Published in final edited form as:

Nutr Cancer. 2015 ; 67(8): 1253–1259. doi:10.1080/01635581.2015.1082108.

Dietary Inflammatory Index and risk of esophageal squamous cell cancer in a case-control study from Iran

Nitin Shivappa^{1,2}, James R. Hébert^{1,2}, and Bahram Rashidkhani³

¹Cancer Prevention and Control Program, University of South Carolina, Columbia, SC 29208, USA

²Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC 29208, USA

³Department of Community Nutrition, Faculty of Nutrition Sciences and Food Technology, National Nutrition and Food Technology Research Institute (WHO Collaborating Center), Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background—Diet and inflammation have been suggested to be important risk factors for esophageal squamous cell carcinoma (ESCC). In this study, we examined the ability of the dietary inflammatory index (DII) to predict ESCC in a case-control study conducted in Iran.

Methods—This study included 47 ESCC cases and 96 controls hospitalized for acute non-neoplastic diseases. The DII was computed based on dietary intake assessed by a previously validated food frequency questionnaire. Logistic regression models were used to estimate odds ratios (ORs) adjusted for age, energy, sex, BMI, years of education, physical activity, smoking and gastro-esophageal reflux.

Results—Subjects with higher DII scores (i.e., with a more pro-inflammatory diet) had a higher risk of ESCC, with the DII being used as both a continuous variable (OR_{continuous} 3.58, 95% confidence interval, CI, 1.76–7.26; one unit increase corresponding to ≈16% of its range in the current study) and a categorical variable (OR_{dii>1.20 vs 1.20} 8.24, 95% CI 2.03–33.47).

Conclusion—These results indicate that a pro-inflammatory diet is associated with increased risk of ESCC.

Introduction

Esophageal cancer (EC) is the eighth most common cancer worldwide, with an estimated 456,000 new cases in 2012 (3.2% of the total), and the sixth most common cause of death

Address correspondence and reprint requests to: Prof. Bahram Rashidkhani, Phone: (0098) 9127388016, Fax: (0098)(21) 22376467, rashidkhani@yahoo.com, b_rashidkhani@sbmu.ac.ir.

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.

from cancer, with an estimated 400,000 deaths (4.9% of the total) (1). There are two type of esophageal cancer (EC) based on histology – squamous cell carcinoma and adenocarcinoma; both are highly lethal, with a 5-year survival rate <10% (2–4). An esophageal “cancer belt,” primarily squamous cell cancers (ESCC), extends from northeast China to the Middle East (5, 6). In this region (where there is a high incidence of esophageal cancer) esophageal squamous cell carcinoma (ESCC) contributes to more than 90% of all EC cases (7) The latest World Cancer Report indicated the highest prevalence of ESCC to be in Iran (8, 9).

Chronic inflammation – which is characterized by the continuous presence of inflammatory cytokines in circulation and in the tissues – is known to play a key role in the development of various epithelial cancers (10, 11). In particular, it has been shown that chronic inflammation is important in triggering the development of EC, especially epithelial damage involved in ESCC (12, 13).

Evidence of an association between environment (including diet) and EC comes from the profound differences in incidence observed in various parts of the world. The majority of the factors, thus far implicated in EC appear to act directly on the esophagus rather than systemically. There also is growing evidence that specific dietary components influence both inflammation (14–17) and ESCC (18–21). Diet represents a complex set of exposures that often interact, and whose cumulative effect modifies both inflammatory responses and health outcomes. A literature-derived, population-based dietary inflammatory index (DII) was developed to assess the inflammatory potential of an individual’s diet (21), and has been validated with various inflammatory markers, including C-reactive protein (17, 22), interleukin-6 (23–25), and homocysteine (23). Additionally, increasing DII has been shown to be associated with the increased glucose intolerant and dyslipidemic components of metabolic syndrome (22, 26), shift work status in a large population-based survey in the USA (27), increased risk of asthma in Australia (25), colorectal cancer in case-control studies in Spain (28) and in cohort studies in USA (29–31) and pancreatic and prostate cancers in Italy (32, 33).

Our hypothesis is that a higher DII score (indicating a pro-inflammatory diet) increases risk of incident ESCC. In the current study, we thus examined the association between DII and ESCC using a case-control study conducted in Iran (34). This provided original information on a Iranian population where dietary and life-style habits and awareness of diet-related health issues are different from those in North America and Europe, and where most ECs are ESCC.

