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Development of a Food-Based Inflammation Score and Its Associations with Colorectal Neoplasms

By

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Development of a Food-Based Inflammation Score and Its Associations with Colorectal Neoplasms

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M.P.H., George Washington University, 2012
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An abstract of
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James T. Laney School of Graduate Studies of Emory University
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ABSTRACT

Development of a Food-Based Inflammation Score and Its Associations with Colorectal Neoplasms

By Ashley Christine Holmes

The ability to characterize the inflammatory potential of diet is a promising area of cancer prevention, as it is well-accepted that inflammation is implicated in colorectal carcinogenesis and that reducing inflammation reduces risk for colorectal adenoma and cancer. However, no *a priori* food-based inflammation index exists that accounts for national nutrition recommendations and few studies have examined the relationship of diet-related inflammation and risk for colorectal neoplasms.

The purpose of this dissertation was to create a food-based inflammation index to investigate associations of this score with systemic biomarkers of inflammation and risk for colorectal neoplasms. The specific research aims were to: 1) create a food-based inflammation (FBI) score based on current dietary guidelines, 2) investigate associations of the score with systemic inflammation biomarkers, 3) investigate associations of the score with risk of colorectal adenoma, and 4) investigate associations of the score with colorectal cancer incidence. These aims were addressed by using biomarker and food frequency questionnaire data from a subset of REasons for Geographic and Racial Differences in Stroke participants to create the score, then calculating and applying the score to four studies: two studies with available biomarker data, a previously-conducted endoscopy-based case-control study of incident, sporadic colorectal adenoma, and a large prospective cohort study of postmenopausal women.

We selected 18 food groups based on the *2015 Dietary Guidelines for Americans* to comprise the FBI score and observed that a proinflammatory diet (indicated by higher FBI score) was significantly associated with higher circulating C-reactive protein concentrations. We observed a significant positive association between proinflammatory diet and adenoma risk when comparing cases to endoscopy-negative controls, but no association between proinflammatory diet and colorectal cancer incidence in a prospective cohort of older women. The results from this dissertation suggest that the FBI score may be a useful tool for quantifying the inflammatory potential of diet. While our data do not identify an optimal diet for colorectal cancer prevention, these findings support dietary guidelines to meet nutrient needs through healthy eating patterns. Further examination is warranted to clarify the role of diet-related inflammation in the development of colorectal neoplasms and other chronic diseases.

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CHAPTER 1. INTRODUCTION AND BACKGROUND

INTRODUCTION

Colorectal cancer is the third most commonly diagnosed cancer and the second-leading cause of cancer death in the United States among men and women combined (1). Geographic differences and migrant data point to lifestyle exposures, such as diet, adiposity, and physical activity, as playing a role in the etiology of colorectal cancer (2). More specifically, the World Cancer Research Fund's (WCRF) Continuous Update Project has concluded that consumption of dairy products, whole grains, and other fiber-containing foods probably protect against colorectal cancer whereas consumption of processed meats is a convincing cause and consumption of red meats is a probable cause of colorectal cancer (3).

Inflammation is a biological hallmark in the multistep development and progression of cancer (4). While acute inflammation is a normal and protective immune response, a prolonged or uncontrolled inflammatory response—resulting in a state of systemic low-grade inflammation—can cause tissue damage (4-7). Molecules produced from chronic inflammation are involved in sustaining proliferative signaling activity, limiting apoptosis, and generally facilitating the transition from benign neoplasm to malignant tumor (4-7). Strong evidence indicates that chronic inflammation plays a key role in colorectal carcinogenesis: inflammatory bowel disease is an established risk factor for colorectal cancer (8, 9); the use of non-steroidal anti-inflammatory drugs (NSAIDs) has been consistently, strongly associated with lower risk of colorectal neoplasms and recurrence (9-15); and obese individuals, who have elevated circulating levels of proinflammatory cytokines, are at greater risk for colorectal neoplasms than are normal weight individuals (5, 16-18). Moreover, in animal models it was found that induced inflammation promotes the conversion of colon adenomas to adenocarcinomas (19, 20).

Chronic inflammation may be one mechanism by which diet influences colorectal cancer risk. Dietary constituents, such as catechins (found in tea) and omega-3 fatty acids (found in some fish and nuts), have chemopreventive properties that act to decrease proinflammatory cytokines and increase

anticancer immunosurveillance (21). However, individuals do not consume these components in isolation—they consume foods and beverages that comprise meals and, over time, dietary patterns. Examining usual dietary patterns accounts for the interactions of specific nutrients and foods, and may be more useful for classifying dietary exposure as pro- or anti-inflammatory. Two dietary inflammation indices (differing in methodology, construction, and components) have recently been developed and validated to quantify the effect of diet on inflammation and to investigate associations of diet-related inflammation on health outcomes, including risk for colorectal neoplasms (22, 23). While higher (more proinflammatory) scores on both indices have been associated with increased risk for incident colorectal cancer (24-26), only one study has examined the association of a proinflammatory diet on risk for incident adenoma (27), the precursor for colorectal cancer. Unfortunately, neither of these indices account for some of the foods or food groups recommended by the WCRF or the Dietary Guidelines for Americans (e.g., legumes, whole grains, and dairy products) as part of health promotion or disease prevention (28).

Thus, the objective of this dissertation is to create an *a priori* food-based inflammation score—based on current dietary recommendations—to further clarify associations of diet-related inflammation with risk for colorectal neoplasms. The specific research aims are to: 1) develop weights for a food-based inflammation (FBI) score *vis á vis* associations of whole food dietary components with a panel of systemic inflammation biomarkers using data from a national, population-based prospective cohort study; 2) create FBI scores and assess their associations with systemic biomarkers of inflammation using cross-sectional data from two independent studies; 3) investigate associations of the FBI score with incident, sporadic colorectal adenoma in a colonoscopy-based case-control study; and 4) investigate associations of the FBI score with colorectal cancer incidence in a prospective cohort study of postmenopausal women.

BACKGROUND

Colorectal Cancer

Colorectal cancer incidence rates vary geographically. Historically, the disease has been a major health issue in developed countries; however, countries that have experienced rapid economic development and adopted more "Western" lifestyles are now experiencing increasing rates (29). The WCRF reported that almost half of colorectal cancer cases occurred in less developed countries in 2012 (3). This data, along with migrant studies that have observed increasing incidence after immigrating from low- to high-risk countries, implicate environmental exposures (such as diet and tobacco use) in colorectal cancer etiology (2, 9).

Most cases of colorectal cancer develop through an accumulation of genetic and epigenetic alterations in which normal colorectal epithelium is transformed to a benign adenoma and, ultimately, to a malignant tumor over a period of 10–20 years (1, 30-32). This transformation is called the "adenoma-carcinoma" sequence, and may involve chromosomal instability, microsatellite instability, and aberrant methylation as a type of epigenetic instability (33). Between 60–90% of colorectal cancers are estimated to occur via this sequence (33, 34).

Chromosomal instability manifests as gains or losses of large portions of chromosomal material. The mechanisms leading to chromosomal instability are not well-described but are hypothesized to involve hypomethylation and telomere erosion (33). Loss of function of the adenomatous polyposis coli (*APC*) tumor suppressor gene is associated with chromosomal instability and is a common first step in colorectal carcinogenesis (33, 35). Mutation and inactivation of the *APC* gene initiates adenoma formation, as the APC protein can no longer bind to and regulate the β-catenin protein (35). If overexpressed, β-catenin can drive transcription of genes involved in tumor growth (35-37). Other mutations to the *p53* tumor suppressor gene and *KRAS* oncogene are also associated with chromosomal instability and appear to occur early in the adenoma-carcinoma sequence (33).

Microsatellite instability is caused by deficiencies in DNA mismatch repair. Normally, the mismatch repair process can correct errors that occur during DNA replication; however, mutations (in the form of short, repetitive DNA sequences [microsatellites]) can accumulate if the repair process is impaired (38). While microsatellite instability is most often found in individuals with Lynch syndrome (a hereditary cancer syndrome), sporadic colorectal cancers may also occur as a result of deficiencies in repair (39). Unlike chromosomal instability, microsatellite instability is found only in advanced sporadic colorectal adenomas and malignant lesions (40).

Epigenetic instability has been found in both benign neoplasms and tissues adjacent to colorectal tumors (41-43). These epigenetic changes are present in nearly all colorectal cancer cases, most often appearing as DNA hyper- and hypomethylations (33, 44). Aberrant DNA methylation may affect genes involved in apoptosis, cell proliferation, and DNA repair, and may act in tandem with chromosomal and microsatellite instability in colorectal cancer pathogenesis (33, 45). Identifying specific mechanisms responsible for aberrant DNA methylation is an area of active research (46, 47).

Inflammation and Colorectal Cancer

Acute inflammation is a normal, protective response to foreign pathogens or tissue injury that leads to the restoration of tissue structure and function. However, a prolonged or uncontrolled inflammatory response resulting in a state of chronic inflammation can cause tissue damage (4, 48-50). Epidemiologic studies of inflammatory bowel disease (IBD) patients have provided evidence for a link between chronic inflammation and colorectal cancer risk, as these patients have an increased risk of developing colorectal cancer than individuals without IBD. Additionally, this risk increases with greater duration and degree of inflammation (51, 52).

Chronic inflammation is characterized by the infiltration of immune cells to a target tissue, leading to the overproduction of inflammatory cytokines (among other soluble mediators) (5). Cytokines are important cell signaling molecules that can modulate both innate and adaptive immune responses.

The interleukins (IL) are among the most well-studied cytokines, coordinating both pro- and anti-inflammatory responses (53). For example, upon release into the circulation, IL-6 acts in a proinflammatory manner by promoting catabolism in the muscle and liver, triggering production of neutrophils in the bone marrow, and stimulating the production of other molecules involved in inflammation (53), like C-reactive protein (CRP). In contrast, IL-10 acts in an anti-inflammatory manner by decreasing the expression of proinflammatory cytokines (54). Certain cytokines have been implicated in tumor growth and development through promoting cell proliferation and survival pathways, angiogenesis, and the production of reactive oxygen species (ROS) and various growth factors (55-57).

Cytokines act to transmit information via induction of signaling pathways such as nuclear factor kappa-B (NFκB), which controls DNA transcription and cell survival (58). As part of the immune response, proinflammatory cytokines like IL-1 and tumor necrosis factor-alpha (TNF-α) stimulate production of ROS (59, 60). Under normal circumstances, ROS are used to help eliminate pathogens or replace destroyed tissue. In a state of chronic inflammation, these ROS can induce mutations in DNA and are involved in the epigenetic silencing of tumor suppressor genes (20, 56-60). ROS can also recruit other inflammatory molecules and activate the NFκB pathway, thereby increasing the inflammatory response and inducing expression of genes involved in increasing cell proliferation and decreasing apoptosis (58, 59).

Experiments using *in vitro* models have shown that proinflammatory cytokines also stimulate the expression of cyclooxygenase-2 (COX-2), an enzyme responsible for the conversion of prostanoids from arachidonic acid (59, 61). Overexpression of COX-2 increases the production of prostaglandin E2, which can inhibit apoptosis in colon cells and promote metastasis through enhancing tumor invasion (62-65). COX-2 enzymes are upregulated in both colorectal adenoma and cancer and are associated with worse survival among colorectal cancer patients (10-11, 64, 66). Aspirin (10) and other NSAIDs reduce proinflammatory prostaglandin activity by modifying and inhibiting COX-2 enzymes (11, 63). Additionally, NSAIDs have been shown to inactivate the NFκB pathway in colorectal cancer cells (67).

Markers of inflammation have been studied extensively in association with colorectal cancer risk. TNF-α is an activator of NFκB signaling and the β-catenin oncogenic pathway involved in chromosomal instability (68-70). Proinflammatory mediators such as CRP (a nonspecific marker for inflammation), IL-8 (a chemotactic agent for granulocytes and inducer of proinflammatory signaling pathways), and IL-6 are found to be elevated in colorectal tumor tissue compared to normal tissue in *in vivo* and *in vitro* models (71-73). Conversely, significantly lower levels of anti-inflammatory IL-10 have been found in colorectal tumor tissue relative to normal tissue (74). Additionally, elevated systemic levels of these biomarkers have been associated with colorectal cancer risk. One colonoscopy-based cross-sectional study found that higher serum concentrations of IL-6 and TNF-α were significantly associated with prevalence of colorectal adenomas (odds ratio [OR] for IL-6: 1.85; 95% confidence interval [CI]: 1.24, 2.75 and OR for TNF-α: 1.66; 95% CI: 1.10, 2.52 for the highest compared to lowest tertiles) (17). Data from the Shanghai Men's Health Study indicated a positive association between CRP concentration and colorectal cancer risk, with men in the highest tertile of CRP having a nearly two-fold higher risk relative to men in the lowest tertile (OR: 1.88; 95% CI: 1.24, 2.86) (75). Similarly, the Copenhagen General Population Study found that elevated levels of CRP were associated with higher future risk of colorectal cancer (76). Higher serum concentrations of IL-6 have been positively associated with colorectal cancer risk and tumor size (77-80) and elevated serum concentrations of IL-8 have previously been associated with tumor size, stage, and prognosis for several different cancer types (81).

Diet and Colorectal Cancer

Many studies have examined associations of individual nutrients and foods with colorectal cancer risk. In its latest report, the WCRF Continuous Update Project panel deemed consumption of processed meat as a convincing cause, red meat as a probable cause, and whole grains, calcium, dairy products, and fiber-containing foods as probably preventive of colorectal cancer (3). Evidence suggesting a role for vitamin D, multivitamin use, and fruit and vegetable consumption in colorectal cancer prevention was

deemed “limited” (3). However, as individuals do not eat these nutrients and foods in isolation, focus has turned to analyzing associations of dietary patterns with colorectal cancer risk.

Despite differences in pattern construction and study populations, results from observational studies have indicated that adherence to a generally “healthy” diet is associated with decreased risk for colorectal cancer. Dietary patterns that have been examined in association with risk for colorectal cancer include “Western” (characterized by high consumption of sweets, French fries, pizza, refined grains, and red/processed meats), “prudent” (characterized by high consumption of whole grains, fish, poultry, fruits, and vegetables), Mediterranean, and “healthy” diets (based on the Dietary Guidelines for Americans and indicated via the Healthy Eating Index and Alternate Healthy Eating Index) (82). Mehta et al. recently examined the association of a “Western” dietary pattern with colorectal cancer risk in the Nurses’ Health Study and Health Professionals Follow-Up Study, and observed a combined relative risk (RR) of 1.31 (95% confidence interval [CI]: 1.15, 1.48) when comparing the highest vs. lowest quartile of intake (83). Interestingly, a “prudent” dietary pattern was not significantly associated with colon or rectal cancer among Nurses’ Health Study participants (84). Several prospective cohort studies—including the European Prospective Investigation into Cancer and Nutrition (EPIC), Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Prevention Trial, and the NIH-American Association of Retired Persons (NIH-AARP) Diet and Health Study—have generally observed a decreased risk of colorectal cancer in individuals who best adhere to a Mediterranean dietary pattern (85-87). Reedy et al. reported a 20-30% reduction (HR for males: 0.72; 95% CI: 0.62, 0.83; HR for females: 0.80; 95% CI: 0.64, 0.98, comparing highest vs. lowest diet quantiles) in colorectal cancer risk in NIH-AARP participants who adhered to a “healthy” diet, as indicated by higher scores on the Healthy Eating Index (88).

Diet, Inflammation, and Colorectal Cancer

Diet-related issues resulting in obesity, hyperinsulinemia, and gut dysbiosis are ways by which chronic inflammation acts to influence colorectal cancer risk. These three conditions may be linked to colorectal cancer through complex but interrelated pathways.

Basic science research has found that inflammatory pathways involving NFκB are stimulated in states of both insulin resistance and obesity (89-91). Excess energy intake and/or poor diet quality can increase circulating glucose and lipid concentrations, which stimulate insulin secretion and cause repeated bouts of hyperinsulinemia (9). Hyperinsulinemia increases circulating levels of TNF-α and induces expression of NFκB, thereby increasing expression of proinflammatory cytokines such as IL-6 and CRP (58, 92). The subclinical inflammation resulting from activation of NFκB pathways can also stimulate other proinflammatory factors, including prostaglandins (via upregulated COX-2 expression), and various adipokines and cytokines (92). Ultimately, these molecules are thought to have wide-ranging downstream effects that decrease apoptosis and promote proliferation, growth, migration, and invasion of tumor cells (93). Previous studies have found that CRP, TNF-α, and IL-6 are all elevated in obese individuals (91) and decrease after weight loss among the same individuals (94, 95). Another histopathological study found a significant increase ($p \leq 0.001$) in expression of COX-2 in normal mucosa adjacent to colorectal tumor among patients that were overweight, compared to patients with a healthy body mass index (96).

Excess energy intake and poor dietary quality can also modify the composition of the gut microbiome, although research is ongoing to elucidate specific mechanisms linking diet, inflammation, microbiome composition, and host susceptibility to disease (97). Gut dysbiosis, an imbalance between beneficial and harmful bacteria, may lead to increased gut permeability and the secretion of lipopolysaccharides that regulate inflammatory pathways and further promote insulin resistance (98, 99). Increases in specific types of bacteria, such as *Fusobacterium*, can activate the NFκB pathway and down-regulate adaptive immune function (100, 101). Increased amounts of *Fusobacterium* have been found in

both colorectal adenomas and cancer (102) and are associated with microsatellite instability (103). Additionally, Abu-Remaileh et al. identified that chronic inflammation can induce the epigenetic silencing of genes involved in gastrointestinal homeostasis, resulting in both adenomas and cancers in mice (20).

Recently, two indices were created and validated to quantify the effect of diet quality on inflammation and to investigate associations of diet-related inflammation on health outcomes (22, 23). The dietary inflammatory index (DII) is a tool developed by researchers at the University of South Carolina (22). The DII is derived and weighted based on a review of over 2,000 articles examining the relationship between 45 dietary parameters (including carbohydrates, saturated fat, B-complex vitamins, vitamins A, C, and E, zinc, magnesium, phytochemicals, and spices) and six inflammation biomarkers (IL-1β, IL-4, IL-6, IL-10, CRP, and TNF-α). Each of the parameters are weighted and summed to create a total DII score, which is then used to assess the inflammatory potential of an individual's diet (22). Higher (more proinflammatory) DII scores have been associated with increased inflammation biomarker levels (104, 105), increased risk of adenoma in males participating in the PLCO trial (27), and increased risk of colorectal cancer in several large prospective cohort studies (including the Women's Health Initiative and Multiethnic Cohort) (106, 107), among other disease endpoints (108-111). While these results suggest a role for diet-related inflammation in the development of colorectal cancer, construction of the DII is primarily focused on specific nutrients/components in foods; thus, it may be difficult to translate a proinflammatory diet (as described by the DII) to nutritional practice. Another criticism of the DII is that this nutrient-based focus oversimplifies the complex interactions between components in whole foods, particularly as many bioactive components have yet to be identified (112). Finally, application of the DII may be limited by both its proprietary nature and available dietary data, which often do not ask about or calculate consumption of components such as ginger, turmeric, or rosemary.

For these reasons, and because dietary recommendations are made based on foods and food groups rather than nutrients, Harvard researchers created the empirical dietary inflammatory pattern

(EDIP). Using data from the Nurses' Health Study, the EDIP was developed to identify a dietary pattern most predictive of four plasma inflammation biomarkers: CRP, IL-6, TNF-αR2, and adiponectin (23). Though 39 foods/food groups were considered, only 18 were identified as significant predictors of inflammation from regression models: leafy green vegetables, dark yellow vegetables, tomatoes, other vegetables (i.e., vegetables other than leafy green and dark yellow vegetables), fish (other than dark-meat fish), red meats, processed meats, organ meats, refined grains, pizza, snacks, wine, beer, coffee, fruit juice, high-energy beverages, low-energy beverages, and tea (23). However, creating an *a posteriori* dietary pattern, after testing for significance in statistical analyses, is still not representative of total diet or the synergistic effects of total diet and individual characteristics. A higher (proinflammatory) EDIP score has been positively associated with increased levels of proinflammatory biomarkers (113) and colorectal cancer risk (114) in the Nurses' Health Study II and Health Professionals Follow-Up Study.

Gaps in the Literature Addressed by this Dissertation

Research on the etiology, prevention, and treatment of colorectal cancer has progressed over the past few decades; however, further investigation into modifiable risk factors for colorectal cancer—and the mechanisms underlying these risk factors—is warranted. While diet and inflammation are independently related to cancer risk, examining the associations of diet-related inflammation with risk for colorectal neoplasms may offer more specific insights into primary prevention strategies for colorectal cancer. Thus, the objectives of this dissertation are to address these specific gaps in the literature: 1- there is currently no dietary inflammation score that includes some of the major foods/food groups recommended by the Dietary Guidelines for Americans (e.g., legumes, whole grains, nuts, and dairy products are not included in current indices that quantify diet-related inflammation), which is used to inform national health and nutrition policy; and 2- there is little evidence examining the role of dietary inflammation on adenoma risk.

DISSERTATION RESEARCH PLAN

Objectives, Specific Aims, and Study Hypotheses

The projects in this dissertation are to create a food-based inflammation (FBI) score based on the current Dietary Guidelines for Americans, investigate associations of the FBI score with a panel of systemic inflammation biomarkers (CRP, IL-6, IL-8, and IL-10), investigate associations of the FBI score with risk of colorectal adenoma, and investigate associations of the FBI score with colorectal cancer risk. The specific aims are:

Aim 1a: Develop weights for a food-based inflammation (FBI) score using data from a subset of the prospective REasons for Geographic and Racial Differences in Stroke (REGARDS) study (*n*= 539) in which there are baseline measurements for 1- serum concentrations of CRP, IL-6, IL-8, and IL-10; and 2- diet, lifestyle, family and medical history, and other risk factors using a Block 98 food frequency questionnaire (FFQ) and other surveys.

Aim 1b: Using the weights derived from *Aim 1a*, create FBI scores and assess their associations with biomarkers of inflammation using data collected previously from two studies: a pooled colonoscopy-based case-control study (the Markers of Adenomatous Polyps studies I and II [MAPs]; *n*= 456) and baseline data from a randomized, clinical trial of adenoma patients (the Calcium and Colorectal Epithelial Cell Proliferation [CCECP] trial; *n*= 176).

