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Prospective Evaluation of Dietary and Lifestyle Pattern Indices with Risk of Colorectal Cancer in a Cohort of Younger Women

Y. Yue, MS[1], **J. Hur, PhD**[1], **Y. Cao, ScD, MPH**[2,3,4], **F.K. Tabung, PhD**[1,5,6], **M. Wang, PhD**[7,8,9], **K. Wu, MD, PhD**[1], **M. Song, MD, ScD**[1,7,10,11], **X. Zhang, MD, ScD**[10], **Y. Liu, MD**[10,12], **J.A. Meyerhardt, MD, MPH**[10,13], **K. Ng, MD, MPH**[13], **S.A. Smith-Warner, PhD**[1,7,#], **W.C. Willett, MD, DrPH**[1,7,13,#], **E. Giovannucci, MD, ScD**[1,7,13,#]

[1]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA

[2]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, MO

[3]Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO

[4]Division of Gastroenterology, Department of Medicine, Washington University School of Medicine, St. Louis, MO

[5]Division of Medical Oncology, Department of Internal Medicine, The Ohio State University College of Medicine, Columbus, OH

[6]The Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH

[7]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

[8]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[9]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[10]Harvard Medical School, Boston, MA

Correspondence: Edward Giovannucci, MD, ScD, Harvard T.H. Chan School of Public Health, 665 Huntington Ave, Boston, MA 02215 (egiovann@hsph.harvard.edu).

[#]Equal contribution as last authors

Author Contributions:

Concept and design: YY, SSW, WW, and ELG;

Acquisition, analysis, or interpretation of data: YY, JH, YC, SSW, WW, and ELG

Drafting of the manuscript: YY and JH

Critical revision of the manuscript for important intellectual content: all authors

Statistical analysis: YY, YC

Administrative, technical, or material support: SSW, WW, and ELG

Supervision: SSW, WW, and ELG

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[11]Clinical and Translational Epidemiology Unit and Division of Gastroenterology, Massachusetts General Hospital, Boston, MA

[12]Evidence-Based Chinese Medicine, School of Chinese Medicine, Beijing University of Chinese, Medicine, Beijing, P.R. China;

[13]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Abstract

Background: Although colorectal cancer (CRC) incidence in the US is declining overall, its incidence is increasing among those younger than 50 years of age. The reasons underlying the increasing trend are largely unknown, although behavioral changes, such as unhealthy diet and lifestyle factors may be partially responsible.

Design—A prospective cohort study included 94,217 women aged 26–45 years at baseline. Validated anthropometric measures and lifestyle information were self-reported biennially. Exposures were four recommendation-based dietary indices—the Prime Diet Quality Score (PDQS) and three plant-based dietary indices; and two mechanism-based indices—the empirical dietary and lifestyle index for hyperinsulinemia (EDIH and ELIH). We calculated hazard ratios (HRs) and 95% confidence intervals (95%CIs) for overall CRC, and for early-onset and post-age-50 CRC, separately.

Results: We documented 332 cases of CRC during 24 years of follow-up (2,113,655 person-years), with an average age of 52±7 years at diagnosis. Hyperinsulinemic dietary and lifestyle patterns were associated with a higher risk of CRC. Multivariable-adjusted HRs (95%CIs) comparing participants in the highest versus lowest quartile were: 1.67 for EDIH (95%CI: 1.15–2.44, *P*-trend=.01) and 1.51 for ELIH (1.10–2.08, *P-trend*=.01). Moreover, per 75% increment in rank, ELIH appeared to be a stronger risk factor for early-onset CRC (HR=1.86, 95% CI: 1.12–3.07) than post-age-50 CRC (HR=1.20, 95%CI: 0.83, 1.73, P-heterogeneity=0.16). The four recommendation-based indices were not significantly associated with overall, early-onset, or post-age 50 CRC risk (per 75% increment in rank, HRs ranged from 0.90–1.28).

Conclusion: Dietary and lifestyle patterns contributing to hyperinsulinemia were associated with greater CRC risk in younger women. Moreover, the hyperinsulinemic lifestyle showed a suggestively stronger positive association with early-onset CRC risk, compared to post-age-50 CRC diagnosed. Our findings suggest that dietary and lifestyle interventions to reduce insulinemic potential may be effective for CRC prevention among younger women.

Keywords

Dietary and lifestyle pattern; colorectal cancer; young women

Introduction

Colorectal cancer (CRC) is the fourth most commonly diagnosed and second most lethal cancer in the United States[1]. Although men have substantially higher rates of colorectal cancer at older ages, rates are similar between men and women at younger ages (e.g., below 50 years)[2]. Furthermore, early-onset CRC, defined as CRC diagnosed before age 50

years, has increased at an alarming rate and is characterized by a more advanced-stage at diagnosis[3–5].

More than 50% of CRC cases are attributable to modifiable risk factors, such as unhealthy diet, physical inactivity, and excess adiposity[2, 6]. However, the majority of data on dietary and lifestyle factors in relation to CRC risk are based on CRC in older adults and effects of the aforementioned factors on CRC risk in younger adults remain unclear[7]. Recently, obesity and prolonged sedentary time were observed to be positively associated with risk of early-onset CRC (<50 years)[8–10]. However, studies on how diet contributes to the etiology of CRC in younger adults, independent of obesity, is sparse[11–13]. Given emerging data on clinicopathological differences of early- and later-onset CRC[14, 15], it is not apparent that risk factors would be the same.

