SHORT COMMUNICATION

BJC

British Journal of Cancer (2016) 115, 862–865 | doi: 10.1038/bjc.2016.245

Keywords: Mediterranean diet; epidemiology; dietary patterns; colon cancer; rectal cancer; diet; risk

Mediterranean diet and colorectal cancer risk: a pooled analysis of three Italian case–control studies

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Background: Adherence to the Mediterranean diet (MD) is associated with a reduced risk of several cancers. However, studies conducted in Mediterranean regions are scanty.

Methods: To investigate the relation between MD and colorectal cancer risk in Italy, we pooled data from three case–control studies, including a total of 3745 colorectal cancer cases and 6804 hospital controls. Adherence to the MD was assessed using an *a priori* Mediterranean Diet Score (MDS), based on nine components.

Results: Compared with the lowest adherence to the MD (0–2 MDS), the odds ratio (OR) was 0.52 (95% confidence interval (CI) 0.43–0.62) for the highest adherence (7–9 MDS), with a significant inverse trend in risk ($P<0.0001$). The OR for a 1-point increment in the MDS was 0.89 (95% CI 0.86–0.91). The inverse association was consistent across studies, cancer anatomical subsites and strata of selected covariates.

Conclusions: This Italian study confirms a favourable role of MD on colorectal cancer risk.

The role of single foods and nutrients in colorectal carcinogenesis is well documented (World Cancer Research Fund and American Institute for Cancer Research, 2012). However, as dietary components are interrelated and may act synergistically, it may be more informative to investigate the relation of colorectal cancer with dietary patterns.

The Mediterranean diet (MD) is characterised by a frequent consumption of vegetables, legumes, fruit and nuts, cereals, fish, and olive oil as the main seasoning fat; a modest intake of wine, generally during meals; a low-to-moderate consumption of dairy products; and a low consumption of meat (Trichopoulou *et al*, 2000). In terms of nutrients, MD is rich in fibres, antioxidants, folates, flavonoids, and monounsaturated fats (oleic acid), with anticarcinogenic activity (La Vecchia *et al*, 1997; Rossi *et al*, 2010; Praud *et al*, 2014; Rotelli *et al*, 2015).

A high adherence to the MD has been associated with a reduced risk of several cancers, including those of the digestive system (Bosetti *et al*, 2013; Filomeno *et al*, 2014; Praud *et al*, 2014; Schwingshackl and Hoffmann, 2014). A meta-analysis of five cohort and two case–control studies reported a statistically significant 14% reduction of colorectal cancer risk, similar for cohort and case–control studies (Schwingshackl and Hoffmann, 2014). However, only three studies were conducted in countries with typical MD: a Greek (Kontou *et al*, 2012) and an Italian

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Received 17 May 2016; revised 11 July 2016; accepted 18 July 2016; published online 18 August 2016

(Grosso *et al*, 2014) case–control studies and an Italian cohort study (Agnoli *et al*, 2013), part of the European Prospective Investigation into Cancer and Nutrition (Bamia *et al*, 2013).

Thus we assessed the relation between the MD and colorectal cancer risk in Italy.

MATERIALS AND METHODS

Study population. We pooled data from three hospital-based case–control studies on colorectal cancer, including a total of 3745 incident, histologically confirmed colorectal cancer cases and 6804 controls. The oldest study, conducted in 1985–91 in Milan, included 1326 cases (median age 62, range 20–74 years) and 2081 controls (median age 55, range 19–74 years) (La Vecchia *et al*, 1988); the second study, conducted in 1992–96 in Milan, Genoa, Pordenone, Gorizia, Forlì, Latina, and Naples, included 1953 cases (median age 62, range 19–74 years) and 4154 controls (median age 58, range 19–74 years) (Franceschi *et al*, 1997); the third study, conducted in 2008–10 in Milan, Pordenone, and Udine, included 466 cases (median age 67, range 35–80 years) and 569 controls (median age 66, range 31–80 years). Overall, 488 cases were cancers of the proximal colon (appendix, caecum, ascending colon, hepatic flexure, transverse colon), 1078 of the distal colon (splenic flexure, descending, sigmoid colon), 788 of overlapping or not otherwise specified colon, 1383 of rectum (rectum and rectosigmoid junction), and 8 of not otherwise specified colorectum. Controls were subjects who had not recently changed their diet and had been admitted to the same hospitals as cases for a wide spectrum of acute, non-neoplastic conditions unrelated to known colorectal cancer risk factors (28% traumas, 24% other orthopedic disorders, 23% surgical conditions, 12% eye diseases, 12% other illnesses).