> *Hypothesis: Higher (more pro-inflammatory) FBI scores will be associated with higher summary inflammation biomarker z-scores.*

Aim 2: Using the weights derived from *Aim 1a*, create and apply the FBI score in the Minnesota Cancer Prevention Research Unit Case-Control Study (CPRU), a colonoscopy-based case-control study (cases =

558, controls = 1,729), and investigate the association of the score with incident, sporadic colorectal adenoma.

Hypothesis: Higher FBI scores will be associated with higher risk for incident, sporadic adenomatous polyps.

Aim 3: Using the weights derived from *Aim 1a*, create and apply the FBI score in the Iowa Women's Health Study (IWHS; *n*=32,616) cohort to investigate the association of the score with colorectal cancer incidence.

Hypothesis: Higher FBI scores will be associated with higher risk for incident colorectal cancer.

Methods for Aim 1a

REGARDS is a longitudinal study of 30,239 adults ≥45 years of age enrolled between January 2003 and October 2007. Exclusion criteria included race other than white or African-American, inability to speak English, medical conditions preventing long-term participation, residence in or on a waiting list for a nursing home, cognitive impairment based on a telephone interview, and active treatment for cancer. Those who agreed to participate completed self-administered questionnaires (including a Block 98 FFQ to collect dietary data) and underwent an in-home visit where anthropometric data, a medication inventory, and fasting blood were collected. Detailed methodology of the study was previously published (115).

Fasting blood was randomly sampled from 1,104 participants for measurement of additional analytes, including CRP, IL-6, IL-8, and IL-10. These analytes were measured using a second generation, C-terminal enzyme-linked immunosorbent assay (ELISA) by the University of Vermont Laboratory for Clinical Biochemical Research. Since serum samples were collected during an in-home visit (rather than at a hospital/study center) and shipped to Vermont, REGARDS sample handling was compared to "ideal" processing using split samples from participants (116).

Baseline biomarker and FFQ data from eligible REGARDS participants were used to develop the FBI score. We used a panel consisting of three proinflammatory markers (CRP, IL-6, and IL-8) and one anti-inflammatory marker (IL-10) to create a summary inflammation biomarker score by calculating a z-score for each biomarker, and then summing the z-scores for CRP, IL-6, IL-8, and IL-10 (giving IL-10 a negative sign). Components of the FBI score were selected based on biological plausibility and previous literature, and consisted of 18 food groups: processed meat, red meat, white meat, fish, shellfish, nuts, coffee, tea, dairy products, refined and whole grains, beta-carotene-containing foods, lycopene-containing foods, green/leafy vegetables, Brassicaceae, Leguminosae, Rosaceae, and Rutaceae. To create the FBI score, we used linear regression to calculate multivariable-adjusted associations of each food group with the summary biomarker z-score. The beta coefficients for these regressions were then used as weights and multiplied to each participant's weekly intake of the respective food components. The overall FBI score was calculated as the sum of the weighted dietary components of each participant.

Methods for Aim 1b

To evaluate the construct validity of the FBI score, we applied it to baseline biomarker and FFQ data from two previously-conducted studies: the CCECP trial and the pooled MAPs studies.

Participants in the CCECP trial (1990–1994) were in general good health, 30–74 years of age, consumed a "western-style" diet, and had one or more pathology-confirmed colorectal adenoma within the past five years. As the purpose of the trial was to assess the efficacy of supplemental calcium in reducing colorectal epithelial cell proliferation in normal mucosa, exclusion criteria included contraindications to biopsy procedures and calcium supplementation. Further details of the study have previously been published (117). Baseline blood samples (obtained using standard venipuncture methods) of CRP, IL-6, IL-8, and IL-10 were available to create a summary biomarker z-score. Concentrations of the biomarkers were measured at the Emory Multiplexed Immunoassay Core using electrochemiluminescence detection-based immunoassays (117).

The pooled MAPs studies (MAPI: 1995–1997, MAPII: 2002) are identically-designed, colonoscopy-based case-control studies of incident, sporadic colorectal adenoma in North and South Carolina; details of the studies have been previously published (118). Participants included both males and females in general good health between 35 and 74 years of age with no history of colorectal adenoma, cancer (excluding non-melanoma skin cancer), inflammatory bowel disease, or genetic syndromes associated with colorectal neoplasms. A venous blood sample was drawn before each participant underwent outpatient, elective colonoscopy. The only inflammation biomarker available in the MAPs study population was CRP (interquartile range: 4.53 mg/L), measured by latex-enhanced immunonephelometry (118, 119).

Baseline characteristics of REGARDS, CCECP, and MAPs participants were compared using the Pearson's chi-square (χ^2) test for categorical variables and the Student *t* test or ANOVA (as appropriate) for continuous variables, according to FBI score quantiles. Multivariable unconditional logistic regression (the standard method for examining associations of independent variables with a dichotomous outcome) was used to calculate odds ratios (OR) and 95% confidence intervals (CI) as measures of associations of the FBI scores with the summary biomarker z-score category (high vs. low, dichotomized based on median inflammation biomarker z-score in each of the study populations). For these analyses, study-specific cutpoints were used to dichotomize FBI scores in CCECP (due to sample size limitations) and create FBI score quartiles in the pooled MAPs studies. The lowest FBI score quantile was used as the reference in each analysis. The FBI score was also treated as a continuous variable to examine multivariable-adjusted associations with the biomarker z-score category. Selection of potential confounding variables was based on previous literature/biological plausibility, statistical significance, and whether exclusion of the variable from the model affected the estimated association of the primary exposure variable with the outcome by ≥10%. The median value of each FBI score category was used for conducting multivariable-adjusted linear trend tests.

Selection of potential effect modifying variables was based on previous literature/biological plausibility, and included age, sex, race, body mass index (BMI), smoking history, and regular NSAID use. Effect modification was assessed by including FBI score × covariate interaction terms in the multivariable-adjusted models. Sensitivity analyses were conducted to ascertain whether any one food component overly influenced the association of the FBI score with the summary biomarker score. A two-sided p-value ≤ 0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 software (SAS Institute, Inc., Cary, North Carolina).

Methods for Aim 2

The CPRU case-control study was conducted between 1991 and 1994 in the Minneapolis metropolitan area (120-122). Adults in general good health between 35 and 74 years of age with no history of colorectal adenoma, cancer (excluding non-melanoma skin cancer), inflammatory bowel disease, or genetic syndromes associated with colorectal neoplasms were recruited from a large, multicenter gastroenterology practice and scheduled for outpatient, elective endoscopy. Additional controls were randomly selected from the Minneapolis metropolitan area using Minnesota driver's license records, but did not undergo endoscopy procedures. For endoscopy participants, all self-reported demographic, lifestyle, anthropometric, medical history, and dietary data were obtained prior to undergoing the outpatient procedure (122).

The FBI score was created for each participant as previously described. Once created, FBI scores were categorized into quartiles based on the distribution of scores in community controls. Selected characteristics among FBI score quartiles were compared using χ^2 tests for categorical variables and ANOVA for continuous variables. Multivariable unconditional logistic regression was used to estimate OR and 95% CI for associations of the FBI score with incident colorectal adenoma, analyzed as both continuous and categorical (reference: lowest FBI score quartile) variables. Selection of potential confounding variables was based on previous literature/biological plausibility, statistical significance, and whether exclusion of the variable from the model changed the adjusted OR for the primary exposure

variable by ≥10%. The median value of each FBI score quartile was used for conducting multivariable-adjusted linear trend tests. Separate analyses were conducted to compare cases with each of the control groups.

Selection of potential effect modifying variables was based on previous literature/biological plausibility and included age, sex, family history of colorectal cancer, BMI, smoking history, and regular NSAID use. Effect modification was assessed in the multivariable-adjusted models by including interaction terms between the FBI score and respective covariates. A two-sided p-value ≤ 0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 software (SAS Institute, Inc., Cary, North Carolina).

Methods for Aim 3

For the IWHS, 41,836 Iowan women between 55-69 years of age were randomly selected and enrolled to determine whether diet and other lifestyle factors were associated with cancer incidence. At baseline, in 1986, participants completed questionnaires on demographics, medical history, and various diet and lifestyle factors. Detailed methodology of the study was previously published (123). At the end of administrative censoring in December 2010, a total of 1,604 incident colorectal cancer cases were recorded.

The FBI score was created for each participant as previously described, and then categorized into quintiles. Baseline characteristics among score quintiles were described using means and standard deviations for continuous variables and percentages for categorical variables. Cox proportional hazards regression, a standard method for analyzing data from prospective cohort studies with variable lengths of follow-up and dichotomous outcomes, was used to calculate multivariable-adjusted hazard ratios (HR) and 95% CIs to assess associations of the FBI score (analyzed as both a continuous variable and by quintiles [reference: lowest quintile]) with incident colorectal cancer. Selection of potential confounding variables was based on previous literature/biological plausibility, statistical significance, and whether

exclusion of the variable from the model changed the adjusted OR for the primary exposure variable by ≥10%. The proportional hazards assumption was tested by adding an interaction term between FBI score and follow-up time to the model. Median values of each FBI score quintile were used for conducting multivariable-adjusted linear trend tests.

Potential effect modification was assessed in the multivariable-adjusted models by including interaction terms between the FBI score and the following covariates (based on previous literature and biological plausibility): age, hormone replacement therapy use, BMI, pack-years of smoking, and history of type-2 diabetes. Sensitivity analyses were conducted excluding women who: 1- did not respond to a follow-up question on history of NSAID use, and 2- were diagnosed with colorectal cancer within the first two years of follow-up. A two-sided p-value ≤ 0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 software (SAS Institute, Inc., Cary, North Carolina).

Significance and Impact of the Dissertation

This dissertation adds to the literature in several respects. First, although two other indices have been developed to quantify dietary inflammation, neither are based on the Dietary Guidelines for Americans. As these guidelines are used by health professionals and policymakers to provide nutrition advice to Americans, it may be useful to explore whether the foods/food groups recommended by these guidelines have a measurable pro- or anti-inflammatory effect. Thus, our aim of creating a food-based inflammation score is innovative in that it accounts for several dietary components recommended for health promotion by the Dietary Guidelines. Secondly, while there is substantial literature that describes associations between dietary patterns and adenoma risk, only one other study has examined the association of diet-related inflammation with risk for adenoma. Thus, Aim 2 may provide evidence for one mechanism underlying the diet—adenoma connection and will build on this previous literature. Finally, the score could serve as a useful comparison or alternative to previously-published dietary inflammation indices for examining associations of diet-related inflammation with various health outcomes.

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CHAPTER 2: DEVELOPMENT AND APPLICATION OF THE FOOD-BASED INFLAMMATION SCORE

Abstract

Background: Examining dietary patterns to classify dietary exposure as pro- or anti-inflammatory accounts for interactions between specific nutrients and foods, and may clarify mechanisms linking diet to disease risk. We developed weights for a food-based inflammation (FBI) score based on national nutrition recommendations and examined associations of the score with inflammation biomarkers.

Methods: The FBI score was created in the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort (*n*= 539) using: 1- serum biomarker measurements of C-reactive protein and interleukins-6, -8, and -10 (combined to make a summary biomarker z-score), and 2- dietary data from a Block 98 food frequency questionnaire (FFQ). Multivariable-adjusted linear regression was used to calculate associations of 18 food groups selected *a priori* with the summary biomarker z-score; beta coefficients for the regressions were used as weights for each food group. We evaluated construct validity of the FBI score using multivariable-adjusted regression models to investigate associations of the FBI score with the biomarker z-score (dichotomized as high vs. low) in two independent studies (the pooled Markers of Adenomatous Polyps studies [MAPs], *n*= 456 and Calcium and Colorectal Epithelial Cell Proliferation [CCECP] trial, *n*= 176).

Results: The FBI score is the weighted sum of 18 food groups. Compared to participants in the lowest FBI score category, the multivariable-adjusted odds of having a high summary biomarker score in the highest (most proinflammatory) FBI score category was 2.11 (95% CI: 1.22, 3.67) for REGARDS (the population used to develop the score) and 2.31 (95% CI: 1.25, 4.28) for MAPs. The estimate for this association was not statistically significant in CCECP, however.

Discussion: The FBI score is an *a priori*, Dietary Guidelines-based approach that classifies dietary quality based on its inflammatory potential. The FBI score is easy to compute in study populations with FFQ data and may be useful for investigating associations of diet-related inflammation with health outcomes.

Introduction

Inflammation is a crucial protective response to foreign pathogens or tissue injury; however, a prolonged or uncontrolled inflammatory response can cause tissue damage and promote tumor progression (1-4). Chronic inflammation is a fundamental process underlying several conditions including cardiovascular disease, type-2 diabetes, and some cancers (5). Elevated systemic levels of proinflammatory biomarkers such as C-reactive protein (CRP) and cytokines such as interleukin-6 and -8 (IL-6 and IL-8, respectively) have been identified as emerging risk factors for chronic disease (6-8). In contrast, interleukin-10 (IL-10) acts as an anti-inflammatory cytokine and immunoregulatory molecule that decreases the expression of proinflammatory cytokines such as IL-6 (9, 10).

Many factors modulate the inflammatory process, including age, sex, smoking, adiposity, and diet (1, 5, 11-13). The ability to characterize specific dietary factors as having pro- or anti-inflammatory effects is a promising area of chronic disease prevention. For example, fruits, vegetables, and nuts are rich in antioxidants and other bioactive molecules that dilute oxidative stress, suppress the action of transcription factors that activate pathways to increase the expression of genes related to inflammation, and decrease the production of proinflammatory cytokines (14-17). Results from mechanistic studies and clinical interventions of the effects of specific foods (e.g., dairy products) on inflammation biomarkers have been inconsistent and warrant further research (18).

Recently, two dietary inflammation indices were developed and validated to quantify the effect of diet on inflammation and to investigate associations of diet-related inflammation on health outcomes (19, 20). The proprietary Dietary Inflammatory Index (DII) was derived and weighted based on an extensive literature review of over 2000 articles examining the relationship between various dietary parameters and six inflammation biomarkers (CRP, IL-1β, IL-6, and TNF-α [proinflammatory] and IL-4 and IL-10 [anti-inflammatory]). In its final form, the DII accounts for 45 dietary components, including macronutrients, vitamins, minerals, and spices. The weighted dietary components of the DII are ultimately summed to create an overall DII score and assess the inflammatory potential of an individual's diet (19). Higher

(more proinflammatory) DII scores have been associated with increased inflammation biomarker levels (21-23) and increased risk of metabolic syndrome (24), colorectal cancer (25-27), depression (28), and many other disease endpoints (29-31). One criticism of the DII is that its focus on select nutrients and extranutritional compounds oversimplifies the complex biological effects and synergy of bioactive components in food (32). Specific classes of anti-inflammatory phytochemicals can be found in certain botanical categories—for example, isothiocyanates in leafy greens and Brassicaceae (broccoli, Brussels sprouts), terpene in Rosaceae (apples, pears, cherries), and hesperidin in Rutaceae (citrus) (33)—but thousands of bioactive components in foods have yet to be identified. Furthermore, application of the DII is limited by available food frequency questionnaire (FFQ) data, which often do not ask about or calculate consumption of components such as eugenol, turmeric, or saffron. For these reasons, and because nutritional practice makes dietary recommendations based on foods and food groups rather than nutrients, the Empirical Dietary Inflammatory Pattern (EDIP) was created. The EDIP is a data-driven index developed to identify a dietary pattern most predictive of three proinflammatory biomarkers (CRP, IL-6, and TNF-α) and one anti-inflammatory biomarker (adiponectin). Though 39 foods/food groups were considered, only 18 were identified as significant predictors in regression models. Ultimately, the EDIP includes the following food components: leafy green vegetables, dark yellow vegetables, tomatoes, other vegetables (i.e., vegetables other than leafy green vegetables and dark yellow vegetables), fish (other than dark-meat fish), red meats, processed meats, organ meats, refined grains, pizza, snacks, wine, beer, coffee, fruit juice, high-energy beverages, low-energy beverages, and tea. However, the selection of these food groups *a posteriori*, after testing for significance in statistical analyses, is still not representative of total diet or the synergistic and additive effects of total diet and individual characteristics. Furthermore, the EDIP was derived using data from primarily white and well-educated cohorts of health professionals, who are not representative of the general American public (20). An increasing EDIP score has been associated with increased levels of proinflammatory biomarkers (23) and has been applied in studies to predict ovarian (34) and colorectal cancer risk (35).

Though there is now substantial literature on the role of chronic inflammation, its regulation by diet, and applications of the DII and EDIP to assess risk for various disease outcomes, there are several research gaps that allow opportunities for additional exploration of diet-related inflammation. First, the Dietary Guidelines for Americans recommend eating an appropriate mix of foods as part of a healthy dietary pattern, and specifically promote the consumption of food groups like legumes, whole grains, nuts, and dairy products (36)—none of which are accounted for in the DII or EDIP. Because the guidelines focus on a healthful dietary pattern as a means of disease prevention and because inflammation is a risk factor for chronic disease, it may be useful to explore whether a score containing these recommended foods has a measurable pro- or anti-inflammatory effect. Additionally, many studies aggregate the consumption of fruits and vegetables into one or two broad categories, which may limit comparisons between studies where individual fruit and vegetable items are not specified. Thus, the creation of an *a priori*, food-based inflammation score—built on current dietary recommendations and containing multiple fruit and vegetable categories—may serve as a useful comparison or alternative to the previously-published indices. To address these gaps in the literature, we developed a Food-Based Inflammation (FBI) score in the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort to facilitate studies of systemic inflammation and chronic disease outcomes. The FBI score was derived using a panel of four inflammation biomarkers (CRP, IL-6, IL-8, and IL-10) and 18 food groupings, including four botanical categories. We then calculated and applied FBI scores in two independent observational studies to evaluate its construct validity and assess how well the FBI score predicted overall inflammation biomarker levels in the respective populations. To compare the utility and predictive ability of the FBI score, we calculated and applied the previously-validated EDIP to the study populations, as well.

Materials and Methods

Study Population for Development of Scores

REGARDS

The REasons for Geographic and Racial Differences in Stroke (REGARDS) study is a national, population-based longitudinal study of adults aged ≥45 years (n=30,239) with the objective of investigating disparities in stroke mortality by geography and race. Participants were randomly recruited between January 2003 and October 2007, with data on demographic, socioeconomic, lifestyle, and stroke risk factors collected via computer-assisted telephone interview. Exclusion criteria included race other than white or African-American, inability to speak English, medical conditions preventing long-term participation, residence in or on a waiting list for a nursing home, cognitive impairment based on the telephone interview, and active treatment for cancer. Those who agreed to participate then underwent an in-home visit where anthropometric data, a medication inventory, and fasting blood were collected. In addition, self-administered questionnaires were used to collect additional risk factor characteristics, including dietary data from a Block 98 FFQ designed to capture individuals' usual dietary intake by asking respondents to report their frequency of consumption of a list of foods over the last year. Detailed methodology of the study was previously published (37).

Of these participants, 1,104 were randomly sampled and had additional analytes (including CRP, IL-6, IL-8, and IL-10) measured from their fasting blood sample. The biomarkers were measured using a second generation, C-terminal enzyme-linked immunosorbent assay (ELISA; Immutopics, Santa Clara, CA) by the University of Vermont Laboratory for Clinical Biochemical Research. The coefficients of variation (CV) for each biomarker sample were <9.0%. Because serum samples were collected during an in-home visit (rather than at a hospital/study center) and shipped to Vermont, REGARDS sample handling was compared to "ideal" study center processing using split samples from participants. The correlation coefficient between ideal and REGARDS processing of samples was 0.90 (38). Participants who were missing any biomarker data, missing 10% or more of their FFQ data, missing covariate data

(such as age or sex), missing or having implausible total energy intakes estimated from the self-reported FFQs (<500 or >5,000 kilocalories daily), or having history of previous cancer or chronic disease (such as coronary heart disease) were excluded from FBI score development and all observational analyses. The final number of REGARDS participants was 539; a detailed flow chart of sample size ascertainment is shown in Figure 1.

Development of the FBI Score

Baseline biomarker and FFQ data from the 539 eligible REGARDS participants were used to develop the FBI score. We used a panel consisting of CRP, IL-6, IL-8, and IL-10 to create the summary inflammation biomarker score, which accounts for various inflammatory pathways involved in both innate and adaptive immunity. To create a summary biomarker score, we first calculated a z-score ($z = (x - \mu) / \sigma$; where x is an individual's biomarker value, μ is the sample biomarker mean, and σ is the sample standard deviation) for each biomarker, and then summed the z-scores for CRP, IL-6, IL-8, and IL-10 (IL-10 was given a negative sign because of its anti-inflammatory effects).

Components of the FBI score were selected based on biological plausibility and previous literature, and consisted of the following food groups: processed meat, red meat, white meat, fish, shellfish, nuts, coffee, tea, dairy products, refined and whole grains, beta-carotene-containing foods, lycopene-containing foods, green/leafy vegetables, Brassicaceae, Leguminosae, Rosaceae, and Rutaceae. A list of the foods used in the FBI score and their rationale for inclusion are provided in Supplementary Table 1 of Appendix A. To create the FBI score, we used linear regression to calculate multivariable-adjusted associations of each food group with the summary biomarker score. To obtain independent associations of the foods with inflammation, models were adjusted for age, sex, use of hormone replacement therapy (HRT), race, education level, total energy intake, body mass index (BMI) category, smoking status, physical activity level, alcohol intake category, regular dietary supplement use, and regular non-steroidal anti-inflammatory drug (NSAID) use. The beta coefficients for these regressions were then used as weights and multiplied to each participant's weekly intake of the respective food

components. An overall FBI score was then calculated as the sum of the weighted dietary component intakes of each participant. Higher (larger/more positive) scores were considered proinflammatory, while lower (smaller/more negative) scores were considered anti-inflammatory.

Other Study Populations and Data Collection

CCECP and MAPs

To evaluate the construct validity of the FBI score, we applied it to two independent populations: the Calcium and Colorectal Epithelial Cell Proliferation (CCECP) trial and the pooled Markers of Adenomatous Polyps I (1995–1997) and II (2002) studies (MAPs). We did not include shellfish as a component of the calculated FBI scores for these two populations since FFQ data on shellfish consumption was unavailable.

