RESEARCH ARTICLE

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Dietary Inflammatory Index and Odds of Colorectal Cancer in a Case- Control Study from Iran

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Abstract

Background: In Iran, colorectal cancer (CRC) is the third and fourth leading cause of cancer incidence among men and women, respectively. Diet and inflammation have been suggested as important risk factors for CRC. We examined the association between dietary inflammatory index (DII) scores and CRC in a case-control study conducted in Iran. **Methods:** This study included 71 CRC cases and 142 controls hospitalized for acute non-neoplastic diseases. DII scores were computed from dietary intake assessed by a previously validated food frequency questionnaire. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CI) adjusted for age, sex, education, energy intake, exercise, body mass index (BMI), smoking, family history of cancer, and history of aspirin, acetaminophen, and multivitamin use. **Results:** Subjects with higher DII scores (i.e., indicating a more pro-inflammatory diet) had a higher odds of CRC with the DII being used as both a continuous variable (OR continuous = 2.20, 95% CI: 1.22-3.87) and as a categorical variable (OR tertile 3 vs tertile1 = 2.47, 95%CI: 1.10-5.55). **Conclusion:** These results indicate that a pro-inflammatory diet is associated with increased odds of CRC in this Iranian population.

Keywords: Dietary inflammatory index- colorectal cancer- case-control

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Introduction

Chronic inflammation, which is characterized by the continuous presence of inflammatory cytokines in circulation and other tissues, is known to play a key role in the development of colorectal cancer (CRC) (Chung and Chang, 2003; Terzic et al., 2010; Toriola et al., 2013). There is growing evidence that specific dietary components influence both inflammation (Simopoulos, 2002; Santos et al., 2013; Bordoni et al., 2017) and CRC (Michaud et al., 2005; Miller et al., 2010; Stefani et al., 2011; Miller et al., 2013). Among Iranians, CRC is the third and fourth most commonly diagnosed malignancy in males and females, respectively (Safari et al., 2013). In the last few decades, CRC incidence and mortality rates have increased markedly in Iran (Mousavi et al., 2008; Kolahdoozan et al., 2010).

A literature-derived, population-based dietary inflammatory index (DII) was developed to assess the inflammatory potential of individuals' diets (Shivappa et al., 2014), and has been validated with various inflammatory markers, including C-reactive protein (Shivappa et al., 2014; Wirth et al., 2014), interleukin-6 (Ruiz-Canela et al., 2015; Tabung et al., 2015; Wood et al., 2015), and tumor necrosis factor-alpha (Tabung et al., 2015). Additionally, the DII has been shown to be associated with CRC in US (Shivappa et al., 2014; Tabung et al., 2015; Wirth et al., 2015, Harmon et al., 2017) and European (Shivappa et al., 2015a; Zamora-Ros et al., 2015) populations. However, the DII and CRC association has not been examined in a Middle Eastern population to date. In this study, we explore the association between the DII and CRC in a case-control study in Iran (Safari et al., 2013). Previously in this case-control study a "healthy" dietary pattern identified by principal component analyses was significantly associated with a decreased risk of CRC, while an increased CRC risk was observed with the "Western" dietary pattern (Safari et al., 2013). The DII has been used in an Iranian population in the past; with higher DII scores shown to be associated with increased risk of esophageal squamous cell cancer (ESCC) (Shivappa et al., 2015b) and ulcerative colitis (Shivappa et al., 2016). However, considering the incidence of CRC, no work has been done to understand the role of proinflammatory diets in Iranian populations.

We hypothesized that participants with more-

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proinflammatory diets (i.e., higher DII scores) would have a greater risk of CRC. This study provided original information on an Iranian population where dietary and lifestyle habits and awareness of diet-related health issues are different from those in North America and Europe.

Materials and Methods

Participant recruitment

This hospital-based case–control study was conducted from September 2008 through January 2010 in 19 CRC surgical units of the Cancer Institute of Imam Khomeini Hospital Complex and three major general hospitals (Shariati, Imam Hussein and Taleghani) in the city of Tehran, Iran.

These hospitals are located in different regions of the Tehran municipality and represent populations with different socioeconomic status.

