

Dietary Inflammatory Index (DII) and risk of colorectal cancer in Iowa Women's Health Study

Nitin Shivappa^{1,2}, Anna E Prizment^{3,4}, Cindy K. Blair³, David R. Jacobs, Jr³, Susan E. Steck^{1,2}, James R. Hébert^{1,2}

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

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

³Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN 55454

⁴Masonic Cancer Center, University of Minnesota, Minneapolis, MN, 55455.

Address correspondence and reprint requests to: Dr. James R. Hébert, Professor and Director,
Cancer Prevention and Control Program, University of South Carolina, 915 Greene Street,
Suite 241, Columbia, SC 29208, Telephone: (803) 576-5666, Fax: (803) 576-5624, e-mail:

jhebert@sc.edu

Funding: Iowa Women's Health Study was supported by National Cancer Institute grant R01 CA39742. D.R. Jacobs, Jr., and C.K. Blair were supported from National Cancer Institute grant R01 CA39742. J.R. Hébert was supported by an Established Investigator Award in Cancer Prevention and Control from the Cancer Training Branch of the National Cancer Institute (K05 CA136975). A.E. Prizment was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health Award Number UL1TR000114. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosure: The authors have declared no conflicts of interest.

Running Title: DII predicts colorectal cancer among women.

Total word count = 3382; Abstract word count = 250 (including headings); Number of tables = 4

Abstract:

Background: Colorectal cancer (CRC), the third most common cancer in the United States, has a natural history that usually encompasses several decades. Dietary components have been implicated in the etiology of CRC, perhaps through their effect on inflammation.

Methods: We examined the ability of the dietary inflammatory index (DII) to predict CRC in the Iowa Women's Health Study. The DII was computed based on dietary intake assessed by a 121-item food frequency questionnaire in this cohort of 34,703 women, aged 55–69 years, free of any self-reported prior malignancy at enrollment in 1986. Incident CRC cases were identified through linkage with the State Health Registry of Iowa (a Surveillance, Epidemiology and End Results program member). Cox proportional hazards regression was used to estimate hazard ratios (HR). Through the end of 2010, 1636 incident CRCs were identified, including 1329 colon and 325 rectal cancers.

Results: Multivariable analysis, adjusting for BMI, smoking status, pack-years of smoking, hormone replacement therapy, education, diabetes and total energy intake, revealed positive associations between higher DII and CRC risk (HR for DII_{continuous}: 1.07 per unit increase in DII (corresponding to 0.5 standard deviation unit increase); 95%CI 1.01- 1.13; HR for DII_{quintiles}: Q5vsQ1=1.20; 95%CI 1.01- 1.43). HRs for DII were similar for colon cancer and rectal cancer, though not statistically significant for rectal cancer.

Conclusions: These results indicate that a pro-inflammatory diet, as indicated by higher DII scores, was associated with higher risk of developing CRC.

Impact: Pro-inflammatory diets are associated with increased risk of CRC.

Introduction: Inflammation is a result of the body's response to tissue insult or injury, or the presence of inflammatory stimulants (1, 2). The acute inflammatory response represents an important step in the process of wound healing and tissue regeneration that, under normal circumstances, will lead to recovery within a few days (3, 4). Chronic inflammation is known to be associated with common epithelial cancers, with colorectal (5-7) being the most intensively studied. There is growing evidence that specific dietary components influence both inflammation (8-10) and colorectal cancer (CRC) (11-13).

CRC is the third most common cancer among men and women in the United States. Primarily because of improvements in screening that have resulted in primary prevention of many cancers and detection at an earlier stage in others, the CRC death rate has decreased in the past 20 years (14, 15). Research into the role of diet in inflammation and CRC suggests that diet represents a complicated set of exposures which often interact, and whose cumulative effect modifies both inflammatory responses and health outcomes.

Several dietary indices exist to assess diet quality, but none had focused on diet's effects on inflammation until researchers at the University of South Carolina's Cancer Prevention and Control Program developed the Dietary Inflammatory Index (DII). The DII can be used in diverse populations to assess the inflammatory potential of diet assessed by various dietary assessment tools [e.g., 24 hour dietary recalls, food frequency questionnaires (FFQs) and food records] (16-18). Thus far, the DII has been successful in predicting inflammatory markers [e.g., C-reactive protein (CRP) and interleukin-6 (IL-6)] in several studies including the Seasonal Variation of Blood Cholesterol Levels Study (SEASONS) and the Buffalo Cardio-Metabolic Police Stress Study (BCOPS) in the United States (17, 19), and in a study of asthmatics in Australia (18). However, the DII has not yet been applied to a population with cancer outcomes. The purpose of this study is to examine the association between the DII and CRC in a large prospective cohort of post-menopausal women, the Iowa Women's Health Study (IWHS). Our working hypothesis is that a higher DII score (indicating a pro-inflammatory diet) increases risk of incident CRC, including anatomic subtypes (i.e., colon cancer and rectal cancer).

Materials and Methods:

Full details regarding the IWHS design have been published elsewhere (20). In brief, 41,836 older women, ages 55–69 years, were enrolled in 1986. Incident cancer cases and deaths were identified through annual linkage with the State Health Registry of Iowa (a Surveillance, Epidemiology and End Results program member) and the National Death Index. Emigration from Iowa was less than 1% annually, resulting in nearly complete follow-up of cancer incidence (21). Women with self-reported history of cancer prior to baseline, except non-melanoma skin cancer ($n=3,830$); or extreme energy intake (< 600 kcal or ≥ 5000 kcal per day) or incomplete dietary data (≥ 30 items blank) on the food frequency questionnaire ($n=3,096$) were excluded from the present study, yielding a sample consisting of 35,216 study participants (exclusions were not mutually exclusive). After further exclusion for missing covariates, data from 34,703 women were included in the analysis.

