Research Article

Cancer Epidemiology, Biomarkers & Prevention

Adherence to the World Cancer Research Fund/ American Institute for Cancer Research 2018 Recommendations for Cancer Prevention and Risk of Colorectal Cancer

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Abstract

Background: The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) 2018 diet, nutrition, and physical activity recommendations aim to reduce cancer risk. We examined adherence to the WCRF/AICR recommendations and colorectal cancer risk in two prospective cohorts.

Methods: We followed 68,977 women in the Nurses' Health Study and 45,442 men in the Health Professionals Follow-up Study from 1986 until 2012. We created cumulatively averaged WCRF/AICR scores using updated diet, adiposity, and physical activity data from questionnaires, and used Cox regression to estimate sex-specific HRs and 95% confidence intervals (CI) for incident colorectal cancer.

Results: We documented 2,449 colorectal cancer cases. Men in the highest quintile of the WCRF/AICR lifestyle score had a lower risk of colorectal cancer compared with those in the lowest quintile ($HR_{Q5vsQ1} = 0.64$; 95% CI, 0.52–0.77). The result was weaker in women ($HR_{Q5vsQ1} = 0.86$; 95% CI, 0.72–1.02; $P_{heterogeneity\ by\ sex} = 0.006$). When analyzing the diet recommendations alone, we similarly observed stronger inverse associations in men ($HR_{Q5vsQ1} = 0.74$; 95% CI, 0.61–0.90) compared with women ($HR_{Q5vsQ1} = 0.93$; 95% CI, 0.77–1.12; $P_{heterogeneity\ by\ sex} = 0.06$). In men, the lifestyle score was more strongly inversely associated with risk of distal colon cancer compared with proximal colon or rectal cancer ($P_{common\ effects} = 0.03$); we did not observe significant differences between anatomic locations in women.

Conclusions: The 2018 WCRF/AICR cancer prevention recommendations are associated with lower colorectal cancer risk in men, with weaker results in women.

Impact: Consideration of adiposity and physical activity in conjunction with diet is important for colorectal cancer prevention.

Introduction

Since 1997 and approximately every ten years thereafter, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) has published diet and lifestyle recommendations that aim to reduce cancer risk and improve cancer survival globally. While the Third Expert Report released in 2018 (1) recommends many behaviors included in their previous publications (e.g., high fruit and vegetable consumption, low alcohol consumption, and maintaining a healthy weight), it newly recommends consuming at least 30 g/day of fiber, discourages intake of processed foods high in fat and sugars, and no longer discourages consumption of all energy-dense foods without regard to nutritional composition (2).

Although many components of the WCRF/AICR Third Expert Report have been either positively (e.g., obesity, alcohol; refs. 3, 4) or inversely (e.g., calcium, physical activity; refs. 5, 6) associated with colorectal cancer risk in previous studies, the importance of adhering to these guidelines holistically for colorectal cancer prevention is unclear. We therefore created a lifestyle score based on major recommendations of the WCRF/AICR Third Expert Report and subsequently examined associations between this score and colorectal cancer risk in the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS).

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Materials and Methods

Study population

The NHS is a cohort of 121,701 U.S. female nurses aged 30 to 55 years at the time of initiation in 1976. The HPFS is a cohort of 51,529 U.S. male health professionals aged 40 to 75 years at the time of initiation in 1986. Both cohorts are ongoing (follow-up >90% in each), with collection of updated data on lifestyle and medical information from participants via questionnaire every two years since baseline.

We excluded individuals with a history of cancer (except nonmelanoma skin cancer) or ulcerative colitis and those with missing data on weight or physical activity at baseline. We also excluded those missing >70 items (approximately half of all foods) on the baseline food frequency questionnaire (FFQ) or those with implausible energy intake (women: <500 or >3,500 kcal/day; men: <800 or >4,200 kcal/day) because these individuals may have filled out their questionnaires incorrectly. After these exclusions, there were 68,977 women and 45,442 men in the final analysis. The study protocol was approved by the Institutional Review Boards at Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health (Boston, MA), and those of participating registries as required.

Dietary assessment

We assessed diet using self-administered, semiquantitative FFQs every four years starting in 1986. These FFQs provide standard portion sizes for items, and ask participants to record their frequency of intake, 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 for each food and summing nutrient values across all foods. Estimated intake of foods and nutrients by this FFQ has been validated against intake via multiple weeks of diet records (7–9), with correlations for foods ranging from 0.26 (cruciferous vegetables) to 0.78 (liquor).

Anthropometry and activity assessment

Body mass index (BMI, kg/m^2) was determined by dividing weight (kg) from each biennial questionnaire by height-squared (m^2) reported at baseline. Participants were given a tape measure for waist circumference measurement (inches) in 1986, 1996, and 2000 in NHS and 1987, 1996, and 2008 in HPFS. Physical activity was measured through a separate, validated questionnaire (10, 11), and assessed every two or four years starting in 1986. Sedentary activity was estimated by hours spent watching television, which was measured on the physical activity questionnaire in 1992 and generally every two years thereafter.

2018 WCRF/AICR score construction

We first created a score for the 2018 WCRF/AICR dietary recommendations, which was based on intake of seven components: (i) fruits and vegetables, (ii) dietary fiber, (iii) whole grains and legumes, (iv) refined grains and processed foods, (v) red and processed meats, (vi) sugar-sweetened beverages, and (vii) alcohol. Each component was assigned a score of 1 (adherence), 0.5 (partial adherence), or 0 (nonadherence) based on WCRF/AICR criteria when available or previously published literature otherwise (Table 1). Red and processed meat intake consisted of two subcomponents (red meat intake and processed meat intake), as did sugar-sweetened beverage intake (beverages with added sugars and juices). In both cases, the subcomponents were given scores of 0, 0.5, or 1, which were averaged together to create the component score. The seven dietary component scores were further averaged to calculate the final WCRF/AICR diet score, which ranged from 0 to 1. Foods included in each component are listed in Supplementary Table S1.

The WCRF/AICR lifestyle score consisted of three components: (i) the WCRF/AICR diet score, (ii) adiposity, and (iii) physical activity. Adiposity consisted of three subcomponents (BMI, waist circumference, and weight change) and physical activity consisted of two subcomponents (energy expenditure and sedentary activity). Weight change was calculated as the difference between current weight and weight from the questionnaire ten years earlier (and was therefore calculated only after ten years of follow-up) because long-term differences in weight are more predictive of colorectal cancer risk than short-term changes (12, 13). Each subcomponent was assigned scores of 0, 0.5, or 1 based on WCRF/AICR criteria or previously published literature (Table 1). The subcomponents were averaged to calculate the component scores. The diet, adiposity, and physical activity component scores were summed to calculate the final WCRF/AICR lifestyle score, which ranged from 0 to 3. This operationalization weighed overall diet, adiposity, and physical activity equally; however, in sensitivity analyses, we evaluated a lifestyle score that summed the seven individual dietary component scores, adiposity score, and physical activity score with all nine components having equal weight in the score calculation (range: 0–9). The distributions of component scores in each cohort in 1998 (approximately halfway through follow-up) are provided in Supplementary Table S2. In general, for each component, the mean score was between 0.4 and 0.7, suggesting partial adherence to the recommendations by most participants. The distribution of each component score was similar between men and women.