Since there was no other study on the role on DII on the colorectal cancer (when we started our study), we referred to studies carried out in Uruguay (Stefani et al., 2011) or Canadian adults (Chen et al., 2015), that demonstrated that a healthy dietary pattern decreases the risk of colorectal cancer by 55%.

Cases were patients with pathologically confirmed CRC, diagnosed ≤6 months before the interview, were 40–75 years of age at the time of diagnosis, and had no previous diagnosis of cancer at other anatomic sites, prior history of inflammatory bowel disease, or familial adenomatous polyposis.

All consecutive patients with a histopathology confirmed diagnosis of CRC were included as cases. Diagnosis of CRC was confirmed by per-rectal sigmoidoscopic or endoscopic biopsy. In cases where resection for colorectal malignancy was done as an emergency surgical procedure, the diagnosis was confirmed post operatively. CRC patients with co-existing malignancy (i.e., a different primary) were excluded. Controls were selected randomly from patients admitted to the same hospitals as cases during the same time period for acute, nonneoplastic conditions. The exclusion of controls would be applied only to subjects admitted because of a diet-related disease. They were admitted to the hospitals for various medical conditions (38% for fractures and sprains, 14.1% for osteoarticular disorders, 11.3% for disk disorders, 9.8% for acute surgical conditions (e.g., hernia inguinalis, appendicitis and kidney stone), 7.0% for trauma and injuries, 7.0% for skin diseases and 12.0% for other illnesses; e.g., eye or nose disorders, debridement, removal of plates, pins, screws and wires). Each patient with CRC was matched with two patients in the control group by age (within 5-year categories) and sex. When more than 2 controls were eligible then two controls were randomly selected from the available controls.

Of 267 patients (89 cases and 178 controls) screened for the study based on inclusion and exclusion criteria, 8 cases and 16 controls were excluded. Thirty additional patients (10 cases and 20 controls) with incomplete food frequency questionnaires (FFQ with > 40% of food items not assessed) and whose total energy intakes were outside the range of ± 3 standard deviation from the mean (< 716 and > 3,764 Kcal/d for men and <541 and >3,397 Kcal/d for women) were excluded. The final sample for statistical analysis was 71 cases and 142 controls. Less than 20% of cases and controls were ineligible to participate to the study.

The present study was approved by the Medical Research and Ethics Committee of University Putra Malaysia, Faculty of Medicine and Health Sciences and the Ministry of Health, Treatment Medical and Education of Iran. Written informed consents were obtained from all respondents prior to the interviews.

Data collection

Professionally trained dietitians interviewed all 71 cases and 142 controls deemed to be fully eligible, using a structured, previously validated questionnaire (Mimiran et al., 2010), which focused the respondent on lifestyle behaviors, including diet, in the year before diagnosis (for cases) or interview date (for controls). The interviewer-administered FFQ consists of 125 food items with standard serving sizes. Participants were asked to specify their consumption frequency for each food item on a daily, weekly, monthly or yearly basis. Nutrient consumption was then calculated using the Nutrient Composition of Iranian Foods (NCIF) (Mirmiran et al., 2010) supplemented with the USDA Food Composition Data. The consumption of alcohol was not asked to our participants due to their cultural beliefs and concomitant low levels of intake. Therefore, alcohol was not included in the analysis. Other questions on education, physical activity, family history of CRC, smoking and NSAID use also were asked in the same interview setting. Height was measured to the nearest 0.1 cm and Body weight to the nearest 0.1 kg using a SECA electronic scale. All participants wearing minimal clothes without shoes. Body mass index (BMI) was calculated by dividing each subject's weight, in kilograms, by the square of her/his height, in meters.

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 intake standard database. A complete description of the DII is available elsewhere (Shivappa et al., 2014). 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., 2014). Briefly, the literature relating to the association between dietary components and six different inflammatory markers (IL-1β, IL-4, IL-6, IL-10, TNF-α and C-reactive protein) published from 1950 to 2010 was reviewed. Each of the 45 different food parameters identified as being related to the six inflammatory biomarkers in this massive search was assigned a "food parameter-specific inflammatory effect score" through a process of counting the number of studies reporting pro-inflammatory, anti-inflammatory, and no effects on the six inflammatory markers, and weighting the scores by study design and size of the literature pool. A total of 26 food parameters were available from the FFQ

and therefore could be used to calculate DII (carbohydrate, protein, total fat, fiber, cholesterol, saturated fat, mono-unsaturated fat, poly unsaturated 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).