Therefore, we investigated whether dietary and lifestyle patterns during adulthood are associated with risk of CRC in the Nurses' Health Study (NHS) II, a cohort of younger women (25–42 years at baseline). Associations with risk of CRC overall, before age 50 (early-onset CRC), and post-age-50 were examined. To better capture the complexity and interaction of dietary and lifestyle factors, we used three sets of pattern indices—the Prime Diet Quality Score (PDQS) assessing overall diet quality[16, 17], three plant-based dietary indices[18] emphasizing the quality of plant foods (such as whole grains and foods rich in dietary fiber that have been shown to be associated with lower CRC risk[19]), and two empirical hypothesis-oriented indices assessing the insulinemic potential[20], a key pathway underlying CRC development.

Methods

Study population and design

NHSII is an ongoing prospective cohort study of 116,430 US female nurses aged 25–42 years at the time of initiation in 1989. Information has been updated every two years on demographics, lifestyle factors, and health-related information. Since 1991, dietary information has been updated every four years using validated, self-administered, semiquantitative food frequency questionnaires (FFQs)[21–25]. These FFQs listed standard portion sizes for foods and asked participants to record intake frequency, with nine possible responses ranging from "never or less than once per month" to "six or more times per day." Average daily nutrient intake was calculated by multiplying the frequency of intake by the nutrient content of each food and summing nutrient values across all foods. Height and weight were reported in 1989, and weight was updated biennially. Body mass index (BMI) was calculated accordingly. Participants self-reported average time spent weekly on seven physical activities using validated questionnaires every 2–4 years since 1989[26]. Total physical activity in metabolic equivalent of tasks (MET)-hours/week was calculated by multiplying the MET score and hours/week spent in each activity[27] and summing over all activity items.

The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and of participating registries, as required.

Assessment of dietary and lifestyle pattern indices

We computed five dietary indices for each participant using FFQ data collected over six 4-year data cycles from 1991 to 2015 as follows: the PDQS, plant-based diet index (PDI), healthful PDI (hPDI), unhealthful PDI (uPDI), and Empirical Dietary Index for Hyperinsulinemia (EDIH). In addition, one lifestyle index, the Empirical Lifestyle Index for Hyperinsulinemia (ELIH), was computed as a composite of diet, BMI, and physical activity (Supplementary Table 1). The PDQS[16, 17] is an overall dietary quality score ranging from 0 to 42 that is comprised of 21 food groups; a higher score represents better diet quality. Three plant-based diet scores[18], including overall, healthful, and unhealthful plant-based diets, were computed based on 18 food groups and scores ranged from 18 to 90. The EDIH is a weighted sum of 18 food groups and the ELIH is a weighted sum of 12 food groups, BMI, and physical activity.[20] Higher EDIH and ELIH reflect more hyperinsulinemic dietary and lifestyle patterns. Details of each index are described in the Supplementary Appendix.

Ascertainment of colorectal cancer

Our primary endpoint was incident CRC. Using CRC diagnoses reported on biennial questionnaires, and after obtaining consent, study physicians who were blinded to exposure status reviewed medical records to confirm the diagnosis and extract data on histology, location, stage and grade. We also identified deaths due to CRC by reports from family members, postal authorities, or cross-referencing of the National Death Index, and the cause of death was confirmed by study physicians via death certificate or medical record review. For non-responders who died of CRC, we also obtained consent from next-of-kin and then confirmed the diagnosis via medical record review. We further classified CRC according to age at diagnosis (<50 versus ≥50 years) and examined cancers of the proximal colon (cecum, ascending colon, hepatic flexure, transverse colon, and splenic flexure) and distal colon (descending and sigmoid colon), and rectum separately.

Assessment of covariates

We obtained updated information by biennial questionnaires on body weight and physical activity (as described above), as well as smoking status, multivitamin use, regular use of aspirin, regular use of non-steroidal anti-inflammatory drugs (NSAIDs), menopausal status, and post-menopausal hormone use. Information was also collected on type 2 diabetes mellitus, family history of CRC, and history of lower gastrointestinal endoscopies in the past two years.