Ascertainment of colorectal cancer

Participants self-reported incident colorectal cancer between baseline and 2012 on biennial questionnaires. We requested and received medical records, which were reviewed by a study physician blinded to exposure to confirm cases and extract information on anatomic location. Colorectal cancer cases were defined as primary tumors with International Classification of Diseases-9 codes of 153 and/or 154. Diagnosis of colorectal cancer in participants who died from colorectal cancer but had not reported a diagnosis on a questionnaire was confirmed through next of kin, the National Death Index, death certificates, or medical records. We only included invasive cancers in our analysis.

Other covariates

We used biennial questionnaires to assess smoking, multivitamin use, colorectal cancer screening, regular use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), family history of colorectal cancer, young adult BMI (18 years in men; 21 years in women), self-reported diabetes status, and, in women, menopausal status, and postmenopausal hormone use.

Statistical analysis

We lagged all exposures by two years because changes in diet and lifestyle could result from symptoms of undiagnosed colorectal cancer. Person-time was therefore calculated from age (months) two years after the date of the 1986 questionnaire until

Table 1. Operationalization of WCRF/AICR dietary and lifestyle scores in the Nurses' Health Study and Health Professionals Follow-up Study

Recommendation	Points		
	0	0.5	1
1. Consume 5+ servings of fruits and vegetables per day[a]	<2.5 servings/day	2.5–<5 servings/day	≥5 servings/day
2. Consume 30+ grams/day fiber[a]	<15 g/day	15–<30 g/day	≥30 g/day
3. Include in most meals foods containing whole grains, nonstarchy vegetables, fruit, and pulses such as beans and lentils			
Consume 3+ servings of whole grains or pulses per day[b]	<1.5 servings/day	1.5–<3 servings/day	≥3 servings/day
4. Limit consumption of 'fast foods' and other processed foods high in fat, starches, or sugars			
Avoid intake of refined grains, pastries, sweets, and salty snacks[c]	≥3 servings/day	1.5–<3 servings/day	<1.5 servings/day
5. Limit intake of red and processed meats			
Consume no more than 3 servings/week of red meat[d]	≥6 servings/week	>3–<6 servings/week	≤3 servings/week
Consume little to no processed meat[e]	≥27 g/day	3–<27 g/day	<3 g/day
6. Limit intake of sugar-sweetened beverages[f]			
Limit intake of sodas and other beverages with added sugars	≥1 drinks/day	0–<1 drinks/day	0 drinks/day
Limit intake of juices	≥2 drinks/day	1–<2 drinks/day	<1 drink/day
7. Limit intake of alcoholic beverages[g]			
Men	≥2 drinks/day	>0–<2 drinks/day	0 drinks/day
Women	≥1 drinks/day	>0–<1 drink/day	0 drinks/day
8. Maintain a healthy body weight			
Maintain a healthy BMI[h]	<15 or ≥30	15–<18.5 or 25–<30	18.5–<25
Avoid weight gain[i]	≥10 lb. gained in last 10 years	0–<10 lb. gained in last 10 years	No weight gain in last 10 years
Maintain a healthy waist circumference (men)[j,k]	≥40.2 inches	37–<40.2 inches	<37 inches
Maintain a healthy waist circumference (women)[j]	≥34.6 inches	31.5–<34.6 inches	<31.5 inches
9. Be physically active and limit sedentary behaviors			
Engage in moderate physical activity (PA)[l]	<75 min moderate PA/week	75–<150 min moderate PA/week	≥150 min moderate PA/week
Limit sedentary behaviors[m]	≥20 hours/week TV watching	5–<20 hours/week TV watching	<5 hours/week TV watching

[a]The cutoffs for adherence (i.e., 1 point) for the recommendations on fruits and vegetables and fiber were provided by the Third Expert Report. We considered participants partially adherent if they consumed less than the Third Expert Report's recommended intake but at least half of the recommended amount, and nonadherent if they consumed less than half of the recommended amount.

[b]The cutoff for adherence for the recommendation on whole grains and pulses was not provided by the Third Expert Report. Because the Third Expert Report recommends these foods to be included in "most meals," we considered participants to be adherent if they consumed at least 3 servings per day on average (roughly once per meal), partially adherent if they consumed less than 3 servings per day but more than 1.5 servings per day on average (i.e., less than the recommended intake but at least half of the recommended amount), and nonadherent if they consumed less than 1.5 servings per day (i.e., less than half the amount used to define adherence). We did not include fruits or vegetables in this component because these food groups were considered in component 1.

[c]The Third Expert Report does not provide cutoffs for the recommendation on "fast foods and other processed foods high in fat, starches, or sugars," and instead broadly recommends little intake of these foods. Thus, we considered participants to be adherent if they consumed less than 1.5 servings of these foods per day or less (roughly half a serving per meal or less), partially adherent if they consumed more than 1.5 servings but less than 3 servings per day (i.e., roughly between half and a whole serving per meal), and nonadherent if they consumed 3 servings per day or more. We included in this category foods that are frequently industrially processed and/or contain a large amount of refined grains, saturated fat, and sodium. We did not include foods that overlapped with other WCRF/AICR recommendations, such as processed meats and sugar-sweetened beverages.

[d]The cutoff for adherence for the recommendation on red meat was provided by the Third Expert Report. We considered participants partially adherent if they consumed more than the recommended intake but less than double the recommended amount, and nonadherent if they consumed double the recommended intake or more.

[e]The Third Expert Report does not provide cutoffs for the recommendation on processed meats and instead recommends "very little, if any" consumption. We therefore considered participants to be adherent if they consumed less than 3 g/day (equivalent to approximately 1 serving per week), partially adherent if they consumed more than 3 but less than 27 g/day (roughly between 1 and 7 servings per week), and nonadherent if they consumed 7 servings per week or more (i.e., 1 serving per day or more).

[f]The cutoff for adherence for the recommendation on sugar-sweetened beverages was provided by the Third Expert Report (i.e., "do not consume sugar-sweetened drinks"). We therefore considered participants adherent if they did not consume beverages with added sugar, partially adherent if they consumed less than 1 beverage with added sugar per day, and nonadherent if they consumed more than 1 serving per day. We used different cutoffs for juices because they contain potential chemopreventive agents and are less strongly associated with weight gain and chronic disease risk than beverages with added sugars (61, 62).

[g]The cutoff for adherence for the recommendation on alcohol was provided by the Third Expert Report (i.e., "for cancer prevention, it's best not to drink alcohol"), which also recommends that individuals do not exceed national guidelines if they do drink alcohol. We therefore considered participants adherent if they did not drink alcohol, partially adherent if they did not exceed the 2015–2020 Dietary Guidelines for Americans recommendation on alcohol (up to 2 drinks per day for men and up to 1 drink per day for women; ref. 63), and nonadherent if they exceeded these guidelines.

[h]The Third Expert Report does not provide cutoffs for BMI, but says "it is best to maintain weight within the healthy range throughout adult life." We therefore considered participants to be adherent if their BMI was in the normal range, partially adherent if it was in the overweight or slightly underweight range, and nonadherent if it was in the obese range or severely underweight range.

