RESEARCH ARTICLE

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Validation of a Dietary Inflammatory Index (DII) and Association with Risk of Gastric Cancer: a Case-Control Study

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Abstract

Background: Gastric cancer (GC) is the fifth most common malignancy and the second leading cause of cancer-related deaths worldwide. Studies have shown that dietary components and inflammation are implicated in the etiology of GC. **Methods:** We examined the ability of a dietary inflammatory index (DII) to predict the odds of GC in a case-control study conducted from December 2014 to May 2016. The subjects were 82 cases and 95 controls who attended specialized centers in Tabriz, Iran. DII scores were computed from a validated 168-item food frequency questionnaire. Logistic regression models were used to estimate odds ratios (ORs) adjusted for age, sex, body mass index, education, smoking, alcohol, H.pylori infection, physical activity, aspirin/NSAID use and total caloric intake. **Results:** In the fully adjusted model, subjects with a DII score >-1.77 had nearly 3.5 times higher odds of having GC compared with subjects with DII≤-1.77, (ORDII>-1.77≤-1.77=3.39; 95%CI=1.59, 7.22). Also, for every one-unit increase in DII, there was a corresponding increase in hs-C-reactive protein, tumor necrosis factor-alpha, interleukin (IL)-6 and IL-1b: β=0.09, 0.16, 0.16 and 0.10, respectively; and a corresponding decrease in IL-10: β=-0.11. Conclusion: Subjects who consumed a more pro-inflammatory diet were at increased odds of GC compared to those who consumed a more anti-inflammatory diet.

Keywords: Gastric cancer- inflammation- dietary inflammatory index (DII)- nutritional assessment- validation of DII

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Introduction

Gastric cancer (GC) is the fifth most common malignancy and the second leading cause of cancer-related death worldwide (Siegel et al., 2013; Torre et al., 2015). More than 932,000 new cases of GC are being diagnosed with each year and at least 750,000 thousand patients lose their lives due to this cancer (Parkin et al., 2005; Siegel et al., 2013). In the Iranian population GC is the most common cancer in men and the third most common cancer in women (Malekzadeh et al., 2009; Mousavi et al., 2009). Northern and Northwestern Iran have among the high rates of GC in the world (Malekzadeh et al., 2009). GC is one of the most common malignancies in the world with a multifactorial etiology including infection with Helicobacter pylori (H.pylori), smoking, alcohol consumption, eating habits and genetics (Fei and Xiao, 2006; Fock et al., 2008).

The relationship between inflammation and cancer was introduced for the first time in Western medicine by Rudolph Virchow in 1,863 when he revealed leukocytes in neoplastic tissue (Macarthur et al., 2004). Inflammation is the result of body's response to tissue injury, infection or other factors that produce proinflammatory stimuli (Keibel et al., 2009; Valin and Pablos, 2015). Chronic inflammation is associated with a number of conditions including cancer, autoimmune diseases, diabetes and chronic diseases (Khansari et al., 2009; Fichtner-Feigl et al., 2015; Vahid et al., 2017c). Chronic inflammation and serum levels of C-reactive protein (CRP) have been implicated in GC in some studies (Egi et al., 2007; Fichtner-Feigl et al., 2015; Lin et al., 2015). On the other hand, there is considerable evidence that diet plays an important and central role in the regulating chronic inflammation (Esposito et al., 2006; Giugliano et al., 2006; Galland, 2010; Vahid et al., 2015).

A Western diet containing high concentrations of red meat, dairy products, other high-fat foods and simple carbohydrates is associated with high levels of CRP and interleukin (IL)-6. By contrast, the Mediterranean diet

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containing high concentrations of whole grains, fish, fruit and green leafy vegetables and moderate amounts of alcohol and olive oil and low intake of red meat and butter is associated with low levels of inflammation (Esposito et al., 2004; Dalziel et al., 2006).

To investigate the role of diet in the development of inflammation we used the newly developed Dietary Inflammatory Index (DIITM) (Cavicchia et al., 2009; Shivappa et al., 2014a), which has been shown to be predictive of levels of inflammatory markers (Cavicchia et al., 2009; Shivappa et al., 2014b; Shivappa et al., 2015; Vahid et al., 2017a). The DII can be used to evaluate the potential of diets inflammatory effects in different populations using a variety of assessment instruments such as 24-hour recall interviews, food frequency questionnaires (FFQ) and food record (Shivappa et al., 2014a; Shivappa et al., 2014b; Wirth et al., 2014; Wood et al., 2015). DII has also been shown to be associated with GC in Italy (Shivappa et al., 2016).

