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Dietary Patterns and Risk of Colorectal Cancer: Analysis by Tumor Location and Molecular Subtypes

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Abstract

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Background & Aims—Western and prudent dietary patterns have been associated with higher and lower risks of colorectal cancer (CRC), respectively. However, little is known about associations between dietary patterns and specific anatomic subsite or molecular subtypes of CRC.

Methods—We used multivariable Cox proportional hazards models to examine associations between Western and prudent dietary patterns and CRC risk in the Health Professionals Follow-up Study and Nurses' Health Study.

Results—After up to 32 years of follow-up of 137,217 men and women, we documented 3260 cases of CRC. Among individuals from whom subsite data were available, we observed 1264 proximal colon, 866 distal colon, and 670 rectal tumors. Western diet was associated with an increased incidence of CRC (Ptrend<.0001), with a relative risk (RR) of 1.31 (95% CI, 1.15–1.48, comparing the highest to lowest quartile). The association of Western diet with CRC was evident for tumors of the distal colon (RR, 1.55; 95% CI, 1.22–1.96; Ptrend=.0004) and rectum (RR, 1.35; 95% CI, 1.03–1.77; Ptrend=.01) but not proximal colon (RR, 1.11; 95% CI, 0.91–1.35; Ptrend=.51) when we compared extreme quartiles. In contrast, for the prudent pattern, we observed a RR of 0.86 for overall CRC (95% CI, 0.77–0.95; Ptrend=.01), with similar trends at anatomic subsites. However, the trend appeared stronger among men than women. Among 1285 cases (39%) with tissue available for molecular profiling, Western diet appeared to be more strongly associated with some CRC molecular subtypes (no mutations in KRAS [KRAS wildtype] or BRAF [BRAF wildtype], no or a low CpG island methylator phenotype, and microsatellite stability), although formal tests for heterogeneity did not produce statistically significant results.

Conclusions—Western dietary patterns are associated with an increased risk of CRC, particularly distal colon and rectal tumors. Western dietary patterns also appear more strongly associated with tumors that are KRAS wildtype, BRAF wildtype, have no or a low CpG island methylator phenotype, and microsatellite stability. In contrast, prudent dietary patterns are associated with a lower risk of CRC that does not vary according to anatomic subsite or molecular subtype.

Keywords

red meat; processed meat; colon cancer risk; molecular epidemiology

Introduction

Dietary exposures play a major role in the development of colorectal cancer (CRC).[1] Examining dietary patterns in relation to risk of CRC offers insights beyond associations of individual food groups or nutrients. Dietary pattern data better capture the complexity of food intakes than any one individual food item, and offer the advantage of describing usual consumption of foods in typical diets.[2] Thus, identifying potential associations according to dietary patterns may lead to the development of more practical dietary guidelines for the prevention of chronic disease, including CRC.[3]

Western dietary patterns – characterized by higher intake of red and processed meats, added sugar, and refined grains – have been strongly linked with colorectal cancer in numerous observational studies as well as in a systematic review and meta-analysis.[4–7] In contrast,

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"prudent" patterns – rich in fruits, vegetables, fish, poultry and whole-grain products – are associated with a lower risk of CRC.[4,8]

Despite these data, our understanding of the association between dietary patterns and CRC risk according to anatomic site or molecular subtype remains unclear. Although there were no clear differences in the risk estimates for proximal and distal CRCs in a recent meta-analysis, prior evidence has suggested that increased consumption of red and processed meat as well as low consumption of fruits and vegetables may be more strongly associated with higher risk of distal CRC.[9–11] In addition, emerging data suggest that the association between diet and colorectal cancer may vary according to specific tumor molecular features, such as CpG island methylator phenotype (CIMP) status and microsatellite instability (MSI).[12–16]

Therefore, in two U.S. prospective cohort studies, we hypothesized that Western and prudent dietary pattern scores and risk of colorectal cancer were more strongly associated with distal colon and rectal cancers. In addition, given previous evidence demonstrating that the frequency of CIMP-high, MSI-high, and *BRAF*-mutated cancers increases from rectum to the ascending colon,[17] we also hypothesized that heterogeneity in the association of Western and prudent diets with subsite may be driven by variation in the prevalence of molecular subtypes. Specifically, we examined if there were differential associations between Western and prudent dietary scores with tumors classified according to CIMP, MSI, *KRAS,* or *BRAF* status.

Methods

Study population

Data were drawn from two ongoing cohorts, the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS).[18,19] The HPFS began in 1986 among 51,529 US male podiatrists, dentists, osteopathic physicians, veterinarians, pharmacists, and optometrists aged 40 to 75 years at enrollment. The NHS began in 1976 among 121,700 US female registered nurses aged 30 to 55 years at enrollment. In both cohorts, participants have returned questionnaires every two to four years with greater than 90% follow-up to provide information about lifestyle and dietary factors, medication use, and diagnoses of CRC and other diseases. The Institutional Review Board at the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health approved this study.

