American Journal of Epidemiology

Vol. 186, No. 5
DOI: 10.1093/aje/kwx115
Advance Access publication:
July 28, 2017

Original Contribution

Changes in the Inflammatory Potential of Diet Over Time and Risk of Colorectal Cancer in Postmenopausal Women

Fred K. Tabung, Susan E. Steck*, Yunsheng Ma, Angela D. Liese, Jiajia Zhang, Dorothy S. Lane, Gloria Y. F. Ho, Lifang Hou, Linda Snetselaar, Judith K. Ockene, and James R. Hebert

* Correspondence to Dr. Susan E. Steck, 915 Greene Street, Discovery I Building, Room 454, Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC 29208 (e-mail: ssteck@sc.edu).

Initially submitted January 29, 2016; accepted for publication October 25, 2016.

We examined the associations between changes in dietary inflammatory potential and risk of colorectal cancer (CRC) in 87,042 postmenopausal women recruited from 1993–1998 by the Women's Health Initiative, conducted in the United States. Food frequency questionnaire data were used to compute patterns of change in dietary inflammatory index (DII) scores and cumulative average DII scores over 3 years. Cox regression models were used to estimate hazard ratios for CRC risk. After a median of 16.2 years of follow-up, 1,038 CRC cases were diagnosed. DII changes were not substantially associated with overall CRC, but proximal colon cancer risk was higher in the proinflammatory-change DII group than in the antiinflammatory-stable DII group (hazard ratio = 1.32, 95% confidence interval: 1.01, 1.74). Among nonusers of nonsteroidal antiinflammatory drugs (NSAIDs) ($P_{interaction} = 0.055$), the proinflammatory-stable DII group was at increased risk of overall CRC and proximal colon cancer. Also among nonusers of NSAIDs, risks of overall CRC, colon cancer, and proximal colon cancer were higher in the highest quintile compared with the lowest cumulative average DII quintile (65%, 61%, and 91% higher risk, respectively). Dietary changes toward, or a history of, proinflammatory diets are associated with an elevated risk of colon cancer, particularly for proximal colon cancer and among nonusers of NSAIDs.

colorectal cancer; dietary patterns; inflammation; Women's Health Initiative

Abbreviations: CI, confidence interval; CRC, colorectal cancer; DII, dietary inflammatory index; FFQ, food frequency questionnaire; HR, hazard ratio; NSAID, nonsteroidal antiinflammatory drug; PA, physical activity; WHI, Women's Health Initiative; WHI-DM, Women's Health Initiative Dietary Modification Trial; WHI-OS, Women's Health Initiative observational study.

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in American women after lung and breast cancers (1). The etiology of CRC involves a complex interaction of cellular and molecular processes with environmental factors (including dietary factors). Diet may thus be a crucial modifiable factor affecting CRC development. Dietary patterns simultaneously take into account many aspects of diet and provide a more comprehensive assessment of exposure than would individual foods or nutrients. Dietary patterns may therefore be more predictive of disease processes and outcomes than the evaluation of single nutrients or foods, given that nutrients and foods are consumed in combination (2–4). Most dietary patterns derived through data-driven approaches or indices created from dietary recommendations (e.g., Healthy Eating Index), research findings (e.g., Dietary Approaches to Stop Hypertension), or culinary/foodway traditions (e.g., Mediterranean diet) have been shown to be associated with CRC risk (5–9), and these findings often vary by anatomic subsite of CRC. Modifying or improving dietary behaviors may represent an important public health strategy for CRC prevention. While the Women's Health Initiative (WHI) reported no effect of a low-fat dietary-pattern intervention on CRC (10–12), analyses of the WHI Observational Study (WHI-OS) reported significantly lower CRC risk among individuals adhering to the American Cancer Society's nutrition and physical activity (PA) guidelines (13).

Given the role of chronic inflammation in carcinogenesis (14, 15), dietary patterns associated with inflammation may

influence CRC risk. Indeed, we previously reported that a more proinflammatory diet, as measured by the dietary inflammatory index (DII) (16–19), calculated using data from a single baseline food frequency questionnaire (FFQ), was associated with higher risk of CRC after an average 11.3 years of follow-up in the WHI (20). In addition, intake of unhealthy diets may influence CRC risk when consumed over long periods of time (21). In a previous study using data from the WHI-OS and Women's Health Initiative Dietary Modification Trial (WHI-DM), we found modest decreases in DII scores over time (22). Therefore, changes in dietary behavior or the cumulative history of diet over time may be more predictive of CRC risk than is diet assessed at one time point. In the present study, we used DII scores to construct patterns of change over time in dietary inflammatory potential, as well as the cumulative average dietary inflammatory potential, and evaluated the association of both exposures with CRC risk.

METHODS

Study population

The WHI was designed to address the major causes of morbidity and mortality among postmenopausal women. The design of the WHI has been described previously (23). Briefly, WHI investigators enrolled 161,808 postmenopausal women 50–79 years of age with a predicted survival of >3 years, in 40 sites in the United States in 1993–1998. Subjects were enrolled into the WHI-OS ($n = 93,676$) or one or more of 4 clinical trial groups, which included the WHI-DM, with 29,294 women randomly assigned to a usual-diet comparison group and 19,541 women assigned to an intervention group. The intervention design set a goal of 20% of energy intake as fat and increased intake of vegetables, fruits, and whole grains. Women who were ineligible for or unwilling to enroll in the clinical trial components were invited to be part of the prospective cohort of women in the WHI-OS (23). Follow-up for the WHI is ongoing, and we used data from women with follow-up until August 29, 2014, for this investigation. The WHI protocol was approved by the institutional review boards at the Clinical Coordinating Center at the Fred Hutchinson Cancer Research Center (Seattle, Washington) and at each of the 40 Clinical Centers (23).

Dietary assessment

During screening for the WHI, all participants completed a standardized self-administered 122-item FFQ developed for the WHI to estimate average daily nutrient intake over the previous 3-month period. This served as the baseline measure. Follow-up measures included: FFQ completed by all WHI-DM participants at year 1; FFQ completed annually from year 2 until study end (approximately 14 years) in one-third of DM participants randomly selected each year; and FFQ completed at year 3 for approximately 90% of WHI-OS participants. There were an average of 2 FFQs per participant in the WHI-OS and 3 FFQs per participant in the WHI-DM. Therefore, to maximize the number of WHI-DM participants with FFQs at one time point (other than year 1), we created a composite FFQ for year 3 that included an average of FFQs in years 2, 3, and 4. We did not use FFQs from year 4 onward because the sample sizes of WHI-DM participants with FFQs became progressively smaller. Second, we did not include baseline FFQ data for WHI-DM participants in the analyses due to the upward bias in baseline mean percent energy from fat as a result of the >32% energy from fat eligibility criterion (24–26). For the present study, we included FFQs from the WHI-OS and WHI-DM control groups but not from the WHI-DM intervention group, because the intervention group participants were actively undergoing dietary changes while the control group participants were asked to follow their usual diets (26–28).