Statistical analysis

After we excluded women with a prior diagnosis of cancer (except non-melanoma skin cancer) or inflammatory bowel disease at baseline, and those with implausible energy intake (<500 or >3,500 kcal/day), a total of 94,217 women were included in the final analyses. Person-years of follow-up accrued from the return date of the first FFQ until the date of CRC diagnosis, death, or end of follow-up (June 1, 2015), whichever came first. To better represent long-term exposures and reduce within-person variation, cumulative averages of each dietary and lifestyle index were computed from all previous questionnaires up to the start of each 2-year follow-up interval[28]. Women were ranked into quartiles

by absolute scores for each index. To reduce the influence of outlying observations in some indices while keeping the continuous nature of the scores, we adopted a rank-based approach[29], where for each index, we transformed each value to its percentile in the empirical distribution of the scores for that index over our study population. This approach resulted in comparable distributions for each index, regardless of their different ranges on the absolute scale. We then conducted continuous analyses based on the percentiles; results are given for an increment corresponding to the difference in the medians of the first and fourth quartiles (a 75% percentile increment). Time-dependent Cox proportional hazards models were used to examine associations of dietary and lifestyle indices with risk of CRC, using the lowest quartile as the reference group. Models were stratified by age (months) and follow-up cycle (2-year intervals) and adjusted for energy intake (kcal/day). Multivariable models further included total alcohol consumption (continuous), height (continuous), race (white/nonwhite), family history of CRC (yes/no), history of diabetes (yes/no), smoking pack-years (continuous), regular use of aspirin (yes/no), regular use of NSAIDs (yes/no), multivitamin use (yes/no), menopausal status and hormone use (premenopausal, never hormone use/post-menopausal, ever hormone use), and history of lower endoscopy within past 10 years (yes/no). For the five dietary indices, we further adjusted for BMI (continuous) and physical activity in MET-hours/week (continuous). Tests for trends were conducted using the median of each index quartile as a continuous variable.

To examine potential differential associations of dietary and lifestyle indices with CRC risk by age at diagnosis (<50 versus ≥50 years), proportional hazards models were used with a data duplication method for heterogeneity[30]. Statistical significance of heterogeneity by age was evaluated by the likelihood ratio test. In addition, we explored potential effect modification by participant characteristics including overweight status, physical activity, smoking status, current regular aspirin/NSAID use, current multivitamin use, and alcohol consumption. Tests for interaction were obtained using the Wald test of cross-product interaction terms between each index, modelled as a continuous variable, and potential effect modifiers.

Finally, to address the potential issue that early symptoms of undiagnosed CRC may alter behavior, we performed sensitivity analyses using baseline indices without updates, as well as a 2-year lag between indices and CRC[31]. To examine associations in a subgroup with less influence by genetic factors and environmental clustering in early life, an additional sensitivity analysis was conducted among participants without a family history of CRC.

Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Statistical tests were two-sided, and *P* values <0.05 were considered statistically significant.

Results

The age-standardized characteristics according to each index are shown in Table 1 and Supplementary Table 2. Participants scoring higher for the PDQS and PDI were more physically active and more likely to take multivitamins and less likely to drink alcohol (PDQS only). Women with higher EDIH and ELIH scores (more hyperinsulinemic) had higher BMI, were more likely to have a history of type 2 diabetes, were less physically

active, and were less likely to take multivitamins or drink alcohol. The EDIH was weakly correlated with the PDQS (Spearman r=−0.30), PDI (r=−0.08), and UPDI (r=0.06), and moderately inversely correlated with hPDI (r=−0.58). The ELIH was only weakly associated with the dietary indices, with the exception of the EDIH (Spearman r=0.41, range for other indices: −0.21 to 0.08) (Supplementary Table 3).

During 2,113,655 person-years of follow-up, 332 women were diagnosed with CRC, and 111 were diagnosed before age 50 (early-onset CRC). The mean age at diagnosis was 52 years (SD=7; range: 34–66 years) for all cases, 45 years (SD=4) for early-onset cases, and 56 years (SD=4) for post-age-50 cases. The early-onset cases were more likely to have advanced TNM stage (65.9%) than the post-age-50 cases (51.8%). The PDQS and three plant-based diet indices were not associated with CRC risk (Table 2 and Supplementary Table 4). For the EDIH, comparing women in the highest with the lowest quartile, CRC risk was 67% higher (multivariable hazard ratio $[HR]_{Q4\ vs.\ Q1}$=1.67, 95% confidence interval [CI]: 1.15–2.44, *P* for trend=0.01). For the same comparison for ELIH, CRC risk was 51% higher (multivariable $HR_{Q4\ vs.\ Q1}$=1.51, 95% CI: 1.10–2.08, *P* for trend=0.01).

No significant differences were noted in associations for each index by age at diagnosis (all *P* for heterogeneity by age ≥0.16) (Table 3 and Supplementary Table 5). However, per 75% increment in rank, ELIH showed a stronger positive association for early-onset CRC (HR=1.86, 95% CI:1.12–3.07) than post-age-50 CRC (HR=1.20, 95% CI: 0.83–1.73; *P* for heterogeneity=0.16). The EDIH showed a suggestive positive association with post-age-50 CRC (per 75% increment in rank, multivariable HR=1.51, 95% CI: 1.00–2.29).

For each dietary and lifestyle index, we found no evidence of heterogeneity in the associations across cancers of the proximal colon, distal colon, and rectum (all *P* for heterogeneity by subsite ≥0.30) (Table 4). However, a strong positive association for the ELIH was observed for the distal colon (multivariable HR=1.91, 95% CI: 1.09–3.34).

