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Association between dietary inflammatory index and gastric cancer risk in an Italian case-control study

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Abstract

Background—In this study, we explored the association between the dietary inflammatory index (DII) and gastric cancer risk in an Italian case-control study.

Materials and Methods—Cases were 230 patients with incident, histologically confirmed cases of gastric cancer from the Greater Milan area, northern Italy. Controls were 547 frequency-matched subjects admitted to the same network of hospitals as cases for a wide spectrum of acute, non-neoplastic conditions. The DII was computed using a reproducible and valid 78-item food frequency questionnaire. Odds ratios (**OR**) were estimated through logistic regression models conditioned on age and sex and adjusted for recognised confounding factors, including total energy intake.

Results—Subjects with the most pro-inflammatory diet had a higher risk of gastric cancer compared to subjects with the most anti-inflammatory diet ($OR_{\text{Quartile4vs1}} = 2.35$, 95% confidence interval, 1.32, 4.20; $p\text{-trend} = 0.004$).

Conclusion—These results indicate that a pro-inflammatory diet, as indicated by higher DII score, was associated with gastric cancer risk.

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Keywords

DII; diet; inflammation; gastric cancer; case-control; Italy

Introduction

Gastric cancer represents the fifth most common cancer and the third-leading cause of cancer death worldwide, with almost 1 million cases and over 700,000 deaths estimated in 2012 (1). In Italy, it is the fourth most common cause of cancer death, after lung, colorectal and breast cancers (2). The major recognized risk factor is *Helicobacter pylori* infection; however, considerable evidence is accumulating on the role of diet and nutrition in the risk of gastric cancer (3–6).

Various dietary components have different effect on inflammation (7–9). The relation between diet and gastric cancer has been studied widely (5, 10); however, the possible relation between inflammation deriving from dietary exposure and gastric cancer risk has not yet been investigated.

Chronic inflammation is a persistent condition in which tissue destruction and repair occur simultaneously (11, 12). Evidence from previous studies suggests an important role of chronic inflammation in gastric cancer (13–15). A meta-analysis of 5 case-control studies, showed polymorphism of interleukin (IL)-17A G197A to be associated with gastric cancer (16). In another meta-analysis, increased pre-treatment serum C-reactive protein level ($> 10\text{mg/L}$) was significantly associated with poor prognosis in gastric cancer patients, either in early or advanced stages (17).

A literature-derived dietary inflammatory index (DII) was developed to assess the inflammatory potential of an individual's diet (18). The DII has been validated with various inflammatory markers, including C-reactive protein (19), interleukin-6 (20, 21), and homocysteine (21). The DII has been shown to be associated with metabolic syndrome and its components (22–24), anthropometric measurements and cardiovascular disease in Spain (25–27); bone mineral density among postmenopausal women in Iran (28). Concerning digestive tract cancers, DII is related to an increased risk of colorectal cancer in three cohort studies in from the USA (29–31) and in two cancer case-control studies, in Spain (32) and Italy (33), esophageal squamous cell cancer in three case-control studies (34–36) and pancreatic cancer in one case-control study (37). In addition to cancer incidence DII also was found to be associated with digestive cancer mortality in three cohort studies (38–40).

This study examined the association between the DII and gastric cancer risk in a case-control study conducted in Italy (41). This is the first study to explore this association.

Methods

Design and Participants

Data were from a case-control study of gastric cancer conducted between 1997 and 2007 in the Greater Milan area, Northern Italy (41). Cases were 230 patients (143 men and 87

women; median age, 63 y; range, 22–80 y), admitted to major teaching and general hospitals in the study area with incident, histologically confirmed gastric cancer (Ninth Revision of the International Classification of Diseases: 151.0–151.9), diagnosed no longer than 1 y before the interview, and with no previous diagnosis of cancer. The control group included 547 patients (286 men and 261 women; median age, 63 y; range, 22–80 y), frequency matched to cases by age and sex (with a ratio of 2:1 for men and 3:1 for women), admitted to the same hospitals as cases for a wide spectrum of acute, non-neoplastic conditions that are unrelated to known or potential risk factors for gastric cancer. Additionally we excluded subjects who were admitted for conditions associated with long-term dietary modifications such as diabetes and cardiovascular diseases. Among controls, 20% were admitted for traumas, 23% for other orthopaedic conditions, 22% for acute surgical, and 35% for other miscellaneous disorders. Less than 5% of cases and controls approached refused to be interviewed.