In the current study, we examined the relationship between DII scores and the risk of GC. We also validated the DII by examining the association between DII scores and serum concentrations of inflammatory factors. Our hypothesis is that higher DII scores (indicating a pro-inflammatory diet) are associated with increased risk of GC and higher levels of inflammatory markers.

Materials and Methods

Participants

This hospital based case-control study was conducted at specialized centers in Northwest of Iran from December 2014 to May 2016. The study included 82 patients with GC and 95 controls. The cases were patients with GC who were diagnosed by a gastroenterologist within the previous month. These patients were selected with the simple random sampling procedure. In this procedure, we prepared an exhaustive list (sampling frame) of all the patients of interest. From this list, the sample is drawn so that each patient has an equal chance of being drawn during each selection round. Controls were randomly selected from among other patients' caregivers attending the same clinics. Controls were frequency matched on sex and age (±5 year). Data on cases and controls were collected at the same time and interviewed in the same setting. After providing written and verbal explanations about the methodology of the study, informed consent was received from all participants. The study protocol was approved by the local Ethics Review Committee at Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Inclusion and exclusion criteria

Inclusion criteria included the following: a) the absence of malignancy (only in control group), b) not following a special diets such as vegetarian, or the diets resulted in the weight reduction or increase during the year prior to the interview, c) the absence of conditions such as pregnancy, lactation or a history of cancer (in control group), and neurological, gastrointestinal, hepatic, endocrine, immune, kidney and heart disorders and diseases, d) to be in the age range of 20-80 years and e) willingness to cooperate in the study.

Exclusion criteria included the following: a) not to adhere to the study protocol, b) major diet changes during the study, including diets aimed at weight increase or decrease, c) reported intake energy report >5500 or less than 800 kcal/day.

Assessment of inflammatory markers and blood samples
Participant Preparation

The participant should not be on any corticosteroids, anti-inflammatory medications or pain killers, for at least 48 hours prior to collection of specimen.

Blood tests

After fasting for 10–12 hours, venous blood samples (10 mL) were taken in vacutainer tubes under sterile conditions from participants between 08:30–10:30 am. Serum was obtained from freshly drawn, rapidly centrifuged. Serum was quickly frozen at −70°C and stored until processed.

The serum levels of inflammatory markers including tumor necrosis factor-alpha (TNF- α) (pg/ml), IL-4 (pg/ml), IL-10 (pg/ml), IL-1β (pg/ml), high-sensitivity C-reactive protein (hsCRP) (mg/l) and IL-6 (pg/ml) for all participants was measured using kits produced by Pishtaz Teb Zaman Diagnostics Co., Ltd and Shanghai Crystal Day Biotech Co., Ltd and provided by Negin Salamat Saba Co. Also, H.pylori infection was assessed by H.pylori Immunoglobulin G (IgG).

Assessment of dietary intake

In this study, dietary intakes of the subjects over the past year were evaluated by a semi-quantitative, valid and reliable FFQ questionnaire (Mirmiran et al., 2010). This FFQ queried about the average consumption frequency of 168 food items. To calculate the DII, it was necessary to have the intake information of some food items such as ginger and saffron which originally are not included in the FFQ. Therefore, some additional questions regarding such food items were asked during the interview. Participants were asked to report the frequency of consumption of each food item in the last year according to the standard size units (standard serving size) in the questionnaire. In the case group, it was specified that they should be responding to their diet prior to their GC diagnosis. According to the questionnaire, depending on the type of food, subjects indicated their intake of the food items per day, week, month or year, or as never.

Then, the information obtained from the questionnaires was analyzed using Nutritionist IV (First Databank, Hearst Corp., SanBruno, CA, USA) to calculate the average daily intake of energy and nutrients. The DII was calculated according to the daily intake of food items affecting the profile of inflammation.

Calculation of DII Scores

FFQ-derived dietary data were used to calculate DII scores for all participants. The DII is based on literature published through 2010 linking diet to inflammation. Individuals' intakes of food parameters on which the DII is based are then compared to a world standard database.