Patients were interviewed in hospital by trained interviewers, using structured questionnaires collecting information on sociodemographic factors, lifestyle habits (including smoking and alcohol drinking), anthropometric measures, physical activity, medical history, and family history of cancer. Information on patients' usual diet in the 2 years before diagnosis/interview was assessed through food frequency questionnaires, collecting information on weekly consumption of 29 foods in the first study (D'Avanzo *et al*, 1997), and 78 or 56 foods, respectively, in the other two studies, (Franceschi *et al*, 1993). Occasional intake (1–3 times per month) was coded as 0.5 per week. The questionnaire of the first study was tested for reproducibility (D'Avanzo *et al*, 1997), and those of the other two studies for reproducibility (Franceschi *et al*, 1993; Franceschi *et al*, 1995; Pearson's correlation coefficients for most foods 60–80%) and validity (Decarli *et al*, 1996; subjects correctly classified within one quintile of nutrients were 73%). Intake of nutrients and total energy were computed using Italian food composition databases (Gnagnarella *et al*, 2004).

The study protocols were approved by the ethical boards, and all participants signed an informed consent. Refusal to participate was $<5\%$ for either cases or controls.

Supplementary Table S1 gives the distribution of cases and controls according to main characteristics.

Mediterranean Diet Score (MDS). Adherence to the traditional MD was assessed through an *a priori* defined score (Trichopoulou *et al*, 2003), based on nine dietary components. For components frequently consumed in the MD (vegetables, legumes, fruit/nuts, cereals, fish/seafood, and a high monounsaturated to saturated fat ratio), participants with consumption above or equal to the study- and sex-specific median value among controls were assigned a value of 1 and 0 otherwise. For components less frequently consumed in the MD (dairy and meat/meat products), participants with consumption above or equal to the median value were assigned a value of 0 and 1 otherwise. For alcohol, a value of 1 was assigned to moderate drinkers (drinking below the study- and sex-specific median intake) and a value of 0 to non-drinkers and drinkers with an intake above the median values. Supplementary Table S2 shows the study- and sex-specific median values of each component of the MD among controls. The MDS was calculated for each subject by adding up the points for each of the nine components and ranged between 0 (lowest adherence) and 9 (highest adherence).

Statistical analysis. Odds ratios (ORs) of colorectal cancer and the corresponding 95% confidence intervals (CIs) were estimated through unconditional logistic regression models, including categorical terms for age, sex, calendar period, centre, education, body mass index, occupational physical activity, family history of intestinal cancer, and study-specific total energy intake. Further adjustment for smoking did not change ORs. The few missing values for adjusting covariates were imputed as median values, but the risk estimates did not change when missing values were considered as indicators or when we restricted the analyses to the individuals with complete data only. Tests for linear trend were based on the likelihood-ratio test between the models with and without a linear term for the score.

RESULTS

High *vs* low consumption of vegetables (OR 0.69, 95% CI 0.63–0.75), legumes (OR 0.69, 95% CI 0.64–0.76), fruit and nuts (OR 0.79, 95% CI 0.73–0.87), fish (OR 0.78, 95% CI 0.71–0.85), monounsaturated to saturated fatty acid ratio (OR 0.87, 95% CI 0.80–0.95), and low *vs* high consumption of meat (OR 0.86, 95% CI 0.79–0.94) were associated with a significantly reduced risk of colorectal cancer. Alcohol intake was not related (OR 1.06, 95% CI 0.96–1.18), and high *vs* low intake of cereals/potatoes (OR 1.12, 95% CI 1.02–1.24) and low *vs* high intake of milk/dairy products (OR 1.09, 95% CI 1.00–1.19) significantly increased colorectal cancer risk (Table 1).

