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Article

Comprehensive Assessment of Diet Quality and Risk of Precursors of Early-Onset Colorectal Cancer

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Abstract

Background: The role of poor diet quality in the rising incidence of colorectal cancer (CRC) diagnosed younger than age 50 years has not been explored. Based on molecular features of early-onset CRC, early-onset adenomas are emerging surrogate endpoints. **Methods:** In a prospective cohort study (Nurses' Health Study II), we evaluated 2 empirical dietary patterns (Western and prudent) and 3 recommendation-based indexes (Dietary Approaches to Stop Hypertension [DASH], Alternative Mediterranean Diet [AMED], and Alternative Healthy Eating Index [AHEI]-2010) with risk of early-onset adenoma overall and by malignant potential (high-risk: $\geq$1 cm, tubulovillous or villous histology, high-grade dysplasia, or $\geq$3 adenomas), among 29 474 women with 1 or more lower endoscopy before age 50 years (1991–2011). Multivariable logistic regressions were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). **Results:** We documented 1157 early-onset adenomas with 375 at high risk. Western diet was positively associated, whereas prudent diet, DASH, AMED, and AHEI-2010 were inversely associated with risk of early-onset adenoma. The associations were largely confined to high-risk adenomas (the highest vs lowest quintile: Western, OR = 1.67, 95% CI = 1.18 to 2.37; prudent, OR = 0.69, 95% CI = 0.48 to 0.98; DASH, OR = 0.65, 95% CI = 0.45 to 0.93; AMED, OR = 0.55, 95% CI = 0.38 to 0.79; AHEI-2010, OR = 0.71, 95% CI = 0.51 to 1.01; all $P_{trend} \leq .03$), driven by those identified in the distal colon and rectum (all $P_{trend} \leq .04$, except AMED: $P_{trend} = .14$). **Conclusion:** Poor diet quality was associated with an increased risk of early-onset distal and rectal adenomas of high malignant potential. These findings provide preliminary but strong support to the role of diet in early-onset CRC.

Despite falling sharply or leveling off in older adults (1), colorectal cancer (CRC) has increased among young adults aged younger than 50 years (early-onset) in 9 high-income countries over the past 2 decades, including the United States. Largely driven by the rise in distal colon and rectal tumors (1,2), early-onset CRCs are diagnosed at more advanced stages with more aggressive clinicopathological characteristics compared with CRC diagnosed at older ages (3). In contrast to the vast accumulated

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evidence on the etiopathogenesis of older-onset CRC (4), risk factors for early-onset CRC remain largely unknown.

Poor diet quality has been linked to elevated risk of older-onset CRC (5-8). Increasing evidence points to hyperinsulinemia (9), chronic inflammation (10), and gut dysbiosis (11-13) as the plausible mechanisms linking diet and CRC. Prior evidence on obesity and sedentary behaviors has indirectly implicated the role of lifestyle factors, likely tied to unhealthy diet, in the etiology of early-onset CRC (14,15). In the United States, diet quality declined steadily between 1985 and 2006 (16) and has remained stable thereafter. Further, diet quality among younger adults is consistently poorer compared with the older population (17). Based on data from the National Health and Nutrition Examination Survey 1999-2016, the estimated overall diet quality of younger individuals in the United States showed modest improvement, but more than half of youth still had poor-quality diets (18). Yet, the health impact of poorer diet among the younger population, including its role in early-onset colorectal neoplasia, has not been well examined, in part because of the lack of cohort studies that followed younger adults for an extensive period of time with validated dietary assessment.

The majority (approximately 80%) of early-onset CRCs exhibits microsatellite stable (MSS) phenotypes (19,20), leading to the postulation that adenomas but not serrated polyps are the precursors of early-onset CRC. In a recent analysis from the Genetics and Epidemiology of Colorectal Cancer Consortium (21), compared with CRC diagnosed after age 65 years, early-onset CRC was more likely to present with a molecular subtype (MSS or microsatellite instability low, non-CpG island methylator phenotype, *BRAF* and *KRAS* wild type) arising from the adenoma-carcinoma sequence (22). These findings lend additional support to the etiological relevance of adenomas, particularly those of high-malignant potential (23), in understanding the etiology of early-onset CRC.

We therefore conducted a comprehensive analysis in the Nurses' Health Study II (NHSII) to elucidate the role of diet quality, as measured by empirical dietary patterns as well as recommendation-based indexes, in early-onset CRC using early-onset adenoma and that of high-malignant potential as surrogate endpoints. The NHSII, a well-established, large, ongoing prospective cohort of young women with detailed documentation of endoscopic history and indications and family history, as well as validated assessment of dietary intake and lifestyle factors, provides a unique opportunity to address these knowledge gaps.

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Methods

Study Population

The NHSII is a prospective cohort study of 116 430 US female nurses aged 25 to 42 years at enrollment in 1989. Participants were followed biennially with self-administered questionnaires on demographics, lifestyle factors, and medical diagnoses. Dietary intake was assessed every 4 years through mailed food frequency questionnaires (FFQs). Return of the completed questionnaire implied informed consent to participate in the study. Overall, the active follow-up rate was approximately 90% (24).

In the current analysis, study baseline was set as 1991, the time of initial FFQ assessment. We excluded participants who had diagnoses of CRC, inflammatory bowel disease, or a previous history of colorectal polyps prior to baseline and each biennial follow-up cycle. After additional exclusions were made for those who had missing data on any of the exposures or reported implausible energy intake (<600 or >3500 kcal/d), 59 013 participants were identified to have undergone at least 1 lower endoscopy before 2011 (the end of follow-up). We further restricted to 29 474 women younger than age 50 years for our primary analyses (Supplementary Figure 1, available online). The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health and those of participating state cancer registries as required.

Ascertainment of Colorectal Adenoma

On each biennial questionnaire, participants reported whether they had undergone lower endoscopy and the corresponding reason(s). Investigators masked to exposure information reviewed all the retrieved medical records and extracted data on anatomical location, size, histological type, and number of polyps. If more than 1 adenoma was diagnosed, size and histology were categorized by the largest and most advanced polyp, respectively. Cases and noncases were defined every 2 years and updated through the 2011 questionnaire cycle: all confirmed newly diagnosed adenomas (tubular, villous, tubulovillous, or with high-grade dysplasia) were considered as cases and individuals who had a lower endoscopy but reported no adenomas as noncases.

We further categorized adenomas according to their malignant potential (25). High-risk adenomas were defined as adenomas with any of the following features: 1 cm or more in size, tubulovillous or villous histology, high-grade dysplasia, and the presence of 3 or more adenomas. Low-risk adenomas included all other adenomas. We defined advanced adenomas considering only size and histology (26). Adenomas in the cecum, ascending colon, hepatic flexure, and transverse colon were classified as proximal adenomas; those in splenic flexure, descending colon, and sigmoid colon as distal colonic adenomas; and those in the rectum or rectosigmoid junction as rectal adenomas, respectively (27).