To calculate DII for the participants of this study, the dietary data were first linked to the regionally representative world database that provided an estimate of a mean intake and standard deviation for each food parameter (Shivappa et al., 2015a,b). 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 was 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-specific inflammatory effect score, which is derived from the literature review, as described above, 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., 2015). The steps are depicted and described in Figure 1.

Statistical Analyses

The DII was analyzed both as a continuous variable and as tertiles with cut points derived from controls. The DII, as tertiles, was examined across the following characteristics: age, sex, education, exercise, BMI, smoking, family history of cancer in first-degree and second-degree relatives, history of aspirin or acetaminophen use and history of multivitamin intake. The Kolmogorov-Smirnov test was used to evaluate the normal distribution of quantitative variables. Student t-tests or χ^2 tests were used for continuous and categorical variables, respectively. Odds ratios and 95% confidence intervals (OR; 95% CI) were estimated using logistic regression models, adjusting only for age and sex, and then fitting a model with additional adjustment for education, leisure-time physical activity, BMI, smoking, family history of cancer, history of using aspirin, acetaminophen, and multivitamins. Energy adjustment was done using the residual method (Willett and Stampfer, 1986). P-value for trend was determined with value of the median DII in each tertile. After testing for interaction, analyses were carried out stratified by sex. Because of relatively small sample sizes, for the sex-stratified analyses, categories of DII were calculated based on the median levels of DII. Statistical tests were performed using SAS® 9.3 (SAS Institute Inc., Cary, NC); all p values were based on two-sided tests.

Results

DII scores in this study ranged from -2.48 (most anti-inflammatory score) to +4.17 (most pro-inflammatory score). Table 1 shows the socio-demographic and lifestyle characteristics of the 71 cases and 142 controls. Because of the frequency-matched design, controls and cases were similar on age and sex. The mean age of respondents at diagnosis of CRC was 59.9±10.3 years for men and 55.6±10.3 years for women. Although there was not a statistical difference between cases and controls in terms of education, leisure time physical activity or smoking status, results suggest that controls were better educated, more physically active during leisure time and more likely to have never smoked. Cases were more likely than controls to have a family history of CRC in first- (p=0.004) and second-degree relatives (p=0.003). The mean BMI appeared to be slightly higher in cases than controls, but did not differ statistically. Cases had significantly higher mean DII scores compared to controls (0.16±0.62 vs -0.08±0.51, p-value=0.003). Control characteristics across categories of DII are provided in Table 2. There were some differences in sociodemographic factors, and lifestyle habits across DII categories. In particular, participants in the third tertile of DII were significantly more likely to be female.

Table 1. Characteristics of Patients in an Iranian Colorectal Cancer Case-Control Study, 2008-10 (n=213).

Characteristics	Controls N =142	Cases N =71	**P-value
Age, (years): mean ± sd	57.7±10.5	58.2±10.5	*
Sex, n (%)			*
Male	70 (49.3)	35 (49.3)	
Female	72 (50.7)	36 (50.7)	
Body Mass Index, (kg/m2): mean ± sd	26.7±4.2	27.2±4.2	0.36
Dietary Inflammatory Index (DII): mean ± sd*	-0.08±0.51	0.16±0.62	0.003
Family history of CRC in first degree, n (%)	2 (1.4)	7 (9.9)	0.004
Family history of CRC in second degree, n (%)	1 (0.7)	6 (8.5)	0.003
Education, n (%)			0.15
No formal education	36 (25.4)	28 (39.4)	
Elementary	45 (31.7)	22 (31.0)	
Junior/Senior High School	19 (9.2)	7 (9.9)	
Diploma/College/University	42 (29.6)	14 (19.7)	
Leisure-time physical activity, n (%)			0.5
Never	44 (31.0)	32 (45.1)	
Rarely	39 (27.5)	20 (28.2)	
Sometimes	37 (26.1)	14 (19.7)	
Always	21 (14.8)	5 (7.0)	
Smoking n (%)			0.95
Never smoker	101 (71.1)	57 (80.3)	
Former smoker	15 (10.6)	8 (11.3)	
Current smoker	26 (18.3)	6 (8.4)	
Non-steroidal anti-inflammatory drugs use n (%)			
Ibuprofen	22 (15.5)	5 (7.1)	0.08
Aspirin	16 (11.3)	1 (1.4)	0.01
Acetaminophen	29 (20.42)	4 (5.6)	0.05
Baby aspirin	19 (13.4)	15 (21.1)	0.15

