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ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Dr. Osamu Toyoshima is a Director of Toyoshima Endoscopy Clinic in Tokyo, Japan. Dr. Toyoshima graduated from the University of Tokyo with his master´s degree in Medicine. After graduating, he joined the Department of Gastroenterology and Surgical Oncology at the University of Tokyo Hospital and engaged in clinical practice and medical research. After that, he established the Toyoshima Endoscopy Clinic with his father, Dr. Hiroshi Toyoshima. Toyoshima Endoscopy Clinic is an endoscopy-specialized clinic, which performs 10000 endoscopies annually. Dr. Osamu Toyoshima mainly conducts research using clinical data from Toyoshima Endoscopy Clinic. He is an expert in the field of gastroenterology, especially of gastric cancer risk evaluation based on the endoscopic gastritis and of quality indicators of colonoscopy such as colorectal polyp detection.

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ORIGINAL ARTICLE

Case Control Study

Food groups, diet quality and colorectal cancer risk in the Basque Country

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Abstract

BACKGROUND

The results obtained to date concerning food groups, diet quality and colorectal cancer (CRC) risk vary according to criteria used and the study populations.

AIM

To study the relationships between food groups, diet quality and CRC risk, in an adult population of the Basque Country (North of Spain).

METHODS

This observational study included 308 patients diagnosed with CRC and 308 age- and sex-matched subjects as controls. During recruitment, dietary, anthropometric, lifestyle, socioeconomic, demographic and health status information was collected. Adherence to the dietary recommendations was evaluated utilizing the Healthy Eating Index for the Spanish Diet and the MedDietScore. Conditional logistic regressions were used to evaluate the associations of food group intakes, diet quality scores, categorized in tertiles, with CRC risk.

RESULTS

The adjusted models for potential confounding factors showed a direct association between milk and dairy products consumption, in particular high-fat cheeses [odds ratio (OR) third tertile *vs* first tertile = 1.87, 95% confidence intervals (CI): 1.11-3.16], and CRC risk. While the consumption of fiber-containing foods, especially whole grains (OR third tertile *vs* first tertile = 0.62, 95%CI: 0.39-0.98), and fatty fish (OR third tertile *vs* first tertile = 0.53, 95%CI: 0.27-0.99) was associated with a lower risk for CRC. Moreover, higher MD adherence was associated with a reduced CRC risk in adjusted models (OR third tertile *vs* first tertile = 0.40, 95%CI: 0.20-0.80).

CONCLUSION

Direct associations were found for high-fat cheese, whereas an inverse relation was reported for fiber-containing foods and fatty fish, as well as adherence to a Mediterranean dietary pattern.

Key words: Colorectal cancer; Food group; Dietary quality; Mediterranean diet; Risk-factors; Case-control study

Core tip: This matched case-control study supports the role of diet in colorectal cancer (CRC) risk. The results suggest that high consumption of high-fat cheeses is associated with CRC risk, whereas, a high intake of fiber-containing foods, especially whole grains, and fatty fish, as well as adherence to the Mediterranean dietary pattern, was associated with a lower risk for CRC. Future studies are needed to better understand the influence of the dietary habits on CRC prevention in this population that can provide leads for the design and tailoring of future interventions, and guide counselling strategies for promoting a healthy lifestyle.

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INTRODUCTION

Colorectal cancer (CRC) is a major public health challenge worldwide. CRC is the third-most commonly diagnosed malignancy and the fourth leading cause of cancer deaths in the world, accounting for approximately 1.8 million new cases and almost 900000 deaths in 2018[1]. In Europe, CRC is the leading malignancy in terms of incidence and the second in mortality in both sexes[2]. CRC is linked to western lifestyles, in particular, to diet, physical inactivity, smoking, alcohol consumption, and body weight[3,4].

Epidemiological evidence suggests that dietary factors may both protect against and promote the development of CRC. A comprehensive review[5] shows robust evidence about the protective role of dietary fiber. Other foods, such as milk or garlic, also may be protective. Conversely, red meat and processed meat intake and alcoholic drinks increase CRC risk. This food group approach has the advantage of reducing some of the problems inherent to analyses of nutrient intake (*e.g.*, inaccuracy and incompleteness of food-composition tables). Furthermore, it offers an advantage from a preventive perspective since food group results are easier to transform into dietary recommendations than those of nutrients[6].

In this regard, foods are not consumed in isolation but as part of a dietary pattern; therefore, the actual effect of diet on disease risk may be observed only when all components are considered jointly[6]. For this purpose, several diet quality indexes have been developed using point systems to measure whole diet quality based on the alignment of food choices with dietary recommendations. Some of these indices have been used to begin assessing the relationships between overall diet quality and CRC risk, and the results show that high scores in these indices are associated with a lower CRC risk[7-10]. However, the results vary considerably according to the index used and other factors such as sex and age. Therefore, there is a need to further examine these relationships in diverse population studies.

The current case-control study was undertaken in the North of Spain to elucidate the relationships between food group consumption, diet quality and CRC risk, and identify possible differences in consumption depending on tumor location, in an adult population that participated in a CRC screening programme (CRCSP) in the Basque Country. To our knowledge, this is the first study in the Basque country population, in which both CRC incidence and mortality have increased in recent years[11]. There are few studies in this regard in Spain[12,13]. And both in these Spanish studies and in others carried out in other Mediterranean countries controls were apparently healthy subjects without clinical symptoms or signs of any type of cancer[14].