Assessment of Diet Quality

Every 4 years since 1991, participants self-reported average food intake over the preceding year via validated semiquantitative FFQs (28). Briefly, to capture food consumption frequency, 9 response options were provided, ranging from "never or less than once per month (referred to never)" to "6 or more times per day". Total nutrient intake was calculated as the sum of consumption frequency of each food item multiplied by the corresponding nutrient composition in the standard portion size.

Food items on the FFQ were categorized into 40 groups, and factor analysis was performed to derive 2 dominant dietary patterns: Western and prudent diet (29) for which the reproducibility and validity have been documented (30).

To capture the adherence to major dietary recommendations, we derived Dietary Approaches to Stop Hypertension (DASH) (31), Alternative Mediterranean Diet (AMED) (32), and Alternative Healthy Eating Index-2010 (AHEI-2010) (33). The DASH score consisted of 8 components and ranged from 8 to 40. The AMED score consisted of 9 components and ranged from 0 to 9. The AHEI-2010 score consisted of 11 items and ranged from 0 to 110. Scoring methods and dietary components are provided in Supplementary Table 1 (available online). For the 3 indexes, a higher score reflects higher diet quality.

Statistical Analysis

We calculated the cumulative average of all dietary scores available from 1991 to the questionnaire cycle (2 years) prior to the most recent endoscopy to represent long-term intake reflecting true changes and reduce random within-person variation by increasing the number of measurements (34). As primary analyses, we first investigated the associations between diet quality (Western and prudent patterns; DASH, AMED, and AHEI-2010 scores, all in period-specific quintiles) and risk of early-onset adenoma overall and according to high-risk vs low-risk adenoma. The associations between each of the dietary indexes and early-onset adenoma were evaluated in different models in the entire study population. As secondary analyses, we further examined the associations by anatomical location, size, and histology. We evaluated the associations according to malignant potential in 2 logistic regressions using the same reference group: 1 for high-risk vs no adenoma, and the other for low-risk vs no adenoma, and similarly for comparisons according to size and histology. Joint association of Western and prudent dietary patterns with risk of early-onset high-risk adenoma was further tested to take into account the combination of 2 distinct dietary patterns. Because some of these early-onset adenomas will be first captured through average-risk screening if they have not had an endoscopy at younger ages (35,36), we performed sensitivity analyses stratified by age of endoscopy (younger than 45 years vs 45 years and older). Also, we conducted a sensitivity analysis among only those who had a colonoscopy to address the likelihood of proximal adenoma not being detected if participants only had a sigmoidoscopy. To replace missing data for exposure in the subsequent cycles, we carried forward nonmissing dietary intake values from the prior questionnaire cycle. Missing data for covariates were treated similarly.

Similar to prior work (27,37-39), we identified the case-control sets every 2 years among participants with a lower endoscopy during the same period. Once a participant was diagnosed with an adenoma, she was censored in all subsequent follow-up cycles (27). To account for the possibility that an individual may have undergone multiple endoscopies over the study period and to handle time-varying exposure and covariates efficiently, we constructed a new record for each 2-year follow-up period during which a participant underwent a lower endoscopy, using Andersen-Gill data structure. Age-adjusted and multivariable logistic regressions for clustered data (PROC GENMOD) were used to account for repeated observations and estimate odds ratios (ORs) and 95% confidence intervals (CIs). Tests for trend were conducted using the median of each quintile of dietary patterns and scores as a continuous variable.

In age-adjusted models, we controlled for age, total caloric intake, time period of endoscopy, number of reported endoscopies, time in years since the most recent endoscopy, and reason for the current endoscopy. In multivariable models, we additionally adjusted for the following potential confounders: height (40), body mass index (41), history of CRC in a first-degree relative (42), menopausal status (43), menopausal hormone use (44), personal history of type 2 diabetes (45), pack-years of smoking (46), physical activity in metabolic equivalent of task-hours (47), current use of multivitamin (48), and regular use ($\geq$2 times per week) of aspirin (49) or nonsteroidal anti-inflammatory drugs (50). For the DASH diet, we additionally adjusted for alcohol intake. All analyses were performed using SAS 9.4 (SAS Institute, Inc, Cary, NC). Two-sided *P* values less than .05 were considered statistically significant.

Results

Among 29 474 women who reported a lower endoscopy between 1991 and 2011 when they were younger than age 50 years, those with a higher Western dietary pattern score were more likely to have higher pack-years of smoking and less likely to exercise or use multivitamins (Table 1). In contrast, participants with greater adherence to the prudent dietary pattern and DASH, AMED, and AHEI-2010 indexes tended to engage in healthier behaviors.

We documented 1157 cases of early-onset adenomas from 1991 to 2011. Compared with those in the lowest quintile of Western dietary pattern, individuals in the highest quintile had an increased risk of early-onset adenoma, after adjusting for a list of putative CRC risk factors (multivariable $OR_{Q5\ vs\ Q1} = 1.38$, 95% CI = 1.13 to 1.68, $P_{trend} = .003$; Table 2). In contrast, a higher prudent pattern score was associated with a lower risk of early-onset adenoma ($OR_{Q5\ vs\ Q1} = 0.81$, 95% CI = 0.66 to 0.99, $P_{trend} = .03$). For the same comparison, there were also suggestions of inverse associations between adherence to the DASH ($OR_{Q5\ vs\ Q1} = 0.84$, 95% CI = 0.69 to 1.04, $P_{trend} = .04$), AMED ($OR_{Q5\ vs\ Q1} = 0.80$, 95% CI = 0.65 to 0.99, $P_{trend} = .07$), and AHEI-2010 ($OR_{Q5\ vs\ Q1} = 0.85$, 95% CI = 0.69 to 1.04, $P_{trend} = .11$) and risk of early-onset adenoma. In a sensitivity analysis among only those who had a colonoscopy, effect estimates were slightly attenuated, but the overall direction of association was consistent (Supplementary Table 2, available online).