Assessment of dietary information

Participants self-reported average food intake over the preceding year through semi-quantitative food frequency questionnaires (FFQ), which have been previously validated and described in detail.[3,20] Briefly, to capture frequency of food consumption, nine response options were provided, ranging from "never or less than once per month" to "6 or more times per day." Total caloric and nutrient intake were calculated by summing up energy and nutrient intakes from all foods. For this analysis, we used information from the HPFS FFQs administered in 1986, 1990, 1994, 1998, 2002, 2006, and 2010. For the NHS, we used data from the FFQs administered in 1980, 1984, 1986, 1990, 1994, 1998, 2002, 2006, and 2010.

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At baseline, we excluded participants with implausibly high or low caloric intakes (i.e., <800 or >4,200 kcal/d for men; <600 or >3,500 kcal/d for women; n=430), those with a high number of blanks on their FFQ (≥ 70 for the HPFS; ≥ 60 for the NHS), participants with missing dietary pattern data, and participants with a history of ulcerative colitis (n=1,519) or cancer (except for non-melanoma skin cancer) prior to baseline (1986 for the HPFS and 1980 for the NHS; n=2,998).

Assessment of colorectal cancer cases and subsite information

In both cohorts, incident cases of CRC were reported by participants through 2012 follow-up. A study physician, blinded to exposure information, reviewed all records to confirm incident cases, as well as to extract data on histological type, anatomic location, and stage of the cancer. Tumors were classified as proximal if they were removed from the cecum to the transverse colon, distal if they were removed from the splenic flexure to the sigmoid colon, and rectal if they were removed from the rectosigmoid junction to the anal canal (excluding anal squamous cell carcinoma). In the case that study participants who died from CRC were not captured during our regular follow-up questionnaires were identified and confirmed through information from various sources including next-of-kin, the National Death Index, death certificates, and medical records.

Molecular marker assessment

Among CRC cases with available tumor tissue, we retrieved formalin-fixed paraffin-embedded (FFPE) tissue blocks from hospitals throughout the U.S as previously detailed.[21] Normal and tumor sections from all CRC cases were reviewed by a pathologist (S.O.). The baseline characteristics of participants with CRC whose tumors we analyzed were overall similar to those of participants whose tumors we did not analyze, although participants with tumor tissue available were less likely to be postmenopausal in women (**Supplementary** Table 1).

DNA was extracted from paraffin-embedded archival tumor and normal tissues. We performed real-time polymerase chain reaction (PCR) and pyrosequencing targeted for *KRAS* codons 12, 13, 61, and 147 as previously described.[22,23] MSI status was determined using 10 microsatellite markers (D17S250, D18S55, D18S56, D18S67, D18S487, D2S123, D5S346, BAT25, BAT26, and BAT40), also as previously described.[24] Tumors were classified as MSI-high if 30% or more of the markers demonstrated instability. We quantified DNA methylation using PCR in eight CIMP-specific promoters [*MLH1, NEUROG1, RUNX3*, *CACNA1G, CDKN2A* (p16), *CRABP1, IGF2,* and *SOCS1*].[25] We classified tumors as CIMP-high if six or more promoters were methylated, and as CIMP-low/negative if zero to five promoters were methylated.[26] Finally, we performed PCR and pyrosequencing targeted towards the *BRAF* codon 600 mutation.[27]

Statistical Analysis

Two dietary patterns – named “Western” and “prudent” – were derived by principal component analysis (PCA) as previously described and validated with good reproducibility.[7,28] To briefly summarize, foods from the FFQ were classified into approximately 40 food groups based on nutrient profiles or culinary usage. Foods that did

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not fit into any of the groups were left as individual categories (*e.g.* pizza, French fries, and tea). Each alcoholic beverage (wine, liquor, beer) type was also included separately as food groups. Vitamin and mineral supplements were not included in the definition of the patterns. Factor analysis was then performed using an orthogonal rotation procedure (the Varimax function in SAS) to produce two maximally uncorrelated factors, based upon the largest eigenvalues and scree plot. Factor loadings were then derived from the correlations between food groups and the two derived factors. Each participant was then assigned two factor scores, determined by adding the reported frequencies of food group intakes, weighted by the factor loadings for each factor. These factor scores were then standardized using a z-score scale, with a mean of 0 and standard deviation of 1. Higher scores indicated stronger adherence to that particular pattern. To capture long-term habitual consumption, we calculated the cumulative average of factor scores,[3] which were then categorized into quartiles, to maximize our power for molecular subtype analysis.