MATERIALS AND METHODS

Study subjects

This is an observational, matched case-control study in a population group residing in the Basque Country (North of Spain). Participants in this study were recruited from among patients attending any of the three hospitals of the Osakidetza/Basque Health Service (Basurto, Galdakao and Donostia) members of the Basque Country CRCSP. To be eligible for this CRCSP, the patients had to be aged between 50 and 69, asymptomatic for colorectal symptoms and registered with the Osakidetza/Basque Health Service[11]. These inclusion criteria were applied to both case and control group, that is, controls fulfilled the same eligibility criteria defined for the cases, with the exception of the disease (outcome). Recruitment and data collection for the present study were conducted between 2014 and 2016.

All the patients who were newly diagnosed with CRC (n = 601) were invited to participate in this study. Of those, 283 refused to participate in the study, and 10 were excluded due to missing information. Ultimately, 308 subjects (66.2% men) consented to participate in the survey and completed all the questionnaires. In addition, for each case, three age- (± 9.0 years) and sex-matched control patients were randomly sought from the list of CRC-free subjects (n = 1836) who participated in the CRCSP during the same period as the cases. The matched controls were patients with positive results

(abnormal) for immunochemical fecal occult blood test and negative colonoscopy results (normal). The participation rate of the controls was 37.6%, and 17 subjects were excluded due to missing information. Finally, the matched case-to-control ratio was 1:1, and the final data set included 308 cases who were diagnosed with CRC and 308 age- and sex-matched controls. Further details on recruitment and data collection have been described elsewhere[15]. The main advantage of the present study compared to other above-mentioned researches[12-14] is that we confirmed that controls were free of the disease through colonoscopy. Colonoscopy was used as diagnostic criteria to identify the cases in order to avoid false positives and negatives.

The pathological staging was based on the 7th edition of the AJCC cancer staging manual[16] as follows: I (57.1%), IIA (13.6%), IIB (1.0%), IIC (0.3%), IIIA (7.5%), IIIB (14.6%), IIIC (1.9%), IVA (2.9%), and IVB (1.0%). The location of the cancer was distal in 76% and proximal (to the splenic flexure of the colon) in 24.0% of the samples. Concerning the tumor grade classification, we adopted a two-grade classification that was divided into low grade (well or moderately differentiated) (80.5%) and high grade (poorly differentiated, anaplastic, or undifferentiated) (4.5%); the percentage of missing data for this classification was 14.9%.

Some of the cases had undergone surgical resection (73.7%) and/or adjuvant treatments, chemotherapy (34.1%), and chemotherapy and radiation (6.8%). The percentages of subjects according to the type of surgical procedure were as follows: 26.3% sigmoidectomy, 17.5% right hemicolectomy resection, 18.8% low anterior resection, 6.5% left hemicolectomy resection, 2.3% transverse colectomy, 1.0% abdominoperineal resection, 1.0% total colectomy, and 0.3% transanal endoscopic operation. The cases were invited to take part in this survey at least one month after finishing their last treatment (surgery, chemotherapy or radiotherapy) (median, 1.3 years; range, 0.1 to 4.2 years). All the clinical data were obtained from the Basque Country's population-based CRCSP database, which links patient medical records and clinical databases and reviewed by expert staff. This review allowed the monitorization of all cases from the submission of the sample through the analysis, colonoscopy, pathology and follow-up.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving patients were approved by the Clinical Research Ethics Committee of the Basque Country (reference numbers PI2011006 and PI2014042). Written informed consent was obtained from all the study participants. Consenting participants self-completed and returned a detailed food frequency questionnaire (FFQ) and one general questionnaire. The questions referred to the behaviors before participating in the CRCSP. Assistance from the study staff was available to help the patients to understand the items on the questionnaires. The quality management applied in the present study has been described in a previous article[15].

Dietary assessment

Diets were assessed using a short FFQ that was a modified version of the Rodríguez *et al*[17] (2008) questionnaire. This adaptation was validated with multiple 24-h recalls in the Basque general population[18] and in CRC diagnosed patients in a pilot of the present study[19]. It consists of 67 items and requires the subjects to recall the number of times each food item was consumed either per week or per month. This FFQ included specific questions about the frequency of intake of alcoholic beverages. Moreover, the respondents could also record the consumption of other foods that were not included on the food list.

Consumption frequencies were standardized to "per day" and multiplied by standard serving sizes (grams)[20]. For items that included several foods, each food's contribution was estimated with weighting coefficients that were obtained from the usual consumption data[21]. Food items were then regrouped according to nutritional characteristics[22] and considering the potential contribution of food to the pathogenesis of CRC[23,24]. Details on the items included in each food group are shown in Table 1. All food items that were consumed were entered into DIAL 2.12 (2011 ALCE INGENIERIA)[25], a type of dietary assessment software, to estimate energy intake (kilocalories/day, kcal/d).

Adherence to the dietary recommendations was evaluated utilizing the Healthy Eating Index for Spanish Diet (HEISD)[26] and the MedDietScore (MDS)[27], as previously described[19]. The theoretical range of the HEISD is 0-100 and of the MDS 0-55, higher values of these scores indicate greater adherence to the dietary recommendations for the Spanish population and the Mediterranean diet pattern, respectively. HEISD was divided into the following categories: Poor diet (< 50 points), needs improvement (50-80 points) and proper diet (> 80 points)[26]; and the MDS into