Participants in CCECP were in general good health, 30–74 years of age, consumed a "western-style" diet, and had a history of one or more pathology-confirmed sporadic colorectal adenoma within the past five years. The purpose of the trial was to assess the efficacy of two doses of supplemental calcium in reducing colorectal epithelial cell proliferation in the normal mucosa over six months. Accordingly, exclusion criteria included contraindications to biopsy procedures and calcium supplementation; further details of the study were previously published (39). For our cross-sectional study, we used baseline data from self-administered questionnaires to obtain information on participant demographics, lifestyle factors, medical history, medication use, and diet (via a semi-quantitative Willett FFQ) as well as baseline blood samples to measure CRP, IL-6, IL-8, and IL-10. Venipuncture was performed using standardized methods; concentrations of CRP, IL-6, IL-8, and IL-10 were measured at the Emory Multiplexed Immunoassay Core (EMIC) using electrochemiluminescence detection-based immunoassays. The average intra-assay CV for the biomarkers was 11.5% (39).

The pooled MAPs studies are colonoscopy-based case-control studies of incident, sporadic colorectal adenoma in North and South Carolina. These studies were pooled because they were

identically designed; details of the studies have been previously published (40). In brief, participants scheduled for elective, outpatient colonoscopies were recruited from private gastroenterology clinics and included adults in general good health between 35 and 74 years of age with no history of colorectal adenoma, cancer (excluding non-melanoma skin cancer), inflammatory bowel disease, or genetic syndromes associated with colorectal neoplasms. Participants completed questionnaires on demographics, lifestyle, anthropometrics, and diet (via a Willett semi-quantitative FFQ) and had a venous blood sample drawn before undergoing outpatient, elective colonoscopy. For MAPs, the only inflammation biomarker available was CRP. Venous high-sensitivity CRP (hsCRP) was measured by latex-enhanced immunonephelometry, and the intra-assay CV was 4% (40, 41).

Like REGARDS, participants in CCECP or MAPs who were missing any biomarker data, missing 10% or more of their FFQ data, missing covariates (e.g., age and sex), or missing/with implausible total energy intakes estimated from the self-reported FFQs (<500 or >5,000 kilocalories daily) were excluded from final analyses. The final number of CCECP and MAPs participants were 176 and 456, respectively. Institutional review boards respective to each study site approved study protocols, and all participants provided written informed consent.

Creation of the EDIP

Based on available FFQ information, we calculated the EDIP in each of the three study populations to compare our results with a previously-developed dietary inflammation score. Methods for calculating the EDIP have previously been published (33) and are described briefly here. First, reduced rank regression was used to create a dietary pattern associated with an inflammation biomarker panel (CRP, IL-6, TNF-α receptor 2, and adiponectin) from 39 food groups. Stepwise linear regression was then used to identify food groups that significantly contributed (p=0.05) to the inflammatory dietary pattern: processed meats, red meats, organ meats, other fish, other vegetables, refined grains, high-energy beverages, low-energy beverages, tomatoes, beer, wine, tea, coffee, dark yellow vegetables, leafy/green vegetables, snacks, fruit juice, and pizza. The food groups that were not statistically significant and thus

not retained in the EDIP were: dark meat fish, poultry, eggs, butter, margarine, low-fat dairy products, high-fat dairy products, liquor, fruit, cruciferous vegetables, legumes, potatoes, French fries, whole grains, nuts, oil/vinegar salad dressings, mayonnaise/other creamy salad dressings, chowder or cream soup, sweets/desserts, condiments, and olive oil. Intake of food groups identified as significant was weighted by the beta coefficients derived from the final stepwise regression model and summed to create an overall EDIP score for each participant. To reduce the magnitude of the scores, the overall EDIP score was then rescaled by dividing by 1000 for statistical analyses. Larger (more positive) EDIP scores represent proinflammatory diets and smaller EDIP scores represent anti-inflammatory diets. Our constructed EDIP included 16 of the 18 food groups (missing high- and low-energy beverages) for REGARDS analyses, 13 of the 18 food groups (missing high- and low energy beverages, organ meats, beer, and wine) for CCECP analyses, and 15 of the 18 food groups (missing high- and low energy beverages and organ meats) for MAPs analyses.

Statistical Analyses

For REGARDS, CCECP, and MAPs, baseline characteristics of participants were compared using the chi-square (χ^2) test for categorical variables and the Student *t* test or ANOVA (as appropriate) for continuous variables, according to FBI score quantiles. Correlations between each of the dietary components of interest were assessed with the use of a Pearson correlation coefficient (Appendix A, Supplementary Table 2 for selected components). After creating FBI and EDIP scores in REGARDS, we categorized each into quartiles. Multivariable unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for associations of the FBI and EDIP scores with the summary biomarker z-score category (high vs. low, dichotomized based on the median inflammation biomarker z-score). The median value of each FBI and EDIP score category was used for conducting linear trend tests, also adjusted for multiple covariates. Study-specific cutpoints were used to dichotomize FBI and EDIP scores in CCECP (due to sample size restrictions) and create FBI and EDIP score quartiles in MAPs. Multivariable unconditional logistic regression and linear trend tests were then performed for

CCECP and MAPs. Quartile agreement between the FBI and EDIP scores was described using frequency data for the REGARDS study population (Appendix A, Supplementary Table 3); weighted kappa statistics were also calculated to assess agreement between quantiles of the FBI and EDIP scores in each of the three study populations (Appendix A, Supplementary Table 4).

Based on previous literature and biological plausibility, potential confounding variables considered included age, sex, use of HRT in females, race, education, total energy intake, physical activity, alcohol intake, BMI (weight (kg)/height (m^2)), smoking status, adenoma case/control status (MAPs only), self-reported dietary supplement use, and self-reported NSAID use. Inclusion in the final models required meeting one or more of the following criteria: biological plausibility, statistical significance, and/or whether inclusion or exclusion of the variable from the model changed the adjusted odds ratio for the primary exposure variable by ≥10%. The final adjusted models controlled for: age (years; continuous; based on biological plausibility and statistical significance), sex (male/female; based on biological plausibility), use of hormone replacement therapy (yes/no; based on biological plausibility), race (black/white in REGARDS only; based on statistical significance), education (some high school, high school graduate, some college, or college graduate in REGARDS only; based on statistical significance), total energy intake (kilocalories/day; continuous; based on biological plausibility), physical activity level (sedentary, moderate, or active; based on biological plausibility), alcohol intake category (none, moderate: ≤1 drink [14 grams/day] for women and ≤2 drinks for men, or heavy: >1 drink for women and >2 drinks per day for men; based on biological plausibility), BMI category (normal: BMI <25; overweight: BMI <30; obese: BMI ≥30; based on biological plausibility, statistical significance, and effect on odds ratio), smoking status (current or former/never; based on biological plausibility and statistical significance), regular dietary supplement use (≥3 times per week; yes/no; based on biological plausibility), and regular NSAID use (≥3 times per week; yes/no; based on biological plausibility and statistical significance).

Potential effect modification of the association between the FBI score and summary biomarker score by age (<population mean or ≥population mean age), sex, race (black/white; REGARDS only), BMI category, smoking history, and regular NSAID use was assessed by including FBI score × covariate interaction terms in the multivariable-adjusted models.

To assess the sensitivity of the associations in how the FBI score was created, we removed each food component from the *a priori* score one at a time to ascertain whether any component overly influenced the association of the FBI score with the summary biomarker score. All analyses were conducted using SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, North Carolina). Results of all statistical tests were considered significant at $p \leq 0.05$.

Results

Selected descriptive characteristics of the eligible REGARDS population, from which our FBI score was developed, are presented in Table 1. Means and standard deviations (SD) are reported for continuous variables, whereas percentages are reported for categorical variables. Compared to participants in the lowest (most anti-inflammatory; Quartile 1) FBI score quartile, those in Quartile 4 (most proinflammatory) were more likely to be black and use dietary supplements on a regular basis. Participants differed in terms of overall inflammation biomarker z-score (mean difference: 1.27 [95% CI: 0.60, 1.94; Quartile 4 vs. Quartile 1]), and consumption of most food groups, including processed meats, nuts, coffee, and most fruit and vegetable categories. The mean difference in FBI scores between Quartile 4 and Quartile 1 was 0.91 (95% CI: 0.84, 0.98).

The individual food components and rationale for inclusion in the FBI score are described in Supplementary Table 1 (Appendix A); the weights obtained from REGARDS for each food group of interest are listed in Table 2. A negative weight indicates an overall anti-inflammatory effect whereas a positive weight indicates an overall proinflammatory effect. Based on the weights derived from

REGARDS, intake of processed meat, red meat, fish, shellfish, whole grains, refined grains, and lycopene foods made positive contributions to the inflammation biomarker score; intake of white meat, nuts, coffee, beta carotene foods, green/leafy vegetables, Brassicaceae, Leguminosae, and Rosaceae made negative contributions to the inflammation biomarker score. The intake of tea made a weak positive contribution to the inflammation biomarker score whereas intake of dairy products and Rutaceae made a weak negative contribution to the overall FBI score (Table 2). Generally, components of the FBI score were weakly correlated with each other; no Pearson correlation coefficient was greater than 0.44 (Appendix A, Supplementary Table 2).

Tables 3 and 4 show selected descriptive characteristics of the CCECP and MAPs populations, based on FBI score quantile. Compared to CCECP participants with a low (anti-inflammatory) FBI score, participants with a high FBI score were more likely to be male and less likely to be college graduates (Table 3). Circulating biomarker levels did not differ among FBI score categorization in CCECP. Relative to participants in Quartile 1, MAPs participants in the highest FBI score quartile were less likely college graduates and more likely to be male and currently smoke (Table 4). There were no significant differences in mean circulating CRP levels based on FBI score categorization in MAPs. Participants with high FBI scores consumed less white meat, nuts, and fruits and vegetables than participants with low FBI scores in both study populations. The mean differences in FBI scores were 0.89 (95% CI: 0.78, 1.00; Quantile 2 vs. Quantile 1) and 1.17 (95% CI: 1.10, 1.24; Quartile 4 vs. Quartile 1) for CCECP and MAPs, respectively.

Associations of the FBI and EDIP scores with the inflammation biomarker z-score are presented in Table 5. Compared to participants in the lowest (most anti-inflammatory) FBI score category, the multivariable-adjusted odds of having a high summary biomarker score in the highest (most proinflammatory) FBI score category was 2.11 (95% CI: 1.22, 3.67) for REGARDS. The multivariable-adjusted odds of having a high CRP score in the most proinflammatory FBI score category was 2.31 (95% CI: 1.25, 4.28) for MAPs compared to the reference category. The FBI score was not associated

with high summary biomarker score in CCECP (OR: 0.78; 95% CI: 0.39, 1.53). Application of the EDIP was not associated with high summary biomarker score in any of our study populations. Tests for linear trend were significant for the summary biomarker score across quartiles of FBI scores in REGARDS ($p<0.01$) and MAPS ($p=0.01$), but not across quartiles of EDIP scores in the study populations (Table 5); the odds ratios for the association between the dietary scores (after assigning the median of each diet score quartile to the respective quartile and treating each quartile exposure as continuous) and high summary biomarker score are provided in Figure 2. Results from models that included interaction terms (between FBI score and categories of age, race, sex, smoking status, BMI, and regular NSAIDs use) were not included in the tables because none of the terms were significant.

Supplementary Table 3 (Appendix A) shows the frequencies and percentages of participants who were in the same or different quartiles of the FBI and EDIP scores for the REGARDS study population. Only 22.2% of individuals classified in the lowest (most anti-inflammatory) FBI score quartile were classified in the corresponding EDIP quartile; 25.4% of individuals in the highest FBI score quartile were in the corresponding EDIP quartile. Kappa statistics indicated low agreement between quartile categorization of the FBI and EDIP scores for REGARDS ($\kappa=-0.02$) and fair agreement between quantiles of FBI and EDIP scores for CCECP and MAPs ($\kappa=0.33$ and $\kappa=0.32$, respectively; Appendix A, Supplementary Table 4).

In sensitivity analyses in which individual components of the FBI score were removed one at a time, we found no substantial differences from the associations reported in the tables (data not shown).

Discussion

There is a great deal of evidence to support the role of diet and lifestyle factors as modulators of inflammation (15, 17, 42-44). Using a racially- and geographically-diverse cohort, we developed a food-based inflammation score to investigate associations of diet-related contributions to systemic

inflammation and applied the score to biomarkers of inflammation in two other study populations to evaluate its construct validity and avoid statistical overfitting in the REGARDS cohort. Our results suggest that, collectively, multiple dietary components are more strongly associated with inflammation than are any individual food items, and support the application of the FBI score in other studies to classify the inflammatory potential of an individual's diet. Furthermore, deriving inflammation weights for distinct categories of fruits and vegetables may provide more specific insight into areas of nutritional intervention or modification by which an individual may reduce systemic inflammation.

Several of our results warrant further discussion. First, some of our FBI components were correlated with each other (beta-carotene foods with Brassicaceae and Leguminosae; fish with shellfish and refined grains) which may be due to these foods sharing similar bioactive components or because they are frequently eaten together (Appendix A, Supplementary Table 2). Among our FBI score components, fish and shellfish were positively associated with the summary inflammation biomarker score. This may be due to cooking method (e.g., frying in oil rather than baking) or the fact that many waters from which fish are caught and eaten are contaminated with pollutants (45, 46). Tea was also found to be weakly positively associated with our summary biomarker score and may reflect how this beverage is commonly prepared with sugar in the southeastern United States. Regardless of these differences from our *a priori* hypotheses about the direction of the weights of the individual food components, the associations of each food component with the summary biomarker score were not as strong as the associations of our overall FBI score with the summary biomarker score. Thus, a "whole diet" or "dietary pattern" approach may be better than evaluating single foods or nutrients in studies of systemic inflammation.

Two other indices have been used to describe dietary effects on inflammatory processes: the DII and EDIP. While the DII has been applied in over 100 studies, we were unable to construct it in our study populations given limitations in obtaining many of its dietary parameters from our available FFQ data. Additionally, given that the DII is comprised of nutrients and other bioactive compounds, it is not directly

comparable with our FBI score. Another critical difference between the DII and FBI score is the methodology behind which these scores were developed. The weights that the DII uses to classify dietary parameters as either pro- or anti-inflammatory are derived from summaries of previous literature (19); the weights that the FBI score uses are derived directly from associations with circulating biomarker levels. Regardless, both the DII and FBI can be used to discern dietary patterns that best predict variation in biomarkers of inflammation.

The EDIP and FBI score have seven dietary components in common: processed meat, red meat, refined grains, tea, coffee, leafy greens, and beta-carotene foods (described as "dark yellow vegetables" in the EDIP). Nevertheless, agreement between the two dietary scores was relatively low in all three study populations and is likely due to differences in how the scores were constructed. Components of the EDIP were identified using an *a posteriori* approach based on associations with specific inflammation biomarkers and maximizing explained variation in those associations (20). Components of the FBI score were identified using an *a priori* approach reflective of national nutritional advice; consequently, the score contains more food groups that could account for diet quality and variability (e.g., fruits, nuts, and dairy products). While the EDIP was developed using data from cohorts of mostly white health professionals, the FBI score was developed in a multiracial and socioeconomically-diverse cohort. The FBI score may thus be better representative of national demographics and have greater utility in studies of diet-related inflammation in the general adult population.

Compared to the lowest (anti-inflammatory) quartile, the highest FBI score quartile was directly associated with having a high inflammation biomarker score in the multivariable-adjusted analyses of two of our study populations: REGARDS (the population we used to develop the score) and MAPs. The estimate for this association was not statistically significant in CCECP, however. Overall, we observed stronger associations between the FBI and summary biomarker scores than with the EDIP and summary biomarker scores. In addition to the differences in score construction described previously, weaker associations between the EDIP and summary biomarker scores may be attributable to limitations in our

FFQ data, as we were unable to create complete EDIP scores in the CCECP and MAPs populations. Though the EDIP and FBI scores may not be completely interchangeable for measuring the inflammatory potential of diet, both could be used as a proxy for inflammation biomarkers in studies of diet and disease and warrant further application.

Certain characteristics of our study populations may have limited our analyses and conclusions. In CCECP participants, we found no statistically significant associations of the FBI score with the inflammation biomarker z-score. This could be due to chance because of our small sample size (*n*=176), or the fact that this population was relatively homogenous in terms of both demographics and intake of dietary variables of interest. In the MAPs population, CRP was the only biomarker measured and available for analyses, even though we developed the FBI score using a panel of biomarkers. Though CRP is a nonspecific marker of inflammation, it is widely-considered a good indicator of inflammatory processes given its role in mediating both acute and innate immune responses (47, 48). In addition, circulating CRP levels are stable over time, correlate with other inflammation biomarkers, and are commonly-measured in clinical practice (48-50). While several cohort studies have observed higher circulating CRP concentrations in non-Hispanic black participants (compared with white participants), the clinical and public health implications of these race-based differences have not been determined (51-53). Larger studies that include more dietary variation and measurement of inflammation biomarkers are needed to better assess these possible associations.

A general limitation in this study is the use of semi-quantitative FFQs to quantify dietary consumption. Though estimated dietary intakes from FFQs are considered representative of habitual intake (frequency of consumption over the course of a year), they are prone to recall bias, their food lists are finite, and little detail is collected on portion sizes, methods of cooking, or combinations of foods in certain meals. Because of limited FFQ data, we were unable to create complete EDIP scores; for example, we did not have data on consumption of organ meats for the EDIP score in CCECP and MAPs or beer and wine in CCECP. Another potential limitation is the assumption that the weights derived from

the associations of the individual food components with the summary biomarker score are totally representative of food-related inflammatory responses. However, given that the population (REGARDS) from which we derive these weights is racially, geographically, and economically diverse, the weights may be good approximations for developing a population-based FBI score. Additional strengths of this study include the collection of multiple biomarkers of inflammation (incorporating several different inflammatory pathways) in the REGARDS population; the use of an inflammation biomarker panel that may allow for more sensitive identification of at-risk individuals for interventions; the use of distinct fruit and vegetable categories to assess and interpret associations of specific fruit and vegetable intake with inflammation and to better account for variation in fruit and vegetable consumption between study populations; and the application of the FBI score to two independent study populations. Given that the food weights derived from REGARDS are point estimates (rather than ranges), the true associations between the FBI score and inflammation biomarkers in our validation studies are likely to be less precise.

In conclusion, our findings, taken in context with other studies of diet and inflammation, suggest that a whole foods-based approach may be useful for investigating associations of dietary contributions with systemic inflammation. Using our weights, the FBI score is easy to compute in study populations with FFQ data and could be used in other studies to investigate associations of diet-related inflammation with various health outcomes.

Figure 1: Sample ascertainment in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study population for deriving food-based inflammation (FBI) score weights

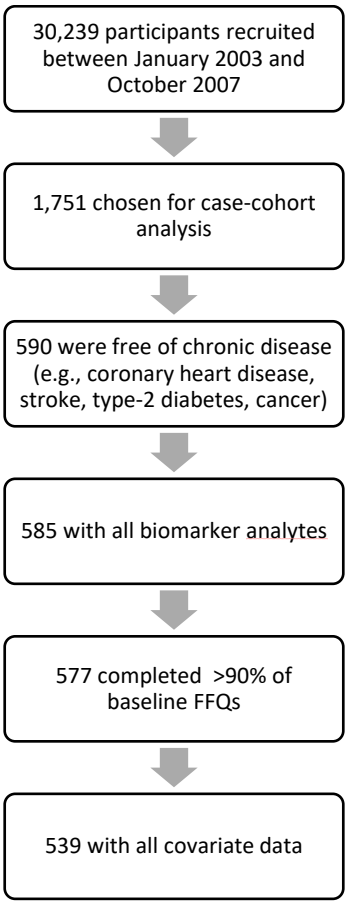

Table 1: Participant characteristics in the REGARDS cohort among selected FBI score quartiles

Variable[1]	**REGARDS total (*n* = 539)**	**FBI Quartile 1[2] (*n* = 134)**	**FBI Quartile 2[2] (*n* = 135)**	**FBI Quartile 3[2] (*n* = 139)**	**FBI Quartile 4[2] (*n* = 131)**	***p*-value[3]**
Demographics and Medical						
Age (years)	66.4 (11.9)	66.1 (11.5)	66.9 (12.4)	68.1 (11.9)	64.6 (11.8)	0.10
Male (%)	47	43	47	46	56	0.12
White race, %	57	57	61	65	46	0.01
College graduate, %	38	42	42	39	30	0.07
Regular NSAID use (≥3/week), %	15	13	14	17	17	0.68
Regular dietary supplement use (≥3/week), %	50	45	44	55	58	0.04
Physical activity (sedentary), %	34	28	34	34	40	0.60
Currently smoke, %	14	8	14	14	19	0.12
Body mass index, (obese), %	37	30	36	37	41	0.30
Alcohol (non-drinkers), %	61	64	57	58	62	0.84
Total energy intake (kilocalories/day)	1,760 (772)	2,000 (759)	1,810 (800)	1,510 (637)	1,720 (806)	<0.01
High-sensitivity C-reactive protein (mg/L)	3.27 (3.65)	2.46 (2.62)	3.38 (3.91)	3.28 (3.39)	3.97 (4.35)	<0.01
Interleukin-6 (pg/mL)	3.31 (1.98)	2.84 (1.79)	3.32 (2.15)	3.33 (1.90)	3.75 (1.99)	<0.01
Interleukin-8 (pg/mL)	3.42 (7.96)	2.83 (1.78)	3.01 (2.48)	3.28 (5.11)	4.60 (14.9)	0.26
Interleukin-10 (pg/mL)	11.8 (15.0)	13.4 (23.9)	10.7 (9.40)	12.4 (12.6)	10.7 (8.80)	0.38
Biomarker z-score	-.001 (2.15)	-0.64 (2.06)	0.06 (1.95)	-0.04 (1.68)	0.63 (2.65)	<0.01
Components of FBI Score						
Processed meat (servings/week)	2.29 (2.47)	1.48 (1.42)	2.26 (2.19)	1.87 (1.83)	3.59 (3.49)	<0.01
Red meat (servings/week)	3.68 (4.16)	3.42 (4.57)	3.99 (4.46)	3.66 (3.73)	3.63 (3.84)	0.74
White meat (servings/week)	3.27 (3.77)	5.31 (5.64)	3.29 (3.38)	2.15 (1.85)	2.35 (2.08)	<0.01
Fish (servings/week)	1.92 (2.45)	2.08 (2.39)	2.00 (2.50)	1.30 (1.32)	2.32 (3.17)	<0.01
Shellfish (servings/week)	0.52 (1.24)	0.58 (1.58)	0.55 (1.47)	0.45 (0.72)	0.51 (1.02)	0.85
Nuts (servings/week)	3.21 (5.44)	7.45 (8.95)	3.18 (2.85)	1.38 (1.64)	0.85 (1.28)	<0.01
Coffee (servings/week)	10.3 (10.3)	11.8 (11.1)	13.0 (10.9)	11.5 (9.78)	4.88 (7.01)	<0.01
Tea (servings/week)	4.36 (6.87)	5.05 (7.45)	3.72 (6.01)	3.92 (5.62)	4.79 (8.14)	0.31