[i]The Third Expert Report does not provide cutoffs for the recommendation on weight gain and instead broadly recommends to "avoid weight gain throughout adulthood." Because long-term weight gain is most strongly associated with cancer risk (12, 13), we considered participants adherent if they did not gain weight in the past 10 years, partially adherent if they gained less than 10 pounds in the past 10 years, and nonadherent if they gained more than 10 pounds over the past 10 years. We chose these cutoffs based on the distribution of weight gain in the study population over the study period.

[j]The cutoff for adherence for the recommendation on waist circumference was provided by the Third Expert Report, which adopts the guidelines of the World Health Organization (WHO). The cutoff for partial adherence was additionally provided by WHO guidelines (64).

[k]Waist circumference was not measured until 1987 in HPFS, so this component was excluded from the body weight component score calculation in 1986.

age at death, colorectal cancer diagnosis, loss to follow-up, or end of follow-up (June 1, 2012 for NHS and January 1, 2012 for HPFS). We used 1986 as the baseline for NHS because this was the first year that physical activity was comprehensively measured. We calculated cumulative averages of WCRF/AICR scores. Specifically, at each time point, the main exposure was the average of that cycle's and all previous cycles' WCRF/AICR scores. This was done to represent long-term exposure and reduce random within-person variation in exposure (14). We carried forward nonmissing exposure and covariate data from the previous data cycle to replace missing data in the next cycle.

Our primary analyses used Cox regression (15) to estimate HRs and 95% confidence intervals (CI) for associations between WCRF/AICR scores (in quintiles) and incident colorectal cancer overall and by subsite (colon, proximal colon, distal colon, and rectal cancer). We stratified the baseline hazard by age and calendar year and adjusted for total energy intake, regular NSAID or aspirin use, family history of colorectal cancer, previous colorectal cancer screening, history of polyps, smoking, multivitamin use, supplemental calcium use, young adult BMI, and, in women, menopausal status and postmenopausal hormone use. For analyses of the diet score alone, we additionally adjusted for physical activity (we did not adjust for BMI because it may be on the causal pathway between diet and colorectal cancer risk, although we included BMI in the models in a sensitivity analysis). We did not find violations of the proportional hazards assumption for any associations of colorectal cancer risk for either score ($P > 0.34$ for all). We also modeled the scores as continuous variables after determining that all primary associations were consistent with linearity, which we tested by comparing a model with restricted cubic splines for the exposure to a model with only a linear term for the exposure using the likelihood ratio test (16, 17). We tested for heterogeneity in the associations by sex by pooling results from NHS and HPFS in a random effects meta-analysis, and evaluating the Q statistic. To examine possible differences in associations between WCRF/AICR scores and risk of proximal colon, distal colon, and rectal cancers, we ran Cox models with a data augmentation method and performed a test of heterogeneity comparing models that assume separate associations for these subtypes with a model that assumes a common association (18).

We explored potential effect modification of associations with total colorectal cancer risk by age at diagnosis, regular aspirin or NSAID use, family history of colorectal cancer, smoking, regular multivitamin use, young adult overweight, total calcium intake, self-reported diabetes, and, in women, oral contraceptive use and postmenopausal hormone use. We also explored possible effect modification by obesity status and physical activity for diet scores. These analyses were conducted by running regression models with interaction terms between the continuous scores and the variable of interest.

In secondary analyses, we reevaluated all primary analyses with different latency periods to determine how lifestyle during different exposure windows preceding diagnosis was associated with colorectal cancer risk. We analyzed scores constructed solely on the most recent questionnaires (i.e., simple update), as well as with 4–8, 8–12, and 12–16 years latencies, where the index scores analyzed at each follow-up interval were constructed from lagged questionnaire data (19).

All analyses were done using SAS version 9.4 for UNIX. We calculated two-sided 95% CIs for all statistical tests.

Results

Over 24 years of follow-up, we documented 2,449 colorectal cancer cases (1,298 in NHS and 1,151 in HPFS). For both the WCRF/AICR lifestyle and diet scores, individuals in the highest quintile (most adherent) were less likely to be current smokers and were more likely to undergo colorectal cancer screening and take supplemental calcium than those in the lowest quintile (least adherent); men in the highest quintile were more likely to take multivitamins regularly than those in the lowest quintile (Table 2). In 1998, approximately halfway through follow-up, few participants were current smokers (6% of men and 11% of women), though nearly half were former smokers (45% of both men and women); most participants either abstained from alcohol (men: 43%; women: 48%) or drank <1 alcoholic beverage per day (men: 37%; women: 41%), took multivitamin supplements daily (men: 59%, women: 56%) and had been screened previously for colorectal cancer (men: 55%; women: 49%).

We observed a strong inverse association for colorectal cancer risk when comparing men in the highest quintile of the WCRF/AICR lifestyle score to the lowest quintile (multivariable-adjusted $HR_{Q5vsQ1} = 0.64$, 95% CI: 0.52–0.77), and a weaker, statistically nonsignificant inverse association in women (multivariable-adjusted $HR_{Q5vsQ1} = 0.86$, 95% CI: 0.72–1.02). Results were similar when scores were modeled as continuous variables (Table 3). Because there was significant heterogeneity by sex ($P_{heterogeneity} = 0.006$), we present only sex-stratified results. In men, we observed differences by tumor location, with stronger results for distal colon cancer ($HR_{Q5vsQ1} = 0.47$; 95% CI: 0.33–0.68) than for proximal colon cancer ($HR_{Q5vsQ1} = 0.82$; 95% CI: 0.58–1.15; $P_{common\ effect} = 0.03$). We did not observe differences in associations by tumor location in women. We did not observe any associations between the lifestyle score and rectal cancer risk in either cohort.

When examining only the WCRF/AICR diet recommendations, we observed a significantly lower risk of colorectal cancer

[l]The cutoff for adherence for the recommendation on physical activity was provided by the Third Expert Report, which adopts guidelines of the WHO. We considered participants partially adherent if their physical activity was half or more than the recommendation but less than the recommendation, and nonadherent if they were less than half as physically active as recommended. We assumed that 1 minute of vigorous physical activity is equal to 2 minutes of moderate physical activity, and categorized activities as vigorous or moderate as defined previously (65).

[m]The Third Expert Report does not provide cutoffs for the recommendation on sedentary activity and instead broadly recommends to "limit sedentary habits." We used TV watching as a proxy for sedentary habits, which has been associated with chronic disease risk previously (57–59) and considered participants adherent if they watched TV less than 5 hours per week (roughly less than 45 minutes per day), partially adherent if they watched TV more than 5 but fewer than 20 hours per week (roughly between 45 minutes and 3 hours per day), and nonadherent if they watched TV more than 20 hours per week (roughly more than 3 hours per day). These categories were also chosen because of how the questionnaires assessed TV watching. TV watching was not measured until 1992 in NHS and HPFS, so this subcomponent was excluded from the physical activity component score calculation in 1986 and 1990.

