0.70 (0.50-0.97)*	0.032*	0.73 (0.54-0.99)*	0.041*
Model 1	0.70 (0.50-0.97)*	0.032*	0.76 (0.58-1.00)	0.051
Model 2	0.71 (0.50-0.99)*	0.050*	0.76 (0.58-0.99)*	0.048*
Men				
Events/non-events (*n*)	57/3,071	-	57/3,071	-
Crude model	0.86 (0.64-1.16)	0.323	0.85 (0.66-1.10)	0.213
Model 1	0.80 (0.58-1.11)	0.185	0.83 (0.65-1.07)	0.154
Model 2	0.85 (0.62-1.17)	0.315	0.84 (0.65-1.08)	0.174
Women				
Events/non-events (*n*)	40/4,145	-	40/4,145	-
Crude model	0.75 (0.55-1.01)	0.059	0.69 (0.50-0.96)*	0.028*
Model 1	0.75 (0.55-1.02)	0.064	0.70 (0.50-0.97)*	0.030*
Model 2	0.72 (0.51-1.02)	0.064	0.69 (0.50-0.95)*	0.023*

Prevalent T2D				
Events/non-events (*n*)	50/3,527	-	50/3,527	-
Crude model	0.69 (0.51-0.93)*	0.014*	0.81 (0.60-1.07)	0.142
Model 1	0.68 (0.50-0.92)*	0.012*	0.81 (0.62-1.07)	0.138
Model 2	0.71 (0.53-0.96)*	0.024*	0.81 (0.62-1.06)	0.123
Non-prevalent T2D				
Events/non-events (*n*)	47/3,689	-	47/3,689	-
Crude model	0.89 (0.64-1.23)	0.475	0.69 (0.50-0.95)*	0.021*
Model 1	0.90 (0.64-1.27)	0.550	0.72 (0.53-0.97)*	0.028*
Model 2	0.87 (0.61-1.24)	0.443	0.71 (0.52-0.95)*	0.021*

Model 1 adjusted for age (years, continuous) and sex.

Model 2 was model 1 plus intervention group (MedDiet + EVOO, MedDiet + nuts, low-fat control), family history of cancer (yes/no), education level (primary or secondary/high school university or graduate), history of diabetes (yes/no), baseline energy intake (Kcal/day, continuous) and treatment with aspirin (yes/no) at baseline. Model 2 for 2018 WCRF/AICR score was further adjusted for current smoker (yes/no), former smoker (yes/no), never smoker (yes/no).

All models were stratified by node. *p-value <0.05

Abbreviations: HR, Hazard Ratio; CI, confidence interval; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research; T2D, type 2 diabetes; MedDiet, Mediterranean Diet; EVOO, extra virgin olive oil.

References

1. Monteiro, C.A.; Cannon, G.; Moubarac, J.-C.; Levy, R.B.; Louzada, M.L.C.; Jaime, P.C. The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. *Public Health Nutr.* **2018**, *21*, 5–17.
2. Romaguera, D.; Vergnaud, A.-C.; Peeters, P.H.; van Gils, C.H.; Chan, D.S.M.; Ferrari, P.; Romieu, I.; Jenab, M.; Slimani, N.; Clavel-Chapelon, F.; et al. Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. *Am. J. Clin. Nutr.* **2012**, *96*, 150–63.
3. Aranceta Bartrina, J.; Aranceta Bartrina, J.; Arija Val, V.; Maíz Aldalur, E.; Martínez de la Victoria Muñoz, E.; Ortega Anta, R.M.; Pérez-Rodrigo, C.; Quiles Izquierdo, J.; Rodríguez Martín, A.; Román Viñas, B.; et al. Guías alimentarias para la población española (SENC, 2016); la nueva pirámide de la alimentación saludable. *Nutr. Hosp.* **2016**, *33*, 1–48.

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Chapter 3

Association between dairy product consumption and colorectal cancer risk in adults: a systematic review and meta-analysis of epidemiologic studies.

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UNIVERSITAT ROVIRA I VIRGILI
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SUPPLEMENT

Association Between Dairy Product Consumption and Colorectal Cancer Risk in Adults: A Systematic Review and Meta-Analysis of Epidemiologic Studies

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ABSTRACT

Dairy product consumption may decrease colorectal cancer (CRC) risk, but very few studies have evaluated the association between different types of dairy products and CRC location. The aim of this systematic review and meta-analysis was to examine the associations between dairy product consumption and CRC incidence. Summary RRs and ORs with 95% CIs were estimated. A total of 15 cohort studies and 14 case-control studies comprising a total of >22,000 cases were included in the quantitative synthesis. The cohort studies showed a consistent significant decrease in CRC risk associated with higher consumption of total dairy products (RR: 0.80; 95% CI: 0.70, 0.91) and total milk (RR: 0.82; 95% CI: 0.76, 0.88) compared with the CRC risk associated with lower consumption. These studies also showed a significant protective association between low-fat milk consumption and CRC (RR: 0.76; 95% CI: 0.66, 0.88), but only for colon cancer (RR: 0.73; 95% CI: 0.61, 0.87). Cheese consumption was inversely associated with the risk of CRC (RR: 0.85; 95% CI: 0.76, 0.96) and proximal colon cancer (RR: 0.74; 95% CI: 0.60, 0.91). No significant associations with CRC were found for the consumption of low-fat dairy products, whole milk, fermented dairy products, or cultured milk. Most of these associations were not supported by the case-control studies. In conclusion, high consumption of total dairy products and total milk was associated with a lower risk of developing CRC at any anatomic location, including the proximal and distal colon and the rectum. Low-fat milk consumption was associated with a lower risk of CRC, but this association was restricted to colon cancer. Cheese consumption was associated with the prevention of CRC, specifically proximal colon cancer. Further studies on larger samples and with longer follow-up periods, along with appropriately designed and executed clinical trials, are warranted to determine whether dairy product consumption affects CRC development. *Adv Nutr* 2019;10:S190–S211.

Keywords: dairy, milk, yogurt, cheese, colorectal cancer, systematic review, meta-analysis, prospective studies, case-control studies, adults

Introduction

In 2016, there were 1.7 million incident cases of colon and rectal cancer, with 830,000 deaths worldwide (1). Over the next 15 years, the global burden of colorectal cancer (CRC) is expected to increase by 60% and cause 1.1 million deaths (2).

It has been suggested that factors such as body weight/adiposity, physical activity, and diet are leading risk factors for CRC (3). Several studies have shown that a healthy dietary pattern, such as that in the Mediterranean diet, characterized by high intakes of vegetables, fruits, whole grains, nuts, and olive oil; moderate intakes of fish, poultry, and low-fat dairy foods; and low intakes of red meat, processed meat, and sugar-sweetened drinks, may decrease the risk of CRC (4, 5).

Although there is considerable evidence to suggest that the consumption of processed meat and alcohol are risk factors for CRC, evidence for an association between the consumption of dairy products and the risk of CRC is not as strong. The latest report from the Continuous Update Project (CUP), led by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), concluded that there is strong evidence that the consumption of dairy products may help to protect against CRC (3). However, the risk of CRC associated with the consumption of different types of dairy products (i.e., yogurt, cultured milk, or hard cheese), as well as the consumption of dairy product subtypes and their fat composition (i.e., low-fat or high-fat dairy products, low-fat or full-fat yogurt, and skim/semiskim or whole milk), remains unclear (6–19).

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Although most current dietary guidelines advocate the consumption of fat-free or low-fat dairy products in the context of a healthy diet to prevent chronic diseases (20–23), evidence has shown no association between the consumption of full-fat dairy products and either the risk of CRC (6, 12, 19) or a reduction in the risk (14). Therefore, further research on the association between the consumption of milk foods and the risk of CRC should be of considerable interest in terms of public health.

The aim of this systematic review and meta-analysis was to extend the available evidence and combine all the results from prospective cohorts and case-control studies in adults so that the association between the consumption of specific types of dairy products and CRC incidence could be examined. We also investigated whether these associations depended on the CRC subsite (colon or rectal) and colon cancer location (proximal or distal colon).

Methods

Design

This systematic review and meta-analysis study was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (24). The results are presented following the "Meta-Analysis of Observational Studies in Epidemiology" (25) and the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement" guidelines (see the PRISMA checklist in the **Supplementary Data**) (26). The protocol for the systematic review and meta-analysis is available in PROSPERO (www.crd.york.ac.uk; identifier: CRD42017057490).

Study selection

We systematically searched for published case-control and prospective cohort studies evaluating the associations between the consumption of total dairy products (and their subtypes) and the incidence of CRC (total CRC, colon or rectal cancer, and proximal or distal colon cancer). One review author (LB) searched for relevant keywords and medical subject heading terms related to the consumption of dairy products (i.e., "dairy" or "dairy products") and subtypes of dairy products (i.e., "milk" or "yogurt" or "yoghurt" or "cheese" or "cultured milk products") in combination with keywords related to CRC events (i.e., "colorectal cancer" or "colorectal neoplasms"). No restrictions on the study design or language of the publication were considered. The MEDLINE (PubMed), Cochrane Library, CINAHL, and ScienceDirect databases were searched up to 4 June, 2018 (see all search strategies in **Supplemental Table 1**). We also carried out a manual search of the bibliographies of the articles we assessed and contacted the authors of unavailable sources.

All studies that met the following criteria were considered for inclusion in the meta-analysis: *1*) those conducted in humans (>18 y old); *2*) those written in English, Spanish, or French; *3*) those in which the outcome of interest was CRC, colon, or rectal cancer; *4*) those that provided estimates of the OR or RR (such as the HR or risk ratio) with the corresponding 95% CIs, or gave sufficient data for these values to be calculated; *5*) those in which the estimates were adjusted for age; *6*) those that evaluated the consumption of dairy products through the use of validated food questionnaires; and *7*) those that assessed the consumption of any subtype or total dairy product (cow, goat, or sheep milk; skim, low-fat, or full-fat milk; total, low-fat, or full-fat yogurt; cheese; and full-fat dairy, sweetened dairy, or other dairy products) as the exposure variable. For the dose-response analysis we required the following criteria to be met: *1*) a quantitative measure of intake had to be provided; *2*) when there were several publications from the same study, we selected the publication with the largest number of cases; and *3*) if all the information required was not provided in the paper, we used the publication that provided enough information for a dose-response analysis to be conducted. The following types of publications were excluded: *1*) nonoriginal papers (reviews, commentaries, editorials, or letters); *2*) ecologic assessments and correlation studies; *3*) cross-sectional studies; *4*) meta-analysis studies; *5*) non-peer-reviewed articles; *6*) off-topic studies; *7*) studies on CRC mortality; *8*) studies lacking specific CRC data; *9*) animal and mechanistic studies; *10*) studies conducted in children, adolescents, or pregnant women; *11*) supplements to the main manuscript; *12*) duplicate publications; and *13*) low-quality studies.

Data extraction

First, we removed duplicate works from the databases mentioned above and from the manual search. Second, the titles and abstracts were screened for eligibility independently and in duplicate by 2 researchers (NB and LB) at the Human Nutrition Unit to exclude obviously irrelevant studies. After the primary screening, the full texts of potentially relevant

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Supplemental Data, Supplemental Tables 1–3, and Supplemental Figures 1–15 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
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reports were retrieved, and the inclusion and exclusion criteria and the quality of the study were assessed by 2 researchers (NR-E and LB) (see the PRISMA flow diagram, **Figure 1**) with the use of a data extraction form developed for this study. If the 2 review authors could not reach agreement, a third author (JS-S) was consulted to make a decision.

The data extracted for each individual study included the following: first author of the article, name of the journal in which the article was published, year of the study, title of the article, study dates, sample size, population characteristics (age, sex, and health status), country of recruitment, covariates included in the fully adjusted models, dietary assessment method, outcome and outcome assessment method, language of the publication, endpoint variables, exposure variables (type of dairy product consumed and intake range), statistical methods and statistical software used, endpoint data, funding sources, and frequency of data collection. For case-control studies, the length of the study period and the number of cases and controls were collected, and for cohort studies, the follow-up period and number of events were collected.

Study quality assessment

To evaluate the validity of the individual studies, 2 reviewers (NR-E and LB) worked independently to determine the quality of the included studies based on the use of the Newcastle-Ottawa Scale (NOS) for cohort or case-control studies (27). The evaluation was based on the following criteria: *1*) the study selection (maximum 4 points); *2*) the adequacy of the outcome in cohort studies and the adequacy of the exposure in case-control studies (maximum 3 points); and *3*) the comparability of the studies (maximum 2 points). Depending on the score assigned, the studies were categorized as either high quality or low quality. The maximum score was 9, and a high score ($\geq$6) indicated high methodologic quality. A consensus was reached between the reviewers if there were any discrepancies.

Statistical analysis

To calculate the summary risk estimates and 95% CIs for the highest compared with the lowest categories of consumption of dairy products and dairy product subtypes, we conducted both random ($\geq$5 study comparisons) and fixed ($<$5 study comparisons) effects analyses. We natural log–transformed and pooled the RRs/HRs (cohort studies) and ORs (case-control studies) through the use of the generic inverse variance method. When the highest level of consumption was considered as the reference category, we recalculated the estimate (RR and 95% CI) of the highest category (28). A 2-tailed $P < 0.05$ was considered statistically significant. The heterogeneity among studies was assessed with the use of Cochran's Q statistic and quantified with the I^2 statistic ($P < 0.10$ was considered significant, and $I^2 \geq 50\%$ was interpreted as substantial heterogeneity).

When the results of the studies were stratified by subgroups, such as sex, they were treated as separate studies. We carried out prespecified stratified analyses for the study design (prospective cohort and case-control studies) and outcome (CRC, colon cancer, proximal or distal colon cancer, and rectal cancer).

Analyses were performed with Review Manager (RevMan) version 5.3 (The Nordic Cochrane Center) and STATA version 14.0 (StataCorp LP) software.

We performed linear and nonlinear dose-response analyses with data from the cohort studies. We carried out generalized least-squares trend estimation modeling and spline curve modeling (MKspline STATA command). This method requires at least 3 quantitative exposure levels or quantiles. To impute missing data, such as the number of participants and cases, in each quantile, we used the method of Bekkering et al. (29). For studies that did not include the total number of participants in each quantile but reported the total number of participants, we divided the total sample size by the number of quantiles. When the number of cases in each category was not given, we used the RR to impute the number of cases.

For studies that reported the range of consumption of dairy products but not the mean or median intake, we calculated the midpoint. For those reporting open-ended lower or upper boundaries, we assumed a range equal to the adjacent range. If the consumption of dairy products was given in grams/day, we converted the intake into servings/day based on the use of standard units: 200 g for total dairy products, 200 g for milk (1 glass), 125 g for yogurt (1 commercial serving), and 30 g for cheese. When the intakes were reported in densities (grams $\cdot$ 1000 kcal^{-1} $\cdot$ day^{-1}), we recalculated the reported intakes by considering the mean energy intake specified in the publication (30). If the study reported the consumption of cheese in slices/day, we regarded each slice as 25 g (17). If the estimated risks for skim and semiskim milk were reported separately, we considered only the measure for skim milk (18) because this is the most widely consumed type of milk. When hard cheese and other types of cheese, such as cottage or cream cheese, were reported individually, we used the estimates for hard cheese (17, 31) so that our results were comparable to the current evidence. When both baseline and repeated measurement analyses were reported, we used the repeated measurements because they more accurately represent changes in dietary consumption (32). When the fully adjusted model was not adjusted for age, we used the age-adjusted estimates (32).

To determine whether our results were robust, we performed a sensitivity analysis by recalculating the summary estimates after excluding 1 study at a time (**Supplemental Tables 2** and **3**).

Results

Study selection

Figure 1 shows the flow diagram summarizing the identification and selection of the relevant publications. Of the 780

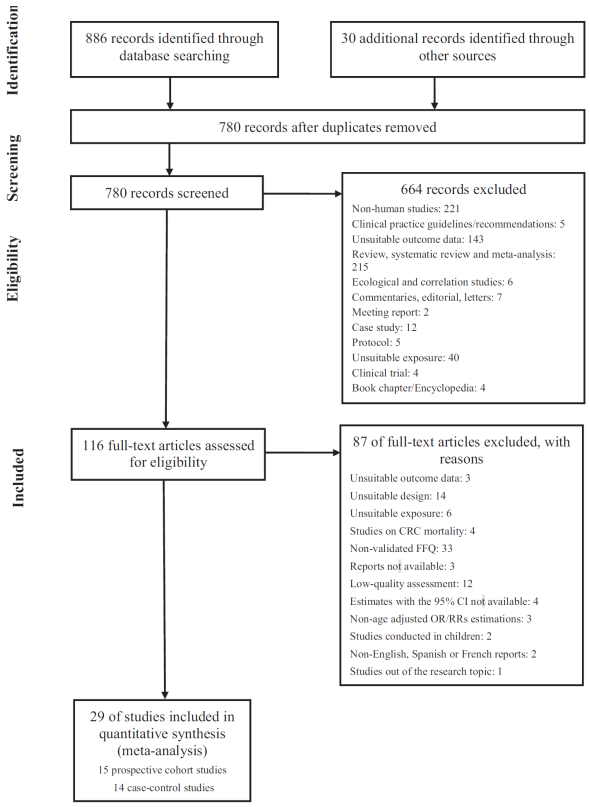

FIGURE 1 Flow of information through the different phases of the identification and selection of relevant studies examining the associations between the consumption of dairy products and the risk of CRC in adults. CRC, colorectal cancer.

reports remaining after duplicates were removed, 29 studies were included in the meta-analysis: 15 prospective cohort studies (6, 8, 11, 14, 17–19, 30, 32–38) and 14 case-control studies (28, 31, 39–50).

Study characteristics

Tables 1 and **2** show the main characteristics of the studies selected. In total, the cohort studies included 1,371,848 participants (66% women, 31% men, and 3% undefined) with 11,733 cases recorded during follow-up periods that ranged from 4 to 14.8 y (Table 1). The case-control studies included 10,921 cases and 13,398 controls (Table 2).

Of the cohort studies, 6 were conducted in the United States, 2 in Norway, 3 in Sweden, 1 in China, 1 in Italy, 1 in Spain, and 1 in each of 10 different European countries. The case-control studies were conducted in 9 countries (China, Italy, the Netherlands, France, the United States, Japan, Canada, Australia, and Korea).

All cohort and case-control studies were conducted in adults. Most of the studies obtained funding only from agencies, but 1 study was agency-industry funded, 1 reported industry funding, 3 did not report the funding source, and 1 did not report receiving a specific grant.

High consumption compared with low consumption analyses

Prospective cohort studies.

Total dairy products. Eight cohort study comparisons (11, 17–19, 30, 36) were used to assess the association between the highest and the lowest consumption of total dairy products and CRC risk; 910,047 individuals and 8424 cases were included. The summary RR for CRC was 0.80 (95% CI: 0.70, 0.91; $I^2 = 45\%$; P-heterogeneity = 0.08) (**Figure 2** and **Supplemental Figure 1**). Significant inverse associations were also observed for colon cancer (summary RR: 0.76; 95% CI: 0.66, 0.87; $I^2 = 14\%$; P-heterogeneity = 0.33; $n = 7$) (**Figure 3** and **Supplemental Figure 2**), proximal colon cancer (summary RR: 0.75; 95% CI: 0.63, 0.89; $I^2 = 63\%$; P-heterogeneity = 0.04; $n = 4$) (**Figure 4**), distal colon cancer (summary RR: 0.73; 95% CI: 0.62, 0.88; $I^2 = 10\%$; P-heterogeneity = 0.34; $n = 4$) (Figure 4), and rectal cancer (summary RR: 0.83; 95% CI: 0.71, 0.96; $I^2 = 32\%$; P-heterogeneity = 0.22; $n = 4$) (**Figure 5**).

High-fat dairy products. Two cohort studies (14, 19), comprising 67,924 participants and 895 cases, were used to analyze the effects of the highest compared with the lowest consumption of high-fat dairy products on CRC risk. The pooled RR was 0.68 (95% CI: 0.53, 0.87), with substantial

TABLE 1 Characteristics of the 15 prospective cohort studies included in the meta-analysis examining the associations between the consumption of dairy products and the risk of CRC[1]

Study, year (ref.)	Study cohort and characteristics (age, y)	No. of participants (M/W)	No. of incident cases	Follow-up length, y	Exposure	RR	Adjustments to the RR	Funding source	NOS quality score
Bostick et al., 1993 (6)	USA: Iowa Women's Health Study (55–69)	35,216 W	212 CC	5	Total dairy (milk products, excluding butter): >25 vs <8 servings/wk Fat-containing dairy (excluding butter): >14 vs <4 serving/wk	CC: 0.72 (95% CI: 0.38, 1.36) CC: 0.78 (95% CI: 0.45, 1.36)	Age, total energy intake, height, parity, low-fat meat intake, total vitamin E intake, and a total vitamin E × age interaction term	Agency	6
Kearney et al., 1996 (8)	USA: Health Professionals Follow-up Study (40–75)	47,935 M	203 CC	6	Milk, whole or skim/low fat: >1/d vs <1/mo (237 mL) Ice cream: >1/d vs <1/mo (1/2 cup) Hard cheese: >1/d vs <1/mo (1 slice) Fermented dairy products (yogurt, sour cream, cottage cheese, cream cheese, hard cheese, Swiss, American, cheddar, etc.): >1/d vs <1/mo (median intake)	CC: 0.87 (95% CI: 0.52, 1.44) CC: 0.93 (95% CI: 0.42, 2.04) CC: 1.35 (95% CI: 0.67, 2.75) CC: 1.09 (95% CI: 0.70, 1.72)	Age, total calories, family history of colon cancer, previous polyp, screening, past history of smoking, alcohol consumption, aspirin use, physical activity, BMI, red meat, saturated fat, and dietary fiber intakes	Agency-industry	6
Gaard et al., 1996 (33)	Norway (20–53)	25,638/24,897	143 CC	11.4	Milk (any type): ≥4 vs <1 glasses/d	CC (M): 0.72 (95% CI: 0.25, 2.07) CC (W): 1.24 (95% CI: 0.35, 4.40)	Age and attained age	Agency	7
Singh et al., 1998 (34)	USA: Adventist Health Study (25–100)	32,051	157 CC	6	Nonfat milk: ≥1 serving/wk vs never Low-fat milk: ≥1 serving/wk vs never Whole milk: ≥1 serving/wk vs never Cheese (excluding cottage cheese): ≥2 servings/wk vs never to <2 servings/mo Cottage cheese: ≥2 servings/wk vs never to <2 servings/mo	CC: 0.78 (95% CI: 0.48, 1.28) CC: 0.97 (95% CI: 0.66, 1.42) CC: 1.04 (95% CI: 0.69, 1.59) CC: 1.31 (95% CI: 0.84, 2.03) CC: 0.74 (95% CI: 0.49, 1.11)	Age at baseline, sex, BMI, physical activity, parental history of colon cancer, current smoking, past smoking, alcohol consumption, and aspirin use	Agency	6
Sellers et al., 1998 (35)	USA: Iowa Women's Health Study (mean of 61.7)	35,216 W	241 CC	10	Total dairy: >20 vs ≤10 servings/wk High-fat dairy (including whole milk, cream, sour cream, ice cream, cheeses, butter, pizza, cream sauce, and cheese sauce): >9 vs ≤4.5 servings/wk	CC (NFH): 0.70 (95% CI: 0.40, 1.00) CC (FH): 0.70 (95% CI: 0.40, 1.40) CC (NFH): 0.90 (95% CI: 0.60, 1.30) CC (FH): 0.70 (95% CI: 0.40, 1.30)	Age at baseline, total energy intake, and history of rectal colon polyps	Agency	6

(*Continued*)

TABLE 1 (*Continued*)

Study, year (ref.)	Study cohort and characteristics (age, y)	No. of participants (M/W)	No. of incident cases	Follow-up length, y	Exposure	RR	Adjustments to the RR	Funding source	NOS quality score
					Low-fat dairy (includes skim milk, ice milk, and yogurt): >7 vs ≤2.5 servings/wk	CC (NFH): 0.80 (95% CI: 0.50, 1.10) CC (FH): 0.90 (95% CI: 0.50, 1.60)			
Terry et al., 2002 (11)	Sweden: Swedish Mammography Screening Cohort (median 55)	61,643 W	572 CRC, 371 CC (164 PC, 121 DC) and 191 R	11.3	Total dairy: Q4 vs Q1	CRC: 0.97 (95% CI: 0.73, 1.29) CC: 1.03 (95% CI: 0.72, 1.47) PC: 1.32 (95% CI: 0.77, 2.28) DC: 0.71 (95% CI: 0.38, 1.30) R: 1.04 (95% CI: 0.64, 1.71)	Age, BMI, education level, total energy and quartiles of red meat, alcohol, and energy-adjusted folic acid and vitamin C intake. Individual dairy products were mutually adjusted	Agency	6
					Low-fat dairy: Q4 vs Q1	CRC: 0.94 (95% CI: 0.91, 1.23) CC: 1.01 (95% CI: 0.72, 1.42) PC: 1.00 (95% CI: 0.60, 1.66) DC: 0.84 (95% CI: 0.45, 1.56) R: 0.79 (95% CI: 0.49, 1.27)			
					Fermented dairy (yogurt and cultured milk): Q4 vs Q1	CRC: 0.90 (95% CI: 0.72, 1.13) CC: 0.76 (95% CI: 0.57, 1.01) PC: 0.67 (95% CI: 0.44, 1.03) DC: 0.80 (95% CI: 0.47, 1.35) R: 1.28 (95% CI: 0.87, 1.89)			
					Nonfermented dairy (milk and cheese): Q4 vs Q1	CRC: 0.99 (95% CI: 0.76, 1.29) CC: 1.10 (95% CI: 0.79, 1.52) PC: 1.43 (95% CI: 0.87, 2.37) DC: 0.64 (95% CI: 0.37, 1.10) R: 0.83 (95% CI: 0.53, 1.31)			
McCullough et al., 2003 (36)	USA: Cancer Prevention Study (CPS) II Nutrition Cohort (50–74)	60,866/66,883	683 CRC	~4	Dairy (skim milk, low-fat milk, whole milk, cheese, yogurt and ice-cream): ≥2 servings/d vs <2 servings/wk	CRC (M): 0.96 (95% CI: 0.67, 1.38) CRC (W): 1.11 (95% CI: 0.68, 1.83) CRC (all population): 1.00 (95% CI: 0.75, 1.34) PC (M): 0.49 (95% CI: 0.24, 1.03) DC (M): 1.18 (95% CI: 0.55, 2.57) CC (M): 0.84 (95% CI: 0.54, 1.29) R (M): 1.22 (95% CI: 0.64, 2.33)	Age, smoking, BMI, education, physical activity, family history of CRC, total energy, percentage saturated fat, fruit intake, vegetable intake, long-term multivitamin use, and HRT use	NA	6
					Milk (skim, low-fat and whole milk): ≥1.1 vs 0 serving/d	CRC (M): 0.86 (95% CI: 0.66, 1.11) CRC (W): 1.18 (95% CI: 0.84, 1.65) CRC (all population): 0.96 (95% CI: 0.78, 1.18) PC (M): 0.68 (95% CI: 0.42, 1.09) DC (M): 0.92 (95% CI: 0.54, 1.58) CC (M): 0.81 (95% CI: 0.60, 1.10) R (M): 0.89 (95% CI: 0.54, 1.47)			

(*Continued*)

TABLE 1 (*Continued*)

