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Et al.

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Running head: Dietary inflammatory index and colorectal cancer

Abstract:

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 into the Women's Health Initiative. 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 16.2 years 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 pro-inflammatory change DII compared to the anti-inflammatory stable DII groups (hazard ratio, 1.32; 95% confidence interval, 1.01, 1.74). Among non-users of nonsteroidal anti-inflammatory drugs (NSAID) ($P_{interaction}$=0.055) the pro-inflammatory stable DII group was at increased risk of overall CRC and proximal colon cancer. Also among non-users of NSAID, risks of overall CRC, colon cancer, and proximal colon cancer were higher in the highest quintile compared to the lowest cumulative average DII quintile (65%, 61%, and 91% increased risk, respectively). Dietary changes towards, or a history of, pro-inflammatory diets are associated with an elevated risk of colon cancer, particularly for proximal colon cancer and among non-users of NSAID.

Key words: colorectal cancer, dietary patterns, Women's Health Initiative, inflammation

List of abbreviations

CRC	Colorectal cancer
DII	Dietary inflammatory index
DM	WHI Dietary Modification Trial

FFQ	Food frequency questionnaire
NSAID	Non-steroidal anti-inflammatory drugs
OS	WHI Observational Study
PA	Physical activity
WHI	Women's Health Initiative

INTRODUCTION

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 CRC public health prevention strategy. 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 reported significantly lower CRC risk among individuals adhering to the American Cancer Society's nutrition and physical activity 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 pro-inflammatory diet, as measured by the dietary inflammatory index (DII) (16-19) calculated using data from a single baseline food frequency questionnaire, 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 Observational Study (OS) and Dietary Modification (DM) Trial, 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; compared to diet assessed at one time point. In the current 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 to 79 years old with a predicted >3 year survival, in 40 sites in the United States between 1993 and 1998. Subjects were enrolled into the OS (n= 93,676) or one or more of four Clinical Trial groups, that included the DM with 29,294 women randomly assigned to a usual-diet comparison group and 19,541 women assigned to an intervention group. The intervention set a goal of 20% of energy intake as fat with increased intake of vegetables, fruits, and

whole grains. Women who proved to be ineligible for, or who were unwilling to enroll in the Clinical Trial components were invited to be part of the prospective cohort of women in the 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, WA) and at each of the 40 Clinical Centers (23).

Diet assessment

During screening for the WHI, all participants completed a standardized self-administered 122-item food frequency questionnaire (FFQ) developed for the WHI to estimate average daily nutrient intake over the previous three-month period. This served as the baseline measure. Follow-up measures included: an FFQ completed by all DM participants at Year 1; an FFQ completed annually from year 2 until study end (approximately fourteen years) in a third of DM participants randomly selected each year; and an FFQ completed at Year 3 for ≈90% of OS participants. There was an average of two FFQs per participant in the OS and three FFQs per participant in the DM. Therefore to maximize the number of DM participants with an FFQ 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 onwards because the sample sizes of DM participants with FFQs became progressively smaller. Secondly, we did not include baseline FFQ data for 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 current study, we included FFQs from the OS and DM control group but

not from the 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 was 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 four 24-hour dietary recall interviews and four days of food diaries recorded within the WHI (27).

The dietary inflammatory index (DII)

Details of the development (16) and construct validation (17-19) of the DII have been described. A summary of the steps taken to create the DII are provided in Web Figure 1 (16). An extensive literature search was performed to identify articles published in peer-reviewed journals reporting on the association between dietary factors and six 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 datasets 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 anti-inflammatory to maximally pro-inflammatory, with a higher DII score indicating a more pro-inflammatory diet and a lower (i.e., more negative) DII score indicating a more anti-inflammatory 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 were defined as cancers of the cecum, ascending colon, right colon, hepatic flexure of colon, and transverse colon (International Classification of Diseases=C18.0, 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 (International Classification of Diseases=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 utilized data from 122,970 women participating in the WHI OS and 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), any cancer (including CRC) diagnosed within three years from baseline during the follow-up period (n=3,348), 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 ≥5000 kcal/day) (n=4,106) or extreme body mass index values (<15kg/m^2 or > 50kg/m^2) (n=588), as well as participants with single FFQs (n=13,517). Frequencies and percentages were computed to describe the distribution of covariates across quintiles of cumulative average DII assessed from baseline to Year 3.