In stratification analysis by other CRC risk factors, the positive associations for the EDIH and ELIH with risk of CRC were seen only among current regular users of aspirin/NSAIDs (per 75% increment in rank, HR_{EDIH}=2.15, 95% CI: 1.15–4.01, *P*-interaction=0.04; multivariable HR_{ELIH}=2.84, 95% CI: 1.64–4.91, *P*-interaction<0.01). Moreover, we observed strong positive associations of the EDIH and ELIH with risk of CRC among current non-users of multivitamins (per 75% increment in rank, HR_{EDIH}=1.97, 95% CI: 1.14–3.38, *P*-interaction=0.04; multivariable HR_{ELIH} = 2.24, 95% CI: 1.41–3.55, *P*-heterogeneity=0.02) (Table 5). Similar interactions were observed in the cross-classification analysis using a common reference group in Supplementary Table 6.

No statistically significant effect modification was observed for the associations between PDQS or PDI and CRC risk by current regular users of aspirin/NSAIDs or multivitamin, or any of the indices and CRC risk by other participant characteristics, including BMI, physical activity, smoking status, and alcohol consumption.

Sensitivity analyses using either the baseline assessment for each index or a 2-year lag (16 CRC cases excluded) or when restricting the study population to women without a family history of CRC (43 CRC cases excluded) showed similar results (Supplementary

Table 7) to the main findings. We also conducted analyses among women with a family history of CRC. Albeit limited by sample size, compared to women without a family history of CRC, a weaker association was observed for the EDIH (per 75% increment in rank, HR_{EDIH}=1.04, 95% CI: 0.36–2.97), while a stronger association was observed for ELIH (per 75% increment in rank, HR_{ELIH}=2.10, 95% CI: 0.85–5.18) among those with a family history of CRC.

Discussion

In a large prospective cohort study of 94,217 women, we evaluated the associations of four recommendation-based dietary indices, and two mechanism-based dietary and lifestyle indices with CRC risk. We found that dietary and lifestyle patterns with high insulinemic potential as indicated by high EDIH and ELIH scores were associated with higher CRC risk, whereas neither the PDQS nor three plant-based diet indices were significantly associated with CRC risk. In addition, we found suggestive evidence that the ELIH was more strongly associated with early-onset CRC, while the EDIH was more strongly associated with post-age-50 CRC. The findings, therefore, indicate the importance of the insulin signaling pathway for CRC in the younger adult population.

Accumulating evidence shows that a healthy diet as indicated by recommendation-based dietary indices has been associated with lower risk of CRC, especially in men[32, 33]. A recent review of 24 (17 cohorts and 7 case-control) studies examined the association between recommendation-based dietary indices and CRC, and found associations were not consistent and generally weak in women[33]. Previous studies have mainly focused on later-onset CRC[32, 34, 35] with limited information on early-onset CRC. We have found the PDQS and plant-based diet indices to be associated with coronary heart disease[17, 36] and diabetes[37], the latter of which is also a risk factor for CRC[38]. However, some components of these indices are weighted towards factors that are critical for heart disease, such as lipids and minerals (potassium, sodium) that may be less important for cancer[39–41]. In the current study, we found no associations of the PDQS and plant-based diet with CRC risk, overall or when stratified by age.

The EDIH and ELIH assessed the insulinemic potential of diet and lifestyle[20]. C-peptide, a marker for insulin secretion, has been consistently associated with higher risk of colorectal neoplasia[42–44]. In a previous study within NHS I, we showed that participants in the highest quintile of the EDIH had a 22% higher risk of CRC than those in the lowest quintile (HR=1.22, 95% CI: 1.03–1.45); a similar association was shown for the ELIH for the same comparison (HR=1.28, 95% CI: 1.09–1.51)[45]. In the current analyses, positive associations were also found for the EDIH and ELIH with overall CRC risk. Interestingly, when the associations were examined according to age at diagnosis, the EDIH was only associated with post-age-50 CRC, whereas the ELIH was more strongly associated with early-onset CRC, although differences in the associations by age group were not statistically significant. The ELIH also showed stronger associations with distal colon cancer, which occurs in a higher proportion of early-onset CRC[46]. These differences may be explained by obesity, which is captured in the ELIH but not in the EDIH, consistent with a previous study of

women in which obesity was primarily associated with early-onset CRC, but not post-age-50 CRC[9].

Stratification analysis showed potentially different roles of diet and lifestyle in CRC by multivitamin use and aspirin/NSAID use. Multivitamin supplements contain several nutrients, including vitamin D, folic acid and calcium, which have been hypothesized to reduce CRC risk[47–49]. However, in the current study, multivitamin supplements were less likely to have benefits among those who already have a healthy diet and lifestyle (e.g. the lowest quartile of EDIH and ELIH). Regular use of aspirin or NSAIDs have an anti-inflammatory effect, another potential pathway in colorectal carcinogenesis[50]. There could be a synergistic effect between hyperinsulinemic and proinflammatory pathways as in obesity or the metabolic syndrome. Indeed, the protective effect with low insulinemic dietary or lifestyle pattern was attenuated without aspirin or NSAIDs use (Supplementary Table 6). Importantly, given the number of tests performed and limited number of CRC cases, any potential effect modification that we observed may also be due to chance.