A complete description of the DII is available elsewhere (Shivappa et al., 2014a). A description of validation work, including DII derived from both dietary, recalls and a structured questionnaire similar to an FFQ and related to interval values of hs-CRP also is available (Shivappa et al., 2014a). Briefly, to calculate DII for the participants of this study, the dietary data were first linked to the regionally representative world database we constructed that provided a robust estimate of a mean and standard deviation for each parameter (Shivappa et al., 2014a). These then become the multipliers to express an individual's exposure relative to the "standard global mean" as a z-score. This is achieved by subtracting the "standard global mean" from the amount reported and dividing this value by the standard deviation. To minimize the effect of "right skewing" (a common occurrence with dietary data), this value is then converted to a centered percentile score. The centered percentile score for each food parameter for each individual was then multiplied by the respective food parameter effect score, which is derived from the literature review, in order to obtain a food parameter-specific DII score for an individual. All of the food parameter-specific DII scores are then summed to create the overall DII score for every participant in the study (Shivappa et al., 2014a). DII= b1*n1+b2*n2..... b31*n31, where b refers to the literature-derived inflammatory effects score for each of the evaluable food parameters and n refers to the food parameter-specific centered percentiles, which were derived from this case-control's dietary data. Of the theoretically possible list of 45 food parameters, a total of 31 were available from this FFQ and therefore could be used to calculate DII (energy, carbohydrate, protein, total fat, fiber, saturated fat, monounsaturated fat, polyunsaturated fat, omega-3, omega-6, niacin, thiamin, riboflavin, vitamin B12, vitamin B6, iron, magnesium, selenium, zinc, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, beta-carotene, garlic, ginger, onion, turmeric, saffron, pepper).

Assessment of other variables

For all participants the required information about age (year), sex (male/female), place of birth (rural/urban), smoking (yes/no), alcohol consumption (yes/no), aspirin/NSAID use (yes/no), regular physical activity (yes/no), education (diploma and low literate/ higher than diploma), family history of cancer (yes/no) and other variables of interest were collected through general information questionnaire during the interviews.

The weight of each participant was measured with the least clothes using a SECA digital scale with a100-gram accuracy. The height was measured without shoes in standing position, leaning against the wall and shoulder blades under normal circumstances with an accuracy of .5 cm by the mean of a tape mounted on the wall. Body Mass Index (BMI) was calculated by dividing weight (in kilograms) by the square of height (square meters).

During several training sessions, the principal investigators trained a nutrition expert, who was not aware of the study objectives, about how to complete the general information questionnaire and FFQ, and to do the anthropometric measurements.

Statistical Analyses

Descriptive analyses were carried out using paired t-test for continuous variables and χ^2-square test for categorical variables. DII (as dichotomous) was examined across the following characteristics: age, sex, BMI, education, smoking, alcohol, H.pylori infection, physical activity, aspirin/NSAID use and family history of cancer. Analyses focusing on the association of DII scores and inflammatory markers were carried out using DII as a continuous variable. For analyses focusing on GC as outcome the DII was analyzed both as a continuous variable and as a dichotomous variable, categorized based on the median value of the DII for the controls (-1.77). The inflammatory markers were log transformed. Beta estimates and 95% confidence intervals (CI) for the inflammatory markers were estimated using linear regression and odds ratios (OR) and 95% confidence intervals for GC as outcome were estimated using logistic regression models, adjusting only for age and then fitting a model with additional adjustment for sex, BMI, education, smoking, alcohol, H.pylori infection, physical activity, aspirin/NSAID use and total caloric intake. The partial correlation was used to estimate coefficients between DII and serum levels of inflammatory factors in the subjects. The covariates were chosen a priori. statistical tests were performed using SAS® 9.3 (SAS Institute Inc., Cary, NC); all p values were based on two-sided tests.

Results

Table 1 shows the distribution of 82 cases of GC and 95 controls according to selected variables. Cases were older, had higher BMI, DII score compared to controls. The mean DII value among cases was -0.97 (SD=0.87); among controls it was -1.74 (SD=0.92), indicating a more pro-inflammatory diet for cases (p-value=<0.01). Control characteristics by DII categories are provided in Table 2. In particular, participants in DII> -1.77 category had higher rates of H.pylori infection, were slightly overweight, and had lower education. However, the results were not significant except for H.pylori infection.

Partial correlation coefficients between DII and serum levels of inflammatory factors in the subjects are shown in Table 3. According to this table, in model 1 adjusted for age and gender, acceptable correlation were seen between the DII and inflammatory markers like hs-CRP, TNF-α, Il-6, and Il-1β and the inverse correlation was seen between the DII and Il-10. In model 2 after multivariable adjustments, the results were almost identical. In model 1 and 2, there was no significant correlation between the DII and Il-4.