Study, year (ref.)	Study cohort and characteristics (age, y)	No. of participants (M/W)	No. of incident cases	Follow-up length, y	Exposure	RR	Adjustments to the RR	Funding source	NOS quality score
Larsson et al., 2005 (14)	Sweden: Swedish Mammography Cohort (40–76)	60,708 W	798 CRC, 543 CC (246 PC, 170 DC, 127 unknown), 249 R and 6 C+R	14.8	High-fat dairy food consumption: ≥4 vs <1 serving/d	CRC: 0.59 (95% CI: 0.44, 0.79) PC: 0.84 (95% CI: 0.50, 1.42) DC: 0.28 (95% CI: 0.14, 0.56) R: 0.62 (95% CI: 0.37, 1.02)	Stratified by age at recruitment and the year of entry into the cohort. Adjusted for age, BMI, education, total energy intake and quintiles of intakes of folate, vitamin B-6, cereal fiber and red meat	Agency	7
					Whole milk: ≥1 serving/d vs never or seldom	CRC: 1.08 (95% CI: 0.90, 1.29) PC: 1.58 (95% CI: 1.15, 2.16) DC: 0.72 (95% CI: 0.47, 1.10) R: 0.99 (95% CI: 0.72, 1.37)			
					Full-fat cultured milk: ≥1 serving/d vs never or seldom	CRC: 0.81 (95% CI: 0.66, 1.00) PC: 0.80 (95% CI: 0.56, 1.15) DC: 0.71 (95% CI: 0.44, 1.13) R: 0.91 (95% CI: 0.62, 1.31)			
					Cheese: ≥3 vs <1 serving/d	CRC: 0.65 (95% CI: 0.44, 0.96) PC: 0.76 (95% CI: 0.39, 1.50) DC: 0.24 (95% CI: 0.07, 0.82) R: 0.89 (95% CI: 0.46, 1.71)			
					Butter: ≥15 g/d vs never or seldom	CRC: 0.80 (95% CI: 0.64, 1.00) PC: 1.10 (95% CI: 0.75, 1.61) DC: 0.63 (95% CI: 0.37, 1.08) R: 0.75 (95% CI: 0.50, 1.11)			
Larsson et al., 2006 (17)	Sweden: Cohort of Swedish Men (45–79)	45,306 M	449 CRC, 276 CC (124 PC, 131 DC, 21 unspecified) and 173 R	6.7	Total dairy (except butter): ≥7 vs <2 servings/d	CRC: 0.46 (95% CI: 0.30, 0.71) CC: 0.44 (95% CI: 0.25, 0.76) PC: 0.37 (95% CI: 0.16, 0.88) DC: 0.43 (95% CI: 0.20, 0.93) R: 0.48 (95% CI: 0.23, 0.99)	Stratified by age at baseline. Adjusted for education, family history of CRC, BMI, exercise, history of diabetes, cigarette smoking, aspirin use, multivitamin supplement use, total energy and quartiles of saturated fat, total vitamin D, alcohol, fruit, vegetable, and red meat intake	Agency	7
					Milk (low-fat, medium-fat and whole): ≥1.5 glasses/d vs <2 glasses/d	CRC: 0.67 (95% CI: 0.51, 0.87) CC: 0.65 (95% CI: 0.46, 0.91) PC: 0.76 (95% CI: 0.45, 1.30) DC: 0.53 (95% CI: 0.33, 0.87) R: 0.69 (95% CI: 0.45, 1.06)			
					Cultured milk (sour milk and yogurt): ≥1 serving/d vs never	CRC: 1.07 (95% CI: 0.86, 1.34) CC: 1.17 (95% CI: 0.88, 1.56) PC: 1.10 (95% CI: 0.72, 1.69) DC: 1.26 (95% CI: 0.84, 1.91) R: 0.94 (95% CI: 0.66, 1.33)			
					Cream and sour cream: ≥2 vs <0.5 serving/wk	CRC: 0.84 (95% CI: 0.65, 1.09) CC: 0.72 (95% CI: 0.52, 1.01) PC: 0.70 (95% CI: 0.42, 1.17) DC: 0.72 (95% CI: 0.45, 1.14) R: 1.12 (95% CI: 0.74, 1.70)			
					Hard cheese: ≥3 slices/d vs <4 slices/wk	CRC: 0.79 (95% CI: 0.56, 1.12) CC: 0.78 (95% CI: 0.51, 1.21) PC: 0.76 (95% CI: 0.40, 1.43) DC: 0.87 (95% CI: 0.45, 1.70) R: 0.80 (95% CI: 0.45, 1.41)			
					Cottage or cream cheese: ≥1 serving/mo vs never	CRC: 0.68 (95% CI: 0.40, 1.16) CC: 0.88 (95% CI: 0.48, 1.59) PC: 0.98 (95% CI: 0.42, 2.29) DC: 0.93 (95% CI: 0.40, 2.17) R: 0.36 (95% CI: 0.11, 1.15)			

(*Continued*)

TABLE 1 (*Continued*)

Study, year (ref.)	Study cohort and characteristics (age, y)	No. of participants (M/W)	No. of incident cases	Follow-up length, y	Exposure	RR	Adjustments to the RR	Funding source	NOS quality score
Park et al., 2007 (30)	USA: Multiethnic Cohort Study (45–75)	85,903/ 105,108	2110 CRC (1138 M, 972 W)	7.3	Total dairy: ≥161 vs <33 g · 1000 $kcal^{-1} \cdot d^{-1}$ Milk: ≥122 vs <11 g · 1000 $kcal^{-1} \cdot d^{-1}$	CRC (M): 0.80 (95% CI: 0.64, 0.99) CRC (W): 0.81 (95% CI: 0.65, 1.00) CRC (M): 0.78 (95% CI: 0.63, 0.96) CRC (W): 0.85 (95% CI: 0.68, 1.06)	Stratified by ethnicity and time since cohort entry. Adjusted for age at cohort entry, pack-years of cigarette smoking, family history of CRC, physical activity, history of intestinal polyps, use of NSAIDs, BMI, total energy intake, dietary fiber intake, regular multivitamin use and HRT use	Agency	6
Lee et al., 2009 (37)	China: Shanghai Women's Health Study (SWHS) (40–70)	73,224 W	394 CRC (236 CC and 158 R)	7.4	Milk: ≥200 vs 0 g/d	CRC: 0.80 (95% CI: 0.50, 1.20) CC: 0.80 (95% CI: 0.40, 1.30) R: 0.80 (95% CI: 0.40, 1.70)	Age, education, income, survey season, tea consumption, NSAID use, energy intake, and fiber intake	Agency	8
Pala et al., 2011 (38)	Italy: Italian European Prospective Investigation into Cancer and Nutrition cohort (EPIC-Italy cohort) (mean of 51)	14,178/31,063	289 CRC (215 CC and 74 R)	12	Yogurt: T3 vs T1 (median intake)	CRC (entire cohort): 0.65 (95% CI: 0.48, 0.89) CRC (M): 0.47 (95% CI: 0.28, 0.81) CRC (W): 0.69 (95% CI: 0.47, 1.03)	Stratified by diet questionnaire. Adjusted for energy, animal fat, red meat intake, dietary calcium, dietary fiber, simple sugars, BMI, alcohol consumption, smoking, education level, recreational activity (excluding sports), sporting and type of work.	Agency	6

(*Continued*)

TABLE 1 (*Continued*)

Study, year (ref.)	Study cohort and characteristics (age, y)	No. of participants (M/W)	No. of incident cases	Follow-up length, y	Exposure	RR	Adjustments to the RR	Funding source	NOS quality score
Murphy et al., 2013 (18)	10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom): European Prospective Investigation into Cancer and Nutrition (EPIC) (≥35)	142,141/334,981	4513 CRC, 2868 CC (1298 PC, 1266 DC, 304 unspecified or overlapping) and 1645 R	11	Total milk (whole-fat, skimmed, semiskim, and not specified): ≥325 vs <9 g/d	CRC: 0.81 (95% CI: 0.73, 0.90) CC: 0.80 (95% CI: 0.70, 0.91) PC: 0.84 (95% CI: 0.69, 1.02) DC: 0.78 (95% CI: 0.63, 0.96) R: 0.84 (95% CI: 0.70, 0.99)	Stratified by age (1-y categories), sex and center. Adjusted for total energy intake, BMI, physical activity index, smoking status and intensity, education status, ever-use of contraceptive pill, ever-use of HRT, menopausal status, alcohol consumption, intakes of red and processed meat and fiber.	Agency	6
					Cheese (all kinds of fresh, fermented, and matured cheese): ≥56 vs <5 g/d	CRC: 0.87 (95% CI: 0.76, 0.99) CC: 0.83 (95% CI: 0.71, 0.97) PC: 0.73 (95% CI: 0.58, 0.93) DC: 0.91 (95% CI: 0.71, 1.17) R: 0.95 (95% CI: 0.76, 1.18)			
					Yogurt (natural and flavored yogurt in all cohorts, and, additionally, fermented milk in Sweden, Norway, and Denmark)	CRC: 0.90 (95% CI: 0.81, 0.99) CC: 0.88 (95% CI: 0.77, 1.00) PC: 0.94 (95% CI: 0.79, 1.13) DC: 0.84 (95% CI: 0.69, 1.02) R: 0.93 (95% CI: 0.79, 1.10)			
					Total dairy	CRC: 0.77 (95% CI: 0.70, 0.86) CC: 0.75 (95% CI: 0.66, 0.86) PC: 0.75 (95% CI: 0.62, 0.91) DC: 0.74 (95% CI: 0.61, 0.90) R: 0.81 (95% CI: 0.69, 0.96)			
					Whole milk (excluding Norway)	CRC: 0.86 (95% CI: 0.72, 1.02) CC: 0.83 (95% CI: 0.67, 1.03) PC: 0.92 (95% CI: 0.68, 1.26) DC: 0.82 (95% CI: 0.59, 1.14) R: 0.90 (95% CI: 0.68, 1.20)			
					Semiskim milk (excluding Norway, Germany, and Greece)	CRC: 0.85 (95% CI: 0.75, 0.97) CC: 0.84 (95% CI: 0.71, 0.99) PC: 0.97 (95% CI: 0.77, 1.22) DC: 0.73 (95% CI: 0.57, 0.95) R: 0.87 (95% CI: 0.70, 1.08)			
					Skim milk [excluding Norway, Germany, Greece, Florence (Italy), Varese (Italy), and Turin (Italy)]	CRC: 0.78 (95% CI: 0.67, 0.90) CC: 0.72 (95% CI: 0.60, 0.88) PC: 0.68 (95% CI: 0.51, 0.90) DC: 0.79 (95% CI: 0.59, 1.05) R: 0.87 (95% CI: 0.69, 1.10)			

(*Continued*)

TABLE 1 (*Continued*)

Study, year (ref.)	Study cohort and characteristics (age, y)	No. of participants (M/W)	No. of incident cases	Follow-up length, y	Exposure	RR	Adjustments to the RR	Funding source	NOS quality score
Barrubés et al., 2018 (19)	Spain: PREDIMED trial (55–80)	7,216	97 CRC	6	Total dairy products (all types of milk, yogurt and cheese; custard; whipped cream; butter; and ice-cream): 564 vs 206 g/day	CRC: 0.55 (95% CI: 0.31, 0.99)	Stratified by recruitment center. Adjusted for intervention group, sex, age, leisure time physical activity, smoking status, family history of cancer, education level, history of diabetes, use of aspirin treatment and cumulative average consumption of vegetables, fruits, legumes, cereals, fish, meat, olive oil and nuts, and alcohol.	Agency	7
					Whole-fat dairy products (includes whole-fat milk and whole-fat yogurt): 114 vs 0 g/d	CRC: 1.01 (95% CI: 0.62, 1.64)			
					Low-fat dairy products (includes semiskim/skim milk and low-fat yogurt): 495 vs 67 g/d	CRC: 0.62 (95% CI: 0.36, 1,07)			
					Total yogurt (low-fat and whole-fat yogurt): 128 vs 8 g/d	CRC: 0.94 (95% CI: 0.56, 1.59)			
					Low-fat yogurt: 122 vs 1 g/d	CRC: 1.06 (95% CI: 0.65, 1.73)			
					Whole-fat yogurt: 45 vs 0 g/d	CRC: 0.86 (95% CI: 0.51, 1.46)			
					Cheese (includes all types of cheese: petit suisse, ricotta, cottage, spreadable, and semicured/cured cheeses): 44 vs 11 g/d	CRC: 1.23 (95% CI: 0.74, 2.06)			
					Total milk (semiskim/skim milk and whole milk): 449 vs 117 g/d	CRC: 0.63 (95% CI: 0.36, 1.10)			
					Low-fat milk (semiskim and skim milk): 407 vs 15 g/d	CRC: 0.54 (95% CI: 0.32, 0.92)			
					Whole milk: 60 vs 0 g/d	CRC: 1.06 (95% CI: 0.64, 1.75)			
					Concentrated full-fat dairy products (butter, whipped cream, and all types of cheese): 45 vs 11 g/d	CRC: 1.11 (95% CI: 0.66, 1.86)			
					Sugar-enriched dairy products (condensed milk, milkshakes, ice cream, and custard): 14 vs 0 g/d	CRC: 0.98 (95% CI: 0.55, 1.75)			
					Fermented dairy products (all types of yogurt and cheeses) 166 vs 36 g/d	CRC: 0.90 (95% CI: 0.53, 1.53)			
Bakken et al., 2018 (32)	Norway: Norwegian Women and Cancer (NOWAC) Cohort Study (median 51)	81,675 W	872 CRC (617 CC, 255 R)	6	Total milk (whole-fat milk, semiskim milk, extra-semiskim milk, and skim milk from a glass): >240 g/d vs never/seldom	CRC: 0.81 (95% CI: 0.66, 0.98) CC: 0.75 (95% CI: 0.59, 0.95) R: 0.94 (95% CI: 0.67, 1.34)	Age	No specific grant	6

[1]CC, colon cancer; CRC, colorectal cancer; DC, distal colon cancer; FH: positive family history of colon cancer; HRT, hormone replacement therapy; M, men; NA, not available; NFH, no family history of colon cancer; NOS, Newcastle-Ottawa Scale; NSAID, nonsteroidal anti-inflammatory drug; PC, proximal colon cancer; PREDIMED, Prevención con Dieta Mediterránea; Q, quartile; R, rectal cancer; ref, reference; T, tertile; W, women.

TABLE 2 Characteristics of the 14 case-control studies included in the meta-analysis examining the associations between the consumption of dairy products and the risk of CRC[1]

Study, year (ref)	Study characteristics (age, y)	No. of cases and endpoint	Sex, no. of cases (M/W)	No. controls and type	Exposure	OR	Adjustments to OR	Funding source	NOS quality score
Lee et al., 1989 (39)	China	203 CRC (132 CC, 71 R)	121/82	426 H	Total milk (fresh whole milk equivalent, including cheese, condensed and evaporated milk): high vs low intake	CRC: 0.92 (95% CI: 0.60, 1.34) CC: 0.81 (95% CI: 0.49, 1.33) R: 1.12 (95% CI: 0.59, 2.10)	Age, sex, Chinese dialect group, and occupational group	Agency	6
Centonze et al., 1994 (40)	Italy (34–90)	119 CRC	66/53	119 C	Dairy products (milk, cheese, and milk products): ≥263 vs 130 g/d	CRC: 0.60 (95% CI: 0.30, 1.18)	Age, sex, level of education, smoking status, and past dietary modification	NA	6
					Milk (fat milk and skim milk): ≥173 vs 6 g/d	CRC: 0.62 (95% CI: 0.23, 1.62)			
					Milk products (mozzarella, fior di latte, and fresh curd cheese): ≥70 vs 31 g/d	CRC: 0.91 (95% CI: 0.46, 1.79)			
					Cheese (fresh cheese and hard cheese): ≥105 vs 55 g/d	CRC: 0.71 (95% CI: 0.37, 1.37)			
					Fresh curd cheese: ≥5 vs 4 g/d	CRC: 1.09 (95% CI: 0.62, 1.94)			
Kampman et al., 1994 (41)	The Netherlands (up to 75 at age of diagnosis)	232 CC	NA	259 C	Fermented dairy products (buttermilk, yogurt, curds, and kefir): >242 vs ≤22 g/d	CC: 1.06 (95% CI: 0.61, 1.82)	Age, gender, urbanization level, family history, cholecystectomy, total energy intake, energy-adjusted intake of fat, dietary fiber, vitamin C, and alcohol	Industry	6
					Buttermilk: >113 vs ≤113 g/d	CC: 0.94 (95% CI: 0.59, 1.50)			
					Yogurt: >91 g/d vs never	CC: 1.49 (95% CI: 0.89, 2.49)			
					Hard cheese: >49 vs ≤19 g/d	CC: 1.18 (95% CI: 0.69, 2.01)			
					Unfermented dairy products (whole-fat milk, skim/low-fat milk, custards, evaporated milk, and porridge)	CC: 1.59 (95% CI: 0.89, 2.85)			

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TABLE 2 (*Continued*)

Study, year (ref)	Study characteristics (age, y)	No. of cases and endpoint	Sex, no. of cases (M/W)	No. controls and type	Exposure	OR	Adjustments to OR	Funding source	NOS quality score
					Whole milk: >50 g/d vs never	CC: 0.95 (95% CI: 0.54, 1.68)			
					Skim/low-fat milk: >185 g/d vs nonusers	CC: 1.15 (95% CI: 0.71, 1.84)			
Boutron et al., 1996 (31)	France (30–75)	171 CRC	109/62	309 C	Total milk	CRC: 1.20 (95% CI: 0.60, 2.2)	Age, sex, and caloric intake	Agency	6
					Low-fat milk: Q5 vs Q1	CRC: 1.00 (95% CI: 0.50, 1.90)			
					Cheese: Q5 vs Q1	CRC: 1.20 (95% CI: 0.60, 2.20)			
					Cottage cheese: level 3 vs level l	CRC: 1.20 (95% CI: 0.80, 1.90)			
					Yogurt: level 3 vs level 1	CRC: 1.00 (95% CI: 0.60, 1.60)			
Shannon et al., 1996 (42)	USA (30–62)	424 CC	238/186	414 C	Total dairy	CC (M): 0.92 (95% CI: 0.49, 1.71)	Age at diagnosis and total energy intake	Agency	6
					M: >3.32 vs 0–1.2 servings/d	CC (W): 0.40 (95% CI: 0.21, 0.79)			
					W: >2.8 vs 0–1.3 servings/d				
					High-fat dairy	CC (M): 0.73 (95% CI: 0.41, 1.30)			
					M: >1.46 vs 0–0.42 servings/d	CC (W): 0.92 (95% CI: 0.47, 1.83)			
					W: >1.14 vs 0–0.21 servings/d				
					Low-fat dairy	CC (M): 1.00 (95% CI: 0.58, 1.71)			
					M: >1.42 vs 0–0.14 servings/d	CC (W): 0.61 (95% CI: 0.34, 1.09)			
					W: >1.51 vs 0–0.30 servings/d				
					Yogurt	CC (M): 1.27 (95% CI: 0.69, 2.36)			
					M: >1 vs 0 servings/wk	CC (W): 0.65 (95% CI: 0.37, 1.16)			
					W: >1 vs 0 servings/wk				
Boutron-Ruault et al., 1999 (43)	France (30–79)	171 CRC	109/62	309 C	Milk: Q4 vs Q1	CRC: 1.0 (95% CI: 0.6, 1.8)	Age and caloric intake, categories established by sex	Agency	6
					Cottage cheese and yogurt: Q4 vs Q1	CRC: 1.10 (95% CI: 0.60, 1.90)			
					Cheese: Q4 vs Q1	CRC: 0.90 (95% CI: 0.50, 1.50)			

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TABLE 2 (*Continued*)

Study, year (ref)	Study characteristics (age, y)	No. of cases and endpoint	Sex, no. of cases (M/W)	No. controls and type	Exposure	OR	Adjustments to OR	Funding source	NOS quality score
Kampman et al., 2000 (44)	USA (30–79)	1993 CC	1095/888	2410 C	Total dairy M: 3.5 vs 0.7 W: 2.7 vs 0.5 Low-fat dairy M: 2.26 vs 0.04 W: 2.06 vs 0.09 High-fat dairy M: 1.35 vs 0.15 W: 0.89 vs 0.11 Cheese M: 0.52 vs 0.08 W: 0.51 vs 0.08 Yogurt: 0 vs >0	CC (M): 0.8 (95% CI: 0.6, 1.1) CC (W): 0.7 (95% CI: 0.5, 0.9) CC (M): 0.8 (95% CI: 0.6, 1.0) CC (W): 0.7 (95% CI: 0.5, 1.0) CC (M): 1.1 (95% CI: 0.8, 1.5) CC (W): 0.9 (95% CI: 0.6, 1.2) CC (M): 0.9 (95% CI: 0.7, 1.2) CC (W): 0.8 (95% CI: 0.7, 1.1) CC (M): 1.0 (95% CI: 0.8, 1.2) CC (W): 1.1 (95% CI: 0.9, 1.3)	Age, BMI, family history of a first-degree relative with CRC, use of aspirin, use of NSAIDs, energy intake, long-term vigorous physical activity, and dietary fiber intake	Agency	6
Satia-Abouta et al., 2004 (45)	USA: North Carolina Colon Cancer Study (NCCCS) (40–80)	613 CC	321/292	996 C	Dairy products Caucasian: 21.7 vs 4.2 servings/wk African-American: 14 vs 1.4 servings/wk	CC (Caucasian): 1.0 (95% CI: 0.6, 1.7) CC (African-American): 1.8 (95% CI: 1.0, 3.3)	Stratified by ethnicity. Adjusted for total energy when the total energy met the criteria for covariate inclusion. Other potential confounders examined included age, gender, education, BMI (year prior to diagnosis), smoking history, physical activity, family history of colon cancer, NSAID use, intake of fat, carbohydrates, dietary fiber, vitamin C, vitamin E, β-carotene, calcium, folate, fruits, and vegetables. The set of confounders in the logistic models varied for each food group	Agency	6
Murtaugh et al., 2006 (28)	USA (30–79)	1698 CC 752 R	CC: 934/764 R: 447/305	1,861 C (CC) 960 C (R)	Total dairy: low vs high intake	CC (FF): 1.05 (95% CI: 0.78, 1.43) CC (Ff/ff): 0.87 (95% CI: 0.65, 1.17) R (FF): 1.32 (95% CI: 0.83, 2.10) R (Ff/ff): 1.54 (95% CI: 1.00, 2.38)	Race, sex, age, lifetime physical activity, BMI, smoking, and energy, calcium, and fiber intake	Agency	6

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TABLE 2 (*Continued*)

Study, year (ref)	Study characteristics (age, y)	No. of cases and endpoint	Sex, no. of cases (M/W)	No. controls and type	Exposure	OR	Adjustments to OR	Funding source	NOS quality score
					High-fat dairy: low vs high intake	CC (FF): 0.85 (95% CI: 0.66, 1.11) CC (Ff/ff): 0.65 (95% CI: 0.51, 0.82) R (FF): 0.97 (95% CI: 0.65, 1.45) R (Ff/ff): 1.19 (95% CI: 0.83, 1.71)			
					Low-fat dairy: low vs high intake	CC (FF): 1.32 (95% CI: 0.98, 1.78) CC (Ff/ff): 0.90 (95% CI: 0.68, 1.19) R (FF): 1.16 (95% CI: 0.75, 1.80) R (Ff/ff): 1.41 (95% CI: 0.94, 2.11)			
Mizoue et al., 2008 (46)	Japan: Fukuoka Colorectal Cancer Study (median of 61)	836 CRC	502/334	831 C	Total dairy foods: ≥300 vs <50 g/d	CRC: 0.76 (95% CI: 0.48, 1.18)	Residence, sex, age, job, parental history of CRC, smoking, alcohol drinking, BMI, leisure-time physical exercise, and intakes of energy, vegetable, fruit, and red meat	Agency	6
					Milk: ≥200 vs <50 g/d	CRC: 0.60 (95% CI: 0.40, 0.91)			
					Dairy foods other than milk: ≥100 vs <10 g/d	CRC: 1.39 (95% CI: 0.95, 2.02)			
Williams et al., 2009 (47)	USA: North Carolina Colon Cancer Study-Phase II (40–79)	Caucasian: 720 R	Caucasian: 418/302	Caucasian: 800 C	Total dairy Caucasian: 17.4 vs 3.6 servings/wk African-American: 13.3 vs 1.5 servings/wk	Caucasian (R): 0.47 (95% CI: 0.32, 0.69) African-American (R): 1.18 (95% CI: 0.53, 2.62)	Stratified by race. Adjusted for age, sex, education, income, BMI 1 year previous, physical activity, family history, NSAID use, and total energy intake	Agency	6
		African-American: 225 R	African-American: 117/108	African-American: 159 C	Cheese Caucasian: 5.9 vs 0.6 servings/wk African-American: 4.6 vs 0.2 servings/wk	Caucasian (R): 0.73 (95% CI: 0.50, 1.06) African-American (R): 1.04 (95% CI: 0.44, 2.46)			
					Milk Caucasian: 12.7 vs 1.4 servings/wk African-American: 8.6 vs 0.6 servings/wk	Caucasian (R): 0.66 (95% CI: 0.46, 0.95) African-American (R): 0.90 (95% CI: 0.41, 1.95)			
					Yogurt: consumers vs nonconsumers	Caucasian (R): 0.69 (95% CI: 0.53, 0.89) African-American (R): 1.08 (95% CI: 0.62, 1.87)			

(*Continued*)

TABLE 2 (*Continued*)

Study, year (ref)	Study characteristics (age, y)	No. of cases and endpoint	Sex, no. of cases (M/W)	No. controls and type	Exposure	OR	Adjustments to OR	Funding source	NOS quality score
Sun et al., 2011 (48)	Canada (20–74)	1760 CRC (488 from NL and 1272 from ON)	NA	2481 C (651 from NL and 1830 from ON)	Total dairy products (all foods in dairy categories) NL: 25.9 vs 2.4 servings/wk ON: 25.5 vs 3.1 servings/wk Milk (nonfat or skim milk, low-fat milk and whole milk) NL: 17 vs 0 servings/wk ON: 14.9 vs 0.6 servings/wk Nonmilk dairy products (yogurt, cheese, and cream) NL: 11.4 vs 0.3 servings/wk ON: 11.5 vs 1.1 servings/wk Yogurt NL: 5 vs 0 servings/wk ON: 3.5 vs 0 servings/wk Cheese NL: 7 vs 0 servings/wk ON: 10 vs 0.5 servings/wk	NL (CRC): 0.89 (95% CI: 0.55, 1.45) ON (CRC): 0.78 (95% CI: 0.60,1.00) NL (CRC): 0.96 (95% CI: 0.58, 1.57) ON (CRC): 0.78 (95% CI: 0.60, 1.00) NL (CRC): 1.12 (95% CI: 0.67, 1.89)ON (CRC): 0.98 (95% CI: 0.76, 1.26) NL (CRC): 1.02 (95% CI: 0.75, 1.39) ON (CRC): 0.85 (95% CI: 0.68, 1.07) NL (CRC): 1.25 (95% CI: 0.76, 2.05) ON (CRC): 0.90 (95% CI: 0.70, 1.14)	Stratified by province. Adjusted for total energy intake, age, sex, BMI, physical activity, first-degree relatives with CRC, polyps, diabetes, reported colon screening procedure, cigarette smoking, alcohol drinking, education attainment, household income, marital status, regular use of NSAID, regular use of multivitamin supplements, reported HRT (females only), and intakes of fruits, vegetables, and red meat	Agency	7
Green et al., 2014 (49)	Australia: Western Australian Bowel Health Study (WABOHS) (40–79)	854 CRC (281 PC, 260 DC, 313 R)	526/328	948 C	Total milk: ≥2 vs <1 cup/d	CRC: 1.02 (95% CI: 0.71, 1.46) PC: 0.96 (95% CI: 0.57, 1.62) DC: 0.85 (95% CI: 0.49, 1.49) R: 1.24 (95% CI: 0.77, 1.98)	Age group, sex, energy intake from food, alcohol intake, smoking status, use of multivitamins, diabetes, physical activity during the ages of 19–34 y, BMI at age 40 y, socioeconomic status, tea and coffee intake	Agency	6
Chun et al., 2015 (50)	Korea (20–80)	150 CRC	94/56	116 C	Milk and dairy products: 5.3 vs <1.1 servings/wk	CRC: 2.42 (95% CI: 1.10, 5.31)	Energy intake, sex, age, household income, education, smoking, alcohol consumption frequency, exercise frequency, dietary fiber and red meat	NA	6

[1] C, community controls; CC, colon cancer; CRC, colorectal cancer; DC, distal colon; FF, FF *FokI* genotype; Ff/ff, Ff/ff *FokI* genotype; H, hospital controls; HRT, hormone replacement therapy; M, men; NA, not available; NL, subjects in Newfoundland and Labrador; NOS, Newcastle-Ottawa Scale; NSAID, nonsteroidal anti-inflammatory drug; ON, subjects in Ontario; PC, proximal colon; Q, quantile; R, rectal cancer; ref, reference; W, women.

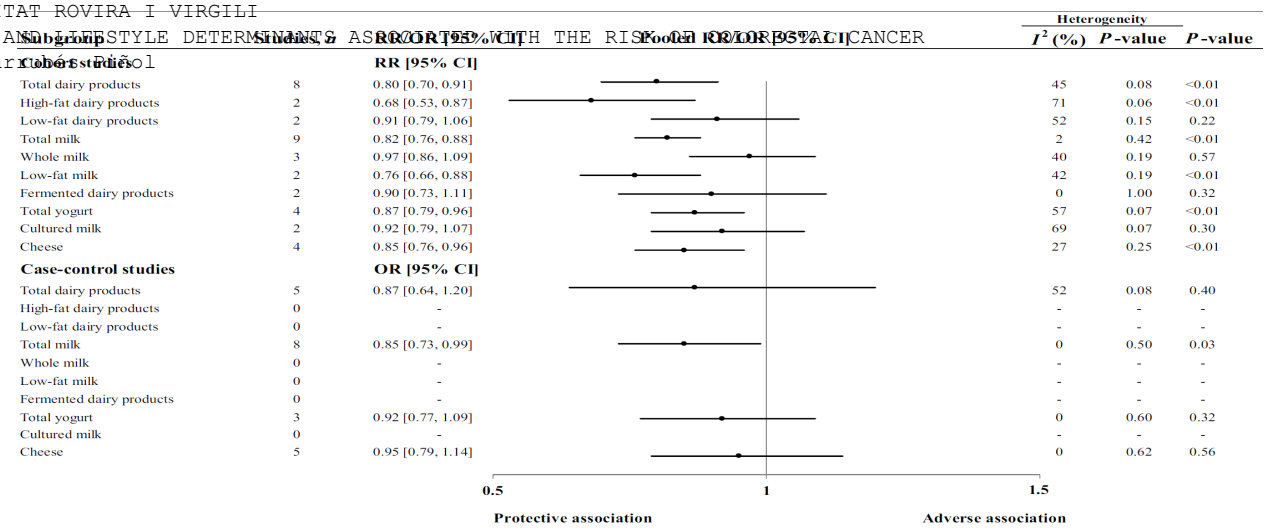

FIGURE 2 Summary estimates (RRs for cohort studies and ORs for case-control studies, with the corresponding 95% CIs; log scale) examining the associations between the consumption of dairy products and the risk of CRC. The meta-analysis included prospective cohort and case-control studies analyzing the consumption of total dairy products, high-fat dairy products, low-fat dairy products, total milk, whole milk, low-fat milk, fermented dairy products, total yogurt, cultured milk, or cheese. CRC, colorectal cancer; MetS, metabolic syndrome.

heterogeneity (I^2 = 71%; *P*-heterogeneity = 0.06) (Figure 2). The summary RR for colon cancer was 0.82 (95% CI: 0.62, 1.08; I^2 = 0%; *P*-heterogeneity = 0.77; *n* = 3) (Figure 3).