Dietary intake data were collected using a FFQ at baseline. This 121-item FFQ was adapted from the 126-item instrument developed by Willett and colleagues (22). Questions related to supplements were part of this FFQ. 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. Developing the DII involved screening ≈ 6000 scientific articles published from 1950-2010 on diet and six inflammatory markers [i.e., CRP, interleukin (IL)-1 β , IL-4, IL-6, IL-10, and tumor necrosis factor (TNF)- α]. Of these, nearly 2000 articles from cell culture and laboratory animal experiments, and cross-sectional, longitudinal and intervention trials in humans were reviewed and scored. Finally, 11 data sets were obtained from around the world to which individual dietary intakes could be compared to determine the final DII score. Individual intakes of food parameters on which the DII is based are then compared to a world standard database. A complete description of the detailing development of the DII is available elsewhere (16, 23). Briefly, to calculate DII for the participants of this study, the dietary data were first linked to the world

database that provided a robust estimate of a mean and standard deviation for each parameter (16). This was achieved by subtracting the “standard global mean” from the intake reported via the FFQ and dividing this value by the standard deviation (both calculated from the world database) to get ‘z’ scores. To minimize the effect of “right skewing”, these ‘z’ scores were 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 (inflammatory potential for each food parameter), which was 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 were then summed to create the overall DII score for each participant in the study (16). A description of validation work, including both dietary recalls and a structured questionnaire similar to an FFQ, also is available (17).

The DII was calculated from foods and supplements and from foods only. The foods-only DII was based on 37 parameters available in the IWHS FFQ. DII attributable to supplements only was calculated by creating a new variable that presents the difference between the food + supplements DII and the food-only DII. If the difference is zero, then either the woman did not take a vitamin supplement, or the associated nutrient (e.g., calcium) was either not part of the DII or it had a negligible effect on DII. If the nutrient is considered anti-inflammatory, then the difference variable should be negative (as virtually all supplements in the calculated DII are anti-inflammatory) and represent a supplement user. Supplements commonly used in this study were calcium (46%), multivitamin (33%), vitamin C (12% seasonally, 17% monthly), and vitamin E (15%).

Associations with DII of demographics, lifestyle factors, self-reported diabetes mellitus, and anthropometric characteristics were examined using general linear models or χ^2 tests (see Table 1 for specific variables). The distribution of 30 different food groups was examined across quintiles of DII to characterize low (anti-inflammatory) vs high (pro-inflammatory) DII in terms of food intake.

Both food + supplements DII and the food-only DII were analyzed both as continuous variables and by quintiles of exposure in relation to CRC outcome variables. For analyses examining the effect of supplement use alone, the reference category represents non-supplement users; categories 1-3 represent tertiles of the supplement-associated DII among supplement users. Category 1 represents women with the greatest contribution from supplements to the DII score. Outcome variables included CRC overall and both colon (ICD-O codes-(18.0-18.9)) and rectum (ICD-O codes-19.9 and 20.9) subsites. Proximal and distal colon cancers defined by codes 18.0 to 18.5 and 18.6 to 18.7, respectively, also were examined. Person-years of exposure time were accumulated from baseline until first CRC diagnosis, move from Iowa, death, or administrative censoring on 12/31/2010. Hazard ratios and 95% confidence intervals (HR; 95% CI) were estimated using Cox proportional hazards regression models, adjusting only for age in the crude model and additionally adjusting for body mass index [BMI = weight (kg)/weight (m)²], smoking status, pack-years of smoking, education, hormone replacement therapy (HRT) use, total energy intake and history of diabetes in another. The covariates were chosen *a priori*, as they previously were shown to be strong risk factors for CRC in this cohort. Further adjustment for alcohol intake and physical activity did not substantially change the results; therefore, these variables were not included in the final model. A linear test for trend was conducted by including the median value for each DII quintile as a continuous term into the regression model (and for tertiles in the supplements-only analyses). The assumption of proportional hazards was tested by adding to the model an interaction term between follow-up time and DII; there was no evidence that these assumptions were violated.

Finally, to examine whether adjustment for aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) use affects a DII-CRC association, we conducted a sensitivity analysis for the CRC outcome by including only those women who replied to the 1992 follow-up questionnaire about the use of aspirin and other NSAIDs (N=26,152 still at risk and 998 CRC cases; NSAIDs use was not queried at baseline) and adjusting for ever use of these medications. For this analysis, all cancer cases diagnosed before 1992

were excluded, and the analytical cohort was followed from the time of the 1992 survey until the end of follow-up. Statistical tests were performed using SAS[®] 9.3, (SAS Institute Inc., Cary, NC); all statistical tests were two-sided and $p < 0.05$ was considered statistically significant.

Results:

The food + supplements DII had a mean (SD) value of -0.87 ($SD = \pm 2.02$), while the food-only DII mean was -0.06 ($SD = \pm 1.94$). The food + supplements DII was positively correlated with the food-only DII ($r = 0.82$); however, it was inversely correlated with DII from supplements only ($r = -0.25$).

Decreasing trends were observed for energy and dietary fiber intake across DII quintiles (Table 1.).

Increasing trends were observed across quintiles of DII for percent energy from fat and proportion of women with $BMI \geq 30 \text{ kg/m}^2$, current smokers and those reporting low levels of physical activity. Table 2 describes the distribution of servings of 30 food groups across DII quintiles, with percentage difference between quintiles 5 and 1. The food groups that showed the greatest reduction ($\geq 60\%$) from quintile 1 to quintile 5 are vegetables other than green leafy vegetables or potatoes (65%), low-fat dairy (63%), green leafy vegetables (62%), fish/seafood (62%), nuts (61%), fruits (61%) and whole grains (60%); and the food groups that showed greatest increase ($\geq 20\%$) were butter (56%), beer (37%), coffee (36%), fried food (29%) and liquor (24%). Food groups that differed little ($\leq 5\%$) across DII quintiles include refined grains, nitrate-processed meat, high-fat dairy, and chocolate.