Trained interviewers collected information during their hospital stay using a structured questionnaire on socio-demographic characteristics, anthropometric characteristics, life-style habits, including tobacco smoking and alcohol drinking, personal medical history. Subjects' usual diet prior to cancer diagnosis or hospital admission (for controls) was assessed using an interviewer-administered food frequency questionnaire (FFQ), consisting of 78 items on foods, including the most common Italian recipes, and 5 items on alcoholic beverages. Subjects were asked to indicate the average weekly frequency of consumption of each dietary item; intakes lower than once a week, but at least once a month, were coded as 0.5 per week. Nutrient and total energy intake was determined using an Italian food composition database. The FFQ showed reproducibility (42, 43) and validity (44) with Spearman correlation coefficients between 0.60 and 0.80 for most food items and nutrients.

In order to compute the DII score, dietary information for each study participant were first linked to the regionally representative database that provided a robust estimate of a mean and a standard deviation for each of the 45 parameters (i.e., foods, nutrients, and other food components) considered (18). These parameters then were used to derive the subject's exposure relative to the standard global mean as a z-score, derived by subtracting the mean of the regionally representative database from the amount reported, and dividing this value by the parameter's standard deviation. To minimize the effect of "right skewing," this value was converted to a centered percentile score, which was then multiplied by the respective food parameter effect score (derived from a literature review on the basis of 1943 articles). All of these food parameter-specific DII scores were then summed to create the overall DII score for every subject in the study. The DII computed on this study's FFQ includes data on 31 of the 45 possible food parameters comprising the DII: carbohydrates, proteins, fats, alcohol, fibers, cholesterol, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, omega 3, omega 6, niacin, thiamin, riboflavin, vitamin B6, iron, zinc, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, beta carotene, anthocyanidins, flavan3ols, flavonols, flavanones, flavones, isoflavones, caffeine, and tea.

The DII was analysed both as a continuous variable, with each point corresponding to 10% of its range (4.78 to −4.71), and by quartiles of exposure computed among controls. Odds ratios (ORs) and the corresponding 95% confidence intervals were estimated using

conditional logistic regression models conditioned on study centre and quinquennia of age, and adjusted for education (<7, 7–11, 12 years, categorically), year of interview, body mass index (BMI) (<20, 20–24.9, 25–29.9, 30 kg/m²), smoking (never smoker, ex-smoker, current smoker of <15 and 15 cigarettes/day, categorically), and total energy intake (quintiles; <1569, 1569–1915, 1916–2229, 2230–2601, >2601 kJ). Stratified analyses were carried out according to sex, age (<65, 65 years), education (<7 and 7y), BMI (<25, 25 kg/m²) and tobacco smoking (never and former smokers and current smokers). Given the small number subjects with family history of gastric cancer, this variable was not included as a covariate in the model. Linear tests for trend were performed using the median value within each quartile as an ordinal variable (45). Statistical tests were performed using SAS[®] 9.3 (SAS Institute Inc., Cary, NC).

Results

The distribution of 230 gastric cancer cases and 547 controls according to age, education, and other selected variables is presented in Table 1. By design, cases and controls had a similar age (p value=0.99) and sex (p value=0.01) distribution. Cases were more frequently current and ex-smokers and no differences were observed with education and BMI.

Characteristics of control subjects across quartiles of DII are provided in Table 2. There were small non-significant differences in socio-demographic characteristics, anthropometric measures, and lifestyle habits across quartiles of DII.

