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Abstract

Background & Aims: Diet may contribute to the increasing incidence of colorectal cancer (CRC) before age 50 (early-onset CRC). Microbial metabolism of dietary sulfur produces hydrogen sulfide (H_2S), a gastrointestinal carcinogen that cannot be easily measured at scale. As a result, evidence supporting its role in early neoplasia is lacking.

Methods: We evaluated long-term adherence to the sulfur microbial diet, a dietary index defined *a priori* based on increased abundance of 43 bacterial species involved with sulfur metabolism, with risk of CRC precursors among 59,013 individuals who underwent lower endoscopy in the Nurses' Health Study II (NHSII, 1991–2015), a prospective cohort study with dietary assessment every four years through validated food frequency questionnaires and an assessment of dietary intake during adolescence in 1998. The sulfur microbial diet was characterized by intake high in processed meats and low in mixed vegetables and legumes, foods previously linked to CRC development. Multivariable logistic regression for clustered data was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

Results: We documented 2,911 cases of early-onset adenoma. After adjusting for established risk factors, higher sulfur microbial diet scores were associated with increased risk for early-onset adenomas ($OR_{Q4vs.Q1}$=1.31, 95% CI: 1.10 to 1.56, P_{trend}=0.02), but not serrated lesions. Compared to the lowest, women in the highest quartile of sulfur microbial diet scores had significantly increased risk of early-onset adenomas with greater malignant potential ($OR_{Q4vs.Q1}$=1.65 for villous/tubulovillous histology, 95% CI: 1.12 to 2.43; P_{trend}=0.04). Similar trends for early onset-adenoma were observed based on diet consumed during adolescence. In contrast, there was no clear association for adenomas identified after age 50.

Conclusion: Our findings in a cohort of young women support a role for dietary interactions with gut sulfur-metabolizing bacteria in early-onset colorectal carcinogenesis, possibly beginning in adolescence.

Lay Summary

Diets high in processed meats and low in vegetables and legumes, in tandem with microbial sulfur metabolism in the colon, can increase risk for colon polyps before age 50.

Keywords

FFQ; colorectal carcinogenesis; colorectal adenoma; hydrogen sulfide; cancer biogeography

Colorectal cancer (CRC) incidence has increased among persons aged 20–49 years in the US.[1, 2] Early-onset CRC, or CRC before age 50, is typically diagnosed at more advanced stages compared to CRC diagnosed later in life with more aggressive tumors, unique tumor molecular features, and greater years of life lost.[3, 4] Accumulating evidence suggests that early-onset CRC most frequently arises from neoplasia following the conventional adenoma-carcinoma sequence, rather than molecular pathways culminating from the development of sessile serrated adenomas and polyps.[5–7] Given the alarming rise in early-onset CRC, which stands in stark contrast to sharp declines in CRC after age 50, the early identification of individuals at risk for the most common early CRC precursor lesion, the colorectal adenoma, is a high unmet need.

Prior work has identified the emerging contribution of poor diet to risk of colorectal neoplasia,[8, 9] particularly before age 50.[10] However, the mechanisms remain underexplored. We recently demonstrated that diet-mediated alterations in specific microbes and patterns of community metabolism could modify CRC risk. Specifically, in an independent cohort (Health Professionals Follow-up Study), we derived a particular pattern of food intake associated with the enrichment of sulfur-metabolizing microbes in humans. Greater carriage of these bacteria may result in an increase in the microbial production of pro-carcinogenic hydrogen sulfide (H_2S).[11–13] 2 The sulfur microbial diet was characterized by foods previously linked to CRC risk (e.g., increased processed meats and decreased vegetables and legumes), and long-term adherence to this pattern was associated with increased risk for CRC in a cohort of older men.[14]

Thus, to investigate whether diet-induced alterations of specific gut microbial populations can influence the development of early-onset CRC, we performed a prospective investigation in a well-established cohort of young women with detailed information on adult and adolescent diets, endoscopic history, medical diagnoses, and CRC family history to link the sulfur microbial diet and risk of precursor adenomatous lesions as validated surrogate endpoints.

Methods

Study population

The Nurses' Health Study II (NHSII) is a prospective cohort study of 116,429 female nurses aged 25 to 42 years at enrollment in 1989. Participants are followed with detailed biennial questionnaires on demographics, lifestyle factors, medical diagnoses, medication use, and other exposures of interest. Cumulative follow up rate exceeds 90%.[15, 16] This study protocol was approved by the human research committees at the Brigham and Women's Hospital, the Harvard T.H. Chan School of Public Health, and participating state cancer registries as required.

In these analyses, we began follow-up with return of the 1991 questionnaire, the first study cycle for which participants were administered a food frequency questionnaire (FFQ). Prior to baseline and before each biennial follow-up cycle, we excluded participants with CRC, inflammatory bowel disease (IBD), a prior history of colorectal neoplasia/polyps, and either implausible energy intake (<600 or >3500 kcal/d) or missing information on dietary intake. Among 59,013 participants meeting these criteria and who had undergone at least one lower endoscopy prior to the end of follow-up (2015), 30,818 were under the age of 50 and thus included in our primary analysis.

Assessment of colorectal polyps

The primary endpoint was colorectal adenoma or serrated polyp diagnosed prior to age 50. On biennial study questionnaires, participants reported whether they had undergone lower endoscopy and the corresponding reasons for the procedure. For those who reported a diagnosis of colorectal polyp(s), we requested permission to review relevant medical records and pathology reports. Investigators masked to risk factor status reviewed all retrieved records to ascertain information on anatomical site, size, and histology.

If more than one adenoma was diagnosed, size and histology were categorized based on the largest and most advanced adenoma, respectively. Cases and non-cases were identified every two years and updated through the 2015 questionnaire cycle. All confirmed, newly diagnosed adenomas (tubular, villous, tubulovillous, or adenomas with high-grade dysplasia), as well as serrated polyps using World Health Organization criteria[17] (hyperplastic, serrated polyp, serrated adenomas, and serrated/mixed adenomas) were considered as cases. Individuals who had a lower endoscopy with no reported adenomas were non-cases.