The differences in DII scores between baseline to Year 3 in the OS and from Year 1 to composite Year 3 in the DM control group are referred to as "change in DII," while the cumulative average DII score in these time points is referred as "cumulative average DII." To determine the role of patterns of change in the inflammatory potential of diet over time in CRC risk, we calculated the DII and categorized it into quintiles (Q) 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. Anti-inflammatory stable: Q1 or Q2 at both time points or change from Q3 to Q2;
2. Anti-inflammatory change: changes ≤ -2Q;
3. Neutral inflammation stable: changes from Q2 to Q3, Q4 to Q3 or stable at Q3 at both time points;
4. Pro-inflammatory change: changes ≥ 2Q;
5. Pro-inflammatory stable: Q4 or Q5 at either time points, or change from Q3 to Q4.

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.

To determine the role of cumulative history of the inflammatory potential of diet in CRC risk over time, we estimated hazard ratios (HR) 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 HRs by >10% were retained in the final model. These were: age group (years) (50-59, 60-69, 70-79); race/ethnicity [European American, African American, Hispanic, Asian or Pacific Islander, and other race groups (other), missing]; educational levels (less than high school, some high school /General Educational Development, at least some college/graduate education, missing); smoking status (current, past, never, missing); body mass index [weight(kg)/height(m)^2, ≤24.9kg/m^2, 25.0-29.9 kg/m^2, and ≥30kg/m^{2,} missing]; physical activity (PA) was 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 versus <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), arthritis (yes, no, missing); regular use of non-steroidal anti-inflammatory drugs (NSAID) (yes, no, missing);

category and duration of estrogen use and category and duration of combined estrogen and progesterone use both categorized into five groups (none, ≤4.9y, 5.0-10.0y, 10.1-14.9y, and ≥15.0y). NSAID included aspirin and non-aspirin NSAID (non-aspirin salicylates, ibuprofen, indomethacin, naproxen, piroxicam, celecoxib, and others). Regular NSAID use was defined as use of an NSAID or acetaminophen at least two times in each of the two weeks preceding the interview. Details on medication use were collected from baseline questionnaires and were updated at Year 3 clinic visit for the OS and at Years 1, 3, 6, and 9 for DM control group (35, 36). For the current analyses, we used only baseline NSAID data because of the higher amount of missing data at Year 3 (~20%) compared to baseline (~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 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 two-way cross-product terms for these covariates in the models, and 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 α=0.05). Statistical analyses were conducted using SAS® version 9.3 (SAS Institute, Cary, NC), and all tests were two-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 anti-inflammatory stable dietary pattern, 12.3% had anti-inflammatory dietary changes, 14.4% were in the neutral inflammation stable category, 11.3% experienced pro-inflammatory changes, while 32.3% were in the pro-inflammatory stable category. **Table 1** shows the distribution of participants' baseline characteristics across patterns of DII change. In the pro-inflammatory stable category, there was a higher proportion of African Americans (10.7%) or Hispanics (4.8%), participants with < high school education (5.9%), current smokers (7.7%), and obese participants (32.7%), and participants not meeting physical activity recommendations (51.8%) compared to the anti-inflammatory stable category (**Table 1**).

The cumulative average (SD) DII was -1.18 (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 was a higher proportion of African Americans (13.9%) or Hispanics (5.7%), participants with < high school education (7.3%), current smokers (9.1%), and obese participants (35.5%), participants not meeting physical activity recommendations (56.1%) in the highest compared to the lowest cumulative average DII quintile (**Table 2**). Participants in quintile 1, with the

lowest DII scores also had high intakes of fruits, vegetables, nuts and wholegrains (**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 non-users of NSAID, there was significantly higher risk of CRC (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 pro-inflammatory stable category compared to women in the anti-inflammatory stable category. There were no significant associations among regular users of NSAID (**Table 3**). The age-adjusted associations are presented in **Web Table 2**.

Table 4 presents HRs of the association between cumulative average DII and CRC risk. Comparing participants in the highest quintile to those in the lowest quintile of cumulative average DII, 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 non-users of NSAID. For example, among non-users of NSAID, there was a 65% higher risk of CRC (95%CI, 1.19, 2.29; P_{trend}=0.01), and 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 NSAID, 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 towards more pro-inflammatory 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 non-users of NSAID. To the best of our knowledge, this is the first study to characterize the association between changes over time and the cumulative history in the inflammatory potential of diet, and risk of overall CRC 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 pro-inflammatory 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 current study's findings, though 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 limited to 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), by NSAID use. Higher scores (representing a healthier lifestyle pattern) were associated with lower odds of colorectal adenomas among non-users of NSAID, but not among users (3). One other study examining the association between the DII and risk of CRC observed significantly higher risk among non-users of NSAID but not among users (20), while another found that higher DII scores were significantly associated with higher concentrations of inflammation markers only in non-users of NSAID (18).