Methods

The current study was conducted in Kurdistan Province in Iran. Cases were 40–75 years old with histologically confirmed ESCC who were identified from hospital records in the major general hospitals in the area under study (Kurdistan Province, Iran) (34, 35). Controls were selected from the same hospitals and were frequency matched to cases on age (± 5 years) and sex. The control group consisted of participants admitted to the same hospital for a wide spectrum of acute non-neoplastic diseases that were unrelated to smoking, alcohol abuse, and long-term diet modification. Controls were hospitalized mainly due to the following

conditions: trauma (25.9%, mostly fractures and sprains), surgical conditions (20.1%, mostly abdominal such as acute appendicitis and kidney stones), non-traumatic orthopedic conditions (4.2%, mostly disk disorders and back pain), and miscellaneous diseases (49.8%, including acute eye, nose, skin, and throat disorders). Fifty ESCC patients and 100 hospital controls were enrolled in the present study. Seven participants were excluded from the analysis because of their total energy intake being either greater than 3 or less than 3 SD from the mean ($n = 2$ controls), missing body mass index (BMI) values ($n = 3$ cases), and poor responses with regard to dietary questions ($n = 2$ controls), which left 47 cases and 96 controls for final analysis. The National Nutrition and Food Technology Research Institute in Iran reviewed and approved all study and ethical procedures, and informed written consent was obtained from each participant.

Professionally trained dietitians interviewed the 50 cases and 100 controls using structured pretested questionnaires. They evaluated the sociodemographic characteristics (age, sex, education, monthly family income, and place of residence), eating habits (food and beverage temperature and cooking method), smoking history (status, duration, and intensity), medical history, familial cancer history, medication use, and gastroesophageal reflux disease (GERD) symptoms (heartburn and acid regurgitation). Body mass index was calculated by dividing the subjects' weight in kilograms by the square of height in meters. Physical activity was measured using a validated questionnaire listing of different metabolic equivalent (MET) categories (36), and was then expressed as MET-hrs/day to estimate the physical activity level of participants (37).

Participants' dietary intake during the past year was assessed using a valid and reliable semi-quantitative food frequency questionnaire (FFQ) (38). This FFQ consists of 125 food items with standard serving sizes, and participants were asked to specify their consumption frequency for each food item on a daily, weekly, monthly or yearly basis. Nutrients of foods were then calculated using the Nutrients Composition of Iranian Foods (NCIF) (39) supplemented with the USDA Food Composition Data. The consumption of alcohol was not asked to our participants due to their cultural beliefs and was not included in the analysis. The FFQ was interviewer-administered. 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 (21). 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 (21). Briefly, to calculate DII for the participants of this study, the dietary data were first linked to the regionally representative world database that provided a robust estimate of a mean and standard deviation for each parameter (21). 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 (21). Methodology was described in figure 1. $DII = b_1 * n_1 + b_2 * n_2 + \dots + b_{27} * n_{27}$, 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. A total of 27 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, onion and pepper.)

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 entire study (1.20). DII (as dichotomous) was examined across the following characteristics: age, education, physical activity level, body mass index (BMI), smoking, gastro-esophageal reflux using *Student t*-test or χ^2 test for continuous and categorical variables, respectively. We also examined the distribution of various food groups across DII categories separately for cases and controls. Odds ratios and 95% confidence intervals (OR; 95% CI) were estimated using logistic regression models, adjusting only for age and energy, and then fitting a model with additional adjustment for sex, BMI, years of education, physical activity, smoking, and gastro-oesophageal reflux. The covariates were chosen *a priori* as they were shown to be risk factors for ESCC. Statistical tests were performed using SAS® 9.3 (SAS Institute Inc., Cary, NC); all p values were based on two-sided tests.

Results

The DII score in this study ranged from -2.33 (most anti-inflammatory score) to 3.89 (most pro-inflammatory score). Table 1 shows the distribution of 47 cases of ESCC and 96 controls according to selected variables. By design, age and sex distributions were similar in cases and controls. Cases had higher tobacco consumption and symptomatic gastro-esophageal reflux. Controls had higher BMI and years of education. The mean DII value among cases was 1.81 (SD=1.23) and among controls it was 0.76(SD=1.35) indicating a more pro-inflammatory diet for cases.