Low-fat dairy products. Two cohort studies, comprising 68,859 participants and 669 cases (11, 19), were used in the meta-analysis of the effects of the highest compared with the lowest consumption of low-fat dairy products on CRC risk. The overall RRs for CRC (summary RR: 0.91; 95% CI: 0.79, 1.06; I^2 = 52%; *P*-heterogeneity = 0.15) (Figure 2) and colon cancer (summary RR: 0.91; 95% CI: 0.72, 1.15; I^2 = 0%; *P*-heterogeneity = 0.68; *n* = 3) (Figure 3) were not statistically significant.

Total milk. The analysis of the association of the highest compared with the lowest consumption of total milk on CRC risk included 9 cohort study comparisons (1,003,303 individuals and 9118 cases) (17–19, 30, 32, 36, 37). We found evidence of a significant inverse association with the summary RR of CRC (summary RR: 0.82; 95% CI: 0.76, 0.88; I^2 = 2%; *P*-heterogeneity = 0.42) (Figure 2 and **Supplemental Figure 3**). A significant inverse association with no significant heterogeneity was also observed for colon cancer (summary RR: 0.79; 95% CI: 0.72, 0.87; I^2 = 0%; *P*-heterogeneity = 0.96; *n* = 8) (Figure 3 and **Supplemental Figure 4**), proximal colon cancer (summary RR: 0.81; 95% CI: 0.68, 0.96; I^2 = 0%; *P*-heterogeneity = 0.70; *n* = 3) (Figure 4), distal colon cancer (summary RR: 0.75; 95% CI: 0.63, 0.90; I^2 = 25%; *P*-heterogeneity = 0.26; *n* = 3) (Figure 4), and rectal cancer (summary RR: 0.84; 95% CI: 0.73, 0.97; I^2 = 0%; P-heterogeneity = 0.84; *n* = 5) (Figure 5).

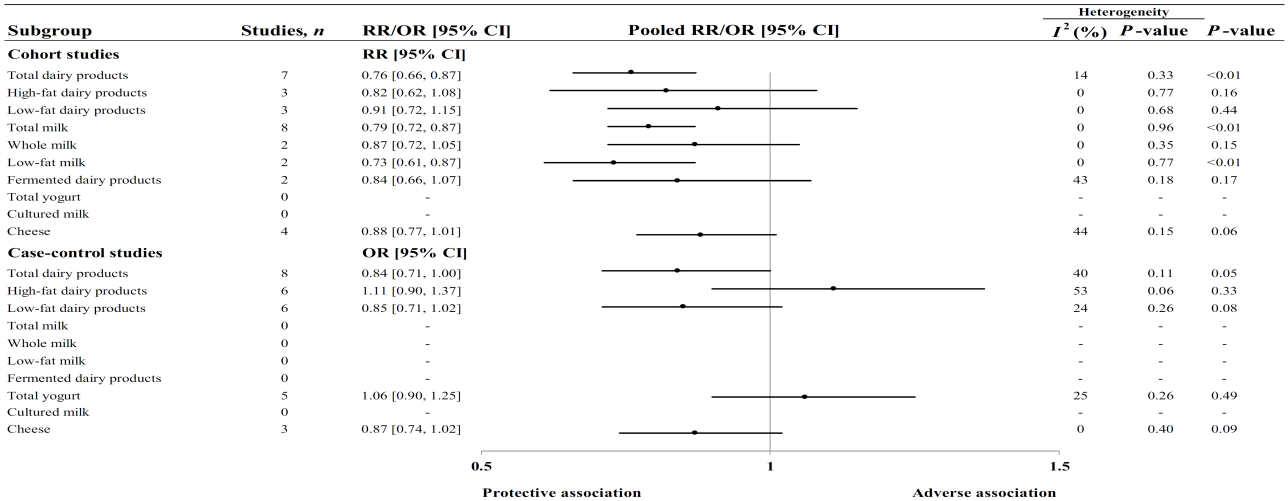

FIGURE 3 Summary estimates (RRs for cohort studies and ORs for case-control studies, with the corresponding 95% CIs; log scale) examining the associations between the consumption of dairy products and the risk of colon cancer. The meta-analysis included prospective cohort and case-control studies analyzing the consumption of total dairy products, high-fat dairy products, low-fat dairy products, total milk, whole milk, low-fat milk, fermented dairy products, total yogurt, cultured milk, or cheese. MetS, metabolic syndrome.

Whole milk. Three cohort studies (14, 18, 19) were used to compare the effects of the highest and the lowest consumption of whole milk on CRC risk (545,046 individuals and 5198 cases). The pooled risk estimate showed an RR of 0.97 (95% CI: 0.86, 1.09), with moderate heterogeneity among the studies (I^2 = 40%; *P*-heterogeneity = 0.19) (Figure 2). We did not observe a significant inverse association with colon cancer risk in the analysis of the highest compared with the lowest consumption (summary RR: 0.87; 95% CI: 0.72, 1.05; I^2 = 0%; *P*-heterogeneity = 0.35; *n* = 2) (Figure 3), proximal colon cancer (summary RR: 1.20; 95% CI: 0.96, 1.49; I^2 = 83%; *P*-heterogeneity = 0.02; *n* = 2) (Figure 4), distal colon cancer (summary RR: 0.78; 95% CI: 0.60, 1.01; I^2 = 0%; *P*-heterogeneity = 0.64; *n* = 2) (Figure 4), or rectal cancer (summary RR: 0.94; 95% CI: 0.76, 1.16; I^2 = 0%; *P*-heterogeneity = 0.66; *n* = 2) (Figure 5).

Low-fat milk. The combined RR for CRC for the highest compared with the lowest consumption of low-fat milk (18, 19) was 0.76 (95% CI: 0.66, 0.88; I^2 = 42%; *P*-heterogeneity = 0.19) (Figure 2). The analysis considered 2 cohorts with a total of 484,338 participants and 3507 cases. The overall RR for colon cancer was 0.73 (95% CI: 0.61, 0.87; I^2 = 0%; *P*-heterogeneity = 0.77; *n* = 2) (Figure 3).

Fermented dairy products. Two cohort studies (11, 19) (68,859 individuals and 669 cases) were included in the meta-analysis of the association between the highest and lowest consumption of fermented dairy products and CRC risk. The summary RR was 0.90 (95% CI: 0.73, 1.11; I^2 = 0%; *P*-heterogeneity = 1.00) (Figure 2). The association for colon cancer was not statistically significant (summary RR: 0.84; 95% CI: 0.66, 1.07; I^2 = 43%; *P*-heterogeneity = 0.18; *n* = 2) (Figure 3).

Total yogurt. Four cohort studies, with a total of 529,579 and 4899 cases (18, 19, 38), were used to compare the overall risk of CRC between the groups with the highest and lowest consumption of total yogurt. The summary RR was 0.87 (95% CI: 0.79, 0.96; I^2 = 57%; *P*-heterogeneity = 0.07) (Figure 2).

Cultured milk. Two cohort studies (14, 17), with a total of 106,014 participants and 1247 cases, were used to analyze the association between the highest and lowest consumption of cultured milk and CRC risk. The summary RR was 0.92 (95% CI: 0.79, 1.07; I^2 = 69%; *P*-heterogeneity = 0.07) (Figure 2). Similarly, for proximal and distal colon cancer (Figure 4) and rectal cancer (Figure 5), the inverse associations were not significant (the *P*-values were 0.52 for proximal colon cancer, 0.92 for distal colon cancer, and 0.55 for rectal cancer).

Cheese. Four prospective cohort studies (14, 17–19) (590,352 participants and 5857 cases) were used to analyze the association between the highest and lowest consumption of cheese and CRC risk. The pooled RR was 0.85 (95% CI: 0.76, 0.96), with no significant heterogeneity between the studies (I^2 = 27%; *P*-heterogeneity = 0.25) (Figure 2). However, the inverse relationship was not statistically significant for colon cancer (summary RR: 0.88; 95% CI: 0.77, 1.01; I^2 = 44%; *P*-heterogeneity = 0.15; *n* = 4) (Figure 3). The RR for proximal colon cancer showed a significant inverse association (summary RR: 0.74; 95% CI: 0.60, 0.91; I^2 = 0%; *P*-heterogeneity = 0.99; *n* = 3) (Figure 4). The inverse relationships for distal colon cancer (summary RR: 0.86; 95% CI: 0.69, 1.09; I^2 = 54%; *P*-heterogeneity = 0.11; *n* = 3) (Figure 4) and rectal cancer (summary RR: 0.93; 95% CI: 0.76, 1.13; I^2 = 0%; *P*-heterogeneity = 0.85; *n* = 3) (Figure 5) were not statistically significant.

Case-control studies.

Total dairy products. Five case-control study comparisons were used to assess the associations between the highest and lowest consumption of total dairy products and the risk of CRC (40, 46, 48, 50). The summary OR was 0.87 (95% CI: 0.64, 1.20), with moderate heterogeneity among the studies (I^2 = 52%; *P*-heterogeneity = 0.08) (Figure 2). The pooled OR was 0.84 (95% CI: 0.71, 1.00) for colon cancer (Figure 3) and 0.63 (95% CI: 0.50, 0.80) for rectal cancer (Figure 5), with no significant heterogeneity (*P*-heterogeneity = 0.11 and 0.15, and *n* = 8 and 4, respectively) among the studies.

High-fat dairy products. We used 6 case-control study comparisons to analyze the association between colon cancer and the highest and lowest intakes of high-fat dairy products (28, 42, 44). The summary OR for colon cancer was 1.11 (95% CI: 0.90, 1.37), with moderate heterogeneity (I^2 = 53%; *P*-heterogeneity = 0.06) (Figure 3). For rectal cancer, the OR was 0.92 (95% CI: 0.71, 1.20; I^2 = 0%; *P*-heterogeneity = 0.45; *n* = 2) (Figure 5).

Low-fat dairy products. We used 6 case-control study comparisons to analyze the association between colon cancer and the highest and lowest intakes of low-fat dairy products (28, 42, 44). The summary OR for colon cancer was 0.85 (95% CI: 0.71, 1.02; I^2 = 24%; *P*-heterogeneity = 0.26) (Figure 3). For rectal cancer, the summary OR was 0.78 (95% CI: 0.58, 1.04; I^2 = 0%; *P*-heterogeneity = 0.53; *n* = 2) (Figure 5).

Total milk. Eight case-control study comparisons (31, 39, 40, 43, 46, 48, 49) were used to analyze the association between the highest and lowest intakes of total milk and CRC risk. We observed a significant inverse association (OR: 0.85; 95% CI: 0.73, 0.99) for CRC, with no important heterogeneity (I^2 = 0%; *P*-heterogeneity = 0.50) (Figure 2). The summary OR for rectal cancer was not statistically significant (OR: 0.88; 95% CI: 0.69, 1.13; I^2 = 40%; *P*-heterogeneity = 0.17; *n* = 4) (Figure 5).

Total yogurt. In the analysis of the highest compared with the lowest intake of total yogurt, the pooled risk estimate for CRC was not significant (OR: 0.92; 95% CI: 0.77, 1.09; I^2 = 0%; *P*-heterogeneity = 0.60). This analysis included 3 case-control study comparisons (31, 48) (Figure 2). For the analysis of colon cancer risk, the summary OR was

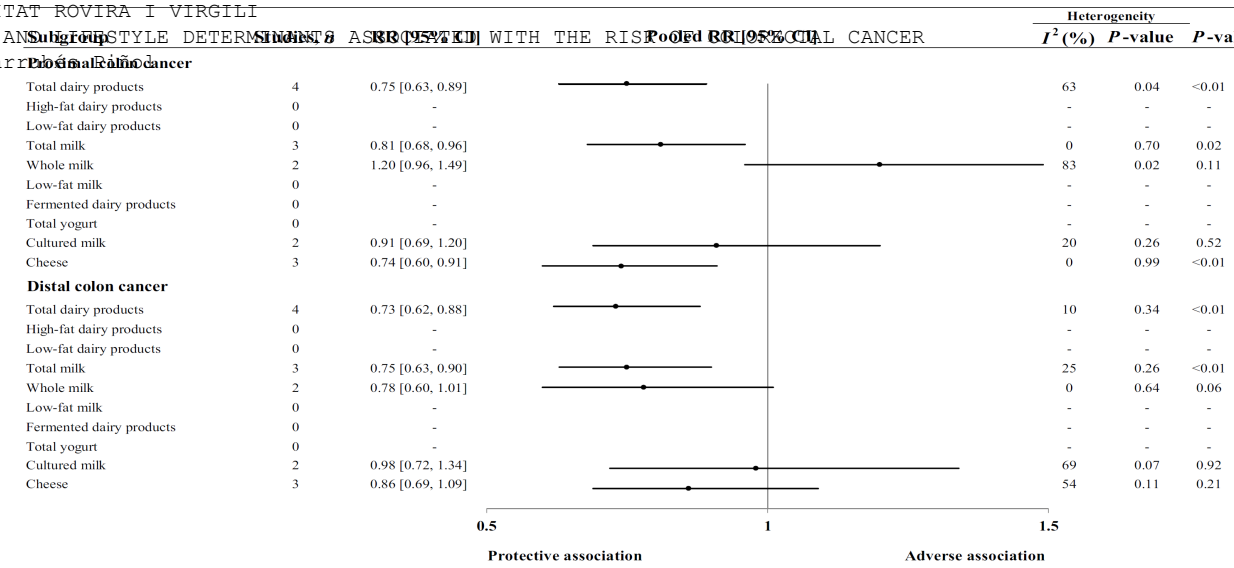

FIGURE 4 Summary estimates (RRs with 95% CIs; log scale) examining the associations between the consumption of dairy products and the risk of colon cancer by subsite (proximal or distal colon). The meta-analysis included prospective cohort studies analyzing the consumption of total dairy products, high-fat dairy products, low-fat dairy products, total milk, whole milk, low-fat milk, fermented dairy products, total yogurt, cultured milk, or cheese. MetS, metabolic syndrome.

1.06 (95% CI: 0.90, 1.25; I^2 = 25%; *P*-heterogeneity = 0.26; n = 5) (Figure 3). The association for rectal cancer was statistically significant (OR: 0.75; 95% CI: 0.59, 0.95; I^2 = 52%; *P*-heterogeneity = 0.15, n = 2) (Figure 5).

Cheese. The combined OR for CRC in the analysis of the highest compared with the lowest consumption of cheese included 5 case-control study comparisons (31, 40, 43, 48). The pooled OR was 0.95 (95% CI: 0.79, 1.14; I^2 = 0%; *P*-heterogeneity = 0.62) (Figure 2). Similarly, we found no evidence of a significant association between colon cancer risk (OR: 0.87; 95% CI: 0.74, 1.02; I^2 = 0%; *P*-heterogeneity = 0.40; n = 3) (Figure 3) or rectal cancer (OR: 0.77; 95% CI: 0.55, 1.09; I^2 = 0%; *P*-heterogeneity = 0.46; n = 2) and the highest and lowest consumption of cheese (Figure 5).

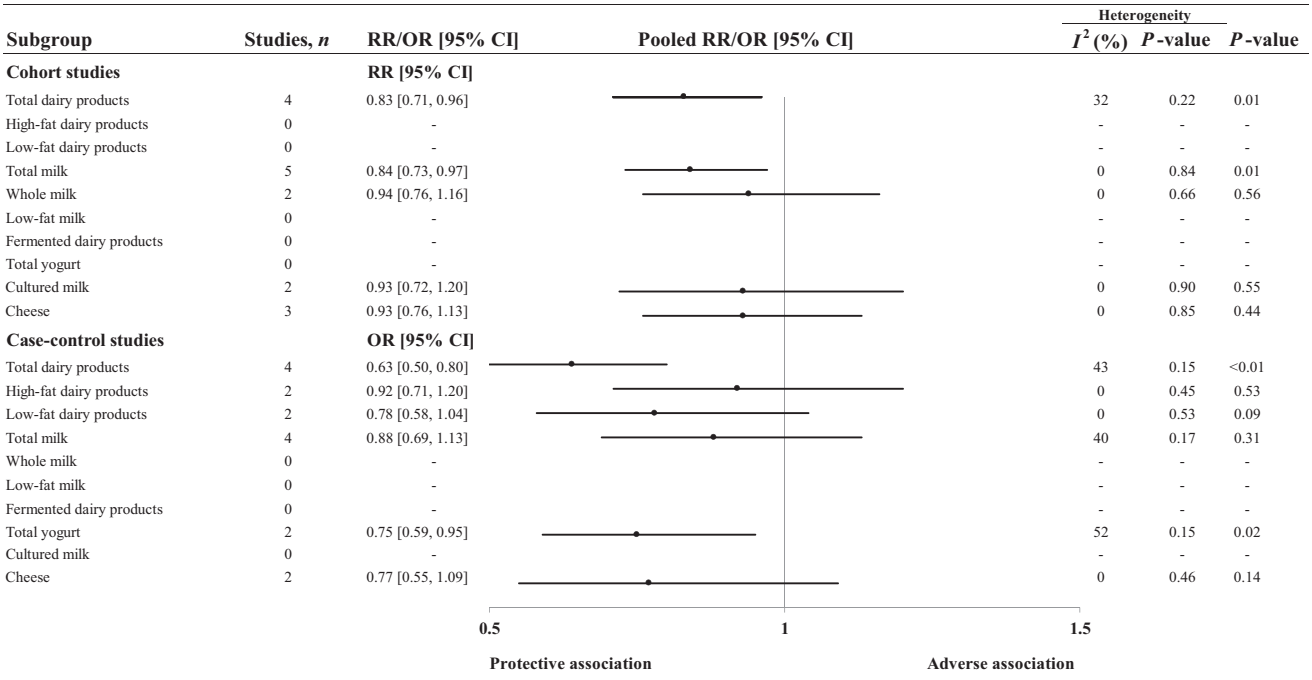

FIGURE 5 Summary estimates (RRs for cohort studies and ORs for case-control studies, with the corresponding 95% CIs; log scale) examining the associations between the consumption of dairy products and the risk of rectal cancer. The meta-analyses included prospective cohort and case-control studies analyzing the consumption of total dairy products, high-fat dairy products, low-fat dairy products, total milk, whole milk, low-fat milk, fermented dairy products, total yogurt, cultured milk, or cheese.

Dose-response analyses

Total dairy products.

The linear RR for CRC per 1 serving increment of total dairy products was 0.92 (95% CI: 0.88, 0.96; $P < 0.001$) (**Supplemental Figure 5**). This inverse association was significant for colon cancer (RR: 0.91; 95% CI: 0.88, 0.95; $P < 0.001$) (**Supplemental Figure 6**) but not for proximal colon cancer ($P = 0.094$) (**Supplemental Figure 7**). The inverse associations for distal colon cancer (RR: 0.88; 95% CI: 0.84, 0.93; $P < 0.001$) (**Supplemental Figure 8**) and rectal cancer (RR: 0.94; 95% CI: 0.88, 0.99; $P = 0.023$) (**Supplemental Figure 9**) were also significant.

Total milk.

The linear RR of CRC per 1 serving increment of total milk was 0.90 (95% CI: 0.86, 0.93; $P < 0.001$) (**Supplemental Figure 10**). There was also a significant linear association for colon cancer (RR: 0.88; 95% CI: 0.84, 0.93; $P < 0.001$) (**Supplemental Figure 11**) and rectal cancer (RR: 0.91; 95% CI: 0.84, 0.97; $P = 0.005$) (**Supplemental Figure 12**).

Total yogurt.

The combined linear RR for CRC for an increment of one serving of yogurt was 0.72 (95% CI: 0.47, 1.10; $P = 0.128$) (**Supplemental Figure 13**).

Cheese.

We detected a significant linear RR for CRC per 1 serving increment of cheese (RR: 0.93; 95% CI: 0.88, 0.98; $P = 0.006$). The linear RR for colon cancer per 1 serving increment was also significant (RR: 0.91; 95% CI: 0.84, 0.99; $P = 0.030$) (**Supplemental Figures 14** and **15**).

Sensitivity analyses

To detect whether the exclusion of a particular study modified the associations observed, we excluded 1 study at a time from the analyses of highest compared with lowest consumption for both the cohort and the case-control studies (Supplemental Tables 2 and 3, respectively). For the cohort studies, after the study by Murphy et al. (18) was removed, the inverse associations between the consumption of total dairy products and the risk of proximal colon, distal colon, and rectal cancer were no longer significant. Likewise, the removal of the same study (18) also decreased the summary RR for proximal colon and rectal cancer for total milk consumption and the pooled RR for CRC for cheese consumption.

In the analysis of total dairy products, the study by Larsson et al. (17) explained most of the observed heterogeneity ($I^2 = 8\%$; P-heterogeneity = 0.36). After the study by Terry et al. (11) was excluded, the heterogeneity was reduced ($I^2 = 44\%$; P-heterogeneity = 0.17). The study by Pala et al. (38) explained most of the heterogeneity among the studies when the association between the consumption of total yogurt and CRC risk ($I^2 = 0\%$; P-heterogeneity = 0.43) was assessed.

For the case-control studies, the heterogeneity in the association between the consumption of total dairy products and CRC risk was no longer significant after the study by Chun et al. (50) was removed ($I^2 = 0\%$; P-heterogeneity = 0.84). The case-control study conducted by Murtaugh et al. (28) accounted for most of the heterogeneity in the analysis of high-fat dairy products and colon cancer risk ($I^2 = 0\%$; P-heterogeneity = 0.52).

Discussion

In this meta-analysis of 29 prospective cohort and case-control studies including >22,000 CRC cases, prospective cohort studies showed an association between a higher consumption of total dairy products and total milk and a consistently and significantly decreased risk of CRC across all CRC subsites. High low-fat milk and cheese consumption was also associated with a decreased risk of CRC. However, this inverse association for low-fat milk was restricted to colon cancer, whereas after stratification by CRC subsite, cheese had a significant association only with proximal colon cancer. Although the high consumption of high-fat dairy products and total yogurt showed a significant inverse association with CRC risk, there was substantial heterogeneity among the few studies that had been conducted. Therefore, these observations should be interpreted cautiously. No significant associations were found between CRC risk and the consumption of low-fat dairy products, whole milk, fermented dairy products, or cultured milk. Most of the associations found were not supported by the case-control studies. This discrepancy may be largely explained by the differences in study design between cohort and case-control studies, differences in categorizing the frequency of dairy product consumption and the amounts of dairy products consumed, and differences in the covariates considered as potential confounders in the statistical models.

Our results are in line with those of a pooled analysis of 10 cohort studies (51) and previous meta-analyses of case-control and cohort studies (52, 53). Likewise, systematic reviews and meta-analyses of prospective studies (54–57) showed a reduced risk of CRC associated with the consumption of total dairy products, milk, or a combination. Our findings are also in accordance with the conclusion of the latest WCRF/AICR report (3).

In our meta-analysis, the consumption of total dairy products and milk was associated with a significant decrease in the risk of both colon and rectal cancers, although these inverse associations were slightly higher for colon cancer. In contrast, most systematic reviews and meta-analyses have shown that the inverse associations between CRC risk and the consumption of milk and total dairy products (54–57) are mainly restricted to colon cancer. To our knowledge, no previous systematic reviews or meta-analyses have assessed the link between CRC risk and the consumption of low-fat and whole milk. Furthermore, the associations between the consumption of dairy products with different fat contents and CRC risk were not documented in the latest report by the CUP panel (3). On the one hand, we found that the

consumption of low-fat milk is associated with a 24% and 27% reduction in the risk of colorectal and colon cancer, respectively, with no significant heterogeneity among the studies. On the other hand, we did not observe a significant association between whole-milk consumption and CRC risk. These results are, therefore, of great importance, because despite the lack of scientific evidence, most dietary recommendations encourage the consumption of low-fat dairy products.

We found that cheese consumption may decrease the risk of CRC, particularly proximal colon cancer. These results are consistent with the conclusions of the latest CUP report (3). We also augmented the current evidence for these associations by our finding of a linear relationship between cheese consumption and CRC. Ralston et al. (55) found no evidence of a significant inverse relationship between solid cheese consumption and CRC. These discrepancies could be explained by the inclusion of 2 large cohort studies assessing cheese consumption, and because CRC risk was included in our study but not in Ralston's systematic review and meta-analysis (18, 19).

The protective association we found between yogurt consumption and CRC risk is inconsistent with other evidence (54, 55). As previously mentioned, this result should be taken with caution since there was substantial heterogeneity among the studies analyzed. Similarly, the inverse association between high-fat dairy products and CRC risk showed substantial heterogeneity, and the summary risk estimate included only 2 studies (14, 19).

The mechanisms involved in the possible decrease in CRC risk are unclear. The most-studied chemopreventive agent in dairy products is calcium, because dairy products are one of the main contributors of calcium in the diet. According to the hypothesis of Newmark et al. (58), fatty acids and bile acids in the colon may play an important role in the initial steps of colorectal carcinogenesis. Calcium might protect against CRC by the colonic sequestration of secondary bile acids such as deoxycholic acid and phospholipids. These components have been shown to promote colorectal tumors in animal models, probably by regulating protein kinase C (59, 60). On the other hand, calcium could lead to differentiation in normal cells and apoptosis in transformed cells (61, 62). Conjugated linoleic acid, which is naturally present in dairy products, might also have a protective effect against CRC by inhibiting cell proliferation, modifying the fluidity of cell membranes, decreasing the production of inflammatory mediators, and stimulating the immune response (63–66). Other components, such as butyric acid (62, 67), lactoferrin (68), and vitamin D (52, 69), in fortified dairy foods might also have protective effects.

Our systematic review and meta-analysis has several strengths: *1*) we identified prospective cohort and case-control studies through a systematic search; *2*) we used a quantitative NOS scale to exclude low-quality studies; and *3*) all of the studies in our analysis used a validated food-frequency questionnaire to assess dairy product consumption.

Despite the high quality of the studies we analyzed, we also acknowledge some limitations, such as potential residual confounding because of the observational nature of the studies included or the possibility that not all the studies were adjusted for important dietary variables. Moreover, some of the dietary assessments were self-reported, which may affect the reliability of the reported intakes. However, the use of validated food-frequency questionnaires could reduce this bias. Although some heterogeneity among studies was observed, this heterogeneity was explained by the removal of individual studies. For studies reporting both skim and semiskim milk and different types of cheese separately, we considered only the values for skim milk and hard cheese, so the risk estimates might be somewhat overestimated. Since we were not able to search all available databases, we cannot ignore the possibility that some references may have been missed. Finally, given the observational nature of the present meta-analysis, our results cannot support causal relationships between dairy product consumption and CRC risk.

Conclusions

Our systematic review and meta-analysis of observational studies shows a consistent inverse association between higher consumption of dairy products and total milk and the risk of CRC at all sites. Low-fat milk consumption was associated with a decreased risk of CRC, although this inverse association was restricted to the colon. This systematic review and meta-analysis is the first to evaluate the association between subtypes of milk and CRC risk. An inverse association between cheese consumption and the risk of CRC, particularly proximal colon cancer, was also found. No harmful effects associated with the consumption of any type of dairy product, including whole-fat dairy products, were observed. Therefore, it seems reasonable to claim that the consumption of dairy foods, especially low-fat milk and cheese, might be related to a lower risk of CRC. Further prospective studies with large samples and long follow-up periods, as well as clinical trials that take into account the long latency period of CRC, known difficulties with dietary compliance, and other complexities such as the high economic cost, are needed to clarify the associations between CRC, including the differences in CRC risk across subsites, and the fat and sugar contents of dairy products.

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LB, NB, NB-T, NR-E and JS-S had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and drafted the manuscript; NB ans JS-S: study concept and design; LB: statistical analyses; LB, NB, NB-T, NR-E and JS-S: critically revised the manuscript for important intellectual content and read and approved the final manuscript.

References

1. Fitzmaurice C, Akinyemiju TF, Al Lami FH, Alam T, Alizadeh-Navaei R, Allen C, Alsharif U, Alvis-Guzman N, Amini E, Anderson BO, et al.

Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016. JAMA Oncol 2018;4(11):1553–68.
2. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut 2017;66:683–91.
3. World Cancer Research Fund/American Institute for Cancer Research. Diet, nutrition, physical activity and cancer: a global perspective. Continuous Update Project Expert Report 2018.
4. Schwingshackl L, Hoffmann G. Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies. Cancer Med 2015;4:1933–47.
5. Feng Y-L, Shu L, Zheng P-F, Zhang X-Y, Si C-J, Yu X-L, Gao W, Zhang L. Dietary patterns and colorectal cancer risk. Eur J Cancer Prev 2017;26:201–11.
6. Bostick RM, Potter JD, Sellers TA, McKenzie DR, Kushi LH, Folsom AR. Relation of calcium, vitamin D, and dairy food intake to incidence of colon cancer among older women. The Iowa Women's Health Study. Am J Epidemiol 1993;137:1302–17.
7. Kampman E, Goldbohm RA, Brandt PA Van Den, Van P. Fermented dairy products, calcium, and colorectal cancer in the Netherlands Cohort Study. Cancer Res 1994;54(12):3186–90.
8. Kearney J, Giovannucci E, Rimm EB, Ascherio A, Stampfer MJ, Colditz GA, Wing A, Kampman E, Willett WC. Calcium, vitamin D, and dairy foods and the occurrence of colon cancer in men. Am J Epidemiol 1996;143:907–17.
9. Pietinen P, Malila N, Virtanen M, Hartman TJ, Tangrea JA, Albanes D, Virtamo J. Diet and risk of colorectal cancer in a cohort of Finnish men. Cancer Causes Control 1999;10:387–96.
10. Järvinen R, Knekt P, Hakulinen T, Aromaa A. Prospective study on milk products, calcium and cancers of the colon and rectum. Eur J Clin Nutr 2001;55:1000–7.
11. Terry P, Baron JA, Bergkvist L, Holmberg L, Wolk A. Dietary calcium and vitamin D intake and risk of colorectal cancer: a prospective cohort study in women. Nutr Cancer 2002;43:39–46.
12. Lin J, Zhang SM, Cook NR, Lee I-M, Buring JE. Dietary fat and fatty acids and risk of colorectal cancer in women. Am J Epidemiol 2004;160:1011–22.
13. Sanjoaquin MA, Appleby PN, Thorogood M, Mann JI, Key TJ. Nutrition, lifestyle and colorectal cancer incidence: a prospective investigation of 10 998 vegetarians and non-vegetarians in the United Kingdom. Br J Cancer 2004;90:118–21.
14. Larsson SC, Bergkvist L, Wolk A. High-fat dairy food and conjugated linoleic acid intakes in relation to colorectal cancer incidence in the Swedish Mammography Cohort. Am J Clin Nutr 2005;82:894–900.
15. Lin J, Zhang SM, Cook NR, Manson JE, Lee I-M, Buring JE. Intakes of calcium and vitamin D and risk of colorectal cancer in women. Am J Epidemiol 2005;161:755–64.
16. Kesse E, Boutron-Ruault MC, Norat T, Riboli E, Clavel-Chapelon F. Dietary calcium, phosphorus, vitamin D, dairy products and the risk of colorectal adenoma and cancer among French women of the E3N-EPIC prospective study. Int J Cancer 2005;117:137–44.
17. Larsson SC, Bergkvist L, Rutegård J, Giovannucci E, Wolk A. Calcium and dairy food intakes are inversely associated with colorectal cancer risk in the Cohort of Swedish Men. Am J Clin Nutr 2006;83:667–73.
18. Murphy N, Norat T, Ferrari P, Jenab M, Bueno-de-Mesquita B, Skeie G, Olsen A, Tjønneland A, Dahm CC, Overvad K, et al. Consumption of dairy products and colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). PLoS One 2013;8:e72715.
19. Barrubés L, Babio N, Mena-Sánchez G, Toledo E, Ramírez-Sabio JB, Estruch R, Ros E, Fitó M, Arós F, Fiol M, et al. Dairy product consumption and risk of colorectal cancer in an older Mediterranean population at high cardiovascular risk. Int J Cancer 2018;143(6):1356–66.
20. Eckel RH, Jakicic JM, Ard JD, Hubbard VS, de Jesus JM, Lee IM, Lichtenstein AH, Loria CM, Millen BE, Houston Miller NAmerican College of Cardiology American/Heart Association Task Force on Practice Guidelines, et al. American College of Cardiology American/Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology American/Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(25 Suppl 2):S76–99.
21. National Health and Medical Research Council. Australian Dietary Guidelines. Canberra: National Health and Medical Research Council; 2013.
22. US Department of Health and Human Services and US Department of Agriculture. 2015–2020 Dietary Guidelines for Americans. [Internet]. 8th ed. 2015. Available from: http://health.gov/dietaryguidelines/2015/guidelines/.
23. Aranceta Bartrina J, Arija Val V, Maíz Aldalur E, Martínez de la Victoria Muñoz E, Ortega Anta RM, Pérez-Rodrigo C, Quiles Izquierdo J, Rodríguez Martín A, Román Viñas B, Salvador i Castell G,, et al. Guías alimentarias para la población española (SENC, 2016); la nueva pirámide de la alimentación saludable. Nutr Hosp 2016;33:1–48.
24. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. [Internet]. Oxford: Cochrane Collaboration; 2011. Available from: www.handbook.cochrane.org.
25. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000;283(15):2008–12.
26. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. PLoS Med 2009;6:e1000097.
27. Wells G, Shea B, O'Connel D. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute; 2014.
28. Murtaugh MA, Sweeney C, Ma K-N, Potter JD, Caan BJ, Wolff RK, Slattery ML. Vitamin D receptor gene polymorphisms, dietary promotion of insulin resistance, and colon and rectal cancer. Nutr Cancer 2006;55:35–43.
29. Bekkering GE, Harris RJ, Thomas S, Mayer A-MB, Beynon R, Ness AR, Harbord RM, Bain C, Smith GD, Sterne JAC. How much of the data published in observational studies of the association between diet and prostate or bladder cancer is usable for meta-analysis? Am J Epidemiol 2008;167:1017–26.
30. Park S-Y, Murphy SP, Wilkens LR, Nomura AMY, Henderson BE, Kolonel LN. Calcium and vitamin D intake and risk of colorectal cancer: the Multiethnic Cohort Study. Am J Epidemiol 2007;165:784–93.
31. Boutron MC, Faivre J, Marteau P, Couillault C, Senesse P, Quipourt V. Calcium, phosphorus, vitamin D, dairy products and colorectal carcinogenesis: a French case-control study. Br J Cancer 1996;74:145–51.
32. Bakken T, Braaten T, Olsen A, Hjartåker A, Lund E, Skeie G. Milk and risk of colorectal, colon and rectal cancer in the Norwegian Women and Cancer (NOWAC) Cohort Study. Br J Nutr 2018;119:1274–85.
33. Gaard M, Tretli S, Løken EB. Dietary factors and risk of colon cancer: a prospective study of 50,535 young Norwegian men and women. Eur J Cancer Prev 1996;5:445–54.
34. Singh PN, Fraser GE. Dietary risk factors for colon cancer in a low-risk population. Am J Epidemiol 1998;148:761–74.
35. Sellers TA, Bazyk AE, Bostick RM, Kushi LH, Olson JE, Anderson KE, Lazovich D, Folsom AR. Diet and risk of colon cancer in a large prospective study of older women: an analysis stratified on family history (Iowa, United States). Cancer Causes Control 1998;9:357–67.
36. McCullough ML, Robertson AS, Rodriguez C, Jacobs EJ, Chao A, Carolyn J, Calle EE, Willett WC, Thun MJ. Calcium, vitamin D, dairy products, and risk of colorectal cancer in the Cancer Prevention Study II Nutrition Cohort (United States). Cancer Causes Control 2003;14:1–12.
37. Lee S-A, Shu XO, Yang G, Li H, Gao Y-T, Zheng W. Animal origin foods and colorectal cancer risk: a report from the Shanghai Women's Health Study. Nutr Cancer 2009;61:194–205.

38. Pala V, Sieri S, Berrino F, Vineis P, Sacerdote C, Palli D, Masala G, Panico S, Mattiello A, Tumino R, et al. Yogurt consumption and risk of colorectal cancer in the Italian European prospective investigation into cancer and nutrition cohort. Int J Cancer 2011;129:2712–9.
39. Lee HP, Gourley L, Duffy SW, Estève J, Lee J, Day NE. Colorectal cancer and diet in an Asian population—a case-control study among Singapore Chinese. Int J Cancer 1989;43:1007–16.
40. Centonze S, Boeing H, Leoci C, Guerra V, Misciagna G. Dietary habits and colorectal cancer in a low-risk area. Results from a population-based case-control study in southern Italy. Nutr Cancer 1994;21:233–46.
41. Kampman E, van 't Veer P, Hiddink GJ, van Aken-Schneijder P, Kok FJ, Hermus RJ. Fermented dairy products, dietary calcium and colon cancer: a case-control study in the Netherlands. Int J Cancer 1994;59:170–6.
42. Shannon J, White E, Shattuck AL, Potter JD. Relationship of food groups and water intake to colon cancer risk. Cancer Epidemiol Biomarkers Prev 1996;5:495–502.
43. Boutron-Ruault MC, Senesse P, Faivre J, Chatelain N, Belghiti C, Méance S. Foods as risk factors for colorectal cancer: a case-control study in Burgundy (France). Eur J Cancer Prev 1999;8:229–35.
44. Kampman E, Slattery ML, Caan B, Potter JD. Calcium, vitamin D, sunshine exposure, dairy products and colon cancer risk (United States). Cancer Causes Control 2000;11:459–66.
45. Satia-Abouta J, Galanko JA, Martin CF, Ammerman A, Sandler RS. Food groups and colon cancer risk in African-Americans and Caucasians. Int J Cancer 2004;109:728–36.
46. Mizoue T, Kimura Y, Toyomura K, Nagano J, Kono S, Mibu R, Tanaka M, Kakeji Y, Maehara Y, Okamura T, et al. Calcium, dairy foods, vitamin D, and colorectal cancer risk: the Fukuoka Colorectal Cancer Study. Cancer Epidemiol Biomarkers Prev 2008;17:2800–7.
47. Williams CD, Satia JA, Adair LS, Stevens J, Galanko J, Keku TO, Sandler RS. Dietary patterns, food groups, and rectal cancer risk in whites and African-Americans. Cancer Epidemiol Biomarkers Prev 2009;18:1552–61.
48. Sun Z, Wang PP, Roebothan B, Cotterchio M, Green R, Buehler S, Zhao J, Squires J, Zhao J, Zhu Y, et al. Calcium and vitamin D and risk of colorectal cancer: results from a large population-based case-control study in Newfoundland and Labrador and Ontario. Can J Public Heal 2011;102:382–9.
49. Green CJ, de Dauwe P, Boyle T, Tabatabaei SM, Fritschi L, Heyworth JS. Tea, coffee, and milk consumption and colorectal cancer risk. J Epidemiol 2014;24:146–53.
50. Chun YJ, Sohn S-K, Song HK, Lee SM, Youn YH, Lee S, Park H. Associations of colorectal cancer incidence with nutrient and food group intakes in Korean adults: a case-control study. Clin Nutr Res 2015;4:110.
51. Cho E, Smith-Warner SA, Spiegelman D, Beeson WL, van den Brandt PA, Colditz GA, Folsom AR, Fraser GE, Freudenheim JL, Giovannucci E, et al. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. J Natl Cancer Inst 2004;96:1015–22.
52. Norat T, Riboli E. Dairy products and colorectal cancer. A review of possible mechanisms and epidemiological evidence. Eur J Clin Nutr 2003;57:1–17.
53. Huncharek M, Muscat J, Kupelnick B. Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: a meta-analysis of 26,335 cases from 60 observational studies. Nutr Cancer 2009;61:47–69.
54. Aune D, Lau R, Chan DSM, Vieira R, Greenwood DC, Kampman E, Norat T. Dairy products and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. Ann Oncol 2012;23:37–45.
55. Ralston RA, Truby H, Palermo CE, Walker KZ. Colorectal cancer and nonfermented milk, solid cheese, and fermented milk consumption: a systematic review and meta-analysis of prospective studies. Crit Rev Food Sci Nutr 2014;54:1167–79.
56. Vieira AR, Abar L, Chan D, Vingeliene S, Polemiti E, Stevens C, Greenwood D, Norat T. Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. Ann Oncol Off J Eur Soc Med Oncol 2017;28(8):1788–802
57. Schwingshackl L, Schwedhelm C, Hoffmann G, Knüppel S, Laure Preterre A, Iqbal K, Bechthold A, De Henauw S, Michels N, Devleesschauwer B, et al. Food groups and risk of colorectal cancer. Int J Cancer 2018;142:1748–58.
58. Newmark HL, Wargovich MJ, Bruce WR. Colon cancer and dietary fat, phosphate, and calcium: a hypothesis. J Natl Cancer Inst 1984;72:1323–5.
59. Govers MJ, Termont DS, Lapré JA, Kleibeuker JH, Vonk RJ, Van der Meer R. Calcium in milk products precipitates intestinal fatty acids and secondary bile acids and thus inhibits colonic cytotoxicity in humans. Cancer Res 1996;56:3270–5.
60. Holt PR, Moss SF, Whelan R, Guss J, Gilman J, Lipkin M. Fecal and rectal mucosal diacylglycerol concentrations and epithelial proliferative kinetics. Cancer Epidemiol Biomarkers Prev 1996;5:937–40.
61. Lamprecht SA, Lipkin M. Cellular mechanisms of calcium and vitamin D in the inhibition of colorectal carcinogenesis. Ann N Y Acad Sci 2001;952:73–87.
62. Pufulete M. Intake of dairy products and risk of colorectal neoplasia. Nutr Res Rev 2008;21:56–67.
63. Parodi PW. Cows' milk fat components as potential anticarcinogenic agents. J Nutr 1997;127:1055–60.
64. Kritchevsky D. Antimutagenic and some other effects of conjugated linoleic acid. Br J Nutr 2000;83:459–65.
65. Bassaganya-Riera J, Hontecillas R, Beitz DC. Colonic anti-inflammatory mechanisms of conjugated linoleic acid. Clin Nutr 2002;21:451–9.
66. Bassaganya-Riera J, Hontecillas R, Horne WT, Sandridge M, Herfarth HH, Bloomfeld R, Isaacs KL. Conjugated linoleic acid modulates immune responses in patients with mild to moderately active Crohn's disease. Clin Nutr 2012;31:721–7.
67. Williams L, Williams EA, Coxhead JM, Mathers JC. Anti-cancer effects of butyrate: use of micro-array technology to investigate mechanisms. Proc Nutr Soc 2017;62:107–15.
68. Tsuda H, Kozu T, Iinuma G, Ohashi Y, Saito Y, Saito D, Akasu T, Alexander DB, Futakuchi M, Fukamachi K, et al. Cancer prevention by bovine lactoferrin: from animal studies to human trial. BioMetals 2010;23:399–409.
69. Garland CF, Gorham ED. Dose-response of serum 25-hydroxyvitamin D in association with risk of colorectal cancer: a meta-analysis. J Steroid Biochem Mol Biol 2017;168:1–8.

Supplementary data

Supplemental table 1. Search strategy (databases and search terms)

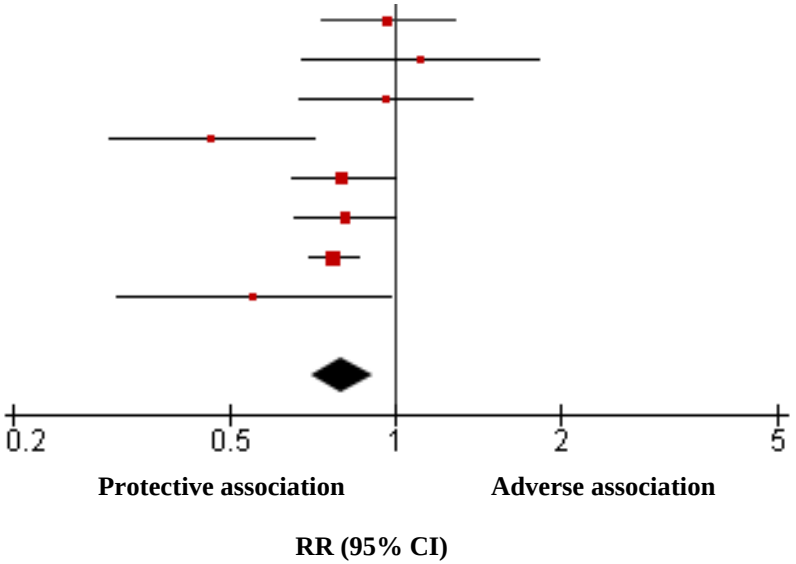
MEDLINE (through PUBMED)	
(("dairy"[All Fields] OR "dairy products"[MeSH Terms] OR ("dairy"[All Fields] AND "products"[All Fields])) OR ("milk"[All Fields] OR "milk"[MeSH Terms]) OR ("yogurt"[MeSH Terms] OR "yogurt"[All Fields] OR "yoghurt"[All Fields]) OR ("cheese"[MeSH Terms] OR "cheese"[All Fields]) OR ("cultured milk products"[MeSH Terms] OR ("cultured"[All Fields] AND "milk"[All Fields] AND "products"[All Fields]) OR "cultured milk products"[All Fields] OR ("cultured"[All Fields] AND "milk"[All Fields]) OR "cultured milk"[All Fields])) AND (("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields]) OR (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) AND "sigma"[All Fields]) OR (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) AND "rectal"[All Fields]))	
COCHRANE	
#1	MeSH descriptor: [Colorectal Neoplasms] explode all trees
#2	colorectal
#3	neoplasms
#4	colorectal neoplasms
#5	cancer
#6	colorectal cancer
#7	#2 and #3
#8	#2 and #5
#9	#1 or #4 or #6 or #7 or #8
#10	MeSH descriptor: [Neoplasms] explode all trees
#11	#3 or #5 or #10
#12	sigma
#13	#11 and #12
#14	rectal
#15	#11 and #14
#16	dairy
#17	MeSH descriptor: [Dairy Products] explode all trees
#18	products
#19	#16 and #18
#20	#16 or #17 or #19
#21	milk
#22	MeSH descriptor: [Milk] explode all trees
#23	#21 or #22
#24	MeSH descriptor: [Yogurt] explode all trees
#25	yogurt
#26	yoghurt
#27	#24 or #25 or #26
#28	MeSH descriptor: [Cheese] explode all trees
#29	cheese
#30	#28 or #29
#31	MeSH descriptor: [Cultured Milk Products] explode all trees
#32	cultured
#33	cultured milk products
#34	cultured milk
#35	#18 and #21 and #32
#36	#21 and #32
#37	#31 or #34 or #35 or #36
#38	(#20 or #23 or #27 or #30 or #37) and (#9 or #13 or #15)
SCIENCE DIRECT	
TITLE-ABSTR-KEY((("dairy") OR ("milk") OR ("yogurt") OR ("yoghurt") OR ("cheese")) AND (("cancer" OR "neoplasms") AND (colorectal OR colon OR sigma OR rectum)))	
CINAHL	
S1	colorectal neoplasms
S2	colorectal
S3	neoplasms
S4	colorectal cancer
S5	cancer
S6	s2 AND s3
S7	s2 AND s5
S8	s1 OR s6 OR s4 OR s7
S9	sigma
S10	s3 OR s5
S11	s10 AND s9
S12	rectal
S13	s10 AND s12
S14	dairy
S15	dairy products
S16	products
S17	s14 AND s16
S18	s14 OR s15 OR s17
S19	milk
S20	yogurt
S21	yoghurt
S22	s20 OR s21
S23	cheese
S24	cultured milk products
S25	cultured
S26	milk
S27	products
S28	s25 AND s26 AND s27
S29	S25 AND s26
S30	s24 OR s28 OR s29
S31	s18 OR s19 OR s20 OR s23 OR s30
S32	s8 OR s11 OR s13
S33	s31 AND s32

Supplementary data

Study	*n* participants	*n* cases	Weight, %	RR (95% CI)
Terry et al., 2002 (11)	61,643	572	12.7	0.97 (0.73-1.29)
McCullough et al., 2003 W (36)	66,883	262	5.7	1.11 (0.68-1.82)
McCullough et al., 2003 M (36)	60,866	421	9.3	0.96 (0.67-1.38)
Larsson et al., 2006 (17)	45,306	449	7.1	0.46 (0.30-0.71)
Park et al., 2007 M (30)	85,903	1,138	16.9	0.80 (0.64-0.99)
Park et al., 2007 W (30)	105,108	972	17.1	0.81 (0.65-1.00)
Murphy et al., 2013 (18)	477,122	4,513	26.8	0.77 (0.69-0.85)
Barrubés et al., 2018 (19)	7,216	97	4.4	0.55 (0.31-0.98)
Total 95% CI	**910,047**	**8,424**	**100**	**0.80 (0.70-0.91)**

I^2= 45% (P= 0.08)

Test for overall effect: Z= 3.42 (P= 0.0006)



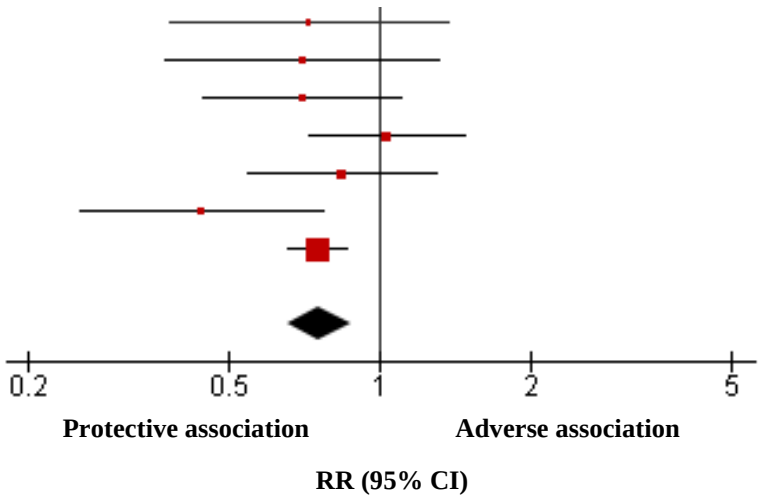
Supplemental figure 1. RRs and 95% CIs (log scale) for fully adjusted random-effects models evaluating the associations between the consumption of total dairy products and the risk of CRC in the meta-analysis of 8 prospective cohort studies (high vs. low intake). The pooled risk estimate is represented by the black diamond. CI: confidence interval, CRC: colorectal cancer, M: only in men, RR: relative risk, W: only in women.

Supplementary data

Study	*n* participants	*n* cases	Weight, %	RR (95% CI)
Bostick et al., 1993 (6)	35,216	212	4.8	0.72 (0.38-1.36)
Sellers et al., 1998 FH (35)	4,239	61	5.0	0.70 (0.37-1.31)
Sellers et al., 1998 NFH (35)	22,698	180	8.9	0.70 (0.44-1.11)
Terry et al., 2002 (11)	61,643	371	13.8	1.03 (0.72-1.47)
McCullough et al., 2003 (36)	60,866	302	9.7	0.84 (0.54-1.30)
Larsson et al., 2006 (17)	45,306	276	6.2	0.44 (0.25-0.77)
Murphy et al., 2013 (18)	477,122	2,868	51.6	0.75 (0.66-0.86)
Total 95% CI	**707,090**	**4,270**	**100**	**0.76 (0.66-0.87)**

I^2= 14% (P= 0.33)

Test for overall effect: Z= 3.79 (P= 0.0002)



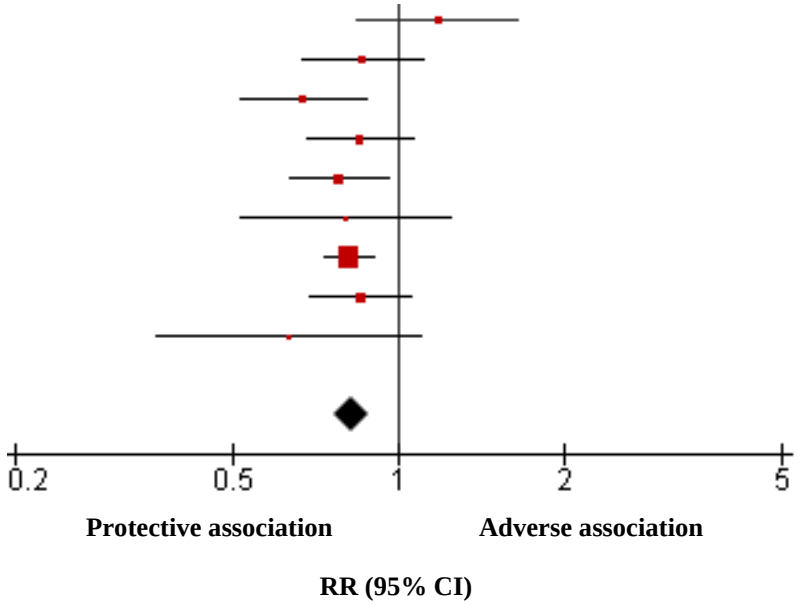
Supplemental figure 2. RRs and 95% CIs (log scale) for fully adjusted random effects models evaluating the associations between the consumption of total dairy products and the risk of colon cancer in the meta-analysis of 7 prospective cohort studies (high vs. low intake). The pooled risk estimate is represented by the black diamond. CI: confidence interval, FH: positive family history of colon cancer, NFH: no family history of colon cancer, RR: relative risk.

Supplementary data

Study	*n* participants	*n* cases	Weight, %	RR (95% CI)
McCullough et al., 2003 W (36)	66,883	262	4.5	1.18 (0.84-1.65)
McCullough et al., 2003 M (36)	60,866	421	7.5	0.86 (0.66-1.12)
Larsson et al., 2006 (17)	45,306	449	7.1	0.67 (0.51-0.88)
Park et al., 2007 W (30)	105,108	972	10.3	0.85 (0.68-1.06)
Park et al., 2007 M (30)	85,903	1,138	11.4	0.78 (0.63-0.96)
Lee et al., 2009 (37)	73,224	394	2.7	0.80 (0.52-1.24)
Murphy et al., 2013 (18)	477,122	4,513	43.4	0.81 (0.73-0.90)
Bakken et al., 2018 (32)	81,675	872	11.5	0.85 (0.69-1.05)
Barrubés et al., 2018 (19)	7,216	97	1.6	0.63 (0.36-1.10)
Total 95% CI	**1,003,303**	**9,118**	**100**	**0.82 (0.76-0.88)**

I^2= 2% (P= 0.42)

Test for overall effect: Z= 5.49 (P<0.00001)



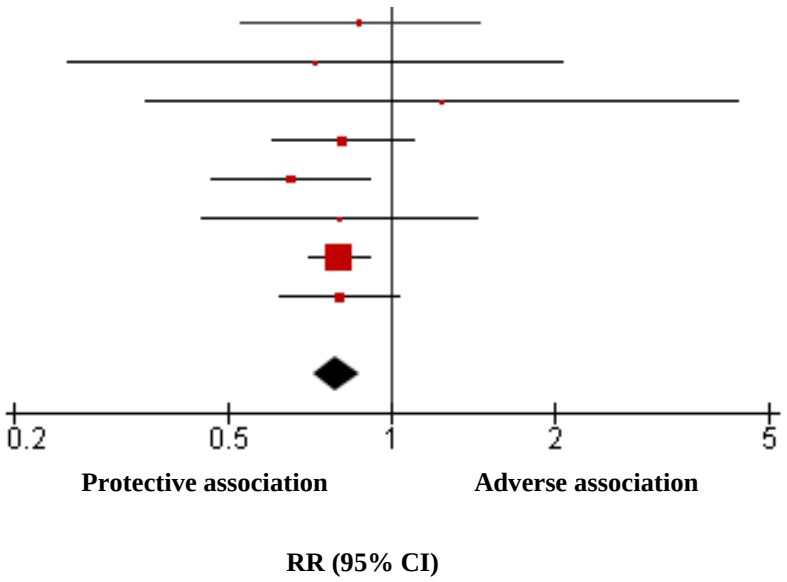
Supplemental figure 3. RRs and 95% CIs (log scale) for fully adjusted random effects models evaluating the associations between the consumption of total milk and the risk of CRC in the meta-analysis of 9 prospective cohort studies (high vs. low intake). The pooled risk estimate is represented by the black diamond. CI: confidence interval, CRC: colorectal cancer, M: only in men, RR: relative risk, W: only in women.