The link between inflammation and CRC is supported by findings from several studies showing either a lower risk of CRC with regular use of NSAID (39, 40), or a positive association between higher concentrations of inflammation markers and higher CRC risk (41, 42). Other potential mechanisms through which a pro-inflammatory 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 pro-inflammatory 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, 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 five 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 contribute to high DII scores in this population, though 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 anti-inflammatory.

Strengths of the current 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 central adjudication of CRC diagnosis. Limitations include known measurement error in using an FFQ for the assessment of diet and its inflammatory potential over time (though we use ≥2 FFQs measured several years apart). Though 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, anthocyanidins) are anti-inflammatory. 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 -6.62 to +5.39 range of cumulative average DII in the current study is comparable to the range of -5.4 to +5.8 obtained in another study using

data from fifteen 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 towards the intake of more pro-inflammatory diets and a history of pro-inflammatory diets over a 3-year period are associated with higher risk of colon cancer, particularly proximal colon cancer and especially among non-users of NSAID. Future work may test interventions designed to reduce the inflammatory potential of diet as a means for colon cancer prevention, especially targeted to non-users of NSAID.

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TABLES AND FIGURES

Table 1. Frequencies (%) of participant's baseline characteristics across patterns of change in dietary inflammatory potential; Women's Health Initiative, 1993-2014

Characteristic	Patterns of change[a] in quintiles of the dietary inflammatory index[b]									
	Anti-inflammatory stable		Anti-inflammatory change		Neutral inflammation stable		Pro-inflammatory change		Pro-inflammatory stable	
	n	%	n	%	n	%	n	%	n	%
Age groups (years)										
<50-59	8006	30.9	3941	37.0	3869	30.9	3359	34.3	10028	35.6
60-69	12348	47.7	4752	44.6	5695	45.5	4309	44.0	12414	44.1
70-79	5533	21.4	1968	18.4	2953	23.6	2131	21.7	5736	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	3025	10.7
Hispanic/Latino	398	1.5	303	2.8	327	2.6	398	4.1	1340	4.8
European American	23235	89.8	9033	85.6	11059	88.4	8166	83.3	22653	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										
< High school	508	2.0	371	3.5	458	3.7	402	4.1	1661	5.9
Some high school/GED	11798	45.6	5538	51.9	6838	54.6	5313	54.2	16375	58.1
Some years of college/graduate	13439	51.9	4683	43.9	5136	41.0	3984	40.7	9911	35.2
Missing	142	0.5	69	0.7	85	0.7	100	1.0	231	0.8
Smoking status										
Never	13146	50.8	5330	50.0	6577	52.5	5016	51.2	14503	51.5
Former	11691	45.2	4602	43.1	5165	41.2	4168	42.5	11307	40.1
Current	914	3.5	660	6.2	693	5.6	514	5.6	2176	7.7
Missing	136	0.5	69	0.7	82	0.7	71	0.7	192	0.7
Body mass index[c]										
Normal weight (≤24.9)	10783	41.7	3957	37.1	4439	35.5	3334	34.1	9074	32.2
Overweight (25.0-29.9)	8994	34.7	3770	35.3	4461	35.6	3474	35.4	9884	35.1
Obese (≥30)	6110	23.6	2934	27.6	3617	28.9	2991	30.5	9220	32.7
Physical activity, minutes/week										
Not meeting physical activity recommendations	8492	32.8	4509	42.3	5577	44.6	4048	41.3	14599	51.8
Meeting physical activity recommendations	17365	67.1	6136	57.6	6920	55.3	5731	58.5	13505	47.9
Missing	31	0.1	16	0.1	20	0.1	20	0.2	74	0.3
Regular NSAID use[d]										
No	9875	38.2	4423	41.5	4690	37.5	3982	40.6	11901	42.2
Yes	15063	58.2	5759	54.0	7359	58.8	5366	54.8	14410	51.1
Missing	949	3.6	479	4.5	468	3.7	451	4.6	1867	6.7