Control characteristics across by DII categories are provided in Table 2. There were some differences in sociodemographic factors, and lifestyle habits across DII categories. In particular, participants in DII> 1.20 category had lower BMI, physical activity, tobacco exposure and were slightly older, more likely to be men and educated. However the results were not significant except for BMI.

Odds ratios (OR) and 95% confidence intervals (CI) for the risk of ESCC according to cut-point of DII are shown in Table 3. Results obtained from modeling DII as a continuous variable in relation to risk of ESCC showed a positive association after adjustment for age (OR=3.10 CI=1.83–5.24) and in the multivariate analyses (OR=3.58 CI=1.76–7.26). When analysis was carried out with DII expressed as a dichotomous variable, and adjusting for age, subjects with DII score >1.20 were at 655% times higher risk of having ESCC

compared to subjects with DII = 1.20 ($OR_{DII > 1.20 / 1.20} = 7.55$; $CI = 2.63-21.70$). After multivariate adjustment, subjects with DII > 1.20 were at 724% higher risk of having ESCC compared to subjects with DII = 1.20 ($OR_{DII > 1.20 / 1.20} = 8.24$; $CI = 2.03-33.47$).

Discussion

In this case-control study, we observed that subjects with the higher DII (i.e., those who had the most pro-inflammatory diets) were at increased risk of developing ESCC, a result supporting our hypothesis that consuming a more pro-inflammatory diet, is associated with an increased risk of ESCC.

Consumption of food items such as vegetables and fruits have been shown to reduce inflammation (40), while others, such as red and processed meat, increase inflammation (41). Indeed, in this case-control study a healthy dietary pattern characterized by high consumption of fruits, raw vegetables and fish showed protective effects on ESCC (34), whereas an unfavorable effect of a westernized dietary pattern rich in animal products, sugar, sweet and fried potatoes has been observed (34). Consuming a diet in concordance with the principles of the Mediterranean dietary pattern was found to be protective against ESCC in this study (35).

Similarly, previous studies that have examined the effect of specific food items on ESCC have reported inverse associations for olive oil, fish and other seafood, whole grains and fruits (35, 42) and increased risks for high consumption of red and processed meat (20, 43–45).

A limitation of this approach is that these foods or nutrients are usually consumed in combination; thus, dietary correlations may attenuate or accentuate the real effects of each food or nutrient under study. In formulating the DII, a different approach was taken by focusing on the functional effects of foods and nutrients. As such, it relies on reviewing and scoring of the peer-reviewed literature on the subject of diet and inflammation. Moreover, it standardizes individuals' dietary intakes of pro- and anti-inflammatory food constituents to world referent values, which results in values that are not dependent on the units of consumption and can be used for comparison across studies.

One of the possible mechanisms for the observed direct association of the DII with ESCC is through the effect of pro-inflammatory diet on the levels of various inflammatory cytokines such as Ki-67, vascular endothelial growth factor and interleukin-8, all of which forms an important component of the esophageal tumor micro-environment. These cytokines may have an important role in cancer development, growth and progression (46) by promoting proliferation, angiogenesis, and carcinogenesis and by recruiting immune cells to the tumor site (47).

Inflammation also alters the extracellular matrix and provides structural support to developing tumors (47). Hypoxia is a common state in inflamed tissues which causes DNA damage and induces tumorigenic factors which result in further progression of cancer (47).