Supplementary data

Study	*n* participants	*n* cases	Weight, %	RR (95% CI)
Kearney et al., 1996 (8)	47,935	203	3.8	0.87 (0.52-1.45)
Gaard et al., 1996 M (33)	25,638	84	0.9	0.72 (0.25-2.07)
Gaard et al., 1996 W (33)	24,897	63	0.6	1.24 (0.35-4.40)
McCullough et al., 2003 (36)	60,866	302	10.7	0.81 (0.60-1.10)
Larsson et al., 2006 (17)	45,306	276	8.5	0.65 (0.46-0.91)
Lee et al., 2009 (37)	73,224	236	2.8	0.80 (0.44-1.44)
Murphy et al., 2013 (18)	477,122	2,868	57.3	0.80 (0.70-0.91)
Bakken et al., 2018 (32)	81,675	617	15.3	0.80 (0.62-1.03)
Total 95% CI	**836,663**	**4,649**	**100**	**0.79 (0.72-0.87)**

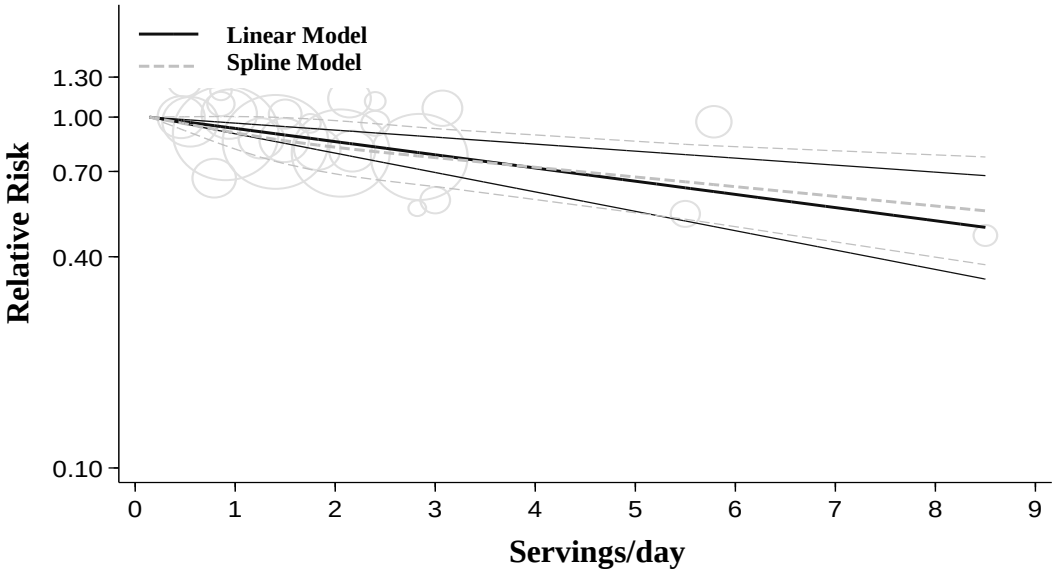
I^2= 0% (P= 0.96)

Test for overall effect: Z= 4.63 (P<0.00001)



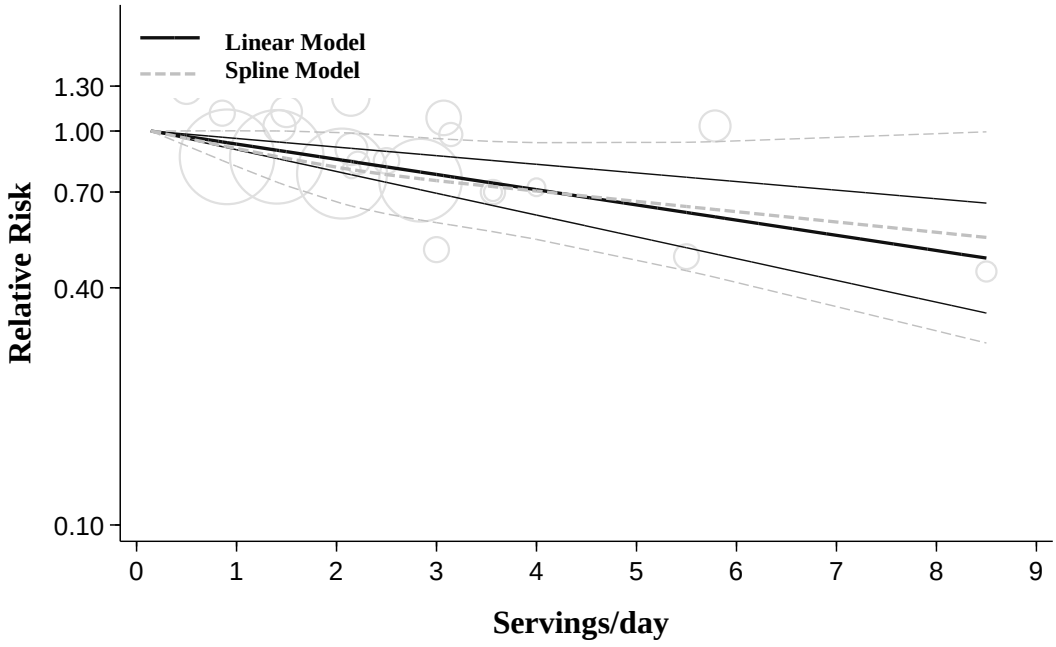
Supplemental figure 4. RRs and 95% CIs (log scale) for fully adjusted random effects models evaluating the associations between the consumption of total milk and the risk of colon cancer in the meta-analysis of 8 prospective cohort studies (high vs. low intake). The pooled risk estimate is represented by the black diamond. CI: confidence interval, M: only in men, RR: relative risk, W: only in women.

Supplementary data



Linear RR per 1 serving increment: 0.92 [95%CI, 0.88 to 0.96]; *P*<0.001.
Departure from linearity= 0.420. Random effects dose-response model

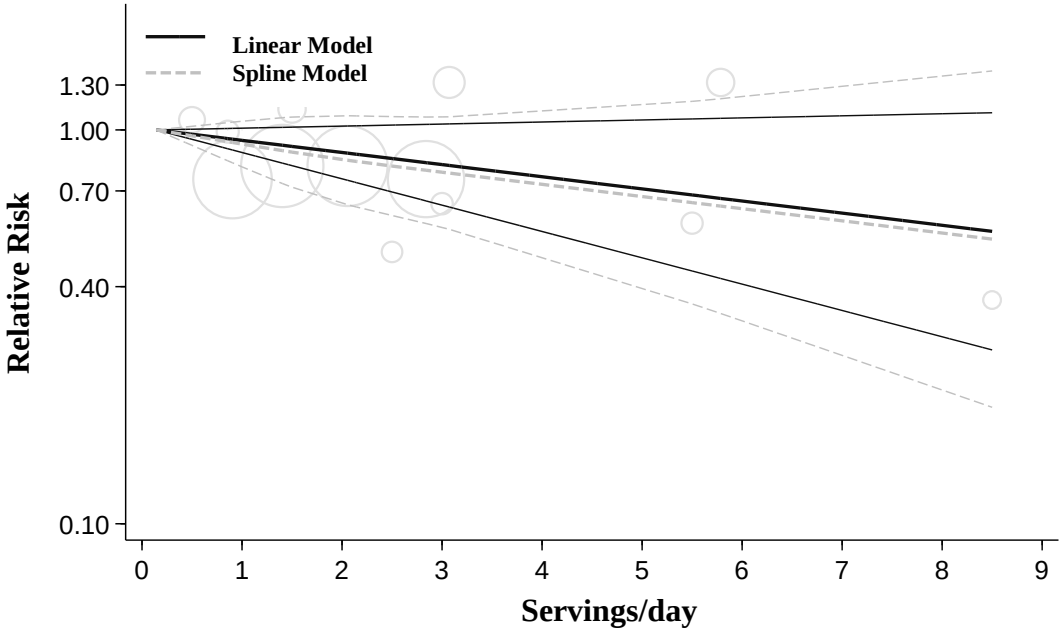
Supplemental figure 5. Linear and nonlinear dose-response analysis of the association between an increase of one serving/day of total dairy products and the risk of colorectal cancer. Each study was centered on the baseline reference dose for the estimation of risk for dose increases.



Linear RR per 1 serving increment: 0.91 [95%CI, 0.88 to 0.95]; *P*<0.001.
Departure from linearity= 0.471. Random effects dose-response model.

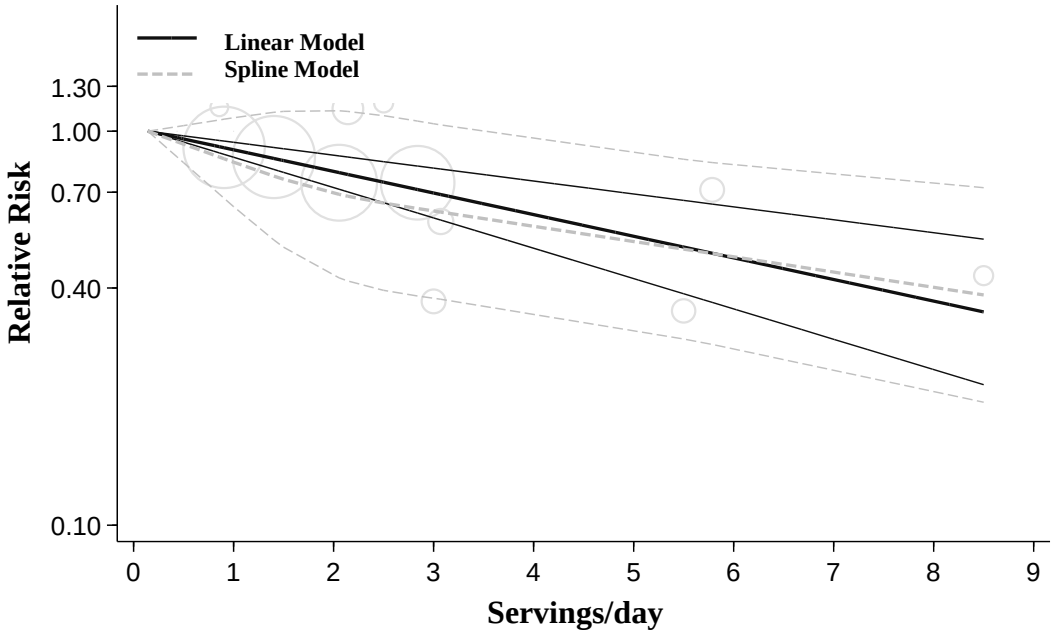
Supplemental figure 6. Linear and nonlinear dose-response analysis of the association between an increase of one serving/day of total dairy products and the risk of colon cancer. Each study was centered on the baseline reference dose for the estimation of risk for dose increases.

Supplementary data



Linear RR per 1 serving increment: 0.93 [95%CI, 0.86 to 1.01]; *P*=0.094
Departure from linearity= 0.805. Random effects dose-response model

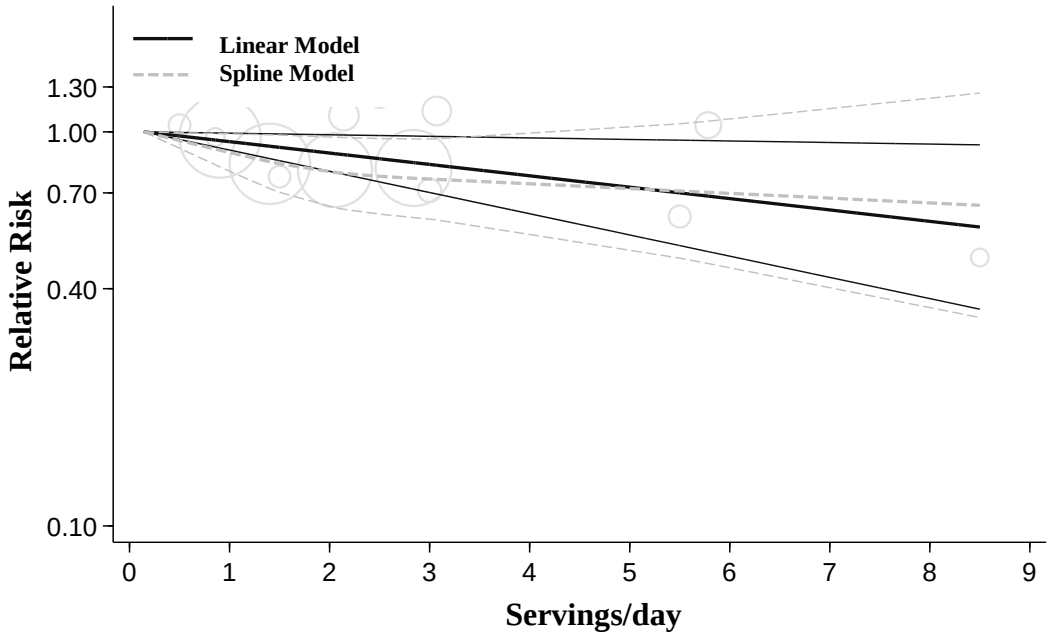
Supplemental figure 7. Linear and nonlinear dose-response analysis of the association between an increase of one serving/day of total dairy products and the risk of proximal colon cancer. Each study was centered on the baseline reference dose for the estimation of risk for dose increases.



Linear RR per 1 serving increment: 0.88 [95%CI, 0.84 to 0.93]; *P*<0.001
Departure from linearity= 0.473. Random effects dose-response model

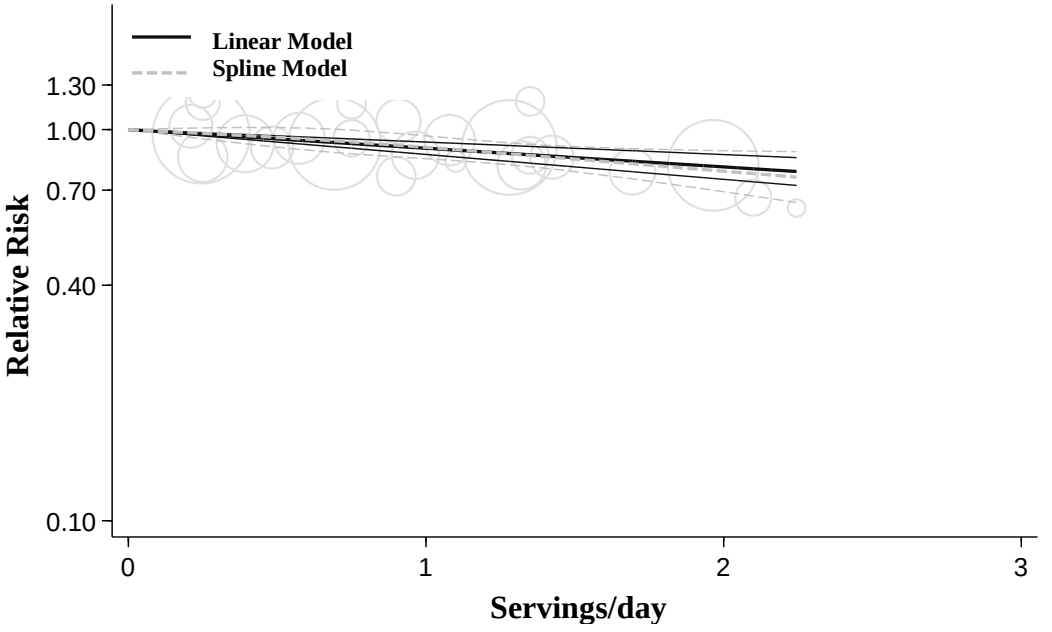
Supplemental figure 8. Linear and nonlinear dose-response analysis of the association between an increase of one serving/day of total dairy products and the risk of distal colon cancer. Each study was centered on the baseline reference dose for the estimation of risk for dose increases.

Supplementary data



Linear RR per 1 serving increment: 0.94 [95%CI, 0.88 to 0.99]; *P*=0.023
Departure from linearity= 0.194. Random effects dose-response model

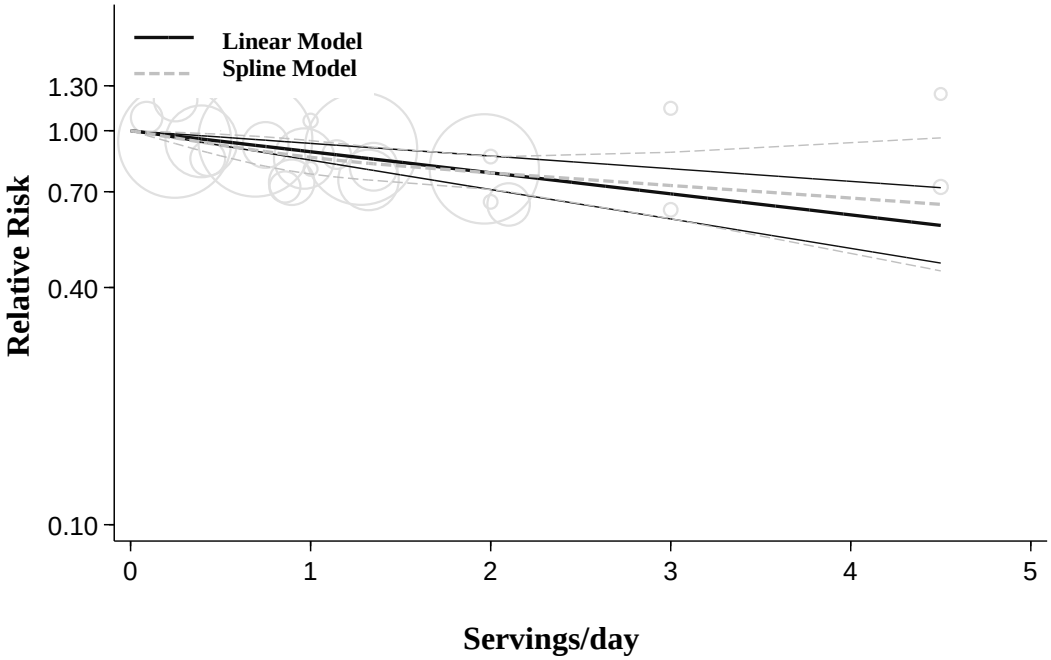
Supplemental figure 9. Linear and nonlinear dose-response analysis between increasing one serving/day of total dairy products and the risk of rectal cancer. Each study was centered on the baseline reference dose for the estimation of risk for dose increases.



Linear RR per 1 serving increment: 0.90 [95%CI, 0.86 to 0.93]; *P*<0.001
Departure from linearity= 0.666. Random effects dose-response model

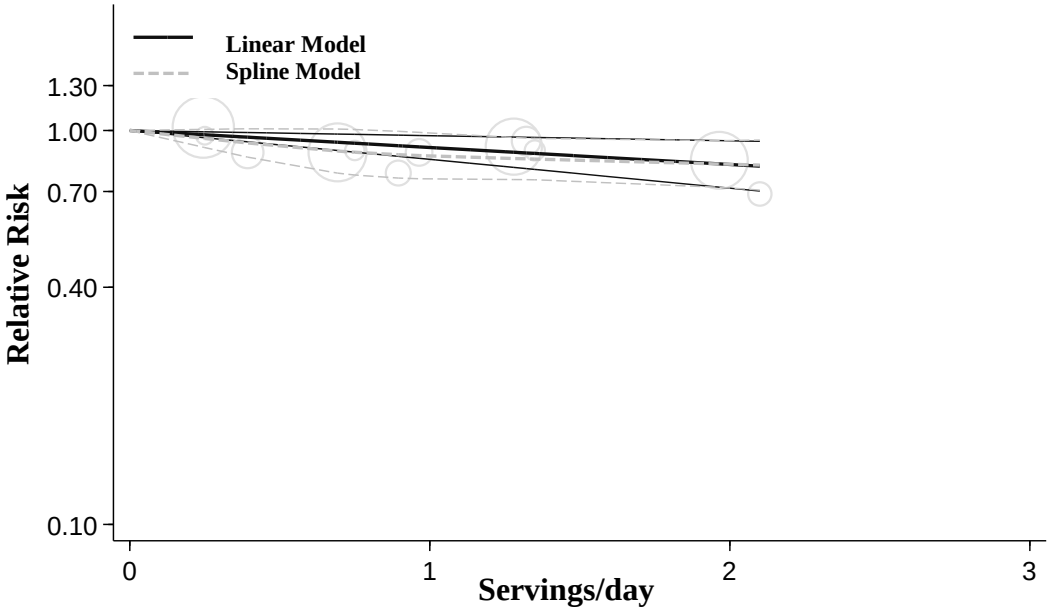
Supplemental figure 10. Linear and nonlinear dose-response analysis of the association between an increase of one serving/day of total milk and the risk of colorectal cancer. Each study was centered on the baseline reference dose for the estimation of risk for dose increases.

Supplementary data



Linear RR per 1 serving increment: 0.88 [95%CI, 0.84 to 0.93]; *P*<0.001
Departure from linearity= 0.452. Random effects dose-response model

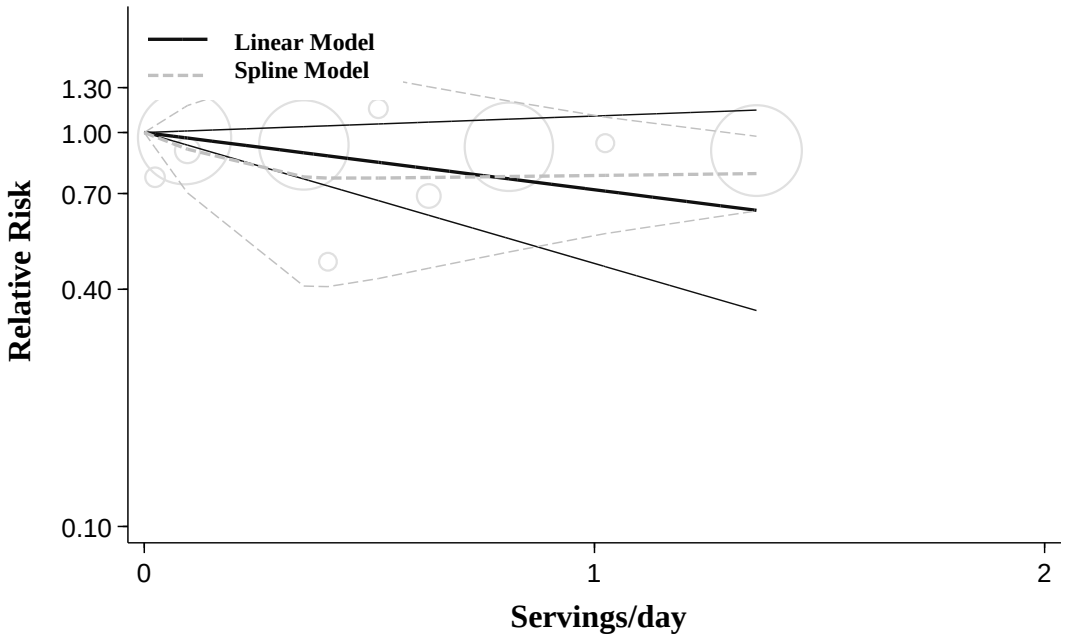
Supplemental figure 11. Linear and nonlinear dose-response analysis of the association between an increase of one serving/day of total milk and the risk of colon cancer. Each study was centered on the baseline reference dose for the estimation of risk for dose increases.



Linear RR per 1 serving increment: 0.91 [95%CI, 0.84 to 0.97]; *P*<0.01
Departure from linearity= 0.399. Random effects dose-response model

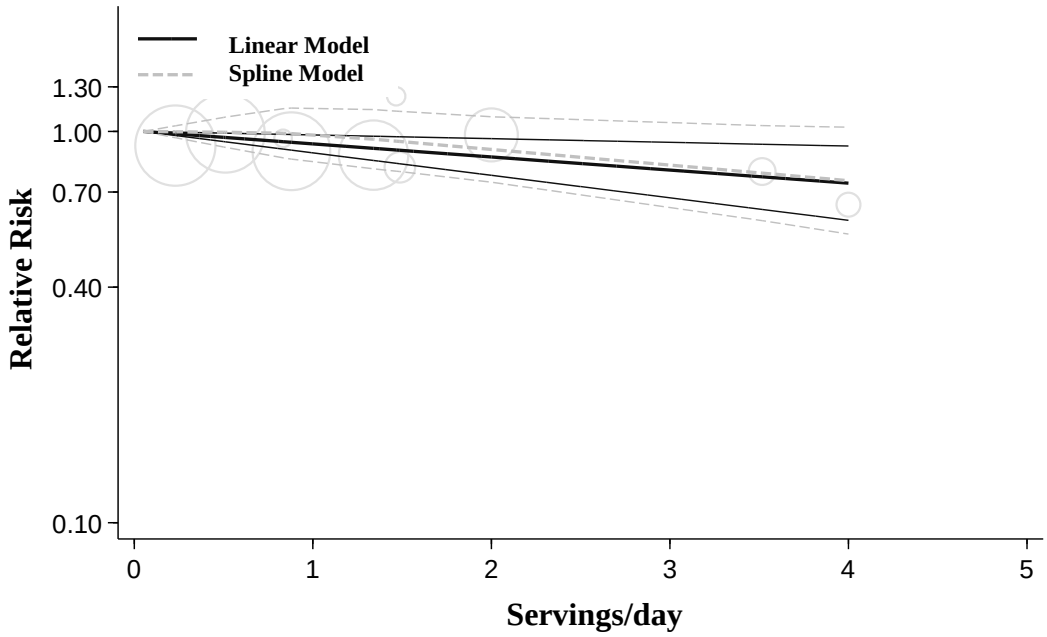
Supplemental figure 12. Linear and nonlinear dose-response analysis of the association between an increase of one serving/day of total milk and the risk of rectal cancer. Each study was centered on the baseline reference dose for the estimation of risk for dose increases.

Supplementary data



Linear RR per 1 serving increment: 0.72 [95% CI, 0.47 to 1.10]; *P*=0.128
Departure from linearity= 0.521. Random effects dose-response model

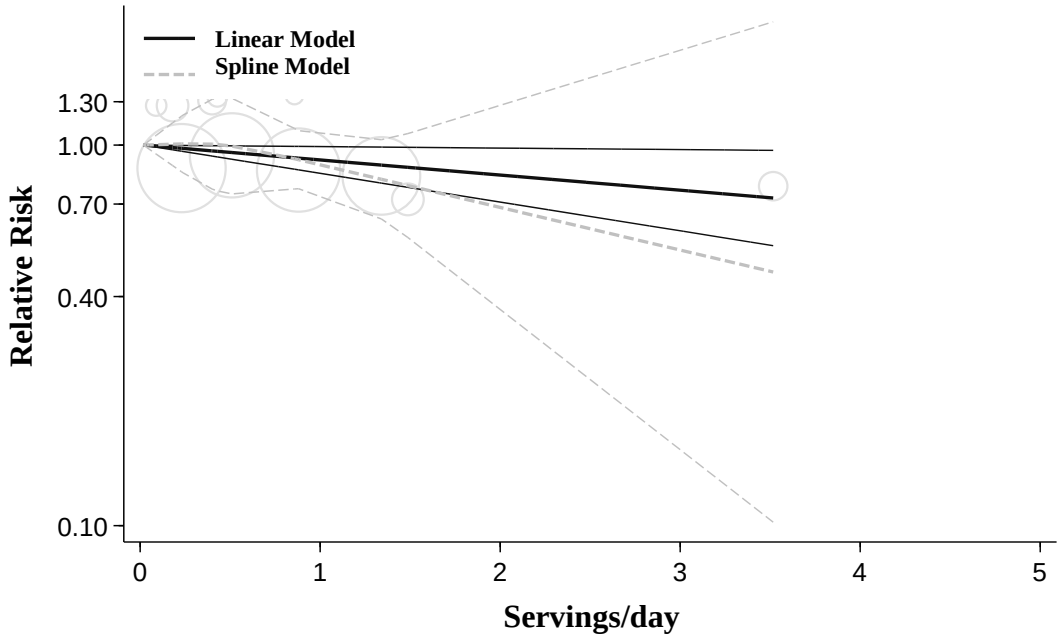
Supplemental figure 13. Linear and nonlinear dose-response analysis of the association between an increase of one serving/day of total yogurt consumption and the risk of colorectal cancer. Each study was centered on the baseline reference dose for the estimation of risk for dose increases.



Linear RR per 1 serving increment: 0.93 [95% CI, 0.88 to 0.98]; *P*<0.01
Departure from linearity= 0.458. Random effects dose-response model

Supplemental figure 14. Linear and nonlinear dose-response analysis of the association between an increase of one serving/day of total cheese and the risk of colorectal cancer. Each study was centered on the baseline reference dose for the estimation of risk for dose increases.

Supplementary data



Linear RR per 1 serving increment: 0.91 [95% CI, 0.84 to 0.99]; *P*=0.030
Departure from linearity= 0.678. Random effects dose-response model

Supplemental figure 15. Linear and nonlinear dose-response analysis of the association between an increase of one serving/day of total cheese consumption and the risk of colon cancer. Each study was centered on the baseline reference dose for the estimation of risk for dose increases.