Table 3 shows the ORs of gastric cancer for the highest versus the lowest DII quartile, as well as for an increment of 1 unit of DII, overall and in strata of selected covariates. Subjects in the upper quartiles of DII had an increased OR for gastric cancer compared to subjects in the lowest quartile (OR_{Quartile4vs1} = 2.35, 95% C.I.=1.32, 4.20; P_{trend}=0.004). A positive association also was observed when considering continuous OR (1.19, 95% CI=1.06, 1.34; P value=0.004). Apparently stronger associations were observed between DII and gastric cancer among females (OR_{Quartile4vs1} = 2.57, CI 1.07, 6.18; P_{trend}=0.04), subjects aged <65years (OR_{Quartile4vs1} = 2.85, CI 1.28, 6.34; P_{trend}=0.01), less educated (OR_{Quartile4vs1} = 3.64, CI 1.33, 9.96; P_{trend}=0.01), non-overweight (OR_{Quartile4vs1} = 2.50, CI 1.12, 5.61; P_{trend}=0.01) and smokers (OR_{Quartile4vs1} = 2.62, CI 1.16, 5.92; P_{trend}=0.03), in the absence, of significant heterogeneity.

Discussion

We observed positive associations between gastric cancer and inflammatory potential of diet as expressed by increasing DII in a southern European population. This result supports the hypothesis that individuals with a pro-inflammatory diet have a higher risk of developing gastric cancer.

Previous results from this study indicate foods such as vegetables and fruits and dietary patterns rich in these items, as well as various compounds, including flavonoids and proanthocyanidins to be inversely related to gastric cancer risk (46, 47). All of these dietary factors contribute to lower DII values (18). Conversely, dietary patterns rich in meats, animal fat, starchy food and refined cereals, which contribute to higher DII values (18), were

positively related to gastric cancer risk (41). The apparently weaker effect among the obese could be explained by the fact that obesity in itself is a very pro-inflammatory condition (48, 49) thereby both exacerbating and masking the effects of pro-inflammatory diet. The stratified results, including those for BMI, should be viewed with caution because the test for heterogeneity was not significant because of small sample sizes within strata.

The positive relationship between increasing inflammatory potential of diet and gastric cancer is consistent with a body of evidence from previous studies examining the effect of various dietary components on gastric cancer. Several epidemiologic, experimental, and animal studies suggests that high intake of fresh fruits and vegetables, lycopene and lycopene-containing food products, and potentially vitamin C and selenium may reduce the risk for gastric cancer (10, 50) while high intake of nitrosamines, processed meat products, salt and salted foods, were associated with increased risk for gastric cancer (10, 50, 51). A systematic review and dose-response meta-analyses of prospective cohort studies indicated that a diet rich in fruit and white vegetable intake is associated with reduced risk of gastric cancer (50) while concordant positive association was observed with high-salt foods and alcohol intake (50). In a meta-analyses on dietary patterns, a ~2-fold lower gastric cancer risk for a 'Prudent/healthy' diet-rich in fruits and vegetables as compared to a 'Western/unhealthy' diet-rich in starchy foods, meat and fats was observed (52). In a case-control study from Uruguay, an increased risk of gastric cancer was observed for rice, salted meat, stewed meat, white bread, potatoes, and tubers. On the other hand, raw vegetables, total fruits, legumes, and black tea were inversely associated with gastric cancer risk (53). In another case-control study conducted in Siberia, increased intake of foods rich in carbohydrate, particularly mono- and disaccharides, as well as reduced consumption of food rich in polysaccharides, was associated with lower risk of diffuse type of gastric cancer (54). The diet and gastric cancer association has been less consistently reported in cohort studies (50, 55). The divergent results between case-control and cohort studies may be due to recall bias in retrospective studies. However, the association may have been underestimated in prospective studies because of the limited variability of dietary intakes within each cohort, and the changes in diet during the relatively long periods between data collection and disease occurrence (56).

One of the possible mechanisms through which the observed positive association between DII and gastric cancer risk could occur is through the effect of diet-related chronic inflammation in the upregulation of various cytokines and chemokines and the recruitment of numerous hematopoietic populations to inflamed gastric tissues. In addition, chronic inflammation stimulates the recruitment of progenitor cell populations to the stomach and their subsequent engraftment (13). Cytokines also can stimulate the recruitment and activation of inflammatory cells like neutrophils and macrophages, which when activated produce inflammatory mediators, including reactive oxygen species (ROS). These mediators impart oxidative stress on the cells in the gastric epithelium. Vitamin C, which is an important anti-inflammatory component, neutralizes this oxidative stress reaction (15, 57). Our results could be biased by the fact that cases were more likely to be smokers and smoking is a strongly pro-inflammatory state and is also a very well known risk factor for gastric cancer (58, 59).