*Matched variables of the study. **P-values were estimated using chi-square ($\chi 2$) statistics, independent t-test for the difference between case and control groups.

Table 2. Participant Characteristics by Level of Dietary Inflammatory Index (DII) among Controls, Iranian Colorectal Cancer Case-Control Study, 2008-10 (n=142).

	Tertile 1 ≤ -0.30	Tertile 2 -0.29 to 0.18	Tertile 3 >0.18	P-Value[a,b]
Age, (years): mean ± sd	57.8±9.4	57.1±10.8	58.3±11.3	0.83
Sex, n (%):				0.01
Males	32 (66.7)	21 (44.7)	17 (36.2)	
Females	16 (33.3)	26 (55.3)	30 (63.8)	
Body Mass Index (kg/m2): mean ± sd	26.8±4.0	27.1±4.5	26.1±4.	0.45
Education, n (%)				0.49
No formal education	10 (20.8)	9 (19.2)	17 (36.2)	
Elementary	20 (41.7)	18 (38.3)	13 (27.7)	
Junior/Senior High School	5 (10.4)	5 (10.6)	3 (6.4)	
Diploma/College/University	13 (27.1)	15 (31.9)	14 (29.8)	
Leisure-time physical activity, n (%)				0.43
Never	12 (25.0)	16 (34.0)	16 (34.0)	
Rarely	12 (25.0)	10 (21.3)	17 (35.2)	
Sometimes	14 (29.2)	13 (27.8)	10 (21.3)	
Always	10 (20.8)	7 (14.9)	4 (8.5)	
Smoking, n (%)				0.12
Never smoker	29 (60.4)	34 (72.3)	38 (80.8)	
Former smoker	6 (12.5)	7 (14.9)	2 (4.3)	
Current smoker	13 (27.1)	6 (12.8)	7 (14.9)	

[a], Student t-test was used for continuous variables; [b], Chi-square test was used for categorical variables

ORs and 95% CIs for the risk of CRC are shown in Table 3. Results obtained from modeling DII as a continuous variable in relation to risk of CRC showed a positive association after adjustment for age and sex (OR=2.24; 95% CI=1.29-3.87); and were nearly identical in the multivariable analyses (OR=2.20; 95% CI=1.22-3.96). When analyses were carried out with DII expressed as tertiles, and adjusting for age, subjects in tertile 3 had an OR of 2.63 (95% CI= 1.27-5.39) in comparison to subjects in tertile 1. Again, after multivariable adjustment, results were essentially identical as in the model adjusting only for age (OR tertile 3vs1=2.47; 95% CI=1.10-5.55).

Test for interaction between DII and sex was statistically significant (P-value <0.0001), ORs and 95% CIs for the risk of CRC stratified by sex are shown in Table 4. The DII was found to be strongly associated with CRC among males, while no association was observed among females.

Discussion

In this Iranian case-control study, we found that subjects with a higher DII score (i.e., those who had more pro-inflammatory diets) were at increased odds of CRC compared to subjects with more anti-inflammatory diets. This result supports accumulating evidence showing that consuming a more pro-inflammatory diet is associated with increased CRC risk. Previously, the DII has been shown to be positively associated with CRC in three cohort studies in the US (Shivappa et al., 2014; Tabung et al., 2015; Wirth et al., 2015) and in two case-control studies in Europe (Shivappa et al., 2015a; Zamora-Ros et al., 2015). This is the first study in a Middle-Eastern

Table 3. Odds Ratios and 95% Confidence Intervals for the Association between DII and Colorectal Cancer in an Iranian Case-Control Study, 2008-10 (n=213).