Supplementary data

Supplemental table 2. Sensitivity analysis excluding one study at a time (cohort studies)

TOTAL DAIRY			
Colorectal cancer (RR [95% CI]= 0.80 [0.70, 0.91], I^2 (%)= 45, *P*-value= 0.08)			
Excluded study or subgroup	**RR (95% CI)**	**I^2 (%)**	***P*-value**
Terry et al., 2002 (only women) (11)	0.77 (0.68, 0.89)	43	0.10
McCullough et al., 2003 (men) (36)	0.78 (0.68, 0.90)	48	0.07
Mc Cullough et al., 2003 (women) (36)	0.78 (0.69, 0.89)	45	0.09
Larsson et al., 2006 (only men) (17)	0.81 (0.74, 0.89)	8	0.36
Park et al., 2007 (men) (30)	0.80 (0.68, 0.93)	53	0.05
Park et al., 2007 (women) (30)	0.79 (0.68, 0.93)	53	0.05
Murphy et al., 2013 (18)	0.80 (0.67, 0.96)	51	0.06
Barrubés et al., 2018 (19)	0.81 (0.71, 0.92)	47	0.08
Colon (RR [95% CI]= 0.76 [0.66, 0.87], I^2 (%)= 14, *P*-value= 0.33)			
Excluded study or subgroup	**RR (95% CI)**	**I^2 (%)**	***P*-value**
Bostick et al., 1993 (6)	0.76 (0.64, 0.90)	28	0.23
Sellers et al., 1998 (positive family history) (35)	0.76 (0.64, 0.90)	27	0.23
Sellers et al., 1998 (no family history) (35)	0.76 (0.64, 0.91)	27	0.23
Terry et al., 2002 (only women) (11)	0.73 (0.65, 0.82)	0	0.58
McCullough et al., 2003 (men) (36)	0.75 (0.62, 0.89)	26	0.24
Larsson et al., 2006 (only men) (17)	0.77 (0.69, 0.87)	0	0.68
Murphy et al., 2013 (18)	0.75 (0.60, 0.95)	27	0.23
Proximal colon (RR [95% CI]= 0.75 [0.63, 0.89], I^2 (%)= 63, *P*-value= 0.04)			
Excluded study or subgroup	**RR (95% CI)**	**I^2 (%)**	***P*-value**
Terry et al., 2002 (only women) (11)	0.71 (0.59, 0.85)	44	0.17
McCullough et al., 2003 (men) (36)	0.77 (0.65, 0.92)	70	0.04
Larsson et al., 2006 (only men) (17)	0.78 (0.65, 0.93)	62	0.07
Murphy et al., 2013 (18)	0.77 (0.52, 1.13)	75	0.02
Distal colon (RR [95% CI]= 0.73 [0.62, 0.88], I^2 (%)= 10, *P*-value= 0.34)			
Excluded study or subgroup	**RR (95% CI)**	**I^2 (%)**	***P*-value**
Terry et al., 2002 (only women) (11)	0.74 (0.61, 0.88)	40	0.19
McCullough et al., 2003 (men) (36)	0.72 (0.60, 0.86)	0	0.41
Larsson et al., 2006 (only men) (17)	0.76 (0.63, 0.91)	0	0.50
Murphy et al., 2013 (18)	0.71 (0.47, 1.07)	39	0.19
Rectum (RR [95% CI]= 0.83 [0.71, 0.96], I^2 (%)= 32, *P*-value= 0.22)			
Excluded study or subgroup	**RR (95% CI)**	**I^2 (%)**	***P*-value**
Terry et al., 2002 (only women) (11)	0.81 (0.69, 0.95)	43	0.17
McCullough et al., 2003 (men) (36)	0.81 (0.70, 0.95)	33	0.23
Larsson et al., 2006 (only men) (17)	0.48 (0.23, 1.00)	8	0.34
Murphy et al., 2013 (18)	0.92 (0.65, 1.29)	50	0.13
HIGH-FAT DAIRY			
Colon cancer (RR [95% CI]= 0.82 [0.62, 1.08], I^2 (%)= 0, *P*-value= 0.77)			
Excluded study or subgroup	**RR (95% CI)**	**I^2 (%)**	***P*-value**
Bostick et al., 1993 (6)	0.83 (0.60, 1.15)	0	0.48
Sellers et al., 1998 (no family history) (35)	0.74 (0.50, 1.11)	0	0.79
Sellers et al., 1998 (positive family history) (35)	0.86 (0.63, 1.18)	0	0.68

Supplementary data

LOW-FAT DAIRY			
Colon cancer (RR [95% CI]= 0.91 [0.72, 1.15], I^2 (%)= 0, *P*-value= 0.68)			
Excluded study or subgroup	**RR (95% CI)**	**I^2 (%)**	***P*-value**
Sellers et al., 1998 (no family history) (35)	0.98 (0.73, 1.32)	0	0.74
Sellers et al., 1998 (positive family history) (35)	0.91 (0.71, 1.18)	0	0.38
Terry et al., 2002 (only women) (11)	0.83 (0.60, 1.15)	0	0.74
TOTAL MILK			
Colorectal cancer (RR [95% CI]= 0.82 [0.76, 0.88], I^2 (%)= 2, *P*-value= 0.42)			
Excluded study or subgroup	**RR (95% CI)**	**I^2 (%)**	***P*-value**
McCullough et al., 2003 (men) (36)	0.82 (0.75, 0.89)	12	0.33
Mc Cullough et al., 2003 (women) (36)	0.80 (0.75, 0.86)	0	0.85
Larsson et al., 2006 (only men) (17)	0.83 (0.77, 0.89)	0	0.56
Park et al., 2007 (women)	0.82 (0.75, 0.89)	13	0.33
Park et al., 2007 (men) (30)	0.82 (0.76, 0.90)	12	0.34
Lee et al., 2009 (only women) (37)	0.82 (0.75, 0.89)	14	0.32
Murphy et al., 2013 (18)	0.82 (0.74, 0.91)	13	0.33
Bakken et al., 2018 (32)	0.81 (0.75, 0.89)	12	0.33
Barrubés et al., 2018 (19)	0.82 (0.76, 0.88)	4	0.40
Colon cancer (RR [95% CI]= 0.79 [0.72, 0.87], I^2 (%)= 0, *P*-value= 0.96)			
Excluded study or subgroup	**RR (95% CI)**	**I^2 (%)**	***P*-value**
Kearney et al., 1996 (only men) (8)	0.79 (0.71, 0.87)	0	0.93
Gaard et al., 1996 (33)	0.79 (0.71, 0.87)	0	0.92
McCullough et al., 2003 (men) (36)	0.79 (0.71, 0.87)	0	0.92
Larsson et al., 2006 (only men) (17)	0.80 (0.72, 0.89)	0	1.00
Lee et al., 2009 (only women) (37)	0.79 (0.71, 0.87)	0	0.91
Murphy et al., 2013 (18)	0.80 (0.70, 0.91)	0	0.93
Bakken et al., 2018 (32)	0.79 (0.71, 0.88)	0	0.92
Proximal cancer (RR [95% CI]= 0.81 [0.68, 0.96], I^2 (%)= 0, *P*-value= 0.70)			
Excluded study or subgroup	**RR (95% CI)**	**I^2 (%)**	***P*-value**
McCullough et al., 2003 (men) (36)	0.81 (0.68, 0.96)	0	0.70
Larsson et al., 2006 (only men) (17)	0.81 (0.68, 0.98)	0	0.42
Murphy et al., 2013 (18)	0.71 (0.50, 1.02)	0	0.76
Distal colon (RR [95% CI]= 0.75 [0.63, 0.90], I^2 (%)= 25, *P*-value= 0.26)			
Excluded study or subgroup	**RR (95% CI)**	**I^2 (%)**	***P*-value**
McCullough et al., 2003 (men) (36)	0.73 (0.60, 0.89)	51	0.15
Larsson et al., 2006 (only men) (17)	0.80 (0.66, 0.97)	0	0.57
Murphy et al., 2013 (18)	0.68 (0.47, 0.97)	55	0.14
Rectum (RR [95% CI]= 0.84 [0.73, 0.97], I^2 (%)= 0, *P*-value= 0.84)			
Excluded study or subgroup	**RR (95% CI)**	**I^2 (%)**	***P*-value**
McCullough et al., 2003 (men) (36)	0.84 (0.72, 0.97)	0	0.71
Larsson et al., 2006 (only men) (17)	0.86 (0.74, 1.00)	0	0.91
Lee et al., 2009 (only women) (37)	0.84 (0.73, 0.97)	0	0.70
Murphy et al., 2013 (18)	0.84 (0.67, 1.07)	0	0.70
Bakken et al., 2018 (32)	0.82 (0.71, 0.96)	0	0.85
WHOLE-MILK			
Colorectal cancer (RR [95% CI]= 0.97 [0.86, 1.09], I^2 (%)= 40, *P*-value= 0.19)			

Supplementary data

Excluded study or subgroup	**RR (95% CI)**	**I^2 (%)**	***P*-value**
Larsson et al., 2005 (only women) (14)	0.88 (0.75, 1.04)	0	0.44
Murphy et al., 2013 (18)	1.08 (0.91, 1.28)	0	0.95
Barrubés et al., 2018 (19)	0.96 (0.85, 1.09)	69	0.07
TOTAL YOGURT			
Colorectal cancer (RR [95% CI]= 0.87 [0.79, 0.96], I^2 (%)= 57, *P*-value= 0.07)			
Excluded study or subgroup	**RR (95% CI)**	**I^2 (%)**	***P*-value**
Pala et al., 2011 (women) (38)	0.88 (0.80, 0.97)	64	0.06
Pala et al., 2011 (men) (38)	0.89 (0.81, 0.98)	0	0.43
Murphy et al., 2013 (18)	0.68 (0.52, 0.89)	40	0.19
Barrubés et al., 2018 (19)	0.87 (0.79, 0.95)	71	0.03
CHEESE			
Colorectal cancer (RR [95% CI]= 0.85 [0.76, 0.96], I^2 (%)= 27, *P*-value= 0.25)			
Excluded study or subgroup	**RR (95% CI)**	**I^2 (%)**	***P*-value**
Larsson et al., 2005 (only women) (14)	0.88 (0.78, 0.99)	2	0.36
Larsson et al., 2006 (only men) (17)	0.86 (0.76, 0.97)	48	0.14
Murphy et al., 2013 (18)	0.81 (0.64, 1.02)	47	0.15
Barrubés et al., 2018 (19)	0.84 (0.74, 0.94)	2	0.36

Supplementary data

Supplemental table 3. Sensitivity analysis excluding one study at a time (case-control studies)

TOTAL DAIRY			
Colorectal cancer (RR [95% CI]= 0.87 [0.64, 1.20], I^2 (%)= 52, *P*-value= 0.08)			
Excluded study or subgroup	**OR (95% CI)**	**I^2 (%)**	***P*-value**
Centonze et al., 1994 (40)	0.94 (0.66, 1.34)	60	0.06
Mizoue et al., 2008 (46)	0.93 (0.61, 1.42)	64	0.04
Sun et al., 2011 NL (48)	0.89 (0.59, 1.34)	64	0.04
Sun et al., 2011 ON (48)	0.94 (0.59, 1.51)	62	0.05
Chun et al., 2015 (50)	0.78 (0.64, 0.94)	0	0.84
Colon cancer (RR [95% CI]= 0.84 [0.71, 1.00], I^2 (%)= 40, *P*-value= 0.11)			
Excluded study or subgroup	**OR (95% CI)**	**I^2 (%)**	***P*-value**
Shannon et al., 1996 (women) (42)	0.88 (0.77, 1.01)	6	0.38
Shannon et al., 1996 (men) (42)	0.83 (0.69, 1.01)	48	0.07
Kampman et al., 2000 (men) (44)	0.84 (0.69, 1.04)	47	0.08
Kampman et al., 2000 (women) (44)	0.87 (0.72, 1.06)	36	0.15
Satia Abouta et al., 2004 Caucasian (45)	0.83 (0.68, 1.01)	48	0.07
Satia Abouta et al., 2004 African (45)	0.84 (0.69, 1.02)	48	0.07
Murtaugh et al., 2006 Ff/ff (28)	0.79 (0.68, 0.93)	11	0.35
Murtaugh et al., 2006 FF (28)	0.82 (0.67, 1.00)	46	0.09
Rectal cancer (RR [95% CI]= 0.63 [0.50, 0.80], I^2 (%)= 43, *P*-value= 0.15)			
Excluded study or subgroup	**OR (95% CI)**	**I^2 (%)**	***P*-value**
Murtaugh et al., 2006 FF (28)	0.59 (0.45, 0.78)	55	0.11
Murtaugh et al., 2006 Ff/ff (28)	0.62 (0.47, 0.82)	62	0.07
Williams et al., 2009 Whites (47)	0.75 (0.56, 1.01)	0	0.44
Williams et al., 2009 African (47)	0.60 (0.47, 0.76)	26	0.26
HIGH-FAT DAIRY			
Colon cancer (RR [95% CI]= 1.11 [0.90, 1.37], I^2 (%)= 53, *P*-value= 0.06)			
Excluded study or subgroup	**OR (95% CI)**	**I^2 (%)**	***P*-value**
Shannon et al., 1996 (women) (42)	1.12 (0.89, 1.41)	60	0.04
Shannon et al., 1996 (men) (42)	1.17 (0.95, 1.43)	49	0.10
Kampman et al., 2000 (women) (44)	1.16 (0.93, 1.46)	49	0.10
Kampman et al., 2000 (men) (44)	1.09 (0.84, 1.42)	61	0.03
Murtaugh et al., 2006 Ff/ff (28)	1.04 (0.88, 1.22)	0	0.52
Murtaugh et al., 2006 FF (28)	1.07 (0.81, 1.41)	62	0.03
LOW-FAT DAIRY			
Colon cancer (RR [95% CI]= 0.85 [0.71, 1.02], I^2 (%)= 24, *P*-value= 0.26)			
Excluded study or subgroup	**OR (95% CI)**	**I^2 (%)**	***P*-value**
Shannon et al., 1996 (women) (42)	0.88 (0.73, 1.06)	23	0.27
Shannon et al., 1996 (men) (42)	0.83 (0.67, 1.02)	36	0.18
Kampman et al., 2000 (women) (44)	0.89 (0.73, 1.09)	19	0.29
Kampman et al., 2000 (men) (44)	0.86 (0.66, 1.10)	35	0.19
Murtaugh et al., 2006 FF (28)	0.85 (0.69, 1.04)	38	0.17
Murtaugh et al., 2006 Ff/ff (28)	0.77 (0.64, 0.92)	0	0.76

Supplementary data

TOTAL MILK			
Colorectal cancer (RR [95% CI]= 0.85 [0.73, 0.99], I^2 (%)= 0, *P*-value= 0.50)			
Excluded study or subgroup	**OR (95% CI)**	**I^2 (%)**	***P*-value**
Lee et al., 1989 (39)	0.84 (0.71, 0.99)	3	0.40
Centonze et al., 1994 (40)	0.86 (0.74, 0.99)	0	0.43
Boutron et al., 1996 (31)	0.83 (0.72, 0.97)	0	0.51
Boutron-Ruault M-C et al., 1999 (43)	0.84 (0.72, 0.98)	0	0.42
Mizoue et al., 2008 (46)	0.90 (0.76, 1.05)	0	0.78
Sun et al., 2011 ON (48)	0.89 (0.74, 1.06)	0	0.46
Sun et al., 2011 NL (48)	0.84 (0.72, 0.98)	2	0.41
Green et al., 2014 (49)	0.82 (0.70, 0.96)	0	0.52
Rectal cancer (RR [95% CI]= 0.88 [0.69, 1.13], I^2 (%)= 40, *P*-value= 0.17)			
Excluded study or subgroup	**OR (95% CI)**	**I^2 (%)**	***P*-value**
Lee et al., 1989 (39)	0.84 (0.64, 1.10)	54	0.11
Williams et al., 2009 African (47)	0.88 (0.67, 1.14)	60	0.08
Williams et al., 2009 Whites (47)	1.13 (0.81, 1.59)	0	0.79
Green et al., 2014 (49)	0.77 (0.58, 1.03)	9	0.34
TOTAL YOGURT			
Colorectal cancer (RR [95% CI]= 0.92 [0.77, 1.09], I^2 (%)= 0, *P*-value= 0.32)			
Excluded study or subgroup	**OR (95% CI)**	**I^2 (%)**	***P*-value**
Boutron et al., 1996 (31)	0.91 (0.75, 1.09)	0	0.35
Sun et al., 2011 ON (48)	1.01 (0.78, 1.32)	0	0.95
Sun et al., 2011 NL (48)	0.87 (0.71, 1.07)	0	0.56
Colon cancer (RR [95% CI]= 1.06 [0.90, 1.25], I^2 (%)= 25, *P*-value= 0.26)			
Excluded study or subgroup	**OR (95% CI)**	**I^2 (%)**	***P*-value**
Kampman et al., 1994 (41)	1.03 (0.89, 1.20)	14	0.32
Shannon et al., 1996 (women) (42)	1.09 (0.95, 1.23)	0	0.50
Shannon et al., 1996 (men) (42)	1.04 (0.86, 1.26)	39	0.18
Kampman et al., 2000 (men) (44)	1.04 (0.79, 1.38)	40	0.17
Kampman et al., 2000 (women) (44)	1.09 (0.83, 1.43)	38	0.19
CHEESE			
Colorectal cancer (RR [95% CI]= 0.95 [0.79, 1.14], I^2 (%)= 0, *P*-value= 0.62)			
Excluded study or subgroup	**OR (95% CI)**	**I^2 (%)**	***P*-value**
Centonze et al., 1994 (40)	0.97 (0.80, 1.18)	0	0.60
Boutron et al., 1996 (31)	0.93 (0.76, 1.13)	0	0.55
Boutron-Ruault M-C et al., 1999 (43)	0.95 (0.78, 1.16)	0	0.45
Sun et al., 2011 NL (48)	0.90 (0.74, 1.11)	0	0.74
Sun et al., 2011 ON (48)	1.02 (0.76, 1.35)	0	0.52
Colon cancer (RR [95% CI]= 0.87 [0.74, 1.02], I^2 (%)= 0, *P*-value= 0.4)			
Excluded study or subgroup	**OR (95% CI)**	**I^2 (%)**	***P*-value**
Kampman et al., 1994 (41)	0.84 (0.71, 1.00)	0	0.51

Supplementary data

Kampman et al., 2000 (men) (44)	0.85 (0.69, 1.04)	42	0.19
Kampman et al., 2000 (women) (44)	0.95 (0.75, 1.21)	0	0.38

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VI. Discussion

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VI. DISCUSSION

Each Chapter of the present doctoral thesis includes a discussion section. However, some aspects that could not be deeply addressed in the articles, as well as new evidence after their publication are further discussed in this section. Furthermore, limitations and strengths of our articles are also provided.

1. GENERAL DISCUSSION

Within the frame of the PREDIMED study, the present doctoral dissertation provides new prospective evidence on the associations between the consumption of different subtypes of dairy products, considering their composition in sugar and fat, and the risk of developing CRC. Moreover, the present thesis provides updated meta-analytical evidence of the available scientific literature on the associations between the consumption of different types of dairy products and CRC incidence in adults. Finally, the associations between adhering to cancer-specific and healthy lifestyle recommendations and CRC risk in the context of the PREDIMED trial are also addressed.

The findings of this thesis suggest that high total dairy product consumption was inversely associated with CRC incidence in elderly Spanish individuals with CVD risk, and especially, of importance was the intake of low-fat milk, which was the main driver behind the inverse association. However, the intake of other dairy product subtypes (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) was not significantly associated with CRC risk.

In addition, the systematic-review and meta-analysis of observational studies included in the present thesis showed that higher consumption of total dairy products and total milk was consistently inversely related to CRC risk at all site. Moreover, cheese consumption was inversely associated with the risk of CRC and proximal colon cancer, and low-fat milk consumption was associated with decreased colon cancer risk in adults. No significant associations were found between CRC and the consumption of low-fat dairy products, whole milk, fermented dairy products or cultured milk.

Our results concerning the consumption of dairy products and the associated CRC risk in the PREDIMED study, are in agreement with the last *Diet, nutrition, physical activity and colorectal cancer report* [144], in which dairy products (this category includes evidence from total dairy, milk, cheese and calcium intakes) are judged to decrease CRC risk with strong evidence. Likewise, the

most current systematic reviews and meta-analyses of prospective studies have reported that total dairy product or milk consumption is inversely associated with CRC risk [130,187].

However, although an inverse association between dairy product consumption, and especially milk, and CRC risk is suggested based on prospective cohort studies conducted in healthy populations [165,179–186], there is insufficient evidence in older individuals at high cardiovascular risk. Simultaneously, case-control studies investigating the associations between dairy product consumption and CRC risk have shown inconclusive results [168,169,178,170–177].

In our prospective observational cohort study, cheese intake was not significantly associated with the risk of developing CRC, probably due to the limited number of CRC cases, and because of the low consumption of fermented dairy in our cohort. This discrepancy might be also explained by differences in the populations studied, the dietary assessment tools used, and types of cheese assessed. Besides, bioaccessibility and bioavailability of the nutrients contained in dairy foods might be different depending on the nature of the food matrix [236]. For instance, the high lactose content in milk in comparison to fermented dairy products might decrease the bioavailability of calcium [237], which seems to be the main contributor to the potential protective effect of dairy products against CRC. Likewise, we hypothesized that fat content in full-fat milk might mitigate the potential benefits of the other bioactive components [238]. In this regard, it is necessary to emphasize that in the recent systematic review and meta-analysis of prospective studies by Schwingshackl [130], inverse associations with CRC risk for both low and high-fat dairy product intakes were found.

Altogether, the results of this thesis expand the associations between dairy product consumption and CRC incidence to other populations, suggesting that low-fat milk intake might decrease CRC in elderly individuals with CVD risk. In addition, the consumption of other subtypes of dairy foods including whole-fat dairy products was not associated with CRC risk. As outlined in the Introduction section of the present thesis, in the last decades, most dietary worldwide guidelines have encouraged the consumption of low-fat dairy products instead of their full-fat counterparts. This might be probably the main cause for the low consumption of whole-fat milk (a median 1.7% of the total milk intake) in our cohort. Thus, our findings also suggest that there is currently not enough scientific data to make strong dietary recommendations that promote avoiding full-fat dairy product consumption.

On the other hand, the results regarding the consumption of dairy products and CRC risk based on the PREDIMED study were supported by the findings of the systematic-review and meta-analysis included in the present doctoral thesis. After conducting a systematic review and meta-analysis of all available scientific literature on dairy product consumption and the associated risk of developing CRC, we found that the highest intake of low-fat milk, compared to the lowest, was

related to 26% lower risk of CRC, although only for colon cancer. Furthermore, the consumption of total dairy products was significantly associated with 20% decreased CRC risk. It is also important to note that, the cohort studies analyzed in our systematic-review and meta-analyses showed a lower risk of CRC associated with higher cheese consumption, which is in accordance with the last WCRF/AICR conclusions [144].

From a mechanistic point of view, dairy product may decrease CRC risk by several mechanisms. However, the most widely studied anticarcinogenic component in dairy products and probably the main contributor to this protective effect is its calcium content. An established mechanism proposed for calcium action is its capability to bind unconjugated bile acids and free fatty acids, lessening their toxic effects on the colorectum [239]. Basic and clinical studies suggest that intracellular calcium may also reduce proliferation and promote colonic epithelial differentiation, likely by influencing different cell-signaling pathways [240,241]. Calcium may also prevent colonic K-Ras mutations and inhibit heme-induced promotion of colon carcinogenesis [242,243]. Epidemiological evidences also indicate the importance for CRC risk of some dietary components found in dairy products such as vitamin D in enriched dairy products, and calcium [222,244–246]. On the other hand, other components naturally present in dairy products such as conjugated linoleic acid, butyric acid, lactoferrin, folate and lactic acid bacteria in fermented foods have been also suggested to exert protective effects against colorectal carcinogenesis by different mechanisms [247–252].

Finally, adhering to emergent lifestyle scores, such as the 2018 WCRF/AICR and the LRL scores, may substantially reduce CRC risk in the PREDIMED study. The second prospective work included in the present dissertation, which focuses on the associations between following healthy lifestyle recommendations and the associated CRC risk, showed that adhering to the 2018 WCRF/AICR recommendations and following healthier behavior patterns, calculated as LRL score, may considerably help to reduce by almost 50% the risk of developing CRC in an elderly Mediterranean population at high CVD risk. Even though the WCRF/AICR score was specifically designed in a context of cancer prevention, our results suggest that using other scores based on healthy lifestyle patterns such as the LRL index, which was developed to evaluate the impact of an overall healthy lifestyle pattern on all-cause mortality (comprising cancer and CVD mortality), might also be a useful tool to prevent CRC, especially in elderly individuals. These results are of great importance since, as far as we are aware, this is the first study based on the LRL score focusing on CRC incidence. Another great advantage of this prospective observational cohort study from the PREDIMED trial is that, it provides scientific evidence in a population under-studied in this field. Furthermore, most studies on which the WCRF/AICR recommendations are based on, are focused on a general adult population.

Additionally, our results suggest that synergy between the various factors of each score might be one of the main mechanisms for the decreased CRC risk, thereby showing that the sum of all

components might be more than the action of each one individually. On the other hand, SSB consumption was shown to be independently associated with CRC risk in our analyses, which is in accordance with the WCRF/AICR conclusions [144]. This recognized international organism states that SSB intake is mostly linked to weight gain, which increases CRC risk. However, other potential mechanisms suggested in the literature should be further explored.

According to the results of the present doctoral thesis, owing to the evidence on the benefits that the consumption of low-fat milk might have on the risk of CRC in elderly individuals with CVD risk, and the lack of evidence on an increased CRC derived from full-fat dairy consumption, it is suggested that there are no consistent reasons to advice against whole-fat dairy product intake in this population. Hence, although further prospective research on the topic is warranted, the recommendation to drink milk might be reasonable. In addition, adopting healthier lifestyle habits that not keep diet in mind, but also other lifestyle factors, should be of primary interest for preventing the risk of developing CRC in Mediterranean elderly individuals with overweight or obesity who have CVD risk.

2. LIMITATIONS AND STRENGTHS

The results from the present doctoral thesis should be interpreted considering some **limitations**:

- With respect to the PREDIMED-studies:

- The causality of the observed associations in the observational cohorts within the context of the PREDIMED study cannot be established due to the observational nature of the study design.
- Regarding the observational cohort studies from the PREDIMED trial, it might be difficult to generalize the results to other populations because we studied an older Mediterranean population at high cardiovascular risk. However, the inverse associations observed in both works have been previously recognized, especially for dairy product intake, in young individuals from different populations. Thus, our results expand the evidence to the previous findings reported on these associations.
- Because the consumption of dairy product has been associated to a decreased risk of obesity and T2D, both conditions highly prevalent in older populations, we cannot discard that the inverse associations that we observed might have been mediated by these metabolic conditions.
- Although dietary variables were assessed by using a validated FFQ, potential measurement errors are unavoidable. Further, although the intervention arm was considered as a potential

confounder in our main statistical models, we cannot discard residual confounding due to the dietary interventions.

- 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 had an impact on the outcomes.
- Since the score components in the second Chapter of the present thesis were added, they contributed equally to the total score. The fact that not all the components of the WCRF/AICR score are associated with the risk of CRC might have weakened the associations observed.
- Because CRC was a secondary outcome in the PREDIMED trial, we did not have enough CRC cases to investigate CRC cases separately or by tumor site with enough statistical power. This lack of statistical power might also explain the lack of association found between individual components consistently associated with decreased CRC risk.

▸ With respect to the meta-analysis:

- Despite the high-quality of the studies we analyzed in our systematic-review and meta-analysis, owing to the observational nature of the studies included and due to the possibility, that not all the studies were adjusted for important dietary variables potential residual confounding cannot be ruled out.
- Some of the dietary assessments were self-reported, which might affect the reliability of the reported intakes. However, the use of validated FFQs could have decreased this bias.
- There was some statistical heterogeneity among the studies included in the systematic review and meta-analysis. Nevertheless, this heterogeneity was explained by the removal of individual studies.
- Because we were not able to search for all available databases, we cannot ignore the possibility that some references may have been missed in the systematic search.
- Given the observational nature of the studies included in the systematic review and meta-analysis, the results cannot support causal relationships between dairy product consumption and CRC risk.

The present investigation has also several **strengths**:

▸ With respect to the PREDIMED-studies:

- The large-scale prospective design with a long follow-up period and a large sample of the observational cohorts based on the PREDIMED trial.

- CRC cases in the PREDIMED were ascertained and confirmed by an independent Event Adjudication Committee annually.
- Food consumption in the PREDIMED study was assessed by using a validated FFQ.
- We had the ability to control for several potential confounders in our statistical analyses.
- In the observational cohort study assessing dairy product intake and CRC risk, to minimize errors in diet measurements caused by within-person variation and dietary changes, we took advantage of the repeated measurements of intake, and we calculated the cumulative average for dietary variables.
- We confirmed the robustness of our results by testing our primary results with different approaches and sensitivity analyses.

  - With respect to the meta-analysis:

- For the systematic review and meta-analysis we a) identified prospective cohort and case-control studies through a systematic search, b) used a quantitative NOS scale to exclude low-quality studies, and 3) all the studies in our analyses used a validated FFQ to assess dairy product consumption.

VII. Conclusions

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VII. CONCLUSIONS

The main goals of this thesis were a) to investigate the associations between the consumption of different subtypes of dairy products and the risk of developing CRC in the PREDIMED trial, b) to assess the associations between cancer-based recommendations and healthier lifestyle patterns with CRC in the PREDIMED study, and c) to meta-analyze all the available scientific evidence on dairy product consumption and CRC risk in adults. Because prospective evidences studying the association between dairy product consumption and CRC incidence in elderly individuals was limited, and because of the lack of prospective studies assessing the CRC risk associated with healthier lifestyle recommendations in elderly individuals, this thesis has contributed to increase the scientific epidemiological knowledge in this field.

In this section, the conclusions of the present dissertation are presented in response to each of the hypotheses raised at the beginning of the present thesis.

- **Hypothesis 1:** *Consumption of different subtypes of dairy products, considering their sugar and fat content might be differently associated with the risk of CRC in the PREDIMED study.*

  - Within the frame of the PREDIMED cohort of older Spanish individuals at high CVD risk, high total dairy product consumption was inversely associated with CRC incidence, and the intake of low-fat milk was supposed to be the main driver behind this inverse association. However, 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.

- **Hypothesis 2:** *High adhesion to a priori lifestyle scores (the WCRF/AICR and the LRL scores) might decrease the risk of developing CRC in the PREDIMED study.*

  - Adherence to the most recent 2018 WCRF/AICR recommendations, as well as accomplishing a cluster of LRL factors, was inversely associated with CRC incidence in elderly Spanish individuals at high CVD risk.
  - In terms of the WCRF/AICR score, greater adherence to the SSB recommendation was strongly and inversely associated with a statistically significant decreased risk of developing CRC. Neither the other individual recommendations of the WCRF/AICR score nor the individual components of the LRL score were significantly associated with CRC risk in elderly Spanish individuals at high CVD risk.

- **Hypothesis 3:** *The consumption of dairy products and the risk of developing CRC might be associated in different ways depending on the type of dairy product and CRC subsite and location.*

    - Higher consumption of total dairy products and total milk was consistently inversely related to CRC risk at all sites, cheese consumption was inversely associated with the risk of CRC and proximal colon cancer, and low-fat milk consumption was associated with decreased colon cancer risk in adults. No significant associations were found between CRC and the consumption of low-fat dairy products, whole milk, fermented dairy products or cultured milk. The associations between different subtypes of dairy products and CRC risk differed by colon cancer location and subsite.

VIII. Global and future insights

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VIII. GLOBAL AND FUTURE INSIGHTS

CRC might be prevented in nearly half of new cases through lifestyle changes. Although the increase in the incidence and mortality of CRC in future decades is unavoidable due to the development and westernization of nutritional and lifestyle habits, scientific evidence suggests that reducing adiposity, increasing PA, adhering to a healthy diet, decreasing alcohol intake and reducing smoking, among other factors, could substantially reduce the risk of CRC.