Lesions were further segregated based on malignant potential,[18] characterized by their histology (tubulovillous/villous vs. tubular) and size (≥1 vs. <1 cm). Adenomas resected from the cecum, ascending colon, hepatic flexure, and transverse colon were considered proximal, while those from the splenic flexure, descending colon, and sigmoid colon were distal adenomas. Rectal or rectosigmoid junction were defined as rectal adenomas.

Assessment of dietary intake and the derivation of the sulfur microbial diet

Every 4 years from 1991 through 2011, participants self-reported adult dietary intake on a semi-quantitative food frequency questionnaire (FFQ), which included approximately 130 food items with specified serving sizes using common portions (e.g., 1 orange or 2–3 celery sticks). To capture the frequency of food consumption, nine response categories were provided, from “never or less than once per month” to “≥6 times per day” which was then converted to servings per day. The validity in assessing habitual dietary intake has been previously published.[19] In 1998, diet during adolescence was assessed using a slightly abbreviated high school FFQ, a 124-item questionnaire specifically designed to ascertain intake of specific food items consumed between 1960 and 1982 when participants were typically between ages 13–18 years. The details of this dietary instrument as well as its validity and reproducibility have previously been described in detail.[20–23]

In a prior investigation from an independent cohort,[14] we identified 43 different sulphur-metabolizing bacterial species based on carriage of genes coding for at least two well-known sulfur-metabolizing enzymes in each taxon's pangenome (Supp. Table 1). Detailed methods have been previously described.[14, 24] In brief, we used self-reported FFQs like those administered in the NHSII to link the intake of various foods with the log-transformed abundance of these microbes in stool by performing a reduced rank regression followed by a stepwise linear regression. The component food groups included processed meat, liquor, and low-calorie drinks (each positively associated with the relative enrichment of sulfur-metabolizing bacteria), as well as beer, fruit juice, legumes, mixed (other) vegetables, and sweets/desserts (each negatively associated; Supp. Table 2). Participants were scored according to their adherence to this pattern of intake, dubbed the sulfur microbial diet, by summing the intake of putative foods weighted by their regression coefficients. Higher sulfur microbial diet scores reflect closer adherence to a diet predicted to enrich for sulfur-metabolizing bacteria.

Assessment of covariates

Height and weight were reported at study inception, and weight was updated biennially. Body mass index (BMI) was calculated as weight in kilograms/height in meters. Physical activity was self-reported using validated questionnaires every 2–4 years.[25] We also assessed and updated family history of CRC among first-degree relatives, menopausal status and hormone use, personal history of type 2 diabetes, the age they started or stopped smoking, the number of cigarettes smoked daily, current use of multivitamin, regular use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), and the number of, time since, and reason for prior endoscopies.

Statistical analysis

To capture long-term habitual intake and to dampen measurement errors from random intra-individual variance, we calculated the cumulative average of all sulfur microbial diet scores available from 1991 until the two-year questionnaire cycle prior to the most recent endoscopy by averaging each score across all prior assessments. Due to the possibility that an individual may have undergone multiple lower endoscopies during follow-up and to efficiently account for time-varying exposures, we used an Andersen-Gill data structure with a new record constructed for each two-year follow up period in which a participant underwent an endoscopic procedure. Exposure and covariate information were captured at the time of questionnaire return. Upon first diagnosis of a polyp, participants were censored in all subsequent cycles. For all analyses using high school diet as an exposure of interest, the study baseline was set to 1998 (when the high school FFQ was administered).

We employed logistic regressions for clustered data (where each participant represents one cluster) to estimate age- and multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Tests for linear trend were conducted using the median value for each quantile as a continuous variable. Covariates were chosen *a priori* and updated on a time-varying basis among major CRC risk factors and confounders including age (five-year intervals), time period (two-year intervals), first-degree family history of CRC (yes/no), height (continuous), BMI (continuous, quintiles), menopausal status (premenopausal,

postmenopausal), menopausal hormone use (never, past, current), 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 tasks (METs, quintiles), current use of multivitamin (yes/no), regular use of aspirin or NSAIDs (each yes/no), number of reported endoscopies (continuous), time in years since the most recent endoscopy (continuous), and reason for the most recent endoscopy (screening, symptoms, missing). Given our primary exposure, we also adjusted for total caloric intake (quartiles). To assess whether the sulfur microbial diet was linked to risk of older-onset adenomas, we performed a separate secondary analysis among individuals aged≥50 years.

Where possible, for analyses considering high school diet, we used covariates most proximate to the exposure: total caloric intake at age 13–18 (continuous), BMI at age 18 (continuous), pack-years of smoking before age 20 (continuous), physical activity at grade 9–12 (continuous), and multivitamin use at age 13–18 (yes/no). Liquor (positive association) and beer (negative association) are both used to calculate the sulfur microbial diet score for habitual adult dietary intake,[14] but given that type of alcohol was not captured in the high school FFQ, high school sulfur microbial diet scores were calculated either without alcohol (primary) or assuming alcohol consumption was all beer, all liquor, or equally split between both.

We conducted several pre-specified secondary analyses to link the sulfur microbial diet to polyp size and histology. For missing data, we carried forward non-missing covariate data from one previous data cycle. SAS 9.4 was used for all analyses. Two-sided *p*-values <0.05 were considered statistically significant. All authors had access to the study data and reviewed and approved the final manuscript.

Results

Among 30,818 women aged <50 years at the time of their lower endoscopy between 1991 and 2015, we found that women more closely adhering to the sulfur microbial diet tended to have a higher BMI (Q4 27.1 vs. Q1 24.2 kg/m^2), were more likely to have ever smoked (35.3 vs. 31.8%), exercised less frequently (20.0 vs. 26.0 MET-hours/week) and were more likely to be regular users of non-aspirin NSAIDs (37.8 vs. 30.2%) and less likely to use multivitamins (50.8 vs. 58.6%; Table 1). These trends were consistent when compared to participant characteristics at the study midpoint (Suppl. Table 3).