An important strength of this study is that it is one of the first studies in Iran, which has a high incidence of ESCC, to explore the association between the inflammatory property of diet and ESCC. Controls were selected carefully by ensuring that none of them had any condition related to diet or other major risk factors of ESCC. However, in addition to the strengths there are certain weaknesses that need to be considered. First, dietary measurement error may lead to underestimation of results. In addition, the measurement error in confounders will lead to residual confounding (48). Although we cannot entirely rule out residual confounding due to imprecise measurement of important covariates, it is unlikely that errors in measuring the covariates would be so extreme because the crude and multivariable results were essentially the same. Secondly, because of the small number of participants, associations with wide confidence intervals for the DII were found when models were fit using DII as both continuous and as a dichotomous variable (however, the results were significant, despite this constraint). Thirdly, as with other case-control studies, recall bias and selection bias were inevitable. In case-control studies, there is the possibility that cases may recall their diets differently after a cancer diagnosis. However, our participants were generally of low literacy and socioeconomic status with little knowledge about the role of diet and nutrients in the cancer risk, which should have reduced the possibility of recall bias. Moreover, using hospital controls and administering validated FFQs by trained interviewers in a hospital setting might have further reduced the recall bias and improved comparability of information of cases and controls. With regard to the selection bias, high participation rates (94% among cases and 91% among controls) in this study minimized the potential for selective participation according to the lifestyle practices (such as diet). Fourthly, absence of data on alcohol consumption is another limitation; study participants refrained from reporting alcohol intake as consuming alcohol is legally prohibited in Iran (38).

In conclusion, subjects who consumed a more pro-inflammatory diet were at increased risk of ESCC compared to those who consumed a more anti-inflammatory diet. 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 foods or processed foods rich in saturated fat or trans fatty acids, may be a strategy for reducing risk of ESCC.

Acknowledgments

We are grateful to all field investigators, staffs and participants of the present study. This study was supported by a grant from National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, IRAN. J.R. Hebert was supported by an Established Investigator Award in Cancer Prevention and Control from the Cancer Training Branch of the National Cancer Institute (K05 CA136975).

References

1. GLOBOCAN 2012 (IARC). Section of Cancer Surveillance. Dec 29. 2014
2. Launay L, Dejardin O, Pornet C, Morlais F, Guittet L, Launoy G, et al. Influence of socioeconomic environment on survival in patients diagnosed with esophageal cancer: a population-based study. *Dis Esophagus*. 2012 Nov-Dec;25(8):723–30. Epub 2012/02/02. eng. [PubMed: 22292704]

3. Taccioli C, Chen H, Jiang Y, Liu XP, Huang K, Smalley KJ, et al. Dietary zinc deficiency fuels esophageal cancer development by inducing a distinct inflammatory signature. *Oncogene*. 2012 Oct 18; 31(42):4550–8. Epub 2011/12/20. eng. [PubMed: 22179833]
4. Allen JW, Richardson JD, Edwards MJ. Squamous cell carcinoma of the esophagus: a review and update. *Surg Oncol*. 1997 Dec; 6(4):193–200. Epub 1998/10/17. eng. [PubMed: 9775405]
5. Rasool S, B AG, Syed Sameer A, Masood A. Esophageal cancer: associated factors with special reference to the Kashmir Valley. *Tumori*. 2012 Mar-Apr;98(2):191–203. Epub 2012/06/09. eng. [PubMed: 22677984]
6. Khuroo MS, Zargar SA, Mahajan R, Banday MA. High incidence of oesophageal and gastric cancer in Kashmir in a population with special personal and dietary habits. *Gut*. 1992 Jan; 33(1):11–5. Epub 1992/01/01. eng. [PubMed: 1740265]
7. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA: A Cancer Journal for Clinicians*. 2011; 61(2):69–90. [PubMed: 21296855]
8. World Health Organization. The global burden of disease: 2004 update. WHO; 2008.
9. Munoz N. Epidemiological aspects of oesophageal cancer. *Endoscopy*. 1993 Nov; 25(9):609–12. Epub 1993/11/01. eng. [PubMed: 8119215]
10. Keibel A, Singh V, Sharma MC. Inflammation, microenvironment, and the immune system in cancer progression. *Curr Pharm Des*. 2009; 15(17):1949–55. [PubMed: 19519435]
11. Pan MH, Lai CS, Dushenkov S, Ho CT. Modulation of inflammatory genes by natural dietary bioactive compounds. *J Agric Food Chem*. 2009 Jun 10; 57(11):4467–77. [PubMed: 19489612]
12. O'Sullivan KE, Phelan JJ, O'Hanlon C, Lysaght J, O'Sullivan JN, Reynolds JV. The role of inflammation in cancer of the esophagus. *Expert review of gastroenterology & hepatology*. 2014 May 23.:1–12. [PubMed: 24857183]
13. Corley DA, Kerlikowske K, Verma R, Buffler P. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. *Gastroenterology*. 2003 Jan; 124(1):47–56. [PubMed: 12512029]
14. de Mello VD, Schwab U, Kolehmainen M, Koenig W, Siloaho M, Poutanen K, et al. A diet high in fatty fish, bilberries and wholegrain products improves markers of endothelial function and inflammation in individuals with impaired glucose metabolism in a randomised controlled trial: the Sysdimet study. *Diabetologia*. 2011 Nov; 54(11):2755–67. eng. [PubMed: 21870174]
15. Khoo J, Piantadosi C, Duncan R, Worthley SG, Jenkins A, Noakes M, et al. Comparing effects of a low-energy diet and a high-protein low-fat diet on sexual and endothelial function, urinary tract symptoms, and inflammation in obese diabetic men. *J Sex Med*. 2011 Oct; 8(10):2868–75. eng. [PubMed: 21819545]
16. Luciano M, Mottus R, Starr JM, McNeill G, Jia X, Craig LC, et al. Depressive symptoms and diet: their effects on prospective inflammation levels in the elderly. *Brain Behav Immun*. 2012 Jul; 26(5):717–20. eng. [PubMed: 22056839]
17. Shivappa N, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, et al. A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). *Public health nutrition*. 2014 Aug; 17(8):1825–33. [PubMed: 24107546]
18. Lin Y, Yngve A, Lagergren J, Lu Y. Dietary intake of lignans and risk of adenocarcinoma of the esophagus and gastroesophageal junction. *Cancer causes & control: CCC*. 2012 Jun; 23(6):837–44. [PubMed: 22527161]
19. Terry P, Lagergren J, Ye W, Wolk A, Nyren O. Inverse association between intake of cereal fiber and risk of gastric cardia cancer. *Gastroenterology*. 2001 Feb; 120(2):387–91. [PubMed: 11159879]
20. Qu X, Ben Q, Jiang Y. Consumption of red and processed meat and risk for esophageal squamous cell carcinoma based on a meta-analysis. *Annals of epidemiology*. 2013 Dec; 23(12):762–70 e1. [PubMed: 24176821]
21. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hebert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public health nutrition*. 2014 Aug; 17(8):1689–96. [PubMed: 23941862]