Using Cox proportional hazards models, we examined the association between Western and prudent dietary patterns and risk of CRC. All analyses were adjusted for total caloric intake (kcal per day) and stratified by age (in months), year of questionnaire return, and sex (in the analysis using combined cohorts). In multivariable analysis, we adjusted for several risk factors for CRC including body mass index (kg/m^2), pack years of smoking (never, 0–4 years, 5–19 years, 20–39 years, or ≧40 years), family history of CRC in any first-degree relative (yes or no), previous lower gastrointestinal endoscopy (yes or no), menopausal hormone use [(for women only) never, past current], physical activity [quintiles of metabolic-equivalent task (MET) hours per week], and regular aspirin or NSAID use (≥2 tablets/wk). To derive physical activity, NHS and HPFS participants were asked to complete a previously validated questionnaire,[29,30] which is a self-reported measure of average weekly recreational physical activity (including walking or hiking, jogging, running, bicycling, swimming, tennis, squash or racquetball, calisthenics or rowing, weight lifting, and heavy outdoor work) throughout the past year. There were 13 response categories ranging from none to >40 hours per week. As in prior analyses,[31,32] the number of hours spent on each activity was then multiplied by its intensity, for a total MET-hours per week score.

To examine whether the association between dietary patterns and risk of CRC differed according to anatomic location or molecular subtype, we used Cox proportional hazards regression models with a duplication method for competing risks data and computed relative risks (RR) and 95% confidence intervals (CI). We tested for heterogeneity by using a one degree-of-freedom likelihood ratio test, comparing a model that allows for separate associations of dietary patterns and risk of CRC according to anatomic and molecular subtypes with a model that assumes a common association.[33] To test for trend, participants were assigned to the median value of their dietary pattern quartile and then this variable was entered into the models as a continuous term. In a secondary analysis, among cases with available tumor tissue, we examined associations between dietary patterns and specific molecular subtypes.

Prior to pooling data from the two cohorts, we examined the possible heterogeneity between cohorts, using the Q statistic for the association between the prudent and Western dietary

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patterns and overall incidence of CRC. We used SAS software version 9.3 (SAS Institute Inc.) All statistical tests were two-sided. A p value of 0.05 was considered statistically significant.

Results

Among 137,217 participants (47,449 men and 89,768 women), we documented 3,260 CRC cases that developed during 3,646,068 person-years of follow-up. Among CRC cases in the HPFS and the NHS with available data on anatomic location, we identified 1,264 proximal colon, 866 distal colon, and 670 rectal tumors.

Two major dietary patterns were identified by factor analysis and were labeled Western and prudent. The Western dietary pattern was characterized by red and processed meats, high-fat dairy products (such as whole milk and cream), refined grains, and desserts, while the prudent dietary pattern was characterized by high intakes of vegetables, fruits, whole grains, and fish.[34] The characteristics of the patterns were stable across repeated FFQs and in both cohorts. Consistent with the prior analyses,[5,7] Western pattern scores were associated with less healthy behaviors whereas prudent pattern scores were associated with healthier behaviors (Table 1). In particular, participants with high Western scores were less likely to have a history of screening lower endoscopy and were more likely to smoke. In contrast, those with high prudent scores tended to smoke less and exercise more.

We first examined the association between Western and prudent dietary pattern scores with the overall risk of CRC. Western dietary pattern scores were directly associated with overall incidence of CRC in both men (HPFS) and women (NHS) (P_{trend} = 0.04 and 0.002, respectively) (Table 2). In contrast, prudent dietary pattern scores appeared to be inversely associated with overall risk of CRC, although tests for linear trend were only statistically significant in men and not women (P_{trend} = 0.03 and 0.24, respectively) (Table 3). Although when compared to the women, our results for the prudent dietary pattern appeared slightly stronger among men, we did not observe statistically significant heterogeneity between cohorts (P=0.83 for the Western dietary pattern; P=0.26 for the prudent dietary pattern). Thus we combined data from both cohorts. In the combined cohort, compared to those in the lowest quartile of Western dietary pattern, the multivariable RR for CRC was 1.31 (95% CI, 1.15–1.48) for those in the highest quartile (P_{trend} < 0.0001) (Table 2). For the prudent pattern, compared to those in the lowest quartile of pattern scores, the multivariable RR for CRC was 0.86 (95% CI, 0.77–0.95) for those in the highest quartile (P_{trend} = 0.01) (Table 3).