During the follow-up period (mean \pm SD = 19.6 ± 7.0 years), 1636 incident CRCs were identified, including 1329 colon and 325 rectal cancer cases. Of the 1329 colon cancer cases, 903 were proximal colon and 388 were distal colon. When analyses were carried out using continuous DII, a 1-unit increment in DII (corresponding to a 0.5 standard deviation increase) showed significant positive associations with risk of overall CRC after adjusting for age (HR=1.09; 95%CI 1.03 - 1.14). After additional adjustment for BMI, smoking status, pack-years of smoking, education, HRT use, total energy intake and history of diabetes, the HR was slightly attenuated (1.07; 95%CI 1.01 - 1.13). In a sensitivity analysis restricted to

responders to the 1992 follow-up questionnaire, additional adjustment for the use of aspirin or other NSAIDs did not materially alter the results ($HR_{\text{continuous}}=1.10$; 95%CI 1.03 - 1.19; $HR_{\text{quintile 5vs 1}}=1.31$; 95%CI 1.05 - 1.63). In addition, the DII–CRC association was stronger among women who did not use aspirin or any other NSAIDs (30% of all women). Compared to the first quintile, the HRs were 1.39 (95%CI 1.03 - 1.14); 1.37 (95%CI 1.03 - 1.14); 1.62 (0.98 - 2.67); and 2.02 (95%CI, 1.21 - 3.39) (p-trend= 0.008) for the second, third, fourth and fifth quintile, respectively.

For analysis focusing on specific anatomic subsites, a significant positive association was observed with colon cancer after age adjustment ($HR=1.08$; 95%CI 1.02 - 1.13), with slight attenuation observed after additional adjustment for other variables ($HR=1.05$; 95%CI 0.99 - 1.12). For rectal cancer, HRs for DII were of similar magnitude as for colon cancer, but did not achieve statistical significance, consistent with the smaller number of cases (Table 3).

Analysis with DII expressed as quintiles revealed significantly higher risk for women in the fifth quintile compared to women in the first quintile for overall CRC ($HR=1.20$; 95%CI 1.01 - 1.43, p-trend=0.03). Effect sizes were similar for colon and rectal cancers analyzed separately, though did not reach statistical significance (Table 3). Additional analyses were carried out with subtypes of colon cancer. The DII as a continuous variable showed a statistically significant association with proximal colon cancer ($HR=1.08$; 95%CI 1.02- 1.16) in the crude model adjusted for age, but this was attenuated and no longer statistically significant with additional adjustment for other covariates ($HR=1.06$; 95%CI 0.98 - 1.14). Similar to colon cancer, the risk of proximal colon cancer increased across the DII quintiles (p-trend = 0.01). Similar associations between the continuous DII and distal colon cancer were observed ($HR_{\text{age-adjusted}}=1.06$; 95% CI 0.96-1.18; $HR_{\text{multivariable adjustment}}=1.05$; 95% CI 0.93 - 1.18), though there was no evidence for a linear trend across DII quintiles (p-trend = 0.33).

When analyses were carried out with DII from food groups only there was minimal change in the effect size of the association for colorectal cancer ($HR_{\text{continuous}}=1.07$; 95%CI 1.01-1.15; $HR_{\text{quintile 5vs 1}}=1.16$; 95%CI 0.95-1.42) and for cancer subtypes (Table 4.).

supplements only (i.e., obtained subtracting the food-only DII from the food + supplements DII) women in category 2 appeared to have lower risk of CRC (HR_{category 2vs4}=0.84; 95%CI 0.73-0.98) than women in category 3 (HR_{category 3vs4}=0.89; 95%CI 0.77-1.03), suggesting a non-linear relationship in which an increasing benefit from the supplement is observed at moderate doses. However, there was no apparent benefit for more heavily exposed women (i.e., for in category 1 (HR_{category 1vs4}=0.94; 95%CI 0.82-1.09) (Table 4).

Discussion:

In this large, population-based, prospective cohort study of older women, consuming a more pro-inflammatory diet, as reflected in higher DII scores, was associated with increased risk of CRC. Results were suggestive of a positive association between the DII and colon (both proximal and distal) and rectal cancers separately, after adjustment for multiple covariates.

In support of the asserted pro-inflammatory effect of higher DII, the DII-CRC association was accentuated among women who did not use aspirin or other NSAIDs (30% of all women). This was hypothesized *a priori* because NSAIDs exert a stronger anti-inflammatory effect than what might be expected through a moderately anti-inflammatory diet (characterized by low DII). Therefore, an unbiased estimate of the true impact of anti-inflammatory diet may be seen by restricting to non-NSAIDs users. Anti-inflammatory diet may confer protection against CRC among non-users of NSAIDs and therefore may be promising as a new approach for CRC prevention, especially in people who cannot tolerate NSAIDs.

The DII, which is based on evidence available in the biomedical literature, is different from other dietary indices, virtually all of which fall into three main categories: 1. Those derived from specific dietary prescriptions based on some external standard [e.g., Healthy Eating Index (HEI) which was derived from the adherence to the United States Dietary guidelines (24)]; 2. Those derived empirically from findings within particular study populations [e.g., computing a pattern using principal component analysis

(PCA)(13)] or 3. Those that link to particular cultural patterns of dietary intake (e.g., the Mediterranean diet score (25)). Previously, studies have been conducted to examine various dietary patterns and indices in relation to CRC in women (13, 26). In a study conducted in the NIH-AARP cohort, significant associations were observed between CRC incidence and the HEI-2005, but not the Alternate HEI or Mediterranean diet scores after adjustment for multiple confounders (26). A case-control study conducted by Miller et al., compared HEI-2005 and PCA-derived patterns of dietary intake and their association with CRC (13). The results showed significant associations between low HEI-2005 scores and a dietary pattern high in meat, potatoes, and refined grains and CRC risk among women (12). There are areas of substantial overlap in the diets that characterize these different dietary patterns; however, there also are differences among dietary pattern scores. Which food groups contribute to prediction of CRC in one score but not in another is a topic for further investigation.