Beta estimates and 95% confidence intervals for DII and inflammatory markers are shown in table 4. For every one-unit increase in DII, there was a corresponding increase in hsCRP (mg/l), TNF-alpha (pg/ml), IL-6 (pg/ml) and IL-1b (pg/ml): β= 0.09 (95%CI: 0.006, 0.17); 0.16 (95%CI 0.05, 0.26); 0.16 (95%CI: 0.06, 0.27) and 0.10 (95%CI: 0.02, 0.19), respectively, and a corresponding decrease in IL-10 (pg/ml) β= -0.11 (95%CI: -0.21, -0.005).

ORs and 95% CIs for the risk of GC according to dichotomized DII scores are shown in Table 5. Results

Table 1. Distribution of 82 Gastric Cancer Cases and 95 Controls According to Selected Variables, Tabriz, Iran, 2014-2016[a]

	Mean±SD or N (%)		
	Controls (n=95)	Cases (n=82)	P-value[b]
Age (years)	51.36±11.81	48.33±10.74	0.07
Body Mass Index (BMI, kg/m^2)	26.36±5.12	24.96±2.71	0.02
Dietary Inflammatory Index (DII)	-0.97±0.87	-1.74±0.92	>0.001
Sex			0.98
Females	52 (54.74)	45 (54.88)	
Males	43 (45.26)	37 (45.12)	
Education			0.24
Diploma or less	67 (70.53)	51 (62.20)	
Higher than diploma	28 (29.47)	31 (37.80)	
Smoking			0.82
Never smoker	80 (84.21)	68 (82.93)	
Ever smoker	15 (15.79)	14 (17.07)	
Alcohol			0.41
Non drinker	86 (90.53)	71 (86.59)	
Drinker	9 (9.47)	11 (13.41)	
H.pylori infection			0.002
Negative	46 (51.58)	21 (25.61)	
Positive	49 (51.58)	61 (74.39)	
Regular Physical Activity			0.03
Yes	30 (31.58)	14 (17.07)	
No	65 (68.42)	68 (82.93)	
Aspirin/NSAID use			0.83
No	86 (90.53)	75 (91.46)	
Yes	9 (9.47)	7 (8.54)	
Cancer history in an immediate family member			0.41
Yes	11 (11.58)	13 (15.85)	
No	84 (88.42)	69 (84.15)	

[a], ANOVA was used for continuous variables and Chi-square was used for categorical variables;[b], Based on the t-test of difference in means (continuous variables) or proportions (categorical variables).

obtained from modeling DII as a continuous variable in relation to risk of gastric showed a positive association after adjustment for age (OR=2.65; 95% CI=1.79-3.91) and in the multivariable analysis (OR=2.65, CI=1.73-4.07). When the analysis was carried out with DII expressed as a dichotomous variable, and adjusting for age, subjects with DII score >-1.77 were at 4.6 times higher odds of having gastric cancer compared to subjects with DII ≤-1.77 (ORDII > -1.77/≤-1.77 =4.60; 95% CI=2.29-9.25). After multivariable adjustment, subjects with DII >-1.77 were at 3.39 times higher odds of having gastric cancer compared to subjects with DII ≤-1.77 (ORDII > -1.77/≤-1.77 =3.39; 95%CI=1.59, 7.22).

Discussion

In this case-control study, which was designed to assess the relationship between the inflammatory potential of diet, as assessed by the DII, and the risk of GC, we found that subjects with higher DII scores (i.e., indicating

Table 2. Distribution of 95 Control Characteristics Across Categories of DII, Tabriz, Iran, 2014-2016[a]

	Mean±SD or N (%)		
	DII ≤ -1.77 (n=48)	DII >-1.77 (n=47)	P-value [b]
Age (years)	48.8±11.58	47.8±9.91	0.64
Sex			0.35
Females	24 (50.00)	28 (59.57)	
Males	24 (50.00)	19 (40.43)	
Body Mass Index (BMI, kg/m^2)	24.55±2.45	25.37±2.92	0.14
Education			0.2
Diploma or less	31 (64.58)	36 (76.60)	
Higher than diploma	17 (35.42)	11 (23.40)	
Smoking			0.74
Never smoker	41 (85.42)	39 (82.98)	
Ever smoker	7 (14.58)	8 (17.02)	
Alcohol			0.31
Non drinker	42 (87.50)	44 (93.62)	
Drinker	6 (12.5)	3 (6.38)	
H.pylori infection			>0.001
No	31 (64.58)	15 (31.91)	
Yes	17 (35.42)	32 (68.09)	
Regular Physical Activity			0.61
Yes	14 (29.17)	16 (34.04)	
No	34 (70.83)	31 (65.96)	
Aspirin/NSAID use			0.75
No	43 (89.58)	43 (91.49)	
Yes	5 (10.42)	4 (8.51)	
Cancer history in an immediate family member			0.72
Yes	5 (10.42)	6 (12.77)	
No	43 (89.58)	41 (87.23)	

[a], ANOVA was used for continuous variables and Chi-square was used for categorical variables; [b], Based on the t-test of difference in means (continuous variables) or proportions (categorical variables); DII, Dietary Inflammatory Index.