In the current study, a major strength was the novelty of evaluating risk of CRC in a younger cohort, while assessing risks separately for early-onset versus post-age-50 CRC. Second, recall and selection bias were minimized because of the prospective design and excellent follow-up rate[51]. Third, the exposures were cumulatively updated over time and have been validated, minimizing misclassification, and reflecting long-term dietary and lifestyle patterns.

The present study also had some limitations. First, we did not have genetic information to confirm predisposition to CRC. However, we conducted a sensitivity analysis among women without a CRC family history, which supported our primary findings. Second, we had a limited number of CRC cases, especially for early-onset CRC. Third, this cohort included mainly white women. Thus, the generalizability of our findings to other populations warrants further investigation.

In conclusion, in this US cohort of younger women, hyperinsulinemic dietary and lifestyle scores (reflecting higher insulinemic potential) were associated with higher CRC risk, with the hyperinsulinemic lifestyle showed a suggestively stronger positive association with early-onset CRC. Nonsignificant associations were observed for two sets of recommendation-based diet indices—PDQS and plant-based diet indices—and risk of overall, early-onset, and post-age-50 CRC. Our findings suggest that a healthy diet and lifestyle with low insulinemic potential may be effective for reduction of CRC risk in younger women. The importance of elucidating modifiable factors for preventing early-onset CRC cannot be overstated due to the potential for life-years gained in this younger population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Conflict of Interest Disclosures:

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Table 1

Participant characteristics (weighted by person-years of follow-up) in the lowest and highest dietary and lifestyle index quartiles in the Nurses' Health Study II, 1991–2015

	Overall population	Prime Diet Quality Score[1]		Plant-based Diet Index[1]		Empirical Dietary Index for Hyperinsulinemia[2]		Empirical Lifestyle Index for Hyperinsulinemia[2]	
		Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4
Score range		2, 19	24, 37	28, 51	58, 85	−1.4, 0.3	0.5, 4.8	−0.5, 1.1	1.4, 4.5
Participant characteristics[3]									
Age, years	46.7 (7.9)	45.9 (7.9)	47.5 (7.8)	46.3 (8.0)	47.1 (7.7)	47.4 (7.8)	46.1 (7.9)	46.2 (7.9)	47.3 (7.8)
White, %	92.9	91.3	93.5	91.6	93.8	93.6	92.4	93.3	92.6
Body mass index, kg/m^2	26.4 (6.1)	27.3 (6.8)	25.6 (5.5)	28.0 (6.9)	24.9 (5.2)	24.4 (4.7)	28.4 (7.1)	21.5 (2.5)	34.1 (6)
Family history of CRC, %	7.7	7.6	7.7	7.7	7.4	8.3	6.8	7.6	7.9
History of diabetes, %	3.6	4.2	3.0	5.7	2.0	1.7	6.0	1.0	9.4
History of lower endoscopy, %[4]	24.8	22.9	24.9	24.0	22.5	28.8	19.2	25.1	24.4
Ever smokers, %	34.5	35.2	35.8	37.5	32.4	40.4	31.8	36.7	33.6
Total activity, MET-hrs/week	21.9 (23.5)	15.4 (17.9)	30.1 (28.8)	18.7 (21.3)	26.1 (26.8)	28.1 (28.1)	18.5 (21.3)	30.7 (31.7)	15.4 (16.2)
Regular aspirin use, %	10.9	11.1	10.5	11.6	10.6	10.3	11.2	9.7	12.7
Regular NSAID use, %	29.2	31.0	26.2	30.4	27.0	26.7	31.4	24.6	36.4
Multivitamin use %	53.5	44.7	60.3	49.8	56.2	58.1	47.2	56.4	49.9
Postmenopausal, %	39.4	42.4	37.4	44.6	34.7	42.1	35.4	37.8	41.6
Dietary intake									
Drinkers of alcohol, %	69.3	60.5	75.0	67.1	69.4	79.6	59.3	78.3	57.8
Alcohol consumption among drinkers, g/day	5.3 (6.8)	4.6 (7.1)	5.8 (6.8)	5.6 (8.0)	5.2 (6.0)	7.1 (8.4)	4.3 (6.2)	6.7 (7.7)	3.9 (6.3)
Red meat, servings/week	6.0 (4.8)	7.7 (5.6)	4.1 (3.8)	6.4 (5.8)	5.2 (4.4)	3.2 (2.9)	9.0 (5.8)	4.7 (4)	7.2 (5.5)
Carbohydrate, % of energy	50.4 (6.9)	49.2 (7.2)	52.5 (6.8)	46.3 (7)	55 (6.3)	53.0 (7.5)	47.6 (7.1)	51.7 (7.2)	48.8 (6.7)
Fat, % of energy	31.2 (5.3)	33.5 (5.1)	28.5 (5.0)	33.6 (5.5)	28.7 (4.9)	28.8 (5.4)	33.8 (5.2)	30.1 (5.5)	32.5 (5.1)
Dietary fiber, g/day[5]	19.0 (5.2)	14.7 (3.2)	23.6 (5.4)	15.8 (4.3)	22.4 (5.6)	22.1 (6.2)	16.5 (3.9)	20.3 (5.9)	17.9 (4.6)
Dietary folate, mcg/day[5]	521(242)	415 (216)	625 (251)	472 (245)	563 (240)	594 (253)	443 (221)	550 (246)	489 (239)
Dietary calcium, mg/day[5]	1,103 (420)	921 (383)	1257 (426)	1100 (442)	1085 (403)	1229 (447)	950 (362)	1155 (434)	1052 (410)

Abbreviations: CRC, colorectal cancer; MET, metabolic equivalent of tasks; NSAID, non-steroidal anti-inflammatory drugs; Q, Quartile.