Previous studies also have examined the effect of specific food items, such as red meat (12, 27), and nutrients, such as folate (28) and zinc (29), and their association with CRC. A limitation of this approach is that these whole foods or nutrients are usually consumed with other food items and nutrients; thus, dietary intercorrelations may attenuate or accentuate the actual effects of the whole food or nutrient under study. A very high correlation between nutrients and among foods can result in instability in risk estimation due to multicollinearity and possible loss of statistical power. In formulating the DII (16, 23), an entirely different approach was taken by focusing on the functional effects of foods and nutrients. As such, it relies on careful review and scoring of the medical literature in specific relation to inflammation. Also, in contrast to more culture-bound indices, it standardizes individuals' dietary intakes of pro- and anti-inflammatory food constituents to world referent values for easy comparison across populations.

One of the possible mechanisms for the positive association of the DII with CRC in IWHS might be through the effect of pro-inflammatory diet on insulin resistance through increasing systemic inflammation (30, 31). Consumption of food items such as meat and butter have been shown to increase

systemic inflammation by increasing levels of high-sensitivity CRP, E-selectin and soluble vascular cell adhesion molecule-1 (30) which then are responsible for increasing insulin resistance (31). Increasing insulin resistance is associated with CRC by increasing circulating levels of insulin, triglycerides, and non-esterified fatty acids (32, 33) which promote excessive proliferation of colonic epithelial cells and exposes them to reactive oxygen species, thereby increasing risk of CRC. Another theory suggests the role of diet on local inflammation and oxidation in the colon; local inflammation and oxidative stress as a result of activation of the COX-2 enzyme in colonic epithelial cells results in focal proliferation and mutagenesis (34). As mentioned previously, there are various dietary factors which have different effects on inflammation; for example, red meat consumption increases inflammation and green leafy vegetables reduce inflammation (32, 33). Supporting our findings, previous work in the IWHS examining diet and CRC has shown significant inverse associations between anti-inflammatory food parameters such as vitamin D (35), magnesium (36), and vitamin E (37) intake and colon cancer and between catechins and rectal cancer (38). A significant positive association was observed between sugar, meat and fat intake and colon cancer (39).

We observed reduced levels of mean fiber and energy intake in quintile 5 compared to quintile 1, this could be because people with lower DII scores consume higher amounts of food in general; this overall higher intake would encompass many anti-inflammatory dietary components that also would contribute to higher overall energy intake. We found that the addition of micronutrients from supplements to the DII scoring had an impact on the mean DII, though did not materially change effect estimates of the DII with colorectal cancer. We also observed inconsistent associations with CRC when the supplements-associated DII was considered (i.e., the difference between the food + supplements DII and the food-only DII shown in Table 4).

Previous published results with DII include the SEASONS study, where we tested DII with two dietary assessment tools, the 24 HR recall and 7-Day Dietary Record (7DDR). For the 24HR recall we had

information on 44 of the 45 food parameters and for 7DDR we had information on 28 of the 45 food parameters. We observed a significant association between DII and CRP (> 3mg/l) for both tools; (1-point increase in score was associated with an increased odds of elevated hs-CRP using either dietary assessment method (OR: 1.08; 95% CI 1.01, 1.16 for 24HR and OR: 1.10; 95% CI 1.02, 1.19 for 7DDR)(17). In an Australian study we calculated DII from FFQ and we had information on 25 food parameters, where we observed for every unit increase in DII score the odds of being asthmatic increased by 70% (OR: 1.70, CI: 1.03, 2.14, p=0.020). Also in that study, logIL-6 was significantly positively associated with DII (β = 0.13, 95% CI: 0.05, 0.21; p=0.002) (18).

Strengths of the present study include: large sample size, prospective data collection with extended follow-up, near-complete case ascertainment, ability to adjust for multiple potential confounding factors, and consideration of CRC risks overall and by anatomic subsite. One recognized limitation is that dietary data were collected by a single FFQ at baseline. However, adult dietary patterns appear to remain relatively stable over time (40-45) and there was no specific dietary intervention applied to participants during the course of the study. Also, evidence from other studies suggests that modest changes in diet over adulthood may have a minimal effect on estimated CRC risk (11).

In conclusion, older women who consumed a more pro-inflammatory diet were at increased risk of CRC compared to women who consumed a more anti-inflammatory diet. Our results provide further evidence for the benefits of a diet high in vegetables and fruits, nuts, low-fat dairy, fish, and whole grains and low in fried foods, processed meats, refined grains, and alcohol. The logical next steps would be to use DII to predict incidence of other inflammation-related cancers, cardiovascular diseases and to examine effects on mortality among women. The results from the current study are restricted to women, so using DII in studies with men would help to discern the generalizability of DII across the sexes. It also would be interesting to compare the results of DII with other indices with CRC and other cancers as outcomes.

Acknowledgement. The authors are thankful to the IWHS staff for assistance in data preparation.

