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Evolutionary Concordance Lifestyle- and Diet- and Mediterranean Diet-Pattern Scores and Risk of Incident Colorectal Cancer in Iowa Women

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Abstract

Background: Whereas diet and lifestyle are strongly implicated in the etiology of colorectal cancer (CRC), single exposures generally are weakly and inconsistently associated with the disease. Exposure patterns may be more helpful for investigating diet- and lifestyle-CRC associations. Evolutionary-concordance diet and Mediterranean diet pattern scores were previously found to be inversely associated with colorectal adenoma.

Methods: To investigate associations of these diet scores and an evolutionary-concordance lifestyle score (comprising smoking status, physical activity, and body mass index) with incident CRC, we analyzed data from the prospective Iowa Women's Health Study. Diet and lifestyle scores were calculated for each participant and categorized into quintiles, and associations estimated using Cox proportional hazards models.

Results: Of the 35,221 55–69-year-old cancer-free women at baseline, 1,731 developed CRC during follow-up. The multivariable-adjusted hazard ratio comparing persons in the highest relative to the lowest quintile of the lifestyle score was 0.66 (95% confidence interval (CI), 0.56–0.78; $P_{trend} < 0.01$). Although the estimated associations of the evolutionary-concordance diet and Mediterranean diet scores alone with CRC were null, relative to those in the lowest tertiles of both the evolutionary-concordance diet and lifestyle scores, those in the highest tertiles of both scores were at the lowest risk ($P_{interaction} < 0.01$).

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Disclosure of Potential Conflicts of Interest

None of the authors has a conflict of interest to disclose.

Conclusions: Our findings suggest that a more evolutionary-concordant lifestyle, alone and in interaction with a more evolutionary-concordant diet pattern, may be inversely associated with CRC risk.

Impact: These results support further investigation of CRC etiology using evolutionary-concordance dietary and lifestyle pattern scores.

Keywords

Colorectal Neoplasms; Diet; Lifestyle; Paleolithic Diet; Mediterranean Diet; Cohort Studies

Introduction

International ecologic and migration studies clearly underscore the importance of environmental exposures—especially diet and physical activity—in the etiology of colorectal cancer (CRC), the second leading cause of cancer deaths in the US (1,2). However, the evidence for many individual dietary and lifestyle factors remains weak and inconsistent. This suggests that individual factors may contribute only modestly to CRC risk, but collectively they may substantially affect it. Accordingly, several diet patterns and scores to represent them were developed, such as the Mediterranean diet score (3). Recently, we developed a “Paleolithic diet” pattern score, and in parallel analyses for the Mediterranean diet pattern score, found both diet patterns to be strongly, inversely associated with biomarkers of oxidative stress and inflammation (4), colorectal adenoma (5), and all-cause, all-cancer, and all-cardiovascular disease mortality (6).

The Paleolithic diet pattern score was developed to help address the evolutionary discordance hypothesis: that the rapid increases in many chronic diseases (including CRC) during the 20th century may be a result of recent changes in diet and lifestyle relative to those of our pre-historic ancestors (7). Anthropologists have described the composition of a Paleolithic diet, the general diet *Homo sapiens* living in the range of environments of evolutionary adaptedness would have had prior to the development of agriculture (8). The Paleolithic diet pattern is characterized as rich in fruits, vegetables, lean meats, eggs, and nuts; excluding grains, dairy products, and refined fats and sugar; and very low in salt. In addition, Paleolithic lifestyle patterns include substantial amounts of physical activity, no smoking, and energy balances resulting in lean body masses (9). Given the constraints in investigating Paleolithic diet or lifestyle patterns in the modern context (e.g., limited wild foods intakes, food preparation methods, types of physical activity), herein we refer to them as evolutionary-concordance diet and lifestyle patterns rather than “Paleolithic” (our re-termed evolutionary-concordance diet pattern score is identical to our above-noted, previously-reported Paleolithic diet score). To the best of our knowledge, there are no reported studies of an evolutionary-concordance lifestyle pattern in relation to a chronic disease, or of separate or combined associations of evolutionary-concordance diet and lifestyle patterns with CRC.