Table 1 Food group definitions

Food group	Food items
Red and processed meat	
Red meat	Beef, pork and lamb, minced meat, hamburgers, meatballs
Processed meat	Ham, sausage, salami, mortadella, black pudding or blood sausage
Egg	Egg
Fish	White fish (hake, grouper, sole, cod) and fatty fish (sardine, tuna, salmon, mackerel)
Milk/dairy products	
Non-cheese products	Whole milk, semi-skimmed milk, skimmed milk, whole yogurt, skimmed yogurt and dairy desserts
Cheese	Burgos cheese, curd, cottage and cheeses low in calories, mature, semi-mature and creamy cheese
Fiber-containing foods	
Fruits	Orange, tangerine, apple, pear, banana, peach, raisins, prunes, dried figs... natural fruit juices
Vegetables	Salads, green beans, chard, spinach... garnish vegetables (eggplant, mushrooms, peppers...), garlic, onion
Whole grains	Whole grain pasta, brown rice, whole grain cookies, whole breakfast cereals (Muesli, All-Bran)
Nuts	Walnuts, almonds, hazelnuts, peanuts
Fat	Vegetable oils (olive, sunflower, corn, soy), butter, margarine, mayonnaise
Sweet and added sugar	Chocolate, breakfast cereals, cookies, muffins, donuts, honey, sugar, commercial fruit juice, soft-drinks, cakes, pies
Alcoholic beverages	Beer, wine, hard cider, vermouth, whiskey, rum, gin, brandy, cocktails

the following ones: Low adherence to MD (0-34 points) and high adherence (> 35 points). The cut-off point of MDS was established taking into account that scores below 34 points were associated with a higher risk of coronary heart disease, being the relative odds ≥ 1.42[27].

General questionnaire

A general questionnaire was used to gather information on weight status (self-reported weight and height) and environmental factors [demographic factors: Age and sex; and lifestyle information: Physical exercise (PE) and smoking consumption]. These questions were taken from the Spanish Health Questionnaire[28]. Body mass index (BMI) estimated from self-reported height and weight was classified according to the World Health Organization criteria for those under 65 years of age[29] and according to the criteria proposed by Silva Silva Rodrigues *et al*[30] for those 65 years and older.

Additionally, socioeconomic and health status data were assessed with two indices that were obtained from the clinical databases developed by the Health Department of the Basque Government, namely the socioeconomic deprivation index (DI) and predictive risk modelling (PRM), respectively. The first one was estimated using the MEDEA project criteria[31], as has been described elsewhere[12] and was divided into quintiles (Q), with the first being the least disadvantaged and the fifth being the most disadvantaged. The DI was successfully assigned to 80.2% of participants, while the quality of the registered information did not permit the linking of the remaining 19.8%.

The PRM is an index that is based on Adjusted Clinical Groups[32], Diagnostic Cost Groups/Hierarchical Condition Categories[33] and Clinical Risk Groups[34]. This index combines information about diagnoses, prescriptions, previous costs and the use of specific procedures. It is capable of predicting the use of health resources[35], and it was stratified into four levels (L); the first included participants with a risk of high health resource consumption and the fourth included those with low health resource consumption. The PRM was successfully assigned to 95.1% of participants, while the quality of the registered information did not permit the linking of the remaining 4.9%.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, United States) and STATA 13.0 (StataCorp LP, TX, United States). Categorical variables are shown as a percentage, and continuous variables are shown as the means and standard deviations (SD). Normality was

checked using the Kolmogorov-Smirnov-Lilliefors test. Differences between continuous variables were calculated with a Wilcoxon test, and a McNemar's test was used for categorical variables.

Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (95%CI) for CRC risk according to tertiles of food group intakes and diet quality scores for unadjusted and adjusted models. Intake of all food groups and total diet quality scores were categorized into tertiles by the distribution in the control population, taking into account sex differences when they were significant. The lowest tertile was used as the reference group. Tertile cut-offs for HEISD were: 1st tertile (T_1), 69; 2nd tertile (T_2), 69-74.5 and 3rd tertile (T_3), > 74.5; and for MDS: T_1, < 35; T_2, 35-37 and T_3, > 37.

Based on known risk factors for CRC[36-38], covariates in adjusted models included age, sex, weight status, energy intake, PE level, smoking status, intensity of smoking (in current and past smokers) and time not smoking (in past smokers), DI and PRM. Quantitative covariates (cigarettes/d and years not smoking) were dichotomized by mean or median, according to the normality test. We used the cut-off of Romaguera *et al*[39] to create two PE levels expressed in min/d of cycling/sports: Sedentary-light (< 15 min/d) and moderate-vigorous (≥ 15 min/d). Age was dichotomized using the same age ranges that were used in the sample selection process (50-59 years old *vs* 60-69 years old). Qualitative ones, such as DI and PRM were dichotomized taking into account the distribution of frequencies to obtain similar sample sizes for each category (DI, Q_{1-3} *vs* Q_{4-5}; PRM, L_{3-4} *vs* L_{1-2}). Energy intake was included as a quantitative variable in the adjusted models. We included participants with missing data for the covariates as a separate category. The reference categories were those that, according to the literature, have a lower CRC risk. All tests were 2-sided, and *P* values less than 0.05 were considered statistically significant.

RESULTS

Comparisons of general characteristics between the cases and the controls are presented in Table 2. Significant differences between the cases and the controls were found for educational level, smoking and weight status, with a higher percentage of cases with low-medium educational level, past or current smoking status and with overweight/obesity compared to the controls ($P < 0.01$).

Table 3 shows food group intakes expressed as mean values and standard deviations according to case-control status. No significant differences were found between the two groups for the majority of foods groups, except for a higher consumption of eggs and a lower intake of whole grains in the cases than the controls ($P < 0.05$).

The ORs for CRC risk by the main food group and food subgroup intakes are presented in Table 4 and 5, respectively. The adjusted ORs for CRC risk increased with higher red and processed meat, eggs, milk/dairy products intakes; whereas it decreased with higher fiber-containing foods and nut intakes. The food group with the highest adjusted OR for CRC risk was milk/dairy products. Fish consumption showed an association with CRC risk in the unadjusted analysis but not in the adjusted analysis. For some of these food groups, specifically for red and processed meat, fish, eggs and nuts, the null value 1 was contained in the confidence interval. Concerning the food subgroup intakes, the ORs for CRC risk increased with higher high-fat cheese intakes, while it decreased with higher fatty fish, in the adjusted analysis.