The strengths of this study include the almost complete participation of both cases and controls, which should reduce the role of selection bias. Hospital controls may have different dietary habits as compared with the general population. However, we excluded from the comparison group subjects admitted for conditions associated with long-term dietary modifications (e.g., diabetes, cardiovascular diseases). Other strengths are the use of a reproducible and valid FFQ (42, 44) and the similar setting of interviews for cases and controls, which should limit information bias. Also, the DII score, which takes into account both pro- and anti-inflammatory food parameters that characterize virtually all human diets, accurately reflects the relationship of the inflammatory potential of whole diet. In addition to being subject to construct validation testing against inflammatory markers in both the SEASONS Study (19) and the Women's Health Initiative (20), the DII previously has been shown to be associated with prostate, pancreatic, colorectal, endometrial, esophageal and hepatocellular cancers in a similar Italian population (22, 24, 32, 34, 60, 61).

Despite its strengths, this hospital study was based on a relatively small number of cases, thus not allowing meaningful analysis by separate histological type or tumour site. Further, we had no information on *Helicobacter pylori* infection, probably a necessary factor for gastric cancer (6, 62). It should be noted that any case-control study would have limited ability to measure *H. pylori* because blood samples obtained at cancer diagnosis are of limited value for ascribing exposure during the relevant etiologic period. As with all case-control studies, another limitation is the recall bias where participants had to remember what they ate 2 years prior to diagnosis. Given the limited knowledge and attention paid in the population to specific relations between diet and stomach cancer, bias in the recall of food intake by cases should be limited. The use of hospital controls may be criticized because their dietary habits may differ from those of the general population (45). However, given the same interview setting, information provided by hospital controls should be reasonably comparable with that obtained from cases (63).

In conclusion, this study indicates a potential role of inflammatory potential of diet on gastric cancer risk, more studies should be conducted on this topic to confirm this association.

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Table 1

Distribution of 230 gastric cancer cases and 547 controls according to selected variables, Italy, 1997–2007

	Cases	Controls
	N. (%)	N. (%)
Sex		
Male	143 (62.2)	286 (52.3)
Female	87 (37.8)	261 (47.7)
Age (years)		
<50	39 (17.0)	97 (17.7)
50–60	58 (25.2)	137 (25.1)
60–70	86 (37.4)	202 (36.9)
70	47 (20.4)	111 (20.3)
Education (years) ^a		
<7	95 (41.8)	236 (43.5)
7–11	86 (37.9)	174 (32.0)
12	46 (20.3)	133 (24.5)
Body mass index (kg/m ²) ^a		
<20	12 (5.3)	33 (6.1)
20–25	106 (46.9)	216 (39.4)
25–30	82 (36.3)	223 (40.9)
30	26 (11.5)	73 (13.6)
Smoking		
Never smokers	96 (41.8)	261 (47.8)
Ex-smokers	75 (32.8)	167 (30.6)
Current smokers		
<15 cigarettes/day	25 (10.9)	49 (9.0)
15 cigarettes/day	33 (14.4)	69 (12.6)

^aThe sum does not add up to a total of 100% because of some missing values.

Table 2

Participants' characteristics across quartiles of dietary inflammatory index (DII) among 547 controls. Italy, 1997–2007.