Table 2. Age-standardized lifestyle characteristics and dietary intake in the highest and lowest quintiles of WCRF/AICR lifestyle and diet scores among men in the HPFS and women in the NHS in 1998[a]

	WCRF/AICR Lifestyle scores (range: 0–3)				WCRF/AICR Diet scores (range: 0–1)			
	Men		Women		Men		Women	
	Q1 (n = 5,268)	Q5 (n = 6,105)	Q1 (n = 10,204)	Q5 (n = 11,894)	Q1 (n = 5,589)	Q5 (n = 6,047)	Q1 (n = 10,555)	Q5 (n = 11,166)
Score	1.16 (0.25)	2.47 (0.13)	0.96 (0.20)	2.31 (0.15)	0.34 (0.05)	0.70 (0.07)	0.38 (0.04)	0.70 (0.06)
Lifestyle characteristics								
Age (years)	64.8 (9.3)	64.8 (9.4)	64.7 (7.1)	64.8 (7.1)	64.7 (9.4)	64.9 (9.3)	64.7 (7.1)	64.8 (7.1)
BMI (kg/m^2)	29.3 (4.1)	23.2 (1.5)	29.8 (5.0)	22.2 (2.1)	26.2 (3.4)	25.3 (3.4)	24.9 (4.3)	25.3 (4.5)
Waist circumference (inches)	42.7 (4.3)	35.3 (2.5)	39.1 (5.3)	30.0 (3.5)	39.0 (4.1)	37.5 (4.0)	33.9 (5.4)	33.4 (5.6)
Weight gain in past 10 years (lb., %)								
None	38	48	26	36	38	47	25	34
>0–<10	22	36	18	39	29	30	28	29
≥10	40	16	56	25	32	24	47	37
Physical activity (MET-hours/wk)	14.5 (17.5)	46.3 (32.5)	6.3 (6.3)	30.1 (20.9)	24.8 (25.2)	38.4 (32.0)	13.1 (13.3)	21.7 (19.4)
TV watching (hours/wk, %)								
<5	34	63	18	48	39	54	26	37
5–<20	43	34	53	46	45	37	55	49
≥20	23	4	29	6	15	10	19	14
Current smokers (%)	9	4	12	8	12	2	19	5
Past smokers (%)	49	38	46	43	49	39	45	42
Aspirin/NSAID use (%)	53	46	65	51	51	48	59	56
Multivitamin use (%)	53	64	53	58	52	66	53	58
Family history of CRC (%)	13	14	16	15	13	14	15	15
Screened for CRC (%)	49	56	45	51	47	57	44	52
Supplemental calcium intake (mg/day)	85 (218)	138 (274)	247 (307)	414 (384)	71 (182)	159 (309)	257 (303)	413 (389)
Postmenopausal hormone ever use (%)	–	–	61	72	–	–	64	70
Dietary characteristics								
Energy intake (kcal/day)	1,970 (575)	1,974 (534)	1,766 (469)	1,754 (448)	2,016 (542)	1,969 (538)	1,790 (443)	1,757 (439)
Fruits and vegetables (serv/day)	4.2 (2.5)	6.4 (3.1)	4.2 (2.3)	6.1 (2.9)	3.2 (1.6)	7.4 (3.2)	3.3 (1.8)	6.9 (3.1)
Fiber (g/day)	20.8 (8.7)	28.9 (11.1)	18.3 (7.2)	24.4 (9.3)	17.5 (6.2)	32.2 (11.3)	15.6 (5.6)	27.4 (9.6)
Whole grains, legumes, nuts (serv/day)	1.2 (1.0)	2.2 (1.5)	1.1 (1.0)	1.8 (1.2)	0.9 (0.7)	2.6 (1.6)	0.8 (0.7)	2.2 (1.3)
Unhealthy, processed foods (serv/day)	3.9 (2.3)	3.2 (2.0)	3.6 (2.1)	2.9 (1.8)	4.2 (2.2)	2.8 (1.9)	3.9 (2.0)	2.5 (1.7)
Red meat (serv/day)	0.7 (0.5)	0.4 (0.3)	0.5 (0.4)	0.3 (0.3)	0.7 (0.4)	0.3 (0.3)	0.5 (0.3)	0.3 (0.3)
Processed meat (g/day)	10.9 (11.1)	5.1 (7.5)	8.4 (9.6)	4.4 (6.8)	11.8 (11.2)	4.4 (7.7)	8.8 (10.0)	4.1 (6.9)
Beverages with added sugar (drinks/day)	0.4 (0.7)	0.2 (0.4)	0.4 (0.8)	0.2 (0.5)	0.5 (0.8)	0.2 (0.3)	0.5 (0.8)	0.2 (0.4)
Juices (drinks/day)	0.7 (0.8)	0.8 (0.9)	0.7 (0.8)	0.9 (0.9)	0.8 (0.8)	0.7 (0.8)	0.8 (0.8)	0.7 (0.8)
Alcohol (drinks, %)								
0	51	45	57	46	41	54	32	68
>0–1	32	36	35	43	33	33	46	29
>1–2	8	12	4	7	11	9	11	2
>2	9	6	4	4	15	3	11	1

[a]Mean (SD) or % presented.

in men (HR_{Q5vsQ1} = 0.74, 95%: 0.61–0.90), but not in women (HR_{Q5vsQ1} = 0.93; 95%: 0.77–1.12; Table 4). In men, similar to the lifestyle score, the diet score was most strongly associated with distal colon cancer risk (HR_{Q5vsQ1} = 0.60; 95% CI: 0.42–0.85; $P_{common\ effect}$ = 0.06); we did not observe differences by tumor subtype in women. The results for the diet score for colorectal cancer risk were nearly identical when adjusting for BMI.

When we constructed the lifestyle score by including each dietary component as a separate component in the score (instead of using one overall diet score) plus BMI and physical activity, results were similar overall (Supplementary Table S3), although in women the associations for colorectal cancer (HR_{Q5vsQ1} = 0.80; 95% CI: 0.66–0.96) and distal colon cancer (HR_{Q5vsQ1} = 0.65; 95% CI: 0.46–0.93) were statistically significant. However, results using the continuous score were similar to or slightly weaker than those from our primary analysis.

We did not observe effect modification for the WCRF/AICR scores and colorectal cancer risk by most participant characteristics, although we observed that a one-interquartile range (IQR) increase in WCRF/AICR lifestyle score was more strongly inversely associated with colorectal cancer risk in women with overweight at age 18 (HR = 0.71; 95% CI: 0.55–0.92) than in women without overweight at age 18 (HR = 0.96; 95% CI: 0.87–1.05; $P_{heterogeneity}$ = 0.05; Table 5). We additionally observed a stronger inverse association for the lifestyle score in men with total calcium intake below the median (<843 mg/day; HR = 0.71; 95% CI: 0.63–0.79) than in those with intake above the median (≥843 mg/day; HR = 0.88; 95% CI: 0.78–1.01; $P_{heterogeneity}$ = 0.004). Results for both scores appeared stronger in women who were current smokers than in those who were former or never smokers, although we did not observe statistically significantly heterogeneous results across smoking strata for either score.

