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Inflammatory potential of diet and risk of colorectal cancer: a case–control study from Italy

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Abstract

Diet and inflammation have been suggested to be important risk factors for colorectal cancer (CRC). In the present study, we examined the association between the dietary inflammatory index (DII) and the risk of CRC in a multi-centre case–control study conducted between 1992 and 1996 in Italy. The study included 1225 incident colon cancer cases, 728 incident rectal cancer cases and 4154 controls hospitalised for acute non-neoplastic diseases. The DII was computed based on dietary intake assessed using a validated seventy-eight-item FFQ that included assessment of alcohol intake. Logistic regression models were used to estimate the OR adjusted for age, sex, study centre, education, BMI, alcohol drinking, physical activity and family history of CRC. Energy intake was adjusted using the residual method. Subjects with higher DII scores (i.e. with a more pro-inflammatory diet) had a higher risk of CRC, with the DII being used both as a continuous variable ($OR_{continuous}$ 1·13, 95 % CI 1·09, 1·18) and as a categorical variable ($OR_{quintile\ 5\ v.\ 1}$ 1·55, 95 % CI 1·29, 1·85; P for trend $<0·0001$). Similar results were observed when the analyses were carried out separately for colon and rectal cancer cases. These results indicate that a pro-inflammatory diet is associated with an increased risk of CRC.

Key words: **Diet: Inflammation: Colorectal cancer: Italy**

Colorectal cancer (CRC) is the second most common cancer both among Italian men (after prostate cancer), with an age-standardised incidence rate of 84·1 cases per 100 000 per year in 2006–9, and among women (after breast cancer), with a rate of 52·1 cases per 100 000 per year[1]. It also is the second most common cause of cancer death after lung cancer in both men and women[2].

Inflammation is the body's reaction to any kind of tissue injury or insult, and it is the direct response to inflammatory stimulants such as cytokines[3,4]. Chronic inflammation, which is characterised by the continuous presence of inflammatory cytokines in the circulation and in the tissues, is known to play a key role in the development of various epithelial cancers, with the strongest association evident in CRC[5–7].

There is growing evidence that specific dietary components influence both inflammation[8–11] and CRC[11–13]. Research on the role of diet in inflammation has suggested that diet represents a complicated set of exposures that often interact, and whose cumulative effect modifies both inflammatory responses and health outcomes. The literature-derived, population-based dietary inflammatory index (DII) was developed to assess the inflammatory potential of an individual's diet[14]. It has been validated with various inflammatory markers, including C-reactive protein[15,16], IL-6[17,18] and homocysteine[17]. Additionally, the DII has been shown to be associated with the glucose intolerance and dyslipidaemic components of the metabolic syndrome[16,19]; shift work status in a large population-based survey in the USA[20]; bone mineral density among postmenopausal women in Iran[21]; asthma in Australia[18]; CRC in a case–control study in Spain[22] and in cohort studies of women in the USA[23,24]; and pancreatic and prostate cancers in Italy[25,26].

Our hypothesis is that a higher DII score (indicating a pro-inflammatory diet) increases the risk of CRC incidence.

Abbreviations: CRC, colorectal cancer; DII, dietary inflammatory index.

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Therefore, in the present study, we examined the association between the DII and the risk of CRC using a large multi-centre case–control study conducted in Italy[27]. This provided original information on the association between the DII and the risk of CRC in a southern European population, which may differ from North America and Spain where other DII and CRC investigations have been conducted, due to differences in dietary and lifestyle habits and awareness of diet-related health issues[22–24].