We documented 2,911 cases of early-onset colorectal neoplasia diagnosed over 45,843 lower endoscopies, including 1,242 conventional adenomas, 1,669 serrated lesions, 230 polyps with advanced histology, and 200 with size ≥1cm. Compared with those in the lowest quartile, women in the highest quartile of sulfur microbial diet scores had an increased risk of early-onset conventional adenoma, even after adjusting for putative CRC risk factors (multivariable-adjusted $OR_{Q4vs.Q1}$=1.31, 95% CI: 1.10 to 1.56, P_{trend}=0.02; Table 2). In contrast, sulfur microbial diet scores were not associated with serrated lesions ($OR_{Q4vs.Q1}$=0.90, 95% CI: 0.77 to 1.05, P_{trend}=0.08; Suppl. Table 4). This increase in risk appeared to be limited to conventional adenomas of early onset. For 2,233 conventional adenomas cases among 93,862 lower endoscopies in participants age 50 years or greater, we

found no clear relationship (multivariable-adjusted $OR_{Q4vs.Q1}$=0.99, 95% CI: 0.87 to 1.14, P_{trend}=0.68; Table 2).

Notably, the positive association with early-onset conventional adenoma appeared stronger for lesions with advanced histology and thus greater malignant potential. Adherence to the sulfur microbial diet appeared to confer a comparatively greater risk for adenomas characterized by tubulovillous or villous histology ($OR_{Q4vs.Q1}$=1.65, 95% CI: 1.12 to 2.43, P_{trend}=0.04; Table 3) vs. tubular adenomas ($OR_{Q4vs.Q1}$=1.24, 95% CI: 1.02 to 1.50, P_{trend}=0.09). No clear differential relationship between the sulfur microbial diet and the size of early-onset conventional adenoma was observed, though there was a stronger trend towards increased risk of polyps <1 cm ($OR_{Q4vs.Q1}$=1.34, 95% CI: 1.07 to 1.66, P_{trend}=0.06).

The increase in sulfur microbial diet-associated risk for conventional adenomas appeared to be largely driven by neoplasia arising in the proximal colon ($OR_{Q4vs.Q1}$=1.58, 95% CI: 1.17 to 2.14, P_{trend}=0.01; Table 4). Similar to their overall risk estimates, we saw no clear relationship between the sulfur microbial diet and serrated lesions when stratified by size or location (Suppl. Table 4).

Interestingly, when we assessed greater adherence to the sulfur microbial diet during adolescence, we observed a positive association for early-onset conventional adenomas. Specifically, compared to scores below the median, the OR for high school sulfur microbial diet scores above the median was 1.13 for early-onset conventional adenomas (95% CI: 0.95 to 1.35; P_{trend}=0.03; Table 5). Similarly, risk estimates were greater for adherence to the sulfur microbial diet during high school and polyps of advanced histology (OR=1.27, 95% CI: 0.79 to 2.04, P_{trend}=0.17) and/or in the proximal colon (OR=1.26, 95% CI: 0.93 to 1.71, P_{trend}=0.47; Suppl. Table 5), though neither estimate reached statistical significance. Estimates remained similar in several sensitivity analyses in which we assumed high school alcohol consumption was either all beer, all liquor, or evenly split between both (data not shown).

Conclusions

In a large prospective cohort study, we found that long-term adherence to a diet that co-occurs with human gut microbial communities enriched for sulfur-metabolizing bacteria was associated with an increased risk of early-onset conventional adenoma, a surrogate endpoint for CRC. This risk was particularly elevated for lesions with a higher likelihood to progress to CRC due to advanced histopathology and those arising in the proximal colon. In contrast, there was no association for adenomas diagnosed after age 50. Finally, our data suggest that additive risk of early-onset adenoma conferred by this sulfur microbial diet may begin with dietary intake during adolescence, or alternatively, that there is substantial risk latency between dietary exposure and adenoma occurrence. Taken together, we offer additional supportive evidence linking specific detrimental microbiome configurations with diet-associated differences in chronic digestive tract disease risk at an epidemiologic scale.

Our primary findings are biologically plausible via microbial hydrogen sulfide (H_2S) generation and significantly extend prior population-level work demonstrating the role of diet in both early-onset colorectal neoplasia,[10] as well as later-onset CRC.[14] This study was motivated by prior mechanistic studies that demonstrated the harmful impact of dietary sulfur economy and microbial sulfur metabolism in the human gut. Specifically, in the presence of microbially-generated H_2S, the mucus bilayer in the colon becomes fragmented, promoting inflammation and carcinogenesis.[26–30] Components of the sulfur microbial diet, such as processed meats, can also individually fuel this process by contributing sulfur-containing amino acids found in meats and preservatives that serve as biochemical substrates.[13] Conversely, plant-based sulfur sources, such as those found in legumes and vegetables, are distinct from animal-based sources, composed primarily of glucosinolate compounds more likely to be cancer protective[31–33].

An association between the sulfur microbial diet and risk for conventional adenomas before age 50 (as compared to serrated lesions) is further supported by emerging evidence that the majority of early-onset CRCs exhibit microsatellite stable (MSS) or MSI-low, non-CpG island methylator phenotypes (CIMP, *BRAF* and *KRAS* wild type). They are thus more likely to originate from completion of the conventional adenoma-carcinoma sequence as opposed to serrated pathways.[5, 634] Similarly, differences in embryologic origins[35] or variable responses to dietary risk factors[36, 37] could help explain the heterogeneity in risk of early-onset adenomas compared to those occurring at or after age 50 years, particularly in younger persons for whom poor diet quality is widely and increasingly prevalent.[38, 39] Finally, observed differences in proportion of diet-attributable risk by anatomic region may be driven by biogeographical differences in microbial ecology (i.e., differences in host-microbe interactions along the gastrointestinal tract).[40] Taken together, this may suggest that diet-induced alterations of gut sulfur economy may have a more pronounced effect on the initiation of proximal lesions early in life. Our finding of greater risk for proximal conventional adenomas in young women—which extends prior work linking the sulfur microbial diet and distal colorectal tumors in older men—warrants further exploration in future investigations.