The Mediterranean diet, the historically traditional diet in the Mediterranean region where life expectancy was among the highest in the world (10), is characterized by high fruit, vegetable, nut, fish, and whole grain intakes; moderate alcohol and dairy product intakes;

and low red or processed meats and sweets intakes. Three large prospective cohort studies found a more Mediterranean-like diet to be modestly inversely associated with CRC (3,11,12), and an intervention trial found that the Mediterranean diet pattern may reduce colorectal adenoma recurrence (13). Thus, the more well-known, established Mediterranean diet pattern score can serve as a reference for comparisons of various diet pattern-CRC associations.

Accordingly, herein we report an investigation of associations of evolutionary-concordance diet and lifestyle pattern scores and a Mediterranean diet pattern score with incident CRC in the prospective Iowa Women's Health Study (IWHS).

Materials and Methods

Study population and data collection

As described previously (14), the IWHS, established in 1986, is a prospective cohort study of 41,836 55–69-year-old Iowa women. In addition to the original survey, follow-up surveys were mailed in 1987, 1989, 1992, 1997, and 2004. The University of Minnesota Institutional Review Board (IRB) approved the study, and the Emory University IRB also approved the present analysis.

At baseline, study participants provided detailed information on demographics; self-measured anthropometrics; lifestyle, medical and family history; diet; and other factors. A self-administered, 127-food item Willett food frequency questionnaire (FFQ) was used to assess usual food and nutritional supplement intakes over the previous 12 months. Physical activity was assessed via two questions regarding the frequency of partaking in moderate and vigorous physical activities (15), and categorized as low, medium, and high (see Table 2 footnote c). Aspirin and other nonsteroidal anti-inflammatory drug (NSAID) use was not collected until 1992. Diet and physical activity were only comprehensively reassessed in 2004 at which time only 68.3% of the participants remained alive (therefore, only baseline exposure information was used in the present analyses).

Deaths were identified through the State Health Registry of Iowa and the National Death Index. Cancer diagnoses were collected through linkage with the State Health Registry of Iowa, a participant in the National Cancer Institute's Surveillance, Epidemiology, and End Results Program; ascertainment of cancer diagnoses was nearly 100% (16). CRC was defined as adenocarcinoma of the colon or rectum (ICD-O-3 codes: C18.0–18.9, C19.9, and C20.9).

Scores

The evolutionary-concordance and Mediterranean diet pattern scores were constructed in a similar manner, as described previously (4–6) and summarized in Table 1. Generally, each study participant was assigned a quintile rank (and a corresponding score from 1 to 5) of intake for each food category, based on the distribution of all participants' baseline intakes. Higher scores were given for higher intakes of foods considered characteristic of the diet pattern, and lower scores were given for lower-to-no consumption of foods considered not characteristic of the diet pattern. For the evolutionary-concordance diet score, we created

two unique variables. The first, a fruit and vegetable diversity score, was created by summing the total number of different fruits and vegetables that participants reported consuming >1–3 servings/month. Second, since the Paleolithic diet had little dairy food but high amounts of calcium (from wild plant foods), to consider dietary calcium separately from dairy products we used the residuals of a linear regression of total calcium intake on total dairy consumption. The Mediterranean diet score was calculated according to previous literature, although rather than basing it on dichotomizing the component dietary intake categories (high vs. low, based on median intake) as is most common, we based it on quintiles of intakes to facilitate a more direct comparison of the two diet scores (also, we previously reported that basing the scoring on five rather than two categories made no differences in the diet score's associations with various outcomes (4–6)). The components of the dietary scores were not weighted because 1) in our previous studies of dietary scores in which we used as weights estimated associations from meta-analyses of associations of the individual components with colorectal cancer, weighting made no difference (17,18), and 2) the components of Mediterranean diet scores traditionally are not weighted. Therefore, the final, possible unweighted score ranges were 14–70 for the 14-component evolutionary-concordance diet score, and 11–55 for the 11-component Mediterranean diet score, with higher scores indicating higher concordance with a dietary pattern.

For the evolutionary-concordance lifestyle score, we combined physical activity, smoking status, and body mass index (BMI; weight [kg]/height [m]^2) as follows (Supplement Table 1). First, because there were only three categories for each lifestyle variable (rather than five categories as for the dietary variables), to put the lifestyle variables on the same initial scale as the dietary variables, each component was assigned a preliminary score of 1, 3, or 5, for, respectively, low/medium/high physical activity, current/former/never smoking, and BMI ≥30/25-<30/<25 kg/m^2. Then, because the individual lifestyle factors are more strongly associated with CRC risk than are the individual dietary factors, the preliminary scores were weighted by dividing the two "most exposed" category scores by summary relative risks from meta-analyses of associations of physical activity (19), smoking status (20), and BMI (21) with CRC: i.e., 0.89 for medium and high physical activity, 1.05 for current smoker, 1.20 for former smoker, and 1.12 for BMI ≥25 kg/m^2. Finally, the weighted score components were summed. The final possible 3-component lifestyle score range was 2.85–15.62, with higher scores indicating a more evolutionary-concordant lifestyle.