FFQ data were considered complete if all adjustment questions, all summary questions, 90% of the foods, and at least one-half of every food group section were completed (23, 29). The nutrient database, linked to the University of Minnesota Nutrition Data System for Research (30), is based on the US Department of Agriculture Standard Reference Releases and manufacturer information. The WHI FFQ has produced results comparable to those from 4 24-hour dietary recall interviews and 4 days of food diaries recorded within the WHI (27).

Dietary inflammatory index

Details of the development (16) and construct validation (17–19) of the DII have been described previously. A summary of the steps taken to create the DII are provided in Web Figure 1 (available at https://academic.oup.com/aje) (16). An extensive literature search was performed to identify articles published in peer-reviewed journals reporting on the association between dietary factors and 6 inflammation markers (interleukin (IL)-1β, IL-4, IL-6, IL-10, tumor necrosis factor alpha, and C-reactive protein). A total of 1,943 eligible articles published through 2010 were indexed and scored to derive component-specific inflammatory effect scores. In the process of reading and scoring these articles, a total of 45 specific foods and nutrients (components of the DII) were identified.

Actual dietary intake data derived from the WHI FFQ were standardized to a representative global diet database constructed based on 11 data sets from diverse populations in different parts of the world. The standardized dietary intake data were then multiplied by the literature-derived inflammatory effect scores for each DII component, and summed across all components, to obtain the overall DII (16). The DII score characterizes an individual's diet on a continuum from maximally antiinflammatory to maximally proinflammatory, with a higher DII score indicating a more proinflammatory diet and a lower (i.e., more negative) DII score indicating a more antiinflammatory diet. In the WHI FFQ, 32 of the 45 original DII components were available for inclusion in the overall DII score (see Table 1 footnote for the list of all 45 DII components).

Outcomes assessment

The outcome for these analyses was incident CRC, including cancers of the colon (proximal colon, distal colon) and rectum (rectum and rectosigmoid). Reported CRC was verified by centrally trained physician adjudicators after review of medical records and pathology reports (31). Proximal colon cancers

Table 1. Frequencies of Baseline Characteristics Across Patterns of Change in Dietary Inflammatory Potential Among Participants in the Women's Health Initiative, United States, 1993–2014

Characteristic	Patterns of Change[a] in Quintiles of the Dietary Inflammatory Index[b]									
	Antiinflammatory Stable		Antiinflammatory Change		Neutral Inflammation Stable		Proinflammatory Change		Proinflammatory Stable	
	No. of Participants	%	No. of Participants	%	No. of Participants	%	No. of Participants	%	No. of Participants	%
Age group, years										
50–59	8,006	30.9	3,941	37.0	3,869	30.9	3,359	34.3	10,028	35.6
60–69	12,348	47.7	4,752	44.6	5,695	45.5	4,309	44.0	12,414	44.1
70–79	5,533	21.4	1,968	18.4	2,953	23.6	2,131	21.7	5,736	20.3
Race/ethnicity										
Asian or Pacific Islander	960	3.7	333	3.0	243	1.9	296	3.0	635	2.3
African American	917	3.5	782	7.2	705	5.6	751	7.8	3,025	10.7
Hispanic/Latino	398	1.5	303	2.8	327	2.6	398	4.1	1,340	4.8
European American	23,235	89.8	9,033	85.6	11,059	88.4	8,166	83.3	22,653	80.4
Other	320	1.2	174	1.1	154	1.2	164	1.6	459	1.6
Missing	57	0.3	36	0.3	29	0.3	24	0.2	66	0.2
Educational level										
Less than high school	508	2.0	371	3.5	458	3.7	402	4.1	1,661	5.9
High school diploma, GED, or college up to associate's degree	11,798	45.6	5,538	51.9	6,838	54.6	5,313	54.2	16,375	58.1
At least 4 years of college	13,439	51.9	4,683	43.9	5,136	41.0	3,984	40.7	9,911	35.2
Missing	142	0.5	69	0.7	85	0.7	100	1.0	231	0.8
Smoking status										
Never smoker	13,146	50.8	5,330	50.0	6,577	52.5	5,016	51.2	14,503	51.5
Former smoker	11,691	45.2	4,602	43.1	5,165	41.2	4,168	42.5	11,307	40.1
Current smoker	914	3.5	660	6.2	693	5.6	514	5.6	2,176	7.7
Missing	136	0.5	69	0.7	82	0.7	71	0.7	192	0.7
Body mass index[c]										
Normal weight (<25.0)	10,783	41.7	3,957	37.1	4,439	35.5	3,334	34.1	9,074	32.2
Overweight (25.0–29.9)	8,994	34.7	3,770	35.3	4,461	35.6	3,474	35.4	9,884	35.1
Obese (≥30.0)	6,110	23.6	2,934	27.6	3,617	28.9	2,991	30.5	9,220	32.7
Physical activity recommendation met, yes or no										
Not meeting physical activity recommendations	8,492	32.8	4,509	42.3	5,577	44.6	4,048	41.3	14,599	51.8
Meeting physical activity recommendations	17,365	67.1	6,136	57.6	6,920	55.3	5,731	58.5	13,505	47.9
Missing	31	0.1	16	0.1	20	0.1	20	0.2	74	0.3
Regular NSAID use[d]										
No	9,875	38.2	4,423	41.5	4,690	37.5	3,982	40.6	11,901	42.2
Yes	15,063	58.2	5,759	54.0	7,359	58.8	5,366	54.8	14,410	51.1
Missing	949	3.6	479	4.5	468	3.7	451	4.6	1,867	6.7

Abbreviations: DII, dietary inflammatory index; GED, General Educational Development; NSAID, nonsteroidal antiinflammatory drug; WHI, Women's Health Initiative.

[a] The differences in DII scores from baseline to year 3 in the WHI Observational Study and from year 1 to composite year 3 (i.e., years 2, 3, and 4) in the Dietary Modification Trial control group are referred to as "change in DII." We categorized the changes in the DII based on quintile differences between the first and second time points, as follows: 1) antiinflammatory stable: quintile 1 or quintile 2 at both time points or change from quintile 3 to quintile 2; 2) antiinflammatory change: downward change of at least 2 quintiles; 3) neutral inflammation stable: changes from quintile 2 to quintile 3 or from quintile 4 to quintile 3 or stable at quintile 3 at both time points; 4) proinflammatory change: upward change of at least 2 quintiles; and 5) proinflammatory stable: quintile 4 or quintile 5 at either time point, or change from quintile 3 to quintile 4.