Notably, these associations appeared to be stronger for adenomas with higher malignant potential. We found a statistically significant positive association of the Western dietary pattern (multivariable $OR_{Q5\ vs\ Q1} = 1.67$, 95% CI = 1.18 to 2.37, $P_{trend} = .01$) and inverse associations of the prudent pattern ($OR_{Q5\ vs\ Q1} = 0.69$, 95% CI = 0.48 to 0.98, $P_{trend} = .03$), DASH ($OR_{Q5\ vs\ Q1} = 0.65$, 95% CI = 0.45 to 0.93, $P_{trend} = .009$), AMED ($OR_{Q5\ vs\ Q1} = 0.55$, 95% CI = 0.38 to 0.79, $P_{trend} = .007$), and AHEI-2010 scores ($OR_{Q5\ vs\ Q1} = 0.71$, 95% CI = 0.51 to 1.01, $P_{trend} = .01$; Table 3) with early-onset high-risk adenoma (n = 375 cases) but not with low-risk adenoma (n = 733 cases, all $P_{trend} \geq .08$). For early-onset adenoma overall and of high risk, we observed highly comparable results when stratified by age of endoscopy (younger than 45 years vs 45 years and older; data not shown). The stronger associations for high-risk adenoma were driven by large size ($\geq$1 cm) and villous histology (Figure 1). Interestingly, the magnitude of these inverse associations was comparable between participants with or without symptoms (visible blood in stool specimen, positive result for fecal occult blood test, abdominal pain, and diarrhea or constipation) at the time of lower endoscopy (Supplementary Table 3, available online). In joint analyses, among women having the healthiest dietary pattern based on principal component analysis (ie, in the highest quintile of the prudent and the lowest quintile of the Western pattern), a statistically significantly lower risk was observed for early-onset high-risk adenomas, compared with those having the lowest score of the prudent and the highest score of the Western pattern (OR = 0.58, 95% CI = 0.36 to 0.92; Supplementary Table 4, available online).

By anatomical site, we observed stronger associations for the Western dietary pattern (multivariable $OR_{Q4\ vs\ Q1} = 1.65$, 95% CI = 1.14 to 2.38, $P_{trend} = .01$), prudent pattern ($OR_{Q4\ vs\ Q1} = 0.68$, 95% CI = 0.47 to 0.99, $P_{trend} = .04$), DASH ($OR_{Q4\ vs\ Q1} = 0.63$, 95% CI = 0.42 to 0.94, $P_{trend} = .01$), and AHEI-2010 scores ($OR_{Q4\ vs\ Q1} = 0.71$, 95% CI = 0.49 to 1.03, $P_{trend} = .02$), and risk of advanced adenomas in the distal colon and rectum (n = 271 cases; Table 4). However, we did not find any statistically significant

Table 1. Characteristics of participants who had undergone lower endoscopy before age 50 years according to period-specific quintiles of diet quality scores, Nurses' Health Study II, 1991-2011[a]

Characteristic	Western dietary pattern			Prudent dietary pattern			Dietary Approaches to Stop Hypertension			Alternative Mediterranean Diet			Alternative Healthy Eating Index-2010		
	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
Age, y[b]	45.1 (4.5)	45.0 (4.4)	44.9 (4.5)	44.6 (4.6)	45.1 (4.4)	45.2 (4.3)	44.8 (4.6)	45.0 (4.4)	45.2 (4.4)	44.7 (4.6)	45.0 (4.5)	45.1 (4.5)	44.7 (4.6)	44.9 (4.5)	45.3 (4.3)
Height, cm	165 (6.7)	165 (6.6)	165 (6.7)	165 (6.7)	165 (6.6)	165 (6.8)	165 (6.8)	165 (6.6)	165 (6.7)	165 (6.7)	165 (6.8)	165 (6.6)	165 (6.7)	165 (6.7)	165 (6.6)
BMI, kg/m^2	24.0 (4.4)	25.2 (5.2)	27.1 (6.3)	26.0 (6.1)	25.2 (5.3)	24.9 (5.0)	26.3 (6.0)	25.4 (5.4)	24.3 (4.7)	26.2 (5.8)	25.5 (5.4)	24.3 (4.7)	26.3 (6.1)	25.4 (5.3)	24.1 (4.4)
Family history of colorectal cancer, %	17	17	16	15	17	17	15	16	18	16	17	17	16	16	17
History of diabetes, %	1.4	2.7	4.3	3.0	2.7	2.5	3.3	2.9	1.9	3.0	2.9	2.1	3.4	2.9	1.7
Time period of endoscopy after 2001, %	49	52	55	59	50	47	56	51	48	56	51	47	57	52	46
No. of previous lower endoscopies	1.6 (0.9)	1.6 (0.9)	1.6 (0.9)	1.6 (0.9)	1.5 (0.9)	1.6 (1.0)	1.6 (0.9)	1.6 (0.9)	1.6 (0.9)	1.6 (0.9)	1.6 (0.9)	1.6 (0.9)	1.6 (0.9)	1.6 (0.9)	1.6 (0.9)
Time since the most recent lower endoscopy, y	3.4 (2.7)	3.4 (2.8)	3.5 (2.8)	3.6 (3.0)	3.5 (2.9)	3.3 (2.6)	3.6 (3.0)	3.5 (2.9)	3.4 (2.6)	3.6 (3.0)	3.4 (2.8)	3.4 (2.7)	3.6 (2.9)	3.4 (2.8)	3.3 (2.7)
Reasons for endoscopy															
Screening, %	55	51	46	46	51	55	46	52	55	47	50	54	45	51	55
Symptoms, %	43	47	52	52	47	43	52	46	44	50	48	44	53	47	43
Missing, %	2.0	2.3	2.0	2.1	2.1	2.0	2.2	2.1	1.9	2.3	1.9	1.9	2.0	2.2	1.8
Current use of multivitamin, %	62	54	46	48	56	59	44	56	62	47	55	61	49	55	59
Regular use of aspirin, %[c]	11	12	14	12	12	12	12	12	11	12	12	12	13	12	12
Regular use of nonaspirin NSAIDs, %[c]	27	33	36	35	33	30	34	34	29	34	32	30	35	33	29
Postmenopausal, %	16	17	19	19	17	17	19	17	16	19	17	16	18	17	16
Current menopausal hormone therapy, %	60	57	62	59	61	60	60	61	59	60	61	60	60	61	60
Physical activity, MET-h/wk	31.8 (30.6)	20.4 (19.8)	15.9 (17.5)	15.5 (17.2)	21.4 (22.1)	32.0 (30.0)	15.5 (17.5)	21.0 (21.4)	31.0 (28.5)	16.1 (18.1)	21.2 (21.6)	29.8 (28.5)	15.3 (16.2)	21.1 (20.7)	31.9 (30)
Ever smokers, %	34	32	35	30	33	38	36	32	32	33	32	35	29	33	39
Pack-years among ever smokers	10.3 (7.8)	11.8 (9.3)	15.1 (11.3)	14.5 (11.4)	11.7 (9.2)	11.4 (8.3)	15.3 (11.5)	11.5 (9.0)	10.4 (8.0)	14.8 (11.2)	11.7 (9.1)	10.6 (8.0)	14.7 (11.4)	11.7 (9.2)	10.8 (8.1)
Dietary intake															
Calories, kcal/d	1937 (464)	1730 (474)	1951 (520)	1938 (520)	1737 (469)	1929 (473)	1619 (463)	1835 (470)	2070 (451)	1578 (434)	1826 (463)	2124 (465)	1970 (488)	1798 (490)	1743 (467)
Red and processed meat, svg/wk	3.7 (2.8)	5.8 (3.1)	9.4 (4.4)	8.6 (4.3)	5.8 (3.4)	4.4 (3.3)	7.7 (4.0)	6.4 (3.7)	4.2 (3.2)	7.1 (3.7)	6.3 (3.9)	5.1 (3.9)	9.1 (4.1)	6.1 (3.2)	3.1 (2.4)
Fruit, svg/d	2.0 (1.1)	1.2 (0.7)	0.8 (0.6)	0.8 (0.6)	1.2 (0.6)	2.0 (1.1)	0.6 (0.4)	1.2 (0.6)	2.1 (1.0)	0.7 (0.5)	1.2 (0.7)	1.9 (1.0)	0.8 (0.6)	1.2 (0.7)	1.9 (1.1)
Vegetable, svg/d	4.7 (2.5)	3.3 (1.6)	2.9 (1.5)	2.1 (1.0)	3.2 (1.1)	6.0 (2.4)	2.2 (1.1)	3.4 (1.5)	5.2 (2.3)	2.1 (1.0)	3.5 (1.6)	5.2 (2.2)	2.5 (1.2)	3.5 (1.7)	4.8 (2.4)
Alcohol, g/d	4.5 (6.6)	3.5 (5.5)	2.8 (5.3)	2.5 (5.3)	3.6 (5.5)	4.6 (6.5)	3.1 (5.8)	3.7 (5.9)	3.9 (5.7)	2.5 (5.8)	3.6 (5.9)	5.0 (5.8)	2.3 (6.2)	3.7 (5.8)	5.0 (5.4)
Total folate, μg/d	630 (235)	526 (222)	428 (191)	426 (195)	534 (226)	625 (231)	426 (215)	537 (227)	621 (223)	453 (230)	534 (231)	590 (217)	441 (201)	526 (222)	611 (244)
Total calcium, mg/d	1322 (422)	1128 (398)	911 (327)	959 (359)	1140 (410)	1230 (423)	920 (387)	1134 (398)	1293 (383)	1048 (437)	1121 (408)	1157 (380)	989 (365)	1125 (413)	1235 (438)
Total vitamin D, IU/d	489 (223)	404 (216)	304 (181)	325 (186)	411 (219)	451 (225)	319 (214)	411 (219)	467 (207)	362 (227)	405 (225)	427 (199)	332 (185)	401 (211)	468 (238)
Dietary fiber, g/d	23.7 (5.9)	18.7 (4.0)	15.9 (3.3)	14.6 (2.9)	19.1 (3.4)	24.8 (5.3)	14.8 (3.1)	19.0 (3.8)	24.2 (5.3)	15.0 (3.5)	19.2 (4.3)	23.4 (5.2)	14.9 (3.0)	19.0 (3.6)	24.6 (5.7)