Latency analyses generally did not suggest modification by time for associations between the WCRF/AICR lifestyle scores and colorectal cancer outcomes in either sex (Supplementary Table S4). However, they did suggest slightly stronger inverse associations in men between the diet score and colorectal cancer risk with longer time between diet and diagnosis. For 0–4, 4–8, 8–12, and 12–16 year lags, we observed HRs (95% CI) of 0.75 (0.62–0.91), 0.75 (0.61–0.92), 0.73 (0.58–0.91), and

Table 3. Associations (HRs, 95% CIs) between WCRF/AICR lifestyle scores (in quintiles and continuously) and risk of colorectal cancer outcomes among men in the HPFS and women in the NHS

	Q1	Q2	Q3	Q4	Q5	Continuous[a]	P_{trend}[b]	$P_{heterogeneity}$[c]
Mean (SD) score								
Men	1.10 (0.27)	1.61 (0.11)	1.92 (0.07)	2.18 (0.10)	2.51 (0.14)			
Women	0.90 (0.22)	1.37 (0.11)	1.70 (0.09)	2.01 (0.11)	2.36 (0.16)			
Total colorectal cancer								
Men								
No. of cases	277	256	240	195	183			
Age-adjusted	1.00 (ref)	0.87 (0.73–1.03)	0.78 (0.66–0.93)	0.65 (0.54–0.78)	0.59 (0.49–0.71)	0.75 (0.69–0.81)	<0.0001	
MV-adjusted[d]	1.00 (ref)	0.90 (0.76–1.07)	0.83 (0.69–0.99)	0.70 (0.58–0.85)	0.64 (0.52–0.77)	0.78 (0.72–0.85)	<0.0001	
Women								0.006
No. of cases	269	268	260	248	253			
Age-adjusted	1.00 (ref)	0.89 (0.75–1.06)	0.83 (0.70–0.98)	0.77 (0.64–0.91)	0.75 (0.63–0.89)	0.86 (0.79–0.93)	0.0002	
MV-adjusted[e]	1.00 (ref)	0.94 (0.79–1.12)	0.90 (0.76–1.07)	0.86 (0.72–1.02)	0.86 (0.72–1.02)	0.92 (0.85–1.00)	0.06	
Total colon cancer								
Men								
No. of cases	230	196	193	146	142			
Age-adjusted	1.00 (ref)	0.80 (0.66–0.97)	0.76 (0.63–0.92)	0.58 (0.47–0.72)	0.55 (0.44–0.67)	0.72 (0.66–0.79)	<0.0001	
MV-adjusted[d]	1.00 (ref)	0.83 (0.68–1.00)	0.80 (0.65–0.97)	0.62 (0.50–0.77)	0.58 (0.47–0.73)	0.75 (0.68–0.82)	<0.0001	
Women								0.002
No. of cases	215	213	195	193	207			
Age-adjusted	1.00 (ref)	0.88 (0.73–1.07)	0.77 (0.63–0.94)	0.74 (0.61–0.90)	0.76 (0.62–0.92)	0.87 (0.79–0.95)	0.003	
MV-adjusted[e]	1.00 (ref)	0.92 (0.76–1.11)	0.83 (0.68–1.00)	0.81 (0.67–0.99)	0.84 (0.69–1.03)	0.92 (0.84–1.02)	0.10	
Proximal colon cancer								
Men								
No. of cases	79	94	91	63	68			
Age-adjusted	1.00 (ref)	1.10 (0.81–1.48)	1.03 (0.76–1.40)	0.72 (0.52–1.01)	0.76 (0.55–1.06)	0.83 (0.72–0.95)	0.009	
MV-adjusted[d]	1.00 (ref)	1.12 (0.83–1.52)	1.06 (0.78–1.45)	0.77 (0.55–1.09)	0.82 (0.58–1.15)	0.86 (0.74–1.00)	0.05	
Women								0.41
No. of cases	139	124	114	134	135			
Age-adjusted	1.00 (ref)	0.78 (0.61–0.99)	0.68 (0.53–0.87)	0.78 (0.62–0.99)	0.75 (0.59–0.95)	0.88 (0.78–1.00)	0.04	
MV-adjusted[e]	1.00 (ref)	0.81 (0.63–1.03)	0.73 (0.56–0.93)	0.85 (0.67–1.09)	0.83 (0.64–1.06)	0.94 (0.83–1.06)	0.30	
Distal colon cancer								
Men								
No. of cases	97	71	64	52	47			
Age-adjusted	1.00 (ref)	0.70 (0.51–0.95)	0.62 (0.45–0.85)	0.51 (0.36–0.71)	0.43 (0.30–0.61)	0.66 (0.57–0.76)	<0.0001	
MV-adjusted[d]	1.00 (ref)	0.72 (0.53–0.99)	0.66 (0.47–0.91)	0.55 (0.38–0.77)	0.47 (0.33–0.68)	0.69 (0.59–0.80)	<0.0001	
Women								0.04
No. of cases	69	85	77	52	65			
Age-adjusted	1.00 (ref)	1.14 (0.83–1.56)	0.99 (0.72–1.38)	0.65 (0.45–0.93)	0.77 (0.55–1.08)	0.84 (0.71–0.98)	0.02	
MV-adjusted[e]	1.00 (ref)	1.20 (0.87–1.65)	1.05 (0.75–1.46)	0.70 (0.48–1.01)	0.83 (0.59–1.19)	0.87 (0.74–1.03)	0.10	
Rectal cancer								
Men								
No. of cases	47	60	47	49	41			
Age-adjusted	1.00 (ref)	1.20 (0.82–1.77)	0.90 (0.60–1.35)	0.97 (0.65–1.46)	0.79 (0.52–1.20)	0.86 (0.72–1.03)	0.09	
MV-adjusted[d]	1.00 (ref)	1.27 (0.86–1.88)	0.98 (0.65–1.48)	1.07 (0.71–1.62)	0.89 (0.58–1.39)	0.91 (0.76–1.10)	0.33	
Women								0.95
No. of cases	54	55	65	55	46			
Age-adjusted	1.00 (ref)	0.93 (0.64–1.36)	1.06 (0.74–1.52)	0.85 (0.59–1.24)	0.71 (0.48–1.06)	0.81 (0.68–0.97)	0.02	
MV-adjusted[e]	1.00 (ref)	1.03 (0.70–1.50)	1.23 (0.85–1.78)	1.03 (0.70–1.51)	0.90 (0.60–1.36)	0.92 (0.76–1.10)	0.37	

[a]Per one interquartile range increase in the WCRF/AICR lifestyle score.
[b]*P* value for the continuous WCRF/AICR lifestyle score.
[c]$P_{heterogeneity}$ between NHS and HPFS for the continuous WCRF/AICR lifestyle score.
[d]Adjusted for total energy intake (kcal/day, quintiles), NSAID/aspirin use [≥2 pills/week vs. <2 pills/week (ref)], family history of colorectal cancer [yes vs. no (ref)], previous colorectal cancer screening via colonoscopy or sigmoidoscopy [yes vs. no (ref)], history of polyps [yes vs. no (ref)], smoking [never smoker (ref), >0–<10, ≥10–<20, ≥20–<30, ≥30–<40, ≥40–<50, ≥50 pack-years), multivitamin use [regular use vs. nonuse (ref)], supplemental calcium intake [none (ref), >0–<200, ≥200–<400, ≥400–<600, ≥600 mg/day], and young adult body mass index [<25 (ref), ≥25–<27.5, ≥27.5–<30, ≥30 kg/m^2].
[e]Adjusted for same as multivariable models in men + menopausal status [postmenopausal vs. not (ref)], and postmenopausal hormone use [never use (ref), past use, current use].