Table 3. Partial Correlation Coefficient between DII and Serum Levels of Inflammatory Factors in the Subjects (N=177)

	Partial correlation coefficient	P-value
Model 1		
High-sensitivity C-reactive protein (mg/L)	0.328	>0.001
Tumor necrosis factor-alpha (pg/ml)	0.373	>0.001
Interleukin-6 (pg/ml)	0.337	>0.001
Interleukin-1 beta (pg/ml)	0.326	>0.001
Interleukin-4 (pg/ml)	0.046	0.544
Interleukin-10 (pg/ml)	-0.333	>0.001
Model 2		
High-sensitivity C-reactive protein (mg/L)	0.315	>0.001
Tumor necrosis factor-alpha (pg/ml)	0.356	>0.001
Interleukin-6 (pg/ml)	0.307	>0.001
Interleukin-1 beta (pg/ml)	0.302	>0.001
Interleukin-4 (pg/ml)	0.001	0.986
Interleukin-10 (pg/ml)	-0.291	>0.001

Model 1, Adjusted for the effects of confounding factors as age and gender; Model 2, Adjusted for the effect of confounding factors such as age, gender, education level, physical activity, smoking, alcohol consumption, use of aspirin/NSAID drugs, Helicobacter pylori infection, family history of gastric cancer, body mass index and energy intake; DII, Dietary Inflammatory Index.

Table 4. Beta estimates and confidence intervals for the association between DII and inflammatory markers, Tabriz, Iran, 2014-2016

	Beta estimates for continuous DII [a,b]	P-value	Beta estimates for continuous DII[a,c]	P-value
C-reactive protein (mg/l)d	0.07 (-0.009, 0.15)	0.08	0.09 (0.006, 0.17)	0.04
Tumor necrosis factor-alpha (pg/ml)	0.15 (0.05, 0.26)	0.003	0.16 (0.05, 0.26)	>0.001
Interleukin (IL)-6 (pg/ml)d	0.17 (0.07, 0.27)	0.001	0.16 (0.06, 0.27)	>0.001
IL-1b (pg/ml)	0.10 (0.01, 0.18)	0.02	0.10 (0.02, 0.19)	>0.001
IL-4 (pg/ml)	0.05 (-0.11, 0.22)	0.55	0.02 (-0.15, 0.19)	0.82
IL-10 (pg/ml)	-0.13 (-0.23, -0.02)	0.02	-0.11 (-0.21, -0.005)	0.04

[a], Beta estimates and 95% confidence intervals (CI) for the inflammatory markers were estimated using linear regression; [b], Age adjusted; [c], Additionally adjusted for sex, BMI, education, smoking, alcohol, H.pylori infection, physical activity, aspirin/NSAID use and energy; [d], Log transformed; DII, Dietary Inflammatory Index; IL, Interleukin.

Table 5. Odds Ratios and Confidence Intervals for the Association between DII and Gastric Cancer, Tabriz, Iran, 2014-2016.

	Dietary Inflammatory Index (categorical) OR (95% CI)		P-Value	DII (Continuous) OR (95% CI)	P-Value
DII	DII≤-1.77	DII>-1.77			
Age-adjusted	1 (ref.)	4.60 (2.29, 9.25)	<0.0001	2.65 (1.79, 3.91)	<0.0001
Multivariable-adjusted [a]	1 (ref.)	3.39 (1.59, 7.22)	0.002	2.65 (1.73, 4.07)	<0.0001

[a], Adjusted for age, sex, BMI, education, smoking, alcohol, H.pylori infection, physical activity, aspirin/NSAID use and energy; DII, Dietary Inflammatory Index; OR, Odds Ratio

a pro-inflammatory diet) were at increased risk of GC. This result supported our hypothesis that consuming a more pro-inflammatory diet is associated with an increased risk of GC. We also observed a significant relationship between IL-6, hsCRP, IL-1b, TNF-alpha and DII scores. This indicates that the DII can predict inflammatory markers in chronic inflammatory states. Also, Table 3 showed an acceptable correlation between the DII and serum levels of inflammatory factors in both models. We found no association between DII scores and Il-4; however, there was a suggestion of reverse association.