Supplementary Table 1 describes food group intakes of cases according to tumor location and their matched controls. Food group intakes were not substantially different between proximal and distal cancer cases, except for fish, milk/dairy products and fat. The fish consumption was higher in both case subgroups (proximal and distal cancer cases) in comparison with their matched controls ($P < 0.001$). However, the milk/dairy products intake was higher in proximal tumor cases and was lower in distal tumor cases than in their matched controls ($P < 0.001$). Finally, the fat intake was higher in proximal tumor cases in comparison with their matched controls ($P < 0.05$). The sample sizes did not allow the assessment of food group intakes related to disease risk, stratifying according to the tumor location.

The components and total scores of the HEISD and MDS are displayed in Table 6. According to HEISD, 91.9% of the participants (cases and controls) followed a diet classified as "needs improvement", 7.6% followed a "good diet" and 0.5 followed a "poor diet". Significant differences were neither observed in the HEISD classification nor the components scores nor in the total score. However, the total score for this

Table 2 General characteristics of the sample studied

Characteristics	Cases (*n* = 308)		Controls (*n* = 308)		*P* value
Sex, men, *n* (%)	204 (66.2)		204 (66.2)		
Age, yr, mean SD	61.5	5.2	61.1	5.5	0.093
Schooling, %					
No education/primary education	36.7		29.2		
Technical/secondary education	48.0		44.5		
University degree	15.3		26.3		0.005
Economic activity, %					
Working	27.9		32.1		
Unemployed	5.2		3.2		
Retired	58.8		56.2		
Housework	8.1		8.4		0.496
Last work, %					
Employer or businessman/women	19.2		17.9		
Steady salaried employee	75.0		71.8		
Temporary salaried employee or member of a cooperative	0.6		4.5		
Household help and other activities without salary	5.1		5.8		0.073
Smoking status, %					
Never	27.9		38.6		
Past/current	72.1		61.4		0.004
Time to quit smoking					
≥ 11 yr	67.2		66.7		
< 11 yr	32.8		33.3		0.931
Intensity of smoking[1]					
≤ 15 cigarettes/d	50.7		33.1		
> 15 cigarettes/d	49.3		66.9		0.003
Physical exercise, %					
< 15 min/d of cycling/sports	79.2		65.9		
≥ 15 min/d of cycling/sports	20.8		34.1		< 0.001
BMI, %					
Underweight	6.5		7.8		0.033
Normal weight	26.0		34.1		
Overweight/obesity	67.5		58.1		
Energy intake (kcal/d), mean SD	1769.9	383.4	1736.6	388.2	0.172
DI,%[2]					
$Q_{1\text{-}3}$	47.1		65.6		
$Q_{4\text{-}5}$	18.8		29.5		< 0.001
PRM,%[2]					
$L_{1\text{-}2}$	15.6		12.3		
$L_{3\text{-}4}$	83.4		79.2		< 0.001

[1]Percentages were calculated excluding never smokers.
[2]Valid percentages. BMI: Body mass index; DI: Deprivation index (This index was successfully assigned to 80.2% of the study sample); L: Level; PRM: Predictive risk modelling (This index was successfully assigned to 95.1% of the study sample); Q: Quintile; SD: Standard deviation.

Table 3 Food group intakes of the sample studied

Food groups, g/d	Cases (*n* = 308)		Controls (*n* = 308)		*P* value
	mean	SD	mean	SD	
Red and processed meat	70.9	36.6	66.0	39.7	0.064
Red meat	49.7	30.5	46.1	31.0	0.130
Processed meat	21.2	16.6	19.9	17.2	0.155
Total fish	76.8	39.2	77.6	40.9	0.540
White fish	40.9	25.2	44.1	27.4	0.055
Fatty fish	35.9	22.6	33.6	24.1	0.236
Eggs	20.8	12.7	18.7	11.5	0.038
Milk/dairy products	264.7	153.4	271.0	119.4	0.310
Non-cheese dairy products	246.0	152.4	253.8	118.5	0.203
Total cheeses	18.8	17.4	17.1	16.8	0.172
Fresh cheeses[1]	6.9	10.3	7.1	13.3	0.867
Other cheeses[2]	11.7	11.8	10.1	10.7	0.172
Fiber-containing foods	570.3	243.9	564.8	214.1	0.761
Fruits (including natural juices)	330.2	202.5	322.6	168.2	0.791
Vegetables	202.1	88.8	200.6	90.9	0.803
Whole grains	14.4	19.9	18.8	23.4	0.012
Fat	35.5	6.9	34.6	6.4	0.064
Nuts	9.1	10.1	10.9	10.5	0.055
Sweets and added sugar	108.3	95.4	110.7	116.5	0.969
Alcoholic beverages	103.4	100.7	96.8	105.9	0.269

[1]Fresh cheeses, *e.g.*, Burgos cheese and cheeses low in calories.
[2]Other cheeses, mature, semi-mature and creamy cheeses. SD: Standard deviation.

dietary quality index and the score of diet variety components were higher for cases with the proximal location of cancer than for their matched controls ($P < 0.05$) (Supplementary Table 2). No association was found between this index and risk of CRC, in the conditional logistic regressions.