Table 1, continued

Variable[1]	**REGARDS total (*n* = 539)**	**FBI Quartile 1[2] (*n* = 134)**	**FBI Quartile 2[2] (*n* = 134)**	**FBI Quartile 3[2] (*n* = 134)**	**FBI Quartile 4[2] (*n* = 131)**	***p*-value[3]**
Components of FBI Score						
Dairy products (servings/week)	9.36 (8.21)	10.3 (9.53)	10.4 (8.45)	8.75 (7.14)	7.94 (7.36)	0.03
Refined grains (servings/week)	23.8 (17.2)	24.4 (17.2)	22.9 (16.3)	21.5 (14.8)	26.5 (19.9)	0.10
Whole grains (servings/week)	4.87 (5.89)	5.80 (5.88)	4.62 (5.58)	3.41 (3.77)	5.74 (7.57)	<0.01
Beta-carotene foods[4] (servings/week)	0.78 (1.16)	1.44 (1.85)	0.79 (0.72)	0.45 (0.45)	0.42 (0.81)	<0.01
Green/leafy vegetables[5] (servings/week)	3.42 (4.31)	5.46 (5.53)	3.60 (3.69)	2.68 (3.69)	1.94 (3.15)	<0.01
Brassicaceae[6] (servings/week)	1.47 (1.82)	2.63 (2.50)	1.52 (1.75)	0.90 (0.88)	0.85 (1.09)	<0.01
Leguminosae[7] (servings/week)	2.01 (1.90)	3.11 (2.46)	2.24 (1.92)	1.47 (1.13)	1.20 (1.17)	<0.01
Rosaceae[8] (servings/week)	2.75 (3.42)	4.86 (4.86)	3.09 (2.88)	1.80 (2.33)	1.26 (1.42)	<0.01
Rutaceae[9] (servings/week)	3.10 (4.54)	4.12 (6.17)	2.90 (4.05)	2.54 (3.48)	2.87 (3.86)	0.02
Lycopene foods[10] (servings/week)	1.35 (2.01)	1.60 (2.05)	1.23 (1.43)	1.07 (1.10)	1.54 (2.98)	0.09
Food-Based Inflammation (FBI) Score[2]	-0.36 (0.40)	-0.88 (0.41)	-0.41 (0.06)	-0.20 (0.06)	0.03 (0.14)	<0.01
Empirical Dietary Inflammatory Pattern (EDIP)[11]	-18.8 (28.1)	-16.5 (22.0)	-17.5 (25.1)	-19.2 (26.7)	-22.3 (36.8)	0.36

Abbreviations: REGARDS, REasons for Racial and Geographic Differences in Stroke; FBI, food-based inflammation; NSAID, non-steroidal anti-inflammatory drug

1. Values for variables are mean (standard deviation), unless otherwise indicated.
2. The FBI score was created using multivariable-adjusted linear regression of the associations of the dietary components with the summary inflammation biomarker z-score. The beta coefficients of the regressions were used as weights for contributions of the dietary components to an overall FBI score. The FBI score was ultimately calculated as the sum of the weighted dietary component intakes of each participant, and then categorized into quartiles [Quartile 1 is most anti-inflammatory; Quartile 4 is most proinflammatory].
3. P-values calculated using ANOVA for continuous variables and χ^2 tests for categorical variables comparing FBI score quartiles; significant at $p \leq 0.05$.
4. Beta-carotene foods include carrots, sweet potatoes, orange/yellow squash and pumpkins.
5. Green/leafy vegetables include collards, mustard/turnip greens, romaine lettuce, and spinach.
6. Brassicaceae include broccoli, Brussels sprouts, cabbage, and cauliflower.
7. Leguminosae include black, kidney, lima, snap and broad beans, peas, and lentils.
8. Rosaceae include apples, apricots, peaches, pears, and strawberries.
9. Rutaceae include grapefruits, oranges, and tangerines.
10. Lycopene foods include tomatoes, salsa, and tomato paste, sauce, and juice.
11. For the EDIP, intake of food groups was weighted by beta coefficients derived from a stepwise regression model, and then summed to create an overall EDIP score for each participant. This EDIP score was then rescaled for statistical analyses.

Table 2: Food components and weights derived in REGARDS study for creation of the FBI score

Components in the FBI score	Weights[1]
Processed meat	0.0348
Red meat	0.0053
White meat	-0.0459
Fish	0.0465
Shellfish	0.0171
Nuts	-0.0446
Coffee	-0.0074
Tea	0.0003
Dairy products	-0.0002
Whole grains	0.0084
Refined grains	0.0023
Beta-carotene foods[2]	-0.0943
Green/leafy vegetables[3]	-0.0020
Brassicaceae[4]	-0.0214
Leguminosae[5]	-0.0484
Rosaceae[6]	-0.0294
Rutaceae[7]	-0.0003
Lycopene foods[8]	0.0032

Abbreviations: REGARDS, REasons for Racial and Geographic Differences in Stroke; FBI, food-based inflammation

1. Weights are beta coefficients derived from linear regression of each dietary component with the summary inflammation biomarker z-score and adjusted for age, sex, use of hormone replacement therapy, race, education, total energy intake, body mass index category, smoking status, physical activity category, alcohol intake category, regular dietary supplement use, and regular non-steroidal anti-inflammatory drug use.
2. Beta-carotene foods include carrots, sweet potatoes, orange/yellow squash and pumpkins.
3. Green/leafy vegetables include collards, mustard/turnip greens, romaine lettuce, and spinach.
4. Brassicaceae include broccoli, Brussels sprouts, cabbage, and cauliflower.
5. Leguminosae include black, kidney, lima, snap and broad beans, peas, and lentils.
6. Rosaceae include apples, apricots, peaches, pears, and strawberries.
7. Rutaceae include grapefruits, oranges, and tangerines.
8. Lycopene foods include tomatoes, salsa, and tomato paste, sauce, and juice.

Table 3: Participant characteristics in the CCECP trial among selected FBI score categories

Variable[1]	**CCECP: FBI Quantile 1[2] (*n* = 88)**	**CCECP: FBI Quantile 2[2] (*n* = 88)**	**p-value[3]**
Demographics and Medical			
Age (years)	59.9 (8.30)	58.3 (10.8)	0.27
Male (%)	54	73	<0.01
White race, %	100	100	0.99
College graduate, %	38	19	<0.01
Regular NSAID use (≥3/week), %	32	25	0.31
Regular dietary supplement use (≥3/week), %	38	34	0.54
Physical activity (sedentary), %	30	35	0.45
Currently smoke, %	14	24	0.10
Body mass index (obese), %	31	36	0.73
Alcohol (non-drinkers), %	33	43	0.11
Total energy intake (kcal/d)	2,120 (634)	2,020 (705)	0.33
High-sensitivity C-reactive protein (mg/L)	3.37 (3.97)	3.33 (4.04)	0.94
Interleukin-6 (pg/mL)	2.41 (1.48)	2.72 (1.88)	0.23
Interleukin-8 (pg/mL)	5.89 (2.77)	6.25 (3.04)	0.41
Interleukin-10 (pg/mL)	4.09 (5.58)	5.12 (11.1)	0.43
Biomarker z-score	-0.08 (2.09)	0.09 (2.53)	0.62
Components of Food-Based Inflammation (FBI) Score			
Processed meat (servings/week)	5.75 (2.01)	6.87 (2.49)	<0.01
Red meat (servings/week)	12.6 (2.59)	12.2 (2.99)	0.41
White meat (servings/week)	17.0 (3.22)	15.1 (2.84)	<0.01
Fish (servings/week)	10.1 (2.25)	8.81 (1.94)	<0.01
Nuts (servings/week)	2.51 (1.32)	1.81 (0.93)	<0.01
Coffee (servings/week)	4.97 (2.92)	5.03 (3.03)	0.88
Tea (servings/week)	1.99 (1.60)	1.52 (1.20)	0.03
Dairy products (servings/week)	27.8 (5.55)	25.6 (4.81)	<0.01
Refined grains (servings/week)	46.1 (11.2)	46.8 (10.9)	0.70
Whole grains (servings/week)	16.8 (3.95)	14.8 (4.30)	<0.01
Beta-carotene foods[5] (servings/week)	14.5 (2.42)	10.9 (1.87)	<0.01
Green/leafy vegetables[6] (servings/week)	8.66 (2.14)	6.75 (1.96)	<0.01
Brassicaceae[7] (servings/week)	10.4 (2.53)	8.17 (2.15)	<0.01
Leguminosae[8] (servings/week)	11.6 (2.59)	9.29 (2.02)	<0.01
Rosaceae[9] (servings/week)	17.4 (3.57)	14.1 (2.76)	<0.01
Rutaceae[10] (servings/week)	9.77 (3.13)	7.82 (3.22)	<0.01
Lycopene foods[11] (servings/week)	8.10 (2.03)	6.46 (1.91)	<0.01
Food-Based Inflammation (FBI) score[2,4]	-2.63 (0.41)	-1.74 (0.33)	<0.01
Empirical Dietary Inflammatory Pattern (EDIP)[12]	-2.61 (3.36)	-0.37 (2.56)	<0.01

Footnotes for Table 3

Abbreviations: CCECP, Calcium and Colorectal Epithelial Cell Proliferation trial; FBI, food-based inflammation; NSAID, non-steroidal anti-inflammatory drug

1. Values for variables are mean (standard deviation), except where indicated.
2. The FBI score was created using multivariable-adjusted linear regression of the associations of the dietary components with the summary inflammation biomarker z-score. The beta coefficients of the regressions were used as weights for contributions of the dietary components to an overall FBI score. The FBI score was ultimately calculated as the sum of the weighted dietary component intakes of each participant, and then dichotomized [Quantile 1 is anti-inflammatory; Quantile 2 is proinflammatory].
3. P-values calculated using ANOVA for continuous variables and χ^2 tests for categorical variables comparing FBI score quartiles; significant at $p \leq 0.05$.
4. The FBI score was calculated as described in footnote 2, then categorized into quartiles [Quartile 1 is most anti-inflammatory; Quartile 4 is most proinflammatory].
5. Beta-carotene foods include carrots, sweet potatoes, orange/yellow squash, and pumpkins.
6. Green/leafy vegetables include collards, mustard/turnip greens, romaine lettuce, and spinach.
7. Brassicaceae include broccoli, Brussels sprouts, cabbage, and cauliflower.
8. Leguminosae include black, kidney, lima, snap and broad beans, peas, and lentils.
9. Rosaceae include apples, apricots, peaches, pears, and strawberries.
10. Rutaceae include grapefruits, oranges, and tangerines.
11. Lycopene foods include tomatoes, salsa, and tomato paste, sauce, and juice.
12. For the EDIP, intake of food groups was weighted by beta coefficients derived from a stepwise regression model, and then summed to create an overall EDIP score for each participant. This EDIP score was then rescaled for statistical analyses.

Table 4: Participant characteristics in the MAPs study populations among selected FBI score quartiles

Variable[1]	**FBI Quartile 1[2] (*n* = 128)**	**FBI Quartile 2[2] (*n* = 109)**	**FBI Quartile 3[2] (*n* = 108)**	**FBI Quartile 4[2] (*n* = 111)**	***p*-value[3]**
Demographics and Medical					
Age (years)	57.9 (8.25)	56.0 (8.81)	57.1 (9.81)	55.6 (8.59)	0.18
Male (%)	39	42	56	63	<0.01
White race, %	95	92	92	92	0.64
College graduate, %	34	33	23	16	<0.01
Regular NSAID use (≥3/week), %	26	17	18	13	0.07
Regular dietary supplement use (≥3/week), %	16	18	12	8	0.13
Physical activity (sedentary), %	32	37	36	32	0.73
Currently smoke, %	13	26	26	39	<0.01
Body mass index, (obese), %	26	28	31	30	0.82
Alcohol (non-drinkers), %	52	44	52	54	<0.01
Total energy intake (kilocalories/day)	2,150 (840)	1,830 (624)	1,790 (647)	1,800 (715)	<0.01
High-sensitivity C-reactive protein (mg/L)	4.44 (5.09)	4.17 (4.45)	4.13 (3.86)	4.92 (4.57)	0.55
Components of FBI Score					
Processed meat (servings/week)	1.37 (1.88)	1.28 (2.22)	2.14 (2.56)	3.77 (4.53)	<0.01
Red meat (servings/week)	4.00 (4.09)	3.65 (3.20)	3.30 (2.49)	3.98 (3.06)	0.33
White meat (servings/week)	6.25 (4.40)	4.78 (2.21)	4.50 (2.32)	3.50 (2.20)	<0.01
Fish (servings/week)	6.90 (3.04)	6.42 (2.60)	6.76 (2.51)	6.86 (2.25)	0.51
Nuts (servings/week)	2.23 (1.43)	1.72 (1.11)	1.79 (1.28)	1.60 (0.96)	<0.01
Coffee (servings/week)	4.16 (2.83)	3.95 (2.87)	4.31 (2.84)	4.47 (2.90)	0.59
Tea (servings/week)	3.97 (2.40)	3.15 (2.49)	3.39 (2.56)	3.68 (2.64)	0.07
Dairy products (servings/week)	9.78 (9.59)	9.56 (11.9)	10.0 (10.5)	11.5 (13.3)	0.58
Refined grains (servings/week)	22.7 (6.32)	22.2 (5.41)	22.1 (5.84)	23.4 (6.43)	0.38
Whole grains (servings/week)	11.6 (4.69)	9.86 (4.02)	9.26 (4.30)	8.89 (3.76)	<0.01

Table 4, continued

Variable[1]	**FBI Quartile 1[2] (*n* = 128)**	**FBI Quartile 2[2] (*n* = 109)**	**FBI Quartile 3[2] (*n* = 108)**	**FBI Quartile 4[2] (*n* = 111)**	***p*-value[3]**
Components of FBI Score					
Beta-carotene foods[4] (servings/week)	8.98 (2.96)	6.95 (2.14)	5.94 (2.16)	4.77 (1.73)	<0.01
Green/leafy vegetables[5] (servings/week)	8.93 (2.86)	7.46 (2.56)	7.06 (2.54)	5.87 (2.28)	<0.01
Brassicaceae[6] (servings/week)	8.97 (2.99)	7.52 (2.08)	6.44 (1.87)	5.23 (1.76)	<0.01
Leguminosae[7] (servings/week)	7.69 (4.30)	5.55 (2.33)	4.25 (2.33)	2.76 (1.91)	<0.01
Rosaceae[8] (servings/week)	7.52 (4.79)	5.20 (3.48)	3.74 (2.61)	2.04 (1.92)	<0.01
Rutaceae[9] (servings/week)	5.31 (5.37)	4.39 (5.05)	3.75 (5.05)	3.01 (3.91)	<0.01
Lycopene foods[10] (servings/week)	2.78 (2.03)	2.56 (1.92)	1.97 (1.53)	1.51 (1.23)	<0.01
Food-Based Inflammation (FBI) Score[2]	-1.60 (0.34)	-1.08 (0.08)	-0.81 (0.09)	-0.43 (0.17)	<0.01
Empirical Dietary Inflammatory Pattern (EDIP)[11]	-2.05 (2.11)	-1.39 (2.08)	-0.92 (1.90)	0.26 (1.86)	0.03

Abbreviations: MAPs, Pooled Markers of Adenomatous Polyps studies; FBI, food-based inflammation; NSAID, non-steroidal anti-inflammatory drug

1. Values for variables are mean (standard deviation), except where indicated.
2. The FBI score was created using multivariable-adjusted linear regression of the associations of the dietary components with the summary inflammation biomarker z-score. The beta coefficients of the regressions were used as weights for contributions of the dietary components to an overall FBI score. The FBI score was ultimately calculated as the sum of the weighted dietary component intakes of each participant, and then dichotomized [Quantile 1 is anti-inflammatory; Quantile 2 is proinflammatory].
3. P-values calculated using ANOVA for continuous variables and χ^2 tests for categorical variables comparing FBI score quartiles; significant at $p \leq 0.05$.
4. The FBI score was calculated as described in footnote 2, then categorized into quartiles [Quartile 1 is most anti-inflammatory; Quartile 4 is most proinflammatory].
5. Beta-carotene foods include carrots, sweet potatoes, orange/yellow squash, and pumpkins.
6. Green/leafy vegetables include collards, mustard/turnip greens, romaine lettuce, and spinach.
7. Brassicaceae include broccoli, Brussels sprouts, cabbage, and cauliflower.
8. Leguminosae include black, kidney, lima, snap and broad beans, peas, and lentils.
9. Rosaceae include apples, apricots, peaches, pears, and strawberries.
10. Rutaceae include grapefruits, oranges, and tangerines.
11. Lycopene foods include tomatoes, salsa, and tomato paste, sauce, and juice.
12. For the EDIP, intake of food groups was weighted by beta coefficients derived from a stepwise regression model, and then summed to create an overall EDIP score for each participant. This EDIP score was then rescaled for statistical analyses.

Table 5: Adjusted associations of the FBI and EDIP scores with "high" summary inflammation biomarker z-score in three study populations

	FBI score quantile					EDIP score quantile				
	1	2	3	4	*P*-trend[1]	1	2	3	4	*P*- trend[1]
REGARDS[2]										
Crude OR (95% CI)	1.00	1.60 (0.99, 2.61)	1.80 (1.11, 2.92)	2.47 (1.51, 4.05)		1.00	1.11 (0.69, 1.79)	1.45 (0.90, 2.34)	1.74 (1.07, 2.82)	
Adjusted OR (95% CI)[3]	1.00	1.54 (0.91, 2.61)	1.59 (0.93, 2.72)	2.11 (1.22, 3.67)	<0.01	1.00	1.13 (0.67, 1.91)	1.13 (0.67, 1.91)	1.35 (0.79, 2.30)	0.35
CCECP										
Crude OR (95% CI)	1.00	0.93 (0.52, 1.68)	— †	— †		1.00	1.22 (0.68, 2.20)	— †	— †	
Adjusted OR (95% CI)[4]	1.00	0.78 (0.39, 1.53)	— †	— †	0.46	1.00	0.98 (0.50, 1.92)	— †	— †	0.94
MAPs										
Crude OR (95% CI)	1.00	1.65 (0.98, 2.76)	1.56 (0.93, 2.62)	1.98 (1.18, 3.35)		1.00	1.30 (0.77, 2.17)	1.41 (0.84, 2.37)	1.96 (1.15, 3.32)	
Adjusted OR (95% CI)[5]	1.00	2.12 (1.17, 3.82)	1.68 (0.93, 3.03)	2.31 (1.25, 4.28)	0.01	1.00	0.98 (0.56, 1.73)	1.18 (0.67, 2.09)	1.50 (0.83, 2.70)	0.17

Abbreviations: FBI, food-based inflammation; EDIP, empirical dietary inflammatory pattern; OR, odds ratio; 95% CI, 95% confidence interval; REGARDS, REasons for Geographic and Racial Differences in Stroke study; CCECP, Calcium and Colorectal Epithelial Cell Proliferation trial; MAPs, Markers of Adenomatous Polyps studies

— † Quantiles not assigned due to small sample size.

1. *P*-trend calculated by assigning the median of each diet score quantile to each quantile, and treating this quantile exposure as continuous. *P*-trend significant at $p \leq 0.05$.
2. Calculation and application of FBI score in REGARDS is not informative (as it was developed in this study population) but is included for direct comparison with the EDIP.
3. FBI score model adjusted for age, sex, hormone replacement therapy (HRT) use, race, education level, total energy intake, smoking status, alcohol intake category, physical activity level, body mass index (BMI) category, regular dietary supplement use, and regular non-steroidal anti-inflammatory drug (NSAID) use. EDIP model adjusted for all previous covariates except alcohol intake category, as beer and wine consumption are components of the EDIP score.
4. FBI and EDIP models adjusted for age, sex, HRT use, total energy intake, smoking status, alcohol intake category, physical activity level, BMI category, and regular NSAID use. EDIP score did not contain alcohol, as we were unable to specify beer and wine components.
5. FBI score model adjusted for age, sex, HRT use, total energy intake, smoking status, alcohol intake category, physical activity level, BMI category, regular dietary supplement use, and regular NSAID use. EDIP model adjusted for all previous covariates except alcohol intake category.

Figure 2: Trend test[1] for quartiles of the FBI and EDIP scores with "high" summary inflammation biomarker score in the REGARDS and MAPs populations

Abbreviations: FBI, food-based inflammation; EDIP, empirical dietary inflammatory pattern; OR, odds ratio; 95% CI, 95% confidence interval; REGARDS, REasons for Geographic and Racial Differences in Stroke; MAPs, Markers of Adenomatous Polyps studies

1. Linear trend modeled by assigning the median of each diet score quartile to each quartile, then treating this quartile exposure as continuous.
2. Calculation and application of FBI score in REGARDS is not informative, as it was developed in this study population, but is included for direct comparison with the EDIP. Model adjusted for age, sex, hormone replacement therapy (HRT) use, race, education level, total energy intake, smoking status, alcohol intake category, physical activity level, body mass index (BMI) category, regular dietary supplement use, and regular non-steroidal anti-inflammatory drug (NSAID) use.
3. Model adjusted for age, sex, HRT use, race, education level, total energy intake, smoking status, physical activity level, BMI category, regular dietary supplement use, and regular NSAID use.
4. Model adjusted for age, sex, HRT use, total energy intake, smoking status, alcohol intake category, physical activity level, BMI category, regular dietary supplement use, and regular NSAID use.
5. Model adjusted for age, sex, HRT use, total energy intake, smoking status, physical activity level, BMI category, regular dietary supplement use, and regular NSAID use.