[b] DII components available in the WHI food frequency questionnaire were, among antiinflammatory components: alcohol, beta-carotene, caffeine, fiber, folic acid, magnesium, niacin, riboflavin, thiamin, zinc, monounsaturated fatty acid, polyunsaturated fatty acid, omega-3 fatty acid, omega-6 fatty acid, selenium, vitamin B6, vitamin A, vitamin C, vitamin D, vitamin E, onion, green/black tea, and isoflavones. Among proinflammatory components: vitamin B12, iron, carbohydrates, cholesterol, total energy, total fat, saturated fat, trans fat, and protein. The following components, all antiinflammatory, were not available in the WHI food frequency questionnaire: ginger, turmeric, garlic, oregano, pepper, rosemary, eugenol, saffron, flavan-3-ol, flavones, flavonols, flavonones, and anthocyanidins.

[c] Body mass index was calculated as weight (kg)/height $(m)^2$.

[d] Regular use of NSAIDs was defined as use at least 2 times in each of the 2 weeks preceding the interview.

were defined as cancers of the cecum, ascending colon, right colon, hepatic flexure of colon, and transverse colon (*International Classification of Diseases for Oncology, Second Edition*, codes C18.0 and C18.2–18.4), and distal colon cancers were defined as cancers of the splenic flexure of colon, descending colon, left colon, and sigmoid colon (codes C18.5–18.7). Survival time was defined as days from enrollment or randomization until CRC diagnosis, while censoring time was defined as days from enrollment or randomization until death or last contact occurring on or before August 29, 2014, in participants without CRC.

Statistical analysis

We used data from 122,970 women participating in the WHI-OS and in the WHI-DM control group. Exclusion criteria included women with CRC at baseline or missing CRC status at baseline ($n = 2,118$), women reporting any cancer at or prior to baseline ($n = 9,232$), women reporting any cancer (including CRC) diagnosed within 3 years from baseline during the follow-up period ($n = 3,348$), with CRCs diagnosed as second primaries during follow-up ($n = 66$), women with reported total energy intake values judged to be implausible (≤600 kcal/day or ≥5,000 kcal/day) ($n = 4,106$) or with extreme body mass index values (<15 or >50) ($n = 588$), and participants with single FFQs ($n = 13,517$).

The differences in DII scores between baseline and year 3 in the WHI-OS and from year 1 to composite year 3 in the WHI-DM control group were referred to as "change in DII," while the cumulative average DII score in these time points was referred to as "cumulative average DII." To determine the role in CRC risk of patterns of change in the inflammatory potential of diet over time, we calculated the DII and categorized it into quintiles at both time points (32). We then further categorized the changes in the inflammatory potential of diet based on quintile differences between the first and second time points, as follows:

1. Antiinflammatory stable: quintile 1 or 2 at both time points or change from quintile 3 to quintile 2;
2. Antiinflammatory change: downward change of at least 2 quintiles;
3. Neutral inflammation stable: changes from quintile 2 to quintile 3 or from quintile 4 to quintile 3 or stable at quintile 3 at both time points;
4. Proinflammatory change: upward change of at least 2 quintiles; and
5. Proinflammatory stable: quintile 4 or quintile 5 at either time point, or change from quintile 3 to quintile 4.

The names given to these categories of DII changes were meant to be qualitative only. We decided to use quintiles for constructing this 5-level exposure variable in order to maximize the contrast between DII change scores while maintaining a sufficiently large sample size within each quantile of DII change to observe an association.

Frequencies and percentages were computed to describe the distribution of covariates across categories of change in DII score and across quintiles of cumulative average DII assessed from baseline to year 3. To determine the role of cumulative history of the inflammatory potential of diet in CRC risk over time, we estimated hazard ratios for newly incident overall CRC, colon (proximal/distal) cancer, and rectal cancer, using multivariable-adjusted Cox regression models by quintiles of cumulative average DII scores (33) and by patterns of DII changes adjusted for multiple covariates. We excluded all CRC cases diagnosed prior to year 3 to establish appropriate temporality between exposure and outcome.

Potential baseline confounders that changed hazard ratios by >10% were retained in the final model. These were 10-year age group (within ages 50–79 years); race/ethnicity (European American, African American, Hispanic, Asian or Pacific Islander, and other race groups (other), missing); educational level (less than high school diploma, high school diploma/General Educational Development certificate/college up to associate's degree, at least 4 years of college, missing); smoking status (current, past, never, missing); body mass index (calculated as weight (kg)/height $(m)^2$; ≤24.9, 25.0–29.9, ≥30.0, missing); physical activity, categorized based on public health recommendations (34) as meeting or not meeting PA recommendations (≥150 minutes/week of moderate intensity PA or ≥75 minutes/week of vigorous intensity PA vs. <150 minutes/week of moderate intensity PA or <75 minutes/week of vigorous intensity PA, respectively), or missing PA; (3) history of diabetes (yes, no, missing), hypertension (yes, no, missing), or arthritis (yes, no, missing); regular use of nonsteroidal antiinflammatory drugs (NSAIDs) (yes, no, missing); category and duration of estrogen use and category and duration of combined estrogen and progesterone use, both categorized into 5 groups (none, ≤4.9 years, 5.0–10.0 years, 10.1–14.9 years, and ≥15.0 years). NSAIDs included aspirin and nonaspirin NSAIDs (nonaspirin salicylates, ibuprofen, indomethacin, naproxen, piroxicam, celecoxib, and others). Regular NSAID use was defined as use of an NSAID or acetaminophen at least 2 times in each of the 2 weeks preceding the interview. Details on medication use were collected from baseline questionnaires and were updated at the year 3 clinic visit for the WHI-OS and at years 1, 3, 6, and 9 for the WHI-DM control group (35, 36). For the present analyses, we used only baseline NSAID data because of the higher amount of missing data at year 3 (approximately 20%) compared with baseline (approximately 5%). Data on potential confounders were collected through self-administration of standardized questionnaires on demographics, medical history, and lifestyle factors. Certified staff performed physical measurements, including blood pressure, height, and weight (23). For missing data, we included a separate missing category for categorical variables and assigned the median for continuous variables. Data from a total of 87,042 participants were therefore available for the final analyses (76.1% in the OS and 23.9% in the WHI-DM control group).