For a combined evolutionary-concordance diet and lifestyle score, we categorized the diet score according to quintiles, and assigned the quintiles scores equal to their quintile rank (i.e., did not weight it since the diet score was minimally associated with risk), and then summed the diet and the weighted physical activity, smoking status, and BMI components (i.e., a four-component score). The final possible 4-component combined score range was 3.85–20.62.

Statistical analysis

For our analyses, we excluded participants with a history of cancer (other than non-melanoma skin cancer) at baseline (n=3,830), and those who left >10% of the FFQ questions blank (n=2,499) or had implausible total energy intakes (<600 or >5,000 kcal/day; n=286),

leaving an analytic cohort of 35,221. Follow-up time was calculated as the time between the date of completing the baseline questionnaire and age at first CRC diagnosis, date when they moved from Iowa, or date of death; if none of these events occurred, the participant was assumed to be alive, cancer-free, and living in Iowa, and censored at the end of follow up (December 31, 2012) (22).

Participants' characteristics, by score quintiles, were summarized and compared using the χ^2 test for categorical variables and analysis of variance for continuous variables. Cox proportional hazards regression was used to calculate hazards ratios (HR) and 95% confidence intervals (CI) to estimate associations of the various baseline scores with incident CRC. The scores were analyzed as continuous and categorical variables (quintiles) based on the distributions of all participants' scores at baseline. The median value of each diet score quintile was used for conducting all trend tests. Correlations between scores were assessed using Pearson correlation coefficients.

Based on previous literature and biological plausibility, the following variables were considered as potential confounders: age (years; continuous), family history of CRC in a first-degree relative (yes/no), smoking status (current, past, never smoker), education (<high school, high school, >high school), BMI (continuous), physical activity (low, medium, high), total energy intake (kcal/day; continuous), arthritis (yes/no), hormone replacement therapy (HRT) use (current, past, never use), and for the lifestyle score model, the evolutionary-concordance diet score was also considered. Criteria for inclusion in the final models were biological plausibility and/or whether inclusion/exclusion of the variable from the model changed the adjusted HR for the primary exposure variable by ≥10%. The covariates for the final adjusted models are noted in the Tables' footnotes.

To assess potential interaction of the two diet scores with the lifestyle score, we categorized the scores into tertiles (rather than quintiles, due to sample size constraints), and conducted a joint/combined analysis in which the reference group was participants in the first tertile of each score.

To assess whether associations differed by categories of other risk factors not included in the scores, we conducted separate analyses within each category of: age (≤/> median age of 61 years), family history of CRC in a first-degree relative (yes/no), education (≤ high school/ >high school), total energy intake (≤/> median of 1,717.4 kcal/day), and HRT use (current or past/never).

To assess the sensitivity of the associations to various considerations, we repeated the analyses with the following variations: 1) excluded participants who died or were diagnosed with CRC within one or two years of follow up, 2) censored participants upon reaching the ages of 75 and 80 years, 3) used a lifestyle score composed of unweighted components, and 4) used a Mediterranean diet score based on dichotomized components. Also, because NSAID use is considered causally related to colorectal carcinogenesis, but information on it was not collected until 1992, we repeated the analyses using 1992 as baseline, and assessed whether inclusion of aspirin and other NSAID use in the models materially affected the

estimated associations. Finally, we investigated whether removing and replacing each component of each score one at a time materially affected the observed associations.

All analyses were conducted using SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, North Carolina). All *P*-values were 2-sided. A *P*-value ≤0.05 or a 95% CI that excluded 1.0 was considered statistically significant.