	Energy adjusted-DII (Tertiles) OR (95% CI)				Energy adjusted-DII	
DII	Tertile 1	Tertile 2	Tertile 3	P_{trend}-value[a]	(Continuous)[b] OR (95% CI)	P-Value
	≤ -0.30	-0.29 to 0.18	>0.18			
Cases/controls	15/48	18/47	38/47		71/142	
Age and sex adjusted	1 (ref.)	1.24 (0.56, 2.75)	2.62 (1.27, 5.39)	0.006	2.24 (1.29, 3.87)	0.004
Multivariate-adjusted [c]	1 (ref.)	1.32 (0.54, 3.21)	2.47 (1.10, 5.55)	0.02	2.20 (1.22, 3.96)	0.01

[a], p-value for trend derived using the median approach; [b], One unit increase corresponding to ≈34% of its range in the current study; [c], Adjusted for age, sex, education, exercise, BMI, smoking, family history of cancer, history of aspirin use, history of acetaminophen use and history of multivitamin intake.

Table 4. Odds Ratios and 95% Confidence Intervals for the Association between DII and Colorectal Cancer Stratified by Sex in an Iranian Case-Control Study, 2008-10 (n=213).

	Energy Adjusted-DII (Tertiles) OR (95% CI)		P_{trend}-value[a]	Energy adjusted-DII (Continuous)[b] OR (95% CI)	P-Value[c]
DII	DII	DII			<0.0001
	≤ -0.23	>-0.23			
Males (N=105)					
Cases/controls	3/35	32/35		35/70	
Multivariate-adjusted [d]	1 (ref.)	33.95 (3.72, 309.44)	0.0003	21.67 (4.71, 99.79)	
Females (N=108)					
	DII	DII			
	≤ 0.06	>0.06			
Cases/controls	21/36	15/36		36/72	
Multivariate-adjusted [d]	1 (ref.)	0.60 (0.22, 1.61)	0.15	0.43 (0.17, 1.11)	

[a], p-value for trend derived using the median approach; [b], One unit increase corresponding to ≈34% of its range in the current study; [c], P-value for interaction between DII and sex; [d], Adjusted for age, education, exercise, BMI, smoking, family history of cancer, history of aspirin use, history of acetaminophen use and history of multivitamin intake.