GED=General educational development, NSAID=non-steroidal anti-inflammatory drugs;
[a]The differences in dietary inflammatory index (DII) scores from baseline to year 3 in the Observational Study and from year 1 to composite year 3 (i.e., years 2,3&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 (Q) differences between the first and second time points, as follows: **1) anti-inflammatory stable**: Q1 or Q2 at both time points or change from Q3 to Q2; **2) anti-inflammatory change**: changes ≤ -2Q; **3) neutral inflammation stable**: changes from Q2 to Q3, Q4 to Q3 or stable at Q3 at both time points; **4) pro-inflammatory change**: changes ≥ 2Q; and **5) pro-inflammatory stable**: Q4 or Q5 at either time points, or change from Q3 to Q4;
[b]DII components available in the Women's Health Initiative (WHI) food frequency questionnaire (FFQ) were: (**anti-inflammatory components)**: alcohol, beta-carotene, caffeine, fiber, folic acid, magnesium , niacin, riboflavin, thiamin, zinc, monounsaturated fatty acid (fa) polyunsaturated fa, omega 3 fa, omega 6 fa, selenium, vitamins B6, A, C, D, E, onion, green/black tea, isoflavones, (**pro-inflammatory components**): vitamin B12, iron, carbohydrates, cholesterol, total energy, total fat, saturated fat, trans fat, protein. The following components, **all anti-inflammatory**, were not available in the WHI FFQ: ginger, turmeric, garlic, oregano, pepper, rosemary, eugenol, saffron, flavan-3-ol, flavones, flavonols, flavonones, anthocyanidins;
[c]Weight (kg)/height (m)^2
[d]Regular use of NSAID was defined as use at least 2 times in each of the 2 weeks preceding the interview.

Table 2. Frequencies (%) of participant's baseline characteristics across quintiles of cumulative average DII[a,b] (baseline[c] and Year 3); Women's Health Initiative, 1993-2014

Characteristic	Quintile 1 (-6.62, < -3.25) (more anti-inflammatory)		Quintile 2 (-3.25, < -2.17)		Quintile 3 (-2.17, < -0.84)		Quintile 4 (< -0.84, 0.97)		Quintile 5 (0.97, 5.39) (more pro-inflammatory)	
	n	%	n	%	n	%	n	%	n	%
Age groups (years)										
<50-59	5483	31.5	5368	30.8	5732	32.9	6102	35.1	6518	37.4
60-69	8286	47.6	8063	46.3	7892	45.3	7711	44.3	7566	43.5
70-79	3639	20.9	3977	22.9	3785	21.8	3595	20.6	3325	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	1038	6.0	1445	8.3	2412	13.9
Hispanic/Latino	260	1.5	334	2.0	501	2.9	672	3.9	999	5.7
European American	15543	89.3	15613	89.7	15127	86.9	14535	83.5	13328	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										
< High school	275	1.6	498	2.9	590	3.4	767	4.4	1270	7.3
Some high school/GED	7386	42.4	8789	50.5	9338	53.6	9767	56.1	10582	60.8
Some years of college/graduate	9654	55.5	7998	45.9	7365	42.3	6733	38.7	5403	31.0
Missing	93	0.5	123	0.7	116	0.7	141	0.8	154	0.9
Smoking status										
Never	8642	49.6	8977	51.6	9043	51.9	8986	51.6	8924	51.3
Former	8124	46.7	7552	43.4	7294	41.9	7181	41.3	6782	39.0
Current	550	3.2	780	4.4	950	5.5	1116	6.4	1591	9.1
Missing	92	0.5	99	0.6	122	0.7	125	0.7	112	0.6
Body mass index[d]										
Normal weight (≤24.9)	7670	44.1	6707	38.5	6201	35.6	5782	33.2	5227	30.0

Overweight (25.0-29.9)	5953	34.2	6140	35.3	6277	36.1	6216	35.7	5997	34.5
Obese (≥30)	3785	21.7	4561	26.2	4931	28.3	5410	31.1	6185	35.5
Physical activity, minutes/week										
Not meeting physical activity recommendations	4887	28.1	6818	39.2	7436	42.7	8315	47.8	9769	56.1
Meeting physical activity recommendations	12501	71.8	10571	60.7	9942	57.1	9051	52.0	7592	43.6
Missing	20	0.1	19	0.1	31	0.2	42	0.2	48	0.3
Regular NSAID use[e]										
No	6833	39.3	6621	38.1	6835	39.3	7179	41.2	7403	42.5
Yes	9894	56.8	10171	58.4	9813	56.4	9319	53.5	8760	50.3
Missing	681	3.9	616	3.5	761	4.3	910	5.3	1246	7.2