Each covariate in the final models for both patterns of change in DII and cumulative average DII was tested for adherence to the proportional hazards assumption using cumulative sums of Martingale-based residuals. None of the covariates violated the proportional hazards assumption. We investigated effect modification of the association between changes in the DII and cumulative average DII and CRC incidence according to education, body mass index, and NSAID use by including 2-way cross-product terms for these covariates

in the models, and we assessed significant effect modification at $P < 0.10$. Confidence intervals that did not include 1 were considered to indicate statistically significant results (i.e., at the nominal $\alpha = 0.05$). Statistical analyses were conducted using SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina), and all tests were 2-sided.

RESULTS

During a median 16.2 years of follow-up, 1,038 incident CRC cases (859 colon and 183 rectal) were identified. In the first 3 years of follow-up, 29.7% of participants were classified as having an antiinflammatory-stable dietary pattern, 12.3% had antiinflammatory dietary changes, 14.4% were in the neutral inflammation-stable category, 11.3% experienced proinflammatory changes, and 32.3% were in the proinflammatory-stable category. Table 1 shows the distribution of participants' baseline characteristics across patterns of DII change. In the proinflammatory-stable category, there was a higher proportion of African Americans (10.7%), Hispanics (4.8%), participants with less than a high school education (5.9%), current smokers (7.7%), obese participants (32.7%), and participants not meeting physical activity recommendations (51.8%) than there were in the antiinflammatory stable category (Table 1).

The cumulative average DII was −1.18 (standard deviation, 2.33), ranging from a minimum of −6.62 to a maximum of 5.39. Table 2 shows the distribution of participants' baseline characteristics in quintiles of cumulative average DII. There were higher proportions of African Americans (13.9%), Hispanics (5.7%), participants with less than a high school education (7.3%), current smokers (9.1%), obese participants (35.5%), and participants not meeting physical activity recommendations (56.1%) in the highest cumulative average DII quintile than in the lowest (Table 2). Participants in quintile 1, with the lowest DII scores, also had high intakes of fruits, vegetables, nuts, and whole grains (Web Table 1).

Table 3 presents the results of the associations between patterns of change in the inflammatory potential of diet and CRC risk for all participants and separately by category of NSAID use. There was no substantial association between changes in DII and overall CRC risk when all participants were considered. However, there were significant differences in the association of changes in DII and CRC risk by category of NSAID use ($P_{interaction} = 0.055$). Among nonusers of NSAIDs, there was significantly higher risk of CRC (hazard ratio (HR) = 1.33, 95% confidence interval (CI): 1.02, 1.73), especially proximal colon cancer (HR = 1.42, 95% CI: 1.01, 2.03), in women classified in the proinflammatory stable category compared with women in the antiinflammatory stable category. There were no significant associations among regular users of NSAIDs (Table 3). The age-adjusted associations are presented in Web Table 2.

Table 4 presents hazard ratios of the association between cumulative average DII and CRC risk. Comparing participants in the highest quintile of cumulative average DII with those in the lowest quintile, there was a higher risk of CRC overall (HR = 1.33, 95% CI: 1.08, 1.64; $P_{trend} = 0.08$). Risk was higher among women with proximal colon cancer but not among women with distal colon cancer or rectal cancer. The term for the interaction between cumulative average DII and NSAID use was not statistically significant ($P_{interaction} = 0.43$); however, based on our findings using the DII change variable, we stratified models by category of NSAID use. Higher risk of CRC overall and by anatomic subsite was limited to nonusers of NSAIDs. For example, among nonusers of NSAIDs, there was a 65% higher risk of CRC (95% CI: 1.19, 2.29; $P_{trend} = 0.01$) and a 61% higher risk of colon cancer (95% CI: 1.12, 2.29; $P_{trend} = 0.02$). Risk was especially pronounced for proximal colon cancer (HR = 1.91, 95% CI: 1.24, 2.96; $P_{trend} = 0.006$). Among regular users of NSAIDs, there was no increase in risk for higher cumulative average DII quintiles (Table 4). The age-adjusted associations are presented in Web Table 3.

DISCUSSION

In this large prospective study, we found that dietary changes toward more proinflammatory diets and a history of higher cumulative average dietary inflammatory potential assessed over a 3-year period were associated with a higher risk of developing CRC, especially proximal colon cancer, after a median 16.2 years of follow-up. The higher risk was mainly limited to nonusers of NSAIDs. To our knowledge, this is the first study to characterize the association of changes over time and the cumulative history in the inflammatory potential of diet with the risk of CRC overall and by anatomic subsite, in categories of NSAID use. There was no statistically significant association between changes in DII over time or cumulative average DII and distal colon cancer or rectal cancer.

Our results from models including all participants are generally similar to previous findings from prospective studies of diet quality and CRC risk (5, 37, 38), where poorer diet quality (here characterized by higher, more proinflammatory DII scores), has been associated with higher CRC risk. We previously examined the association between baseline DII and CRC risk in the WHI, and results were similar to the present study's findings, although smaller in magnitude. In that study, we found a 22% higher risk of overall CRC (HR = 1.22, 95% CI: 1.05, 1.43; $P_{trend} = 0.04$), which was more pronounced in the proximal colon (HR = 1.35, 95% CI: 1.05, 1.67; $P_{trend} = 0.01$) (20). Cumulating dietary measures over time could reduce within-subject variation and improve ability to detect elevated risk.

The differences in CRC risk estimates between NSAID-use categories were clinically meaningful. This is consistent with previous work in which we found similar trends in the association of a combined lifestyle index and colorectal adenomatous polyps (precursor lesions of CRC) according to NSAID use. Higher scores (representing a healthier lifestyle pattern) were associated with lower odds of colorectal adenomas among nonusers of NSAIDs but not among users (3). One other study examining the association between the DII and risk of CRC observed significantly higher risk among nonusers of NSAIDs but not among users (20), while another found that higher DII scores were significantly associated with higher concentrations of inflammation markers only in nonusers of NSAIDs (18).