[1] Higher indices are hypothesized to be healthy.

[2] Higher indices are hypothesized to be unhealthy.

[3] All values other than age have been directly standardized to age distribution (in 5-year age group) and energy intake (in quartiles) of all participants. Mean (SD) is presented for continuous variables.

[4] History of lower endoscopy within the past 10 years.

[5] From food only.

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Table 2

Associations of cumulative average dietary and lifestyle indices with risk of colorectal cancer in the Nurses' Health Study II, 1991–2015

	Q1	Q2	Q3	Q4	P_{trend}[1]	Continuous[2]
Prime Dietary Quality Score						
Median score		20	23	26		
Number of events	93	74	89	76		332
Number of person-years	535255	510499	547363	520538		2113655
Age-adjusted HR (95% CI)[3]	1[Ref]	0.80 (0.59, 1.09)	0.92 (0.68, 1.23)	0.76 (0.56, 1.05)	0.16	0.86 (0.64, 1.15)
Multivariable-adjusted HR (95% CI)[4]	1[Ref]	0.81 (0.60, 1.11)	0.96 (0.71, 1.30)	0.80 (0.57, 1.11)	0.29	0.91 (0.67, 1.24)
Overall Plant-based Diet Index						
Median score	48	53	56	61		
Number of events	71	86	98	77		332
Number of person-years	525415	516694	537951	533595		2113655
Age-adjusted HR (95% CI)[3]	1[Ref]	1.21 (0.88, 1.66)	1.36 (0.99, 1.86)	1.06 (0.74, 1.51)	0.63	1.03 (0.75, 1.42)
Multivariable-adjusted HR (95% CI)[4]	1[Ref]	1.25 (0.91, 1.72)	1.45 (1.05, 2.00)	1.16 (0.81, 1.67)	0.28	1.14 (0.82, 1.59)
Empirical Dietary Index for Hyperinsulinemia						
Median score	0.2	0.3	0.4	0.7		
Number of events	68	86	88	90		332
Number of person-years	528809	528938	528538	527370		2113655
Age-adjusted HR (95% CI)[3]	1[Ref]	1.36 (0.98, 1.87)	1.45 (1.05, 2.01)	1.67 (1.18, 2.38)	<0.01	1.45 (1.04, 2.00)
Multivariable-adjusted HR (95% CI)[4]	1[Ref]	1.38 (0.99, 1.92)	1.46 (1.04, 2.06)	1.67 (1.15, 2.44)	0.01	1.41 (0.99, 2.01)
Empirical Lifestyle Index for Hyperinsulinemia						
Median score	1.0	1.1	1.3	1.6		
Number of events	69	82	74	107		332
Number of person-years	529808	528792	528009	527046		2113655
Age-adjusted HR (95% CI)[3]	1[Ref]	1.17 (0.84, 1.61)	1.02 (0.73, 1.42)	1.43 (1.05, 1.94)	0.02	1.33 (1.00, 1.77)
Multivariable-adjusted HR (95% CI)[5]	1[Ref]	1.19 (0.86, 1.65)	1.05 (0.75, 1.47)	1.51 (1.10, 2.08)	0.01	1.40 (1.03, 1.89)

Abbreviations: CI, confidence interval; HR, hazard ratio; Q, Quartile.

[1]P for linear trend across quartiles was calculated using the median of each quartile as a continuous variable.

[2]Continuous analyses used rank-order indices for a 75 percentile increment in rank (e.g., median of first to fourth quartile).

[3]Adjusted for total energy intake (continuous). Age (months) and follow-up cycle (2-year intervals) were included as stratification variables.

[4]Additionally adjusted for total alcohol consumption (continuous), height (continuous), race (white/nonwhite), body mass index (continuous), family history of colorectal cancer (yes/no), history of diabetes (yes/no), smoking pack-years (continuous), physical activity (continuous), regular use of aspirin (yes/no), regular use of nonsteroidal anti-inflammatory drugs (yes/no), multivitamin use (yes/no), menopausal status and menopausal hormone therapy (premenopausal, never hormone use/postmenopausal, ever hormone use), and history of lower endoscopy (yes/no).

[5]Additionally adjusted for factors listed in [4], except for body mass index and physical activity.