Results

In the analytic cohort, 1,731 participants developed CRC during follow-up. Selected baseline characteristics of the study participants according to quintiles of the evolutionary-concordance and Mediterranean diet scores and the evolutionary-concordance lifestyle score are presented in Tables 2 and 3. Participants in the higher quintiles of both diet scores were more likely to be more educated, use HRT, and be more physically active. Also, they had higher mean total calcium and dietary fiber intakes, and lower total and saturated fat intakes. Participants in the higher evolutionary-concordance diet score quintiles had lower mean total energy, alcohol, protein, and carbohydrate intakes, whereas those in the higher Mediterranean diet score quintiles had higher alcohol, protein, and carbohydrate intakes. Exclusive of variables included in the evolutionary-concordance lifestyle score, participants in the higher quintiles of the score were more likely to be more educated and had higher mean total energy, calcium, fat, dietary fiber, protein, and carbohydrate intakes and lower alcohol intakes.

The evolutionary-concordance and Mediterranean diet scores ranged from 19–68 and 12–52, respectively. The correlation between the two diet scores was r=0.68 ($P<0.01$). The lifestyle and combined evolutionary-concordance diet and lifestyle scores ranged from 2.85–15.62 and 3.85–20.62, respectively. The correlations between the lifestyle score and the evolutionary-concordance and Mediterranean diet scores were each r=0.17 ($P<0.01$).

Associations of the scores with incident CRC are presented in Table 4. Adjustment for multiple covariates minimally affected the estimated associations; only the multivariable-adjusted associations are presented. When the lifestyle score was treated as a continuous variable, there was a statistically significant 4% lower risk for each point increase in the score; when the score was analyzed according to quintiles, there was a statistically significant trend of decreasing risk with an increasing score, and a statistically significant 34% lower risk for those in the upper relative to the lower quintile. On the other hand, whether the diet scores were treated as continuous or categorical variables, their estimated associations with CRC were at or close to the null. The association of the combined evolutionary-concordance diet and lifestyle score with CRC was similar to that for the lifestyle score alone. However, as shown in Table 5, being in the upper tertile of both the evolutionary-concordance diet and lifestyle scores was associated with lower risk (HR, 0.72; 95% CI, 0.60–0.87) than was being in the upper tertile of only one or the other of the scores (e.g., lifestyle only: HR, 0.81 [95% CI, 0.66–0.99], and diet only: HR, 1.01 [95% CI, 0.84–1.21]; $P_{interaction}<0.01$). However, the estimated risk for those in the upper tertile of both the Mediterranean diet and evolutionary-concordance lifestyle scores was not substantially

different from that for those in the upper tertile of the lifestyle score/lowest tertile of the Mediterranean diet score (both were about 25% lower).

There were no consistent, clear patterns of differences in associations of any of the scores with incident CRC according to age, family history of CRC in a first-degree relative, education, total energy intake, or HRT use (Supplement Tables 2 and 3).

In sensitivity analyses, excluding those who died or were diagnosed with CRC within one or two years of follow up, or censoring participants upon reaching the ages of 75 or 80 years had negligible impact on our estimated associations (Supplement Table 4). The unweighted version of the lifestyle score was somewhat more strongly inversely associated with CRC than was the weighted score, which was our *a priori*, and thus more conservative score (Supplement Table 5). Dichotomizing the Mediterranean diet score components had no appreciable effect on the findings for the score (Supplement Table 6). When we used 1992 as baseline and compared the results from when we included or excluded aspirin and other NSAID use from the model, the results (Supplement Table 7) were nearly identical to each other and similar to those shown in Table 4. Removing and replacing each component of the diet scores one at a time did not materially affect the observed associations for the scores, whereas removal of physical activity and BMI from the lifestyle score modestly attenuated the associations of the score with CRC (Supplement Table 8).

Discussion

Our findings suggest that a more evolutionary-concordant lifestyle, alone and in interaction with a more evolutionary-concordant diet pattern, may be inversely associated with CRC risk. However, our findings do not support that more evolutionary-concordant- or Mediterranean-like diet patterns among those with poor lifestyle patterns are associated with CRC risk among older, white Iowa women. This is the first reported study of associations of evolutionary-concordance lifestyle and diet scores with incident CRC.