Table 2. Frequencies of Baseline Characteristics Across Quintiles of Cumulative Average Dietary Inflammatory Index[a,b] (Baseline[c] and Year 3) Among Participants in the Women's Health Initiative, United States, 1993–2014

Characteristic	Quintile 1 (More Antiinflammatory)		Quintile 2		Quintile 3		Quintile 4		Quintile 5 (More Proinflammatory)	
	No. of Participants	%	No. of Participants	%	No. of Participants	%	No. of Participants	%	No. of Participants	%
Age group, years										
50–59	5,483	31.5	5,368	30.8	5,732	32.9	6,102	35.1	6,518	37.4
60–69	8,286	47.6	8,063	46.3	7,892	45.3	7,711	44.3	7,566	43.5
70–79	3,639	20.9	3,977	22.9	3,785	21.8	3,595	20.6	3,325	19.1
Race/ethnicity										
Asian or Pacific Islander	779	4.5	465	2.7	447	2.6	448	2.6	328	1.9
African American	551	3.2	734	4.2	1,038	6.0	1,445	8.3	2,412	13.9
Hispanic/Latino	260	1.5	334	2.0	501	2.9	672	3.9	999	5.7
European American	15,543	89.3	15,613	89.7	15,127	86.9	14,535	83.5	13,328	76.6
Other	238	1.3	220	1.2	245	1.4	265	1.5	300	1.7
Missing	37	0.2	42	0.2	49	0.2	42	0.2	42	0.2
Educational level										
Less than high school	275	1.6	498	2.9	590	3.4	767	4.4	1,270	7.3
High school diploma, GED, or college up to associate's degree	7,386	42.4	8,789	50.5	9,338	53.6	9,767	56.1	10,582	60.8
At least 4 years of college	9,654	55.5	7,998	45.9	7,365	42.3	6,733	38.7	5,403	31.0
Missing	93	0.5	123	0.7	116	0.7	141	0.8	154	0.9
Smoking status										
Never smoker	8,642	49.6	8,977	51.6	9,043	51.9	8,986	51.6	8,924	51.3
Former smoker	8,124	46.7	7,552	43.4	7,294	41.9	7,181	41.3	6,782	39.0
Current smoker	550	3.2	780	4.4	950	5.5	1,116	6.4	1,591	9.1
Missing	92	0.5	99	0.6	122	0.7	125	0.7	112	0.6
Body mass index[d]										
Normal weight (<25.0)	7,670	44.1	6,707	38.5	6,201	35.6	5,782	33.2	5,227	30.0
Overweight (25.0–29.9)	5,953	34.2	6,140	35.3	6,277	36.1	6,216	35.7	5,997	34.5
Obese (≥30.0)	3,785	21.7	4,561	26.2	4,931	28.3	5,410	31.1	6,185	35.5
Physical activity recommendations met, yes or no										
Not meeting physical activity recommendations	4,887	28.1	6,818	39.2	7,436	42.7	8,315	47.8	9,769	56.1
Meeting physical activity recommendations	12,501	71.8	10,571	60.7	9,942	57.1	9,051	52.0	7,592	43.6
Missing	20	0.1	19	0.1	31	0.2	42	0.2	48	0.3
Regular NSAID use[e]										
No	6,833	39.3	6,621	38.1	6,835	39.3	7,179	41.2	7,403	42.5
Yes	9,894	56.8	10,171	58.4	9,813	56.4	9,319	53.5	8,760	50.3
Missing	681	3.9	616	3.5	761	4.3	910	5.3	1,246	7.2

Abbreviations: DII, dietary inflammatory index; GED, General Educational Development; NSAID, nonsteroidal antiinflammatory drug; WHI, Women's Health Initiative.

[a] The cumulative average DII was the average of the DII scores at baseline (year 1 for the Dietary Modification Trial control group) and year 3. Lower (more negative) DII scores indicate antiinflammatory diets whereas higher (more positive) DII scores indicate proinflammatory diets. Quintile 1: −6.62 to −3.26; quintile 2: −3.25 to −2.18; quintile 3: −2.17 to −0.85; quintile 4: −0.84 to 0.96; and quintile 5: 0.97 to 5.39.

[b] DII components available in the WHI food frequency questionnaire were, among antiinflammatory components: alcohol, beta-carotene, caffeine, fiber, folic acid, magnesium, niacin, riboflavin, thiamin, zinc, monounsaturated fatty acid, polyunsaturated fatty acid, omega-3 fatty acid, omega-6 fatty acid, selenium, vitamin B6, vitamin A, vitamin C, vitamin D, vitamin E, onion, green/black tea, and isoflavones. Among proinflammatory components: vitamin B12, iron, carbohydrates, cholesterol, total energy, total fat, saturated fat, trans fat, and protein. The following components, all antiinflammatory, were not available in the WHI food frequency questionnaire: ginger, turmeric, garlic, oregano, pepper, rosemary, eugenol, saffron, flavan-3-ol, flavones, flavonols, flavonones, and anthocyanidins.

[c] Year 1 and composite year 3 for the Dietary Modification Trial control group.

[d] Body mass index was calculated as weight (kg)/height $(m)^2$.

[e] Regular use of NSAIDs was defined as use at least 2 times in each of the 2 weeks preceding the interview.

Table 3. Multivariable-Adjusted[a] Hazards Ratios of the Association Between Patterns of Change in Dietary Inflammatory Potential and Colorectal Cancer Risk Stratified by Nonsteroidal Antiinflammatory Drug Use, Women's Health Initiative, United States, 1993–2014

Tumor Location[c]	Patterns of Change[b] in Quintiles of the Dietary Inflammatory Index									
	Antiinflammatory Stable		Antiinflammatory Change		Neutral Inflammation Stable		Proinflammatory Change		Proinflammatory Stable	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
All Participants										
Colorectal cancer	1.00	Referent	1.09	0.88, 1.34	1.07	0.88, 1.31	1.10	0.89, 1.37	1.06	0.90, 1.26
Colon cancer	1.00	Referent	1.11	0.88, 1.40	1.14	0.92, 1.44	1.11	0.87, 1.41	1.07	0.89, 1.29
Proximal colon cancer	1.00	Referent	1.11	0.84, 1.47	1.06	0.81, 1.39	1.32	1.01, 1.74	1.05	0.84, 1.31
Distal colon cancer	1.00	Referent	0.98	0.61, 1.58	1.42	0.95, 1.13	0.81	0.47, 1.38	1.13	0.79, 1.63
Rectal cancer	1.00	Referent	0.98	0.60, 1.60	0.71	0.43, 1.20	1.06	0.64, 1.75	0.98	0.67, 1.44
Nonusers of NSAIDs										
Colorectal cancer	1.00	Referent	1.09	0.77, 1.53	1.04	0.74, 1.46	1.25	0.88, 1.76	1.33	1.02, 1.73
Colon cancer	1.00	Referent	1.05	0.72, 1.52	1.07	0.75, 1.55	1.20	0.82, 1.75	1.30	0.97, 1.75
Proximal colon cancer	1.00	Referent	1.13	0.72, 1.78	0.84	0.51, 1.37	1.34	0.85, 2.11	1.42	1.01, 2.03
Distal colon cancer	1.00	Referent	0.86	0.40, 1.87	1.79	0.98, 3.27	1.20	0.58, 2.49	1.09	0.62, 1.93
Rectal cancer	1.00	Referent	1.24	0.54, 2.81	0.76	0.29, 1.96	1.43	0.62, 3.30	1.42	0.74, 2.72
Regular Users of NSAIDs										
Colorectal cancer	1.00	Referent	1.09	0.83, 1.43	1.12	0.87, 1.43	1.08	0.81, 1.43	0.83	0.66, 1.03
Colon cancer	1.00	Referent	1.13	0.83, 1.54	1.19	0.91, 1.57	1.10	0.80 1.51	0.86	0.66, 1.11
Proximal colon cancer	1.00	Referent	1.13	0.78, 1.64	1.28	0.92, 1.77	1.40	0.98, 2.00	0.74	0.53, 1.02
Distal colon cancer	1.00	Referent	0.87	0.45, 1.69	0.97	0.55, 1.72	0.53	0.24, 1.21	1.13	0.70, 1.82
Rectal cancer	1.00	Referent	0.96	0.52, 1.78	0.76	0.41, 1.43	1.01	0.53, 1.92	0.71	0.41, 1.21