[a]29 474 women with a total of 43 961 observations. BMI = body mass index; MET = metabolic equivalent of task; NSAID = nonsteroidal anti-inflammatory drug; Q1 = lowest quintile; Q3 = middle quintile; Q5 = highest quintile; svg = serving.
[b]All values other than age have been directly standardized to age distribution (in 5-year age group) of all the participants. Mean (SD) was presented for continuous variables.
[c]Regular use was defined as 2 or more times per week.

Table 2. Diet quality and risk of early-onset (aged younger than 50 years) adenoma, NHSII, 1991-2011[a]

Diet quality	Quintile					P_{trend}[d]
	1 (lowest)	2	3	4	5 (highest)	
Dietary pattern						
Western dietary pattern						
No. of cases	183	213	223	238	300	
Unadjusted OR (95% CI)	1 (Referent)	1.14 (0.93 to 1.39)	1.12 (0.92 to 1.37)	1.18 (0.97 to 1.43)	1.41 (1.17 to 1.70)	.001
Age-adjusted OR (95% CI)[b]	1 (Referent)	1.13 (0.92 to 1.38)	1.11 (0.91 to 1.36)	1.18 (0.96 to 1.43)	1.42 (1.17 to 1.71)	.001
Multivariable OR (95% CI)[c]	1 (Referent)	1.11 (0.91 to 1.36)	1.10 (0.89 to 1.35)	1.16 (0.94 to 1.42)	1.38 (1.13 to 1.68)	.003
Prudent dietary pattern						
No. of cases	297	263	214	201	182	
Unadjusted OR (95% CI)	1 (Referent)	0.99 (0.83 to 1.17)	0.86 (0.72 to 1.03)	0.85 (0.71 to 1.02)	0.81 (0.67 to 0.97)	.01
Age-adjusted OR (95% CI)[b]	1 (Referent)	0.97 (0.81 to 1.15)	0.83 (0.69 to 1.00)	0.82 (0.68 to 0.99)	0.79 (0.65 to 0.95)	.007
Multivariable OR (95% CI)[c]	1 (Referent)	0.97 (0.82 to 1.15)	0.84 (0.70 to 1.02)	0.84 (0.69 to 1.02)	0.81 (0.66 to 0.99)	.03
Recommendation-based dietary index						
Dietary Approaches to Stop Hypertension						
No. of cases	272	260	227	201	197	
Unadjusted OR (95% CI)	1 (Referent)	1.01 (0.85 to 1.20)	0.88 (0.73 to 1.05)	0.86 (0.71 to 1.03)	0.85 (0.71 to 1.03)	.04
Age-adjusted OR (95% CI)[b]	1 (Referent)	0.99 (0.83 to 1.18)	0.84 (0.70 to 1.01)	0.81 (0.67 to 0.99)	0.81 (0.66 to 0.98)	.008
Multivariable OR (95% CI)[c]	1 (Referent)	1.00 (0.84 to 1.20)	0.86 (0.72 to 1.04)	0.85 (0.69 to 1.03)	0.84 (0.69 to 1.04)	.04
Alternative Mediterranean Diet						
No. of cases	293	236	221	210	197	
Unadjusted OR (95% CI)	1 (Referent)	0.88 (0.74 to 1.05)	0.82 (0.69 to 0.98)	0.88 (0.73 to 1.05)	0.81 (0.67 to 0.97)	.11
Age-adjusted OR (95% CI)[b]	1 (Referent)	0.86 (0.72 to 1.02)	0.79 (0.66 to 0.95)	0.83 (0.68 to 1.00)	0.76 (0.62 to 0.92)	.01
Multivariable OR (95% CI)[c]	1 (Referent)	0.88 (0.74 to 1.05)	0.82 (0.68 to 0.98)	0.86 (0.71 to 1.04)	0.80 (0.65 to 0.99)	.07
Alternative Healthy Eating Index-2010						
No. of cases	287	245	246	197	182	
Unadjusted OR (95% CI)	1 (Referent)	0.92 (0.77 to 1.09)	1.00 (0.84 to 1.19)	0.84 (0.70 to 1.01)	0.84 (0.69 to 1.01)	.30
Age-adjusted OR (95% CI)[b]	1 (Referent)	0.90 (0.76 to 1.07)	0.98 (0.82 to 1.17)	0.82 (0.68 to 0.99)	0.82 (0.67 to 0.99)	.03
Multivariable OR (95% CI)[c]	1 (Referent)	0.91 (0.76 to 1.08)	0.99 (0.83 to 1.19)	0.85 (0.70 to 1.03)	0.85 (0.69 to 1.04)	.11