Physical inactivity, smoking, and obesity plausibly increase CRC risk, and all three have been consistently directly associated with CRC in epidemiologic studies. Physical activity increases gut motility, enhances immune functions, and reduces prostaglandin, insulin, and insulin-like growth factor levels (23). Smoking delivers carcinogens and increases oxidative stress (24). Excess adiposity increases inflammation, circulating insulin, and insulin resistance (25). In systematic reviews with meta-analyses, the meta-relative risk for physical activity (27 studies) was 0.89 (95% CI, 0.81–0.99) (19); for being a current or former smoker (45 and 47 studies), 1.05 (95% CI, 0.94–1.18) and 1.20 (95% CI, 1.11–1.30), respectively (20); and for BMI (13 studies), 1.12 (95% CI, 1.03–1.22) (21).

Evolutionary-concordant and Mediterranean diet patterns have several components that could plausibly reduce CRC risk. Both are high in fruits and vegetables, which may help improve oxidative balance and reduce inflammation, increase dietary fiber intake, and reduce total energy intake, although support for each in epidemiologic studies is mixed (2,26,27). Both diet patterns are also low in red, processed, and fatty meats, which may increase CRC risk via several mechanisms (28,29). Of possible relevance to our study is that

stronger associations of dietary patterns with CRC were frequently reported in men, but not women (30,31); the possible reasons(s) for this is unclear, but may be related to biological differences (32) or differential diet measurement (33).

The evolutionary-concordance ("Paleolithic") diet pattern was examined in one case-control study of incident, sporadic colorectal adenoma (5), one cross-sectional study of biomarkers of inflammation and oxidative stress (4), and one prospective cohort study of mortality (6). In the colorectal adenoma case-control study (n=564 cases identified via outpatient colonoscopy, 1,202 colonoscopy-negative controls, and 535 community controls), which collected dietary information via a Willett FFQ, the multivariable-adjusted odds ratios (OR) comparing those in the highest relative to the lowest quintiles of the Paleolithic (evolutionary-concordance) diet score were 0.71 (95% CI, 0.50–1.02; P_{trend}=0.02) when comparing the cases to the endoscopy-negative controls, and 0.84 (95% CI, 0.56–1.26; P_{trend}=0.14) when comparing the cases to the community controls (5). Of possible relevance to our study is that the estimated inverse associations were stronger among men, and close to the null among women. In the pooled cross-sectional study (n=646) of elective outpatient colonoscopy populations, dietary information was collected via a Willett FFQ, and because inflammation is thought to be causally related to colorectal carcinogenesis, and oxidative stress is closely linked with inflammation, concentrations of circulating high sensitivity C-reactive protein (hsCRP), a marker of inflammation, and F_2-isoprostanes, a marker of oxidative stress, were measured (4). Diet patterns considered more evolutionary-concordant were inversely associated with both biomarkers. The findings for hsCRP did not differ substantially by sex, but the findings for F_2-isoprostanes were stronger among women. In the REasons for Geographic and Racial Differences in Stroke (REGARDS) study, a longitudinal cohort of black and white men and women ≥45 years of age, diet was assessed using a Block 98 FFQ (6). In the analytic cohort (n=21,423), for those in the highest relative to the lowest quintiles of the "Paleolithic" (evolutionary-concordance) diet score, the multivariable-adjusted HRs for all-cause, cancer, and cardiovascular disease mortality were, respectively, 0.77 (95% CI, 0.67–0.89; P_{trend}<0.01), 0.72 (95% CI, 0.55–0.95; P_{trend}=0.03), and 0.78 (95% CI, 0.61–1.00; P_{trend}=0.06). There were no substantial differences in the findings by sex. Within each of these three studies, the findings for the evolutionary-concordance and Mediterranean diet scores were very similar to each other.

While, to the best of our knowledge, there are no previous reports of an evolutionary-concordance diet score-incident CRC association, three prospective cohort studies investigated Mediterranean diet score-incident CRC associations, finding inverse associations. The European Prospective Investigation into Cancer and Nutrition study (12), the Nurses' Health Study (3), and the NIH-American Association of Retired Persons Diet and Health Study (11) found 11–12% lower risk among women in the highest relative to the lowest Mediterranean diet score group, although none of the findings was statistically significant.