Methods

A case–control study of CRC was conducted between January 1992 and June 1996 in six Italian regions: provinces of Pordenone and Gorizia in north-eastern Italy; urban areas of Milan and Genoa; provinces of Forlì in the North; Latina and the urban area of Naples in the Centre South[27]. Cases were subjects with histologically confirmed CRC diagnosed no longer than 1 year before the interview and with no previous diagnoses of cancer at other sites. Overall, 1225 subjects with colon cancer (688 men and 537 women, median age 62 years, range 19–74 years) and 728 subjects with rectal and recto-sigmoid junction cancers (437 men and 291 women, median age 62 years, range 23–74 years) were included (Table 1). Controls were patients with no history of cancer, admitted to major teaching and general hospitals in the same catchment areas as cases for acute non-neoplastic conditions unrelated to hormonal or digestive tract diseases or to long-term modifications of diet. They included 2073 men and 2081 women aged 19–74 years (median age 58 years), belonging to the following diagnostic categories: traumas, mostly fractures and sprains (27%); other orthopaedic disorders, such as low back pain and disc disorders (24%); acute surgical conditions (18%); eye diseases (24%); other miscellaneous diseases, such as ear, nose, throat, skin and dental conditions (7%). The same structured questionnaire and coding manual were used in each centre, and all interviewers were centrally trained and routinely supervised. The present study was approved by the appropriate ethics committee, and performed in accordance with the ethical standards laid down in the guidelines of the 1964 Declaration of Helsinki.

The questionnaire included information on sociodemographic characteristics, such as education and occupation, lifetime smoking and alcohol-drinking habits, physical activity, anthropometric measures at various ages, a problem-oriented personal medical history, and family history of cancer. A reproducible[28] and validated[29] FFQ was used to assess the patient's usual diet in the 2 years preceding cancer diagnosis (for cases) or hospital admission (for controls). The FFQ included the average weekly consumption of seventy-eight food items or food groups and of five alcoholic beverages. Intakes lower than once per week, but at least once per month, were coded as 0·5 per week.

FFQ-derived dietary data were used to calculate DII scores for each study subject. A complete description of the DII is available elsewhere[14]. Briefly, to calculate the DII for the subjects in the present study, the dietary data were first linked to a world database that provided a robust estimate of the mean and standard deviation for each food parameter included in the DII. These parameters then became the multipliers to express a subject's exposure relative to the

Table 1. Characteristics of 4154 controls across quintiles of the energy-adjusted dietary inflammatory index (DII) in Italy during 1992–6
(Mean values and standard deviations; number of subjects and percentages)

	DII quintiles*										
	≤ −1·05		−1·04 to −0·33		−0·32 to 0·38		0·39 to 1·22		>1·22		
Characteristics	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*P*
Age (years)											0·05
Mean	56·8		56·1		56·6		56·5		55·5		
SD	10·5		10·7		11·2		11·3		12·5		
Sex											<0·0001
Male	371	42·3	473	54·1	416	50·3	432	54·3	381	48·8	
Female	505	57·7	402	45·9	411	49·7	363	45·7	400	51·2	
BMI (kg/m^2)											0·05
<25	397	45·3	370	42·3	379	45·8	390	49·1	371	47·5	
25–30	347	39·6	387	44·2	319	38·6	314	39·5	300	38·4	
>30	132	15·1	118	13·5	129	15·6	91	11·4	110	14·1	
Education (years)											0·12
<7	465	53·1	469	53·6	489	59·1	464	58·4	418	53·5	
7–11	260	29·7	253	28·9	207	25·0	214	26·9	222	28·4	
≥12	151	17·2	153	17·5	131	15·8	117	14·7	141	18·1	
Physical activity (at the workplace)											0·0002
Low	266	30·4	288	32·9	263	31·8	253	31·8	301	38·5	
Medium	382	43·6	335	38·3	297	35·9	299	37·6	254	32·5	
High	228	26·0	252	28·8	267	32·3	243	30·6	226	28·9	
Alcohol consumption											<0·0001
No	193	22·03	166	18·97	179	21·64	160	20·13	219	28·04	
Yes	605	69·06	657	75·09	600	72·55	599	75·35	521	66·71	
In the past	78	8·90	52	5·94	48	5·80	36	4·53	41	5·25	

* ANOVA and χ^2 tests were used for continuous and categorical variables, respectively.