We considered the possibility that a history of endoscopy may have influenced our results. Thus, we restricted the cohort to individuals without a prior endoscopy and observed similar results. Compared to individuals in the lowest quartile of Western dietary pattern, the multivariate HR for colorectal cancer was 1.32 (95% CI, 1.15–1.51) for those in the highest quartile of Western dietary pattern (P_{trend}=0.0002). In contrast, compared to individuals in the lowest quartile of prudent dietary pattern, the multivariate HR for colorectal cancer was 0.87 (95% CI, 0.76–0.98) for those in the highest quartile of Prudent dietary pattern (P_{trend}=0.06). We also considered the possibility that a history of regular aspirin/NSAID use may have influenced our results by restricting the cohort to individuals without a history of

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regular use of aspirin/NSAIDs. Comparing extreme quartiles for the Western dietary pattern, the multivariate HR for colorectal cancer was 1.34 (95% CI, 1.13–1.58, P_{trend}=0.001). In contrast, comparing extreme quartiles for the prudent dietary pattern, the multivariate HR for colorectal cancer was 0.83 (95% CI, 0.72–0.96, P_{trend}=0.03).

We then examined the association of the two dietary patterns with risk of CRC by anatomic subsite. The association of Western diet with cancer incidence was evident for tumors of the distal colon (P_{trend} = 0.0004) and rectum (P_{trend} =0.01) but not proximal colon (P_{trend} =0.51) (Table 2) although a formal test for heterogeneity between distal colon and rectal tumors versus proximal colon tumors was not statistically significant ($P_{heterogeneity}$=0.13). In contrast, there was no evidence of differences by anatomic subsite for prudent dietary pattern scores ($P_{heterogeneity}$=0.24) (Table 3).

Finally, because of evidence for a stronger association between Western dietary pattern and distal colorectal tumors (compared to proximal tumors), we next examined the association between dietary patterns and risk of CRC according to molecular features that have been associated with tumor subsite. We utilized cases with available tumor tissue data as follows: 1,285 tumors for *KRAS* mutation status, 1,267 for MSI status, 1,233 for CIMP status, and 1,284 for *BRAF* mutation, which represented at most 39% of the tumors in the overall analysis. For the Western dietary pattern, we observed stronger associations comparing extreme quartiles as well as statistically significant trends (ptrend ≤ 0.03) for MSS, *KRAS*-wildtype, *BRAF*-wildtype, and CIMP-negative/low tumors than for MSI-high, *KRAS*-mutant, *BRAF*-mutant, CIMP-high tumors (Table 4). Nevertheless, formal tests for heterogeneity were all nonsignificant ($p_{heterogeneity} \geq 0.28$). We did not observe evidence of heterogeneity by these molecular subtypes for the prudent dietary pattern (Table 5).

Discussion

In two large U.S. prospective cohorts, we found that participants with higher long-term Western dietary pattern scores had a greater risk of CRC whereas those with higher prudent dietary pattern scores had a decreased risk of CRC. Notably, the association between Western diet and CRC appeared more evident for distal colon and rectal tumors compared to proximal colon tumors, although the formal statistical test for heterogeneity was not significant. In addition, our results suggest that Western dietary patterns are more strongly associated with *KRAS*-wildtype, *BRAF*-wildtype, CIMP-negative/low, and MSS tumors, although, again, formal tests for heterogeneity by molecular subtype were not statistically significant.

Our data are consistent with a recent meta-analysis reporting that Western dietary patterns are associated with an increased risk of CRC whereas prudent patterns are associated with lower risk.[4] Similarly, based on review of available data, the World Health Organization concluded that consumption of red and processed meat is probably carcinogenic and carcinogenic, respectively, to humans.[35] In addition, our findings that Western diet has a stronger link to distal and rectal tumors agrees with four prior studies in the U.S. and Japan that examined the relationship between Western diet and risk of CRC according to subsite.[5,8,36,37] In contrast, our results differ from two studies that reported no material

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relationship between Western diet and site-specific risk of CRC. However, these studies were limited in power and failed to detect an overall increased association.[6,38] Furthermore, a number of prior analyses have indicated that the positive relationship between processed meat consumption and cancer risk was stronger for the distal colon than for the proximal colon.[11,39] Finally, our data are concordant with broad epidemiological trends in the developing world which reflect an increasing Westernization of their diet. The incidence of distal colon cancer tumors has increased in Asian populations, especially urbanized areas compared to rural areas. In contrast, proximal tumor rates have stabilized.[40]

The mechanism by which Western diet may be more strongly linked to distal colorectal tumors rather than proximal tumors remains uncertain but may be related to heterogeneity in carcinogenic processes in different sites of the large bowel. Considerable evidence suggests that proximal colon tumors are associated with the serrated carcinogenic pathway characterized by specific molecular alterations such as CIMP-high, MSI-high, and *BRAF* mutations.[12,17,35,36] In contrast, tumors arising in the distal colon and rectum more commonly originate through the traditional chromosomal instability pathway characterized by *APC* mutations.[37,38] This theory may be supported by data from a case-control study revealing that components of a Western diet – including greater red meat consumption – were most strongly associated with CRC characterized by *TP53* mutations compared to *TP53*-wildtype tumors.[45] In addition, a Dutch case-control study found that red meat consumption was more strongly associated with MSI-low/MSS carcinomas compared to MSI-high tumors.[13] Although we observed a similar trend towards a stronger association of Western diet with MSS cancer risk, compared to that with MSI-high cancer risk, the difference was not statistically significant, in part due to a limited statistical power in the case set with available tumor molecular data. Finally, divergent results by anatomic subsite may additionally be explained by findings that the proximal colon, distal colon, and rectum each contains distinct microbial communities,[46,47] derives from different embryological origins (midgut vs. hindgut),[48] and is exposed to varied levels of metabolites such as short-chain fatty acids and bile acids.[49]