Abbreviation: CI, confidence interval; DII, dietary inflammatory index; HR, hazard ratio; NSAID, nonsteroidal antiinflammatory drugs.

[a] All models adjusted for age, race/ethnicity, educational level, smoking status, diabetes, hypertension, arthritis, regular NSAID use (except when stratified by NSAID use), category and duration of estrogen use, category and duration of estrogen/progesterone use, body mass index, physical activity, and total energy intake.

[b] The differences in DII scores from baseline to year 3 in the Observational Study and from year 1 to composite year 3 (i.e., years 2, 3, and 4 combined) in the Dietary Modification Trial control group are referred to as "change in DII." We categorized the changes in the DII based on quintile differences between the first and second time points, as follows: 1) antiinflammatory stable: quintile 1 or quintile 2 at both time points or change from quintile 3 to quintile 2; 2) antiinflammatory change: downward change of at least 2 quintiles; 3) neutral inflammation stable: changes from quintile 2 to quintile 3 or from quintile 4 to quintile 3 or stable at quintile 3 at both time points; 4) proinflammatory change: upward change of at least 2 quintiles; and 5) proinflammatory stable: quintile 4 or quintile 5 at either time point, or change from quintile 3 to quintile 4.

[c] *International Classification of Diseases for Oncology, Second Edition*, codes used to define location of colon cancer included C18.0 (cecum), C18.2 (ascending colon, right colon), C18.3 (hepatic flexure of colon), C18.4 (transverse colon), C18.5 (splenic flexure of colon), C18.6 (descending colon, left colon), and C18.7 (sigmoid colon); rectal cancer included all rectum and rectosigmoid cases.

The link between inflammation and CRC is supported by findings from several studies showing either a lower risk of CRC with regular use of NSAIDs (39, 40) or a positive association between higher concentrations of inflammation markers and higher CRC risk (41, 42). Other potential mechanisms through which a proinflammatory diet may increase risk of CRC include components of the metabolic syndrome, especially insulin resistance or glucose intolerance (43, 44), and influences on the microbiota. A high and sustained proinflammatory potential of the diet may compromise the host-microbiota mutualism, favoring the proliferation of toxic bacteria that have been suggested to promote colorectal carcinogenesis (45).

It is interesting to note that intakes of major food groups deemed healthy (e.g., vegetables, fruits, and whole grains) were higher among DII quintile 1 and lower among DII quintile 5, while less healthy food groups (e.g., red meat) did not increase consistently across the 5 quintiles (Web Table 1). This suggests that it may be the absence of certain healthy food groups, rather than excesses of unhealthy food groups, that contributes to high DII scores in this population, although the list of unhealthy foods in Web Table 1 is by no means comprehensive. The DII score in this study is comprised of mostly macronutrients, micronutrients, and phytochemicals, not foods or food groups, so DII scores represent a balance of a multitude of dietary factors, with the majority being antiinflammatory.

Strengths of the present study include the ability to account for changes in the inflammatory potential of diet over time by using the DII; use of a large, well-characterized population with a long follow-up period and sufficiently large sample size to allow stratification of analyses in categories of NSAID; the inclusion of women of diverse race/ethnic groups; and the

Table 4. Multivariable-Adjusted[a] Hazards Ratios of the Association Between Cumulative Average Dietary Inflammatory Index and Colorectal Cancer Risk Stratified by Nonsteroidal Antiinflammatory Drug Use, Women's Health Initiative, United States, 1993–2014

Tumor Location[c]	Quintiles of Cumulative Average Dietary Inflammatory Index[b]										P_{trend}[d]
	Quintile 1 (More Antiinflammatory Diet)		Quintile 2		Quintile 3		Quintile 4		Quintile 5 (More Proinflammatory Diet)		
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	
All Participants											
Colorectal cancer	1.00	Referent	1.14	0.93, 1.39	1.22	1.00, 1.49	0.93	0.75, 1.15	1.33	1.08, 1.64	0.08
Colon cancer	1.00	Referent	1.15	0.92, 1.44	1.24	0.99, 1.54	0.95	0.75, 1.21	1.37	1.09, 1.73	0.06
Proximal colon cancer	1.00	Referent	1.28	0.98, 1.66	1.25	0.96, 1.64	0.96	0.72, 1.28	1.35	1.02, 1.79	0.30
Distal colon cancer	1.00	Referent	0.88	0.56, 1.38	1.27	0.83, 1.93	0.88	0.55, 1.39	1.35	0.87, 2.11	0.19
Rectal cancer	1.00	Referent	1.06	0.67, 1.69	1.14	0.72, 1.82	0.79	0.47, 1.31	1.10	0.67, 1.80	0.90
Nonusers of NSAIDs											
Colorectal cancers	1.00	Referent	1.15	0.83, 1.61	1.38	1.00, 1.89	0.97	0.69, 1.37	1.65	1.19, 2.29	0.01
Colon cancer	1.00	Referent	1.09	0.76, 1.57	1.30	0.92, 1.85	0.99	0.69, 1.44	1.61	1.12, 2.29	0.02
Proximal colon cancer	1.00	Referent	1.17	0.75, 1.83	1.34	0.87, 2.08	1.02	0.64, 1.62	1.91	1.24, 2.96	0.006
Distal colon cancer	1.00	Referent	1.11	0.57, 2.17	1.35	0.71, 2.57	0.98	0.49, 1.96	1.16	0.57, 2.35	0.88
Rectal cancer	1.00	Referent	1.37	0.60, 3.11	1.64	0.74, 3.65	0.73	0.28, 1.89	1.70	0.74, 3.90	0.53
Regular Users of NSAIDs											
Colorectal cancer	1.00	Referent	1.10	0.85, 1.43	1.12	0.86, 1.45	0.83	0.62, 1.11	1.07	0.80, 1.43	0.69
Colon cancer	1.00	Referent	1.17	0.88, 1.56	1.18	0.88, 1.58	0.86	0.62, 1.19	1.13	0.82, 1.56	0.86
Proximal colon cancer	1.00	Referent	1.35	0.96, 1.90	1.24	0.87, 1.76	0.87	0.59, 1.29	0.91	0.60, 1.37	0.10
Distal colon cancer	1.00	Referent	0.63	0.33, 1.20	1.07	0.61, 1.89	0.69	0.36, 1.33	1.52	0.85, 2.74	0.09
Rectal cancer	1.00	Referent	0.89	0.49, 1.59	0.95	0.53, 1.72	0.72	0.38, 1.37	0.82	0.42, 1.61	0.46