[a]CI = confidence interval; NHSII = Nurses' Health Study II; OR = odds ratio.
[b]Adjusted for age (continuous), total caloric intake (in quintiles), time period of endoscopy (in 2-year intervals), number of reported endoscopies (continuous), time in years since the most recent endoscopy (continuous), and reason for the current endoscopy (screening, symptoms, missing).
[c]Additionally adjusted for height (continuous), body mass index (in quintiles), family history of colorectal cancer (yes, no), menopausal status (premenopausal, postmenopausal), menopausal hormone use (never, past, current use of menopausal hormones), personal history of type 2 diabetes (yes, no), pack-years of smoking (never, 1-4.9, 5-19.9, 20-39.9, ≥40 pack-years), physical activity (in metabolic equivalent of task-hours per week, quintiles), current use of multivitamin (yes, no), regular use of aspirin (yes, no), and regular use of nonsteroidal anti-inflammatory drugs (yes, no). For Dietary Approaches to Stop Hypertension, we additionally adjusted for alcohol intake (0, 0.1-14.9, ≥15 g/d).
[d]Calculated using the median of each quintile as a continuous variable.

associations for diet quality and risk of advanced adenoma in the proximal colon (n = 93 cases).

Discussion

In this large prospective cohort study of young women, Western diet was associated with an increased risk of early-onset adenoma, whereas intake more consistent with the prudent pattern and healthy DASH, AMED, and AHEI-2010 scores was associated with a lower risk. The associations were largely confined to high-risk adenomas, especially those in the distal colon and rectum. Coupled with secular trends toward low diet quality that is more prevalent among young adults in the United States (16), our findings suggest poor diet may partially contribute to the rapid increase in early-onset CRC.

Human nutrition has changed dramatically over the past century, represented by increased intake of meat, fats, oils, and added sugars and sweeteners, as well as reduced consumption of vegetables and whole grains (51). In addition to exploring the role of specific dietary elements in human health, researchers are increasingly focused on overall diet quality (52). Poor diet quality has been considered a putative CRC risk factor in older individuals. A meta-analysis of 40 studies showed that Western diet was associated with an increased risk of CRC, whereas a prudent pattern was associated with a lower risk (53). Findings have been mixed for recommendation-based indexes (52,54), together with no association observed in our parallel cohort of older women (52). Studies of early-onset CRC have been limited to case-control studies (55,56) from Pakistan and Italy. Our analyses are thus among the first prospective investigations of diet in early-onset colorectal neoplasia. The consistent findings across a posteriori dietary patterns and recommendation-based indexes, driven by high-risk adenomas, lend substantial support to the important and potentially stronger role of diet in early-onset than late-onset colorectal carcinogenesis.

Increases in early-onset CRC were primarily driven by distal colon and rectal tumors between 2004 and 2013, with incidence having increased by approximately 2% annually (57). Intriguingly, we observed stronger associations between diet quality and early-onset advanced adenomas in the distal colon and rectum, compared to those in the proximal colon. These results were in line with prior findings on diet quality demonstrating a prominent association for distal colon and rectal tumors in older adults (54,58). Proximal CRC is more likely to progress through the serrated neoplasia pathway (59), whereas

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Table 3. Diet quality and risk of early-onset (aged younger than 50 years) adenoma according to malignant potential, NHSII, 1991-2011[a]