There are several strengths to this study. First, our dietary data were prospectively collected with follow-up rates exceeding 90%, lowering effects of recall or selection bias, and our dietary instruments have been well-validated.[3,20] Second, by examining dietary patterns, we were less likely to produce statistically significant results by chance compared to analyses assessing the associations of many individual food items and nutrients with CRC risk. Third, detailed data on a wide range of exposures allowed us to adjust for multiple confounding factors, although residual confounding cannot be excluded.

We also acknowledge limitations to this study. Our diet data were derived from questionnaires, allowing for possible measurement error. Nonetheless, questionnaire-based diet data collection can capture long-term dietary intakes better than food diaries in limited time periods.[3] Despite the large size of the two cohorts, we had limited power to detect heterogeneity in the associations of dietary patterns with CRC tumor molecular subtypes. Nevertheless, our molecular pathological epidemiology database offers a unique opportunity to integrate long-term dietary data with molecular features of colorectal tumors collected from participants across the U.S.[43] Finally, because our participants were all health

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professionals and are mostly Caucasian, generalizability of our study findings to other populations needs to be examined.

In summary, we have shown that higher Western dietary pattern scores are associated with a greater risk of CRC, particularly distal colorectal tumors and tumors that are *KRAS*-wildtype, *BRAF*-wildtype, CIMP-low, and MSS. In contrast, higher prudent dietary pattern scores are associated with a lower risk of CRC that did not appear to vary according to anatomic subsite or molecular subtype. Our data support the latest guidelines promoting high consumption of whole grains, fruits, and vegetables and low intakes of processed and red meat for primary prevention of CRC. Additional studies are needed to confirm our findings and to further characterize the complex mechanisms underlying the well-documented relationship between Western diet and CRC.

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Abbreviations

BMI	body mass index
CI	confidence interval
CIMP	CpG Island Methylator Phenotype
CRC	colorectal cancer
FFPE	formalin-fixed paraffin-embedded
FFQ	food frequency questionnaire
HPFS	Health Professionals Follow-up Study
MSI	microsatellite instability
MSS	microsatellite stable
NHS	Nurses' Health Study
PCA	principal component analysis

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PCR	polymerase chain reaction
RR	relative risk
SD	standard deviation

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Table 1

Age-standardized characteristics of the Health Professionals Follow-up Study and Nurses' Health Study participants in 1994 and 1990, respectively, according to Western and prudent dietary pattern intake

Characteristic	Western Dietary Pattern				Prudent Dietary Pattern			
	HPFS		NHS		HPFS		NHS	
	Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4
Age (mean)	61.4	61.0	56.4	56.2	61.1	61.3	56.2	56.4
Pack-years smoked (mean)	9.2	18.3	12.1	15.5	16.1	11.0	17.8	10.6
Current smoker, %	3	13	13	23	12	5	27	12
Family history of colorectal cancer, %	14	13	16	17	13	14	16	17
History of previous endoscopy, %	22	16	28	22	17	21	23	27
Current multivitamin use, %	47	39	44	32	39	47	33	44
Regular aspirin/NSAID use, %*	42	46	45	51	42	45	48	44
Postmenopausal, %†			79	77			78	79
Menopausal hormone use, %†			38	30			32	36
Body mass index, kg/m^2 (mean)	25.4	26.5	25.3	26.3	26.1	25.8	25.5	26.0
Physical activity, MET-hours/wk‡ (mean)	37.7	34.4	17.6	10.9	26.4	44.8	9.9	18.3
Dietary intake (means)								
Unprocessed red meat, servings/d	0.25	0.94	0.31	0.76	0.59	0.52	0.53	0.50
Processed red meat, servings/d	0.07	0.54	0.09	0.40	0.33	0.20	0.26	0.17
Poultry, servings/d	0.40	0.42	0.42	0.36	0.31	0.52	0.27	0.51
Fruit, servings/d	3.07	2.42	2.44	2.29	1.65	3.86	1.52	3.28
Vegetable, servings/d	3.64	3.48	3.49	3.34	1.85	5.54	1.95	5.10
Alcohol, g/d	7.5	14.2	5.6	5.0	11.2	10.6	5.9	4.8
Folate, µg/d	625	449	499	367	451	618	376	490
Calcium, mg/d	1023	831	1151	835	863	975	900	1062
Vitamin D, IU/d	540	379	420	271	408	499	309	376
Dietary fiber, g/d	28	19	21	16	18	29	15	22

*Regular users are defined as ≥2 standard (325-mg) tablets of aspirin or ≥ 2 tablets of NSAIDs per week.