22. Wirth MD, Burch J, Shivappa N, Violanti JM, Burchfiel CM, Fekedulegn D, et al. Association of a dietary inflammatory index with inflammatory indices and metabolic syndrome among police officers. *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine*. 2014 Sep; 56(9):986–9. [PubMed: 25046320]
23. Shivappa N, Hebert JR, Rietzschel ER, De Buyzere ML, Langlois M, Debruyne E, et al. Associations between dietary inflammatory index and inflammatory markers in the Asklepios Study. *The British journal of nutrition*. 2015 Feb; 113(4):665–71. [PubMed: 25639781]
24. Tabung FK, Steck SE, Zhang J, Ma Y, Liese AD, Agalliu I, et al. Construct Validation of the Dietary Inflammatory Index among Postmenopausal Women. *Annals of Epidemiology*. (0)
25. Wood LG, Shivappa N, Berthon BS, Gibson PG, Hebert JR. Dietary inflammatory index is related to asthma risk, lung function and systemic inflammation in asthma. *Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology*. 2015 Jan; 45(1):177–83. [PubMed: 24708388]
26. Alkerwi A, Shivappa N, Crichton G, Hebert JR. No significant independent relationships with cardiometabolic biomarkers were detected in the Observation of Cardiovascular Risk Factors in Luxembourg study population. *Nutrition research*. 2014 Dec; 34(12):1058–65. [PubMed: 25190219]
27. Wirth MD, Burch J, Shivappa N, Steck SE, Hurley TG, Vena JE, et al. Dietary inflammatory index scores differ by shift work status: NHANES 2005 to 2010. *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine*. 2014 Feb; 56(2):145–8. [PubMed: 24451608]
28. Zamora-Ros R, Shivappa N, Steck SE, Canzian F, Landi S, Alonso MH, et al. Dietary inflammatory index and inflammatory gene interactions in relation to colorectal cancer risk in the Bellvitge colorectal cancer case-control study. *Genes & nutrition*. 2015 Jan.10(1):447. [PubMed: 25488145]
29. Shivappa N, Prizment AE, Blair CK, Jacobs DR, Steck SE, Hébert JR. Dietary Inflammatory Index and Risk of Colorectal Cancer in the Iowa Women's Health Study. *Cancer Epidemiology Biomarkers & Prevention*. 2014 Nov 1; 23(11):2383–92. 2014.
30. Tabung, Fred K.; Steck, Susan E.; Ma, Yunsheng; Liese, Angela D.; Zhang, Jiajia; Caan, Bette, et al. The Association between Dietary Inflammatory Index and Risk of Colorectal Cancer among Postmenopausal Women: Results from the Women's Health Initiative. *Cancer Causes and Control*. 2014 In Press.
31. Wirth MD, Shivappa N, Steck SE, Hurley TG, Hébert JR. The dietary inflammatory index is associated with colorectal cancer in the National Institutes of Health–American Association of Retired Persons Diet and Health Study. *British Journal of Nutrition*. 2015 FirstView: 1–9.
32. Shivappa N, Bosetti C, Zucchetto A, Montella M, Serraino D, La Vecchia C, et al. Association between dietary inflammatory index and prostate cancer among Italian men. *The British journal of nutrition*. 2014 Nov 17.:1–6. [PubMed: 25400225]
33. Shivappa N, Bosetti C, Zucchetto A, Serraino D, La Vecchia C, Hebert JR. Dietary inflammatory index and risk of pancreatic cancer in an Italian case-control study. *The British journal of nutrition*. 2014 Dec 17.:1–7. [PubMed: 25515552]
34. Hajizadeh B, Rashidkhani B, Rad AH, Moasheri SM, Saboori H. Dietary patterns and risk of oesophageal squamous cell carcinoma: a case-control study. *Public Health Nutr*. 2010 Jul; 13(7): 1107–12. Epub 2010/03/02. eng. [PubMed: 20188004]
35. Jessri M, Rashidkhani B, Hajizadeh B, Jacques PF. Adherence to Mediterranean-style dietary pattern and risk of esophageal squamous cell carcinoma: a case-control study in Iran. *Journal of the American College of Nutrition*. 2012 Oct; 31(5):338–51. [PubMed: 23529991]
36. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR Jr, Montoye HJ, Sallis JF, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Medicine and science in sports and exercise*. 1993 Jan; 25(1):71–80. [PubMed: 8292105]
37. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Medicine and science in sports and exercise*. 2000 Sep; 32(9 Suppl):S498–504. [PubMed: 10993420]