Our study has several strengths. First, in a cohort distinct from which the sulfur microbial diet was derived, we had a unique opportunity to explore the dietary determinants of early-onset CRC precursors, lending greater generalizability to this novel and emerging dietary risk factor. Second, information on dietary intake, including assessments of both habitual adult and adolescent diets, and colorectal neoplasia were regularly updated and prospectively collected among participants with high follow-up rates, limiting ascertainment and selection bias. Third, we also collected contemporaneous information on multiple known risk factors for CRC that may confound the relationship between the sulfur microbial diet and early-onset colorectal neoplasia risk.

We acknowledge several limitations. We cannot eliminate the possibility of residual confounding in an observational study. However, our findings were robust to multivariable analysis inclusive of several major CRC risk factors. We did not routinely assess if individuals had a known hereditary cancer syndrome (e.g., Lynch syndrome or familial adenomatous polyposis). However, most cases of early-onset CRC are sporadic with only

15% having a documented germline mutation[41] and even fewer occurring among individuals with a confirmed (and rare) hereditary cancer syndrome/known genetic predisposition.[42, 43] Additionally, adherence to the sulfur microbial diet among possible hereditary cancer syndrome cases and non-cases would likely be non-differential, which would have biased our results towards the null, and reassuringly, risk estimates remained robust even after adjusting for first-degree family history of CRC (updated biennially). We did not routinely assess reasons for screening beyond canonical lower GI alarm symptoms (i.e., change in bowel habits, unexplained weight loss, or lower GI bleeding) or family history, and thus, alternative reasons for early endoscopic evaluation may be incompletely captured. As before,[14] the sulfur microbial diet was derived based on variation in the abundance of sulfur-metabolizing bacteria of sufficient prevalence in the healthy human gut. Thus, our analysis did not specifically examine, for example, *Fusobacterium* species. However, such strongly cancer-associated taxa are more commonly found among individuals with late-stage colorectal neoplasia,[44–47] outside the scope of this investigation on precursor lesions in young persons. Finally, our study enrolled female nurses aged 25–42, and the generalizability of our findings exploring predictors of colorectal polyps among men or in other age groups is unknown. However, it is worth noting that our initial effort linking the sulfur microbial diet to CRC incidence was conducted in a cohort of older men.[14] Further, our observations address a possible underlying biological mechanism relating substrate availability to microbially-mediated tumorigenesis (e.g., the confluence of cancer-promoting dietary sulfur components and microbes that can metabolize them), a process that is unlikely to differ significantly among different populations. In support of this assertion, large-scale studies, including the Human Microbiome Project 1 and the Integrative Human Microbiome Project or HMP2 have not demonstrated systematic sex-based differences in gut microbial communities.[48, 49]

In conclusion, we found that higher sulfur microbial diet scores in early adulthood, and perhaps during adolescence, were associated with increased risk of early-onset conventional adenomas, particularly those with higher-risk histological features. Epidemiologic validation or further mechanistic work are needed to determine the underlying biology that explains observed heterogeneity in the anatomic location and histopathology of sulfur-induced CRC precursor lesions. How other gut microbial determinants, including body composition and other lifestyle factors (e.g., physical activity and medications), may influence the link between diet-induced enrichment of carcinogenic microbes, whether dietary modification can modulate long-term carriage of harmful gut bacteria, and how these complex interactions may culminate in a viable disease prevention strategy remains to be determined.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ASA	aspirin or acetylsalicylic acid
BMI	body mass index
CI	confidence interval
CIMP	CpG island methylator phenotype
CRC	colorectal cancer
EC	Enzyme Commission
FFQ	food frequency questionnaire
GI	gastrointestinal
H_2S	hydrogen sulfide
KRAS	Kirsten Rat Sarcoma
MET	metabolic equivalent of tasks
MSS	microsatellite stable
MSI	microsatellite instability
NHS II	Nurses' Health Study II
OR	odds ratio

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What You Need to Know

Background & Context

Early-onset colorectal cancer (CRC) before age 50 years is rising for largely unknown reasons, and emerging evidence suggests CRC risk attributable to diet may be partially mediated through activities of gut microbial communities and bacterial sulfur metabolism contributing to carcinogenesis.

New Findings

Long-term adherence to a sulfur microbial diet, a pattern of intake linked to 43 gut microbes associated with sulfur metabolism, may be associated with increased risk for adenomas prior to age 50, particularly those with advanced histology/greater malignant potential, and risk may begin as early as adolescence.

Limitations

We focused on microbes of sufficient prevalence and abundance in healthy gut communities and thus, did not specifically examine cancer-associated *Fusobacterium* species.

Impact

These findings support a relationship between diet-induced alterations of the gut microbiome and risk for precancerous lesions in younger populations as early as adolescence. Targeting at-risk patients with directed guidance to favorably alter this ecology through dietary modulation may be a viable and low-risk preventative strategy.