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'standard global mean' as a *z*-score. This was achieved by subtracting the 'standard global mean' from the amount reported and dividing this value by the standard deviation. To minimise the effect of 'right skewing', this value was then converted to a centred percentile score. The centred percentile score for each food parameter for each subject was then multiplied by the respective food parameter effect score in order to obtain a food parameter-specific DII score. All of the food parameter-specific DII scores were then summed up to create the overall DII score for each study subject. Data were available for thirty-one of the forty-five food parameters included in the development of the DII score, i.e. carbohydrate, protein, fat, alcohol, fibre, cholesterol, SFA, MUFA, PUFA, *n*-3, *n*-6, niacin, thiamin, riboflavin, vitamin B_6, Fe, Zn, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, β-carotene, anthocyanidins, flavan-3-ol, flavonol, flavonones, flavones, isoflavones, caffeine and tea. Previously, we showed that DII scores can range from a maximally pro-inflammatory value of +7·98 to a maximally anti-inflammatory value of −8·87[14].

Height and weight were self-reported. BMI was calculated as weight (kg) divided by height (m) squared, and categorised into normal weight (BMI $<25{\cdot}0\,kg/m^2$), overweight ($25{\cdot}0\,kg/m^2 <$ BMI $< 30{\cdot}0\,kg/m^2$) and obese (BMI $\geq 30{\cdot}0\,kg/m^2$). The DII was analysed both as a continuous variable (i.e. for a one-unit increment in the DII corresponds to approximately 7 % of its global range) and by quintiles of exposure, determined on the basis of the entire study population. The DII was also examined across the strata of selected factors such as age, education, BMI and physical activity for the controls and cases separately using the ANOVA test for continuous variables or the χ^2 test for categorical variables. The OR and the corresponding 95 % CI were estimated using logistic regression models, adjusting only for age, and then additionally for sex, study centre (Pordenone/Gorizia, Milan, Genoa, Forlì, Naples and Latina), education (<7, 7–11 and ≥12 years), BMI (<25·0, 25·0–29·9 and $\geq 30{\cdot}0\,kg/m^2$), alcohol drinking (0, 1–21 and >21 drinks/week) and history of CRC (yes/no). Energy intake was adjusted using the residual method[30]. Linear tests for trend were performed using the median value within each quintile as an ordinal variable. Analyses were carried out for CRC and by major subtypes (colon and rectal cancer). Stratified analyses were carried out by sex. Sensitivity analyses were also performed, in which we adjusted risk estimates for smoking and diabetes. Effect modification by age, BMI and physical activity on the association between the DII and CRC was examined. None of these variables interacted with the DII to exert an effect on CRC, and thus the results are not shown. Statistical analyses were performed using SAS® 9·3 (SAS Institute, Inc.).

Results

The DII score in the present study ranged from a maximally pro-inflammatory score of +4·89 to a maximally anti-inflammatory score of −5·40 with a standard deviation of 1·84. Among the cases, the mean DII value was 0·14 (SD 1·39) and among the controls, it was −0·06 (SD 1·38), indicating a more pro-inflammatory diet for the cases. The characteristics of the controls and cases across the quintiles

Table 2. Characteristics of 1953 cases across quintiles of the energy-adjusted dietary inflammatory index (DII) in Italy during 1992–6 (Mean values and standard deviations; number of subjects and percentages)