Abbreviation: CI, confidence interval; DII, dietary inflammatory index; HR, hazard ratio; NSAID, nonsteroidal antiinflammatory drugs.

[a] All models adjusted for age, race/ethnicity, educational level, smoking status, diabetes, hypertension, arthritis, regular NSAID use (except when stratified by NSAID use), category and duration of estrogen use, category and duration of estrogen and progesterone use, body mass index, physical activity, and total energy intake.

[b] The cumulative average DII was the average of the DII scores at baseline (year 1 for the Dietary Modification Trial control group) and year 3.

[c] *International Classification of Diseases for Oncology, Second Edition*, codes used to define location of colon cancer included C18.0 (cecum), C18.2 (ascending colon, right colon), C18.3 (hepatic flexure of colon), C18.4 (transverse colon), C18.5 (splenic flexure of colon), C18.6 (descending colon, left colon), and C18.7 (sigmoid colon); rectal cancer included all rectum and rectosigmoid cases.

[d] The *P* for trend was obtained by assigning the median cumulative average DII for each quintile to all participants in the quintile and inserting this ordinal variable in the multivariable-adjustment model.

central adjudication of CRC diagnosis. Limitations include known measurement error in using FFQs for the assessment of diet and its inflammatory potential over time (although we used ≥2 FFQs measured several years apart). Although we adjusted for many potential confounders, residual or unmeasured confounding is still a possibility. It also is important to note that all of the DII components missing from the WHI FFQ (ginger, turmeric, garlic, oregano, pepper, rosemary, eugenol, saffron, flavan-3-ol, flavones, flavonols, flavonones, and anthocyanidins) are antiinflammatory. However, in the construct validation of the DII in the WHI, the DII computed based on the 32 components significantly predicted concentrations of inflammation markers (18). The range of cumulative average DII in the present study of −6.62 to 5.39 is comparable to the range of −5.4 to 5.8 obtained in another study using data from 15 24-hour dietary recalls with 44 of the 45 DII components (17). These results suggest that in Western populations the range of DII scores may be more dependent on the amount of foods actually consumed rather than on the number of components available for scoring.

In summary, dietary changes toward the intake of more proinflammatory diets and a history of proinflammatory diets over a 3-year period are associated with higher risk of colon cancer, particularly proximal colon cancer and especially among nonusers of NSAIDs. Future work may test interventions designed to reduce the inflammatory potential of diet as a means for colon cancer prevention, especially targeted to nonusers of NSAIDs.

ACKNOWLEDGMENTS

Author affiliations: Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Fred K. Tabung); Department of Epidemiology, Harvard T.H. Chan

School of Public Health, Boston, Massachusetts (Fred K. Tabung); Cancer Prevention and Control Program, University of South Carolina, Columbia, South Carolina (Fred K. Tabung, Susan E. Steck, James R. Hebert); Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, South Carolina (Fred K. Tabung, Susan E. Steck, Angela D. Liese, Jiajia Zhang, James R. Hebert); Center for Research in Nutrition and Health Disparities, Arnold School of Public Health, University of South Carolina, Columbia, South Carolina (Susan E. Steck, Angela D. Liese); Division of Preventive and Behavioral Medicine, University of Massachusetts Medical School, Worcester, Massachusetts (Yunsheng Ma, Judith K. Ockene); Department of Preventive Medicine, Stony Brook University School of Medicine, Stony Brook, New York (Dorothy S. Lane); Feinstein Institute for Medical Research, Manhasset, New York (Gloria Y. F. Ho); Department of Occupational Medicine, Epidemiology and Prevention, Hofstra-Northwell School of Medicine, Great Neck, New York (Gloria Y. F. Ho); Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Lifang Hou); Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Lifang Hou); and Department of Epidemiology, The University of Iowa, Iowa City, Iowa (Linda Snetselaar).

F.K.T. and J.R.H. were supported by National Cancer Institute (grants F31 CA177255 and K05 CA136975, respectively). The Women's Health Initiative program was funded by the National Heart, Lung, and Blood Institute (contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C).