0.62 (0.47–0.81), respectively, comparing men in the highest to men in the lowest quintile of the diet score.

Discussion

In this analysis of two prospective cohorts, we observed a lower risk of colorectal cancer, especially distal colon cancer, with greater adherence to the 2018 WCRF/AICR lifestyle cancer prevention recommendations on diet, body weight, and physical activity in men, with inverse, but weaker associations for the diet recommendations specifically. The WCRF/AICR lifestyle score was weakly, but nonsignificantly, inversely associated with colorectal cancer risk in women, and the diet score was not associated with colorectal cancer risk. A previous case–control study (20)

Table 4. Associations (HRs, 95% CIs) between WCRF/AICR diet scores (in quintiles and continuously) and risk of colorectal cancer outcomes among men in the HPFS and women in the NHS

	Q1	Q2	Q3	Q4	Q5	Continuous[a]	*P* trend[b]	*P* heterogeneity[c]
Mean (SD) score								
Men	0.33 (0.05)	0.43 (0.02)	0.50 (0.02)	0.58 (0.03)	0.71 (0.07)			
Women	0.38 (0.05)	0.48 (0.02)	0.54 (0.02)	0.60 (0.02)	0.71 (0.06)			
Total colorectal cancer								
Men								
No. of cases	245	219	227	234	226			
Age-adjusted	1.00 (ref)	0.80 (0.67–0.96)	0.77 (0.64–0.92)	0.72 (0.60–0.86)	0.67 (0.56–0.80)	0.82 (0.75–0.89)	<0.0001	
MV-adjusted[d]	1.00 (ref)	0.84 (0.70–1.02)	0.83 (0.69–1.00)	0.78 (0.65–0.94)	0.74 (0.61–0.90)	0.86 (0.79–0.94)	0.001	
Women								0.06
No. of cases	241	276	259	272	250			
Age-adjusted	1.00 (ref)	0.97 (0.81–1.15)	0.93 (0.78–1.10)	0.87 (0.73–1.04)	0.79 (0.66–0.95)	0.90 (0.83–0.97)	0.004	
MV-adjusted[e]	1.00 (ref)	1.02 (0.85–1.21)	1.01 (0.84–1.21)	0.99 (0.82–1.18)	0.93 (0.77–1.12)	0.97 (0.89–1.04)	0.38	
Total colon cancer								
Men								
No. of cases	195	177	167	189	179			
Age-adjusted	1.00 (ref)	0.81 (0.66–1.00)	0.70 (0.57–0.87)	0.72 (0.58–0.88)	0.66 (0.54–0.82)	0.81 (0.74–0.90)	<0.0001	
MV-adjusted[d]	1.00 (ref)	0.85 (0.69–1.05)	0.76 (0.61–0.94)	0.78 (0.63–0.96)	0.73 (0.59–0.91)	0.85 (0.77–0.94)	0.002	
Women								0.04
No. of cases	185	210	211	215	202			
Age-adjusted	1.00 (ref)	0.95 (0.78–1.16)	0.96 (0.79–1.17)	0.88 (0.72–1.08)	0.82 (0.67–1.00)	0.91 (0.84–0.99)	0.03	
MV-adjusted[e]	1.00 (ref)	1.01 (0.83–1.23)	1.06 (0.87–1.30)	1.01 (0.82–1.23)	0.97 (0.79–1.20)	0.99 (0.90–1.08)	0.75	
Proximal colon cancer								
Men								
No. of cases	77	67	72	94	85			
Age-adjusted	1.00 (ref)	0.77 (0.56–1.08)	0.76 (0.55–1.05)	0.89 (0.65–1.20)	0.77 (0.56–1.06)	0.92 (0.80–1.06)	0.26	
MV-adjusted[d]	1.00 (ref)	0.79 (0.57–1.11)	0.80 (0.58–1.12)	0.94 (0.69–1.29)	0.84 (0.61–1.17)	0.96 (0.83–1.12)	0.61	
Women								0.64
No. of cases	106	133	139	133	135			
Age-adjusted	1.00 (ref)	1.05 (0.81–1.35)	1.08 (0.84–1.40)	0.92 (0.71–1.19)	0.92 (0.71–1.19)	0.94 (0.84–1.04)	0.23	
MV-adjusted[e]	1.00 (ref)	1.12 (0.86–1.44)	1.20 (0.92–1.55)	1.04 (0.80–1.36)	1.07 (0.82–1.40)	1.01 (0.90–1.12)	0.92	
Distal colon cancer								
Men								
No. of cases	83	71	59	60	58			
Age-adjusted	1.00 (ref)	0.80 (0.58–1.10)	0.61 (0.44–0.86)	0.54 (0.38–0.75)	0.53 (0.38–0.75)	0.71 (0.61–0.83)	<0.0001	
MV-adjusted[d]	1.00 (ref)	0.85 (0.61–1.17)	0.67 (0.47–0.94)	0.59 (0.42–0.83)	0.60 (0.42–0.85)	0.76 (0.64–0.89)	0.0008	
Women								0.05
No. of cases	74	67	68	78	61			
Age-adjusted	1.00 (ref)	0.77 (0.55–1.07)	0.80 (0.57–1.11)	0.85 (0.62–1.18)	0.67 (0.47–0.94)	0.88 (0.76–1.01)	0.07	
MV-adjusted[e]	1.00 (ref)	0.80 (0.57–1.12)	0.87 (0.62–1.21)	0.97 (0.70–1.36)	0.79 (0.55–1.13)	0.95 (0.82–1.10)	0.49	
Rectal cancer								
Men								
No. of cases	50	42	60	45	47			
Age-adjusted	1.00 (ref)	0.76 (0.50–1.14)	1.01 (0.69–1.48)	0.71 (0.47–1.07)	0.69 (0.46–1.04)	0.83 (0.69–0.99)	0.04	
MV-adjusted[d]	1.00 (ref)	0.81 (0.53–1.23)	1.11 (0.75–1.63)	0.80 (0.53–1.22)	0.79 (0.52–1.20)	0.88 (0.72–1.06)	0.17	
Women								0.95
No. of cases	56	66	48	57	48			
Age-adjusted	1.00 (ref)	1.01 (0.71–1.45)	0.80 (0.54–1.17)	0.83 (0.57–1.21)	0.70 (0.47–1.04)	0.84 (0.71–0.98)	0.03	
MV-adjusted[e]	1.00 (ref)	1.05 (0.73–1.51)	0.85 (0.57–1.25)	0.92 (0.63–1.36)	0.80 (0.53–1.21)	0.89 (0.75–1.06)	0.20	

[a]Per one interquartile range increase in the WCRF/AICR lifestyle score.

[b]*P* value for the continuous WCRF/AICR lifestyle score.

[c]$P_{heterogeneity}$ between NHS and HPFS for the continuous WCRF/AICR lifestyle score.