†The percentages of postmenopausal participants as well as hormone use are among women only.

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[‡]Physical activity is represented by the product sum of the metabolic equivalent (MET) of each specific recreational activity and hours spent on that activity per week. METs were assessed in 1986 for the NHS.

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Table 2

Relative risks (RRs) of incident colorectal cancer, overall and by subsite, according to Western dietary pattern score quartiles in the Health Professionals Follow-up Study (1986–2012), the Nurses' Health Study (1980–2012), and the pooled cohort.

	Person- years	Colorectal cancer		Proximal colon cancer		Distal colon cancer		Rectal cancer	
		Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
HPFS: Multivariable- adjusted*									
Quartile 1	259,223	236	1 (referent)	80	1 (referent)	70	1 (referent)	56	1 (referent)
Quartile 2	259,918	275	1.23 (1.03–1.48)	91	1.11 (0.81–1.52)	90	1.46 (1.05–2.03)	46	0.93 (0.62–1.41)
Quartile 3	259,766	270	1.25 (1.02–1.52)	100	1.13 (0.81–1.58)	79	1.38 (0.96–1.99)	60	1.37 (0.90–2.08)
Quartile 4	259,664	268	1.31 (1.03–1.67)	91	0.98 (0.65–1.48)	77	1.55 (1.00–2.41)	59	1.53 (0.92–2.56)
P for trend¶			0.04		0.89		0.09		0.05
NHS: Multivariable- adjusted†									
Quartile 1	652,059	599	1 (referent)	257	1 (referent)	146	1 (referent)	116	1 (referent)
Quartile 2	651,238	547	1.02 (0.90–1.15)	251	1.09 (0.91–1.31)	118	0.91 (0.71–1.16)	105	1.01 (0.77–1.32)
Quartile 3	651,322	514	1.04 (0.91–1.18)	190	0.91 (0.74–1.11)	129	1.06 (0.82–1.37)	116	1.20 (0.91–1.58)
Quartile 4	652,878	551	1.28 (1.10–1.48)	204	1.13 (0.89–1.43)	157	1.46 (1.10–1.95)	112	1.29 (0.93–1.80)
P for trend¶			0.002		0.58		0.006		0.09
Pooled: MV-adjusted‡									
Quartile 1	911,282	835	1 (referent)	337	1 (referent)	216	1 (referent)	172	1 (referent)
Quartile 2	911,156	822	1.09 (0.99–1.20)	342	1.11 (0.95–1.29)	208	1.10 (0.90–1.34)	151	0.98 (0.78–1.22)
Quartile 3	911,088	784	1.11 (1.00–1.24)	290	0.99 (0.83–1.17)	208	1.19 (0.97–1.47)	176	1.24 (0.99–1.56)
Quartile 4	912,542	819	1.31 (1.15–1.48)	295	1.11 (0.91–1.35)	234	1.55 (1.22–1.96)	171	1.35 (1.03–1.77)
P for trend¶			<0.0001		0.51		0.0004		0.01

*Cox proportional hazards models stratified by age and calendar year and adjusted for family history of colorectal cancer in any first-degree relative, history of previous lower gastrointestinal endoscopy, pack-years of smoking (never, 0–4, 5–19, 20–39, or ≥40), body mass index (kg/m^2), physical activity (MET-hours/week), regular aspirin or NSAID use (≥2 tablets/week), and total caloric intake.

†As above and additionally adjusted for menopausal hormone use.

‡As the first, additionally stratified by sex.

¶Tests for trend were conducted using the median value of each category as a continuous variable.

Abbreviations: CI, confidence interval; RR, relative risk; MET, metabolic equivalent task; NSAID, non-steroidal anti-inflammatory drug.

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Table 3

Relative risks (RRs) of incident colorectal cancer, overall and by subsite, according to prudent dietary pattern score quartiles in the Health Professionals Follow-up Study (1986–2012), the Nurses' Health Study (1980–2012), and the pooled cohort.