38. Hosseini-Esfahani F, Jessri M, Mirmiran P, Bastan S, Azizi F. Adherence to dietary recommendations and risk of metabolic syndrome: Tehran Lipid and Glucose Study. *Metabolism: clinical and experimental*. 2010 Dec; 59(12):1833–42. [PubMed: 20667561]
39. Mirmiran P, Hosseini Esfahani F, Mehrabi Y, Hedayati M, Azizi F. Reliability and relative validity of an FFQ for nutrients in the Tehran Lipid and Glucose Study. *Public Health Nutrition*. 2010; 13(05):654–62. [PubMed: 19807937]
40. Defago MD, Elorriaga N, Irazola VE, Rubinstein AL. Influence of food patterns on endothelial biomarkers: a systematic review. *Journal of clinical hypertension*. 2014 Dec; 16(12):907–13. [PubMed: 25376124]
41. Lopez-Garcia E, Schulze MB, Fung TT, Meigs JB, Rifai N, Manson JE, et al. Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. *The American journal of clinical nutrition*. 2004 Oct; 80(4):1029–35. [PubMed: 15447916]
42. Pelucchi C, Bosetti C, Negri E, Lipworth L, La Vecchia C. Olive oil and cancer risk: an update of epidemiological findings through 2010. *Curr Pharm Des*. 2011; 17(8):805–12. [PubMed: 21443483]
43. Chen W, Yang C, Yang L, Qi C, Tian S, Han Y, et al. Association of roasting meat intake with the risk of esophageal squamous cell carcinoma of Kazakh Chinese via affecting promoter methylation of p16 gene. *Asia Pacific journal of clinical nutrition*. 2014; 23(3):488–97. [PubMed: 25164462]
44. Salehi M, Moradi-Lakeh M, Salehi MH, Nojomi M, Kolahehdooz F. Meat, fish, and esophageal cancer risk: a systematic review and dose-response meta-analysis. *Nutrition reviews*. 2013 May; 71(5):257–67. [PubMed: 23590703]
45. Tavani A, La Vecchia C, Gallus S, Lagiou P, Trichopoulos D, Levi F, et al. Red meat intake and cancer risk: a study in Italy. *International journal of cancer Journal international du cancer*. 2000 May 1; 86(3):425–8. [PubMed: 10760833]
46. Liu J, Li Z, Cui J, Xu G, Cui G. Cellular changes in the tumor microenvironment of human esophageal squamous cell carcinomas. *Tumour biology: the journal of the International Society for Oncodevelopmental Biology and Medicine*. 2012 Apr; 33(2):495–505. [PubMed: 22134872]
47. Bonomi M, Patsias A, Posner M, Sikora A. The role of inflammation in head and neck cancer. *Advances in experimental medicine and biology*. 2014; 816:107–27. [PubMed: 24818721]
48. Fewell Z, Davey Smith G, Sterne JA. The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study. *American journal of epidemiology*. 2007 Sep 15; 166(6):646–55. [PubMed: 17615092]