Table 1

Age-standardized characteristics of participants at the time of lower endoscopy before age 50 according to quartiles of sulfur microbial diet scores in the Nurses' Health Study II (NHSII), 1991–2015

	Sulfur microbial diet score (quartile)			
	1 (lowest)	**2**	**3**	**4 (highest)**
Age, years *	45.3 (4.4)	45.3 (4.4)	45.2 (4.5)	45 (4.5)
Height, cm	165 (6.7)	164.8 (6.6)	164.9 (6.6)	165.2 (6.8)
BMI, kg/m²	24.2 (4.8)	24.7 (5)	25.4 (5.3)	27.1 (6.1)
Family history of colorectal cancer, %	16.0	16.2	16.0	15.5
Number of previous endoscopies	1.6 (0.9)	1.6 (0.9)	1.5 (0.9)	1.6 (0.9)
Time since most recent endoscopy, years	3.6 (3.1)	3.7 (3.1)	3.7 (3.2)	3.7 (3.2)
Reasons for endoscopy				
Screening, %	52.9	52.8	51.3	49.4
Symptoms, %	44.9	45.2	46.7	48.3
Missing, %	2.2	2.0	2.0	2.3
Postmenopausal hormone use				
Pre-menopause, %	83.9	83.8	81.7	81.2
No prior use, %	4.9	4.2	4.8	4.5
Current use, %	9.0	9.5	10.9	11.4
Past use, %	2.3	2.5	2.6	3.0
History of diabetes, %	1.4	1.7	2.8	5.3
Ever smokers, %	31.8	31.5	31.5	35.3
Pack-years among prior smokers	11.2 (8.9)	11.7 (9.4)	12.3 (9.9)	13.7 (10.2)
Alcohol intake, g/day	4.6 (7.1)	3.4 (5.2)	3 (4.8)	3.2 (5.7)
Physical activity, MET-hours/week	26 (26.1)	22.1 (22.9)	20.1 (20.9)	20 (21.2)
Regular aspirin use, %	11.8	11.4	11.6	13.0
Regular non-aspirin NSAID use, %	30.2	30.8	33.1	37.8
Multivitamin use, %	58.6	54.4	52.0	50.8
Total calorie intake, kcal/day	2136 (464)	1833 (438)	1680 (436)	1665 (472)
Dietary intake, servings/week				
Processed meat	1.3 (1.3)	1.5 (1.3)	1.6 (1.4)	2 (2)
Liquor	0.2 (0.7)	0.2 (0.7)	0.3 (0.8)	0.4 (1.6)
Low-calorie drinks	2.2 (3.6)	3 (4)	5.1 (5)	17.1 (11.1)
Beer	1.2 (2.9)	0.6 (1.4)	0.5 (1.1)	0.5 (1.2)
Fruit juice	7.5 (6.3)	4.7 (3.8)	3.3 (3)	2.6 (2.9)
Legumes	4.3 (2.8)	2.6 (1.5)	2 (1.4)	1.9 (1.4)
Other vegetables	10.4 (6.8)	6.6 (3.7)	5.2 (3.3)	5.1 (3.6)
Sweets & desserts	9.4 (8.7)	6.6 (5)	5.6 (4.2)	5.8 (4.7)
Alternate Healthy Eating Index 2010 (without alcohol)	47.8 (10.1)	45.1 (9.4)	44.1 (8.9)	43.8 (8.5)

Values are means (SD) for continuous variables. Percentages or Ns or both for categorical variables. Variables standardized to the age distribution of the study population.

Values of polytomous variables may not sum to 100% due to rounding

* Not age adjusted

Abbreviations: g (gram), kcal (kilocalories), kg (kilogram), m (meters), MET (metabolic equivalent of task), NSAID (non-steroidal anti-inflammatory drug)

Table 2.

Sulfur microbial diet and risk of conventional adenoma, NHSII, 1991–2015

	Sulfur microbial diet score (quartile)				P_{trend} §
	1 (lowest)	2	3	4 (highest)	
Before age 50 years	287	302	292	361	
Age-adjusted OR (95% CI)†	1 [Ref]	1.06 (0.90 to 1.25)	1.04 (0.87 to 1.24)	1.33 (1.12 to 1.57)	0.007
Multivariable OR (95% CI)‡	1 [Ref]	1.05 (0.88 to 1.24)	1.03 (0.87 to 1.24)	1.31 (1.10 to 1.56)	0.02
Age 50 years or later	541	590	527	575	
Age-adjusted OR (95% CI)†	1 [Ref]	1.07 (0.95 to 1.21)	0.95 (0.83 to 1.08)	1.03 (0.90 to 1.17)	0.93
Multivariable OR (95% CI)‡	1 [Ref]	1.05 (0.93 to 1.19)	0.93 (0.81 to 1.06)	0.99 (0.87 to 1.14)	0.68

† 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).

‡ 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/week, quintiles), current use of multivitamin (yes, no), regular use of aspirin (yes, no), and regular use of non-steroidal anti-inflammatory drugs (yes, no).

§ Calculated using the median of each quartile as a continuous variable.

Abbreviations: CI (confidence interval), OR (odds ratio)

Table 3.

Sulfur microbial diet and risk of early-onset (age <50 years) conventional adenoma by malignancy risk, NHSII, 1991–2015

	Sulfur microbial diet score (quartile)				P_{trend} [§]
	1 (lowest)	2	3	4 (highest)	
Histology					
Tubulovillous/villous	51	57	49	73	
Age-adjusted OR (95% CI)[†]	1 [Ref]	1.19 (0.80 to 1.77)	1.06 (0.70 to 1.62)	1.61 (1.10 to 2.36)	0.04
Multivariable OR (95% CI)[‡]	1 [Ref]	1.21 (0.81 to 1.80)	1.09 (0.72 to 1.65)	1.65 (1.12 to 2.43)	0.04
Tubular	236	245	243	288	
Age-adjusted OR (95% CI)[†]	1 [Ref]	1.03 (0.86 to 1.24)	1.03 (0.85 to 1.25)	1.27 (1.06 to 1.53)	0.05
Multivariable OR (95% CI)[‡]	1 [Ref]	1.01 (0.84 to 1.22)	1.02 (0.84 to 1.24)	1.24 (1.02 to 1.51)	0.09
Size					
Large (≥1 cm)	49	56	45	50	
Age-adjusted OR (95% CI)[†]	1 [Ref]	1.18 (0.79 to 1.76)	0.99 (0.64 to 1.54)	1.14 (0.75 to 1.74)	0.74
Multivariable OR (95% CI)[‡]	1 [Ref]	1.21 (0.81 to 1.81)	1.02 (0.66 to 1.59)	1.17 (0.76 to 1.81)	0.80
Small (<1 cm)	175	171	155	223	
Age-adjusted OR (95% CI)[†]	1 [Ref]	0.99 (0.80 to 1.23)	0.91 (0.72 to 1.14)	1.36 (1.10 to 1.68)	0.03
Multivariable OR (95% CI)[‡]	1 [Ref]	0.98 (0.78 to 1.21)	0.90 (0.71 to 1.14)	1.34 (1.07 to 1.66)	0.06

[†]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).