References:

1. Keibel A, Singh V, Sharma MC. Inflammation, microenvironment, and the immune system in cancer progression. *Curr Pharm Des.* 2009;15:1949-55.
2. Pan MH, Lai CS, Dushenkov S, Ho CT. Modulation of inflammatory genes by natural dietary bioactive compounds. *J Agric Food Chem.* 2009;57:4467-77.
3. Thun MJ, Henley SJ, Gansler T. Inflammation and cancer: an epidemiological perspective. *Novartis Found Symp.* 2004;256:6-21; discussion 2-8, 49-52, 266-9.
4. Warnberg J, Gomez-Martinez S, Romeo J, Diaz LE, Marcos A. Nutrition, inflammation, and cognitive function. *Ann N Y Acad Sci.* 2009;1153:164-75.
5. Chung Y-C, Chang Y-F. Serum interleukin-6 levels reflect the disease status of colorectal cancer. *Journal of Surgical Oncology.* 2003;83:222-6.
6. Terzic J, Grivennikov S, Karin E, Karin M. Inflammation and colon cancer. *Gastroenterology.* 2010;138:2101-14 e5.
7. Toriola AT, Cheng TY, Neuhauser ML, Wener MH, Zheng Y, Brown E, et al. Biomarkers of inflammation are associated with colorectal cancer risk in women but are not suitable as early detection markers. *International journal of cancer Journal international du cancer.* 2013;132:2648-58.
8. 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;54:2755-67.
9. 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;8:2868-75.
10. 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;26:717-20.
11. Michaud DS, Fuchs CS, Liu S, Willett WC, Colditz GA, Giovannucci E. Dietary glycemic load, carbohydrate, sugar, and colorectal cancer risk in men and women. *Cancer Epidemiol Biomarkers Prev.* 2005;14:138-47.
12. Miller PE, Lazarus P, Lesko SM, Cross AJ, Sinha R, Laio J, et al. Meat-related compounds and colorectal cancer risk by anatomical subsite. *Nutr Cancer.* 2013;65:202-26.
13. Miller PE, Lazarus P, Lesko SM, Muscat JE, Harper G, Cross AJ, et al. Diet index-based and empirically derived dietary patterns are associated with colorectal cancer risk. *J Nutr.* 2010;140:1267-73.
14. Weizman AV, Nguyen GC. Colon cancer screening in 2010: an up-date. [Review] [62 refs]. *Minerva Gastroenterologica e Dietologica.* 2010;56:181-8.
15. Smith RA, Cokkinides V, Brawley OW. Cancer screening in the United States, 2009: a review of current American Cancer Society guidelines and issues in cancer screening. *CA Cancer J Clin.* 2009;59:27-41.
16. Shivappa N, Steck, S. E., Hurley, T. G., Hussey, J. R., Hebert, J. R. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr.* 2013;14:1-8.
17. Shivappa N, Steck, S. E., Hurley, T. G., Hussey, J. R., Ma, Y., Ockene, I. S., Tabung, F., Hebert, J. R. A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). *Public Health Nutr.* 2013;10:1-9.
18. Wood L, Shivappa, N., Berthon, BS., Gibson, PG., Hebert, JR. Dietary inflammatory index is related to asthma risk, lung function and systemic inflammation in asthma. *Clinical & Experimental Allergy.* 2014:n/a-n/a.
19. 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. *J Occup Environ Med.* 2014;18:18.

20. Folsom AR, Kaye SA, Prineas RJ, Potter JD, Gapstur SM, Wallace RB. Increased incidence of carcinoma of the breast associated with abdominal adiposity in postmenopausal women. *Am J Epidemiol.* 1990;131:794-803.
21. Bisgard KM, Folsom AR, Hong CP, Sellers TA. Mortality and cancer rates in nonrespondents to a prospective study of older women: 5-year follow-up. *Am J Epidemiol.* 1994;139:990-1000.
22. Willett WC, Sampson L, Browne ML, Stampfer MJ, Rosner B, Hennekens CH, et al. The use of a self-administered questionnaire to assess diet four years in the past. *Am J Epidemiol.* 1988;127:188-99.
23. Cavicchia PP, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, et al. A new dietary inflammatory index predicts interval changes in high-sensitivity c-reactive protein. *J Nutr.* 2009;139:2365-72.
24. Kennedy ET, Ohls J, Carlson S, Fleming K. The Healthy Eating Index: design and applications. *J Am Diet Assoc.* 1995;95:1103-8.
25. Panagiotakos DB, Pitsavos C, Stefanadis C. Dietary patterns: a Mediterranean diet score and its relation to clinical and biological markers of cardiovascular disease risk. *Nutr Metab Cardiovasc Dis.* 2006;16:559-68.
26. Reedy J, Mitrou PN, Krebs-Smith SM, Wirfalt E, Flood A, Kipnis V, et al. Index-based dietary patterns and risk of colorectal cancer: the NIH-AARP Diet and Health Study. *Am J Epidemiol.* 2008;168:38-48.
27. Parr CL, Hjartaker A, Lund E, Veierod MB. Meat intake, cooking methods and risk of proximal colon, distal colon and rectal cancer: The Norwegian Women and Cancer (NOWAC) cohort study. *International journal of cancer Journal international du cancer.* 2013.
28. Razzak AA, Oxentenko AS, Vierkant RA, Tillmans LS, Wang AH, Weisenberger DJ, et al. Associations between intake of folate and related micronutrients with molecularly defined colorectal cancer risks in the Iowa Women's Health Study. *Nutr Cancer.* 2012;64:899-910.
29. Zhang X, Giovannucci EL, Smith-Warner SA, Wu K, Fuchs CS, Pollak M, et al. A prospective study of intakes of zinc and heme iron and colorectal cancer risk in men and women. *Cancer Causes Control.* 2011;22:1627-37.
30. Esmailzadeh A, Kimiagar M, Mehrabi Y, Azadbakht L, Hu FB, Willett WC. Dietary Patterns and Markers of Systemic Inflammation among Iranian Women. *The Journal of Nutrition.* 2007;137:992-8.
31. Festa A, D'Agostino R, Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic Subclinical Inflammation as Part of the Insulin Resistance Syndrome: The Insulin Resistance Atherosclerosis Study (IRAS). *Circulation.* 2000;102:42-7.
32. Bruce WR, Wolever TM, Giacca A. Mechanisms linking diet and colorectal cancer: the possible role of insulin resistance. *Nutr Cancer.* 2000;37:19-26.
33. Bruce WR, Giacca A, Medline A. Possible mechanisms relating diet and risk of colon cancer. *Cancer Epidemiol Biomarkers Prev.* 2000;9:1271-9.
34. Bruce WR, Giacca A, Medline A. Possible Mechanisms Relating Diet and Risk of Colon Cancer. *Cancer Epidemiology Biomarkers & Prevention.* 2000;9:1271-9.
35. Bostick RM, Potter JD, Sellers TA, McKenzie DR, Kushi LH, Folsom AR. Relation of calcium, vitamin D, and dairy food intake to incidence of colon cancer among older women. The Iowa Women's Health Study. *Am J Epidemiol.* 1993;137:1302-17.
36. Folsom AR, Hong C-P. Magnesium Intake and Reduced Risk of Colon Cancer in a Prospective Study of Women. *American Journal of Epidemiology.* 2006;163:232-5.
37. Bostick RM, Potter JD, McKenzie DR, Sellers TA, Kushi LH, Steinmetz KA, et al. Reduced Risk of Colon Cancer with High Intake of Vitamin E: The Iowa Women's Health Study. *Cancer Research.* 1993;53:4230-7.
38. Arts IC, Jacobs DR, Jr., Gross M, Harnack LJ, Folsom AR. Dietary catechins and cancer incidence among postmenopausal women: the Iowa Women's Health Study (United States). *Cancer Causes Control.* 2002;13:373-82.