	DII quintiles*										
	≤ −1·05		−1·04 to −0·33		−0·32 to 0·38		0·39 to 1·22		>1·22		
Characteristics	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*P*
Age (years)											0·03
Mean	61·9		59·4		60·4		60·4		59·8		
SD	8·5		10·1		9·9		10·0		10·0		
Sex											<0·0001
Male	164	47·5	192	55·3	231	58·5	261	61·3	277	62·9	
Female	181	52·5	155	44·7	164	41·5	165	38·7	163	37·0	
BMI (kg/m^2)											0·71
<25	152	44·1	160	46·1	169	42·8	192	45·1	217	49·3	
25–30	145	42·0	142	40·9	165	41·8	176	41·3	173	39·3	
>30	48	13·9	45	13·0	61	15·4	58	13·6	50	11·4	
Education (years)											0·15
<7	193	55·9	172	49·6	194	49·1	245	57·5	248	56·4	
7–11	79	22·9	100	28·8	115	29·1	104	24·1	114	25·9	
≥12	73	21·2	75	21·6	86	21·8	77	18·1	78	17·7	
Physical activity (at the workplace)											0·49
Low	112	32·5	132	38·0	146	37·1	148	34·7	168	38·2	
Medium	139	40·3	127	36·6	129	32·7	146	34·3	143	32·6	
High	94	27·2	88	25·4	119	30·2	132	31·0	128	29·2	
Alcohol consumption											0·21
No	66	19·1	48	13·8	58	14·7	75	17·6	80	18·2	
Yes	248	71·9	276	79·5	316	80·0	324	76·1	328	74·7	
In the past	31	9·0	23	6·6	21	5·3	27	6·3	31	7·1	

* ANOVA and χ^2 tests were used for continuous and categorical variables, respectively.

of the DII are provided in Tables 1 and 2. There were some significant differences in sociodemographic, anthropometric and lifestyle habits across the quintiles of the DII. Among the controls, subjects in the highest quintile (Q5) were slightly younger and more likely to be male, to have a BMI $<25\,kg/m^2$, to report a low physical activity, and to be less-frequent alcohol drinkers compared with those in the lowest quintile (Q1) (Table 1). Among the cases, subjects in Q5 were younger and more likely to be male compared with those in Q1 (Table 2).

The OR and 95 % CI for CRC according to the quintiles of the DII and as continuous measures of the DII are provided in Table 3. When the analyses were carried out using the DII as a continuous variable, a significant positive association with the risk of CRC was observed (multivariable OR 1·13, 95 % CI 1·09, 1·18). When fit as quintiles, subjects in Q3, Q4 and Q5 were at a higher risk of developing CRC compared with those in Q1 ($OR_{Q3\ v.\ Q1}$ 1·23, 95 % CI 1·03, 1·47; $OR_{Q4\ v.\ Q1}$ 1·39, 95 % CI 1·16, 1·67; $OR_{Q5\ v.\ Q1}$ 1·55, 95 % CI 1·29, 1·85; *P* for trend $<0·0001$). For the analysis focusing on specific anatomic subsites, a significant positive association was observed with colon cancer for both DII as a continuous variable (OR 1·09, 95 % CI 1·04, 1·14) and fit as quintiles ($OR_{Q5\ v.\ Q1}$ 1·39, 95 % CI 1·13, 1·71; *P* for trend=0·0002). A similar positive association was found for rectal cancer ($OR_{continuous}$ 1·12, 95 % CI 1·06, 1·19; $OR_{Q5\ v.\ Q1}$ 1·47, 95 % CI 1·14, 1·90; *P* for trend=0·0004). Additional adjustment for smoking and diabetes did not meaningfully change the risk estimates (data not shown).

When stratified by sex, the DII was associated with CRC in both males and females, but with a stronger association among males ($OR_{Q5\ v.\ Q1}$ 1·90, 95 % CI 1·47, 2·45 in males *v.* $OR_{Q5\ v.\ Q1}$ 1·27, CI 1·00, 1·65 in females; *P* for trend=0·01; Table 4). Among males, the DII was associated with both colon cancer ($OR_{Q5\ v.\ Q1}$ 1·71, 95 % CI 1·27, 2·28) and rectal cancer ($OR_{Q5\ v.\ Q1}$ 1·47, 95 % CI 1·14, 1·90) (Table 4), whereas for females, a significant association was observed with rectal cancer for the DII fit as continuous (OR 1·10, 95 % CI 1·01, 1·19), but no significant association was observed for colon cancer (Table 4).