The results are consistent with the ability of the DII to predict GC that was observed in an Italian case-control study (Shivappa et al., 2016) in which subjects with the most pro-inflammatory diets had a higher risk of GC compared to subjects with the most anti-inflammatory diet (ORQuartile4vs1 = 2.35, 95% confidence interval, 1.32, 4.20; P-trend = 0.004). In previous studies the DII also has been consistently shown to be associated with inflammatory markers like hs-CRP (Cavicchia et al., 2009), IL-6 (Wirth et al., 2014; Tabung et al., 2015; Vahid et al., 2017a; Vahid et al., 2017b), TNF-alpha (Tabung et al., 2015) and homocysteine (Shivappa et al., 2015); hence, this study provides additional evidence that diet plays a role in the regulation of inflammation, even after careful control of a wide variety of potential confounders. Also, in another study, we evaluated validity of DII in women with recurrent abortion (Vahid et al., 2017b). The results of that study Vahid et al., (2017b) showed that the DII can predict Il-6 in chronic inflammatory states. Although in the present study, in addition to Il-6 we have seen a significant association between the DII and other inflammatory markers.

The use of the DII has several unique advantages over other dietary measures and was designed specifically for reference to inflammation (Shivappa et al., 2014a). Despite the limited evidence on the relationship between overall inflammatory effects of diet and GC risk, other studies have reported comparable associations between GC risk and anti-inflammatory foods (e.g., fruits and vegetables) (Pakseresht et al., 2011; Yassibas et al., 2012), nutrients (e.g., fiber, selenium, and folate) (Nemati et al., 2012; Yassibas et al., 2012; Gao et al., 2013), and other bioactive compounds (e.g., flavonoids) (Yassibas et al., 2012; Alberici Pastore et al., 2013).

Previous studies have found that certain nutrients such as omega-3 fatty acids (Lopez-Garcia et al., 2004); fiber (Bo et al., 2006); moderate consumption of wine and alcohol (Imhof et al., 2001); vitamin E (Murphy et al., 2004); vitamin C (Bertran et al., 2005), beta-carotenes (Bertran et al., 2005) and magnesium (Bo et al., 2006) are associated with low levels of inflammation. 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. 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 standardizes 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 (Shivappa et al., 2014a).

The positive association observed between the DII and GC in this case-control study is very encouraging. One of the possible mechanisms for the positive association between the DII and the risk of GC and other chronic inflammatory states might be through the effect of a pro-inflammatory diet on insulin resistance, which is known to increase systemic inflammation (Festa et al., 2000; Vahid et al., 2017c). Previous studies (Egi et al., 2007; Fichtner-Feigl et al., 2015; Lin et al., 2015) have

noted chronic and systemic inflammation's role in GC. This study adds to evidence suggesting that diet-associated inflammation is involved in the etiology of GC. Further work will need to be done to assess attributable risk and delineate the exact mechanism of action.

An important strength of this study is that it is the first one to examine the association between DII scores and GC while validating the index with inflammatory markers in the same study. Another important strength is the use of a validated and reproducible FFQ (Mirmiran et al., 2010), which allowed for a comprehensive assessment of major nutrient sources in the diet, although some measurement error inherent in the FFQ may be present. Also, controls were selected carefully by ensuring that none of them had any condition related to diet or other major risk factors associated with GC. However, in addition to its strengths, the study has certain weaknesses that need to be considered. As with other case-control studies, recall bias and selection bias were inevitable. However, administering validated FFQ by trained interviewer in a hospital setting might have further reduced the recall bias and improved comparability of information of cases and controls.

In conclusion, subjects who consumed a more pro-inflammatory diet were at increased odds of GC compared to those who consumed a more anti-inflammatory diet. Thus, encouraging intake of more anti-inflammatory dietary factors, such as omega-3 fatty acids, plant-based foods rich in fiber, beta-carotenes 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 risk of some cases of GC. Future studies are needed to gain insight into the relationship between diet-associate inflammation and the risk of GC; this would deepen understanding of the role of diet in gastric carcinogenesis. Future research also should test whether changing the inflammatory potential of diet can reduce chronic inflammation and the risk of GC. In so doing, the utility of the DII can be extended to clinical settings to address inflammatory potency of one's diet, and possibly reduce future risk of chronic inflammatory-related diseases.