Diet quality	Quintile					
	1 (lowest)	2	3	4	5 (highest)	P_{trend}[d]
Dietary pattern						
Western dietary pattern						
High-risk adenoma						
No. of cases	52	72	78	72	101	
Unadjusted OR (95% CI)	1 (Referent)	1.36 (0.95 to 1.94)	1.38 (0.97 to 1.96)	1.26 (0.88 to 1.80)	1.67 (1.19 to 2.34)	.01
Age-adjusted OR (95% CI)[b]	1 (Referent)	1.35 (0.95 to 1.94)	1.38 (0.97 to 1.97)	1.26 (0.88 to 1.80)	1.66 (1.19 to 2.33)	.01
Multivariable OR (95% CI)[c]	1 (Referent)	1.33 (0.93 to 1.91)	1.37 (0.96 to 1.97)	1.26 (0.88 to 1.82)	1.67 (1.18 to 2.37)	.01
Low-risk adenoma						
No. of cases	125	131	138	150	189	
Unadjusted OR (95% CI)	1 (Referent)	1.03 (0.80 to 1.32)	1.01 (0.79 to 1.30)	1.09 (0.86 to 1.38)	1.30 (1.03 to 1.63)	.04
Age-adjusted OR (95% CI)[b]	1 (Referent)	1.01 (0.78 to 1.29)	1.00 (0.78 to 1.28)	1.08 (0.85 to 1.38)	1.31 (1.04 to 1.65)	.02
Multivariable OR (95% CI)[c]	1 (Referent)	0.99 (0.77 to 1.28)	0.98 (0.76 to 1.26)	1.05 (0.81 to 1.35)	1.25 (0.97 to 1.59)	.08
Prudent dietary pattern						
High-risk adenoma						
No. of cases	103	81	73	61	57	
Unadjusted OR (95% CI)	1 (Referent)	0.88 (0.65 to 1.18)	0.85 (0.63 to 1.14)	0.74 (0.54 to 1.02)	0.73 (0.53 to 1.01)	.045
Age-adjusted OR (95% CI)[b]	1 (Referent)	0.86 (0.64 to 1.16)	0.82 (0.61 to 1.11)	0.72 (0.52 to 0.99)	0.70 (0.50 to 0.98)	.03
Multivariable OR (95% CI)[c]	1 (Referent)	0.84 (0.62 to 1.13)	0.80 (0.58 to 1.09)	0.70 (0.50 to 0.98)	0.69 (0.48 to 0.98)	.03
Low-risk adenoma						
No. of cases	179	172	135	128	119	
Unadjusted OR (95% CI)	1 (Referent)	1.07 (0.87 to 1.32)	0.90 (0.72 to 1.13)	0.90 (0.71 to 1.13)	0.87 (0.69 to 1.11)	.16
Age-adjusted OR (95% CI)[b]	1 (Referent)	1.05 (0.85 to 1.30)	0.87 (0.69 to 1.10)	0.87 (0.69 to 1.10)	0.86 (0.68 to 1.09)	.13
Multivariable OR (95% CI)[c]	1 (Referent)	1.07 (0.86 to 1.32)	0.90 (0.71 to 1.14)	0.91 (0.72 to 1.16)	0.91 (0.71 to 1.17)	.36
Recommendation-based dietary index						
Dietary Approaches to Stop Hypertension						
High-risk adenoma						
No. of cases	97	77	83	59	59	
Unadjusted OR (95% CI)	1 (Referent)	0.84 (0.62 to 1.13)	0.90 (0.67 to 1.21)	0.70 (0.51 to 0.97)	0.71 (0.52 to 0.99)	.02
Age-adjusted OR (95% CI)[b]	1 (Referent)	0.81 (0.60 to 1.10)	0.85 (0.62 to 1.15)	0.65 (0.47 to 0.91)	0.65 (0.46 to 0.91)	.006
Multivariable OR (95% CI)[c]	1 (Referent)	0.81 (0.59 to 1.10)	0.85 (0.62 to 1.16)	0.65 (0.46 to 0.91)	0.65 (0.45 to 0.93)	.009
Low-risk adenoma						
No. of cases	160	177	133	132	131	
Unadjusted OR (95% CI)	1 (Referent)	1.17 (0.94 to 1.45)	0.87 (0.69 to 1.10)	0.96 (0.76 to 1.21)	0.96 (0.76 to 1.22)	.44
Age-adjusted OR (95% CI)[b]	1 (Referent)	1.15 (0.93 to 1.43)	0.84 (0.66 to 1.06)	0.92 (0.73 to 1.18)	0.94 (0.73 to 1.20)	.29
Multivariable OR (95% CI)[c]	1 (Referent)	1.18 (0.95 to 1.47)	0.88 (0.69 to 1.11)	0.98 (0.77 to 1.26)	1.01 (0.78 to 1.31)	.69
Alternative Mediterranean Diet						
High-risk adenoma						
No. of cases	103	72	74	72	54	
Unadjusted OR (95% CI)	1 (Referent)	0.77 (0.57 to 1.04)	0.79 (0.58 to 1.06)	0.85 (0.63 to 1.16)	0.63 (0.45 to 0.88)	.03
Age-adjusted OR (95% CI)[b]	1 (Referent)	0.74 (0.54 to 1.00)	0.74 (0.54 to 1.00)	0.77 (0.56 to 1.06)	0.55 (0.38 to 0.78)	.005
Multivariable OR (95% CI)[c]	1 (Referent)	0.74 (0.54 to 1.01)	0.73 (0.53 to 1.00)	0.76 (0.55 to 1.06)	0.55 (0.38 to 0.79)	.007
Low-risk adenoma						
No. of cases	175	158	136	129	135	
Unadjusted OR (95% CI)	1 (Referent)	0.99 (0.80 to 1.23)	0.85 (0.68 to 1.07)	0.90 (0.72 to 1.13)	0.93 (0.74 to 1.16)	.76
Age-adjusted OR (95% CI)[b]	1 (Referent)	0.97 (0.78 to 1.20)	0.83 (0.66 to 1.04)	0.87 (0.68 to 1.10)	0.91 (0.71 to 1.16)	.39
Multivariable OR (95% CI)[c]	1 (Referent)	1.00 (0.81 to 1.25)	0.87 (0.69 to 1.10)	0.93 (0.73 to 1.19)	1.00 (0.77 to 1.29)	.91
Alternative Healthy Eating Index-2010						
High-risk adenoma						
No. of cases	103	86	73	54	59	
Unadjusted OR (95% CI)	1 (Referent)	0.90 (0.67 to 1.20)	0.82 (0.61 to 1.12)	0.64 (0.46 to 0.90)	0.76 (0.55 to 1.04)	.02
Age-adjusted OR (95% CI)[b]	1 (Referent)	0.89 (0.66 to 1.18)	0.81 (0.60 to 1.10)	0.63 (0.45 to 0.88)	0.74 (0.53 to 1.03)	.01
Multivariable OR (95% CI)[c]	1 (Referent)	0.87 (0.65 to 1.16)	0.79 (0.58 to 1.07)	0.61 (0.43 to 0.87)	0.71 (0.51 to 1.01)	.01
Low-risk adenoma						
No. of cases	172	147	163	135	116	
Unadjusted OR (95% CI)	1 (Referent)	0.92 (0.73 to 1.15)	1.10 (0.89 to 1.37)	0.96 (0.77 to 1.21)	0.89 (0.70 to 1.13)	.52
Age-adjusted OR (95% CI)[b]	1 (Referent)	0.90 (0.72 to 1.12)	1.09 (0.87 to 1.35)	0.94 (0.75 to 1.19)	0.88 (0.69 to 1.12)	.51
Multivariable OR (95% CI)[c]	1 (Referent)	0.92 (0.73 to 1.15)	1.13 (0.90 to 1.41)	1.01 (0.79 to 1.28)	0.95 (0.74 to 1.23)	.90

[a]High-risk adenoma includes adenoma at or greater than 1 cm, or with tubulovillous or villous histology or high-grade dysplasia, or 3 or more adenomas. CI = confidence interval; NHSII = Nurses' Health Study II; OR = odds ratio.
[b]Adjusted for age (continuous), total caloric intake (in quintiles), time period of endoscopy (in 2-year intervals), number of reported endoscopies (continuous), time in years since the most recent endoscopy (continuous), and reason for the current endoscopy (screening, symptoms, missing).
[c]Additionally adjusted for height (continuous), body mass index (in quintiles), family history of colorectal cancer (yes, no), menopausal status (premenopausal, postmenopausal), menopausal hormone use (never, past, current use of menopausal hormones), personal history of type 2 diabetes (yes, no), pack-years of smoking (never, 1-4.9, 5-19.9, 20-39.9, ≥40 pack-years), physical activity (in metabolic equivalent of task-hours per week, quintiles), current use of multivitamin (yes, no), regular use of aspirin (yes, no), and regular use of nonsteroidal anti-inflammatory drugs (yes, no). For Dietary Approaches to Stop Hypertension, we additionally adjusted for alcohol intake (0, 0.1-14.9, ≥15 g/d).
[d]Calculated using the median of each quintile as a continuous variable.