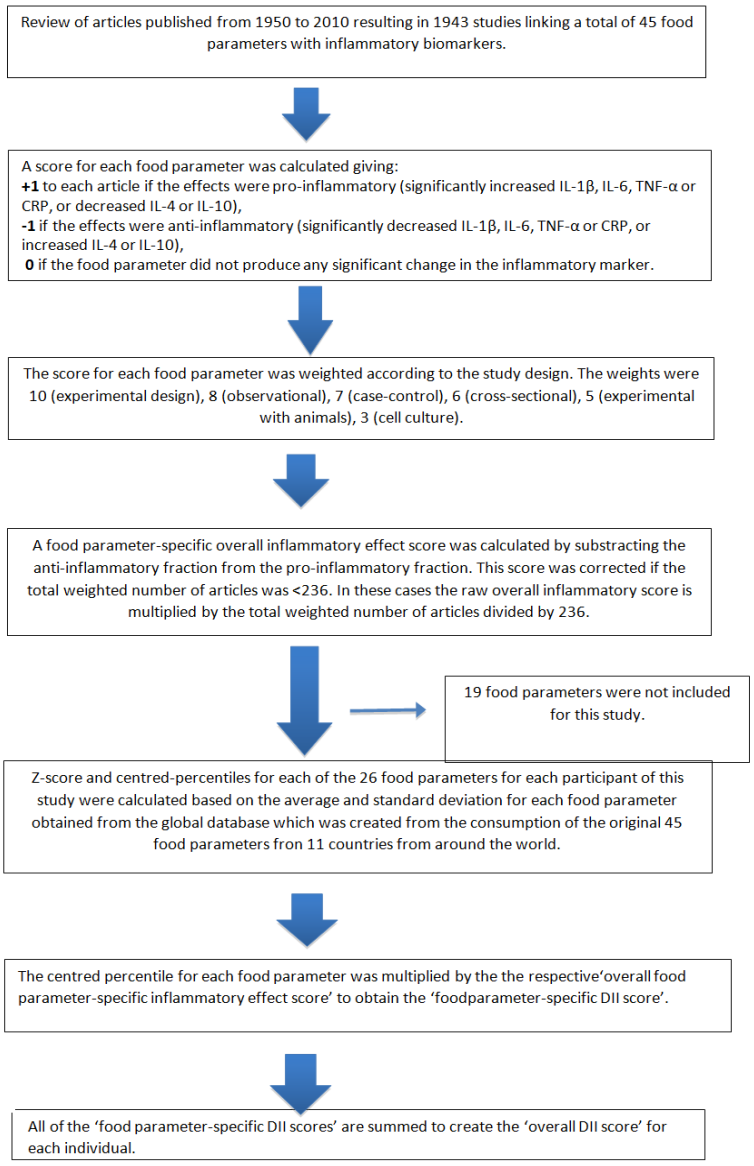

Figure 1. Sequence of Steps in Creating the Dietary Inflammatory Index in the Iranian Colorectal Cancer Case-Control Study

population to examine the DII in relation to CRC. Even though DII scores were distributed across a more limited range in this population (-2.48 to +4.17) than in other studies (ranges reported up to -7.05 to 5.64) (Tabung et al., 2015), a significant positive association was still observed.

Consumption of fiber-rich food items such, vegetables and fruits has been shown to reduce inflammation (Defago et al., 2014; Baena and Salinas, 2015), while other foods, such as red and processed meat, increase inflammation (Lopez-Garcia et al., 2014). Indeed, in a previous report on this Iranian case-control study, a healthy dietary pattern characterized by high consumption of vegetables, fruits, olives and fish was inversely associated with CRC, and in the same study, a Western dietary pattern characterized by the high consumption of red meat and refined grains was associated with increased odds of CRC (Safari et al., 2013). The difference between the previous and the current study is that in the previous study authors examined various dietary patterns such as Healthy and Western, which were determined by categorizing 125 food items into 31 food groups based on the similarity of their nutrient content, use in cooking or their relationship with cancer (Safari et al., 2013). In the current study we considered the inflammatory potential of diet and did not restrict our analysis to any dietary pattern. In this regard, it is important to note that the inflammatory effect score for each food parameter is determined by careful review of literature published from 1950 to 2010 that looked at the association between each of the 45 food parameters and inflammation.

A systematic review of cohort studies from 2000-2011 showed a Western dietary pattern, consisting mainly of red and processed meat and refined grains, is associated with an elevated risk of developing CRC. A healthy or prudent diet, consisting of vegetables, fruits, fish and poultry (Yusof et al., 2012) was found to be protective against CRC. Another systematic review published in 2012 showed that a healthy dietary pattern, characterized by high fruit/vegetables consumption decreased risk of colon cancer, whereas a Western dietary pattern characterized by high red/processed meat consumption increased risk of colon cancer (Magalhaeset al., 2012). In formulating the DII, a new approach to dietary index analyses was taken by focusing on the functional effects of foods and nutrients and scoring the peer-reviewed literature related to diet and inflammation (Shivappa et al., 2014). Moreover, it standardizes individuals' dietary intakes of pro- and anti-inflammatory food constituents to world referent daily intake amounts. This results in values that are not dependent on idiosyncrasies of the units of consumption (e.g., simply expressing exposure in micrograms instead of milligrams results in values that differ by 3 orders of magnitude) and results can be used for direct comparison across studies. We showed in comparison of simulated diets that the DII was found to be highest for a Western, fast-food diet compared to either a Mediterranean or a Macrobiotic (modified Japanese) diet (Steck et al., 2014).

There are several lines of evidence linking inflammation to CRC. Chronic inflammation increases tumorigenesis in experimental models; individuals with chronic inflammation of the colon, such as ulcerative colitis and Crohn's disease are at increased risk of CRC; and the use of NSAIDs has been associated with reduced risk of adenomas, precursors to CRC, in human trials (Jolly et al., 2002; Dube et al., 2007; Ullman and Itzkowitz, 2011; Piazuelo and Lanas, 2015). While chronic NSAIDs use can result in adverse side effects, manipulating diet to improve its inflammatory potential has a much wider safety margin. Evidence from several observational studies comprised of populations from around the world is now building suggesting that the inflammatory potential of diet, as measured by the DII, is associated with risk of CRC (Shivappa et al., 2014; Tabung et al., 2015; Wirth et al., 2015; Shivappa et al., 2015a; Zamora-Ros et al., 2015). Future work examining whether interventions targeted at lowering DII scores can reduce CRC risk is warranted.