Discussion

In the present large case–control study, consuming a more pro-inflammatory diet, as reflected in higher DII scores, was associated with an increased risk of CRC. The results showed a significant positive association between the DII and colon and rectal cancers separately. When stratified by sex, we found positive associations between the DII and CRC for both sexes, with larger effect sizes for males. CI were narrower for males due to a larger sample size relative to that for females.

Overall, the present results are in accordance with those previously obtained from studies showing protective effects of food groups such as vegetables, fruit, fish, total antioxidant capacity of the diet[31], flavonoids[32] and high proanthocyanidin intake[33] on the risk of CRC, all of which include anti-inflammatory components or exert anti-inflammatory effects. Conversely, in a previous case–control study by our

Table 3. OR for the relationship between the dietary inflammatory index (DII) and colorectal cancer among 1953 cases of colorectal cancer, 1225 cases of colon cancer, 728 cases of rectal cancer and 4154 controls in Italy during 1992–6
(Number of cases, odds ratios and 95 % confidence intervals)

	Colorectal cancer					Colon cancer					Rectal cancer				
	Cases (*n*)	OR*	95 % CI	OR†	95 % CI	Cases (*n*)	OR*	95 % CI	OR†	95 % CI	Cases (*n*)	OR*	95 % CI	OR†	95 % CI
DII quintiles															
Q1	345	1	Reference	1	Reference	227	1	Reference	1	Reference	118	1	Reference	1	Reference
Q2	347	1·05	0·88, 1·26	1·03	0·86, 1·23	218	0·98	0·80, 1·21	0·99	0·80, 1·22	129	1·14	0·88, 1·49	1·08	0·83, 1·42
Q3	395	1·23	1·03, 1·47	1·22	1·01, 1·46	256	1·17	0·96, 1·43	1·20	0·98, 1·48	139	1·21	0·93, 1·57	1·15	0·88, 1·50
Q4	426	1·39	1·17, 1·65	1·39	1·16, 1·67	255	1·17	0·96, 1·43	1·23	1·00, 1·51	171	1·54	1·20, 1·98	1·43	1·10, 1·84
Q5	440	1·50	1·26, 1·78	1·55	1·29, 1·85	269	1·28	1·05, 1·56	1·39	1·13, 1·71	171	1·57	1·22, 2·01	1·47	1·14, 1·90
P for trend			<0·0001		<0·0001			0·004		0·0002			<0·0001		0·0004
DII continuous	1953	1·12	1·08, 1·17	1·13	1·09, 1·18	1225	1·07	1·02, 1·12	1·09	1·04, 1·14	728	1·14	1·08, 1·20	1·12	1·06, 1·19

* The logistic regression model controlled for age.
† The logistic regression model additionally controlled for sex, study centre, education, (<7, 7–11 and ≥12 years), BMI (<25·0, 25·0–29·9 and ≥30·0 kg/m^2), alcohol drinking (0, 1–21 and >21 drinks/week), physical activity (low, medium and high) and history of colorectal cancer (yes/no); energy intake was adjusted using the residual method.

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Table 4. OR for the association between the dietary inflammatory index (DII) and colorectal cancer stratified by sex in Italy during 1992–6 (Number of cases, odds ratios and 95 % confidence intervals)