39. Bostick RM, Potter JD, Kushi LH, Sellers TA, Steinmetz KA, McKenzie DR, et al. Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). *Cancer Causes Control*. 1994;5:38-52.
40. Jain M, Howe GR, Harrison L, Miller AB. A study of repeatability of dietary data over a seven-year period. *Am J Epidemiol*. 1989;129:422-9.
41. Jensen OM, Wahrendorf J, Rosenqvist A, Geser A. The reliability of questionnaire-derived historical dietary information and temporal stability of food habits in individuals. *Am J Epidemiol*. 1984;120:281-90.
42. Lindsted KD, Kuzma JW. Long-term (24-year) recall reliability in cancer cases and controls using a 21-item food frequency questionnaire. *Nutr Cancer*. 1989;12:135-49.
43. Mursu J, Steffen LM, Meyer KA, Duprez D, Jacobs DR, Jr. Diet quality indexes and mortality in postmenopausal women: the Iowa Women's Health Study. *Am J Clin Nutr*. 2013;98:444-53.
44. Sijtsma FP, Meyer KA, Steffen LM, Shikany JM, Van Horn L, Harnack L, et al. Longitudinal trends in diet and effects of sex, race, and education on dietary quality score change: the Coronary Artery Risk Development in Young Adults study. *Am J Clin Nutr*. 2012;95:580-6.
45. Thompson FE, Metzner HL, Lamphiear DE, Hawthorne VM. Characteristics of individuals and long term reproducibility of dietary reports: the Tecumseh Diet Methodology Study. *J Clin Epidemiol*. 1990;43:1169-78.

Table 1. Prevalence of characteristics at baseline across quintiles of dietary inflammatory index (DII, with supplements). IWHS, 1986-2010.

Characteristics ^a (mean (SD) or %)	Dietary inflammatory index (with supplements) ^b				
	Quintile 1 <-2.75 Median = -3.29 N= 6,940	Quintile 2 -2.75 to -1.76 Median = -2.26 N= 6,941	Quintile 3 -1.75 to -0.57 Median =-1.21 N= 6,941	Quintile 4 -0.56 to 1.10 Median = 0.23 N= 6,941	Quintile 5 >1.10 Median = 2.13 N= 6,940
Age (years)	62.0 (4.2)	61.7 (4.2)	61.6 (4.2)	61.4 (4.1)	61.2 (4.2)
Total energy intake (kcal/day)	2119.1 (664.5)	2009.5 (631.4)	1816.4 (532.2)	1684.8 (446.7)	1362.9 (406.7)
Total fat (% kcal/day)	31.4 (5.4)	33.5 (5.3)	34.2 (5.5)	34.7 (5.6)	36.0 (6.0)
Dietary fiber (g/1000 kcal/day)	13.5 (3.2)	11.6 (2.9)	10.8 (2.9)	10.5 (2.9)	9.5 (2.8)
Vitamin supplement use (% taking)					
Any	85.0	73.9	65.5	47.3	34.1
Multivitamin	68.9	50.2	35.3	9.9	2.0
Calcium	63.2	53.0	46.6	37.4	29.2
Vitamin C	32.0	21.9	16.9	9.5	3.8
Vitamin E	28.6	19.8	14.9	7.4	2.0
BMI (%) (kg/m ²)					
≤24.9	42.5	40.2	39.4	38.5	38.6
25-30	37.1	37.1	37.4	36.9	36.2
≥30	20.5	22.7	23.2	24.7	25.2
Education (%)					
Less than high school	15.2	16.6	17.6	19.3	21.6
High school	36.4	40.8	42.1	43.7	47.5
More than high school	48.4	42.6	40.3	37.0	30.9
Smoking (%)					
Never	70.3	68.5	65.7	64.6	59.0