This doctoral thesis adds new evidence to the current scientific literature regarding the nutritional epidemiology of CRC. On the one hand, our results allow us to better understand the associations between the consumption of certain foods that are part of a healthy dietary pattern, such as dairy products, with CRC incidence. Additionally, our research also permits to gain understanding of the synergistic association between different lifestyle risk factors and the risk of developing CRC in elderly individuals with cardiovascular risk.

Based on the results found in this dissertation, and considering the available scientific literature on this subject, different aspects are suggested to address in future research, which are necessary to clarify the role that different dietary and lifestyle components may play in the development of CRC, as well as their combined effect:

- Additional prospective studies are needed, both in the general and in specific populations, in other geographical regions that confirm our results on the relationship between dairy consumption and CRC risk, and allow them to be extrapolated to the general population.
- Further prospective studies with large samples and long follow-up periods, as well as clinical trials that take into account the long latency period of CRC, known difficulties with dietary compliance, and other complexities are needed to clarify the associations between CRC risk, including the differences in CRC risk across subsites, and the fat and sugar contents of dairy products.
- Dietary assessment tools used in nutritional epidemiological studies should be improved in order to represent the usual intake. For instance, new varieties of dairy products such as artificially sweetened dairy products are not considered in most studies. Additionally, most of dietary questionnaires do not bear in mind different subtypes of cheese but include them in the same category. On the other hand, some studies do not use standardized serving sizes which difficult comparability and generalization of the results. The results of our research based on the adherence to emergent lifestyle scores need to be replicated in other populations with different dietary and lifestyle patterns. For this purpose, large-prospective cohorts with more events are needed to extend the evidence on lifestyle patterns and CRC risk

- OMICS, and in particular metabolomics, can give us the opportunity to identify biomarkers of dairy food intake and its effects on metabolism in order to better identify the relationship between dairy intake and disease as well as to identify potential pathways implicated in these relationships.

IX. References

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IX. REFERENCES

1. von Meyenfeldt, M. Cancer-associated malnutrition: An introduction. *Eur. J. Oncol. Nurs.* **9**, S35-8 (2005).

2. American Cancer Society. *American Cancer Society. Colorectal Cancer Facts & Figures 2017-2019.* (2017).

3. Mayer, R. J. *Harrison's Principles of Internal Medicine*. (Mc Graw Hill Education, 2018).

4. Li, F. Y. & Lai, M. De. Colorectal cancer, one entity or three. *Journal of Zhejiang University: Science B*. **10**, 219–229 (2009).

5. Bufill, J. A. Colorectal cancer: Evidence for distinct genetic categories based on proximal or distal tumor location. *Annals of Internal Medicine*. **113**, 779–788 (1990).

6. Lee, G. H. *et al.* Is right-sided colon cancer different to left-sided colorectal cancer? - A systematic review. *European Journal of Surgical Oncology*. **41**, 300–308 (2015).

7. Yahagi, M., Okabayashi, K., Hasegawa, H., Tsuruta, M. & Kitagawa, Y. The Worse Prognosis of Right-Sided Compared with Left-Sided Colon Cancers: a Systematic Review and Meta-analysis. *J. Gastrointest. Surg.* **20**, 648–655 (2016).

8. Keum, N. N. & Giovannucci, E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. *Nature Reviews Gastroenterology and Hepatology*. **16**, 713-732 (2019).

9. Drewes, J. L., Housseau, F. & Sears, C. L. Sporadic colorectal cancer: microbial contributors to disease prevention, development and therapy. *Br. J. Cancer* **115**, 273–80 (2016).

10. Flemer, B. *et al.* Tumour-associated and non-tumour-associated microbiota in colorectal cancer. *Gut* **66**, 633–643 (2017).

11. Wei, E. K. *et al.* Comparison of risk factors for colon and rectal cancer. *Int. J. Cancer* **108**, 433–442 (2004).

12. Murphy, N. *et al.* Heterogeneity of Colorectal Cancer Risk Factors by Anatomical Subsite in 10 European Countries: A Multinational Cohort Study. *Clin. Gastroenterol. Hepatol.* **17**, 1323-1331.e6 (2019).

13. Wang, L. *et al.* Risk Factor Profiles Differ for Cancers of Different Regions of the Colorectum. *Gastroenterology* (2020) doi:10.1053/j.gastro.2020.03.054. [Online ahead of print].

14. Mostafa, G. *et al.* Influence of demographics on colorectal cancer. *Am. Surg.* **70**, 259–64 (2004).

15. Yang, L. *et al.* Proximal shift of colorectal cancer with increasing age in different ethnicities. *Cancer Manag. Res.* **10**, 2663–2673 (2018).

16. Murphy, G. *et al.* Sex disparities in colorectal cancer incidence by anatomic subsite, race and age. *Int. J. Cancer* **128**, 1668–1675 (2011).

17. Nelson, R. L., Dollear, T., Freels, S. & Persky, V. The relation of age, race, and gender to the subsite location of colerectal carcinoma. *Cancer* **80**, 193–197 (1997).

18. Murphy, C. C. & Singal, A. G. Establishing a research agenda for early-onset colorectal cancer. *PLoS Medicine*. **15**, e1002577 (2018).

19. Wu, X. *et al.* Subsite-specific colorectal cancer incidence rates and stage distributions among Asians and Pacific Islanders in the United States, 1995 to 1999. *Cancer Epidemiol. Biomarkers Prev.* **13**, 1215–22 (2004).

20. Shin, A. *et al.* Increasing trend of colorectal cancer incidence in Korea, 1999-2009. *Cancer Res. Treat.* **44**, 219–226 (2012).

21. Ervik M, Lam F, Ferley J, et al. Cancer Today. *Int. Agency Res. Cancer.* (2016).

22. Townsend, N. *et al.* Cardiovascular disease in Europe: epidemiological update 2016. *Eur. Heart J.* **37**,

3232–3245 (2016).

23. Bray, F. *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA. Cancer J. Clin.* **68**, 394–424 (2018).

24. Arnold, M. *et al.* Global patterns and trends in colorectal cancer incidence and mortality. *Gut* **66**, 683–691 (2017).

25. Evan, G. & Littlewood, T. A matter of life and cell death. *Science*. **281**, 1317–1322 (1998).

26. Hanahan, D. & Weinberg, R. A. Hallmarks of cancer: The next generation. *Cell*. **144**, 646–674 (2011).

27. Fleming, M., Ravula, S., Tatishchev, S. F. & Wang, H. L. Colorectal carcinoma: Pathologic aspects. *Journal of Gastrointestinal Oncology*. **3**, 153–173 (2012).

28. Pitot, H. C. The molecular biology of carcinogenesis. *Cancer* **72**, 962–970 (1993).

29. Zauber, A. G. *et al.* Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N. Engl. J. Med.* **366**, 687–96 (2012).

30. Carethers, J. M. & Jung, B. H. Genetics and Genetic Biomarkers in Sporadic Colorectal Cancer. *Gastroenterology* **149**, 1177-1190.e3 (2015).

31. Medema, J. P. Cancer stem cells: The challenges ahead. *Nature Cell Biology*. **15**, 338–344 (2013).

32. Munro, M. J., Wickremesekera, S. K., Peng, L., Tan, S. T. & Itinteang, T. Cancer stem cells in colorectal cancer: A review. *Journal of Clinical Pathology*. **71**, 110–116 (2018).

33. Pritchard, C. C. & Grady, W. M. Colorectal cancer molecular biology moves into clinical practice. *Gut* **60**, 116–29 (2011).

34. Levine, J. S. & Ahnen, D. J. Clinical practice. Adenomatous polyps of the colon. *N. Engl. J. Med.* **355**, 2551–2557 (2006).

35. Fearon, E. R. & Vogelstein, B. A genetic model for colorectal tumorigenesis. *Cell*. **61**, 759–767 (1990).

36. Leggett, B. & Whitehall, V. Role of the serrated pathway in colorectal cancer pathogenesis. *Gastroenterology* **138**, 2088–100 (2010).

37. Kedrin, D. & Gala, M. K. Genetics of the serrated pathway to colorectal cancer. *Clin. Transl. Gastroenterology* **6**, e84 (2015).

38. Itzkowitz, S. H. & Yio, X. Inflammation and cancer - IV. Colorectal cancer in inflammatory bowel disease: The role of inflammation. *American Journal of Physiology - Gastrointestinal and Liver Physiology*. 287, G7-17 (2004).

39. Buchner, A. M. & Lichtenstein, G. R. Evaluation and Detection of Dysplasia in IBD: the Role of Chromoendoscopy and Enhanced Imaging Techniques. *Curr. Treat. Options Gastroenterol.* **14**, 73–82 (2016).

40. Jess, T., Rungoe, C. & Peyrin-Biroulet, L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. *Clin. Gastroenterol. Hepatol.* **10**, 639–45 (2012).

41. Oruc, Z. & Kaplan, M. A. Effect of exercise on colorectal cancer prevention and treatment. *World J. Gastrointest. Oncol.* **11**, 348–366 (2019).

42. Graff, R. E. *et al.* Familial Risk and Heritability of Colorectal Cancer in the Nordic Twin Study of Cancer. *Clin. Gastroenterol. Hepatol.* **15**, 1256–1264 (2017).

43. Lin, J. H. *et al.* Association between sex hormones and colorectal cancer risk in men and women. *Clin. Gastroenterol. Hepatol.* **11**, 419-424.e1 (2013).

44. Grodstein, F., Newcomb, P. A. & Stampfer, M. J. Postmenopausal hormone therapy and the risk of colorectal cancer: A review and meta-analysis. *American Journal of Medicine*. **106**, 574–582 (1999).

45. Fernandez, E. *et al.* Oral contraceptives and colorectal cancer risk: a meta-analysis. *Br. J. Cancer* **84**, 722–7 (2001).

46. Murphy, N. *et al.* A Prospective Evaluation of Endogenous Sex Hormone Levels and Colorectal Cancer Risk in Postmenopausal Women. *J. Natl. Cancer Inst.* **107**, (2015).

47. Gunter, M. J. *et al.* Insulin, insulin-like growth factor-I, endogenous estradiol, and risk of colorectal cancer in postmenopausal women. *Cancer Res.* **68**, 329–337 (2008).

48. International Agency for Research on Cancer. *Globocan 2018: Cancer Fact Sheets- Colorectal cancer.* http://gco.iarc.fr/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf (2018).

49. Wolf, A. M. D. *et al.* Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA. Cancer J. Clin.* **68**, 250–281 (2018).

50. Virostko, J., Capasso, A., Yankeelov, T. E. & Goodgame, B. Recent trends in the age at diagnosis of colorectal cancer in the US National Cancer Data Base, 2004-2015. *Cancer* **125**, 3828–3835 (2019).

51. Kasi, P. M. *et al.* Rising Proportion of Young Individuals With Rectal and Colon Cancer. *Clin. Colorectal Cancer* **18**, e87–e95 (2019).

52. Piscitello, A. & Edwards, D. K. Estimating the Screening-Eligible Population Size, aged 45 to 74, at Average Risk to Develop Colorectal Cancer in the United States. *Cancer Prev. Res.* **13**, 443-448 (2020)

53. Siegel, R. L. *et al.* Colorectal cancer statistics, 2020. *CA. Cancer J. Clin.* doi: 10.3322/caac.21601. **[Online ahead of print]**. (2020).

54. Doubeni, C. A. *et al.* Socioeconomic status and the risk of colorectal cancer: an analysis of more than a half million adults in the National Institutes of Health-AARP Diet and Health Study. *Cancer* **118**, 3636–44 (2012).

55. Doubeni, C. A. *et al.* Contribution of behavioral risk factors and obesity to socioeconomic differences in colorectal cancer incidence. *J. Natl. Cancer Inst.* **104**, 1353–62 (2012).

56. Lansdorp-Vogelaar, I. *et al.* Contribution of screening and survival differences to racial disparities in colorectal cancer rates. *Cancer Epidemiol. Biomarkers Prev.* **21**, 728–736 (2012).

57. Ashktorab, H. *et al.* Identification of novel mutations by exome sequencing in African American colorectal cancer patients. *Cancer* **121**, 34–42 (2015).

58. Augustus, G. J. & Ellis, N. A. Colorectal Cancer Disparity in African Americans: Risk Factors and Carcinogenic Mechanisms. *Am. J. Pathol.* **188**, 291–303 (2018).

59. Jasperson, K. W., Tuohy, T. M., Neklason, D. W. & Burt, R. W. Hereditary and Familial Colon Cancer. *Gastroenterology* **138**, 2044–2058 (2010).

60. Butterworth, A. S., Higgins, J. P. T. & Pharoah, P. Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. *Eur J Cancer* **42**, 216–27 (2006).

61. Kravochuck, S. E., Kalady, M. F., Burke, C. A., Heald, B. & Church, J. M. Defining HNPCC and Lynch syndrome: What's in a name? *Gut* **63**, 1525–1526 (2014).

62. Rahner, N. & Steinke, V. Hereditary cancer syndromes. *Dtsch. Arztebl. Int.* **105**, 706–14 (2008).

63. De Rosa, M. *et al.* Genetics, diagnosis and management of colorectal cancer (Review). *Oncol. Rep.* **34**, 1087–1096 (2015).

64. Wong, M. C. S. *et al.* Lower relative contribution of positive family history to colorectal cancer risk with increasing age: A systematic review and meta-analysis of 9.28 million individuals. *American Journal of Gastroenterology* **113**, 1819–1827 (2018).

65. Roos, V. H. *et al.* Effects of Family History on Relative and Absolute Risks for Colorectal Cancer: A Systematic Review and Meta-Analysis. *Clinical Gastroenterology and Hepatology* **17**, 2657-2667.e9 (2019).

66. Lynch, H. T. & De la Chapelle, A. Hereditary colorectal cancer. *N. Engl. J. Med.* **348**, 919–932 (2003).

67. Bonadona, V. *et al.* Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in lynch syndrome. *JAMA - J. Am. Med. Assoc.* **305**, 2304–2310 (2011).

68. Rawla, P., Sunkara, T. & Barsouk, A. Epidemiology of colorectal cancer: Incidence, mortality, survival, and risk factors. *Przeglad Gastroenterologiczny* **14**, 89–103 (2019).

69. Ricciardiello, L., Ahnen, D. J. & Lynch, P. M. Chemoprevention of hereditary colon cancers: time for

new strategies. *Nat. Rev. Gastroenterol. Hepatol.* **13**, 352–61 (2016).

70. Mousavi, S. M., Fallah, M., Sundquist, K. & Hemminki, K. Age- and time-dependent changes in cancer incidence among immigrants to Sweden: colorectal, lung, breast and prostate cancers. *Int. J. cancer* **131**, E122-8 (2012).

71. Lutgens, M. W. M. D. *et al.* Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. *Inflamm. Bowel Dis.* **19**, 789–799 (2013).

72. Olén, O. *et al.* Childhood onset inflammatory bowel disease and risk of cancer: a Swedish nationwide cohort study 1964-2014. *BMJ* **358**, j3951 (2017).

73. Taylor, C. C., Millien, V. O., Hou, J. K. & Massarweh, N. N. Association Between Inflammatory Bowel Disease and Colorectal Cancer Stage of Disease and Survival. *J. Surg. Res.* **247**, 77–85 (2020).

74. Nottage, K. *et al.* Secondary colorectal carcinoma after childhood cancer. *J. Clin. Oncol.* **30**, 2552–2558 (2012).

75. Desautels, D. *et al.* Risk of colorectal cancer after the diagnosis of prostate cancer: A population-based study. *Cancer* **122**, 1254–1260 (2016).

76. Daly, P. E. *et al.* High prevalence of adenomatous colorectal polyps in young cancer survivors treated with abdominal radiation therapy: Results of a prospective trial. *Gut* **66**, 1797–1801 (2017).

77. Yamada, A. *et al.* Risk of gastrointestinal cancers in patients with cystic fibrosis: a systematic review and meta-analysis. *Lancet. Oncol.* **19**, 758–767 (2018).

78. Lagergren, J., Ye, W. & Ekbom, A. Intestinal cancer after cholecystectomy: is bile involved in carcinogenesis? *Gastroenterology* **121**, 542–7 (2001).

79. Zhang, Y. *et al.* Cholecystectomy can increase the risk of colorectal cancer: A meta-analysis of 10 cohort studies. *PLoS One* **12**, e0181852 (2017).

80. Gillessen, S. *et al.* Risk of colorectal cancer in men on long-term androgen deprivation therapy for prostate cancer. *J. Natl. Cancer Inst.* **102**, 1760–70 (2010).

81. Leport, C., Bure, A., Leport, J. & Vilde, J. L. Incidence of colonic lesions in Streptococcus bovis and enterococcal endocarditis. *Lancet (London, England)* **1**, 748 (1987).

82. Abdulamir, A. S., Hafidh, R. R. & Bakar, F. A. The association of Streptococcus bovis/gallolyticus with colorectal tumors: The nature and the underlying mechanisms of its etiological role. *Journal of Experimental and Clinical Cancer Research* **30**, 11 (2011).

83. Kune, G. A. The Melbourne colorectal cancer study: Reflections on a 30-year experience. *Med. J. Aust.* **193**, 648–652 (2010).

84. World Cancer Research Fund/American Institute for Cancer Research. *Diet, nutrition, physical activity and colorectal cancer*. http://www.aicr.org/continuous-update-project/reports/colorectal-cancer-2017-report.pdf (2018).

85. World Cancer Research Fund/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Cancer: a global perspective. Continuous Update Project Expert Report*. dietandcancerreport.org (2018).

86. Dekker, E., Tanis, P. J., Vleugels, J. L. A., Kasi, P. M. & Wallace, M. B. Colorectal cancer. *The Lancet* **394**, 1467–1480 (2019).

87. Genkinger, J. M. *et al.* A pooled analysis of 14 cohort studies of anthropometric factors and pancreatic cancer risk. *Int. J. Cancer* **129**, 1708–1717 (2011).

88. Ma, Y. *et al.* Obesity and Risk of Colorectal Cancer: A Systematic Review of Prospective Studies. *PLoS ONE* **8**, e53916 (2013).

89. Turati, F., Tramacere, I., La Vecchia, C. & Negri, E. A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **24**, 609–17 (2013).

90. Wang, F. & Xu, Y. Body mass index and risk of renal cell cancer: A dose-response meta-analysis of published cohort studies. *Int. J. Cancer* **135**, 1673–1686 (2014).

91. Aune, D. *et al.* Anthropometric factors and endometrial cancer risk: a systematic review and dose-response meta-analysis of prospective studies. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **26**, 1635–48 (2015).

92. Schmid, D., Ricci, C., Behrens, G. & Leitzmann, M. F. Adiposity and risk of thyroid cancer: A systematic review and meta-analysis. *Obesity Reviews*, **16**, 1042–1054 (2015).

93. Chen, G. C. *et al.* Central obesity and risks of pre- and postmenopausal breast cancer: a dose–response meta-analysis of prospective studies. *Obesity Reviews* **17**, 1167–1177 (2016).

94. Hidayat, K., Du, X., Chen, G., Shi, M. & Shi, B. Abdominal obesity and lung cancer risk: Systematic review and meta-analysis of prospective studies. *Nutrients* **8**, 810 (2016).

95. Du, X., Hidayat, K. & Shi, B. M. Abdominal obesity and gastroesophageal cancer risk: Systematic review and meta-analysis of prospective studies. *Bioscience Reports* **37**, BSR20160474 (2017).

96. Freisling, H. *et al.* Comparison of general obesity and measures of body fat distribution in older adults in relation to cancer risk: Meta-analysis of individual participant data of seven prospective cohorts in Europe. *Br. J. Cancer* **116**, 1486–1497 (2017).

97. Dong, Y. *et al.* Abdominal obesity and colorectal cancer risk: Systematic review and meta-analysis of prospective studies. *Bioscience Reports* **37**, BSR20170945 (2017).

98. Renehan, A. G., Tyson, M., Egger, M., Heller, R. F. & Zwahlen, M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* **371**, 569–578 (2008).

99. Song, M. *et al.* Long-term status and change of body fat distribution, and risk of colorectal cancer: a prospective cohort study. *Int. J. Epidemiol.* **45**, 871–83 (2016).

100. Leeners, B., Geary, N., Tobler, P. N. & Asarian, L. Ovarian hormones and obesity. *Hum. Reprod. Update* **23**, 300–321 (2017).

101. Moore, L. L. *et al.* BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. *Int. J. Obes. Relat. Metab. Disord.* **28**, 559–67 (2004).

102. Andreasson, A. *et al.* The prediction of colorectal cancer using anthropometric measures: A Swedish population-based cohort study with 22 years of follow-up. *United Eur. Gastroenterol. J.* **7**, 1250–1260 (2019).

103. Samaras, K., Botelho, N. K., Chisholm, D. J. & Lord, R. V. Subcutaneous and visceral adipose tissue gene expression of serum adipokines that predict type 2 diabetes. *Obesity* **18**, 884–889 (2010).

104. Bruun, J. M., Lihn, A. S., Pedersen, S. B. & Richelsen, B. Monocyte chemoattractant protein-1 release is higher in visceral than subcutaneous human adipose tissue (AT): Implication of macrophages resident in the AT. *J. Clin. Endocrinol. Metab.* **90**, 2282–2289 (2005).

105. Ouchi, N., Parker, J. L., Lugus, J. J. & Walsh, K. Adipokines in inflammation and metabolic disease. *Nature Reviews Immunology* **11**, 85–97 (2011).

106. Riondino, S. *et al.* Obesity and colorectal cancer: Role of adipokines in tumor initiation and progression. *World J. Gastroenterol.* **20**, 5177–5190 (2014).

107. Uyar, G. O. & Sanlier, N. Association of adipokines and insulin, which have a role in obesity, with colorectal cancer. *Eurasian Journal of Medicine* **51**, 190–194 (2019).

108. Giovannucci, E. Insulin and colon cancer. *Cancer Causes and Control* **6**, 164–179 (1995).

109. Calle, E. E. & Kaaks, R. Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms. *Nature Reviews Cancer* **4**, 579–591 (2004).

110. Jiang, Y. *et al.* Diabetes mellitus and incidence and mortality of colorectal cancer: A systematic review and meta-analysis of cohort studies. *Eur. J. Epidemiol.* **26**, 863–876 (2011).

111. Guraya, S. Y. Association of type 2 diabetes mellitus and the risk of colorectal cancer: A meta-analysis and systematic review. *World J. Gastroenterol.* **21**, 6026–6031 (2015).

112. von Wagner, C. *et al.* Type 2 diabetes and colorectal cancer screening: Findings from the English Longitudinal Study of Ageing. *J. Med. Screen.* **27**, 25–30 (2020).

113. Rezende, L. F. M. de *et al.* Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770 000 cancer cases. *Br. J. Sports Med.* **52**, 826–833 (2018).

114. World Health Organization (WHO). *Global recommendations on physical activity for health*. (2010).

115. Ainsworth, B. E. *et al.* 2011 compendium of physical activities: A second update of codes and MET values. *Medicine and Science in Sports and Exercise* **43**, 1575–1581 (2011).

116. Kushi, L. H. *et al.* American Cancer Society guidelines on nutrition and physical activity for cancer prevention. *CA. Cancer J. Clin.* **62**, 30–67 (2012).

117. Hu, F. B. Dietary pattern analysis: A new direction in nutritional epidemiology. *Current Opinion in Lipidology* **13**, 3–9 (2002).

118. Conti, L., Del Cornò, M. & Gessani, S. Revisiting the impact of lifestyle on colorectal cancer risk in a gender perspective. *Critical Reviews in Oncology/Hematology* **145**, 102834 (2020).

119. Grosso, G. *et al.* Possible role of diet in cancer: systematic review and multiple meta-analyses of dietary patterns, lifestyle factors, and cancer risk. *Nutr. Rev.* **75**, 405–419 (2017).

120. Feng, Y. L. *et al.* Dietary patterns and colorectal cancer risk: A meta-analysis. *Eur. J. Cancer Prev.* **26**, 201–211 (2017).

121. Pan, P., Yu, J. & Wang, L. S. Diet and colon: What matters? *Current Opinion in Gastroenterology* **35**, 101–106 (2019).

122. Tangestani, H., Salari-Moghaddam, A., Ghalandari, H. & Emamat, H. Adherence to the Dietary Approaches to Stop Hypertension (DASH) dietary pattern reduces the risk of colorectal cancer: A systematic review and meta-analysis. *Clin. Nutr.* S0261-5614,30050-9. **[Online ahead of print]**. (2020).

123. Zhang, C., Wang, W. & Zhang, D. Association between dietary inflammation index and the risk of colorectal cancer: A meta-analysis. *Nutrition and Cancer* **70**, 14–22 (2018).

124. Cross, A. J., Pollock, J. R. A. & Bingham, S. A. Haem, not protein or inorganic iron, is responsible for endogenous intestinal N-nitrosation arising from red meat. *Cancer Res.* **63**, 2358–60 (2003).

125. Bastide, N. M., Pierre, F. H. F. & Corpet, D. E. Heme iron from meat and risk of colorectal cancer: A meta-analysis and a review of the mechanisms involved. *Cancer Prevention Research* **4**, 177–184 (2011).

126. Gamage, S. M. K., Dissabandara, L., Lam, A. K. Y. & Gopalan, V. The role of heme iron molecules derived from red and processed meat in the pathogenesis of colorectal carcinoma. *Critical Reviews in Oncology/Hematology* **126**, 121–128 (2018).

127. Cross, A. J. & Sinha, R. Meat-related mutagens/carcinogens in the etiology of colorectal cancer. in *Environmental and Molecular Mutagenesis* **44**, 44–55 (2004).

128. Helmus, D. S., Thompson, C. L., Zelenskiy, S., Tucker, T. C. & Li, L. Red Meat-derived heterocyclic amines increase risk of colon cancer: A population-based case-control study. *Nutr. Cancer* **65**, 1141–1150 (2013).

129. Cascella, M. *et al.* Dissecting the mechanisms and molecules underlying the potential carcinogenicity of red and processed meat in colorectal cancer (CRC): An overview on the current state of knowledge. *Infectious Agents and Cancer* **13**, 3 (2018).

130. Schwingshackl, L. *et al.* Food groups and risk of colorectal cancer. *Int. J. Cancer* **142**, 1748–1758 (2018).

131. Händel, M. N. *et al.* Processed meat intake and incidence of colorectal cancer: a systematic review and meta-analysis of prospective observational studies. *European Journal of Clinical Nutrition.* **[Online ahead of print].** (2020) doi:10.1038/s41430-020-0576-9.

132. Gianfredi, V. *et al.* Rectal cancer: 20% risk reduction thanks to dietary fibre intake. systematic review and meta-analysis. *Nutrients* **11**, 1579 (2019).

133. Bingham, S. A. Mechanisms and experimental and epidemiological evidence relating dietary fibre (non-starch polysaccharides) and starch to protection against large bowel cancer. *Proc. Nutr. Soc.* **49**, 153–171 (1990).

134. Slavin, J. L. Mechanisms for the Impact of Whole Grain Foods on Cancer Risk. *J. Am. Coll. Nutr.* **19**, 300S-307S (2000).

135. Pi-Sunyer, X. Do glycemic index, glycemic load, and fiber play a role in insulin sensitivity, disposition index, and type 2 diabetes? *Diabetes Care* **28**, 2978–2979 (2005).

136. Ma, Y. *et al.* Dietary fiber intake and risks of proximal and distal colon cancers: A meta-analysis. *Med. (United States)* **97**, e11678 (2018).

137. Gianfredi, V. *et al.* Is dietary fibre truly protective against colon cancer? A systematic review and meta-analysis. *Int. J. Food Sci. Nutr.* **69**, 904–915 (2018).

138. Cho, E. *et al.* Alcohol Intake and Colorectal Cancer: A Pooled Analysis of 8 Cohort Studies. *Ann. Intern. Med.* **140**, 603-13 (2004).

139. Fedirko, V. *et al.* Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **22**, 1958–72 (2011).

140. McNabb, S. *et al.* Meta-analysis of 16 studies of the association of alcohol with colorectal cancer. *Int. J. Cancer* **146**, 861–873 (2020).

141. Salaspuro, M. Microbial metabolism of ethanol and acetaldehyde and clinical consequences. *Addict. Biol.* **2**, 35–46 (1997).

142. Giovannucci, E. Alcohol, one-carbon metabolism, and colorectal cancer: recent insights from molecular studies. *J. Nutr.* **134**, 2475S-2481S (2004).

143. Seitz, H. K. & Stickel, F. Molecular mechanisms of alcohol-mediated carcinogenesis. *Nature Reviews Cancer* **7**, 599–612 (2007).

144. World Cancer Research Fund International/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Colorectal Cancer*. wcrf.org/colorectal-cancer-2017 (2018).

145. Liang, P. S., Chen, T. Y. & Giovannucci, E. Cigarette smoking and colorectal cancer incidence and mortality: Systematic review and meta-analysis. *International Journal of Cancer* **124**, 2406–2415 (2009).

146. Rothwell, P. M. *et al.* Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet* **376**, 1741–1750 (2010).

147. Johnson, J. R. *et al.* Menopausal hormone therapy and risk of colorectal cancer. *Cancer Epidemiol. Biomarkers Prev.* **18**, 196–203 (2009).

148. Agencia Estatal Boletín Oficial del Estado. Ministerio de la Presidencia, R. con las C. e igualdad. Decreto 2484/1967, de 21 de septiembre, por el que se aprueba el texto del Código Alimentario Español. https://www.boe.es/eli/es/d/1967/09/21/2484/con (2019).

149. Ranganathan, R., Nicklas, T. A., Yang, S. J. & Berenson, G. S. The nutritional impact of dairy product consumption on dietary intakes of adults (1995-1996): The Bogalusa Heart Study. *J. Am. Diet. Assoc.* **105**, 1391–1400 (2005).