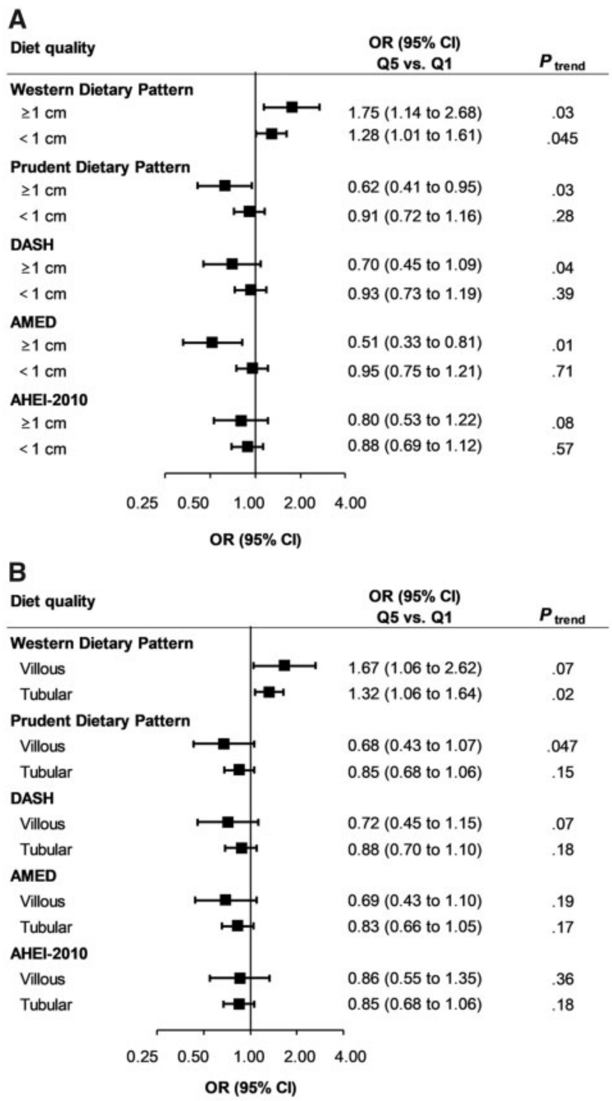

Figure 1. Diet quality and risk of early-onset (aged younger than 50 years) adenoma according to size **(A)** and histology **(B)**, Nurses' Health Study II, 1991-2011. AHEI = Alternative Healthy Eating Index; AMED = Alternative Mediterranean Diet; CI = confidence interval; DASH = Dietary Approaches to Stop Hypertension; OR = odds ratio; Q1 = lowest quintile; Q5 = highest quintile. Odds ratio was adjusted for the covariates denoted in Table 2. P_{trend} was calculated using the median of each quintile as a continuous variable.

the vast majority of distal cancers originate from conventional adenomas associated with molecular alterations such as *APC* and *TP53* mutations (60). Indeed, prior analyses in 2 older cohorts showed that Western dietary pattern was more strongly associated with tumors that were MSS or microsatellite instability low, non-CpG island methylator phenotype, *BRAF* and *KRAS* wild type (58), a molecular subtype common in early-onset CRC (21). Taken together, our findings also indirectly support that diet may exert a stronger influence on neoplasia originating from the traditional adenoma-carcinoma sequence. As incidence for proximal tumors among younger individuals appears to be increasing with similar rates to distal colon and rectal tumors since 2012 (2), studies investigating the role of diet in recent years and other factors are warranted.

One of the potential mechanisms may relate to the summation of individual dietary constituents previously associated with CRC risk. For instance, a Western dietary pattern is high, whereas a prudent pattern and DASH, AMED, and AHEI-2010 scores are low in red and processed meats, which are known to be associated with increased risk of CRC (61). The DASH diet is rich in low-fat dairy products, a good source of dietary calcium. Higher calcium intake has been inversely associated with CRC risk, especially for distal colon cancer (62), which could be attributable to its known functions of reducing cellular proliferation and promoting cell differentiation and apoptosis (63). Secondly, diets may influence risk of adenoma by regulating levels of intestinal inflammation (64) and altering gut microbial composition and diversity (12,13). For advanced adenomas, microbial population shifts similar to CRC have been observed (11). For instance, gut commensals such as *Bifidobacterium animalis* and *Streptococcus thermophilus* that could inhibit potential pathogens in the colon were found to be relatively depleted in both advanced adenomas and CRC tissue (11). Last, unhealthy diets can lead to obesity (65), which is associated with increased risk of early-onset CRC (14), although our results did not change appreciably when body mass index was adjusted for.

Our study has several strengths. First, NHSII, with nearly 30 000 women younger than 50 years with at least 1 prior lower endoscopy and detailed data on indications, provided a unique opportunity to study early-onset adenomas, the most common precursors to early-onset CRC. Prior studies have reported comparable prevalence of adenomas in individuals aged 40-49 years vs 50-59 years who underwent employer-based screening colonoscopy (35,36,66,67). These studies also in part indicated the emerging lower endoscopy practice in the younger individuals. Our similar advanced adenoma detection rate for those aged 40-49 years with the prior report (36) lent additional support for the reliability and generalizability of our data. Second, our dietary data, assessed by FFQ, captured long-term intake and have been validated and collected in a prospective manner, limiting recall or ascertainment bias (68). Regular updates on dietary habits, accrued over 20 years of follow-up, also allowed us to evaluate long-term intake. Third, investigators masked to exposure information reviewed all the retrieved medical records and extracted data on histological subtype, which enabled us to perform subanalysis according to different adenoma subtypes as well as the malignant potential.

Several limitations need to be considered. First, as an observational study, the possibility of residual confounding could not be ruled out. Nevertheless, minimal changes after adjustment for a wide variety of putative risk factors of CRC indicated the robustness of our findings. Second, the dietary data were assessed using FFQs and subject to measurement errors. Using factor analysis to derive dietary patterns requires some decisions, such as the way to group individual food items into food groups, making it subjective to some extent for defining a posteriori dietary pattern. However, dietary measurement errors are expected to be nondifferential for CRC risk (52), and it has been well established that repeated FFQs can accurately capture long-term dietary intake (34). Finally, the generalizability of our findings to other populations, particularly men or other racial and ethnic groups, remains unknown.

In conclusion, higher scores for a Western diet were associated with an increased risk of early-onset adenoma overall, whereas intake of healthier dietary patterns (prudent diet and DASH, AMED, and AHEI-2010 scores) was associated with a lower risk, largely driven by associations for adenomas in the distal colon and rectum that were of high malignant potential. The slightly different associations based on dietary index classification system might inspire future work exploring the specific

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Table 4. Diet quality and risk of early-onset (aged younger than 50 years) advanced adenoma according to anatomical locations, NHSII, 1991-2011[a]