Former	20.3	19.1	19.1	19.7	18.9
Current	9.5	12.5	15.3	15.7	22.1
Alcohol intake (%)					
0 g/day	58.6	54.2	52.7	54.3	55.0
<15 g/day	34.1	39.8	41.1	39.4	38.2
≥15 g/day	7.4	6.0	6.2	6.4	6.8
Level of physical activity ^c (%)					
Low	33.7	42.3	48.4	51.9	61.2
Middle	29.8	30.2	27.4	27.4	22.8
High	36.5	27.5	24.2	20.7	16.1
Hormone therapy use (yes) (%)	43.8	39.9	39.2	36.9	34.0
Diabetes at baseline (yes, %)	6.6	6.4	6.2	5.9	5.3
History of aspirin use (1992 survey, ever %)	73.5	72.7	71.6	71.4	71.0
History of NSAIDs use (1992 survey, ever %)	84.2	83.8	82.6	82.4	81.6

^a All variables are measured at baseline (1986) unless otherwise noted. Some column percentages are presented; they do not always add to 100 because of rounding.

^b Quintile 1 refers to scores indicating the most anti-inflammatory diet and quintile 5 refers to scores indicating the most pro-inflammatory diet.

^c Physical activity level: High- more than 4 times/week for moderate physical activities (e.g., bowling, golf, light sports or physical exercise, gardening, taking long walks) or more than 2 times/week for vigorous physical activities (e.g., jogging, racquet sports, swimming, aerobics, strenuous sports); Middle- more than 2 times/week for moderate physical activities or a few times a month for both moderate and vigorous physical activities; Low- those not belonging to activity level 2 or 3.

Table 2. Distribution of food groups across quintiles of Dietary Inflammatory Index (DII; with supplements)^a. IWHS, 1986-2010.

Food groups (servings/week)	Direction increase with DII ^b	% diff (Q5- Q1)/Q1	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
			Mean	Mean	Mean	Mean	Mean
Other vegetables (other than green leafy vegetables or potatoes)	-	-65%	27.3	19.8	16.0	13.8	9.7
Low fat dairy	-	-63%	10.6	9.1	7.9	6.6	3.9
Green leafy vegetables	-	-62%	7.5	5.5	4.4	3.9	2.8
Fish/seafood	-	-62%	2.6	1.9	1.5	1.3	1.0
Fruit (no juice)	-	-61%	19.9	15.6	12.9	11.2	7.7
Nuts	-	-61%	3.5	2.8	2.2	1.9	1.4
Whole grains	-	-60%	16.8	12.9	10.8	9.3	6.7
Beans without soy	-	-56%	0.7	0.6	0.5	0.4	0.3
Fruit juice	-	-52%	6.6	5.8	5.0	4.5	3.1
Poultry	-	-52%	2.6	2.0	1.8	1.6	1.2
Wine	-	-39%	0.7	0.6	0.5	0.5	0.4
Potatoes	-	-31%	3.5	3.5	3.2	3.1	2.4
Salty snacks	-	-30%	4.5	4.4	3.9	3.7	3.1
Margarine	-	-27%	10.4	10.1	9.6	9.2	7.6
Tea	-	-26%	3.4	3.3	3.0	2.9	2.5
Eggs	-	-24%	2.4	2.4	2.3	2.1	1.8
Sweets without chocolate	-	-22%	8.1	9.1	8.2	7.7	6.3
Low-calorie beverages	-	-20%	2.0	1.8	1.7	1.6	1.6
Red meat	-	-13%	5.8	6.5	6.2	5.9	5.0
Chocolate	0	-3%	0.6	0.8	0.8	0.7	0.6
High-fat dairy	0	-3%	9.6	10.9	10.4	10.2	9.3
Refined grains	0	0%	8.3	8.9	9.0	9.2	8.2
Nitrate processed meat	0	1%	1.8	2.1	2.1	2.0	1.8
French fries	+	6%	0.3	0.4	0.4	0.4	0.4
High-sugar beverages	+	18%	1.2	1.4	1.4	1.4	1.4
Liquor	+	24%	0.8	0.8	0.8	0.9	1.0
Fried food	+	29%	1.8	2.2	2.3	2.3	2.3
Coffee	+	36%	9.9	11.4	11.8	12.1	13.5
Beer	+	37%	0.5	0.6	0.6	0.7	0.7
Butter	+	56%	1.4	1.9	2.0	2.0	2.2

^a The foods listed are meant to give the reader a sense of how dietary intake varies across DII quintiles; though some listed are indeed among the 37 parameters that are used in computation of DII in the IWHS, these are not meant to be a list of contributors to the DII.

^b + indicates increase across quintiles, - indicates decrease across quintiles, 0 indicates no or <5% change.

Table 3. Dietary Inflammatory Index (DII) from food and supplements and colorectal cancer risk; IWHS, 1986-2010.

	# cases	HR ^a , 95% CI	HR ^b , 95% CI	# cases	HR ^a , 95% CI	HR ^b , 95% CI	# cases	HR ^a , 95% CI	HR ^b , 95% CI
	Colorectal cancer			Colon cancer			Rectal cancer		
DII continuous	1636	1.09 (1.03, 1.14)	1.07 (1.01, 1.13)	1329	1.08 (1.02, 1.13)	1.05 (0.99, 1.12)	325	1.10 (0.99, 1.23)	1.11 (0.98, 1.25)
DII quintiles									
Quintile 1	290	1 (referent)	1 (referent)	236	1 (referent)	1 (referent)	58	1 (referent)	1 (referent)
Quintile 2	318	1.11 (0.94, 1.30)	1.04 (0.89, 1.22)	267	1.14 (0.96, 1.34)	1.07 (0.89, 1.28)	54	0.93 (0.64, 1.35)	0.91 (0.62, 1.32)
Quintile 3	335	1.18 (1.01, 1.38)	1.11 (0.95, 1.31)	270	1.17 (0.98, 1.40)	1.10 (0.92, 1.31)	73	1.28 (0.91, 1.81)	1.23 (0.86, 1.76)
Quintile 4	341	1.20 (1.03, 1.40)	1.13 (0.95, 1.33)	270	1.17 (0.98, 1.39)	1.08 (0.89, 1.29)	71	1.24 (0.88, 1.76)	1.25 (0.87, 1.80)
Quintile 5	352	1.29 (1.10, 1.51)	1.20 (1.01, 1.43)	286	1.28 (1.08, 1.53)	1.19 (0.98, 1.45)	69	1.25 (0.88, 1.77)	1.21 (0.81, 1.79)
P-trend		0.001	0.03		0.008	0.10		0.09	0.10