150. Drewnowski, A. & Fulgoni, V. Nutrient profiling of foods: Creating a nutrient-rich food index. *Nutrition Reviews* **66**, 23–39 (2008).

151. FAO. *Milk human nutrition dairy products*. (FAO, 2013).

152. Gil, Á. & Ortega, R. M. Introduction and Executive Summary of the Supplement, Role of Milk and Dairy Products in Health and Prevention of Noncommunicable Chronic Diseases: A Series of Systematic Reviews. *Adv. Nutr.* **10**, S67–S73 (2019).

153. Council, N. H. and M. R. Australian Dietary Guidelines Summary. (2013).

154. Harvard T.H. CHAN. School of Public Health. The Nutition Source. Healthy Eating Plate vs. USDA's MyPlate. *2011*.

155. U.S. Department of Health and Human Services and U.S. Department of Agriculture. *2015-2020 Dietary Guidelines for Americans*. (2015).

156. Fundación Dieta Mediterranea. Ministerio de Agricultura Alimentación y medio Ambiente. Gobierno

de España. ¿Qué es la Dieta Mediterránea? Fundación Dieta Mediterránea. Pirámide de la Dieta mediterranea. *Barcelona* (2015).

157. Gil, A., Ruiz-Lopez, M. D., Fernandez-Gonzalez, M. & Martinez de Victoria, E. [The finut healthy lifestyles guide: beyond the food pyramid]. *Nutr. Hosp.* **31**, 2313–23 (2015).

158. Agencia Española de Consumo, Seguridad Alimentaria y Nutrición. Pirámide NAOS. Ministerio de Sanidad, Consumo y Bienestar Social. (2015).

159. Sociedad Española de Nutrición Comunitaria. Pirámide de la Alimentación Saludable. (2015).

160. Eckel RH, Jakicic JM, Ard, JD, Hubbard VS, de J., JM, Lee IM, Lichtenstein AH, Loria CM, Millen BE, Houston Miller N, Nonas CA, Sacks FM, Smith SC Jr, Svetkey LP, W. T. & SZ., Y. AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology American/Heart Association Task Force on Practice Guidelines. *Circulation* **129**, S76–99 (2013).

161. Aranceta Bartrina, J. *et al.* Guías alimentarias para la población española (SENC, 2016); la nueva pirámide de la alimentación saludable. *Nutr. Hosp.* **33**, 1–48 (2016).

162. Yu, E. & Hu, F. B. Dairy Products, Dairy Fatty Acids, and the Prevention of Cardiometabolic Disease: a Review of Recent Evidence. *Current Atherosclerosis Reports* **20**, 24 (2018).

163. Bostick, R. M. *et al.* Relation of calcium, vitamin D, and dairy food intake to incidence of colon cancer among older women. The Iowa Women's Health Study. *Am. J. Epidemiol.* **137**, 1302–17 (1993).

164. Lin, J., Zhang, S. M., Cook, N. R., Lee, I.-M. & Buring, J. E. Dietary Fat and Fatty Acids and Risk of Colorectal Cancer in Women. *Am J Epidemiol Am. J. Epidemiol.* **160**, 1011–1022 (2004).

165. Larsson, S. C., Bergkvist, L. & Wolk, A. High-fat dairy food and conjugated linoleic acid intakes in relation to colorectal cancer incidence in the Swedish Mammography Cohort. *Am. J. Clin. Nutr.* **82**, 894–900 (2005).

166. Safiri, S. *et al.* The global, regional, and national burden of colorectal cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol. Hepatol.* **4**, 913–933 (2019).

167. Schwingshackl, L., Schwedhelm, C., Galbete, C. & Hoffmann, G. Adherence to mediterranean diet and risk of cancer: An updated systematic review and meta-analysis. *Nutrients* **9**, 1063 (2017).

168. Mizoue, T. *et al.* Calcium, Dairy Foods, Vitamin D, and Colorectal Cancer Risk: The Fukuoka Colorectal Cancer Study. *Cancer Epidemiol. Biomarkers Prev.* **17**, 2800–2807 (2008).

169. Williams, C. D. *et al.* Dietary Patterns, Food Groups, and Rectal Cancer Risk in Whites and African-Americans. *Cancer Epidemiol. Biomarkers Prev.* **18**, 1552–1561 (2009).

170. Sun, Z. *et al.* Calcium and vitamin D and risk of colorectal cancer: results from a large population-based case-control study in Newfoundland and Labrador and Ontario. *Can. J. Public Health* **102**, 382–389 (2011).

171. Cox, B. & Sneyd, M. J. School milk and risk of colorectal cancer: A national case-control study. *Am. J. Epidemiol.* **173**, 394–403 (2011).

172. Green, C. J. *et al.* Tea, coffee, and milk consumption and colorectal cancer risk. *J. Epidemiol.* **24**, 146–53 (2014).

173. Abu Mweis, S. S. *et al.* Food groups and the risk of colorectal cancer. *Eur. J. Cancer Prev.* **24**, 313–320 (2015).

174. Chun, Y. J. *et al.* Associations of Colorectal Cancer Incidence with Nutrient and Food Group Intakes in Korean Adults: A Case-Control Study. *Clin. Nutr. Res.* **4**, 110 (2015).

175. Tayyem, R. F. *et al.* Meats, milk and fat consumption in colorectal cancer. *J. Hum. Nutr. Diet.* **29**, 746–756 (2016).

176. Azzeh, F. S. *et al.* Healthy dietary patterns decrease the risk of colorectal cancer in the Mecca Region, Saudi Arabia: a case-control study. *BMC Public Health* **17**, 607 (2017).

177. Zhang, X. *et al.* Higher intakes of dietary vitamin D, calcium and dairy products are inversely associated with the risk of colorectal cancer: A case-control study in China. *Br. J. Nutr.* **123**, 699–

711 (2020).

178. El Kinany, K. *et al.* Consumption of modern and traditional Moroccan dairy products and colorectal cancer risk: a large case control study. *Eur. J. Nutr.* **59**, 953–963 (2020).

179. Larsson, S. C., Bergkvist, L., Rutegård, J., Giovannucci, E. & Wolk, A. Calcium and dairy food intakes are inversely associated with colorectal cancer risk in the Cohort of Swedish Men. *Am. J. Clin. Nutr.* **83**, 667–73; quiz 728–9 (2006).

180. Park, S.-Y. *et al.* Calcium and Vitamin D Intake and Risk of Colorectal Cancer: The Multiethnic Cohort Study. *Am. J. Epidemiol.* **165**, 784–793 (2007).

181. Lee, S.-A. *et al.* Animal origin foods and colorectal cancer risk: a report from the Shanghai Women's Health Study. *Nutr Cancer* **61**, 194–205 (2009).

182. Pala, V. *et al.* Yogurt consumption and risk of colorectal cancer in the Italian European prospective investigation into cancer and nutrition cohort. *Int. J. Cancer* **129**, 2712–2719 (2011).

183. Thompson, F. E. *et al.* Adolescent and mid-life diet : risk of colorectal cancer in the NIH-AARP Diet and Health Study. *Am. J. Clin. Nutr.* **94**, 1607–1619 (2011).

184. Murphy, N. *et al.* Consumption of dairy products and colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). *PLoS One* **8**, e72715 (2013).

185. Tantamango-Bartley, Y. *et al.* Independent associations of dairy and calcium intakes with colorectal cancers in the Adventist Health Study-2 cohort. *Public Health Nutr.* **20**, 2577–2586 (2017).

186. Bakken, T. *et al.* Milk and risk of colorectal, colon and rectal cancer in the Norwegian Women and Cancer (NOWAC) Cohort Study. *Br. J. Nutr.* **119**, 1274–1285 (2018).

187. Vieira, A. R. *et al.* Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **28**, 1788-1802 (2017).

188. Kant, A. K. Dietary patterns and health outcomes. *J. Am. Diet. Assoc.* **104**, 615–635 (2004).

189. Steck, S. E., Guinter, M., Zheng, J. & Thomson, C. A. Index-Based Dietary Patterns and Colorectal Cancer Risk: A Systematic Review. *Adv. Nutr. An Int. Rev. J.* **6**, 763–773 (2015).

190. Schwingshackl, L., Bogensberger, B. & Hoffmann, G. Diet Quality as Assessed by the Healthy Eating Index, Alternate Healthy Eating Index, Dietary Approaches to Stop Hypertension Score, and Health Outcomes: An Updated Systematic Review and Meta-Analysis of Cohort Studies. *J. Acad. Nutr. Diet.* **118**, 74-100.e11 (2018).

191. Romaguera, D. *et al.* Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. *Am. J. Clin. Nutr.* **96**, 150–63 (2012).

192. Shams-White, M. M. *et al.* Further guidance in implementing the standardized 2018 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Score. *Cancer Epidemiol. Biomarkers Prev.* **29**, 889-894 (2020).

193. Thomson, C. A. *et al.* Nutrition and physical activity cancer prevention guidelines, cancer risk, and mortality in the women's health initiative. *Cancer Prev. Res. (Phila).* **7**, 42–53 (2014).

194. Kabat, G. C., Matthews, C. E., Kamensky, V., Hollenbeck, A. R. & Rohan, T. E. Adherence to cancer prevention guidelines and cancer incidence, cancer mortality, and total mortality: a prospective cohort study. *Am. J. Clin. Nutr.* **101**, 558–569 (2015).

195. Makarem, N., Lin, Y., Bandera, E. V, Jacques, P. F. & Parekh, N. Concordance with World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) guidelines for cancer prevention and obesity-related cancer risk in the Framingham Offspring cohort (1991-2008). *Cancer Causes Control* **26**, 277–286 (2015).

196. Nomura, S. J. O. *et al.* Is adherence to diet, physical activity, and body weight cancer prevention recommendations associated with colorectal cancer incidence in African American women? *Cancer Causes Control* **27**, 869–879 (2016).

197. Jones, P., Cade, J. E., Evans, C. E. L., Hancock, N. & Greenwood, D. C. Does adherence to the World

Cancer Research Fund/American Institute of Cancer Research cancer prevention guidelines reduce risk of colorectal cancer in the UK Women's Cohort Study? *Br. J. Nutr.* **119**, 340–348 (2018).

198. Petimar, J. *et al.* Adherence to the World Cancer Research Fund/American Institute for Cancer Research 2018 Recommendations for Cancer Prevention and Risk of Colorectal Cancer. *Cancer Epidemiol. Biomarkers Prev.* **28**, 1469–1479 (2019).

199. Romaguera, D. *et al.* Adherence to nutrition-based cancer prevention guidelines and breast, prostate and colorectal cancer risk in the MCC-Spain case-control study. *Int. J. Cancer* **141**, 83–93 (2017).

200. Turati, F. *et al.* Adherence to the World Cancer Research Fund/American Institute for Cancer Research recommendations and colorectal cancer risk. *Eur. J. Cancer* **85**, 86–94 (2017).

201. El Kinany, K. *et al.* Concordance with the World Cancer Research Fund/American Institute for Cancer Research recommendations for cancer prevention and colorectal cancer risk in Morocco: A large, population-based case–control study. *Int. J. Cancer* **145**, 1829-1837 (2019).

202. Solans, M., Chan, D. S. M., Mitrou, P., Norat, T. & Romaguera, D. A systematic review and meta-analysis of the 2007 WCRF/AICR score in relation to cancer-related health outcomes. *Annals of Oncology* **31**, 352–368 (2020).

203. Li, Y. *et al.* Impact of Healthy Lifestyle Factors on Life Expectancies in the US Population. *Circulation* **138**, 345–355 (2018).

204. Li, Y. *et al.* Healthy lifestyle and life expectancy free of cancer, cardiovascular disease, and type 2 diabetes: prospective cohort study. *BMJ* **368**, l6669 (2020).

205. Liu, G. *et al.* Influence of Lifestyle on Incident Cardiovascular Disease and Mortality in Patients With Diabetes Mellitus. *J. Am. Coll. Cardiol.* **71**, 2867–2876 (2018).

206. Fijten, G. *et al.* Predictive value of signs and symptoms for colorectal cancer in patients with rectal bleeding in general practice. *Farm Pr.* **12**, 279–286 (1995).

207. Kaminski, M. F. *et al.* Quality indicators for colonoscopy and the risk of interval cancer. *N. Engl. J. Med.* **362**, 1795–1803 (2010).

208. Corley, D. A. *et al.* Adenoma detection rate and risk of colorectal cancer and death. *N. Engl. J. Med.* **370**, 1298–1306 (2014).

209. Nerad, E. *et al.* Diagnostic accuracy of CT for local staging of colon cancer: A systematic review and meta-analysis. *Am. J. Roentgenol.* **207**, 984–995 (2016).

210. Beets-Tan, R. G. H. *et al.* Magnetic resonance imaging for clinical management of rectal cancer: Updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. *Eur. Radiol.* **28**, 1465–1475 (2018).

211. Benson, A. B. *et al.* NCCN Guidelines Insights: Colon Cancer, Version 2.2018. *J. Natl. Compr. Canc. Netw.* **16**, 359–369 (2018).

212. Labianca, R. *et al.* Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* **24**, Suppl 6:vi64-72 (2013).

213. Sargent, D. J. *et al.* Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. *J. Clin. Oncol.* **28**, 3219–26 (2010).

214. Le, D. T. *et al.* Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* **357**, 409–413 (2017).

215. Pagès, F. *et al.* International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study. *Lancet (London, England)* **391**, 2128–2139 (2018).

216. Ma, B. *et al.* What has preoperative radio(chemo)therapy brought to localized rectal cancer patients in terms of perioperative and long-term outcomes over the past decades? A systematic review and meta-analysis based on 41,121 patients. *Int. J. Cancer* **141**, 1052–1065 (2017).

217. Abdel-Rahman, O. & Cheung, W. Y. Integrating Systemic Therapies into the Multimodality Treatment of Resectable Colorectal Liver Metastases. *Gastroenterol. Res. Pract.* **2018**, 4326082 (2018).

218. Algra, A. M. & Rothwell, P. M. Effects of regular aspirin on long-term cancer incidence and metastasis:

A systematic comparison of evidence from observational studies versus randomised trials. *Lancet Oncol.* **13**, 518–527 (2012).

219. Lin, K. J., Cheung, W. Y., Lai, J. Y. C. & Giovannucci, E. L. The effect of estrogen vs. combined estrogen-progestogen therapy on the risk of colorectal cancer. *Int. J. Cancer* **130**, 419–430 (2012).

220. Song, M., Garrett, W. S. & Chan, A. T. Nutrients, foods, and colorectal cancer prevention. *Gastroenterology* **148**, 1244-1260.e16 (2015).

221. Heine-Bröring, R. C. *et al.* Dietary supplement use and colorectal cancer risk: A systematic review and meta-analyses of prospective cohort studies. *Int. J. Cancer* **136**, 2388–2401 (2015).

222. Keum, N., Aune, D., Greenwood, D. C., Ju, W. & Giovannucci, E. L. Calcium intake and colorectal cancer risk: Dose-response meta-analysis of prospective observational studies. *Int. J. Cancer* **135**, 1940–1948 (2014).

223. Liu, Y. *et al.* Vitamin and multiple-vitamin supplement intake and incidence of colorectal cancer: a meta-analysis of cohort studies. *Med. Oncol.* **32**, 1–10 (2015).

224. PDQ Screening and Prevention Editorial Board. *Colorectal Cancer Screening (PDQ®): Health Professional Version*. *PDQ Cancer Information Summaries* (2002).

225. Jeon, J. *et al.* Determining Risk of Colorectal Cancer and Starting Age of Screening Based on Lifestyle, Environmental, and Genetic Factors. *Gastroenterology* **154**, 2152-2164.e19 (2018).

226. Estruch, R. *et al.* Primary prevention of cardiovascular disease with a mediterranean diet supplemented with extra-virgin olive oil or nuts. *N. Engl. J. Med.* **378**, e34 (2018).

227. Martínez-González, M. Á. *et al.* Cohort profile: design and methods of the PREDIMED study. *Int. J. Epidemiol.* **41**, 377–85 (2012).

228. Fernández-Ballart, J. D. *et al.* Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. *Br. J. Nutr.* **103**, 1808–16 (2010).

229. Mataix, V. J. *Tabla de composicion de alimentos [Food composition tables]*. (Universidad de Granada, 2003).

230. Moreiras, O., Carvajal, A., Cabrera, L. & Cuadrado, C. *Tablas de composición de alimentos [Food composition tables]*. vol. 9th (Ediciones Pirámide, 2005).

231. Elosua, R., Marrugat, J., Molina, L., Pons, S. & Pujol, E. Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish men. The MARATHOM Investigators. *Am. J. Epidemiol.* **139**, 1197–209 (1994).

232. Elosua, R. *et al.* Validation of the Minnesota Leisure Time Physical Activity Questionnaire In Spanish Women. Investigators of the MARATDON Group. *Med. Sci. Sports Exerc.* **32**, 1431–7 (2000).

233. *Cochrane handbook for systematic reviews of interventions. Version 5.1.0*. (2011).

234. Stroup, D. F. *et al.* Meta-analysis of Observational Studies in Epidemiology A Proposal for Reporting. *JAMA* 283, 2008-12 (2000).

235. Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G. & PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* **6**, e1000097 (2009).

236. Fardet, A., Dupont, D., Rioux, L.-E. & Turgeon, S. L. Influence of food structure on dairy protein, lipid and calcium bioavailability: A narrative review of evidence. *Crit. Rev. Food Sci. Nutr.* 59, 1987-2010 (2018).

237. Guéguen, L. & Pointillart, A. The bioavailability of dietary calcium. *J. Am. Coll. Nutr.* **19**, 119S-136S (2000).

238. Vargas, A. J. & Thompson, P. A. Diet and Nutrient Factors in Colorectal Cancer Risk. *Nutr. Clin. Pract.* **27**, 613–623 (2012).

239. Newmark, H. L., Wargovich, M. J. & Bruce, W. R. Colon cancer and dietary fat, phosphate, and calcium: A hypothesis. *J. Natl. Cancer Inst.* **72**, 1323–1325 (1984).

240. Wargovich, M. J. & Baer, A. R. Basic and clinical investigations of dietary calcium in the prevention of

colorectal cancer. *Prev. Med. (Baltim).* **18**, 672–679 (1989).

241. Fedirko, V. *et al.* Effects of vitamin D and calcium supplementation on markers of apoptosis in normal colon mucosa: A randomized, double-blind, placebo-controlled clinical trial. *Cancer Prev. Res.* **2**, 213–223 (2009).

242. Llor, X. *et al.* K-ras Mutations in 1,2-Dimethylhydrazine-induced Colonic Tumors: Effects of Supplemental Dietary Calcium and Vitamin D Deficiency. *Cancer Res.* **51**, 4305–4309 (1991).

243. Pierre, F. H. F. *et al.* Calcium and α-tocopherol suppress cured-meat promotion of chemically induced colon carcinogenesis in rats and reduce associated biomarkers in human volunteers. *Am. J. Clin. Nutr.* **98**, 1255–1262 (2013).

244. McCullough, M. L. *et al.* Calcium, vitamin D, dairy products, and risk of colorectal cancer in the Cancer Prevention Study II Nutrition Cohort (United States). *Cancer Causes Control* **14**, 1–12 (2003).

245. Huncharek, M., Muscat, J. & Kupelnick, B. Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: A meta-analysis of 26,335 cases from 60 observational studies. *Nutr. Cancer* **61**, 47–69 (2009).

246. Ma, Y. *et al.* Association between vitamin D and risk of colorectal cancer: A systematic review of prospective studies. *J. Clin. Oncol.* **29**, 3775–3782 (2011).

247. Parodi, P. W. Cows' milk fat components as potential anticarcinogenic agents. *J. Nutr.* **127**, 1055–60 (1997).

248. Kritchevsky, D. Antimutagenic and some other effects of conjugated linoleic acid. *Br. J. Nutr.* **83**, 459–65 (2000).

249. Bassaganya-Riera, J., Hontecillas, R. & Beitz, D. C. Colonic anti-inflammatory mechanisms of conjugated linoleic acid. *Clin. Nutr.* **21**, 451–459 (2002).

250. Norat, T. & Riboli, E. Dairy products and colorectal cancer. A review of possible mechanisms and epidemiological evidence. *Eur. J. Clin. Nutr.* **57**, 1–17 (2003).

251. Tsuda, H. *et al.* Cancer prevention by bovine lactoferrin: from animal studies to human trial. *BioMetals* **23**, 399–409 (2010).

252. Williams, L., Williams, E. A., Coxhead, J. M. & Mathers, J. C. Anti-cancer effects of butyrate: use of micro-array technology to investigate mechanisms. *Proc. Nutr. Soc.* **62**, 107–115 (2017).

X. Appendices

UNIVERSITAT ROVIRA I VIRGILI
DIETARY AND LIFESTYLE DETERMINANTS ASSOCIATED WITH THE RISK OF COLORECTAL CANCER
Laura Barrubés Piñol

1. Scientific contributions

- *Publications derived from the present doctoral thesis:*

Barrubés L, Babio N, Hernández-Alonso P, Toledo E, Ramírez Sabio JB, Estruch R, Ros E, Fitó M, Alonso-Gómez AM, Fiol M, Lapetra J, Serra-Majem L, Pintó X, Ruiz-Canela M, Corella D, Castañer O, Macías-González M, Salas-Salvadó J., et al. Association between the 2018 WCRF/AICR and the Low-Risk Lifestyle Scores with Colorectal Cancer Risk in the Predimed Study. *J Clin Med*. 2020;23;9(4).

Barrubés L, Babio N, Becerra-Tomás N, Rosique-Esteban N, Salas-Salvadó J. Association Between Dairy Product Consumption and Colorectal Cancer Risk in Adults: A Systematic Review and Meta-Analysis of Epidemiologic Studies. Adv Nutr. 2019;10(suppl_2):S190-S211.

Barrubés L, Babio N, Mena-Sánchez G, Toledo E, Ramírez-Sabio JB, Estruch R, Ros E, Fitó M, Arós F, Fiol M, Santos-Lozano JM, Serra-Majem L, Pintó X, Martínez-González MÁ, Sorlí JV, Basora J, Salas-Salvadó J; PREvención con DIeta MEDiterránea Study Investigators. Dairy product consumption and risk of colorectal cancer in an older Mediterranean population at high cardiovascular risk. International Journal of Cancer. 2018;143(6):1356-1366.

- *Other scientific publications*

Paz-Graniel I, Babio N, Serra-Majem L, Vioque J, Zomeño MD, Corella D, Díaz-López A, Pintó X, Bueno-Cavanillas A, Tur JA, Daimiel L, Martínez JA, Becerra-Tomás N, Navarrete-Muñoz EM, Schröder H, Fernández-Carrión R, Ortiz-Andrellucchi A, Corbella E, Riquelme-Gallego B, Gallardo-Alfaro L, Micó V, Zulet M, **Barrubés L**, Fitó M, Ruiz-Canela M, Salas-Salvadó J. Fluid and total water intake in a senior Mediterranean population at high cardiovascular risk: demographic and lifestyle determinants in the PREDIMED-Plus study. Eur J Nutr. 2020; 59(4):1595-1606.

Cano-Ibáñez N, Bueno-Cavanillas A, Martínez-González MÁ, Salas-Salvadó J, Corella D, Freixer GL, Romaguera D, Vioque J, Alonso-Gómez ÁM, Wärnberg J, Martínez JA, Serra-Majem L, Estruch R, Tinahones FJ, Lapetra J, Pintó X, Tur JA, García-Ríos A, García-Molina L, Delgado-Rodríguez M, Matía-Martín P, Daimiel L, Martín-Sánchez V, Vidal J, Vázquez C, Ros E, Bartolomé-Resano J, Palau-Galindo A, Portoles O, Torres L, Miquel-Fiol, Sánchez MTC, Sorto-Sánchez C, Moreno-Morales N, Abete I, Álvarez-Pérez J, Sacanella E, Bernal-López MR, Santos-Lozano JM, Fanlo-Maresma M, Bouzas C, Razquin C, Becerra-Tomás N, Ortega-Azorin C, LLimona R, Morey M, Román-Maciá J, Goicolea-Güemez L, Vázquez-Ruiz Z, **Barrubés L**, Fitó M, Gea A. Eur J Nutr. 2019;16. [Online ahead of print]

Julibert A, Bibiloni MDM, Bouzas C, Martínez-González MÁ, Salas-Salvadó J, Corella D, Zomeño MD, Romaguera D, Vioque J, Alonso-Gómez ÁM, Wärnberg J, Martínez JA, Serra-Majem L, Estruch R, Tinahones FJ, Lapetra J, Pintó X, Lopez-Miranda J, García-Molina L, Gaforio JJ, Matía-Martín P, Daimiel L, Martín-Sánchez V, Vidal J, Vázquez C, Ros E, Toledo E, Becerra-Tomás N, Pórtoles O, Pérez-Vega KA, Fiol M, Torres-Collado L, Tojal-Sierra L, Carabaño-Moral R, Abete I, Sanchez-Villegas A, Casas R, Bernal-López MR, Santos-Lozano JM, Galera A, Ugarriza L, Ruiz-Canela M, Babio N, Coltell O, Schröder H, Konieczna J, Orozco-Beltrán D, Sorto-Sánchez C, Eguaras S, **Barrubés L**, Fitó M, Tur JA; Predimed-Plus Investigators. Total and Subtypes of Dietary Fat Intake and Its Association with Components of the Metabolic Syndrome in a Mediterranean Population at High Cardiovascular Risk. Nutrients. 2019;11(7).

Babio, N; **Barrubés, L**; Salas-Salvadó, J. Importancia del consumo y calidad del desayuno en población infantil y adolescente. Informe científico-técnico (Publicaciones URV). 1ª edición: enero de 2018. ISBN: 978-84-8424-724-1.

Salas-Salvadó J, Becerra-Tomás N, García-Gavilán JF, Bulló M, **Barrubés L**. Mediterranean Diet and cardiovascular disease prevention: What do we know? Progress in Cardiovascular diseases. 2018;61(1):62-67.

Babio N, Alcázar M, Castillejo G, Recasens M, Martínez-Cerezo F, Gutiérrez-Pensado V, Vaqué C, Vila-Martí A, Torres-Moreno M, Sánchez E, **Barrubés L**, Salas-Salvadó J. Risk of eating disorders in patients with celiac disease. Journal of Pediatric Gastroenterology & Nutrition. 2017.

2. Participation in national and international conferences

- *Participation in national conferences*

"Association between dairy product consumption and colorectal cancer risk in adults: a systematic review and meta-analysis of prospective studies". X Symposium Ciber Fisiopatologia de la Obesidad y Nutrición – Obesity and Nutrition in the 21st Century. 20-21 November 2019. Madrid (España). Poster. Abstract book; p. 105.

"Dairy product consumption and risk of colorectal cancer incidence in an elderly Mediterranean population at high cardiovascular risk". V Jornadas Anuales del Colegio de Dietistas-Nutricionistas y II Congreso de la Sociedad Catalana de Alimentación y Dietética Clínica. 17-18 November 2017. Reus (España). Oral presentation.

- *Participation in international conferences*

"Association between dairy product consumption and colorectal cancer risk in adults: a systematic review and meta-analysis of epidemiologic studies". **FENS 2019 – 13th European Nutrition Conference, Federation of European Nutrition Societies**. 15-18 October 2019, Dublin (Ireland). Poster.

"Risk of eating disorders in patients with celiac disease". **IUNS 21st International Congress of Nutrition (ICN). 'From Sciences to Nutrition Security'**. Sociedad Argentina de Nutrición (SAN). 15-20 October 2017, Buenos Aires (Argentina). Poster.

"Dairy product consumption and risk of colorectal cancer incidence in an elderly Mediterranean population at high cardiovascular risk". **IUNS 21st International Congress of Nutrition (ICN). 'From Sciences to Nutrition Security'**. Sociedad Argentina de Nutrición (SAN). 15-20 October 2017, Buenos Aires (Argentina). Poster.

3. Mobility

Length: 3 months (01/04/2019 - 30/06/2019)

Institution : Équipe de Recherche en Épidémiologie Nutritionnelle (EREN). UMR U1153 Inserm / U1125 Inrae / Cnam / Université Paris 13 - Sorbonne Paris Nord. Centre de Recherche en Epidémiologie et Statistiques - Université de Paris (CRESS).

Location: 93017 Bobigny CEDEX. France

Supervision: Dr. Mathilde Touvier

Objectives set during the stay and degree of achievement: During the 3-month stay, it was assessed the association between dairy product consumption (total dairy, cheese, white cheese, yogurt and yogurt-like products) and the risk of developing total cancer, breast cancer, prostate cancer and CRC, in the context of the NutriNet Santé cohort (n=101,279). The objective was to verify whether the relationships observed in the present thesis regarding dairy products may be extrapolated to the general population.

The predoctoral stay in the EREN team allowed to:

- Gain experience in the field of epidemiological research within a relevant international group on the thesis subject.
- Learn how to work with new statistical tools (SAS program®).
- Improve skills at the personal and teamwork level.
- Expand knowledge about the food-to-cancer ratio within a large-scale cohort. Specifically, about the association between the different dairy subtypes and the risk of different types of cancer (specified previously), including CRC, which belongs to the subject of the doctoral thesis.
- Open the doors to possible future collaborations. With the results obtained during the doctoral stay, as a result of the collaboration between the EREN group and the Human Nutrition Unit a publication will be carried out.
- Improve language skills in English and French.
- Obtain a doctoral degree with international mention.

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