Appendix A

Supplementary Table 1: Food-based inflammation (FBI) score components and rationales for inclusion

FBI score components	Rationale for inclusion
Beta carotene-containing foods	Antioxidant function; contain anti-inflammatory bioactive compounds such as campesterol and lignans (54-56)
Coffee	Contains caffeic acid and diterpenes with antioxidant effects; associated with decreased CRP levels (57-59)
Cruciferae	Contain isothiocyanates involved in antioxidant function; anti-inflammatory effect during cell proliferation (60, 61)
Fish	Contains anti-inflammatory omega-3 fatty acids which inhibit omega-6–derived eicosanoids (62-64)
Shellfish	Contains omega-3 fatty acids (10-11); reduced oxidative stress and inflammation in rodent model (64)
Whole grains	Contain short-chain fatty acids (after colonic fermentation) that have anti-inflammatory effects and modulate the immune system (65-67)
Dairy	Consumption associated with decreased levels of pro-inflammatory markers (18, 68)
Leafy greens	Antioxidant function; contain folacin, magnesium, and calcium which may be anti-neoplastic (69, 70)
Leguminosae	Contain isoflavones and vitamin B6 that have anti-inflammatory/anti-thrombotic activity (71, 72)
Lycopene-containing foods	Antioxidant function; decreases NF-kB activation (73-75)
Nuts	Contain nutrients (magnesium, fiber, etc.) that act to decrease pro-inflammatory cytokines (76-78)
Processed meat	Contains heterocyclic amines and other genotoxic molecules produced during production/cooking; contains saturated fat (79, 80)
Red meat	Contains iron (which can act as a pro-oxidant) and saturated fat; associated with microinflammation (65, 79-83)
Refined grains	Increased consumption associated with higher levels of serum CRP, IL-6, and inflammatory conditions (65, 67, 84)
Rosaceae	Contain anti-inflammatory anthocyanins, quercetin, and phenolic acids which can block NF-kB activity (85-88)
Rutaceae	Contain anti-inflammatory and anti-microbial quinoline alkaloids, limonoids, etc. (89, 90)
Tea	Anti-inflammatory; polyphenols can inhibit expression of COX-2 (91, 92)
White meat	Leaner meat low in saturated fats (79, 80)

Supplementary Table 2: Correlations of selected dietary components used to create the FBI score in the REGARDS study population

Components of interest and Pearson correlation coefficients			
Brassicaceae[1]	Beta-carotene foods[2]	Leguminosae[3]	
	0.39	0.32	
Fish	White meat	Shellfish	Refined grains
	0.44	0.43	0.30
Refined grains	Processed meat	Red meat	White meat
	0.35	0.32	0.33
White meat	Fish	Refined grains	
	0.44	0.33	

Abbreviations: FBI, food-based inflammation; REGARDS, REasons for Geographic and Racial Differences in Stroke

1. Brassicaceae include broccoli, Brussels sprouts, cabbage, and cauliflower.
2. Beta-carotene foods include carrots, sweet potatoes, orange/yellow squash, and pumpkins.
3. Leguminosae include black, kidney, lima, snap and broad beans, peas, and lentils.

Supplementary Table 3: Quartile agreement among FBI and EDIP scores in REGARDS study participants[1]

	EDIP score quartile			
	1	2	3	4
FBI score quartile				
1	30 (22.2)	35 (26.1)	36 (26.5)	33 (24.6)
2	36 (26.7)	28 (20.9)	37 (27.2)	34 (25.4)
3	34 (25.2)	35 (26.1)	37 (27.2)	33 (24.6)
4	35 (25.9)	36 (26.9)	26 (19.1)	34 (25.4)
Total	135 (100)	134 (100)	136 (100)	134 (100)

Abbreviations: FBI, food-based inflammation; EDIP, empirical dietary inflammatory pattern; REGARDS, REasons for Geographic and Racial Differences in Stroke

1. Values are *n* (%) of participants in each quartile of the FBI score by quartile of the EDIP score

Supplementary Table 4: Weighted kappa statistics between the dietary scores for three study populations

	REGARDS κ (95% CI)	**CCECP** κ (95% CI)	**MAPs** κ (95% CI)
Dietary Scores			
FBI & EDIP	-0.02 (-0.09, 0.04)	0.33 (0.19, 0.47)	0.32 (0.25, 0.38)

Abbreviations: REGARDS, REasons for Geographic and Racial Differences in Stroke study; CCECP, Calcium and Colorectal Epithelial Cell Proliferation trial; MAPs, Markers of Adenomatous Polyps studies; FBI, food-based inflammation; EDIP, empirical dietary inflammatory pattern

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CHAPTER 3. THE FOOD-BASED INFLAMMATION SCORE AND RISK OF INCIDENT, SPORADIC COLORECTAL ADENOMA

Abstract

Background: It is now well-accepted that inflammation is implicated in colorectal carcinogenesis and that reducing inflammation reduces risk for colorectal neoplasms. The ability to characterize specific dietary patterns as pro- or anti-inflammatory is a promising area of cancer prevention; however, few studies have examined the relationship of diet-related inflammation and risk for incident, sporadic colorectal adenoma. We investigated associations of the food-based inflammation (FBI) score with incident, sporadic colorectal adenoma in a colon-/endoscopy-based case-control study.

Methods: Participants in the Minnesota Cancer Prevention Research Unit (CPRU) study were recruited between 1991 and 1994 and completed detailed questionnaires on diet (assessed using a Willett food frequency questionnaire [FFQ]), medical history, and lifestyle before undergoing elective, outpatient endoscopy procedures. Among 2,421 participants, 684 incident colorectal adenoma cases were identified. We calculated the FBI score, containing 17 foods/food groups, in all eligible participants using data from the FFQ. The FBI score ranged from -6.91 to 0.66. Multivariable-adjusted odds ratios (OR) were estimated using logistic regression.

Results: The multivariable-adjusted OR and 95% confidence interval (CI) in the highest relative to lowest FBI quartiles was 1.37 (CI: 0.95, 1.98; P_{trend}=0.06) and 1.50 (CI: 1.08, 2.08; P_{trend}=0.03) when comparing cases with community and endoscopy-negative controls, respectively. There were no consistent differences in associations of the FBI score with adenoma according to age, sex, family history of colorectal cancer, smoking status, body fatness, or regular non-steroidal anti-inflammatory drug use.

Conclusions: Higher FBI scores were associated with increased risk for adenoma. Further investigation of the role of inflammation and use of the FBI score in larger and more diverse prospective studies of adenoma risk is warranted.

Introduction

Colorectal cancer is the third most commonly diagnosed cancer in the United States among men and women (1). Colorectal carcinogenesis is characterized by several hallmarks, including inflammation, which is involved in tissue dysplasia, tumor initiation, and tumor promotion (2). Conditions like inflammatory bowel disease, Crohn's disease, and ulcerative colitis are well-known risk factors for colorectal cancer (3, 4), and the use of non-steroidal anti-inflammatory drugs (NSAIDs) has been consistently, strongly associated with lower risk of colorectal neoplasms (5-11). Most colorectal cancers arise from the "adenoma-carcinoma" sequence, in which genetic and epigenetic alterations transform normal colorectal epithelium to an adenoma and, ultimately, to a malignant tumor over a period of 10-20 years (1, 12-13). Colorectal adenomas, the precursor lesion to colorectal cancers, are estimated to develop in about 20-50% of Americans older than age 50 (14). Previous studies have demonstrated that colorectal adenomas exhibit histologic inflammatory features (15, 16), and animal models have shown that inflammation promotes the conversion of colorectal adenomas to adenocarcinomas (17-19).

Geographic differences and migrant data point to dietary exposures as playing a role in the etiology of colorectal cancer (20). However, epidemiologic studies examining the associations between specific foods and nutrients with the development of colorectal neoplasms have been inconsistent (21-25), likely due to the complex interactions between foods, nutrients, and other bioactive molecules. Studies that examine total diet or dietary patterns may be more helpful in accounting for these interactions and their overall effects on adenoma risk. Diets characterized by high fruit and vegetable consumption, for example, have been associated with decreased risk of adenoma (23, 26). In contrast, "Western" diet patterns (marked by high consumption of processed grains and meats) have been associated with increased incidence of adenoma (26).

Systemic inflammation may be one process through which diet acts on adenoma risk: consumption of processed meat may form *N*-nitroso compounds that cause oxidative stress (which is intricately linked to inflammation) (27, 28) whereas fruits, vegetables, and nuts are rich in antioxidants

and other bioactive molecules that temper oxidative stress and decrease the production of pro-inflammatory cytokines (29-32). The dietary inflammatory index (DII) and empirical dietary inflammatory pattern (EDIP) are two multicomponent indices developed to measure the inflammatory potential of diet and examine its relationship with various health outcomes (33, 34). Both the DII and EDIP have been used to report associations between proinflammatory diets and increased risk of colorectal cancer (35-38), but to date, only one study has assessed the association of an inflammatory dietary pattern with incident, sporadic colorectal adenoma risk (39).

Given the slow progression from normal epithelium to invasive colorectal cancer, the detection and removal of adenomas is one possible prevention strategy. Because adenomatous polyp removal is invasive and does not prevent all colorectal cancers (1), other strategies for chemoprevention—possibly targeting inflammation—should be considered. While the use of aspirin and other NSAIDs is associated with reduced risk for colorectal neoplasms, these drugs are not recommended for preventive purposes due to potential adverse effects from long-term use (6, 7). Modification of lifestyle factors, such as managing weight, engaging in physical activity, and eating a healthful diet, are independently associated with reductions in systemic inflammation (29, 30) and decreased risk for colorectal neoplasms (1, 5, 20-26). However, information is lacking on the role of diet-mediated inflammation for the prevention of colorectal adenomas. We recently developed a food-based inflammation (FBI) score (based on current dietary recommendations and containing multiple fruit and vegetable categories) to quantify the effect of diet-related systemic inflammation. In this study, we evaluated associations of the FBI score with risk for incident, sporadic colorectal adenoma in a case-control study of Minnesota men and women.

Methods

Study Population and Data Collection

The Minnesota Cancer Prevention Research Unit (CPRU) case-control study was a multi-institution research study conducted between 1991 and 1994 in the Minneapolis metropolitan area (40-

42). Participants were recruited while being scheduled for elective, outpatient endoscopies (colonoscopies or flexible sigmoidoscopies) at 10 hospitals and endoscopy units within a multicenter gastroenterology practice. Eligibility criteria for participation required that patients: be English-speaking adults between 35 and 74 years of age living in the Minneapolis-St. Paul metropolitan area; be in general good health; and have no history of colorectal adenoma, cancer (excluding non-melanoma skin cancer), inflammatory bowel disease, or genetic syndromes associated with colorectal neoplasms. Prior to endoscopy procedure, each participant completed questionnaires on demographics, lifestyle, anthropometrics, medical history (including family history of colon cancer, history of hormone replacement therapy, and non-steroidal anti-inflammatory drug [NSAID] use), and diet via a 166-item Willett semi-quantitative FFQ before undergoing the outpatient procedure. Estimated dietary intakes derived from the FFQ were considered representative of habitual intake, as portion size and frequency of consumption over the last year were assessed (43). Endoscopy procedures were done following a 12-hour fast and bowel cleansing preparation. Endoscopists removed each polyp found during the procedure and recorded its size, shape, and location; study pathologists then histologically examined the polyp according to National Polyp Study protocol (44). The institutional review boards of the University of Minnesota and each endoscopy site approved the study. Written informed consent was obtained from each study participant.

Food-Based Inflammation (FBI) Score

Development and application of the food-based inflammation (FBI) score was previously described in **Chapter 2**. Briefly, the FBI score quantifies the inflammatory potential of an individual's diet using 18 food components (including four botanical groupings), all selected *a priori* (based on previous literature and biological plausibility) and given weights based on associations with a panel of inflammation biomarkers. Components of the FBI score were selected based on previous literature and biological plausibility, and consisted of: processed meat, red meat, white meat, fish, shellfish, nuts, coffee, tea, dairy products, refined and whole grains, beta-carotene-containing foods, lycopene-containing

foods, green/leafy vegetables, Brassicaceae, Leguminosae, Rosaceae, and Rutaceae. In CPRU, we used 17 of the original 18 food components to calculate an overall FBI score, as we did not have data on shellfish consumption. For each CPRU participant, we used baseline FFQ data to derive intake of the food components, multiplied the components by their respective weights, and then summed the weighted components to obtain an overall FBI score. Participants' FBI scores were categorized into quartiles, based on the distribution of scores in community controls. Higher (larger/more positive) scores were considered characteristic of a pro-inflammatory diet, while lower (smaller/more negative) scores were considered characteristic of an anti-inflammatory diet. The FBI score ranged from -6.91 to 0.66 in this population.

Outcome Assessment

Based on the endoscopy and pathology findings, participants were assigned final eligibility and case/control status. Cases (*n*=684) were defined as patients with first ever pathology-confirmed adenoma(s) at complete colonoscopy, and with no new diagnosis of inflammatory bowel disease or invasive carcinoma. Controls were defined as endoscopy patients with no history or findings of adenomatous or hyperplastic polyps (*n*=1,202) at the time of procedure. Because the endoscopy-negative controls may have had gastrointestinal symptoms or a family history of disease that led to being referred for the procedure, additional controls were recruited. These community controls (*n*=535) were randomly selected from the general population in the Minneapolis-St. Paul metropolitan area using Minnesota driver's license records, and frequency-matched to cases with respect to sex, age category (5-year intervals), and zip code. Community controls were included only if they met study eligibility criteria, but did not undergo endoscopy to assess or confirm polyp status. The participation rates for all endoscoped patients and community controls were 68% and 65%, respectively. All self-reported data (including anthropometrics and medical, lifestyle, and dietary history) were collected before case or control status was determined, as previously described (41-42, 45).

Other Scores

To compare our results to a previously-developed diet-related inflammation score, we calculated the empirical inflammatory pattern (EDIP) based on available FFQ information (34). Details on the creation and application of the EDIP have been published and are also described in **Chapter 2**. Briefly, the EDIP assesses diet quality based on its inflammatory potential using 18 food components (34), 15 of which were available in CPRU: processed meats, red meats, fish, pizza, refined grains, snacks, tomatoes, leafy/green vegetables, dark yellow vegetables, other vegetables, coffee, tea, beer, wine, and fruit juice. We did not have data on organ meats or high- and low-energy beverages. Like the FBI score, intake of these food components was derived using FFQ data, weighted, and then summed to create an overall EDIP score. Higher EDIP scores represent pro-inflammatory diets and smaller EDIP scores represent anti-inflammatory diets. The EDIP score of CPRU participants ranged from -15.6 to 10.4. The FBI and EDIP score components and their respective weights are included in Appendix B (Supplementary Table 1).

Statistical Analyses

Participants were excluded from final analyses if they had implausible total energy intakes estimated from the self-reported FFQs (<600 or >5,000 kilocalories daily), failed to respond to 10% or more of the FFQ, or had missing covariate data included in the multivariable-adjusted models. A total of 2,287 participants were included in the analyses, of which 558 were cases, 534 were community controls, and 1,195 were endoscopy-negative controls.

We described selected characteristics among FBI score quartiles using means and standard deviations (SD) for continuous variables and percentages for categorical variables. Descriptive characteristics were compared using chi-square (χ^2) tests for categorical variables and ANOVA for continuous variables. Multivariable unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for associations of the FBI and EDIP scores with colorectal adenoma. Both dietary pattern scores were analyzed as both continuous and categorical variables

(quartiles; based on the distributions of the scores in the controls). The median values of each FBI or EDIP score quartile were used for conducting linear trend tests, also adjusted for multiple covariates. Separate analyses were conducted to compare cases with each of the control groups.

We considered the following potential confounding variables based on previous literature and biological plausibility: age (years; continuous), sex (male/female), use of hormone replacement therapy (HRT) in females (yes/no), race/ethnicity; education (high school graduate or less, some college, college graduate), family history of colorectal cancer in a first-degree relative (yes/no), total energy intake (kilocalories/day; continuous), physical activity level (sedentary, moderately active, active), alcohol intake category (none, moderate: ≤1 drink [14 grams/day] for women and ≤2 drinks for men, or heavy: >1 drink for women and >2 drinks per day for men), body fatness (waist-to-hip ratio, obese: ≥1.0 for men and ≥0.8 for women, or body mass index (BMI) [weight (kg)/height (m^2)] categorized as normal: <25, overweight: <30, or obese: ≥30), smoking status (current, former, or never smoker), regular dietary supplement use (≥3 times per week; yes/no), and regular NSAID use (≥3 times per week; yes/no). Inclusion in the final model required meeting one or more of the following criteria: findings previously reported in the literature, biological plausibility, statistical significance, and whether exclusion of the variable from the model changed the adjusted OR for the primary exposure variable by ≥10%. The final adjusted model controlled for age, sex, body fatness category, smoking status, and regular NSAID use (based on previous literature, biological plausibility, and statistical significance), use of HRT, family history of colorectal cancer, total energy intake, physical activity level, alcohol intake category, and regular dietary supplement use (based on previous literature and biological plausibility).

Potential effect modification was assessed in the multivariable-adjusted models by including interaction terms between the FBI score and the following covariates: age (continuous), sex, family history of colorectal cancer in a first-degree relative (yes/no), BMI (continuous), smoking status (ever/never), and regular NSAID use (yes/no). All analyses were conducted using SAS statistical

software, version 9.4 (SAS Institute, Inc., Cary, North Carolina). Results of all statistical tests were considered significant at $p \leq 0.05$.

Results

Selected characteristics of CPRU participants based on FBI score categorization are presented in Table 1. Compared to individuals in the lowest (most anti-inflammatory) score quartile, participants in the highest FBI score quartile were more likely to be male, sedentary, or currently smoke and less likely to have been college graduates and use dietary supplements or NSAIDs regularly. Participants did not differ in terms of self-reported intake of red meat, coffee, dairy products, or refined grains, although there were significant differences among FBI score quartiles for other food groups of interest. The mean difference in FBI score between the highest (most pro-inflammatory) and lowest quartile was 1.66 (95% CI: 1.60, 1.72).

Age- and multivariable-adjusted associations of the FBI and EDIP scores with colorectal adenoma are presented in Table 2. The FBI score was not associated with incident adenoma in multivariable-adjusted analyses involving community controls, but did approach statistical significance when comparing participants in the highest/most pro-inflammatory quartile to those in the lowest quartile (OR: 1.37; 95% CI: 0.95, 1.98; P_{trend}=0.06). In multivariable-adjusted analyses involving endoscopy-negative controls, adenoma incidence was estimated to be 29% higher per one-point increase in the FBI score (OR: 1.29; 95% CI: 1.09, 1.52). When the FBI score was treated as a categorical variable in this analysis group, the multivariable-adjusted OR of incident adenoma among participants in the highest (most pro-inflammatory) quartile was 1.50 (95% CI: 1.08, 2.08; P_{trend}=0.03) compared to the lowest quartile. When the EDIP score was used as a continuous variable in the age-adjusted analysis involving endoscopy-negative controls, adenoma incidence was estimated to be 7% higher per one-point increase in the EDIP score (OR: 1.07; 95% CI: 1.02, 1.12); this association was not statistically significant after adjusting for potential confounders, though. Ultimately, the EDIP score was not associated with incident

adenoma when used as the primary exposure variable in either analysis involving community and endoscopy-negative controls (P_{trend}=0.20 and P_{trend}=0.73, respectively). There was moderate correlation between the FBI and EDIP scores (Pearson's *r*=0.46).

Table 3 shows associations of the FBI score with incident adenoma, stratified by specific risk factors for colorectal neoplasm. No clear pattern of effect modification was observed and none of the interaction terms between FBI score and risk factors of interest were statistically significant. Patterns of association were weak or inconsistent among most increasing score quartiles; however, a linear trend was observed across categories of FBI score for males and participants older than age 55 in comparisons involving both community and endoscopy-negative controls.

Discussion

Overall, our results suggest that a pro-inflammatory dietary pattern, as indicated by high FBI score, is associated with risk of incident, sporadic colorectal adenoma. We found no association between incident adenoma and another previously-validated dietary inflammation score, the EDIP.

Although it is well-accepted that inflammation plays a critical role in cancer etiology, evidence of its role in the development of colorectal adenoma has been mixed (46, 47). One hypothesized mechanism is that underlying inflammation in pre-neoplastic tissue (e.g., via long-term endotoxin exposure) may cause genetic instability, thereby altering the colorectal epithelium and initiating unchecked proliferation. Recently, Abu-Remaileh et al. demonstrated that chronic inflammation can induce the silencing of genes involved in gastrointestinal homeostasis, resulting in both adenomas and cancers in mice (18). Other mouse models have found that pro-inflammatory cytokines can recruit and induce additional inflammatory mediators involved in anti-apoptotic activities, angiogenesis, and dysregulated cell adhesion—all of which increase risk and progression of cancer (48-50). Despite these results from basic research, epidemiologic studies investigating the association of systemic inflammation biomarkers with

adenoma risk have been inconsistent (47, 51-52); a recent meta-analysis of 14 case-control studies found no statistically significant associations of C-reactive protein, interleukin-6, or tumor necrosis factor-alpha with incident adenoma (46). A systematic review on the effectiveness of anti-inflammatory medications (such as NSAIDs and cyclooxygenase-2 inhibitors) for chemoprevention observed inverse associations between regular medication use and risk for both adenoma and colorectal cancer incidence (6-7, 53). As diet has been found to moderate biomarkers of inflammation in intervention trials (54, 55), the ability to characterize specific dietary patterns as pro- or anti-inflammatory may be a promising area of cancer prevention.