^aAge-adjusted

^bAdjusted for age, BMI, smoking status, pack-years of smoking, HRT use, education, diabetes, and total energy intake.

Table 4. Dietary Inflammatory Index (DII) from foods only, DII from vitamin supplements, and colorectal cancer risk; IWHS, 1986-2010.									
	# cases	HR ^a , 95% CI	HR ^b , 95% CI	# cases	HR ^a , 95% CI	HR ^b , 95% CI	# cases	HR ^a , 95% CI	HR ^b , 95% CI
DII from foods only^c	Colorectal cancer			Colon cancer			Rectal cancer		
Continuous	1636	1.09 (1.03, 1.14)	1.08 (1.01, 1.15)	1329	1.08 (1.02, 1.14)	1.06 (0.99, 1.14)	325	1.11 (0.99, 1.24)	1.13 (0.98, 1.31)
Quintiles^d									
Quintile 1	294	1 (referent)	1 (referent)	237	1 (referent)	1 (referent)	58	1 (referent)	1 (referent)
Quintile 2	323	1.11 (0.95, 1.30)	1.07 (0.90, 1.26)	271	1.15 (0.96, 1.37)	1.10 (0.91, 1.32)	60	1.07 (0.74, 1.54)	1.07 (0.73, 1.56)
Quintile 3	338	1.16 (0.99, 1.36)	1.12 (0.94, 1.33)	268	1.12 (0.94, 1.34)	1.07 (0.88, 1.30)	73	1.35 (0.95, 1.92)	1.37 (0.93, 2.01)
Quintile 4	351	1.21 (1.03, 1.43)	1.16 (0.97, 1.40)	293	1.23 (1.03, 1.47)	1.16 (0.95, 1.43)	61	1.16 (0.80, 1.68)	1.20 (0.79, 1.84)
Quintile 5	330	1.17 (0.99, 1.38)	1.12 (0.91, 1.38)	260	1.12 (0.93, 1.35)	1.06 (0.84, 1.33)	73	1.43 (0.99, 2.05)	1.48 (0.94, 2.34)
P-trend		0.004	0.08		0.02	0.27		0.10	0.1
DII from supplements^e									
Continuous	1636	1.04 (0.99-1.10)	1.02 (0.97-1.08)	1329	1.04 (0.98-1.09)	1.02 (0.96-1.08)	325	1.05 (0.93-1.17)	1.02 (0.91-1.15)
Categories^f									
1 (N=5,824)	273	0.91 (0.79-1.04)	0.94 (0.82-1.09)	226	0.84 (0.69-1.02)	0.84 (0.69-1.03)	52	1.10 (0.74-1.64)	1.10 (0.73-1.64)
2 (N=5,824)	236	0.81 (0.70-0.94)	0.84 (0.73-0.98)	186	0.91 (0.74-1.11)	0.89 (0.72-1.09)	53	1.30 (0.88-1.92)	1.21 (0.81-1.81)
3 (N=5,826)	256	0.89 (0.77-1.02)	0.89 (0.77-1.03)	199	1.09 (0.94-1.27)	1.05 (0.90-1.23)	61	1.08 (0.79-1.49)	1.02 (0.74-1.42)
4 (N=17,229)	871	1 (referent)	1 (referent)	718	1 (referent)	1 (referent)	159	1 (referent)	1 (referent)

P-trend		0.09	0.29		0.15	0.36		0.56	0.88
---------	--	------	------	--	------	------	--	------	------

^a Adjusted for age and the other DII variable

^b Adjusted for age, the other DII variable, BMI, smoking status, pack-years of smoking, HRT use, education, diabetes, and total energy intake.

^c These are for foods only, exclusive of supplement intake

^d Reference category is the lowest (i.e., most anti-inflammatory) quintile; increasing quintiles of DII from food groups represent increasing inflammatory scores

^e This is obtained by subtracting the DII score for foods only from the DII derived by including both foods and supplements.

^f Reference category represents non-supplement users; categories 1-3 represent tertiles of the DII from supplement users. Category 1 represents women with the greatest contribution from supplements to the DII score. DII score median (range): Categories 1: -3.00 (<-2.0552); 2: -1.31 (-2.0552 to -0.7616); 3: -0.34 (-0.7615 to 0.0000); 4: 0.00 (0.0000 to 0.1765)

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association
for Cancer Research

Dietary Inflammatory Index (DII) and risk of colorectal cancer in Iowa Women's Health Study

Nitin Shivappa, Anna E Prizment, Cindy K Blair, et al.

Cancer Epidemiol Biomarkers Prev Published OnlineFirst August 25, 2014.

Updated version

Access the most recent version of this article at:
doi:[10.1158/1055-9965.EPI-14-0537](https://doi.org/10.1158/1055-9965.EPI-14-0537)

Author Manuscript

Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts

[Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, use this link
<http://cebp.aacrjournals.org/content/early/2014/08/23/1055-9965.EPI-14-0537>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.