Table 3

Associations of cumulative average dietary and lifestyle indices with risk of colorectal cancer diagnosed before and after age 50 in the Nurses' Health Study II, 1991–2015[1]

	Age at colorectal cancer diagnosis		P_{het}[2]
	<50 years	≥50 years	
Number of events	111	221	
Prime Dietary Quality Score			
Age-adjusted HR (95% CI)[3]	0.90 (0.55, 1.48)	0.84 (0.59, 1.20)	0.82
Multivariable-adjusted HR (95% CI)[4]	0.90 (0.55, 1.50)	0.91 (0.62, 1.31)	>0.99
Overall Plant-based Diet Index			
Age-adjusted HR (95% CI)[3]	1.13 (0.68, 1.88)	1.03 (0.70, 1.50)	0.75
Multivariable-adjusted HR (95% CI)[4]	1.24 (0.74, 2.08)	1.10 (0.75, 1.62)	0.70
Empirical Dietary Index for Hyperinsulinemia			
Age-adjusted HR (95% CI)[3]	1.34 (0.80, 2.27)	1.50 (1.02, 2.19)	0.72
Multivariable-adjusted HR (95% CI)[4]	1.24 (0.72, 2.16)	1.51 (1.00, 2.29)	0.54
Empirical Lifestyle Index for Hyperinsulinemia			
Age-adjusted HR (95% CI)[3]	1.71 (1.04, 2.81)	1.17 (0.82, 1.66)	0.21
Multivariable-adjusted HR (95% CI)[5]	1.86 (1.12, 3.07)	1.20 (0.83, 1.73)	0.16

Abbreviations: CI, confidence interval; het, heterogeneity; HR, hazard ratio.

[1]Continuous analyses used rank-order indices for a 75 percentile increment in rank (e.g., median of first to fourth quartile)

[2]P for heterogeneity between CRC diagnosed before age 50 years and at age 50 years or older by contrast test.

[3]Adjusted for total energy intake (continuous). Age (months) and follow-up cycle (2-year intervals) were included as stratification variables.

[4]Additionally adjusted for alcohol consumption (continuous), height (continuous), race (white or nonwhite), body mass index (continuous), family history of colorectal cancer (yes/no), history of diabetes (yes/no), smoking pack-years (continuous), physical activity (continuous), regular use of aspirin (yes/no), regular use of nonsteroidal anti-inflammatory drugs (yes/no), multivitamin use (yes/no), menopausal status and menopausal hormone therapy (premenopausal, postmenopausal/never hormone use, and postmenopausal/ever hormone use), and history of lower endoscopy (yes/no).

[5]Additionally adjusted for factors listed in[4], except for body mass index and physical activity.

Table 4

Associations of cumulative average dietary and lifestyle indices with risk of colorectal cancer by subsite in the Nurses' Health Study II, 1991–2015[1]

	Proximal colon	Distal colon	Rectum	Distal colon and rectum	P_{het} by site[2]	P_{het} by site[3]
Number of events	86	94	94	188		
Prime Dietary Quality Score, HR (95% CI)[4]	0.82 (0.46, 1.46)	1.28 (0.74, 2.21)	0.78 (0.45, 1.36)	1.00 (0.67, 1.49)	0.57	0.38
Overall Plant-based Diet Index, HR (95% CI)[4]	1.23 (0.68, 2.22)	1.27 (0.72, 2.24)	1.49 (0.84, 2.64)	1.38 (0.90, 2.10)	0.87	0.75
Empirical Dietary Index for Hyperinsulinemia, HR (95% CI)[4]	1.04 (0.56, 1.94)	1.45 (0.80, 2.64)	1.33 (0.73, 2.42)	1.38 (0.88, 2.18)	0.43	0.71
Empirical Lifestyle Index for Hyperinsulinemia, HR (95% CI)[5]	1.15 (0.65, 2.03)	1.91 (1.09, 3.34)	1.41 (0.82, 2.44)	1.64 (1.10, 2.44)	0.30	0.44

Abbreviation: CI, confidence interval; het, heterogeneity; HR, hazard ratio

[1] Continuous analyses used rank-order indices for a 75 percentile increment in rank (e.g., median of first to fourth quartile).

[2] Tested whether associations differed between proximal colon and the combination of distal colon and rectal cancer.

[3] Tested whether associations differed between proximal colon, distal colon, and rectal cancer.

[4] Age (months) and follow-up cycle (2-year intervals) were included as stratification variables. Adjusted for total energy intake (continuous), alcohol consumption (continuous), height (continuous), race (white or nonwhite), body mass index (continuous), family history of colorectal cancer (yes/no), history of diabetes (yes/no), smoking pack-years (continuous), physical activity (continuous), regular use of aspirin (yes/no), regular use of nonsteroidal anti-inflammatory drugs (yes/no), multivitamin use (yes/no), menopausal status and menopausal hormone therapy (premenopausal, postmenopausal/never hormone use, and postmenopausal/ever hormone use), and history of lower endoscopy (yes/no).

[5] Adjusted for factors listed in[4], except for body mass index and physical activity.