	Person-years	Colorectal cancer		Proximal colon cancer		Distal colon cancer		Rectal cancer	
		Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
HPFS: Multivariable-adjusted*									
Quartile 1	260,363	271	1 (referent)	74	1 (referent)	90	1 (referent)	58	1 (referent)
Quartile 2	259,019	256	0.87 (0.73–1.03)	81	1.00 (0.72–1.39)	80	0.82 (0.60–1.12)	62	1.00 (0.69–1.45)
Quartile 3	260,450	264	0.84 (0.70–1.01)	102	1.15 (0.83–1.60)	81	0.82 (0.59–1.14)	51	0.75 (0.50–1.13)
Quartile 4	258,738	258	0.78 (0.64–0.96)	105	1.17 (0.82–1.67)	65	0.66 (0.45–0.96)	50	0.64 (0.41–1.01)
P for trend¶			0.03		0.29		0.04		0.03
NHS: Multivariable-adjusted†									
Quartile 1	653,901	572	1 (referent)	232	1 (referent)	130	1 (referent)	120	1 (referent)
Quartile 2	649,224	505	0.89 (0.79–1.00)	203	0.85 (0.70–1.03)	129	1.00 (0.78–1.28)	98	0.84 (0.64–1.11)
Quartile 3	652,562	566	0.94 (0.83–1.06)	241	0.93 (0.77–1.12)	151	1.11 (0.87–1.41)	109	0.89 (0.68–1.17)
Quartile 4	651,811	568	0.90 (0.79–1.03)	226	0.82 (0.67–1.01)	140	0.98 (0.76–1.28)	122	0.98 (0.74–1.30)
P for trend¶			0.24		0.11		0.99		0.93
Pooled: Multivariable-adjusted‡									
Quartile 1	914,264	843	1 (referent)	306	1 (referent)	220	1 (referent)	178	1 (referent)
Quartile 2	908,243	761	0.88 (0.80–0.97)	284	0.88 (0.75–1.04)	209	0.93 (0.76–1.13)	160	0.90 (0.72–1.12)
Quartile 3	913,012	830	0.90 (0.82–1.00)	343	0.97 (0.82–1.14)	232	0.99 (0.82–1.21)	160	0.84 (0.68–1.06)
Quartile 4	910,549	826	0.86 (0.77–0.95)	331	0.88 (0.74–1.05)	205	0.85 (0.69–1.05)	172	0.86 (0.68–1.09)
P for trend¶			0.01		0.33		0.15		0.18

*Cox proportional hazards models stratified by age and calendar year and adjusted for family history of colorectal cancer in any first-degree relative, history of previous lower gastrointestinal endoscopy, pack-years of smoking (never, 0–4, 5–19, 20–39, or ≥40), body mass index (kg/m^2), physical activity (MET-hours/week), regular aspirin or NSAID use (≥2 tablets/week), and total caloric intake.

†As above and additionally adjusted for menopausal hormone use.

‡As the first, additionally stratified by sex.

¶Tests for trend were conducted using the median value of each category as a continuous variable.

Abbreviations: CI, confidence interval; RR, relative risk; MET, metabolic equivalent task; NSAID, non-steroidal anti-inflammatory drug.

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Table 4

Multivariable-adjusted relative risks (RRs) of incident CRC by MSI, CIMP, *KRAS*, and *BRAF* status according to the Western dietary pattern in the pooled cohort of the Health Professionals Follow-up Study (1986–2012) and the Nurses' Health Study (1980–2012).

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend} †	$P_{heterogeneity}$ ‡
MSS/MSI-low CRC						
No. of cases (n=1057)	249	271	264	273		
Multivariable RR (95% CI) *	1 (referent)	1.19 (1.00–1.42)	1.22 (1.01–1.47)	1.39 (1.12–1.72)	0.004	
MSI-high CRC						0.28
No. of cases (n=210)	60	59	43	48		
Multivariable RR (95% CI) *	1 (referent)	1.07 (0.75–1.54)	0.87 (0.59–1.30)	1.15 (0.77–1.71)	0.71	
***BRAF*-wildtype CRC**						
No. of cases (n=1088)	265	281	262	280		
Multivariable RR (95% CI) *	1 (referent)	1.15 (0.97–1.37)	1.14 (0.95–1.37)	1.33 (1.08–1.65)	0.01	
***BRAF*-mutant CRC**						0.69
No. of cases (n=196)	51	54	47	44		
Multivariable RR (95% CI) *	1 (referent)	1.19 (0.81–1.76)	1.09 (0.73–1.64)	1.24 (0.81–1.89)	0.40	
CIMP-low/negative CRC						
No. of cases (n=1013)	238	265	253	257		
Multivariable RR (95% CI) *	1 (referent)	1.21 (1.01–1.45)	1.20 (0.99–1.46)	1.31 (1.05–1.64)	0.02	
CIMP-high CRC						0.28
No. of cases (n=220)	66	60	46	48		
Multivariable RR (95% CI) *	1 (referent)	1.00 (0.70–1.42)	0.85 (0.58–1.25)	1.07 (0.72–1.59)	0.92	
***KRAS*-wildtype CRC**						
No. of cases (n=835)	194	224	207	210		
Multivariable RR (95% CI) *	1 (referent)	1.26 (1.03–1.53)	1.23 (1.00–1.52)	1.39 (1.10–1.76)	0.01	
***KRAS*-mutant CRC**						0.33
No. of cases (n=450)	123	114	100	113		
Multivariable RR (95% CI) *	1 (referent)	1.02 (0.78–1.232)	0.94 (0.71–1.24)	1.17 (0.88–1.56)	0.36	