Table 1. Odds ratios (ORs) and 95% confidence intervals (CIs) of colorectal cancer among 3745 cases and 6804 controls according to single components of the Mediterranean Diet Score (MDS): Italy, 1985–2010

Components of the MDS	Comparison level[a]	OR[b] (95% CI)
Vegetables	High *vs* low	0.69 (0.63–0.75)
Legumes	High *vs* low	0.69 (0.64–0.76)
Fruit and nuts	High *vs* low	0.79 (0.73–0.87)
Cereals and potatoes	High *vs* low	1.12 (1.02–1.24)
Fish	High *vs* low	0.78 (0.71–0.85)
Monounsaturated to saturated fatty acid ratio	High *vs* low	0.87 (0.80–0.95)
Alcohol	Moderate *vs* high/non-drinking	1.06 (0.96–1.18)
Meat and meat products	Low *vs* high	0.86 (0.79–0.94)
Milk and dairy products	Low *vs* high	1.09 (1.00–1.19)

[a]High: consumption above or equal to the study- and sex-specific median value; low: consumption below the study- and sex-specific median value; moderate: consumption higher than zero but below or equal to the study- and sex-specific median value.
[b]Estimated from logistic regression models adjusted for age, sex, calendar period, centre, education, body mass index, occupational physical activity, family history of intestinal cancer, and total energy intake.

Compared with a 0–2 MDS (lowest adherence), the OR was 0.52 (95% CI 0.43–0.62) for a 7–9 MDS (highest adherence), with a significant strong inverse trend in risk (Table 2). The OR for a 1-point increment in the MDS was 0.89 (95% CI 0.86–0.91). The corresponding ORs excluding in turn each of the nine components (sensitivity analysis) ranged from 0.87 (95% CI 0.84–0.89) to 0.92 (95% CI 0.89–0.94).

The inverse relation was consistent across strata of age, sex, education, body mass index, physical activity, energy intake, and history of intestinal cancer in first-degree relatives (Supplementary Table S3).

The OR for a 1-point increment in the MSD was 0.90 (95% CI 0.85–0.96) for proximal colon, 0.88 (95% CI 0.84–0.92) for distal colon, 0.85 (95% CI 0.81–0.89) for overlapping and undefined colon, and 0.90 (95% CI 0.86–0.93) for rectal cancer (Table 3).

DISCUSSION

Combining the three Italian studies, the highest adherence to the MD compared with the lowest reduced colorectal cancer risk by about 50%, consistent across the large bowel. We found a stronger inverse association between MD and colorectal cancer than that reported in a Greek case–control study (OR 0.88; Kontou *et al*, 2012) but similar to that found in an Italian case–control study (OR 0.46; Grosso *et al*, 2014) and an Italian cohort study (hazard ratio 0.50; Agnoli *et al*, 2013) and stronger than that found in a meta-analysis (pooled relative risk of 0.86; Schwingshackl and Hoffmann, 2014). However, comparison between studies is difficult because of the differences of dietary habits between various countries, the use of different components and cut points

Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs) of colorectal cancer among 3745 cases and 6804 controls according to the Mediterranean Diet Score (MDS): Italy, 1985–2010

	Cases		Controls		
No. of MDS components	No.[a]	%	No.[a]	%	OR[b] (95% CI)
0–2	529	14.1	736	10.8	1[c]
3	662	17.7	1112	16.4	0.79 (0.68–0.92)
4	910	24.3	1551	22.8	0.76 (0.65–0.87)
5	792	21.2	1573	23.2	0.63 (0.54–0.73)
6	528	14.1	1103	16.2	0.58 (0.49–0.68)
7–9	318	8.5	717	10.6	0.52 (0.43–0.62)
P-value for trend					<0.0001
1-point increment					0.89 (0.86–0.91)

[a]The sum does not add up to the total because of 18 missing values (6 cases and 12 controls) on a few MDS components (i.e., monounsaturated to saturated fatty acid ratio, alcohol, and legumes).
[b]Estimated from logistic regression models adjusted for age, sex, calendar period, centre, education, body mass index, occupational physical activity, family history of intestinal cancer, and total energy intake.
[c]Reference category.