Concerning the MDS, in the total sample, 39.8% showed low adherence to the MD and the remaining percentage had high adherence, without significant differences in the MDS classification between the cases and the controls. However, the scores for whole grains and total index were lower for cases than for controls ($P < 0.05$). This last result was confirmed using conditional logistic regressions, showing that those participants with higher MDS had a lower CRC risk than those with a lower score, in both unadjusted (model I: T_3 *vs* T_1, OR = 0.57, 95%CI: 0.37-0.89, $P = 0.013$) and adjusted models (model II: T_3 *vs* T_1, OR = 0.40, 95%CI: 0.20-0.80, $P = 0.009$). No significant differences were observed in total MDS between cases stratified by tumor location and their matched controls, but the total score was higher for cases with the proximal location of cancer than for those with distal location ($P < 0.05$) (Supplementary Table 2). Moreover, the score for potatoes and whole grain components were lower for cases with the distal location of cancer than for their matched controls ($P < 0.05$).

Table 4 Association between main food group in and colorectal cancer risk

Main food group intakes[1]	No., case/control	Model I[2]	Model II[3]	Model III[4]
		OR (95%CI)	OR (95%CI)	OR (95%CI)
Red and processed meat				
T_1	90/102	1.00	1.00	1.00
T_2	97/103	1.06 (0.72-1.57)	1.02 (0.61-1.72)	1.08 (0.61-1.94)
T_3	121/109	1.32 (0.91-1.93)	1.65 (0.99-2.75)	1.26 (0.71-2.23)
P		0.314	< 0.001	-
Fish				
T_1	95/105	1.00	1.00	1.00
T_2	77/103	0.82 (0.53-1.25)	0.97 (0.56-1.68)	0.83 (0.46-1.51)
T_3	136/105	1.49 (1.01-2.20)	1.06 (0.62-1.79)	1.25 (0.68-2.29)
P		0.008	< 0.001	-
Eggs				
T_1	71/98	1.00	1.00	1.00
T_2	107/116	1.15 (0.77-1.72)	1.04 (0.62-1.76)	0.97 (0.61-1.93)
T_3	130/104	1.55 (1.03-2.33)	1.72 (1.00-2.94)	1.26 (0.71-2.23)
P		0.081	< 0.001	-
Milk/dairy products				
T_1	60/102	1.00	1.00	1.00
T_2	127/104	2.05 (1.35-3.11)	2.02 (1.19-3.42)	1.97 (1.10-3.53)
T_3	121/102	2.00 (1.31-3.05)	2.12 (1.25-3.84)	1.80 (0.95-3.42)
P		< 0.001	< 0.001	-
Fiber-containing foods				
T_1	121/102	1.00	1.00	1.00
T_2	75/101	0.60 (0.39-0.92)	0.47 (0.26-0.85)	0.49 (0.25-0.95)
T_3	112/105	0.86 (0.58-1.28)	0.63 (0.36-1.11)	0.65 (0.35-1.21)
P		0.048	< 0.001	-
Nuts				
T_1	118/103	1.00	1.00	1.00
T_2	118/108	0.97 (0.67-1.42)	0.87 (0.53-1.44)	0.70 (0.37-1.31)
T3	72/97	0.67 (0.43-0.97)	0.58 (0.34-1.00)	0.59 (0.30-1.18)
P		0.074	< 0.001	-
Fat				
T_1	86/100	1.00	1.00	1.00
T_2	101/105	1.12 (0.75-1.67)	0.94 (0.56-1.59)	0.83 (0.45-1.51)
T_3	121/100	1.34 (0.92-1.97)	1.46 (0.85-2.50)	1.25 (0.68-2.29)
P		0.297	< 0.001	-
Sweets and added sugar				
T_1	82/120	1.00	1.00	1.00
T_2	120/103	1.47 (0.99-2.20)	1.67 (0.98-2.86)	1.88 (1.01-3.52)
T_3	106/103	1.30 (0.87-1.94)	1.63 (0.92-2.89)	1.39 (0.72-2.67)

P		0.159	< 0.001	-
Alcoholic beverage				
T_1	90/103	1.00	1.00	1.00
T_2	107/101	1.20 (0.81-1.77)	1.05 (0.63-1.75)	1.10 (0.63-1.92)
T_3	111/104	1.19 (0.83-1.72)	0.82 (0.50-1.36)	0.75 (0.42-1.32)
P		0.558	< 0.001	-

[1]Food groups consumption was categorized into tertiles according to the distribution in controls, and by sexes for food groups with significant differences according to sex; Tertiles of food groups: Red and processed meat, T_1 < 47.7, T_2 47.7-78.5, T_3 > 78.5; Total fish, T_1 < 42.8, T_2 42.8-67.2, T_3 > 67.2; eggs, T_1 < 15.7, T_2 15.7-23.5, T_3 > 23.5; Milk/dairy products, T_1 < 72.0, T_2 72.0-232.1, T_3 > 232.1; Fat, T_1 < 30.8, T_2 30.8-34.8, T_3 > 34.8; Nuts, T_1 < 2.9, T_2 2.9-12.8, T_3 > 12.8; Sweets and added sugar, T_1 < 50.1, T_2 50.1-117.3, T_3 > 117.3; Tertiles of food groups for men: Fiber-containing foods, T_1 < 424.3, T_2 424.3-617.8, T_3 > 617.8; Alcoholic beverages, T_1 < 66.7, T_2 66.7-137.2, T_3 > 137.2; Tertiles of food groups for women: Fiber-containing foods, T_1 < 537.9, T_2 537.9-723.6, T_3 > 723.6; T_1 < 8.3; T_2 8.3-85.7; T_3 > 85.7.

[2]Model I, analyses were performed using crude conditional logistic regression, without taking into account confounding factors.