J.R.H. owns controlling interest in Connecting Health Innovations, LLC, a company planning to license the right to his invention of the dietary inflammatory index from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. The other authors report no conflicts.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015;65(1):5–29.
2. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol*. 2002;13(1):3–9.
3. Tabung FK, Steck SE, Burch JB, et al. A healthy lifestyle index is associated with reduced risk of colorectal adenomatous polyps among non-users of non-steroidal anti-inflammatory drugs. *J Prim Prev*. 2015;36(1):21–31.
4. Jacques PF, Tucker KL. Are dietary patterns useful for understanding the role of diet in chronic disease? *Am J Clin Nutr*. 2001;73(1):1–2.
5. Reedy J, Krebs-Smith SM, Miller PE, et al. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. *J Nutr*. 2001; 144(6):881–889.
6. Miller PE, Cross AJ, Subar AF, et al. Comparison of 4 established DASH diet indexes: examining associations of index scores and colorectal cancer. *Am J Clin Nutr*. 2013; 98(3):794–803.
7. Randi G, Edefonti V, Ferraroni M, et al. Dietary patterns and the risk of colorectal cancer and adenomas. *Nutr Rev*. 2010; 68(7):389–408.
8. Miller PE, Lesko SM, Muscat JE, et al. Dietary patterns and colorectal adenoma and cancer risk: a review of the epidemiological evidence. *Nutr Cancer*. 2010;62(4):413–424.
9. Fung T, Brown LS. Dietary patterns and the risk of colorectal cancer. *Curr Nutr Rep*. 2013;2(1):48–55.
10. Beresford SA, Johnson KC, Ritenbaugh C, et al. Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative randomized controlled dietary modification trial. *JAMA*. 2006;295(6):643–654.
11. Kabat GC, Shikany JM, Beresford SA, et al. Dietary carbohydrate, glycemic index, and glycemic load in relation to colorectal cancer risk in the Women's Health Initiative. *Cancer Causes Control*. 2008;19(10):1291–1298.
12. Thomson CA, Van Horn L, Caan BJ, et al. Cancer incidence and mortality during the intervention and post intervention periods of the Women's Health Initiative dietary modification trial. *Cancer Epidemiol Biomarkers Prev*. 2014;23(12): 2924–2935.
13. Thomson CA, McCullough ML, Wertheim BC, et al. Nutrition and physical activity cancer prevention guidelines, cancer risk, and mortality in the Women's Health Initiative. *Cancer Prev Res (Phila)*. 2014;7(1):42–53.
14. Touvier M, Fezeu L, Ahluwalia N, et al. Association between prediagnostic biomarkers of inflammation and endothelial function and cancer risk: a nested case-control study. *Am J Epidemiol*. 2013;177(1):3–13.
15. Balkwill F. Cancer and the chemokine network. *Nat Rev Cancer*. 2004;4(7):540–550.
16. Shivappa N, Steck SE, Hurley TG, et al. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. 2014;17(8): 1689–1696.
17. Shivappa N, Steck SE, Hurley TG, et al. A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). *Public Health Nutr*. 2014;17(8):1825–1833.
18. Tabung FK, Steck SE, Zhang J, et al. Construct validation of the dietary inflammatory index among postmenopausal women. *Ann Epidemiol*. 2015;25(6):398–405.
19. Shivappa N, Hébert JR, Rietzschel ER, et al. Associations between dietary inflammatory index and inflammatory markers in the Asklepios Study. *Br J Nutr*. 2015;113(4):665–671.
20. Tabung FK, Steck SE, Ma Y, et al. The association between dietary inflammatory index and risk of colorectal cancer among postmenopausal women: results from the Women's Health Initiative. *Cancer Causes Control*. 2015;26(3):399–408.
21. Mulder M, Ranchor AV, Sanderman R, et al. The stability of lifestyle behaviour. *Int J Epidemiol*. 1998;27(2):199–207.
22. Tabung FK, Steck SE, Zhang J, et al. Longitudinal changes in the dietary inflammatory index: an assessment of the inflammatory potential of diet over time in the Women's Health Initiative. *Eur J Clin Nutr*. 2016;70(12):1374–1380.
23. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. *Control Clin Trials*. 1998;19(1):61–109.
24. Prentice RL, Mossavar-Rahmani Y, Huang Y, et al. Evaluation and comparison of food records, recalls, and frequencies for

energy and protein assessment by using recovery biomarkers. *Am J Epidemiol*. 2011;174(5):591–603.
25. Neuhouser ML, Tinker L, Shaw PA, et al. Use of recovery biomarkers to calibrate nutrient consumption self-reports in the Women's Health Initiative. *Am J Epidemiol*. 2008;167(10): 1247–1259.
26. Ritenbaugh C, Patterson RE, Chlebowski RT, et al. The Women's Health Initiative Dietary Modification Trial: overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(9 suppl):S87–S97.
27. Patterson RE, Kristal AR, Tinker LF, et al. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. *Ann Epidemiol*. 1999;9(3):178–187.
28. Tinker LF, Rosal MC, Young AF, et al. Predictors of dietary change and maintenance in the Women's Health Initiative dietary modification trial. *J Am Diet Assoc*. 2007;107(7): 1155–1166.
29. Patterson RE, Neuhouser ML, Hedderson MM, et al. Changes in diet, physical activity, and supplement use among adults diagnosed with cancer. *J Am Diet Assoc*. 2003;103(3): 323–328.
30. Schakel SF. Maintaining a nutrient database in a changing marketplace: keeping pace with changing food products—a research perspective. *J Food Compost Anal*. 2001;14(3): 315–322.
31. Curb JD, McTiernan A, Heckbert SR, et al. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol*. 2003;13(9):S122–S128.
32. Parekh N, Voland RP, Moeller SM, et al. Association between dietary fat intake and age-related macular degeneration in the Carotenoids in Age-Related Eye Disease Study (CAREDS): an ancillary study of the Women's Health Initiative. *Arch Ophthal*. 2009;127(11):1483–1493.
33. Hu FB, Stampfer MJ, Rimm E, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. *Am J Epidemiol*. 1999;149(6):531–540.
34. Office of Disease Prevention and Health Promotion. 2008 physical activity guidelines for Americans. Washington, DC; Department of Health and Human Services. www.health.gov/paguidelines. Published October 2008. Accessed April 8, 2014.
35. Baik CS, Brasky TM, Pettinger M, et al. Nonsteroidal anti-inflammatory drug and aspirin use in relation to lung cancer risk among postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2015;24(5):790–797.
36. Harris RE, Chlebowski RT, Jackson RD, et al. Breast cancer and nonsteroidal anti-inflammatory drugs: prospective results from the Women's Health Initiative. *Cancer Res*. 2003;63(18): 6096–6101.
37. Fung TT, Hu FB, Wu K, et al. The Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets and colorectal cancer. *Am J Clin Nutr*. 2010;92(6):1429–1435.
38. Reedy J, Mitrou PN, Krebs-Smith SM, et al. Index-based dietary patterns and risk of colorectal cancer: the NIH-AARP Diet and Health Study. *Am J Epidemiol*. 2008;168(1):38–48.
39. Dubé C, Rostom A, Lewin G, et al. The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the US Preventive Services Task Force. *Ann Intern Med*. 2007;146(5):365–375.
40. Rostom A, Dubé C, Lewin G, et al. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the US Preventive Services Task Force. *Ann Intern Med*. 2007;146(5):376–389.
41. Toriola AT, Cheng TY, Neuhouser ML, et al. Biomarkers of inflammation are associated with colorectal cancer risk in women but are not suitable as early detection markers. *Int J Cancer*. 2013;132(11):2648–2658.
42. Wu J, Cai Q, Li H, et al. Circulating C-reactive protein and colorectal cancer risk: a report from the Shanghai Men's Health Study. *Carcinogenesis*. 2013;34(12):2799–2803.
43. Bruce WR, Wolever TM, Giacca A. Mechanisms linking diet and colorectal cancer: the possible role of insulin resistance. *Nutr Cancer*. 2000;37(1):19–26.
44. Giovannucci E. Insulin and colon cancer. *Cancer Causes Control*. 1995;6(2):164–179.
45. Candela M, Turroni S, Biagi E, et al. Inflammation and colorectal cancer, when microbiota-host mutualism breaks. *World J Gastroenterol*. 2014;20(4):908–922.