[‡]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/week, quintiles), current use of multivitamin (yes, no), regular use of aspirin (yes, no), and regular use of non-steroidal anti-inflammatory drugs (yes, no).

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

[//]High-risk adenoma includes adenoma ≥1 cm, or with tubulovillous/villous histology or high-grade dysplasia, or ≥3 adenomas.

Abbreviations: CI (confidence interval), cm (centimeter), OR (odds ratio)

Table 4.

Sulfur microbial diet and risk of early-onset (age <50 years) conventional adenoma by location, NHSII, 1991–2015

	Sulfur microbial diet score (quartile)				P_{trend} [§]
	1 (lowest)	2	3	4 (highest)	
Proximal	79	99	87	120	
Age-adjusted OR (95% CI)[†]	1 [Ref]	1.26 (0.94 to 1.70)	1.12 (0.82 to 1.53)	1.60 (1.19 to 2.16)	0.009
Multivariable OR (95% CI)[‡]	1 [Ref]	1.25 (0.93 to 1.69)	1.12 (0.82 to 1.53)	1.58 (1.17 to 2.14)	0.01
Distal	123	110	116	135	
Age-adjusted OR (95% CI)[†]	1 [Ref]	0.92 (0.70 to 1.20)	0.99 (0.75 to 1.31)	1.19 (0.92 to 1.55)	0.25
Multivariable OR (95% CI)[‡]	1 [Ref]	0.90 (0.68 to 1.18)	0.98 (0.74 to 1.30)	1.18 (0.90 to 1.56)	0.27
Rectal	39	43	38	42	
Age-adjusted OR (95% CI)[†]	1 [Ref]	1.13 (0.72 to 1.77)	1.04 (0.65 to 1.66)	1.17 (0.74 to 1.86)	0.99
Multivariable OR (95% CI)[‡]	1 [Ref]	1.12 (0.71 to 1.75)	1.03 (0.64 to 1.65)	1.15 (0.72 to 1.86)	0.92

[†]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).

[‡]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/week, quintiles), current use of multivitamin (yes, no), regular use of aspirin (yes, no), and regular use of non-steroidal anti-inflammatory drugs (yes, no).

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

Abbreviations: CI (confidence interval), OR (odds ratio)

Table 5.

Sulfur microbial diet in high school and risk of early-onset (age <50 years) polyp, NHSII, 1998–2015

	Sulfur microbial diet score (median)		P_{trend} ‖
	Below	Above	
Conventional adenoma	302	342	
Age-adjusted OR (95% CI)†	1 [Ref]	1.15 (0.96 to 1.36)	0.02
Multivariable model 1 OR (95% CI)‡	1 [Ref]	1.13 (0.94 to 1.34)	0.04
Multivariable model 2 OR (95% CI)§	1 [Ref]	1.13 (0.95 to 1.35)	0.03
Serrated lesion	416	412	
Age-adjusted OR (95% CI)†	1 [Ref]	0.98 (0.84 to 1.14)	0.54
Multivariable model 1 OR (95% CI)‡	1 [Ref]	0.96 (0.82 to 1.12)	0.31
Multivariable model 2 OR (95% CI)§	1 [Ref]	0.94 (0.81 to 1.10)	0.25

†Adjusted for age (continuous), total caloric intake at age 13–18 (continuous), 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).

‡Additionally adjusted for height (continuous), body mass index at age 18 (continuous), pack-years of smoking before age 20 (continuous), physical activity at grade 9–12 (continuous), and multivitamin use at age 13–18 (yes, no).

§Additionally adjusted for putative colorectal cancer risk factors in mid-adulthood: 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, 0.1–19.9, ≥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 non-steroidal anti-inflammatory drugs (yes, no).

‖Calculated using the median of each quantile as a continuous variable

Abbreviations: CI (confidence interval), OR (odds ratio)

Supplementary Table 1: List of sulfur-metabolizing bacteria[14]

Acidaminococcus unclassified	*Eubacterium rectale*
Adlercreutzia equolifaciens	*Gordonibacter pamelaeae*
Alistipes finegoldii	*Lachnospiraceae bacterium 5 1 63FAA*
Alistipes putredinis	*Odoribacter splanchnicus*
Anaerotruncus colihominis	*Oxalobacter formigenes*
Bacteroides clarus	*Parabacteroides distasonis*
Bacteroides intestinalis	*Parabacteroides goldsteinii*
Bacteroides ovatus	*Parabacteroides johnsonii*
Bacteroides plebeius	*Parabacteroides merdae*
Bacteroides stercoris	*Parabacteroides unclassified*
Bacteroides uniformis	*Paraprevotella clara*
Bacteroides vulgatus	*Paraprevotella xylaniphila*
Bilophila unclassified	*Parasutterella excrementihominis*
Bilophila wadsworthia	*Roseburia intestinalis*
Burkholderiales bacterium 1 1 47	*Ruminococcus bromii*
Clostridiales bacterium 1 7 47FAA	*Streptococcus australis*
Coprococcus catus	*Streptococcus vestibularis*
Desulfovibrio desulfuricans	*Sutterella wadsworthensis*
Eggerthella lenta	*Veillonella atypica*
Erysipelotrichaceae bacterium 21 3	*Veillonella parvula*
Erysipelotrichaceae bacterium 6 1 45	*Veillonella unclassified*
Eubacterium ramulus	

Species-level identification of microbes suspected to be involved in dietary sulfur metabolism based on prior experimental evidence, as well as the presence of genes encoding for at least two sulfur-metabolizing enzymes.