Table 3. Distribution of subsite-specific colorectal cancer cases and of controls and corresponding odds ratios (ORs) and 95% confidence intervals (CIs), according to the Mediterranean Diet Score (MDS): Italy, 1985–2010

	Controls	Colon cancer (overall)		Proximal colon cancer[a]		Distal colon cancer[a]		Overlapping and undefined colon cancer[a]		Rectal cancer[a]	
No. of MDS components	No.[b]	No.[b]	OR[c] (95% CI)	No.[b]	OR[c] (95% CI)	No.[b]	OR[c] (95% CI)	No.[b]	OR[c] (95% CI)	No.[b]	OR[c] (95% CI)
Overall	6804	2354		488		1078		788		1383	
0–2	736	351	1[d]	79	1[d]	145	1[d]	127	1[d]	177	1[d]
3	1112	397	0.71 (0.59–0.85)	70	0.55 (0.39–0.78)	197	0.85 (0.67–1.08)	130	0.62 (0.47–0.82)	265	0.94 (0.76–1.17)
4	1551	587	0.73 (0.61–0.86)	113	0.63 (0.46–0.86)	276	0.84 (0.67–1.05)	198	0.64 (0.50–0.83)	320	0.81 (0.65–0.99)
5	1573	485	0.57 (0.48–0.67)	107	0.56 (0.41–0.77)	215	0.60 (0.48–0.77)	163	0.50 (0.39–0.65)	305	0.73 (0.59–0.91)
6	1103	328	0.53 (0.44–0.64)	75	0.54 (0.38–0.76)	148	0.58 (0.45–0.75)	105	0.45 (0.33–0.60)	199	0.67 (0.53–0.85)
7–9	717	202	0.49 (0.39–0.60)	43	0.48 (0.32–0.73)	95	0.55 (0.41–0.74)	64	0.39 (0.28–0.54)	115	0.58 (0.44–0.75)
P-value for trend			<0.0001		0.001		<0.0001		<0.0001		<0.0001
1-point increment			0.88 (0.85–0.91)		0.90 (0.85–0.96)		0.88 (0.84–0.92)		0.85 (0.81–0.89)		0.90 (0.86–0.93)

[a]Proximal colon (International Classification of Diseases, vol. 10, ICD-10, C18.0–C18.4), distal colon (ICD-10, C18.5–C18.7), overlapping and undefined colon (ICD-10, C18.8–C18.9) and rectal (ICD-10, C19.9–C20.9) cancer.
[b]The sum does not add up to the total because of some missing values on a few MDS components (i.e. monounsaturated to saturated fatty acid ratio, alcohol, and legumes).
[c]Estimated from logistic regression models adjusted for age, sex, calendar period, centre, education, body mass index, occupational physical activity, family history of intestinal cancer, and total energy intake.
[d]Reference category.

in the MD definition, and the different prevalence of adherence to the MD. The MDS is based on the median consumption among the control group within the study population, and not in absolute terms, and subjects with a higher MDS in this Italian population are likely to have a higher absolute consumption of foods that are typical of the MD.

Limitations of this study include pooling results from studies with different food frequency questionnaire and possible selection and information bias. However, cases and controls were interviewed in the same hospital setting, had similar very high participation rate, and were from comparable catchment area. We excluded from the controls patients admitted for conditions related to known risk factors for colorectal cancer and those with long-term dietary modifications. The strengths of the study include the use of food frequency questionnaires with satisfactory reproducibility (D'Avanzo *et al*, 1997; Franceschi *et al*, 1997) and validity (Decarli *et al*, 1996). Our estimates were adjusted for major confounding variables, and the consistency of the associations across strata of major covariates rules out a major role of residual confounding. Another strength of our study is the large sample size, based on >3700 cases, and the study population with an overall high adherence to MD, allowing for the investigation of high absolute amounts of foods typical of this diet.

Thus this large study conducted in a Mediterranean region confirms a favourable role of MD on colorectal cancer risk.

ACKNOWLEDGEMENTS

We thank Professor Norman Temple for style editing of the manuscript. This work was funded by the Italian Foundation for Cancer Research (FIRC) and the Italian Ministry of Health, General Directorate of European and International Relations. VR was supported by a fellowship from the Italian Foundation for Cancer Research (FIRC no. 18107).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)