In our analysis involving endoscopy-negative controls, we found significant associations of the FBI score with risk for incident adenoma. These results are consistent with findings from other studies that have found inverse associations between various "healthy" diets and adenoma risk (45, 56-58). Although these studies posit inflammation as a potential mechanism, few studies have attempted to characterize the inflammatory potential of diet as it pertains to adenoma risk. Previously the DII—a proprietary tool consisting of 45 food, nutrient, and bioactive component parameters—was applied to participants included in the screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial to assess risk for distal adenoma (33, 39). Ultimately, a higher DII score was associated with both adenoma prevalence (OR: 1.41; 95% CI [1.23, 1.62]) and having multiple adenomas (OR: 1.63; 95% CI [1.26, 2.11]) in males when comparing the most pro-inflammatory quartile with the reference quartile (39). The DII calculates an inflammatory dietary pattern based on weighted results from prior literature involving various food components/parameters (33); however, most dietary patterns postulated to reduce inflammation and adenoma risk are generally identified using exploratory factor and principal component analyses. These patterns are often characterized by low intake of meats and refined grains and high intake of fruits and vegetables (26). While both the FBI and EDIP scores include meat and specific categories of fruits and vegetables, FBI score components were selected *a priori* based on biological plausibility and current dietary guidelines (**Chapter 2**) whereas components of the EDIP were selected

based on statistical associations with specific biomarkers of inflammation (34). Both scores are thus used as proxies for inflammation-related dietary quality and were not specifically designed to evaluate adenoma risk, which may explain the lack of association between the EDIP score and adenoma incidence. Nonetheless, the positive association observed between increasing FBI score and adenoma incidence suggests that dietary mechanisms related to inflammation may be important for adenoma risk. Previous studies examining associations of diet and lifestyle factors with colorectal adenoma observed effect modifications by regular NSAID use; however, the risk reductions associated with healthier diet and lifestyle modifications/patterns were found only in non-users of NSAIDs (57, 59-61). We observed stronger associations of the FBI score with adenoma in regular NSAID users, but these were not statistically significant. Our differential results may be indicative of confounding by indication, as various underlying comorbidities are associated with both poor diet quality and regular NSAID use.

We observed statistically significant associations between the FBI score and incident adenoma in comparisons involving the endoscopy-negative controls but not in comparisons involving the community controls. This may be explained in part by the small sample size in the community control group or differences in demographic characteristics between the two control groups. Compared with community controls, the endoscopy-negative controls were more likely to be younger, female, and have a family history of disease (Appendix B, Supplemental Table 2). Increasing age and male sex are well-known risk factors for colorectal adenoma, and associations of the FBI score with adenoma were stronger among these at-risk groups (although we did not observe any effect modification by these specific characteristics of interest). Two other published scores, the Mediterranean diet score and the Dietary Approaches to Stop Hypertension score, were associated with reduced risk of colorectal adenoma among men only (58). It is possible that dietary risk factors for colorectal adenoma differ by sex, but the mechanisms for these differences are unclear; evaluating sex-specific dietary scores may elucidate some of the risk differences observed between our control groups and between males and females. Additionally, because this study was conducted before widespread use of colonoscopies for screening average-risk individuals (62), the

endoscopy controls may typify a highly-selected group of participants who had gastrointestinal symptoms or a family history of disease which prompted the procedure.

Stronger associations were observed for associations between the FBI score and incident adenoma than between the EDIP score and incident adenoma. Though the FBI and EDIP scores contain seven of the same food components (Supplemental Table 1), several differences in the construction of the scores may have affected the results of this study. As described in **Chapter 2**, the dietary components of each of the scores were identified using different methodological approaches. Based on FFQ data, 17 of 18 dietary components were available to calculate an overall FBI score, whereas only 15 of 18 components were available to calculate an EDIP score. Furthermore, the FBI score contains components that comprise a large part of CPRU participants' self-reported diets (e.g., whole grains and dairy products) which are not included in the EDIP. Ultimately the EDIP—as calculated in this population—may not account for the kinds of dietary variation necessary to observe an association with adenoma risk. Associations of both the FBI and EDIP scores with incident adenoma were attenuated after adjusting for other covariates in analyses involving endoscopy controls; the main covariates driving these attenuations were sex and smoking status for the FBI score and EDIP score, respectively. The EDIP was originally developed in cohorts of health professionals with lower proportions of current smokers than our CPRU population, which may explain the weaker association observed after adjustment.

This study had several strengths and limitations. Strengths included the use of two control groups, the detailed collection and assessment of dietary exposures and other risk factors prior to colon-/endoscopy (thereby reducing the opportunity for recall bias), and the use of standardized, pathological verification of colorectal adenoma (thereby reducing misclassification of cases and controls in the endoscopy groups). One potential limitation is the possibility of undiagnosed adenoma cases within our community control group which may be a cause of outcome misclassification and, along with small sample size in this comparison group, could have attenuated our results. The use of our FBI score to quantify pro- and anti-inflammatory dietary patterns is a major strength: the FBI score uses food-specific

weights to characterize overall diet, is easily-constructed in populations with data on usual food intake, and can be used with a variety of inflammation-related health outcomes. However, the FBI score was derived using FFQ data, which contains finite food lists (limiting potential variation in intake, particularly for combinations of foods in certain dishes/meals) and collects little information on cooking methods (63). Another limitation is that the results of this study may not be generalizable to broader populations, as CPRU participants were mostly white, lived in the same geographic area, and were healthy volunteers already scheduled for outpatient screening procedures; thus, they may be different from non-participants and the general population in terms of sociodemographics, various health characteristics, and likelihood of being recommended for routine colon-/endoscopy.

In conclusion, the present results suggest that a pro-inflammatory dietary pattern, indicated by high FBI score, is associated with risk of colorectal adenoma. However, further investigation and use of the FBI score in larger and more diverse prospective studies of adenoma and other health outcomes is warranted.

Table 1. Selected characteristics of participants in the CPRU case-control study of the FBI score and risk of incident, sporadic colorectal adenoma

Variable[1]	**FBI Quartile 1 ≤ -1.15**	**FBI Quartile 2 -1.14 to -0.76**	**FBI Quartile 3 -0.75 to -0.40**	**FBI Quartile 4 ≥ -0.39**	***p*-value[2]**
Demographics and Medical					
Age (years)	56.6 (10.7)	55.6 (10.9)	54.8 (10.6)	54.1 (11.2)	<0.01
Male (%)	37	42	52	62	<0.01
White race, %	97	97	97	98	0.48
College graduate, %	38	38	31	23	<0.01
Family history of colorectal cancer, %	16	20	14	15	0.07
Regular NSAID use (≥3 times/week), %	36	36	34	27	<0.01
Regular dietary supplement use (≥3 times/week), %	27	27	20	18	<0.01
Physical activity (sedentary), %	38	43	47	53	<0.01
Currently smoke, %	8	13	15	25	<0.01
Obese[3], %	49	51	53	53	0.32
Overweight[4], %	21	19	21	22	
Normal weight[5], %	30	30	26	25	
Alcohol (non-drinkers), %	44	43	39	40	0.07
Total energy intake (kcal/day)	2,350 (732)	2,050 (664)	1,930 (686)	1,841 (748)	<0.01
Components of FBI Score					
Processed meats (servings/week)	1.45 (1.82)	1.71 (2.61)	1.98 (2.46)	3.43 (4.95)	<0.01
Red meat (servings/week)	4.44 (3.67)	4.34 (3.21)	4.34 (3.18)	4.69 (3.61)	0.26
White meat (servings/week)	6.48 (4.54)	5.10 (2.79)	4.15 (2.27)	3.09 (1.93)	<0.01
Fish (servings/week)	2.61 (2.08)	1.96 (1.51)	1.65 (1.25)	1.29 (1.28)	<0.01
Nuts (servings/week)	4.18 (6.51)	2.87 (3.55)	2.23 (2.43)	1.30 (1.54)	<0.01
Coffee (servings/week)	4.67 (2.96)	4.84 (2.91)	4.89 (2.94)	4.63 (3.11)	0.36
Tea (servings/week)	2.34 (1.84)	2.12 (1.69)	1.96 (1.64)	1.70 (1.44)	<0.01
Total dairy (servings/week)	19.1 (12.5)	18.5 (12.3)	18.2 (13.8)	17.1 (13.4)	0.08
Refined grains (servings/week)	19.5 (10.6)	19.9 (10.3)	19.8 (11.6)	20.2 (11.9)	0.75
Whole grains (servings/week)	13.7 (3.66)	12.5 (3.38)	11.4 (3.09)	10.3 (3.12)	<0.01

Table 1, continued

Beta-carotene foods[6] (servings/week)	11.4 (7.48)	5.33 (1.93)	3.12 (1.46)	1.50 (1.00)	<0.01
Green/leafy vegetables[7] (servings/week)	7.71 (5.66)	4.55 (2.62)	3.47 (2.40)	2.09 (1.69)	<0.01
Brassicaceae[8] (servings/week)	5.01 (5.37)	3.01 (2.39)	2.03 (1.64)	1.25 (1.11)	<0.01
Leguminosae[9] (servings/week)	4.83 (3.49)	3.03 (1.92)	2.35 (1.57)	1.50 (1.10)	<0.01
Rosaceae[10] (servings/week)	9.16 (7.10)	5.30 (3.69)	3.59 (2.90)	1.85 (1.91)	<0.01
Rutaceae[11] (servings/week)	7.85 (6.53)	5.67 (5.04)	4.92 (4.91)	3.44 (4.39)	<0.01
Lycopene foods[12] (servings/week)	3.69 (3.82)	2.39 (2.30)	1.95 (2.35)	1.32 (1.47)	<0.01
FBI Score[13]	-1.86 (0.79)	-0.95 (0.11)	-0.58 (0.11)	-0.20 (0.17)	<0.01

Abbreviations: CPRU, Minnesota Cancer Prevention Research Unit; FBI, food-based inflammation; NSAID, non-steroidal anti-inflammatory drug

1. Values for variables are mean (standard deviation), except where indicated.
2. *P*-values calculated using ANOVA for continuous and χ^2 tests for categorical variables comparing FBI score categories; significant at $p \leq 0.05$.
3. Obese defined as waist-to-hip ratio ≥1.0 for men and ≥0.8 for women, or body mass index [weight (kg)/height (m^2)] (BMI) ≥30.
4. Overweight defined as BMI ≥25 and <30.
5. Normal weight defined as BMI ≥18.5 and <25.
6. Beta-carotene foods include carrots, sweet potatoes, orange/yellow squash, and pumpkins.
7. Green/leafy vegetables include collards, mustard/turnip greens, romaine lettuce, and spinach.
8. Brassicaceae include broccoli, Brussels sprouts, cabbage, and cauliflower.
9. Leguminosae include black, kidney, lima, snap and broad beans, peas, and lentils.
10. Rosaceae include apples, apricots, peaches, pears, and strawberries.
11. Rutaceae include grapefruits, oranges, and tangerines.
12. Lycopene foods include tomatoes, salsa, and tomato paste, sauce, and juice.
13. The FBI score was created using multivariable-adjusted linear regression of the associations of the dietary components with the summary inflammation biomarker z-score. The beta coefficients of the regressions were used as weights for contributions of the dietary components to an overall FBI score. The FBI score was ultimately calculated as the sum of the weighted dietary component intakes of each participant.

Table 2. Associations of diet scores with incident, sporadic colorectal adenoma in the CPRU case-control study

	FBI Score						EDIP Score					
			Community Controls (n=1,092)		*Endoscopy-Negative Controls (n=1,753)*				*Community Controls (n=1,092)*		*Endoscopy-Negative Controls (n=1,753)*	
Diet Score Variable	***Quartile Cutpoints***	***n* cases**	**Model 1 OR[1] (95% CI)**	**Model 2 OR[2] (95% CI)**	**Model 1 OR[1] (95% CI)**	**Model 2 OR[2] (95% CI)**	***Quartile Cutpoints***	***n* cases**	**Model 1 OR[1] (95% CI)**	**Model 3 OR[3] (95% CI)**	**Model 1 OR[1] (95% CI)**	**Model 3 OR[3] (95% CI)**
Continuous variable		*558*	1.15 (0.96, 1.37)	1.07 (0.88, 1.30)	1.41 (1.21, 1.64)	1.29 (1.09, 1.52)		*558*	1.04 (0.99, 1.09)	1.01 (0.96, 1.07)	1.07 (1.02, 1.12)	1.03 (0.98, 1.08)
Quartiles												
1	≤ -1.15	*125*	1.00	1.00	1.00	1.00	≤ -3.03	*139*	1.00	1.00	1.00	1.00
2	-1.14 to -0.76	*109*	0.87 (0.61, 1.23)	0.82 (0.57, 1.19)	1.08 (0.79, 1.48)	1.11 (0.80, 1.54)	-3.02 to -1.55	*117*	1.03 (0.73, 1.44)	0.97 (0.68, 1.37)	0.88 (0.66, 1.19)	0.95 (0.70, 1.29)
3	-0.75 to -0.40	*149*	1.16 (0.83, 1.63)	1.14 (0.80, 1.63)	1.23 (0.92, 1.64)	1.12 (0.81, 1.53)	-1.54 to -0.31	*147*	1.28 (0.92, 1.79)	1.26 (0.90, 1.77)	1.05 (0.79, 1.40)	1.02 (0.76, 1.38)
4	≥ -0.39	*175*	1.46 (1.04, 2.04)	1.37 (0.95, 1.98)	1.84 (1.37, 2.46)	1.50 (1.08, 2.08)	≥ -0.30	*155*	1.37 (0.99, 1.91)	1.19 (0.84, 1.68)	1.30 (0.97, 1.73)	1.05 (0.77, 1.42)
***P-trend*[4]**			*0.02*	*0.06*	*<0.01*	*0.03*			*0.03*	*0.20*	*<0.01*	*0.73*

Abbreviations: CPRU, Minnesota Cancer Prevention Research Unit; FBI, food-based inflammation; EDIP, empirical dietary inflammatory pattern; OR, odds ratio; CI, confidence interval.

1. OR from an unconditional logistic regression model adjusted for age only.
2. OR from an unconditional logistic regression model adjusted for age, sex, hormone replacement therapy use, family history of colorectal cancer in a first-degree relative, total energy intake, smoking status, alcohol intake category, physical activity level, body fatness category, regular dietary supplement use, and regular non-steroidal anti-inflammatory drug use.
3. OR from an unconditional logistic regression model adjusted for all covariates in footnote 1 except alcohol intake category (beer and wine are components of the EDIP).
4. *P*-trend calculated by assigning the median of each diet score quartile to each quartile, and treating this quartile exposure as continuous. *P*-trend significant at $p \leq 0.05$.

Table 3. Associations of the FBI score with incident, sporadic colorectal adenomas among cases and community controls according to selected characteristics in the CPRU case-control study

		Adjusted OR[1] (95% CI) among FBI score quartiles				
	n (cases/total)	FBI Q1 ≤ -1.15	FBI Q2 -1.14 to -0.76	FBI Q3 -0.75 to -0.40	FBI Q4 ≥ -0.39	*P for trend*[2]
Selected characteristics						
Sex						
Community controls						
Males	345/640	1.00	0.82 (0.49, 1.39)	1.15 (0.71, 1.88)	1.38 (0.86, 2.22)	*0.05*
Females	213/452	1.00	0.81 (0.48, 1.34)	1.07 (0.64, 1.79)	1.21 (0.67, 2.17)	*0.98*
P for interaction		*0.98*				
Endoscopy-neg. controls						
Males	345/809	1.00	1.19 (0.73, 1.94)	1.06 (0.68, 1.66)	1.67 (1.07, 2.60)	*<0.01*
Females	213/944	1.00	1.03 (0.67, 1.60)	1.04 (0.68, 1.62)	0.98 (0.60, 1.58)	*0.21*
P for interaction		*0.30*				
Age						
Community controls						
<55	204/400	1.00	0.91 (0.49, 1.70)	0.82 (0.46, 1.46)	1.16 (0.64, 2.11)	*0.92*
≥55	354/692	1.00	0.76 (0.49, 1.19)	1.31 (0.84, 2.04)	1.35 (0.86, 2.12)	*0.03*
P for interaction		*0.18*				
Endoscopy-neg. controls						
<55	204/890	1.00	1.05 (0.64, 1.73)	0.98 (0.61, 1.59)	1.03 (0.65, 1.65)	*0.97*
≥55	354/863	1.00	1.03 (0.67, 1.57)	0.93 (0.62, 1.40)	1.40 (0.92, 2.14)	*0.05*
P for interaction		*0.35*				
Family history of colorectal cancer						
Community controls						
No	468/965	1.00	0.78 (0.53, 1.16)	1.03 (0.71, 1.50)	1.23 (0.84, 1.81)	*0.13*
Yes	90/127	1.00	1.14 (0.42, 3.08)	2.40 (0.70, 8.23)	2.50 (0.78, 8.00)	*0.22*
P for interaction		*0.53*				
Endoscopy-neg. controls						
No	468/1,423	1.00	0.99 (0.69, 1.43)	1.04 (0.74, 1.47)	1.33 (0.93, 1.90)	*0.03*
Yes	90/330	1.00	1.61 (0.76, 3.39)	0.96 (0.44, 2.07)	1.37 (0.65, 2.92)	*0.85*
P for interaction		*0.51*				

Table 3, continued

		Adjusted OR[1] (95% CI) among FBI score quartiles				
	n (cases/total)	FBI Q1 ≤ -1.15	FBI Q2 -1.14 to -0.76	FBI Q3 -0.75 to -0.40	FBI Q4 ≥ -0.39	*P for trend*[2]
Selected characteristics						
Body fatness						
Community controls						
Normal or overweight[3]	246/497	1.00	0.91 (0.53, 1.55)	0.99 (0.59, 1.66)	1.14 (0.67, 1.93)	*0.34*
Obese[4]	312/595	1.00	0.74 (0.45, 1.22)	1.24 (0.77, 1.99)	1.48 (0.91, 2.41)	*0.08*
P for interaction		*0.64*				
Endoscopy-neg. controls						
Normal or overweight[3]	246/853	1.00	1.07 (0.67, 1.71)	0.91 (0.58, 1.43)	1.13 (0.71, 1.78)	*0.49*
Obese[4]	312/900	1.00	1.12 (0.71, 1.76)	1.15 (0.75, 1.77)	1.56 (1.01, 2.41)	*0.01*
P for interaction		*0.28*				
Smoking status						
Community controls						
Never/former smokers	444/896	1.00	0.81 (0.55, 1.20)	1.13 (0.77, 1.65)	1.21 (0.81, 1.80)	*0.20*
Current smokers	114/196	1.00	0.88 (0.32, 2.44)	1.28 (0.48, 3.43)	2.14 (0.83, 5.52)	*0.02*
P for interaction		*0.56*				
Endoscopy-neg. controls						
Never/former smokers	444/1,483	1.00	1.04 (0.73, 1.48)	1.02 (0.73, 1.43)	1.27 (0.89, 1.82)	*0.06*
Current smokers	114/270	1.00	1.35 (0.51, 3.58)	1.02 (0.41, 2.55)	1.34 (0.57, 3.17)	*0.44*
P for interaction		*0.93*				
Regular NSAID use[5]						
Community controls						
No	394/767	1.00	0.73 (0.47, 1.14)	0.96 (0.63, 1.48)	1.18 (0.76, 1.83)	*0.37*
Yes	164/325	1.00	1.01 (0.54, 1.89)	1.49 (0.80, 2.77)	1.62 (0.84, 3.11)	*0.06*
P for interaction		*0.69*				
Endoscopy-neg. controls						
No	394/1,156	1.00	1.11 (0.74, 1.67)	1.01 (0.68, 1.48)	1.29 (0.87, 1.90)	*0.33*
Yes	164/597	1.00	1.07 (0.62, 1.86)	1.08 (0.63, 1.83)	1.47 (0.84, 2.57)	*0.04*
P for interaction		*0.96*				

Abbreviations: FBI, food-based inflammation; CPRU, Minnesota Cancer Prevention Research Unit; OR, odds ratio; CI, confidence interval; endoscopy-neg. controls, endoscopy-negative controls; NSAID, non-steroidal anti-inflammatory drug.

1. OR from an unconditional logistic regression model including the following covariates: age, sex, hormone replacement therapy use, family history of colorectal cancer in a first-degree relative, total energy intake, smoking status, physical activity level, body fatness category, regular dietary supplement use, and regular non-steroidal anti-inflammatory drug use.

Footnotes for Table 3, continued

2. *P*-trend calculated by assigning the median of each diet score quartile to each quartile, and treating this quartile exposure as continuous. *P*-trend significant at $p \leq 0.05$.
3. Normal weight defined as body mass index (BMI; [weight (kg)/height (m^2)]) ≥18.5 and <25; overweight defined as BMI ≥25 and <30.
4. Obese defined as waist-to-hip ratio ≥1.0 for men and ≥0.8 for women, or BMI ≥30.
5. Regular NSAID use defined as ≥3 times per week.

Appendix B

Supplementary Table 1. Food components and weights for the FBI and EDIP scores

Components in FBI score	Weights[1]	Components in EDIP score	Weights[2]
Processed meat	0.0348	Processed meat	165.03
Red meat	0.0053	Red meat	140.19
White meat	-0.0459	Organ meat	144.61
Fish	0.0465	Other fish[3]	252.45
Shellfish	0.0171	Snacks[4]	-45.08
Nuts	-0.0446	Pizza	-1175.21
Coffee	-0.0074	Coffee	-83.18
Tea	0.0003	Tea	-42.25
Dairy products	-0.0002	High-energy beverages	156.85
Whole grains	0.0084	Low-energy beverages	94.77
Refined grains	0.0023	Refined grains	-81.21
Beta-carotene foods[5]	-0.0943	Dark yellow vegetables[5]	-165.37
Green/leafy vegetables[6]	-0.002	Green/leafy vegetables[6]	-190.29
Brassicaceae[7]	-0.0214	Other vegetables[8]	136.14
Leguminosae[9]	-0.0484	Fruit juice[10]	-58.95
Rosaceae[11]	-0.0294	Beer	-136.99
Rutaceae[12]	-0.0003	Wine	-249.7
Lycopene foods[13]	0.0032	Tomatoes[13]	167.92

Abbreviations: FBI, food-based inflammation; EDIP, empirical inflammatory dietary pattern.
EDIP weights from: Tabung FK et al. Development and Validation of an Empirical Dietary Inflammatory Index. J Nutr. 2016 Aug;146(8):1560-70.