We observed strong positive association between DII and CRC among males. This result should be viewed with caution because the sample size was underpowered to carry out stratified analyses by any variable. However, the sample size calculation was based on a formula that is described in the supplementary file to provide the acceptable alpha (5%) and beta errors (20%).

In addition to its small sample size, there are several limitations worth noting in the present study. First, the possibility of selection bias is difficult to avoid in hospital-based case–control studies. The present study minimized this problem by a high (approximately 80%) participation rate of eligible subjects who were approached to participate. Errors in self-reported intake estimates, through which cases may recall their diets differently after a disease diagnosis, may be common in case-control studies (Lindsted and Kuzma, 1989; Kuzma and Lindsted, 1989; Holmberg et al., 1996). The probability of recall bias may have been reduced by using hospital controls and administering FFQs by trained interviewers in a hospital setting. We also know that such dietary self-reports may be plagued by disease-independent response sets, such as social approval and social desirability (Hebert et al., 1997; Heber et al., 2002). Having information on measurement errors may help to control for inaccuracies in dietary recall (Hebert et al., 1995; Heitmann et al., 1996; Hebert et al., 1996; Fewel et al., 2007). However, these response sets were not measured in the study, nor do we know how they would function in Iranian culture. Overall, studies conducted to date suggest that diet may be recalled with acceptable levels of misclassification for up to approximately 10 years. However, it seems reasonable to assume that it would be easier for participants to recall diet a year before diagnosis, rather than many years in the past. Although we would expect diet in the year prior to diagnosis to be similar to usual adult diet for the controls (Willett, 1998), this would not apply to any disease-motivated change in diet that may have occurred in the cases. Another limitation is that only 26 of possible 45 food parameters were available for DII calculation. The food parameters that are missing are flavonoids, turmeric, thyme and others that are usually consumed in relatively small amounts or not consumed at all; hence, they may not have had a major impact on the scoring.

A major limitation of this study is it's hospital-based case-control design. Recruitment from a cancer registry

will be representative of all the cancer cases because every cancer case that is reported is recorded in the registry. If referral hospitals have a specific patient profile that may not represent the total population of cases, then the findings may not be generalizable. However, we tried to recruit our cases from 3 referral hospitals that were located in different regions of the Tehran municipality, each of which represented different socioeconomic status (prosperous, intermediate, and deprived). Hence, we do think that our study subjects well represent the Iranian population regarding educational (literacy rate is 80% for adults) and smoking status and body mass index (Azizi et al., 2009). Furthermore, selection of an appropriate control group for a study of diet and disease also may be problematic. One common practice is to use patients with another disease as a control group, with the assumption that the exposure under study (diet or DII) is unrelated to the condition of this control group (for example orthopedics conditions). Because diet may well affect many diseases, it is often difficult to identify disease groups that are definitely unrelated to the aspects of diet under investigation.

One important strength of the study is that this is one of the first in a Middle Eastern population to explore the association between the inflammatory property of diet and CRC. As diets vary considerably across the globe, it is important to examine the association in a variety of populations with different ways of eating. Of note, the range in DII scores in this Iranian population was narrower than in other populations that we have studied in North America. This may be a reflection of the reduced number of DII food parameters available from the dietary data in this study, or a true difference in the heterogeneity of inflammatory potential of diets across populations. Future work with larger study populations and more detailed dietary assessment is warranted to confirm these findings.

In conclusion, it appears that a low DII score is associated with lower CRC risk. Thus, encouraging intake of more anti-inflammatory dietary factors, such as plant-based foods rich in fiber and phytochemicals, and reducing intake of pro-inflammatory factors, such as fried or processed foods rich in saturated fat or trans-fatty acids, may be a strategy for reducing risk of CRC.

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. The subject matter of this paper will have no direct bearing on the work of CHI, nor has any CHI-related activity exerted any influence on this project.

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