[3]Model II, analyses were performed using conditional logistic regression analysis adjusted for age (50-59 years old, 60-69 years old), sex, body mass index (underweight/normal weight, overweight/obesity), energy intake (kcal/d), physical exercise level (< 15 min/d of cycling/sports, ≥ 15 min/d), smoking status and intensity of smoking (never; past: quit smoking ≥ 11 years ago, quit < 11 years ago; Smoker: ≤ 15 cigarettes/d, > 15 cigarettes/d), Deprivation Index (quintile 1-3,quintile 4-5) and Predictive Risk Modelling (level 1-2, level 3-4), including food groups separately; participants with missing data for the confounding variables were included as a separate category for these variables.

[4]Model III, model II including all the mean food groups. CI: Confidence interval; OR: Odd ratio; T: Tertile.

DISCUSSION

The results from this observational study indicate that high consumption of milk/dairy products, in particular high-fat cheeses, is associated with CRC risk, while a high intake of fiber-containing foods, specially whole grains, and fatty fish was associated with a lower risk for CRC. Moreover, a higher MD adherence in general and particularly a higher score for whole grains have been associated with a reduced CRC risk.

As other authors have previously reported[40] milk/dairy products were the food group with the highest adjusted OR for CRC risk, which is not in agreement with the probable evidence of protection of this food group against CRC[5]. Some cohort studies support the protective effect of total dairy products and milk[41-43]. This effect has been hypothetically associated with calcium, vitamin D, fats and other components such as lactoferrin or lactic bacteria in the case of fermented dairy products milk[41,42]. However, case-control studies published to date are heterogeneous and, on average, do not provide evidence of an association between total intake of total dairy products, milk, cheese or yogurt and CRC risk[41]. Regarding milk/dairy products consumption according to anatomical subsites of cases, the intake was higher in proximal tumor cases and lower in distal cases than in their matched controls. Although according to scientific literature, the effect of this food group seems to be similar across all locations of the bowel[43].

In general, epidemiological studies have not found evidence of either reduction or increase of CRC risk specifically associated with the consumption of cheese[41,42]. Although there are few pieces of research on cheese consumption that reported an inverse association with CRC[44] in the present research, high-fat cheeses are shown to be possible risk factors for CRC development. Some studies showed a positive relationship between fatty foods and CRC incidence[45]. Dairy products, *e.g.*, mature, semi-mature and creamy cheeses, are rich in saturated fat, so this relationship might be due to the content of fat in these products. Several studies have suggested that high-fat consumption increases bile acid discharge. Moreover, an increase in the concentration of bile acids above physiological levels has been reported to promote CRC[46,47]. In any case, the association between milk/dairy products consumption and the risk of developing CRC is complex and some researchers indicated that the fat content contained within dairy products does not influence this association[43].

In line with previous studies[48-50], we also found that the consumption of fiber-containing foods was inversely associated with CRC risk. Specifically, consumption of more than 424.3 g/d in men and 537.9 g/d in women of fiber-containing foods decreased CRC risk by about 50% (OR approximately 0.5) compared to lower consumption, in adjusted models. The preventive effect of dietary fiber can be explained by biological mechanisms that include increasing amounts of feces, decreasing gastrointestinal transit time, diluting intestinal cancer-causing factors,

Table 5 Association between food subgroup intakes and colorectal cancer risk

Food subgroup intakes[1]	No., case/control	Model I[2]	Model II[3]	Model III[4]
		OR (95%CI)	OR (95%CI)	OR (95%CI)
Red meat				
T_1	88/101	1.00	1.00	1.00
T_2	103/98	1.20 (0.81-1.79)	1.38 (0.82-2.34)	1.10 (0.62-1.96)
T_3	117/109	1.22 (0.84-1.78)	1.41 (0.87-2.30)	1.17 (0.67-2.03)
P		0.534	< 0.001	-
Processed meat				
T_1	102/103	1.00	1.00	1.00
T_2	82/99	0.84 (0.57-1.24)	0.62 (0.36-1.07)	0.67 (0.38-1.18)
T_3	124/106	1.21 (0.83-1.77)	1.54 (0.91-2.60)	1.54 (0.88-2.70)
P		0.206	< 0.001	-
White fish				
T_1	95/105	1.00	1.00	1.00
T_2	77/103	0.82 (0.53-1.25)	0.97 (0.56-1.68)	0.96 (0.36-2.53)
T_3	136/105	1.49 (1.01-2.20)	1.06 (0.62-1.79)	1.29 (0.74-2.25)
P		0.008	< 0.001	-
Fatty fish				
T_1	119/110	1.00	1.00	1.00
T_2	105/102	1.05 (0.71-1.55)	0.93 (0.56-1.55)	0.89 (0.43-1.69)
T_3	74/96	0.72 (0.49-1.08)	0.50 (0.29-0.87)	0.53 (0.27-0.99)
P		0.145	< 0.001	-
Fresh cheese				
T_1	150/153	1.00	1.00	1.00
T_2	224/33	0.64 (0.32-1.28)	1.06 (0.44-2.55)	1.11 (0.66-1.87)
T_3	134/122	1.11 (0.80-1.55)	1.10 (0.70-1.72)	0.92 (0.58-1.46)
P		0.272	< 0.001	-
Other cheeses				
T_1	96/116	1.00	1.00	1.00
T_2	71/75	1.16 (0.76-1.77)	1.51 (0.86-2.63)	1.83 (1.15-2.89)
T_3	141/117	1.46 (1.01-2.12)	1.85 (1.12-3.05)	1.87 (1.11-3.16)
P		0.112	< 0.001	-
Fruits				
T_1	109/99	1.00	1.00	1.00
T_2	98/110	0.82 (0.56-1.19)	1.08 (0.63-1.85)	1.03 (0.58-1.83)
T_3	101/99	0.92 (0.62-1.37)	0.70 (0.40-1.22)	0.68 (0.37-1.26)
P		0.567	< 0.001	-
Vegetables				
T_1	97/102	1.00	1.00	1.00
T_2	111/103	1.14 (0.76-1.71)	0.98 (0.55-1.73)	1.10 (0.60-2.04)
T_3	100/103	1.03 (0.68-1.57)	0.94 (0.52-1.70)	1.10 (0.58-2.11)