Supplementary Table 2: Components of the sulfur microbial diet pattern (Health Professionals Follow-up Study)[14]

Sulfur microbial diet pattern components with the top factor loadings	**Representative foods**	**β-coefficients (SE)**
Positive associations		
Processed meats	Processed meats, bacon, hot dogs	0.64 (0.25)
Liquor	Vodka, gin	0.31 (0.11)
Low-calorie drinks	Low-calorie cola, other low-energy carbonated beverages	0.38 (0.11)
Negative associations		
Beer	Beer	-0.54 (0.17)
Fruit juice	Apple juice or cider, orange juice, grapefruit juice, other fruit juice	-0.21 (0.12)
Legumes	String beans, peas or lima beans, beans or lentils, tofu or soybeans, alfalfa sprouts	-0.64 (0.19)
Other vegetables	Celery, mushrooms, green pepper, corn, mixed vegetables, eggplant, summer squash	-0.30 (0.10)
Sweets & desserts	Chocolate bars or pieces, candy bars, cookies, brownies, doughnuts, cake, pie, sweet roll, coffee cake, pastries	-0.23 (0.10)

Abbreviations: SE (standard error)

Supplementary Table 3. Participant characteristics at study midpoint in the Nurses' Health Study II (NHSII), 2001

	Sulfur microbial diet score (quartile)			
	1 (lowest) (*n*=1395)	2 (*n*=1396)	3 (*n*=1396)	4 (highest) (*n*=1396)
Age, years*	46 (3.3)	46.1 (3.2)	46.1 (3.2)	45.7 (3.4)
Height, cm	164.9 (6.6)	164.7 (6.5)	165 (6.6)	165 (7)
BMI, kg/m²	24.3 (4.8)	24.7 (5)	25.6 (5.3)	27.3 (6.1)
Family history of colorectal cancer, %	18.7	19.1	19.9	18.4
Number of previous endoscopies	1.6 (0.9)	1.6 (1)	1.6 (0.9)	1.6 (1)
Time since most recent endoscopy, years	3.7 (2.8)	3.6 (2.7)	3.5 (2.6)	3.4 (2.6)
Reasons for endoscopy				
Screening, %	48.7	48.4	48.1	44.2
Symptoms, %	49.0	48.8	50.1	53.3
Missing, %	2.3	2.8	1.9	2.5
Postmenopausal hormone use				
Pre-menopause, %	81.4	82.6	79.6	80.1
No prior use, %	4.3	3.6	3.5	3.3
Current use, %	11.9	11.7	14.5	13.5
Past use, %	2.5	2.2	2.4	3.0
History of diabetes, %	1.6	1.8	2.8	4.1
Ever smokers, %	32.2	31.9	32.6	34.5
Pack-years among prior smokers	11.1 (8.7)	12.2 (9.7)	13.1 (10)	14 (10.7)
Alcohol intake, g/day	4.4 (6.8)	3.3 (4.7)	2.9 (4.7)	3.3 (5.7)
Physical activity, MET-hours/week	24.7 (23.4)	20.5 (20.4)	19.6 (18.8)	18.9 (18.4)
Regular aspirin use, %	11.4	11.5	12.0	12.4
Regular non-aspirin NSAID use, %	32.0	30.2	34.0	36.9
Multivitamin use, %	63.2	56.7	55.0	52.1
Total calorie intake, kcal/day	2145 (445)	1826 (431)	1690 (422)	1671 (454)
Dietary intake, servings/week				
Processed meat	1.3 (1.3)	1.5 (1.3)	1.6 (1.4)	2 (2.1)
Liquor	0.2 (0.6)	0.2 (0.6)	0.2 (0.7)	0.5 (1.6)
Low-calorie drinks	2.2 (3.4)	2.9 (3.8)	5.3 (5.2)	16.6 (11.2)
Beer	1.2 (2.8)	0.7 (1.3)	0.5 (1.2)	0.5 (1.2)
Fruit juice	7.8 (6.1)	4.9 (4)	3.4 (2.9)	2.9 (3)
Legumes	4.4 (3)	2.7 (1.5)	2.2 (1.4)	1.9 (1.4)
Other vegetables	10.4 (6.4)	6.5 (3.4)	5.5 (3.3)	5.1 (3.5)
Sweets & desserts	10 (9)	7.3 (5.2)	5.9 (4.1)	6.1 (4.7)

Alternate Healthy Eating Index 2010 (without alcohol)	47.2 (9.6)	44.3 (9.1)	43.7 (8.7)	43.3 (8.3)

Values are means (SD) for continuous variables. Percentages or Ns or both for categorical variables. Variables standardized to the age distribution of the study population.
Values of polytomous variables may not sum to 100% due to rounding
*Not age adjusted
Abbreviations: g (gram), kcal (kilocalories), kg (kilogram), m (meters), MET (metabolic equivalent of task), NSAID (non-steroidal anti-inflammatory drug)

Supplementary Table 4. Sulfur microbial diet and risk of early-onset (age <50 years) serrated lesion by polyp location and size, NHSII, 1991-2015