[d]Adjusted for total energy intake (kcal/day, quintiles), NSAID/aspirin use [≥2 pills/week vs. <2 pills/week (ref)], family history of colorectal cancer [yes vs. no (ref)], previous colorectal cancer screening via colonoscopy or sigmoidoscopy [yes vs. no (ref)], history of polyps [yes vs. no (ref)], smoking [never smoker (ref), >0–<10, ≥10–<20, ≥20–<30, ≥30–<40, ≥40–<50, ≥50 pack-years], multivitamin use [regular use vs. nonuse (ref)], supplemental calcium intake [none (ref), >0–<200, ≥200–<400, ≥400–<600, ≥600 mg/day], young adult body mass index [<25 (ref), ≥25–<27.5, ≥27.5–<30, ≥30 kg/m^2], and physical activity (MET-hours/wk, quintiles).

[e]Adjusted for same as multivariable models in men + menopausal status [postmenopausal vs. not (ref)], and postmenopausal hormone use [never use (ref), past use, current use].

reported strong inverse associations between adherence to the 2018 WCRF/AICR recommendations and colorectal cancer risk. However, this prior study assessed exposure retrospectively, used a score that did not include weight gain, waist circumference, or sedentary behavior, and did not report sex-specific results, making direct comparison with our study difficult. Some (21–23) but not all (24–26) previous prospective studies that operationalized recommendations of the Second Expert Report reported inverse associations with colorectal cancer risk, with most finding weaker results in women than in men.

The associations we observed between the WCRF/AICR diet scores and colorectal cancer risk were similar to those of other

Table 5. Associations (multivariable HRs, 95% CIs) between continuous WCRF/AICR lifestyle and diet scores[a] and colorectal cancer risk stratified by participant characteristics among men in the HPFS and women in the NHS

	No. of cases		WCRF/AICR Lifestyle score[b]				WCRF/AICR Diet score[c]			
			Men		Women		Men		Women	
	Men	Women	HR (95% CI)	P_{het}[d]	HR (95% CI)	P_{het}[d]	HR (95% CI)	P_{het}[e]	HR (95% CI)	P_{het}[e]
Age at diagnosis										
<65 years	329	409	0.83 (0.72–0.97)	0.49	0.99 (0.86–1.14)	0.29	0.91 (0.77–1.07)	0.41	1.02 (0.89–1.17)	0.40
≥65 years	822	889	0.75 (0.68–0.84)		0.92 (0.83–1.03)		0.84 (0.75–0.93)		0.95 (0.87–1.05)	
Aspirin/NSAID use										
Yes	540	631	0.76 (0.66–0.86)	0.31	0.91 (0.81–1.03)	0.66	0.83 (0.73–0.95)	0.21	0.96 (0.86–1.08)	0.65
No	611	667	0.81 (0.72–0.90)		0.93 (0.83–1.05)		0.89 (0.79–1.00)		0.97 (0.87–1.08)	
Family history of colorectal cancer										
Yes	202	263	0.74 (0.59–0.92)	0.66	0.92 (0.75–1.11)	0.96	0.96 (0.77–1.21)	0.38	1.07 (0.90–1.28)	0.29
No	949	1,035	0.79 (0.72–0.86)		0.92 (0.84–1.02)		0.84 (0.76–0.93)		0.94 (0.86–1.02)	
Smoking[f]										
Current	70	144	0.68 (0.45–1.03)	0.32	0.75 (0.57–0.99)	0.45	1.03 (0.67–1.60)	0.64	0.68 (0.52–0.89)	0.07
Former	606	656	0.76 (0.68–0.86)		0.98 (0.86–1.11)		0.84 (0.74–0.95)		1.00 (0.90–1.12)	
Never	475	498	0.82 (0.71–0.94)		0.95 (0.83–1.09)		0.89 (0.77–1.02)		0.97 (0.86–1.10)	
Multivitamin use										
Yes	622	729	0.76 (0.67–0.86)	0.50	0.90 (0.79–1.02)	0.27	0.90 (0.80–1.02)	0.23	0.92 (0.82–1.03)	0.35
No	529	569	0.80 (0.71–0.91)		0.96 (0.85–1.08)		0.81 (0.71–0.92)		1.00 (0.89–1.11)	
BMI ≥ 25 kg/m^2 in young adulthood										
Yes	254	166	0.76 (0.63–0.91)	0.65	0.71 (0.55–0.92)	0.05	0.84 (0.69–1.02)	0.47	0.84 (0.66–1.06)	0.08
No	897	1,132	0.78 (0.71–0.86)		0.96 (0.87–1.05)		0.86 (0.78–0.95)		0.99 (0.91–1.07)	
Total calcium intake										
High	536	581	0.88 (0.78–1.01)	0.004	1.03 (0.90–1.18)	0.23	0.93 (0.82–1.06)	0.07	1.00 (0.89–1.12)	0.81
Low	615	717	0.71 (0.63–0.79)		0.91 (0.81–1.02)		0.81 (0.71–0.92)		0.98 (0.88–1.09)	
Diabetes										
Yes	150	143	0.97 (0.74–1.27)	0.45	1.08 (0.76–1.54)	0.25	0.69 (0.51–0.92)	0.15	1.07 (0.83–1.37)	0.51
No	1,001	1,155	0.77 (0.71–0.85)		0.98 (0.87–1.10)		0.86 (0.79–0.95)		0.95 (0.88–1.04)	
BMI ≥ 30 kg/m^2										
Obesity	153	289	—	—	—	—	0.88 (0.67–1.16)	0.38	0.90 (0.75–1.07)	0.39
No obesity	998	1,009	—		—		0.87 (0.79–0.96)		0.99 (0.90–1.08)	
Physical activity										
High	399	610	—	—	—	—	0.88 (0.75–1.02)	0.37	1.04 (0.93–1.17)	0.09
Low	752	688	—		—		0.85 (0.76–0.94)		0.91 (0.82–1.02)	
Oral contraceptive use										
Ever	—	526	—	—	0.94 (0.81–1.07)	0.49	—	—	0.99 (0.87–1.12)	0.57
Never	—	772	—		0.93 (0.83–1.03)		—		0.95 (0.86–1.05)	
Postmenopausal hormone use										
Ever	—	477	—	—	0.93 (0.80–1.08)	0.96	—	—	1.00 (0.87–1.14)	0.72
Never	—	821	—		0.92 (0.83–1.03)		—		0.95 (0.86–1.04)	

[a]Per a one-unit increase in the interquartile range for each score.
[b]Adjusted for total energy intake (kcal/day, quintiles), NSAID/aspirin use [≥2 pills/week vs. <2 pills/week (ref)], family history of colorectal cancer [yes vs. no (ref)], previous colorectal cancer screening via colonoscopy or sigmoidoscopy [yes vs. no (ref)], history of polyps [yes vs. no (ref)], smoking [never smoker (ref), >0–<10, ≥10–<20, ≥20–<30, ≥30–<40, ≥40–<50, ≥50 pack-years], multivitamin use [regular use vs. nonuse (ref)], supplemental calcium intake [none (ref), >0–<200, ≥200–<400, ≥400–<600, ≥600 mg/day], and young adult body mass index [<25 (ref), ≥25–<27.5, ≥27.5–<30, ≥30 kg/m^2]; in women, additionally adjusted for menopausal status [postmenopausal vs. not (ref)] and postmenopausal hormone use [never use (ref), past use, current use].
[c]Adjusted for the same covariates as for the WCRF/AICR lifestyle score as well as physical activity (MET-hours/wk, quintiles).
[d]$P_{interaction}$ between the potential effect modifier of interest and the continuous lifestyle score.
[e]$P_{interaction}$ term between the potential effect modifier of interest and the continuous diet score.
[f]*P* values calculated by comparing a model with all two-way interactions between the exposure of interest and each category of smoking to a model without any interactions using the likelihood ratio test.