Figure 1. Sequence of steps in creating the dietary inflammatory index in the Esophageal cancer case-control study in Iran.

Table 1

Characteristics of prostate cancer cases and controls, Iranian Esophageal Squamous Cell Cancer Case-Control Study.

Characteristics	Cases	Controls	P-Value ^{a,b}
	<i>N</i> =47	<i>N</i> =96	
Age, (years): mean $\pm$ sd	58.0 $\pm$ 10.1	58.0 $\pm$ 10.4	0.89
Female n (%)	29 (62)	58 (60)	0.88
Symptomatic gastro-oesophageal reflux- (%)	16 (34)	9 (9)	<0.001
BMI, kg/m ² : mean $\pm$ sd	20.4 $\pm$ 3.2	25.3 $\pm$ 4.2	<0.001
Physical activity, METs/day: mean $\pm$ sd	36.6 $\pm$ 6.7	35.7 $\pm$ 8.0	0.52
Education (%)			0.65
No	41 (87.2)	81 (84.4)	
Yes	6 (12.8)	15 (15.6)	
Smoking ^a (%)			0.60
Nonsmoker	30 (63.8)	67 (69.8)	
Ex-smoker	10 (21.3)	14 (14.6)	
Current smoker	7 (14.9)	15 (15.6)	

^a Student t-test was used for continuous variables

^b Chi-square test was used for categorical variables

Table 2

Participant characteristics by level of dietary inflammatory index (DII) among controls, Iranian Esophageal Squamous Cell Cancer case-control study.

Continuous variables (mean $\pm$ SD)	DII 1.20 (n=72)	DII>1.20 (n=71)	P-Value ^{a,b}
Age (years)	58.0 $\pm$ 10.9	59.9 $\pm$ 10.0	0.30
Body mass Index (kg/m ²)	24.5 $\pm$ 4.8	22.9 $\pm$ 4.2	0.04
Physical activity (METs)	36.2 $\pm$ 8.4	35.5 $\pm$ 6.5	0.61
Sex (%):			0.36
Males	40.0	30.6	
Females	60.0	69.4	
Smoking (%)			0.17
Non-smoker	67.3	72.2	
Ex-smoker	10.9	19.4	
Current smoker	21.8	8.3	
Education (%)			0.54
No	85.5	80.6	
Yes	14.5	19.4	

^a Student t-test was used for continuous variables

^b Chi-square test was used for categorical variables

Table 3

Odds ratios and confidence intervals for the association between DII and ESCC, Iranian Esophageal Squamous Cell Cancer case-control study.

	Dietary Inflammatory Index OR (95% CI)		P-Value	DII (Continuous) ^a OR (95% CI)	P-Value
	DII	1.20	DII>1.20		
Age-adjusted		1 (ref.)	7.55 (2.63, 21.70)	3.10 (1.83, 5.24)	<.0001
Multivariate-adjusted ^b		1 (ref.)	8.24 (2.03, 33.47)	3.58 (1.76, 7.26)	0.0004

^a one unit increase corresponding to ≈16% of its range in the current study.

^b Adjusted for age, energy, sex, BMI, years of education, physical activity, smoking and gastro-oesophageal reflux