	Colorectal cancer					Colon cancer					Rectal cancer				
	Cases (*n*)	OR*	95 % CI	OR†	95 % CI	Cases (*n*)	OR*	95 % CI	OR†	95 % CI	Cases (*n*)	OR*	95 % CI	OR†	95 % CI
Males															
DII quintiles															
Q1	164	1	Reference	1	Reference	101	1	Reference	1	Reference	63	1	Reference	1	Reference
Q2	192	0·97	0·75, 1·24	0·97	0·75, 1·25	116	0·94	0·70, 1·27	0·98	0·73, 1·33	76	1·01	0·71, 1·45	1·08	0·83, 1·42
Q3	231	1·29	1·00, 1·65	1·31	1·02, 1·70	152	1·34	1·01, 1·78	1·41	1·06, 1·89	79	1·06	0·74, 1·51	1·15	0·88, 1·50
Q4	261	1·41	1·11, 1·80	1·46	1·14, 1·88	152	1·23	0·93, 1·63	1·35	1·01, 1·81	109	1·43	1·03, 2·00	1·43	1·10, 1·84
Q5	277	1·82	1·42, 2·33	1·90	1·47, 2·45	167	1·56	1·18, 2·07	1·71	1·27, 2·28	110	1·62	1·16, 2·27	1·47	1·14, 1·90
P for trend			<0·0001		<0·0001			0·0002		<0·0001			0·0003		0·0013
DII continuous	1125	1·17	1·11, 1·24	1·19	1·12, 1·26	688	1·10	1·03, 1·17	1·13	1·06, 1·20	437	1·14	1·08, 1·20	1·16	1·07, 1·25
Females															
DII quintiles															
Q1	181	1	Reference	1	Reference	126	1	Reference	1	Reference	55	1	Reference	1	Reference
Q2	156	1·13	0·87, 1·46	1·12	0·86, 1·46	102	1·03	0·77, 1·38	1·02	0·76, 1·38	53	1·25	0·84, 1·86	1·26	0·84, 1·88
Q3	164	1·14	0·89, 1·46	1·17	0·90, 1·52	104	1·00	0·75, 1·33	1·02	0·76, 1·38	60	1·36	0·92, 2·00	1·36	0·92, 2·01
Q4	165	1·30	1·01, 1·67	1·34	1·03, 1·74	103	1·09	0·81, 1·46	1·13	0·83, 1·52	62	1·55	1·06, 2·27	1·54	1·04, 2·27
Q5	163	1·13	0·88, 1·46	1·27	1·00, 1·65	102	0·98	0·73, 1·32	1·11	0·82, 1·51	61	1·37	0·93, 2·01	1·41	0·95, 2·09
P for trend			0·19		0·04			0·97		0·39			0·06		0·05
DII continuous	828	1·06	1·00, 1·12	1·09	1·03, 1·16	537	1·02	0·96, 1·09	1·06	0·98, 1·14	291	1·14	1·08, 1·20	1·10	1·01, 1·19

* The logistic regression model controlled for age.
† The logistic regression model additionally controlled for study centre, education, (<7, 7–11 and ≥12 years), BMI (<25·0, 25·0–29·9 and ≥30·0 kg/m^2), alcohol drinking (0, 1–21 and >21 drinks/week), physical activity (low, medium and high), history of colorectal cancer (yes/no); energy intake was adjusted using the residual method.

group[27], increased risks of CRC have been associated with food groups such as bread and pasta, potatoes, cakes and desserts, and refined sugar, which would be expected to be more concentrated with pro-inflammatory components such as saturated fat, *trans*-fatty acids and low fibre content.

Previous studies investigating the effect of specific food items on the risk of CRC have reported an increased risk with a high consumption of red and processed meat[12,34,35] and high alcohol drinking[36]. Generally, inverse associations have been found for dairy foods and for foods high in fibre, fruits and vegetables[37]. A limitation of this single food/nutrient-based approach is that these foods or nutrients are usually consumed with other food items and nutrients; thus, dietary interactions may modify the actual effects of the food or nutrient under study. A high correlation between nutrients and among foods can produce instability in risk estimation due to multicollinearity, resulting in the possible loss of statistical power and distortion of risk estimates. In the formulation of the DII, an entirely different approach was taken by focusing on the functional effects of foods and nutrients. As such, the DII relies on reviewing and scoring of the peer-reviewed literature on the subject of diet and inflammation. Also, it standardises individuals' dietary intakes of pro- and anti-inflammatory food constituents to world reference values, resulting in values that are not dependent on units of consumption and can be used for comparison across studies.