P		0.789	< 0.001	-
Whole grains				
T_1	144/128	1.00	1.00	1.00
T_2	83/77	0.92 (0.62-1.38)	0.86 (0.52-1.42)	0.98 (0.58-1.65)
T_3	81/103	0.68 (0.46-1.01)	0.62 (0.37-1.06)	0.62 (0.39-0.98)
P		0.135	< 0.001	

[1]Food groups consumption was categorized into tertiles according to the distribution in controls, and by sexes for food groups with significant differences according to sex; Tertiles of food groups: Red meat, T_1 < 33.5, T_2 33.5-54.9, T_3 > 54.9; Processed meat, T_1 < 11.6, T_2 11.6-22.8, T_3 > 22.8; non-cheese dairy, T_1 < 225.0, T_2 225.0-325.0, T_3 > 325.0; Cheese, T_1 < 7.5, T_2 7.5-20.0, T_3 > 20.0; Vegetables, T_1 < 152.9, T_2 152.9-237.2, T_3 > 237.2;Tertiles of food groups for men: Fruits, T_1 < 207.5, T_2 207.5-392.9, T_3 > 392.9; Whole grains, T_1 < 1.0, T_2 1.0-17.5, T_3 > 17.5; Tertiles of food groups for women: Fruits T_1 < 242.9, T_2 242.9-425.0,: Whole grains, T_1 < 2.0, T_2 2.0-30.0, T_3 > 30.0.

[2]Model I, analyses were performed using crude conditional logistic regression, without taking into account confounding factors.

[3]Model II, analyses were performed using conditional logistic regression analysis adjusted for age (50-59 years old, 60-69 years old), sex, body mass index (underweight/normal weight, overweight/obesity), energy intake (kcal/d), physical exercise level (< 15 min/d of cycling/sports, ≥ 15 min/d), smoking status and intensity of smoking (never; past: quit smoking ≥ 11 years ago, quit < 11 years ago; Smoker: ≤ 15 cigarettes/d, > 15 cigarettes/d), Deprivation Index (quintile 1-3, quintile 4-5) and Predictive Risk Modelling (level 1-2, level 3-4), including food groups separately; Participants with missing data for the confounding variables were included as a separate category for these variables.

[4]Model III, model II including all the mean food groups. CI: Confidence interval; OR: Odd ratio; T: Tertile.

interfering absorption of those, and lowering intestinal acidity[51]. In addition, fermentation of fiber produced butyrate. This short-chain fatty acid showed anti-inflammatory, anti-proliferation and antineoplastic properties in colonocyte cells metabolism through microbiota homeostasis and genetic/epigenetic regulation[52].

Furthermore, our findings suggest that high consumption of whole grains (higher than 17.5 g/d in men and 30.0 g/d in women) may decrease the risk of CRC, after controlling confounding factors. There is convincing evidence that whole grains help to reduce CRC risk[5,53]. The observed reduction in CRC risk associated with high consumption of whole grains may partly be attributed to dietary fiber, resistant starch, and oligosaccharides that can influence the gut environment. Insoluble fiber increases the bulk of luminal contents, diluting potential carcinogens and promoters in the colon and decreasing transit time, and, consequently, reduces the exposure of the colonic epithelium to harmful compounds[54,55]. Additionally, other components such as vitamins (especially B-vitamins), minerals (*e.g.*, magnesium and zinc), phenolic compounds, antinutrients (*e.g.*, tannins), and phytoestrogens may also contribute to this protection[54].

On the other hand, the consumption of fatty fish (higher than 42.8 g/d) was associated with a decreased risk in CRC by about 50% (OR approximately 0.5) compared to lower consumption, after adjusting models for covariates. It should be noted that the Basque Country population has a higher consumption of total fish and fatty fish compared to other Spanish autonomous communities[55,56]. Recent cohort studies have observed that fatty fish was inversely associated with CRC incidence[57,58] and they have related this association with exposure to long-chain n-3 polyunsaturated fatty acids[57]. Evidence from animal and *in vitro* studies indicates that n-3 fatty acids present in fatty fish may inhibit carcinogenesis[59]. High intake of n-3 fatty acids suppresses the production of arachidonic acid-derived eicosanoids such as prostaglandin E2 and leukotriene B431. N-3 fatty acids could also suppress the expression of inducible nitric oxide synthase and nuclear transcription factor κ B (NF-κ B)[60].

In relation to the diet quality, our findings on the MDS and CRC risk are supported by those of other researchers[13,61-63], who found significant associations between lower risk of CRC and adherence to Mediterranean dietary pattern. However the HEISD was not associated with CRC risk, discrepancies in results obtained with the two dietary quality indices analysed are probably due to differences in their constructs and scoring criteria. The overall MDS was inversely associated with CRC risk, being higher the total score in cases with the proximal location of cancer than for those with the distal location. These last results contrast with previous findings, which showed that the protective effects of adherence to the MD were mainly for distal colon and rectal cancer and not for proximal colon cancer[64]. In the total sample, investigation of the separate score components showed that whole grain score was lower for cases than for controls. This result is consistent with that obtained for the association between whole grains consumption and CRC risk.