recommendation-based dietary indices (e.g., Dietary Approaches to Stop Hypertension, Mediterranean diet, etc.), especially in men (27), and inclusion of adiposity and physical activity recommendations strengthened these associations, underscoring the importance of considering these lifestyle factors simultaneously. To some degree, these components may affect colorectal cancer risk through different pathways. For example, alcohol inhibits folate absorption and produces toxic acetaldehyde (28–30), excess adiposity upregulates insulinemic pathways (31, 32) and physical activity reduces inflammatory biomarker concentrations (33). However, diet, adiposity, physical activity, and their downstream biological effects are often highly correlated with each other (34–36). Thus, holistic consideration of lifestyle recommendations may partially account for intercorrelation and synergy between these components, while allowing for detection of their cumulative effects.

The differences in associations between WCRF/AICR scores and colorectal cancer risk by sex may be explained by more prominent roles of some lifestyle factors in colorectal cancer etiology in men than women, which has been observed previously in NHS/HPFS (37, 38) and other prospective studies (27, 39). Although few individual dietary components other than alcohol (40) have demonstrated consistent heterogeneity by sex, heterogeneity in associations for adiposity and colorectal cancer risk by sex has been more consistently observed (41, 42). The precise mechanism for this heterogeneity is unclear, but may be

related to sex hormones. Estrogen is primarily produced in adipose tissue in men and postmenopausal women, and a high estrogen to testosterone ratio is associated with increased risk of colorectal cancer in men, but decreased risk in women (43–45). Because men and women had similar distributions of component scores and of other factors not included in the WCRF/AICR recommendations (but which may indicate general health consciousness, such as colorectal cancer screening and multivitamin use), it is unlikely that the stronger results we observed in men are due to major differences in overall lifestyle or attitudes toward health. In addition, both cohorts were followed in nearly identical periods of time, had nearly identical age distributions at baseline, experienced minimal attrition, and were administered very similar questionnaires that had been validated in each cohort (although adapted for different sexes as appropriate). Thus, differences in results between cohorts are also unlikely to be due to differences in features of their study designs. Finally, although diet was first measured in 1980 in NHS, physical activity was not measured until 1986. We therefore could not create WCRF/AICR scores before this questionnaire cycle. While both cohorts had similar age distributions after this exclusion, some previous studies of dietary factors in NHS that included earlier follow-up periods observed stronger associations with colorectal cancer risk than the current study (46, 47). If the distributions of these factors changed from 1980 to 1986 in NHS, our exclusion of this period could partially explain the weak results we observed.

Associations for distal colon cancer risk were stronger than for proximal colon or rectal cancer risk, especially in men. This possible tumor subtype heterogeneity has been observed for many dietary exposures (48, 49) as well as obesity (50), and may be attributed to these locations' distinct etiologic processes (48, 50, 51), microbial compositions (52, 53), or different interaction with metabolites during digestion (54).

We observed stronger inverse associations for the WCRF/AICR scores among women with overweight at age 21 compared with women without overweight at age 21. While the mechanism for this is unclear, it is worth investigating whether improving lifestyle from young adulthood to late adulthood is most important for colorectal cancer risk in women. We also observed stronger inverse associations for the lifestyle score in men with lower total calcium intake compared with those with higher calcium intake. Calcium has been inversely associated with colorectal cancer risk (5, 55), but is not directly recommended by WCRF/AICR. It is therefore possible that the WCRF/AICR lifestyle recommendations confer a greater benefit in men who do not consume optimal calcium than in men with nearly optimal or optimal calcium intake. Importantly, given the number of tests we conducted in subgroups of participant characteristics, any potential effect modification we observed (as well as the HRs themselves) may also be due to chance.

Strengths of this study include its prospective nature, use of multiple questionnaires for updated data on exposures and confounders, high response rates in both cohorts, and long follow-up that allowed for analyses involving different windows of exposure. However, there are limitations as well. First, we defined adherence to each component based on criteria outlined by the Third Expert Report when available, but this report does not provide absolute cutoffs for all components. For some, the report simply recommends limiting consumption or eating others "in most meals." In these instances, we used previous literature or other rationale to define cutoffs for adherence (e.g., assuming that eating three or more servings of whole grains or pulses per day is consistent with eating these items "in most meals"). Moreover, the Third Expert Report usually did not provide cutoffs for "partial adherence." We created this category to distinguish individuals whose lifestyle habits approached (but fell short of) the recommendations from those whose lifestyle habits more clearly deviated from the recommendations. However, this often required us to create ad hoc partial adherence cutoffs. The categories created by these cutoffs were broad and sometimes simple, and could lead to nondifferential exposure misclassification of participants (because we would not expect this error to be related to future incident colorectal cancer). Despite these issues regarding our score operationalization, there are limitations with other common approaches, including using the median (i.e., even broader categories), quantiles (i.e., difficult to compare across studies), or continuous intake (i.e., difficult to interpret component scores). Our approach allows for easy application in and comparison with other populations. Furthermore, the inclusion of waist circumference, weight gain, and sedentary behavior is a novel addition to most previously operationalized WCRF/AICR scores (20, 26, 56).

Other limitations include the fact that diet, physical activity, and sedentary behavior (reflected by television watching) are measured with error, which could bias results. However, the FFQs and physical activity questionnaires (which include television-watching questions) have been validated previously, with moderate to high correlation coefficients when compared against multiple weighed diet records (7–9) and physical activity diaries (10, 11), respectively. Although television watching captures only one aspect of sedentary behavior (and therefore defining sedentary behavior using only television watching is vulnerable to misclassification), we chose this measure because it is most predictive of adverse health outcomes in these cohorts among all sedentary behaviors (57–59). Self-reported anthropometric measures are generally measured with minimal error in NHS and HPFS (14, 60). In addition, use of cumulative average updated exposures likely reduces some random within-person measurement error (14). However, there could still be nondifferential measurement error of the lifestyle behaviors that were used to create our main exposures, which would likely underestimate the results we observed. Third, we were unable to analyze diet in early adulthood (given the older mean age of participants at baseline), which may be relevant for colorectal cancer risk, particularly in women. Finally, because both cohorts consisted of white health professionals, these results may not be generalizable to other populations.

In summary, adherence to the diet, adiposity, and physical activity recommendations provided by the WCRF/AICR Third Expert Report is associated with lower colorectal cancer risk, especially distal colon tumors, in U.S. men, with weaker and statistically nonsignificant inverse associations observed in women. Dietary recommendations alone were less strongly associated with colorectal cancer risk, suggesting the importance of considering lifestyle more broadly for colorectal cancer prevention. Given that the WCRF/AICR recommendations are designed for global cancer prevention, replication of these findings in non-white and non-U.S. populations is warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

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