The results of the present study support findings from our previous research indicating increased risks of CRC with increasing DII scores among postmenopausal women in two US cohort studies, the Iowa Women's Health Study[23] and the Women's Health Initiative[24]. Previous studies have been conducted to examine other dietary patterns and indices in relation to CRC[13,38,39]. In the National Institutes of Health–American Association of Retired Persons cohort, after adjustment for multiple confounders, significant inverse associations were observed between CRC incidence and the Healthy Eating Index (HEI)-2005, but not the alternate HEI or Mediterranean diet scores[38]. A case–control study conducted in Pennsylvania, USA, showed significant associations between low HEI-2005 scores and dietary patterns high in meat, potatoes and refined grains and the risk of CRC among women[12,13]. In one case–control study, a starch-rich dietary pattern was found to increase the risk of both colon and rectal cancers, whereas the vitamins and fibre pattern reduced the risk of rectal cancer and the unsaturated fats patterns reduced the risk of colon cancer[40].

In addition to CRC, the associations between the DII and cancers of other organ sites, including pancreatic and prostate cancers, have been examined in case–control studies[25,26] conducted in Italy. Similar to the present findings, consuming a more pro-inflammatory diet was associated with increased odds of pancreatic cancer ($OR_{Q5\ v.\ Q1}$ 2·48, 95 % CI 1·50, 4·10) and prostate cancer ($OR_{Q4\ v.\ Q1}$ 1·33, 95 % CI 1·01, 1·76) in those studies[25,26].

One of the possible mechanisms for the positive association between the DII and the risk of CRC (and other cancers) might be through the effect of a pro-inflammatory diet on insulin resistance by increasing systemic inflammation[41].

Consumption of food items such as meat and butter has been shown to affect systemic inflammation by increasing levels of high-sensitivity CRP, E-selectin and soluble vascular cell adhesion molecule-1[42], which then are responsible for increasing insulin resistance[41]. Increasing insulin resistance is associated with CRC by increasing circulating levels of insulin, TAG and NEFA[37,43], which promote excessive proliferation of colonic epithelial cells and expose them to reactive oxygen species, thereby increasing the risk of CRC. Another theory suggests the role of diet on local inflammation and oxidation in the colon; local inflammation and oxidative stress as a result of the activation of the cyclo-oxygenase-2 enzyme in colonic epithelial cells results in focal proliferation and mutagenesis[37].

The strengths of the present study include the large sample size, where both cases and controls came from comparable catchment areas and were interviewed by uniformly trained interviewers in their respective hospital settings. Subjects were unaware of any particular study-related hypothesis in relation to diet and CRC, thereby reducing potential selection and information bias[44]. The FFQ was satisfactorily reliable[28] and validated with a 7 d dietary record[29]. Participation among eligible cases and controls was almost complete, and we excluded from the controls patients who were hospitalised for diseases likely to be related to long-term dietary intakes. The present results were adjusted for several potential confounders that are known risk factors for CRC, including education, alcohol drinking and BMI, in addition to demographic factors and total reported energy intake. After controlling for all of these factors, the associations became stronger after multivariable analyses including terms for energy intake.

In conclusion, Italian men and women who consumed a more pro-inflammatory diet were at an increased risk of CRC compared with those who consumed a more anti-inflammatory diet. The results suggest that encouraging intake of more anti-inflammatory dietary factors, such as plant-based foods rich in fibre and phytochemicals, and reducing intake of pro-inflammatory factors, such as fried foods or processed foods rich in saturated fat or *trans*-fatty acids, may be a strategy for reducing the risk of CRC.

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N. S. was involved in the calculation of DII in this dataset, performed all the analyses and drafted the first version of the manuscript. C. L. V. helped with the analyses, data acquisition, and interpretation of data and critical revision of the manuscript. A. Z., M. M., D. S. and S. E. S. contributed to the data interpretation and drafting of the manuscript. J. R. H. provided expertise and oversight throughout the process. All authors approved the final version.

J. R. H. owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the DII from the University of South Carolina in order to develop computer and smart applications for patient counselling and dietary intervention in clinical settings. N. S. is an employee of CHI. The subject matter of this article will not have any direct bearing on that work, nor has that activity exerted any influence on this project. The rest of the authors declare that they have no conflicts of interest.

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