The reasons for our null results for the two diet scores individually, especially considering the findings from previous studies, are unclear. Possibilities include some of the limitations of our study, including a relatively homogeneous population; that, for the most part, the actual diets of the participants could not be considered to be strongly consistent with either

an evolutionary-concordant or Mediterranean diet pattern; and limited reassessment of exposures during follow up. Other possibilities include chance and that these diet patterns may not reduce risk for CRC, especially among women. As noted above, on the one hand, in our adenoma case-control study, the inverse associations of the diets with adenoma were essentially limited to men; on the other hand, in the REGARDS cohort study, the inverse associations of the diets with all-cause, cancer, and cardiovascular disease mortality did not substantially differ by sex. A comparison of the quintile medians for the components of our diet scores in the IWHS and REGARDS analytic cohorts supports our conjecture about the IWHS population being homogeneous in more ways than geographic location and race. Example first and fifth quintile medians in the IWHS vs. the REGARDS cohorts are: total vegetables, 11.5–43 vs. 6.5–52.6 servings/week; sugar-sweetened beverages, 0–4 vs. 0–11.8 servings/week; and alcohol, 0–12.1 vs. 0–23.1 g/day. However, being in the upper tertile of both the evolutionary-concordance and lifestyle score was associated with modestly lower risk than was being in the highest tertile of only one or the other scores ($P_{\text{interaction}}<0.01$), suggests that diet may contribute to lower CRC risk.

Other investigators have reported associations of separate and combined lifestyle and dietary scores (primarily framed as adherence to lifestyle and dietary recommendations) with CRC. Adherence to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations (regarding BMI, physical activity, and a limited number of dietary intakes) was investigated in three large prospective cohort studies (EPIC, VITAL [VITamins And Lifestyle Study, in Western Washington, USA], and the Black Women's Health Study [BWHS]) (34–37) and one large, pooled (combined n=2,419 cases, 4,723 controls) Italian case-control study (38). Strong, inverse associations were found in each of these studies (the findings were statistically significant in all but the BWHS), and in one (VITAL) of the two (VITAL and the Italian case-control study) that stratified on sex, a stronger inverse association was found among men. Two large, prospective cohort studies (EPIC and the Danish Diet, Cancer and Health Cohort Study) investigated Healthy Lifestyle Index (HLI) recommendations adherence scores (comprised of BMI and/or waist circumference, physical activity, smoking status, alcohol, and a limited number of dietary intakes) (34,37,39). Both found strong, statistically significant associations of the scores with CRC, and in both, the findings were weaker among women than among men. Four of the studies also reported associations of lifestyle and dietary sub-scores with CRC (the HLI in EPIC and WCRF/AICR recommendations adherence scores in VITAL, the BWHS, and the Italian case-control study), all finding the lifestyle sub-scores to be more strongly inversely associated with risk than were the dietary sub-scores (35,36,38,39).

Our study had several limitations, including the known limitations of FFQs (e.g., recall error, limited number of food items, complex task of estimating and calculating intake frequencies, etc.), and not having data on NSAID use until after six years of follow up. However, study strengths included that, to our knowledge, this is the first study of associations of evolutionary-concordance lifestyle and diet scores with incident CRC, the prospective design, large sample size, long follow up, and the standardized, nearly 100% complete information on cancer diagnoses.

In conclusion, our findings suggest that a more evolutionary-concordant lifestyle, alone and in interaction with a more evolutionary-concordant diet pattern, may be inversely associated with CRC risk. However, our findings do not support that more evolutionary-concordant- or Mediterranean-like diet patterns among those with poor lifestyle patterns are associated with CRC risk, at least among older, white Iowa women. Given these findings and the limited existing literature, further investigation of lifestyle scores and evolutionary-concordance and Mediterranean dietary patterns in prospective cohort studies is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CRC	colorectal cancer
IWHS	Iowa Women's Health Study
IRB	Institutional Review Board
FFQ	food frequency questionnaire
NSAID	nonsteroidal anti-inflammatory drug
BMI	body mass index
HR	hazards ratio
CI	confidence interval
HRT	hormone replacement therapy
hsCRP	high sensitivity C-reactive protein
REGARDS	REasons for Geographic and Racial Differences in Stroke
WCRF/AICR	World Cancer Research Fund/American Institute for Cancer Research
VITAL	VITamins And Lifestyle Study
BWHS	Black Women's Health Study
HLI	Healthy Lifestyle Index

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Table 1.