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Table 5

Associations of dietary and lifestyle indices with risk of colorectal cancer by dietary and other lifestyle factors in the Nurses' Health Study II, 1991–2015[1]

	Characteristics		
	BMI (kg/m^2)		
	< 25	**≥25**	**P_{inter}[2]**
Number of events	144	188	
Prime Dietary Quality Score, HR (95% CI)[3]	0.80 (0.50, 1.28)	1.02 (0.67, 1.55)	0.75
Overall Plant-based Diet Index, HR (95% CI)[3]	1.62 (0.98, 2.67)	0.84 (0.54, 1.30)	0.08
Empirical Dietary Index for Hyperinsulinemia[3], HR (95% CI)	1.16 (0.69, 1.96)	1.71 (1.05, 2.78)	0.30
Empirical Lifestyle Index for Hyperinsulinemia, HR (95% CI)[4]	-	-	-
	Physical activity (MET-hours/week)		
	Below median[5]	**Above median[5]**	**P_{inter}[2]**
Number of events	168	164	
Prime Dietary Quality Score, HR (95% CI)[3]	0.89 (0.57, 1.38)	0.93 (0.60, 1.45)	0.92
Overall Plant-based Diet Index, HR (95% CI)[3]	1.00 (0.63, 1.59)	1.34 (0.83, 2.16)	0.52
Empirical Dietary Index for Hyperinsulinemia, HR (95% CI)[3]	1.42 (0.86, 2.37)	1.34 (0.81, 2.20)	0.77
Empirical Lifestyle Index for Hyperinsulinemia, HR (95% CI)[4]	-	-	-
	Smoking status		
	Never	**Ever**	**P_{inter}[2]**
Number of events	204	128	
Prime Dietary Quality Score, HR (95% CI)[3]	0.95 (0.64, 1.40)	0.86 (0.53, 1.42)	0.53
Overall Plant-based Diet Index, HR (95% CI)[3]	1.23 (0.80, 1.88)	0.99 (0.59, 1.68)	0.46
Empirical Dietary Index for Hyperinsulinemia[3]	1.27 (0.80, 2.02)	1.75 (1.00, 3.07)	0.56
Empirical Lifestyle Index for Hyperinsulinemia[4]	1.32 (0.89, 1.94)	1.60 (0.98, 2.59)	0.43
	Regular aspirin/NSAID use		
	Not current	**Current**	**P_{inter}[2]**

Number of events	218	114	
Prime Dietary Quality Score, HR (95% CI)[3]	0.87 (0.60, 1.27)	0.97 (0.56, 1.67)	0.82
Overall Plant-based Diet Index, HR (95% CI)[3]	1.17 (0.78, 1.75)	1.08 (0.61, 1.92)	0.22
Empirical Dietary Index for Hyperinsulinemia, HR (95% CI)[3]	1.19 (0.77, 1.84)	2.15 (1.15, 4.01)	0.04
Empirical Lifestyle Index for Hyperinsulinemia, HR (95% CI)[4]	1.00 (0.69, 1.45)	2.84 (1.64, 4.91)	<0.01
	Multivitamin use		
	Not current	**Current**	**P_{inter}[2]**
Number of events	146	186	
Prime Dietary Quality Score, HR (95% CI)[3]	0.67 (0.42, 1.08)	1.18 (0.77, 1.79)	0.08
Overall Plant-based Diet Index, HR (95% CI)[3]	0.88 (0.54, 1.45)	1.44 (0.92, 2.25)	0.22
Empirical Dietary Index for Hyperinsulinemia, HR (95% CI)[3]	1.97 (1.14, 3.38)	1.07 (0.66, 1.74)	0.04
Empirical Lifestyle Index for Hyperinsulinemia, HR (95% CI)[4]	2.24 (1.41, 3.55)	0.99 (0.66, 1.48)	0.02
	Alcohol drinker		
	No	**Yes**	**P_{inter}[2]**
Number of events	100	232	
Prime Dietary Quality Score, HR (95% CI)[3]	0.59 (0.33, 1.05)	1.14 (0.78, 1.66)	0.12
Overall Plant-based Diet Index, HR (95% CI)[3]	0.92 (0.50, 1.66)	1.29 (0.87, 1.91)	0.53
Empirical Dietary Index for Hyperinsulinemia, HR (95% CI)[3]	2.34 (1.17, 4.67)	1.09 (0.72, 1.64)	0.10
Empirical Lifestyle Index for Hyperinsulinemia, HR (95% CI)[4]	1.44 (0.82, 2.54)	1.33 (0.93, 1.89)	0.74

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent task; NSAID, non-steroidal anti-inflammatory drugs.

[1]Continuous analyses used rank-order indices for a 75 percentile increment in rank (e.g., median of first to fourth quartile).

[2]P for the interaction term between the potential effect modifier of interest and the continuous diet index.

[3]Age (months) and follow-up cycle (2-year intervals) were included as stratification variables. Adjusted for total energy intake (continuous), alcohol consumption (continuous), height (continuous), race (white or nonwhite), body mass index (continuous), family history of colorectal cancer (yes/no), history of diabetes (yes/no), smoking pack-years (continuous), physical activity (continuous), regular use of aspirin (yes/no), regular use of nonsteroidal anti-inflammatory drugs use (yes/no), multivitamin use (yes/no), menopausal status and menopausal hormone therapy (premenopausal, postmenopausal/never hormone use, and postmenopausal/ever hormone use), and history of lower endoscopy (yes/no).The effect modier was not included in the model.

[4]Adjusted for factors listed in[3], except for body mass index and physical activity. The effect modier was not included in the model.

[5] Median is 15 MET-hours/week.