Characteristics	DII quartiles				P-Value ^b
	< -1.47	-1.47,-0.14	-0.13,1.49	>1.49	
	N (%)	N (%)	N (%)	N (%)	
Sex					0.82
Male	74 (54.4)	73 (52.9)	72 (52.9)	67 (48.9)	
Female	62 (45.6)	65 (47.1)	64 (47.1)	70 (51.1)	
Age (years) ^a					0.24
<50	26 (19.1)	21 (15.2)	21 (15.4)	29 (21.2)	
50–60	38 (27.9)	44 (31.9)	29 (21.3)	26 (19.0)	
60–70	50 (36.7)	48 (34.8)	51 (37.5)	53 (38.7)	
70	22 (16.2)	25 (18.1)	35 (25.7)	29 (21.2)	
Education (years)					0.56
<7	54 (39.7)	58 (42.0)	56 (41.2)	68 (49.6)	
7–11	49 (36.0)	49 (35.5)	44 (32.4)	36 (26.3)	
>11	33 (24.3)	31 (22.5)	36 (26.5)	33 (24.1)	
Body mass index					0.63
<20	8 (5.9)	8 (5.8)	10 (7.4)	9 (6.6)	
20 to <25	58 (42.6)	49 (35.5)	47 (34.6)	62 (45.3)	
25 to <30	56 (41.2)	62 (44.9)	59 (43.4)	46 (33.6)	
30	14 (10.3)	19 (13.8)	20 (14.7)	20 (14.6)	
Smoking					0.95
Never smokers	66 (48.5)	63 (45.7)	65 (48.2)	67 (48.9)	
Ex-smokers	42 (30.9)	44 (31.9)	44 (32.6)	37 (27.0)	
Current smokers					
<15	14 (10.3)	11 (8.0)	11 (8.2)	13 (9.5)	
15	14 (10.3)	20 (14.5)	15 (11.1)	20 (14.6)	

^a Chi-square test for categorical variables

Table 3

Odds ratios (OR) of gastric cancer and corresponding 95% confidence intervals (CI) according to quartiles of DII, among 230 cases and 537 controls, overall and in strata of selected covariates. Italy, 1997–2007.

	Cases/Controls	DII quartiles				P _{trend}	P _{interaction}	OR (95% CI) ^d
		< -1.47 1 ^a	-1.47, -0.14 1.17 (0.73, 1.85)	-0.13, 1.49 1.34 (0.81, 2.21)	> 1.49 2.35 (1.32, 4.20)			
Overall	230/547					0.004		1.19 (1.06, 1.34)
Sex							0.53	
Male	142/283	1 ^a	1.17 (0.63, 2.15)	1.45 (0.75, 2.80)	2.15 (0.97, 4.79)	0.05		1.17 (0.99, 1.37)
Female	87/261	1 ^a	1.04 (0.50, 2.18)	1.11 (0.50, 2.47)	2.57 (1.07, 6.18)	0.04		1.24 (1.03, 1.49)
Age (years)							0.44	
<65	105/252	1 ^a	1.01 (0.54, 1.89)	1.28 (0.63, 2.62)	2.85 (1.28, 6.34)	0.01		1.25 (1.06, 1.47)
65	125/295	1 ^a	1.35 (0.66, 2.75)	1.37 (0.66, 2.84)	1.83 (0.76, 4.44)	0.20		1.13 (0.95, 1.34)
Education (years)							0.67	
<7	95/235	1 ^a	1.16 (0.55, 2.46)	1.74 (0.77, 3.96)	3.64 (1.33, 9.96)	0.01		1.33 (1.08, 1.62)
7	135/309	1 ^a	1.29 (0.70, 2.37)	1.23 (0.64, 2.35)	2.20 (1.04, 4.67)	0.05		1.13 (0.97, 1.32)
BMI (kg/m ²)							0.47	
<25	121/250	1 ^a	1.33 (0.66, 2.68)	2.10 (1.04, 4.27)	2.50 (1.12, 5.61)	0.01		1.22 (1.04, 1.44)
25	108/296	1 ^a	0.88 (0.46, 1.68)	0.75 (0.36, 1.58)	1.91 (0.79, 4.65)	0.21		1.13 (0.94, 1.35)
Smoking							0.86	
Never smokers	96/261	1 ^a	1.41 (0.69, 2.92)	1.39 (0.64, 3.02)	2.26 (0.96, 5.34)	0.07		1.18 (1.00, 1.40)
Smokers	133/283	1 ^a	1.14 (0.61, 2.14)	1.39 (0.71, 2.73)	2.62 (1.16, 5.92)	0.03		1.20 (1.02, 1.41)

^aReference category.

^bEstimated from multiple logistic regression models, conditioned on sex and quinquennia of age and adjusted for education, year of interview, body mass index (BMI), smoking, and total energy intake

^cContinuous OR for one unit increment of the DII, corresponding to ≈10% of its range (4.78 to -4.71).