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[*] Cox proportional hazards models stratified by age, sex, and calendar year and adjusted for family history of colorectal cancer in any first-degree relative, history of previous lower gastrointestinal endoscopy, pack-years of smoking (never, 0–4, 5–19, 20–39, or ≥40), body mass index (kg/m^2), physical activity (MET-hours/week), regular aspirin or NSAID use (≥2 tablets/week), and total caloric intake.

[†] Tests for trend were conducted using the median value of each category as a continuous variable.

[‡] We tested for heterogeneity by using a likelihood ratio test, comparing a model that allows separate associations for the two colorectal cancer subtypes with a model that assumes a common association. Abbreviations: CI, confidence interval; CIMP, CpG island methylator phenotype, RR, relative risk; MET, metabolic equivalent task; MSI, microsatellite instability; MSS, microsatellite stability; NSAID, non-steroidal anti-inflammatory drug.

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Table 5

Multivariable-adjusted relative risks (RRs) of incident CRC by MSI, CIMP, *KRAS*, and *BRAF* status according to the prudent dietary pattern in the pooled cohort of the Health Professionals Follow-up Study (1986–2012) and the Nurses' Health Study (1980–2012).

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend} †	$P_{heterogeneity}$ ‡
MSS/MSI-low CRC						
No. of cases (n=1057)	263	256	270	268		
Multivariable RR (95% CI) *	1 (referent)	0.94 (0.79–1.12)	0.92 (0.77–1.10)	0.87 (0.72–1.05)	0.12	
MSI-high CRC						0.59
No. of cases (n=210)	61	38	57	54		
Multivariable RR (95% CI) *	1 (referent)	0.58 (0.39–0.88)	0.80 (0.55–1.15)	0.70 (0.48–1.02)	0.19	
***BRAF*-wildtype CRC**						
No. of cases (n=1088)	273	269	269	277		
Multivariable RR (95% CI) *	1 (referent)	0.95 (0.80–1.12)	0.88 (0.73–1.05)	0.85 (0.71–1.03)	0.07	
***BRAF*-mutant CRC**						0.89
No. of cases (n=196)	55	31	60	50		
Multivariable RR (95% CI) *	1 (referent)	0.55 (0.35–0.86)	0.98 (0.68–1.42)	0.75 (0.51–1.12)	0.50	
CIMP-low/negative CRC						
No. of cases (n=1013)	258	248	248	259		
Multivariable RR (95% CI) *	1 (referent)	0.95 (0.79–1.13)	0.89 (0.74–1.07)	0.88 (0.72–1.06)	0.14	
CIMP-high CRC						0.98
No. of cases (n=220)	61	40	58	61		
Multivariable RR (95% CI) *	1 (referent)	0.62 (0.42–0.93)	0.81 (0.56–1.17)	0.79 (0.55–1.14)	0.48	
***KRAS*-wildtype CRC**						
No. of cases (n=835)	217	181	211	226		
Multivariable RR (95% CI) *	1 (referent)	0.80 (0.65–0.98)	0.87 (0.72–1.06)	0.88 (0.71–1.07)	0.37	
***KRAS*-mutant CRC**						0.30
No. of cases (n=450)	111	118	117	104		
Multivariable RR (95% CI) *	1 (referent)	1.04 (0.80–1.35)	0.93 (0.71–1.21)	0.79 (0.60–1.05)	0.06	

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[*] Cox proportional hazards models stratified by age, sex, and calendar year and adjusted for family history of colorectal cancer in any first-degree relative, history of previous lower gastrointestinal endoscopy, pack-years of smoking (never, 0–4, 5–19, 20–39, or ≥40), body mass index (kg/m^2), physical activity (MET-hours/week), regular aspirin or NSAID use (≥2 tablets/week), and total caloric intake.

[†] Tests for trend were conducted using the median value of each category as a continuous variable.

[‡] We tested for heterogeneity by using a likelihood ratio test, comparing a model that allows separate associations for the two colorectal cancer subtypes with a model that assumes a common association Abbreviations: CI, confidence interval; CIMP, CpG island methylator phenotype, RR, relative risk; MET, metabolic equivalent task; MSI, microsatellite instability; MSS, microsatellite stability; NSAID, non-steroidal anti-inflammatory drug.

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