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Conflict of Interests

The authors declare no conflict of interests.

Disclosure

Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI.

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References

Alberici Pastore C, Paiva Orlandi S, Gonzalez MC (2013). Association between an inflammatory-nutritional index and nutritional status in cancer patients. *Nutr Hosp*, **28**, 188-93.

Babaei M, Mousavi S, Malek M, et al (2005). Cancer occurrence in Semnan Province, Iran: results of a population-based cancer registry. *Asian Pac J Cancer Prev*, **6**, 159-64.

Bertran N, Camps J, Fernandez-Ballart J, et al (2005). Diet and lifestyle are associated with serum C-reactive protein concentrations in a population-based study. *J Lab Clin Med*, **145**, 41-6.

Bo S, Durazzo M, Guidi S, et al (2006). Dietary magnesium and fiber intakes and inflammatory and metabolic indicators in middle-aged subjects from a population-based cohort. *Am J Clin Nutr*, **84**, 1062-9.

Cavicchia PP, Steck SE, Hurley TG, et al (2009). A new dietary inflammatory index predicts interval changes in serum high-sensitivity C-reactive protein. *J Nutr*, **139**, 2365-72.

Dalziel K, Segal L, de Lorgeril M (2006). A mediterranean diet is cost-effective in patients with previous myocardial infarction. *J Nutr*, **136**, 1879-85.

Egi Y, Ito M, Tanaka S, et al (2007). Role of Helicobacter pylori infection and chronic inflammation in gastric cancer in the cardia. *Jpn J Clin Oncol*, **37**, 365-9.

Esposito K, Ciotola M, Giugliano D (2006). Mediterranean diet, endothelial function and vascular inflammatory markers. *Public Health Nutr*, **9**, 1073-6.

Esposito K, Marfella R, Ciotola M, et al (2004). Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA*, **292**, 1440-6.

Fei SJ, Xiao SD (2006). Diet and gastric cancer: a case-control study in Shanghai urban districts. *Chin J Dig Dis*, **7**, 83-8.

Festa A, D'Agostino R Jr, Howard G, et al (2000). Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation*, **102**, 42-7.

Fichtner-Feigl S, Kesselring R, Strober W (2015). Chronic inflammation and the development of malignancy in the GI tract. *Trends Immunol*, **36**, 451-9.

Fock KM, Talley N, Moayyedi P, et al (2008). Asia-Pacific consensus guidelines on gastric cancer prevention. *J Gastroenterol Hepatol*, **23**, 351-65.

Galland L (2010). Diet and inflammation. *Nutr Clin Pract*, **25**, 634-40.

Gao S, Ding LH, Wang JW, et al (2013). Diet folate, DNA methylation and polymorphisms in methylenetetrahydrofolate reductase in association with the susceptibility to gastric cancer. *Asian Pac J Cancer Prev*, **14**, 299-302.

Giugliano D, Ceriello A, Esposito K (2006). The effects of diet on inflammation: emphasis on the metabolic syndrome. *J Am Coll Cardiol*, **48**, 677-85.

Grivennikov SI, Greten FR, Karin M (2010). Immunity, inflammation, and cancer. *Cell*, **140**, 883-99.