Table 6 Diet quality indices in the sample studied

	Cases (*n* = 308)		Controls (*n* = 308)		*P* value
	mean	SD	mean	SD	
HEISD components[1]					
Meats	3.1	1.7	3.1	1.7	0.811
Processed meats	2.8	2.0	3.1	2.2	0.162
Legumes	8.6	2.1	8.5	2.3	0.716
Milk/Dairy	9.8	1.2	9.8	1.1	0.797
Fruits	9.1	1.8	9.1	1.9	0.464
Vegetables	8.9	1.7	8.9	1.6	0.816
Grains	9.9	0.9	9.9	1.9	0.862
Sweets	1.6	3.1	1.6	3.0	0.847
Soft-drink	8.8	2.5	8.7	2.6	0.583
Variety	8.0	1.7	8.0	1.7	0.646
Total HEISD	70.7	7.2	70.8	7.9	0.906
MDS components[2]					
Red meats and processed meats	0.7	1.0	0.8	1.2	0.134
Poultry	2.9	1.2	2.9	1.2	0.335
Fish	3.8	1.1	3.8	1.2	0.771
Legumes	2.4	1.2	2.3	1.1	0.482
Full fat dairy	2.0	1.8	2.0	1.9	0.618
Vegetables	4.9	0.6	4.9	0.5	0.599
Fruits	4.6	1.0	4.6	1.0	0.726
Potatoes	2.2	1.5	2.4	1.5	0.054
Whole grains	2.0	2.2	2.3	2.3	0.044
Alcoholic beverages	4.9	0.4	4.9	0.4	0.729
Olive oil	4.9	0.6	4.8	0.8	0.446
Total MDS	35.3	4.5	36.0	4.3	0.027

[1]Each component can contribute 10 points to the total score and the theoretical range is 0–100.
[2]Each component can contribute five points to the total score and the theoretical range is 0–55. HEISD: Healthy Eating Index for Spanish Diet; MDS: Med Diet Score; SD: Standard deviation.

Our study has several limitations. First, recall bias inherent in a case-control study design cannot be ruled out. The primary concern of this study is the low participation rate, which may have limited the representativeness of study samples. The decision to participate or not may be influenced by several factors, including social, educational and health conditions, which may again correlate with outcome risk factors. Second, self-reported data could be subject to measurement errors and the problem of food omissions due to memory failure and underreporting of unhealthy habits among disease subjects. However, previous validation studies indicate that the self-reported dietary information is reported with sufficient accuracy for use in epidemiology analyses[65]; and it should be noted that dietary changes are usually modest after participating in the CRCSP due to a lack of information and personalized advice[66,67]. Another limitation of this type of study could be the selection of controls (selection bias). To avoid this type of bias, we obtained controls from the same CRCSP and in the same period as cases, thus, it was confirmed that they did not suffer from CRC by colonoscopy.

Despite these limitations, the results allow us to conclude that high consumption of high-fat cheeses is associated with CRC risk, whereas, a high intake of fiber-containing

foods, especially whole grains, and fatty fish, and adherence to the Mediterranean dietary pattern was associated with a lower risk for CRC. Future studies are needed to better understand the influence of the dietary habits on CRC prevention in this population that can provide leads for the design and tailoring of future interventions, and guide counselling strategies for promoting a healthy lifestyle.

ARTICLE HIGHLIGHTS

Research background

Epidemiological evidence suggests that some foods may both protect against and promote the development of colorectal cancer (CRC). However, foods are not consumed in isolation but as part of a dietary pattern; therefore, the actual effect of diet on disease risk may be observed only when all components are considered jointly. For this purpose, several diet quality indexes have been developed using point systems to measure whole diet quality based on the alignment of food choices with dietary recommendations.

Research motivation

Some diet quality indexes have been used to begin assessing the relationships between overall diet quality and CRC risk, and the results show that high scores in these indices are associated with a lower CRC risk. However, the results vary considerably according to the index used and other factors such as sex and age. Therefore, there is a need to further examine these relationships in diverse population studies.

Research objectives

To study the relationships between food groups, diet quality and CRC risk, in an adult population of the Basque Country (North of Spain).

Research methods

This observational study included 308 patients diagnosed with CRC and 308 age- and sex-matched subjects as controls. During recruitment, dietary, anthropometric, lifestyle, socioeconomic, demographic and health status information was collected. Dietary intake was assessed using a short food frequency questionnaire that was adapted and validated for this population. Adherence to the dietary recommendations was evaluated utilizing the Healthy Eating Index for the Spanish Diet and the MedDietScore. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, United States) and STATA 13.0 (StataCorp LP, TX, United States). Conditional logistic regressions were used to evaluate the associations of food group intakes, diet quality scores, categorized in tertiles, with CRC risk.

Research results

The adjusted models for potential confounding factors showed a direct association between milk/dairy products consumption, in particular high-fat cheeses [odds ratio (OR) third tertile *vs* first tertile = 1.87, 95% confidence intervals (CI): 1.11-3.16], and CRC risk. While the consumption of fiber-containing foods, especially whole grains (OR third tertile *vs* first tertile = 0.62, 95%CI: 0.39-0.98), and fatty fish (OR = 0.53, 95%CI: 0.27-0.99) was associated with a lower risk for CRC. Moreover, higher MD adherence was associated with a reduced CRC risk in adjusted models (OR = 0.40, 95%CI: 0.20-0.80).

Research conclusions

Direct associations were found for high-fat cheese, whereas an inverse relation was reported for fiber-containing foods and fatty fish, as well as adherence to a Mediterranean dietary pattern.

Research perspectives

Future studies are needed to better understand the influence of the dietary habits on CRC prevention in this population that can provide leads for the design and tailoring of future interventions, and guide counselling strategies for promoting a healthy lifestyle.

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