DII=dietary inflammatory index, GED=General education development, NSAID=non-steroidal anti-inflammatory drugs;
[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;
[b]DII components available in the Women's Health Initiative (WHI) food frequency questionnaire (FFQ) were: (**anti-inflammatory components)**: alcohol, beta-carotene, caffeine, fiber, folic acid, magnesium , niacin, riboflavin, thiamin, zinc, monounsaturated fatty acid (fa) polyunsaturated fa, omega 3 fa, omega 6 fa, selenium, vitamins B6, A, C, D, E, onion, green/black tea, isoflavones, (**pro-inflammatory components**): vitamin B12, iron, carbohydrates, cholesterol, total energy, total fat, saturated fat, trans fat, protein. The following components, **all anti-inflammatory**, were not available in the WHI FFQ: ginger, turmeric, garlic, oregano, pepper, rosemary, eugenol, saffron, flavan-3-ol, flavones, flavonols, flavonones, anthocyanidins;
[c]Year 1 and composite Year 3 for the Dietary Modification Trial control group;
[d]Weight (kg)/height $(m)^2$
[e]Regular use of NSAID 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[2] cancer risk stratified by NSAID use; Women's Health Initiative, 1993-2014

	Patterns of change[b] in quintiles of the dietary inflammatory index								
Tumor location[c]	Anti-inflammatory stable (Referent)	Anti-inflammatory change		Neutral inflammation stable		Pro-inflammatory change		Pro-inflammatory stable	
	HR	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
All participants									
Colorectal cancer	1.00	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	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	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	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	0.98	0.60, 1.60	0.71	0.43, 1.20	1.06	0.64, 1.75	0.98	0.67, 1.44
Non users of non-steroidal anti-inflammatory drugs									
Colorectal cancer	1.00	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	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	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	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	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 non-steroidal anti-inflammatory drugs									
Colorectal cancer	1.00	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	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	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	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	0.96	0.52, 1.78	0.76	0.41, 1.43	1.01	0.53, 1.92	0.71	0.41, 1.21

NSAID=non-steroidal anti-inflammatory drugs;

[a]All models were 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 dietary inflammatory index (DII) scores from baseline to year 3 in the Observational Study and from year 1 to composite year 3 (i.e., years 2,3&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 (Q) differences between the first and second time points, as follows: **1) anti-inflammatory stable**: Q1 or Q2 at both time points or change from Q3 to Q2; **2) anti-inflammatory change**: changes ≤ -2Q; **3) neutral inflammation stable**: changes from Q2 to Q3, Q4 to Q3 or stable at Q3 at both time points; **4) pro-inflammatory change**: changes ≥ 2Q; and **5) pro-inflammatory stable**: Q4 or Q5 at either time points, or change from Q3 to Q4;

[c]International classification of diseases (ICD)-O-2 codes used to define location of colon cancer include 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 include all rectum and rectosigmoid cases;

Table 4: Multivariable-adjusted[a] hazards ratios of the association between cumulative average dietary inflammatory index and colorectal cancer risk stratified by NSAID use; Women's Health Initiative, 1993-2014

	Quintiles of cumulative average dietary inflammatory index[b]									
Tumor location[c]	Quintile 1 (more anti-inflammatory diet) referent	Quintile 2		Quintile 3		Quintile 4		Quintile 5 (more pro-inflammatory diet)		[d]P_{trend}
	HR	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR
All participants										
Colorectal cancer	1.00	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	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	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	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	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
Non users of non-steroidal anti-inflammatory drugs										
Colorectal cancers	1.00	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	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	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	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	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 non-steroidal anti-inflammatory drugs										
Colorectal cancer	1.00	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	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	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	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	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

NSAID=non-steroidal anti-inflammatory drugs;

[a]All models were 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 cumulative average dietary inflammatory index (DII) was the average of the DII scores at baseline (Year 1 for the Dietary Modification Trial control group) and Year 3;

[e]International classification of diseases (ICD)-O-2 codes used to define location of colon cancer include 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 include all rectum and rectosigmoid cases;

[d]The p value 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-adjusted model;