Diet quality	Quartile 1 (lowest)	2	3	4 (highest)	P_{trend}[d]
Dietary pattern					
Western dietary pattern					
Proximal					
No. of cases	22	22	24	25	
Unadjusted OR (95% CI)	1 (Referent)	0.96 (0.53 to 1.73)	1.00 (0.56 to 1.78)	0.98 (0.55 to 1.75)	.90
Age-adjusted OR (95% CI)[b]	1 (Referent)	0.93 (0.51 to 1.69)	0.97 (0.55 to 1.73)	0.97 (0.55 to 1.73)	.91
Multivariable OR (95% CI)[c]	1 (Referent)	0.93 (0.50 to 1.71)	0.96 (0.53 to 1.75)	0.96 (0.52 to 1.78)	.88
Distal and rectal					
No. of cases	48	65	68	90	
Unadjusted OR (95% CI)	1 (Referent)	1.30 (0.89 to 1.88)	1.30 (0.89 to 1.88)	1.62 (1.14 to 2.31)	.01
Age-adjusted OR (95% CI)[b]	1 (Referent)	1.31 (0.90 to 1.90)	1.33 (0.91 to 1.93)	1.61 (1.13 to 2.30)	.01
Multivariable OR (95% CI)[c]	1 (Referent)	1.30 (0.89 to 1.91)	1.34 (0.91 to 1.97)	1.65 (1.14 to 2.38)	.01
Prudent dietary pattern					
Proximal					
No. of cases	25	25	21	22	
Unadjusted OR (95% CI)	1 (Referent)	1.14 (0.65 to 1.98)	1.02 (0.57 to 1.82)	1.13 (0.64 to 2.01)	.70
Age-adjusted OR (95% CI)[b]	1 (Referent)	1.09 (0.62 to 1.91)	0.97 (0.54 to 1.75)	1.10 (0.62 to 1.95)	.79
Multivariable OR (95% CI)[c]	1 (Referent)	1.10 (0.62 to 1.95)	1.00 (0.55 to 1.82)	1.14 (0.61 to 2.11)	.71
Distal and rectal					
No. of cases	91	73	56	51	
Unadjusted OR (95% CI)	1 (Referent)	0.91 (0.67 to 1.24)	0.75 (0.53 to 1.04)	0.72 (0.51 to 1.02)	.049
Age-adjusted OR (95% CI)[b]	1 (Referent)	0.91 (0.67 to 1.23)	0.73 (0.52 to 1.02)	0.70 (0.49 to 0.99)	.03
Multivariable OR (95% CI)[c]	1 (Referent)	0.89 (0.65 to 1.21)	0.71 (0.50 to 1.01)	0.68 (0.47 to 0.99)	.04
Recommendation-based dietary index					
Dietary Approaches to Stop Hypertension					
Proximal					
No. of cases	33	16	18	26	
Unadjusted OR (95% CI)	1 (Referent)	0.52 (0.29 to 0.95)	0.58 (0.33 to 1.03)	0.92 (0.55 to 1.54)	.83
Age-adjusted OR (95% CI)[b]	1 (Referent)	0.51 (0.28 to 0.95)	0.58 (0.32 to 1.05)	0.92 (0.54 to 1.58)	.81
Multivariable OR (95% CI)[c]	1 (Referent)	0.52 (0.28 to 0.95)	0.59 (0.32 to 1.08)	0.93 (0.53 to 1.65)	.85
Distal and rectal					
No. of cases	78	84	61	48	
Unadjusted OR (95% CI)	1 (Referent)	1.16 (0.85 to 1.58)	0.83 (0.60 to 1.17)	0.72 (0.50 to 1.03)	.04
Age-adjusted OR (95% CI)[b]	1 (Referent)	1.10 (0.80 to 1.51)	0.77 (0.54 to 1.09)	0.63 (0.43 to 0.93)	.007
Multivariable OR (95% CI)[c]	1 (Referent)	1.10 (0.80 to 1.52)	0.77 (0.54 to 1.09)	0.63 (0.42 to 0.94)	.01
Alternative Mediterranean Diet					
Proximal					
No. of cases	30	18	20	25	
Unadjusted OR (95% CI)	1 (Referent)	0.61 (0.34 to 1.10)	0.73 (0.41 to 1.29)	0.94 (0.55 to 1.60)	.84
Age-adjusted OR (95% CI)[b]	1 (Referent)	0.62 (0.34 to 1.13)	0.74 (0.41 to 1.34)	0.94 (0.53 to 1.67)	.94
Multivariable OR (95% CI)[c]	1 (Referent)	0.64 (0.34 to 1.17)	0.76 (0.42 to 1.37)	0.97 (0.54 to 1.76)	.86
Distal and rectal					
No. of cases	80	66	70	55	
Unadjusted OR (95% CI)	1 (Referent)	0.84 (0.61 to 1.17)	0.96 (0.70 to 1.33)	0.78 (0.55 to 1.10)	.34
Age-adjusted OR (95% CI)[b]	1 (Referent)	0.80 (0.57 to 1.11)	0.87 (0.62 to 1.22)	0.67 (0.46 to 0.97)	.11
Multivariable OR (95% CI)[c]	1 (Referent)	0.80 (0.57 to 1.13)	0.86 (0.61 to 1.23)	0.67 (0.45 to 0.99)	.14
Alternative Healthy Eating Index-2010					
Proximal					
No. of cases	30	19	24	20	
Unadjusted OR (95% CI)	1 (Referent)	0.69 (0.39 to 1.23)	0.95 (0.55 to 1.62)	0.86 (0.49 to 1.52)	.93
Age-adjusted OR (95% CI)[b]	1 (Referent)	0.67 (0.38 to 1.19)	0.90 (0.52 to 1.58)	0.82 (0.46 to 1.45)	.64
Multivariable OR (95% CI)[c]	1 (Referent)	0.67 (0.37 to 1.20)	0.91 (0.52 to 1.61)	0.83 (0.47 to 1.49)	.69
Distal and rectal					
No. of cases	91	77	51	52	
Unadjusted OR (95% CI)	1 (Referent)	0.93 (0.68 to 1.26)	0.66 (0.47 to 0.94)	0.74 (0.52 to 1.04)	.01
Age-adjusted OR (95% CI)[b]	1 (Referent)	0.93 (0.69 to 1.26)	0.66 (0.47 to 0.94)	0.74 (0.52 to 1.05)	.02
Multivariable OR (95% CI)[c]	1 (Referent)	0.91 (0.67 to 1.24)	0.64 (0.44 to 0.92)	0.71 (0.49 to 1.03)	.02

[a]Advanced adenoma includes adenoma at or greater than 1 cm, or with tubulovillous or villous histology or high-grade dysplasia. CI = confidence interval; NHSII = Nurses' Health Study II; OR = odds ratio.

[b]Adjusted for age (continuous), total caloric intake (in quintiles), time period of endoscopy (in 2-year intervals), number of reported endoscopies (continuous), time in years since the most recent endoscopy (continuous), and reason for the current endoscopy (screening, symptoms, missing).

[c]Additionally adjusted for height (continuous), body mass index (in quintiles), family history of colorectal cancer (yes, no), menopausal status (premenopausal, postmenopausal), pack-years of smoking (never, 1-20, ≥20 pack-years), physical activity (in metabolic equivalent of task-hours/week, quintiles), current use of multivitamin (yes, no), regular use of aspirin (yes, no), and regular use of nonsteroidal anti-inflammatory drugs (yes, no). For Dietary Approaches to Stop Hypertension, we additionally adjusted for alcohol intake (0, 0.1-14.9, ≥15 g/d).

[d]Calculated using the median of each quartile as a continuous variable.

mechanisms involved. More detailed studies of differences in dietary index adherence and CRC risk by anatomic site in youth are also warranted.

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Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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