Constituents and construction of evolutionary-concordance and Mediterranean diet pattern scores in the prospective Iowa Women's Health Study (n = 35,221), 1986 – 2012[a]

Constituents	Evolutionary-concordance diet score[b]	Mediterranean diet score[c]
Vegetables	Highest intake "best"	Highest intake "best"
Fruits	Highest intake "best"	Highest intake "best"
Lean meats[d]	Highest intake "best"	Highest intake "best"
Fish	Highest intake "best"	Highest intake "best"
Nuts	Highest intake "best"	Highest intake "best"
Fruit & vegetable diversity[e]	Highest intake "best"	
Calcium[f]	Highest intake "best"	
Monounsaturated/saturated fat ratio		Highest intake "best"
Red and processed meats[g]	Lowest intake "best"	Lowest intake "best"
Sodium	Lowest intake "best"	Lowest intake "best"
Dairy foods	Lowest intake "best"	Moderate intake "best"
Grains and starches	Lowest intake "best"	Moderate intake "best"
Baked goods[h]	Lowest intake "best"	
Sugar-sweetened beverages	Lowest intake "best"	
Alcohol	Lowest intake "best"	5 −15 g/day (+5 points) Outside of the range (+1 point)

[a]All constituents measured in servings/week unless otherwise indicated. Highest intake "best": points assigned to each quintile = quintile rank (e.g., highest and lowest quintiles scored +5 and +1 points, respectively); lowest intake "best": points assigned to each quintile = reverse quintile rank (e.g., highest and lowest quintiles scored +1 and +5 points, respectively); moderate intake "best": third quintile scored +5 points, second and fourth quintiles scored +3 points, and first and fifth quintiles scored +1 point.

[b]The evolutionary-concordance diet pattern score had 14 components; range of possible scores, 14 – 70.

[c]The Mediterranean diet pattern score had 11 components; range of possible scores, 11 – 55.

[d]Lean meats included skinless chicken or turkey and lean beef.

[e]Fruit & vegetable diversity calculated by summing the total number of different fruits and vegetables items in the food frequency questionnaire the participants indicated that they ate more than 1 – 3 times per month.

[f]Intake of calcium independent of non-calcium components of dairy foods; calculated as residuals from the linear regression of total calcium intake (mg/day) on dairy-food intake.

[g]Consumption of nitrate-processed meats and non-lean red meat combined.

[h]Baked goods included items such as cake, pie, and other pastry-type foods.

Table 2.

Selected characteristics of participants according to quintiles of the evolutionary-concordance and Mediterranean diet pattern scores at baseline in the Iowa Women's Health Study (n = 35,221), 1986 – 2012

	Evolutionary-concordance diet score quintiles				Mediterranean diet score quintiles			
Characteristics[a]	1 (n = 7,846)	3 (n = 7,695)	5 (n = 6,260)	*P*[b]	1 (n = 8,490)	3 (n = 6,999)	5 (n = 7,036)	*P*[b]
Age, years	61.3 (4.2)	61.6 (4.2)	61.6 (4.2)	<0.01	61.2 (4.2)	61.7 (4.2)	61.5 (4.2)	<0.01
White race, %	99.4	99.3	99	<0.01	99.1	99.2	99.3	0.13
Body mass index, kg/m^2	26.6 (5.0)	27.0 (5.0)	27.0 (5.0)	<0.01	27.1 (5.3)	27.0 (5.0)	26.7 (4.8)	<0.01
First-degree relative with colorectal cancer, %	3.1	3.2	3.4	0.62	3.1	2.8	3	0.27
Current or past HRT use, %	35.2	39	43.8	<0.01	35.6	38.5	42.4	<0.01
Current or past smoker, %	36.8	33.3	33.7	<0.01	35.6	23.7	35.9	<0.01
> High school education, %	31.2	40.7	49.6	<0.01	30.7	40.3	50.4	<0.01
High physical activity[c], %	15.9	24.1	38.9	<0.01	16.8	24.4	35.8	<0.01
Total energy intake, kcal/day	2,021 (605)	1,770 (619)	1,590 (481)	<0.01	1,778 (656)	1,794 (609)	1,784 (509)	<0.01
Total calcium intake[d], mg/day	983 (493)	1,096 (562)	1,259 (580)	<0.01	1,026 (574)	1,086 (542)	1,154 (527)	<0.01
Total fat intake, g/day	82.7 (28.7)	67.0 (26.6)	54.2 (20.0)	<0.01	72.7 (30.6)	68.1 (27.4)	64.3 (23.3)	<0.01
Saturated fat intake, g/day	30.0 (11.2)	23.4 (10.0)	18.1 (7.0)	<0.01	27.1 (12.3)	23.7 (10.0)	21.0 (7.9)	<0.01
Dietary fiber intake, g/day	17.9 (6.8)	19.7 (8.2)	22.2 (8.3)	<0.01	12.6 (7.1)	19.9 (7.7)	23.7 (7.8)	<0.01
Alcohol intake, g/day	4.8 (10.1)	3.6 (8.4)	2.9 (7.7)	<0.01	3.2 (9.8)	3.5 (8.5)	4.9 (7.9)	<0.01
Protein intake, g/day	84.9 (29.2)	80.0 (31.3)	78.6 (27.3)	<0.01	78.4 (31.8)	80.4 (30.8)	85.3 (26.7)	<0.01
Carbohydrates intake, g/day	235 (81)	216 (83)	203 (70)	<0.01	205 (84)	219 (80)	232 (74)	<0.01