1. Weights are beta coefficients derived from linear regression of each dietary component with the summary inflammation biomarker z-score and adjusted for age, sex, use of hormone replacement therapy, race, education, total energy intake, body mass index (BMI) category, smoking status, physical activity category, alcohol intake category, regular dietary supplement use, and regular non-steroidal anti-inflammatory drug use.
2. Weights are beta coefficients derived from stepwise linear regressions used to identify food groups that significantly contributed to an inflammatory dietary pattern and adjusted for BMI.
3. Other fish includes canned tuna, shrimp, lobster, scallops, fish, or other seafood other than dark-meat fish.
4. Snacks include potato chips, corn chips, popcorn, and crackers.
5. Beta-carotene foods and dark yellow vegetables include carrots, sweet potatoes, orange/yellow squash and pumpkins.
6. Green/leafy vegetables include collards, mustard/turnip greens, romaine lettuce, and spinach.
7. Brassicaceae include broccoli, Brussels sprouts, cabbage, and cauliflower.
8. Other vegetables include celery, mushrooms, peppers, corn, mixed vegetables, eggplant, zucchini, alfalfa sprouts, and cucumber.
9. Leguminosae include black, kidney, lima, snap and broad beans, peas, and lentils.
10. Fruit juice includes apple juice or cider, orange juice, grapefruit juice, or other fruit juices.
11. Rosaceae include apples, apricots, peaches, pears, and strawberries.
12. Rutaceae include grapefruits, oranges, and tangerines.
13. Lycopene foods and tomatoes [for EDIP] include tomatoes, salsa, and tomato paste, sauce, and juice.

Supplementary Table 2. Selected characteristics of participants in the CPRU case-control study of the FBI score and risk of incident, sporadic colorectal adenoma

Variable[1]	**Cases (*n*=558)**	**Community Controls (*n*=534)**	**Endoscopy-Negative Controls (*n*=1,195)**	***p*-value[2]**
Age (years)	58.1 (9.67)	57.7 (10.4)	52.9 (11.1)	<0.01
Male	62	55	39	<0.01
White race, %	98	97	97	0.30
Education, %				
High school graduate	37	37	31	0.03
Some college	32	34	36	
College graduate	31	29	34	
Family history of colorectal cancer, %	16	6.9	20	<0.01
Regular NSAID use (≥3 times/week), %	29	30	36	<0.01
Regular dietary supplement use (≥3 times/week), %	18	22	26	<0.01
Physical activity, %				
Sedentary	46	46	45	0.45
Moderately active	27	26	30	
Active	27	28	25	
Smoking status, %				
Never	32	44	46	<0.01
Former	48	41	41	
Current	20	15	13	
Body fatness, %				
Normal weight[3]	22	26	31	<0.01
Overweight[4]	22	21	20	
Obese[5]	56	53	49	
Alcohol consumption, %				
Non-drinkers	39	40	43	<0.01
Moderate drinkers	39	45	44	
Heavy drinkers	22	15	13	
Total energy intake (kcal/day)	2,090 (779)	2,050 (719)	2,000 (718)	0.05
FBI Score[6]	-0.80 (0.70)	-0.86 (0.66)	-0.94 (0.79)	<0.01

Abbreviations: CPRU, Minnesota Cancer Prevention Research Unit; FBI, food-based inflammation; OR, odds ratio; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug.

1. Values for variables are mean (standard deviation), except where indicated.
2. *P*-values calculated using ANOVA for continuous and χ^2 tests for categorical variables comparing groups; significant at *p≤0.05.*
3. Normal weight defined as body mass index (BMI; [weight (kg)/height (m^2)]) ≥18.5 and <25.
4. Overweight defined as BMI ≥25 and <30.
5. Obese defined as waist-to-hip ratio ≥1.0 for men and ≥0.8 for women, or BMI ≥30.
6. The FBI score was created using multivariable-adjusted linear regression of the associations of the dietary components with the summary inflammation biomarker z-score. The beta coefficients of the regressions were used as weights for contributions of the dietary components to an overall FBI score. The FBI score was ultimately calculated as the sum of the weighted dietary component intakes of each participant.

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CHAPTER 4. THE FOOD-BASED INFLAMMATION SCORE AND RISK OF COLORECTAL CANCER IN THE IOWA WOMEN'S HEALTH STUDY

Abstract

Background: Colorectal cancer is the third most commonly diagnosed cancer in the United States among men and women combined. Chronic inflammation may be one mechanism by which diet influences colorectal cancer risk. Here we investigated associations of the food-based inflammation (FBI) score with incident colorectal cancer in a population-based study of postmenopausal Iowan women.

Methods: Participants in the Iowa Women's Health Study (IWHS) were enrolled in 1986 and completed questionnaires on diet (evaluated using a Willett food frequency questionnaire [FFQ]) and lifestyle to identify modifiable risk factors for cancer. We calculated the FBI score, containing 18 foods/food groups, in all eligible participants using data from the FFQ. Among 38,006 participants followed for 22 years, 1,604 incident colorectal cancer cases (including 1,371 colon and 233 rectal cases) were identified through linkage with the State Health Registry of Iowa. Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI).

Results: We observed no significant associations between higher FBI score and incident colorectal cancer risk ($HR_{continuous}$: 1.05; 95% CI: 0.96, 1.15 and $HR_{quintiles}$ for Q5 vs. Q1: 1.07; 95% CI: 0.90, 1.27; P_{trend}: 0.36) in multivariable-adjusted analyses. Results were not substantially different when examining colon and rectal cancer separately, excluding cases that occurred within the first two years of follow-up, and further adjusting for NSAID use.

Conclusions: A proinflammatory diet, as quantified by FBI score, was not associated with increased risk for colorectal cancer in the IWHS. Further investigation of the role of inflammation and use of the FBI score in more diverse prospective studies is warranted to clarify the relationship between diet-related inflammation and incident colorectal cancer.

Introduction

Colorectal cancer is the third most commonly diagnosed cancer worldwide; the lifetime risk for developing colorectal cancer is between 4-5% for both men and women (1). An estimated 95,000 new colon and 49,000 new rectal cancer cases were diagnosed in the United States in 2017, most frequently among individuals between 65–74 years of age (1, 2). In addition to age, other nonmodifiable risk factors include sex, race/ethnicity, and hereditary cancer syndromes (1). Potentially modifiable risk factors for colorectal cancer include smoking, physical inactivity, excess body weight, and diet (1, 3).

Many observational studies and randomized controlled trials have been conducted to identify dietary components that influence cancer risk. The World Cancer Research Fund's Continuous Update Project panel recently reviewed available evidence on the relationship between diet and colorectal cancer and concluded that consumption of processed meats is a convincing cause, consumption of red meats is a probable cause, and consumption of foods containing dietary fiber probably protect against colorectal cancer (3). Dietary patterns have also been linked to colorectal cancer risk: a "Western" pattern—characterized by high intake of processed and red meats, sugar-sweetened beverages, and refined grains—has been associated with increased colorectal cancer incidence while a "prudent" pattern—characterized by high intake of fruits, vegetables, and whole grains—has been inconsistently associated with decreased colorectal cancer incidence (4-8). Unfortunately, given the complex interactions between nutrients and other bioactive components found in food, the specific mechanisms through which diet influences colorectal cancer risk are unclear.

Chronic, systemic low-grade inflammation can promote carcinogenesis by inducing hyperproliferation and decreasing apoptosis in premalignant cells (9-11). This type of inflammation is also implicated in tumor promotion and progression, as pro-inflammatory cytokines produce free radicals and other intermediates that can further damage DNA and enhance angiogenesis (12, 13). Chronic inflammation is one mechanism by which diet could play a role in colorectal cancer development or prevention; for example, fruits and vegetables contain anti-inflammatory components which can help

maintain cell integrity and regulate cell cycle progression [14-16]. The dietary inflammatory index (DII) is a literature-derived proprietary tool designed to describe the inflammatory capacity of an individual's diet based on 45 dietary parameters (including vitamins, minerals, spices, and secondary metabolites of plants) weighted for their effects on systemic inflammation markers (17). Based on available dietary data, an individual's overall DII score can be calculated on a continuum from maximally anti-inflammatory to pro-inflammatory and used to examine how dietary inflammation may influence various health outcomes. A meta-analysis of nine studies (including four large prospective cohort studies) that have used the DII found evidence of an overall positive association between a pro-inflammatory diet and colorectal cancer risk (odds ratio [OR]: 1.40; 95% confidence interval [CI]: 1.26, 1.55) (18). While these results suggest a role for diet-related inflammation in the development of colorectal cancer, construction of the DII is primarily focused on specific nutrients/components in foods; thus, it may be difficult to translate a proinflammatory diet—as described by the DII—to nutritional practice. Another criticism of the DII is that some nutrients/components cannot be calculated from available food frequency questionnaire (FFQ) data (e.g., turmeric and saffron).

We recently developed a food-based inflammation (FBI) score, based on whole foods and food groups specified in the 2015 Dietary Guidelines for Americans, to quantify diet-related inflammation. In previous studies, an increasing FBI score was positively associated with a panel of systemic inflammation markers (**Chapter 2**) and risk of incident colorectal adenoma, the benign precursor to colorectal cancer (**Chapter 3**). In this study, we used the FBI score to investigate associations of baseline dietary inflammatory potential with incident colorectal cancer in the Iowa Women's Health Study (IWHS).

Methods

Study Population

Details of the IWHS have previously been published (19). Briefly, 41,836 postmenopausal women between 55-69 years old were randomly selected from a list of women with Iowa drivers' licenses

and enrolled in the study in 1986 to determine whether diet and other lifestyle factors were associated with cancer incidence. At baseline, participants completed questionnaires on demographics, medical history, and various diet and lifestyle factors. Data on dietary intake over the past year was collected using a 121-item food frequency questionnaire (FFQ, adapted from a 126-item Willett FFQ [20] and including questions on foods, beverages, and supplements), which was then used to calculate FBI scores for the participants. The institutional review board at the University of Minnesota approved the study, and all participants gave written informed consent.

Participants with self-reported history of cancer (except for non-melanoma skin cancer) were excluded from analyses; of the 41,836 women initially enrolled, 38,006 were cancer-free at baseline. Women who failed to respond to 10% or more of the FFQ or reported implausible total energy intakes estimated from the FFQs (<600 or ≥5,000 kilocalories daily) were excluded (n=3,096). We also excluded individuals who were missing potentially confounding covariate data, such as age, smoking history, family history of colorectal cancer, and use of hormone replacement therapy (n=2,633). Our final sample included 32,616 participants (our exclusion criteria were not mutually exclusive).

Outcome Assessment

The outcome of interest was incident colorectal cancer, ascertained via annual linkage with the Iowa Cancer Registry as part of the National Cancer Institute's Surveillance, Epidemiology, and End Results program. Incident cases were defined using WHO *International Classification of Diseases for Oncology* (ICD-O) codes 18.0–20.9. A total of 1,604 incident colorectal cancer cases, including 1,371 colon (838 proximal and 533 distal) and 233 rectal cases, were identified. Person-years of follow-up time were accumulated from baseline (date of completion of the 1986 questionnaire) until the date of the first of the following: incident colorectal cancer diagnosis, move from Iowa (if known), death, or administrative censoring on December 31, 2010. Less than 1% of participants emigrated annually from Iowa, resulting in almost complete follow-up of participants. Deaths were ascertained via linkage with the National Death Index of the National Center for Health Statistics; underlying causes of death as listed

on death certificates were used to ascertain colorectal cancer-specific mortality (ICD-O codes 153.0–154.1).

Food-Based Inflammation (FBI) Score

Details of the development and application of the FBI score were described in **Chapter 2**. In brief, the FBI score is an *a priori* approach that describes the inflammatory potential of an individual's diet using 18 food components (selected based on previous literature and biological plausibility): processed meat, red meat, white meat, fish, shellfish, nuts, coffee, tea, dairy products, refined and whole grains, beta-carotene-containing foods, lycopene-containing foods, green/leafy vegetables, Brassicaceae (e.g., broccoli, Brussels sprouts), Leguminosae (e.g., beans, peas), Rosaceae (e.g., apples, strawberries), and Rutaceae (citrus fruits). Each of the food components were given weights based on multivariable-adjusted associations with a panel of four inflammation biomarkers: C-reactive protein and interleukin-6, -8, and -10. Using baseline FFQ data, we derived intake (servings per week) of the 18 food components, multiplied the components by their respective weights, and then summed the weighted components to create an overall FBI score for each participant. The overall FBI scores were then categorized into quintiles with lower/smaller scores representing anti-inflammatory diets and higher scores representing pro-inflammatory diets.

Statistical Analyses

We described selected demographic, medical, and dietary characteristics among FBI score quintiles using means and standard deviations (SD) for continuous variables and percentages for categorical variables. Cox proportional hazard models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for the incidence of colorectal cancer by FBI score in both age-adjusted and multivariable-adjusted models. The FBI score was analyzed as both a continuous variable and by quintiles. Median values of each FBI score quintile were used for conducting linear trend tests, also adjusted for multiple covariates. The proportional hazards assumption was tested by adding an

interaction term between FBI score and follow-up time to the model; there was no evidence that this assumption was violated.

We considered the following potential confounding variables based on previous literature and biological plausibility: age (years; continuous), use of HRT (yes/no), education (high school graduate or less, some college, college graduate), family history of colorectal cancer in a first-degree relative (yes/no), total energy intake (kilocalories/day; continuous), physical activity level (sedentary, moderately active, active), alcohol intake category (none, moderate: ≤1 drink [14 grams/day] per day, or heavy: >1 drink per day), body mass index (BMI) [weight (kg)/height (m^2)] categorized as normal: <25, overweight: <30, or obese: ≥30), pack-years of smoking (0, 1-19, 20-39, 40+), regular dietary supplement use (≥1 time per week; yes/no), and history of type-2 diabetes (yes/no). The final adjusted model included the following covariates based on findings previously reported in the literature with this cohort, biological plausibility, and statistical significance: age, HRT use, total energy intake, BMI category, pack-years of smoking, and history of type-2 diabetes. Potential effect modification was assessed in the multivariable-adjusted models by including interaction terms between the FBI score and the following covariates: age, HRT use, BMI, pack-years of smoking, and history of type-2 diabetes.

We conducted a sensitivity analysis excluding colorectal cancer cases diagnosed within the first two years of follow-up (n=100) to account for potential protopathic bias. As history of aspirin and NSAID use was not included in baseline questionnaires, we conducted another sensitivity analysis that included only participants who responded to a 1992 follow-up questionnaire (n=26,025) to test whether NSAID use influences associations between the FBI score and colorectal cancer risk. All colorectal cancer cases diagnosed before completion of the 1992 questionnaire were excluded from this analysis. Person-years of follow-up time were accumulated from date of completion of the 1992 questionnaire until date of incident colorectal cancer diagnosis, emigration from Iowa, death, or administrative censoring. We redefined FBI score quintiles based on the distribution of scores of participants in this sensitivity analysis, and adjusted for NSAID use (never, <1 per week, 1 per week, 2-5 times per week, and 6+ times

per week) in addition to the covariates previously described. To assess potential effect modification, we included NSAID use as an interaction term in the multivariable-adjusted models. All analyses were conducted using SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, North Carolina). Results of all statistical tests were considered significant at $p \leq 0.05$.

Results

The average FBI score was -1.08 (SD: 0.65), ranging from -10.4 to 1.34. Baseline characteristics of participants across quintiles of FBI score are presented in Table 1. Compared to participants in the lowest (most anti-inflammatory) quintile, participants in the highest quintile were less likely to meet physical activity requirements and to have completed more than high school. Participants in the highest quintile were also more likely to currently smoke and report eating more weekly servings of processed meat. In general, decreasing trends were observed across quintiles of FBI score for consumption of FBI score components and overall energy intake. Restricting analyses to individuals who responded to the 1992 survey on medication history, all FBI score quintiles reported similar frequency of NSAID use.

Participants were followed for an average of 13.0 (SD: 7.04) years, during which 1,604 incident colorectal cancer cases—including 1,371 colon and 233 rectal cases—were identified. Table 2 illustrates the age- and multivariable-adjusted associations of the FBI score with colorectal cancer risk. In the age-adjusted analysis, when the FBI score was treated as a continuous variable, overall colorectal cancer incidence was estimated to be higher by 7% per one-point increase in FBI score (HR: 1.07; 95% CI: 0.99, 1.16). However, this association was slightly attenuated after additional adjustment for HRT use, BMI category, pack-years of smoking, total energy intake, and history of type-2 diabetes (HR: 1.05; 95% CI: 0.96, 1.15). In the multivariable-adjusted analyses involving specific anatomic subsites, the effect size was similar for incident colon (HR: 1.06; 95% CI: 0.96, 1.17) and incident rectal cancers (HR: 0.99; 95% CI: 0.78, 1.24). Results were not materially different for the sensitivity analysis excluding participants

diagnosed with colorectal cancer within the first two years of follow-up (Appendix C, Supplemental Table 1).

When the FBI score was treated as a categorical variable, the multivariable-adjusted HR of incident colorectal cancer among participants in the highest (most pro-inflammatory) quintile was 1.07 (95% CI: 0.90, 1.27; P_{trend}: 0.36) compared to the lowest quintile. No statistically significant associations were observed for incident colon (HR: 1.09; 95% CI: 0.90, 1.31; P_{trend}: 0.38) or rectal (HR: 0.92; 95% CI: 0.58, 1.47; P_{trend}: 0.83) cancers in multivariable-adjusted analyses comparing the highest to lowest quintiles of FBI score (Table 2). No clear pattern of effect modification was observed and none of the interaction terms between FBI score and risk factors of interest were statistically significant (data not shown). As described in Table 3, the FBI score was not significantly associated with either proximal (n=838) or distal (n=533) colon cancer risk; however, we did observe a stronger effect among participants with incident distal colon cancer when comparing highest to lowest FBI score quintiles in the multivariable-adjusted analyses (distal colon cancer HR: 1.19; 95% CI: 0.88, 1.62; P_{trend}: 0.65; proximal colon cancer HR: 1.01; 95% CI: 0.80, 1.28; P_{trend}: 0.51).

Upon restricting our analysis to participants who responded to the 1992 follow-up questionnaire on NSAID use, we identified 1,257 incident colorectal (1,072 colon and 182 rectal) cancer cases. As illustrated in Supplemental Table 2, results from this sensitivity analysis were not materially different from our main analyses. After adjustment for NSAID use and other covariates, the HR for colorectal cancer incidence was 1.05 (95% CI: 0.95, 1.16) when the FBI score was treated as a continuous variable and 1.03 (95% CI: 0.85, 1.25; P_{trend}: 0.49) when comparing the highest to lowest FBI score quintiles. We observed no effect modification by NSAID use ($P_{interaction}$: 0.60).

Discussion

We observed no substantial associations between a pro-inflammatory diet—as quantified by FBI score—and colorectal cancer incidence (overall or by specific anatomical site) in this population-based cohort of postmenopausal women. Results from sensitivity analyses suggest that exclusion of cases that occurred within the first two years of follow-up and further adjustment for NSAID use would not affect these results.

Our results differ from a 2014 study by Shivappa et al. in this population in which a pro-inflammatory diet, as measured by higher scores on the DII, was positively associated with incident colorectal cancer (HR for highest vs. reference DII quintile: 1.20; 95% CI: 1.01-1.43) (21). Differences in the development and construction of the DII and FBI scores may account for these contrasting results. Components of the DII were selected for their functional properties and weighted based on a review of literature-derived effects on inflammation markers. Components of our FBI score were selected based on foods and food groups described in the 2015 Dietary Guidelines for Americans, including legumes, dairy products, and leafy green vegetables (22). These components were then weighted based on associations with a panel of inflammation markers in the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort (**Chapter 2**). Previous studies that have utilized IWHS data to examine associations between diet and colorectal cancer risk could also explain the differential results between the two dietary inflammation scores in this cohort. Several DII components, such as vitamin E (23), magnesium (24), and calcium and vitamin D (25) were inversely associated with colorectal cancer risk in the IWHS. Conversely, no statistically significant associations between 15 groupings of fruits and vegetables—including seven groups that comprise part of our FBI score—and incident colorectal cancer were observed (26). While the food groups comprising the FBI score contain some DII components, the DII ultimately contains more dietary parameters independently associated with colorectal cancer risk in this population. Nevertheless, results from the Shivappa et al. study point to the importance of obtaining nutrients from whole foods (rather than individual supplements): a DII calculated solely from food

sources yielded a stronger association with incident colorectal cancer (HR for highest vs. reference DII quintile: 1.16; 95% CI: 0.95-1.42) than a DII based only on supplement intake (HR for highest vs. reference DII quartile: 0.91; 95% CI: 0.79-1.04) (21).

Sex-specific differences in biological responses to diet may partially explain the lack of association observed between FBI score and colorectal cancer risk in this population. In general, colorectal cancer incidence is estimated to be 30% higher for males than females (1); however, females are more likely to be diagnosed with proximal (versus distal) colon cancers than men (27, 28). Hypothesized reasons for these disparities include interactions between the differing etiologies of colon cancer by subsite (29-31), the complex effects of sex hormones (32, 33), and differences in exposure to various risk factors such as smoking, central adiposity, and diet (1, 34, 35). Proximal colon tumors more often exhibit microsatellite instability, whereas distal colon tumors exhibit mutations in tumor suppressor genes and other types of chromosomal instability (29, 30, 36). Several studies have reported differing associations of dietary factors with incident colorectal cancer based on tumor location, perhaps due to these underlying molecular mechanisms. For example, a review of cohort studies found that high intake of red and processed meats was more strongly associated with distal colon cancer risk (37). A study using the Multiethnic Cohort observed that dietary fiber intake was inversely associated with distal colon (relative risk [RR]: 0.56; 95% CI: 0.35-0.90) and rectal (RR: 0.52; 95% CI: 0.32-0.84) cancer risk among males (38). Our results are generally consistent with other prospective studies that have described associations of dietary patterns with colorectal cancer risk in females. Weaker associations have been observed between the DII (39), Mediterranean diet (40-42), and Alternate Healthy Eating Index (42, 43) and incident colorectal cancer among females compared to males. Although there was no evidence of effect modification by sex in previous studies that have applied the FBI score (**Chapters 2** and **3**), associations of the FBI score with systemic inflammation markers and incident adenoma were stronger among males. Ultimately, sex-specific dietary patterns (or weights for FBI score components) may be more useful for informing associations between diet and disease.

Characteristics of the IWHS population may have limited our conclusions and generalizeability, as these participants were mostly white, postmenopausal women from the same state. As mentioned previously, the FBI score was developed in the REGARDS cohort, a racially-, geographically-, and socioeconomically-diverse sample of men and women recruited between 2003–2007 using a Block FFQ. Here, we applied the FBI score to baseline FFQ data from 1986. It is conceivable that our results could have been affected by changing consumption patterns (e.g., changes in cooking methods, increased intake of foods containing high-fructose corn syrup, etc.) and food sources/supply (e.g., changes in nutrient content due to changes in plant breeding or processing) between 1986 and the mid-2000s (44), when REGARDS participants completed their FFQs. As our FBI score may reflect more recent dietary trends, it may not be completely appropriate for application and assessment of associations within this group. Additionally, we measured the inflammatory potential of diet based on FFQ data from a single timepoint in this study; since chronic exposure to an unhealthy diet may be more strongly associated with incident colorectal cancer (45, 46), long-term dietary history may be better predictive of disease risk. We also did not have data on colorectal cancer screening history, although regular screenings for individuals at average risk were not recommended until the mid-1990s (47, 48).