Imhof A, Froehlich M, Brenner H, et al (2001). Effect of alcohol

consumption on systemic markers of inflammation. *Lancet*, **357**, 763-7.
Keibel A, Singh V, Sharma MC (2009). Inflammation, microenvironment, and the immune system in cancer progression. *Curr Pharm Des*, **15**, 1949-55.
Khansari N, Shakiba Y, Mahmoudi M (2009). Chronic inflammation and oxidative stress as a major cause of age-related diseases and cancer. *Recent Pat Inflamm Allergy Drug Discov*, **3**, 73-80.
Lin R, Xiao D, Guo Y, et al (2015). Chronic inflammation-related DNA damage response: a driving force of gastric cardia carcinogenesis. *Oncotarget*, **6**, 2856-64.
Lopez-Garcia E, Schulze MB, Manson JE, et al (2004). Consumption of (n-3) fatty acids is related to plasma biomarkers of inflammation and endothelial activation in women. *J Nutr*, **134**, 1806-11.
Macarthur M, Hold GL, El-Omar EM (2004). Inflammation and Cancer II. Role of chronic inflammation and cytokine gene polymorphisms in the pathogenesis of gastrointestinal malignancy. *Am J Physiol Gastrointest Liver Physiol*, **286**, 515-20.
Malekzadeh R, Derakhshan MH, Malekzadeh Z (2009). Gastric cancer in Iran: epidemiology and risk factors. *Arch Iran Med*, **12**, 576-83.
Mirmiran P, Esfahani FH, Mehrabi Y, et al (2010). Reliability and relative validity of an FFQ for nutrients in the Tehran lipid and glucose study. *Public Health Nutr*, **13**, 654-62.
Mousavi SM, Gouya MM, Ramazani R, et al (2009). Cancer incidence and mortality in Iran. *Ann Oncol*, **20**, 556-63.
Murphy RT, Foley JB, Tome MT, et al (2004). Vitamin E modulation of C-reactive protein in smokers with acute coronary syndromes. *Free Radic Biol Med*, 36, 959-65.
Nemati A, Mahdavi R, Naghizadeh Baghi A (2012). Case-control study of dietary pattern and other risk factors for gastric cancer. *Health Promot Perspect*, **2**, 20-7.
Pakseresht M, Forman D, Malekzadeh R, et al (2011). Dietary habits and gastric cancer risk in north-west Iran. *Cancer Causes Control*, **22**, 725-36.
Parkin DM, Bray F, Ferlay J, et al (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, **55**, 74-108.
Sadjadi A, Malekzadeh R, Derakhshan MH, et al (2003). Cancer occurrence in Ardabil: results of a population-based cancer registry from Iran. *Int J Cancer*, **107**, 113-8.
Shivappa N, Hebert JR, Rietzschel ER, et al (2015). Associations between dietary inflammatory index and inflammatory markers in the Asklepios Study. *Br J Nutr*, **113**, 665-71.
Shivappa N, Hebert JR, Rosato V, et al (2016). Dietary inflammatory index and risk of bladder cancer in a large Italian case-control study. *Urology*, **100**, 84-9.
Shivappa N, Steck SE, Hurley TG, et al (2014a). Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*, **17**, 1689-96.
Shivappa N, Steck SE, Hurley TG, et al (2014b). A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). *Public Health Nutr*, **17**, 1825-33.
Siegel R, Naishadham D, Jemal A (2013). Cancer statistics, 2013. *CA Cancer J Clin*, **63**, 11-30.
Somi MH, Farhang S, Mirinezhad SK, et al (2008). Cancer in East Azerbaijan, Iran: results of a population-based cancer registry. *Asian Pac J Cancer Prev*, **9**, 327-30.
Tabung FK, Steck SE, Zhang J, et al (2015). Construct validation of the dietary inflammatory index among postmenopausal women. *Ann Epidemiol*, **25**, 398-405.
Torre LA, Bray F, Siegel RL, et al (2015). Global cancer statistics, 2012. *CA Cancer J Clin*, **65**, 87-108.
Vahid F, Shivappa N, Hekmatdoost A, et al (2017a). Association between maternal dietary inflammatory index (DII) and abortion in Iranian women and validation of DII with serum concentration of inflammatory factors: case-control study. *Appl Physiol Nutr Metab*, **42**, 511-6.
Vahid F, Shivappa N, Hekmatdoost A, et al (2017b). Association between maternal dietary inflammatory index (DII) and abortion in Iranian women and validation of DII with serum concentration of inflammatory factors: Case-control study. *Appl Physiol Nutr Metab,* **42**, 511-16.
Vahid F, Shivappa N, Karamati M, et al (2017c). Association between dietary inflammatory index (DII) and risk of prediabetes: a case-control study. *Appl Physiol Nutr Metab*, **42**, 399-404.
Vahid F, Zand H, Nosrat-Mirshekarlou E, et al (2015). The role dietary of bioactive compounds on the regulation of histone acetylases and deacetylases: a review. *Gene*, **562**, 8-15.
Valin A, Pablos JL (2015). The role of the transcriptional regulation of stromal cells in chronic inflammation. *Biomolecules*, **5**, 2723-57.
Wirth MD, Burch J, Shivappa N, et al (2014). Association of a dietary inflammatory index with inflammatory indices and metabolic syndrome among police officers. *J Occup Environ Med*, **56**, 986-9.
Wood LG, Shivappa N, Berthon BS, et al (2015). Dietary inflammatory index is related to asthma risk, lung function and systemic inflammation in asthma. *Clin Exp Allergy*, **45**, 177-83.
Yassibas E, Arslan P, Yalcin S (2012). Evaluation of dietary and life-style habits of patients with gastric cancer: a case-control study in Turkey. *Asian Pac J Cancer Prev*, **13**, 2291-7.