	Sulfur microbial diet score (quartile)				P_{trend}§
	1 (lowest)	2	3	4 (highest)	
Overall	420	420	414	415	
Age-adjusted OR (95% CI)†	1 [Ref]	0.99 (0.86 to 1.14)	0.98 (0.84 to 1.13)	1.01 (0.87 to 1.17)	0.86
Multivariable OR (95% CI)‡	1 [Ref]	0.96 (0.84 to 1.11)	0.93 (0.80 to 1.08)	0.90 (0.77 to 1.05)	0.08
Size					
Large (≥1 cm)	27	40	40	31	
Age-adjusted OR (95% CI)†	1 [Ref]	1.42 (0.87 to 2.32)	1.42 (0.86 to 2.37)	1.13 (0.65 to 1.98)	0.73
Multivariable OR (95% CI)‡	1 [Ref]	1.44 (0.88 to 2.35)	1.40 (0.83 to 2.36)	1.02 (0.58 to 1.76)	0.94
Small (<1 cm)	369	352	358	371	
Age-adjusted OR (95% CI)†	1 [Ref]	0.94 (0.81 to 1.10)	0.97 (0.83 to 1.13)	1.04 (0.89 to 1.21)	0.89
Multivariable OR (95% CI)‡	1 [Ref]	0.92 (0.79 to 1.08)	0.93 (0.79 to 1.09)	0.93 (0.79 to 1.09)	0.22
Location					
Proximal	149	145	147	143	
Age-adjusted OR (95% CI)†	1 [Ref]	0.95 (0.75 to 1.21)	0.96 (0.75 to 1.23)	0.97 (0.75 to 1.24)	0.66
Multivariable OR (95% CI)‡	1 [Ref]	0.95 (0.75 to 1.21)	0.96 (0.75 to 1.23)	0.93 (0.72 to 1.20)	0.48
Distal	179	182	179	193	
Age-adjusted OR (95% CI)†	1 [Ref]	0.98 (0.80 to 1.22)	0.97 (0.77 to 1.21)	1.08 (0.87 to 1.34)	0.59
Multivariable OR (95% CI)‡	1 [Ref]	0.95 (0.77 to 1.17)	0.90 (0.71 to 1.12)	0.91 (0.73 to 1.14)	0.34
Rectal	143	150	152	138	
Age-adjusted OR (95% CI)†	1 [Ref]	1.08 (0.85 to 1.37)	1.14 (0.89 to 1.45)	1.07 (0.83 to 1.37)	0.66
Multivariable OR (95% CI)‡	1 [Ref]	1.05 (0.82 to 1.33)	1.06 (0.83 to 1.36)	0.90 (0.69 to 1.17)	0.35

†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).

‡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/week, quintiles), current use of multivitamin (yes, no), regular use of aspirin (yes, no), and regular use of non-steroidal anti-inflammatory

drugs (yes, no).

§Calculated using the median of each quartile as a continuous variable.

Abbreviations: CI (confidence interval), OR (odds ratio)

Supplementary Table 5. Sulfur microbial diet in high school and risk of early-onset (age <50 years) conventional adenoma by malignancy risk, NHSII, 1998-2015

	Sulfur microbial diet score (median)		P_{trend}‖
	Below	Above	
Histology			
Tubulovillous/villous	48	56	
Age-adjusted OR (95% CI)†	1 [Ref]	1.21 (0.77 to 1.91)	0.27
Multivariable model 1 OR (95% CI)‡	1 [Ref]	1.26 (0.80 to 2.00)	0.17
Multivariable model 2 OR (95% CI)§	1 [Ref]	1.27 (0.79 to 2.04)	0.17
Tubular	254	286	
Age-adjusted OR (95% CI)†	1 [Ref]	1.13 (0.94 to 1.37)	0.04
Multivariable model 1 OR (95% CI)‡	1 [Ref]	1.10 (0.91 to 1.33)	0.11
Multivariable model 2 OR (95% CI)§	1 [Ref]	1.11 (0.92 to 1.34)	0.09
Size			
Large (≥1 cm)	58	70	
Age-adjusted OR (95% CI)†	1 [Ref]	1.25 (0.84 to 1.85)	0.16
Multivariable model 1 OR (95% CI)‡	1 [Ref]	1.23 (0.82 to 1.85)	0.19
Multivariable model 2 OR (95% CI)§	1 [Ref]	1.28 (0.85 to 1.92)	0.14
Small (<1 cm)	208	219	
Age-adjusted OR (95% CI)†	1 [Ref]	1.05 (0.85 to 1.29)	0.31
Multivariable model 1 OR (95% CI)‡	1 [Ref]	1.02 (0.83 to 1.26)	0.54
Multivariable model 2 OR (95% CI)§	1 [Ref]	1.03 (0.83 to 1.27)	0.51
Location			
Proximal	92	112	
Age-adjusted OR (95% CI)†	1 [Ref]	1.27 (0.94 to 1.72)	0.38
Multivariable model 1 OR (95% CI)‡	1 [Ref]	1.24 (0.92 to 1.68)	0.52
Multivariable model 2 OR (95% CI)§	1 [Ref]	1.26 (0.93 to 1.71)	0.47
Distal	124	121	
Age-adjusted OR (95% CI)†	1 [Ref]	1.01 (0.77 to 1.33)	0.06
Multivariable model 1 OR (95% CI)‡	1 [Ref]	0.97 (0.74 to 1.28)	0.11
Multivariable model 2 OR (95% CI)§	1 [Ref]	0.97 (0.73 to 1.28)	0.10
Rectal	40	45	
Age-adjusted OR (95% CI)†	1 [Ref]	1.12 (0.68 to 1.87)	0.18
Multivariable model 1 OR (95% CI)‡	1 [Ref]	1.14 (0.68 to 1.91)	0.14

Multivariable model 2 OR (95% CI)§	1 [Ref]	1.16 (0.69 to 1.95)	0.13

†Adjusted for age (continuous), total caloric intake at age 13-18 (continuous), 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).

‡Additionally adjusted for height (continuous), body mass index at age 18 (continuous), pack-years of smoking before age 20 (continuous), physical activity at grade 9-12 (continuous), and multivitamin use at age 13-18 (yes, no).

§Additionally adjusted for putative colorectal cancer risk factors in mid-adulthood: 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, 0.1-19.9, ≥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 non-steroidal anti-inflammatory drugs (yes, no).

|| Calculated using the median of each quantile as a continuous variable

Abbreviations: CI (confidence interval), cm (centimeter), OR (odds ratio)