Strengths of this prospective study include its extensive follow-up time, large sample size, and comprehensive case ascertainment as well as the ability to classify colorectal cancer cases by anatomical site. The use of our FBI score to describe the inflammatory potential of overall diet is another strength, as it accounts for the intricate effects and synergy of bioactive components in food and can be easily constructed in populations with FFQ data. However, while estimated intakes from FFQs are considered representative of usual consumption, they are prone to recall bias, have limited food lists, and lack complete information on portion size, mixed dishes, and food preparation methods (49). As a result, the use of semi-quantitative FFQ data allows for potential exposure misclassification and is a limitation in many observational studies of diet and disease.

We did not observe any association between a proinflammatory diet, as indicated by high FBI scores, and colorectal cancer risk in the IWHS. Nonetheless, application and use of the FBI score in future studies with more diverse populations is warranted to further examine the relationship between diet-related inflammation and incident colorectal cancer, as well as other chronic disease outcomes.

Table 1. IWHS participant characteristics across quintiles of FBI score

Variable[1]	**Quintile 1 ≤ -1.47 *n*=6,544**	**Quintile 2 -1.46 to -1.09 *n*=6,587**	**Quintile 3 -1.08 to -0.83 *n*=6,421**	**Quintile 4 -0.82 to -0.59 *n*=6,459**	**Quintile 5 ≥ -0.58 *n*=6,605**
Demographics and Medical					
Age (years)	61.6 (4.21)	61.5 (4.21)	61.4 (4.21)	61.4 (4.19)	61.3 (4.19)
Hormone replacement therapy use (yes), %	39	40	38	39	38
Body mass index categories (kg/m^2), %					
Normal weight (18.6–24.9)	38	39	38	39	37
Overweight (25.0–29.9)	38	37	37	38	37
Obese (≥ 30)	23	23	23	23	24
Education, %					
Less than high school	15	15	17	18	21
High school graduate	47	50	52	55	58
More than high school	38	35	31	27	21
Regular NSAID use (1+/week, 1992 survey, ever), %	39	40	40	40	39
Dietary supplement use (yes), %	37	35	33	32	31
Physical activity (sedentary), %	34	42	47	51	60
Smoking status, %					
Never	69	68	65	65	64
Former	20	19	20	19	18
Current	11	13	15	16	18
Alcohol (non-drinkers), %	53	53	53	55	58
Diabetes at baseline (yes), %	6.6	5.8	6.1	5.8	4.9
Total energy intake (kilocalories/day)	2,230 (670)	1,910 (549)	1,770 (518)	1,650 (503)	1,510 (517)
Components of FBI Score					
Processed meats (servings/week)	1.78 (2.28)	1.72 (2.03)	1.80 (2.02)	1.89 (2.12)	2.53 (3.33)
Red meat (servings/week)	6.60 (4.49)	6.12 (3.83)	5.85 (3.73)	5.64 (3.70)	5.49 (4.00)
White meat (servings/week)	5.65 (4.70)	4.11 (2.88)	3.39 (2.35)	2.76 (1.91)	2.06 (1.61)
Fish (servings/week)	2.46 (2.60)	1.79 (2.07)	1.51 (1.63)	1.23 (1.28)	0.94 (1.19)

Table 1, continued

Variable[1]	**Quintile 1 ≤ -1.47 *n*=6,544**	**Quintile 2 -1.46 to -1.09 *n*=6,587**	**Quintile 3 -1.08 to -0.83 *n*=6,421**	**Quintile 4 -0.82 to -0.59 *n*=6,459**	**Quintile 5 ≥ -0.58 *n*=6,605**
Shellfish (servings/week)	0.19 (0.64)	0.15 (0.40)	0.12 (0.28)	0.10 (0.24)	0.07 (0.22)
Nuts (servings/week)	4.24 (5.88)	2.80 (3.17)	2.29 (2.64)	1.74 (1.95)	1.17 (1.49)
Coffee (servings/week)	12.9 (13.7)	13.0 (13.7)	12.6 (13.4)	12.1 (13.3)	8.70 (11.6)
Tea (servings/week)	3.42 (6.48)	3.05 (6.07)	2.88 (5.82)	2.92 (6.13)	2.96 (6.56)
Total dairy (servings/week)	22.8 (14.5)	19.9 (12.5)	18.0 (11.4)	16.1 (10.3)	12.7 (8.98)
Refined grains (servings/week)	17.6 (14.1)	17.2 (13.4)	16.7 (13.2)	16.8 (12.9)	16.9 (13.7)
Whole grains (servings/week)	10.5 (8.59)	9.01 (7.84)	7.92 (7.39)	7.45 (7.40)	7.41 (8.33)
Beta-carotene foods[2] (servings/week)	6.65 (5.49)	3.60 (1.80)	2.54 (1.37)	1.74 (1.02)	1.06 (0.74)
Green/leafy vegetables[3] (servings/week)	8.65 (6.86)	5.65 (3.42)	4.50 (2.69)	3.59 (2.37)	2.46 (1.90)
Brassicaceae[4] (servings/week)	6.74 (5.57)	4.26 (3.11)	3.27 (2.42)	2.42 (1.73)	1.66 (1.33)
Leguminosae[5] (servings/week)	5.86 (4.00)	3.81 (1.88)	2.97 (1.50)	2.32 (1.21)	1.64 (0.94)
Rosaceae[6] (servings/week)	10.7 (8.21)	7.11 (4.52)	5.66 (3.64)	4.51 (3.03)	2.90 (2.36)
Rutaceae[7] (servings/week)	8.89 (6.87)	7.48 (5.56)	6.77 (5.22)	6.27 (5.05)	5.26 (5.00)
Lycopene foods[8] (servings/week)	5.20 (5.55)	3.75 (3.88)	3.21 (3.29)	2.80 (2.99)	2.40 (4.05)
FBI Score[9]	-2.07 (0.74)	-1.30 (0.11)	-1.00 (0.07)	-0.75 (0.07)	-0.42 (0.16)

Abbreviations: IWHS, Iowa Women's Health Study; FBI, food-based inflammation; NSAID, non-steroidal anti-inflammatory drug

1. Values for variables are mean (standard deviation), except where indicated.
2. Beta-carotene foods include carrots, sweet potatoes, orange/yellow squash, and pumpkins.
3. Green/leafy vegetables include collards, mustard/turnip greens, romaine lettuce, and spinach.
4. Brassicaceae include broccoli, Brussels sprouts, cabbage, and cauliflower.
5. Leguminosae include black, kidney, lima, snap and broad beans, peas, and lentils.
6. Rosaceae include apples, apricots, peaches, pears, and strawberries.
7. Rutaceae include grapefruits, oranges, and tangerines.
8. Lycopene foods include tomatoes, salsa, and tomato paste, sauce, and juice.
9. The FBI score was created using multivariable-adjusted linear regression of the associations of the dietary components with a summary inflammation biomarker z-score. The beta coefficients of the regressions were used as weights for contributions of the dietary components to an overall FBI score. The FBI score was ultimately calculated as the sum of the weighted dietary component intakes of each participant.

Table 2. Food-based inflammation (FBI) score and colorectal cancer risk; IWHS, 1986-2010

	Colorectal Cancer Incidence			Colon Cancer Incidence			Rectal Cancer Incidence		
FBI score variable	***n* cases**	***Age-adjusted HR (95% CI)***	***Multivariable-Adjusted HR[1] (95% CI)***	***n* cases**	***Age-adjusted HR (95% CI)***	***Multivariable-Adjusted HR[1] (95% CI)***	***n* cases**	***Age-adjusted HR (95% CI)***	***Multivariable-Adjusted HR[1] (95% CI)***
Continuous	*1,604*	1.07 (0.99, 1.16)	1.05 (0.96, 1.15)	*1,371*	1.07 (0.98, 1.17)	1.06 (0.96, 1.17)	*233*	1.08 (0.88, 1.32)	0.99 (0.78, 1.24)
Quartiles									
1	*291*	1.00	1.00	*247*	1.00	1.00	*42*	1.00	1.00
2	*271*	1.07 (0.91, 1.27)	1.05 (0.88, 1.25)	*236*	1.10 (0.92, 1.32)	1.10 (0.91, 1.32)	*35*	0.96 (0.61, 1.50)	0.83 (0.51, 1.37)
3	*298*	1.08 (0.92, 1.27)	1.05 (0.89, 1.25)	*260*	1.04 (0.88, 1.24)	1.03 (0.86, 1.24)	*37*	1.57 (1.00, 2.47)	1.31 (0.79, 2.15)
4	*380*	1.15 (0.99, 1.34)	1.11 (0.94, 1.31)	*319*	1.14 (0.96, 1.35)	1.12 (0.94, 1.34)	*58*	1.32 (0.88, 1.97)	1.17 (0.75, 1.82)
5	*364*	1.10 (0.94, 1.28)	1.07 (0.90, 1.27)	*309*	1.10 (0.93, 1.31)	1.09 (0.90, 1.31)	*53*	1.09 (0.73, 1.65)	0.92 (0.58, 1.47)
P-trend[2]	0.36			0.38			0.83		

Abbreviations: IWHS, Iowa Women's Health Study; HR, hazard ratio; CI, confidence interval.

1. Adjusted for age, hormone replacement therapy use, body mass index category, total energy intake, pack-years of smoking, and history of type-2 diabetes.
2. *P*-trend calculated by assigning the median of each FBI score quintile to each quintile, and treating this quintile exposure as continuous. *P*-trend significant at $p \leq 0.05$.

Table 3. Food-based inflammation (FBI) score and colon cancer risk; IWHS, 1986-2010

	Proximal Colon Cancer Incidence			Distal Colon Cancer Incidence		
FBI score variable	***n* cases**	***Age-adjusted HR (95% CI)***	***Multivariable-Adjusted HR[1] (95% CI)***	***n* cases**	***Age-adjusted HR (95% CI)***	***Multivariable-Adjusted HR[1] (95% CI)***
Continuous	*838*	1.07 (0.96, 1.19)	1.06 (0.94, 1.20)	*533*	1.07 (0.92, 1.25)	1.04 (0.87, 1.25)
Quartiles						
1	*155*	1.00	1.00	*92*	1.00	1.00
2	*152*	1.05 (0.83, 1.31)	1.03 (0.81, 1.30)	*84*	1.19 (0.88, 1.61)	1.19 (0.87, 1.63)
3	*150*	1.03 (0.82, 1.29)	1.01 (0.80, 1.28)	*110*	1.04 (0.79, 1.38)	1.03 (0.76, 1.38)
4	*193*	1.13 (0.91, 1.40)	1.11 (0.88, 1.40)	*126*	1.12 (0.85, 1.46)	1.08 (0.81, 1.46)
5	*188*	1.04 (0.84, 1.28)	1.01 (0.80, 1.28)	*121*	1.22 (0.93, 1.60)	1.19 (0.88, 1.62)
P-trend[2]	0.65			0.51		

Abbreviations: IWHS, Iowa Women's Health Study; HR, hazard ratio; CI, confidence interval.

1. Adjusted for age, hormone replacement therapy use, body mass index category, total energy intake, pack-years of smoking, and history of type-2 diabetes.
2. *P*-trend calculated by assigning the median of each FBI score quintile to each quintile, and treating this quintile exposure as continuous. *P*-trend significant at $p \leq 0.05$.

Appendix C

Supplemental Table 1. Food-based inflammation (FBI) score and colorectal cancer risk, excluding cases diagnosed within the first two years of follow-up; IWHS, 1986-2010

	Colorectal Cancer Incidence			Colon Cancer Incidence			Rectal Cancer Incidence		
FBI score variable	***n* cases**	***Age-adjusted HR (95% CI)***	***Multivariable-Adjusted HR[1] (95% CI)***	***n* cases**	***Age-adjusted HR (95% CI)***	***Multivariable-Adjusted HR[1] (95% CI)***	***n* cases**	***Age-adjusted HR (95% CI)***	***Multivariable-Adjusted HR[1] (95% CI)***
Continuous	*1,504*	1.06 (0.98, 1.15)	1.04 (0.95, 1.14)	*1,291*	1.06 (0.97, 1.16)	1.05 (0.95, 1.16)	*213*	1.06 (0.86, 1.30)	0.97 (0.77, 1.23)
Quartiles									
1	*297*	1.00	1.00	*252*	1.00	1.00	*45*	1.00	1.00
2	*263*	1.02 (0.87, 1.21)	1.00 (0.84, 1.19)	*228*	1.03 (0.86, 1.24)	1.02 (0.85, 1.23)	*35*	1.02 (0.65, 1.60)	0.89 (0.55, 1.44)
3	*320*	1.05 (0.90, 1.23)	1.04 (0.88, 1.22)	*282*	1.03 (0.87, 1.23)	1.03 (0.86, 1.23)	*38*	1.42 (0.91, 2.20)	1.22 (0.76, 1.97)
4	*323*	1.13 (0.96, 1.32)	1.09 (0.92, 1.29)	*272*	1.10 (0.92, 1.30)	1.07 (0.89, 1.29)	*51*	1.46 (0.97, 2.19)	1.32 (0.85, 2.05)
5	*301*	1.06 (0.90, 1.25)	1.03 (0.86, 1.23)	*257*	1.08 (0.90, 1.28)	1.06 (0.87, 1.28)	*44*	0.98 (0.64, 1.49)	0.83 (0.52, 1.33)
P-trend[2]	0.49			0.48			0.95		

Abbreviations: IWHS, Iowa Women's Health Study; HR, hazard ratio; CI, confidence interval.

1. Adjusted for age, hormone replacement therapy use, body mass index category, total energy intake, pack-years of smoking, and history of type-2 diabetes.
2. *P*-trend calculated by assigning the median of each FBI score quintile to each quintile, and treating this quintile exposure as continuous. *P*-trend significant at $p \leq 0.05$.

Supplemental Table 2. Food-based inflammation (FBI) score and colorectal cancer risk among NSAID use respondents; IWHS, 1986-2010

	Colorectal Cancer Incidence			Colon Cancer Incidence			Rectal Cancer Incidence		
FBI score variable	***n* cases**	***Age-adjusted HR (95% CI)***	***Multivariable-Adjusted HR[1] (95% CI)***	***n* cases**	***Age-adjusted HR (95% CI)***	***Multivariable-Adjusted HR[1] (95% CI)***	***n* cases**	***Age-adjusted HR (95% CI)***	***Multivariable-Adjusted HR[1] (95% CI)***
Continuous	*1,257*	1.06 (0.97, 1.16)	1.05 (0.95, 1.16)	*1,075*	1.06 (0.96, 1.17)	1.08 (0.96, 1.20)	*182*	1.03 (0.83, 1.29)	0.92 (0.71, 1.19)
Quartiles									
1	*255*	1.00	1.00	*212*	1.00	1.00	*43*	1.00	1.00
2	*213*	0.99 (0.83, 1.20)	0.98 (0.81, 1.18)	*188*	1.00 (0.82, 1.22)	1.00 (0.82, 1.23)	*25*	1.00 (0.61, 1.66)	0.89 (0.52, 1.52)
3	*273*	1.10 (0.93, 1.31)	1.09 (0.91, 1.30)	*238*	1.09 (0.91, 1.31)	1.10 (0.90, 1.34)	*35*	1.27 (0.79, 2.04)	1.07 (0.64, 1.79)
4	*259*	1.09 (0.92, 1.30)	1.07 (0.89, 1.29)	*216*	1.06 (0.87, 1.28)	1.06 (0.86, 1.30)	*43*	1.51 (0.97, 2.34)	1.32 (0.82, 2.14)
5	*257*	1.05 (0.88, 1.24)	1.03 (0.85, 1.25)	*221*	1.06 (0.88, 1.28)	1.07 (0.86, 1.32)	*36*	0.97 (0.61, 1.53)	0.81 (0.48, 1.35)
P-trend[2]	0.49			0.44			0.92		

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; IWHS, Iowa Women's Health Study; HR, hazard ratio; CI, confidence interval.

1. Adjusted for age, hormone replacement therapy use, body mass index category, total energy intake, pack-years of smoking, history of type-2 diabetes, and NSAID use.
2. *P*-trend calculated by assigning the median of each FBI score quintile to each quintile, and treating this quintile exposure as continuous. *P*-trend significant at $p \leq 0.05$.

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CHAPTER 5. DISCUSSION AND FUTURE DIRECTIONS

Summary and Public Health Implications

The goals of this dissertation were to develop weights for and create an *a priori* food-based inflammation (FBI) score to investigate associations of the score with systemic biomarkers of inflammation and risk for colorectal neoplasms.

In the first aim, 18 foods/food groups were selected to comprise the FBI score. Several of these food groups were selected based on specific recommendations in the *2015 Dietary Guidelines for Americans*, including whole grains, dairy products, seafood, legumes, and nuts (1). Biomarker and food frequency questionnaire data from the REasons for Geographic and Racial Differences in Stroke prospective cohort study were then used to create weights for each of the food components of the FBI score. An overall FBI score was calculated by summing the weighted dietary intakes of the 18 food groups.

The FBI score was then calculated in and applied to two previously-conducted studies with available biomarker data to analyze associations of the score with systemic inflammation. To account for multiple inflammatory processes, a panel of inflammation biomarkers (consisting of C-reactive protein [CRP] and interleukins [IL]-6, -8, and -10) was used to create a summary biomarker z-score in the Calcium and Colorectal Epithelial Cell Proliferation trial (CCECP). The FBI score was not associated with the inflammation biomarker z-score in CCECP, perhaps due to sample size limitations. However, a proinflammatory diet, as indicated by higher FBI score, was significantly associated with higher circulating CRP (the only inflammation biomarker measured) in the pooled Markers for Adenomatous Polyps studies. When comparing the FBI score to a previously-published whole foods-based inflammation score, we observed stronger associations between our FBI score and inflammation biomarkers.

In the second aim, we calculated the FBI score in an endoscopy-based case-control study and examined associations of the score with risk for incident, sporadic colorectal adenoma. We observed a significant positive association between increasing FBI score (indicating a proinflammatory diet) and adenoma risk when comparing cases to endoscopy-negative controls. These results are consistent with findings from other studies that have found inverse associations between various "healthy" diets and adenoma risk (2-5), and suggest that dietary mechanisms related to inflammation may be important for adenoma risk.

In the third aim we calculated the FBI score in the Iowa Women's Health Study (IWHS), a large prospective cohort study of postmenopausal women, and observed no association between increasing FBI score and colorectal cancer risk, overall or by anatomic subsite. Our finding of a null association between proinflammatory dietary pattern and incident colorectal cancer risk is consistent with previous studies that have observed weaker associations between whole foods (including dairy products and red and processed meats) and risk of colorectal neoplasia in this population (6-8).

Overall, the results from this dissertation suggest that the FBI score may be a useful tool for quantifying the inflammatory potential of diet. While many dietary patterns aggregate consumption of fruits and vegetables into one or two broad categories, the FBI score is innovative in that it contains seven such categories to better account for specific fruit and vegetable consumption between study populations. Our results also add to the existing literature on diet as a modifiable risk factor for colorectal cancer. Though many studies have posited inflammation as an underlying mechanism by which diet affects risk for colorectal neoplasia, few studies have attempted to characterize the inflammatory potential of diet as it pertains to adenoma risk (9-11). We did not observe a significant association between a proinflammatory diet and colorectal cancer in the IWHS. To date, we have not had the opportunity to study the association between a proinflammatory diet and colorectal cancer risk among men or ethnically-diverse populations.

Future Directions

One of the major strengths in the creation of the FBI score is our utilization of the REGARDS study, a racially-, geographically-, and socioeconomically-diverse population, to develop weights for our FBI score (12). Weights for each food component of the FBI score were developed vis à vis associations with a panel of four inflammation biomarkers: CRP, IL-6, IL-8, and IL-10. However, a panel that includes more biomarkers—such as TNFα, IL-1β, or soluble cell adhesion molecules—may better account for the complexity of diet-related inflammation and immune responses. Though we applied the FBI score in two independent studies to assess its construct validity, we observed a significant association between the score and inflammation in only one of the studies. To further validate the weights obtained from REGARDS for the FBI score, we could create and apply FBI score to larger studies with data available on multiple inflammation biomarkers. Additionally, the external validity of the FBI score weights derived in REGARDS may be limited, as study participants were white or African American adults ≥45 years of age (12). Deriving FBI score weights using data from a nationally-representative sample, such as participants in the National Health and Nutrition Examination Survey, may make the FBI score more generalizable for studies involving younger or multiethnic individuals, for example.

While we observed a significant positive association between increasing FBI score and risk for colorectal adenoma, we did not observe such an association when the FBI score was applied in the IWHS to predict colorectal cancer risk. Because characteristics of the IWHS population (white, postmenopausal women from the same state) may have limited our conclusions and generalizeability (13), application of the FBI score to other cohorts with incident colorectal cancer data would help to clarify what role, if any, diet-related inflammation has in influencing colorectal cancer risk. I would also like to utilize the FBI score to assess how changes in diet quality over time (e.g., replacing low-nutrient/energy-dense foods with nutrient-dense foods) may influence circulating biomarker levels or colorectal cancer risk, as history of dietary exposures may be better predictive of these endpoints than dietary data collected at one time point.

While our data do not identify an optimal diet for colorectal cancer prevention, the findings reported in this dissertation support the *2015 Dietary Guidelines for Americans* recommendations to meet nutrient needs through healthy eating patterns that include consumption of fruits and vegetables from various subgroups, dairy products, and a variety of protein foods (e.g., nuts, legumes) in nutrient-dense forms (1). Our results suggest that inflammation may be an underlying mechanism through which diet may act to modulate the development of colorectal neoplasms. Further examination is warranted to clarify the role of diet-related inflammation in the development of colorectal neoplasms and other chronic diseases. Ultimately, the FBI score could be used to investigate associations of diet-related inflammation with various health outcomes.

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