Abbreviations: HRT, hormone replacement therapy.

[a] Continuous variables presented as mean ± standard deviation, and categorical variables as percentage.

[b] *P* values calculated using the χ^2 test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables.

[c] Physical activity level derived from two questions regarding the frequency of moderate and vigorous physical activity (15), and categorized as high (vigorous activity twice a week or moderate activity >4 times/week), medium (vigorous activity once a week plus moderate activity once a week, or moderate activity 2–4 times/week), and low.

[d] Total = diet + supplements.

Table 3.

Selected characteristics of participants according to quintiles of the evolutionary-concordance lifestyle score at baseline in the Iowa Women's Health Study (n = 35,221), 1986 – 2012

Characteristics[a]	Evolutionary-concordance lifestyle score quintiles			
	1 (n = 7,040)	3 (n = 7,290)	5 (n = 5,137)	*P*[b]
Age, years	61.3 (4.2)	61.4 (4.2)	61.8 (4.3)	<0.01
White race, %	98.8	99.3	99.5	<0.01
Body mass index, kg/m^2	32.5 (5.0)	25.7 (5.1)	22.8 (1.6)	<0.01
First-degree relative with colorectal cancer, %	3.1	3.0	3.2	0.72
Current or past HRT use, %	36.2	39.9	41.2	<0.01
Current or past smoker, %	56.3	35.5	0	<0.01
> High school education, %	33.3	40.7	47.9	<0.01
High physical activity[c], %	0	15.9	50.3	<0.01
Total energy intake, kcal/day	1,787 (624)	1,788 (600)	1,827 (573)	<0.01
Total calcium intake[d], mg/day	1,004 (537)	1,101 (555)	1,202 (552)	<0.01
Total fat intake, g/day	70.3 (28.9)	68.0 (27.5)	67.0 (25.8)	<0.01
Saturated fat intake, g/day	24.7 (10.8)	23.8 (10.5)	23.3 (9.8)	<0.01
Dietary fiber intake, g/day	18.4 (7.6)	19.6 (7.7)	21.7 (8.1)	<0.01
Alcohol intake, g/day	3.5 (9.2)	3.9 (8.7)	2.8 (6.2)	<0.01
Protein intake, g/day	80.9 (31.1)	79.9 (30.1)	81.8 (28.3)	<0.01
Carbohydrates intake, g/day	211 (81)	218 (78)	231 (77)	<0.01

Abbreviations: HRT, hormone replacement therapy.

[a]Continuous variables presented as mean ± standard deviation, and categorical variables as percentage.

[b]*P* values calculated using the χ^2 test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables.

[c]Physical activity level derived from two questions regarding the frequency of moderate and vigorous physical activity (15), and categorized as high (vigorous activity twice a week or moderate activity >4 times/week), medium (vigorous activity once a week plus moderate activity once a week, or moderate activity 2–4 times/week), and low.

[d]Total = diet + supplements.

Table 4.

Multivariable-adjusted associations of evolutionary-concordance diet and lifestyle and Mediterranean diet pattern scores with incident colorectal cancer in the Iowa Women's Health Study (n = 35,221), 1986 – 2012

Score variable	Evolutionary-concordance scores						Mediterranean diet score[a]	
	Diet[a]		Lifestyle[b]		Combined[c]			
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Continuous	1.00	0.99–1.01	0.96	0.94–0.97	0.97	0.95–0.98	1.00	0.99–1.01
Quintiles								
1	1.00		1.00		1.00		1.00	
2	1.02	0.88–1.19	0.87	0.75–1.00	0.92	0.79–1.07	1.10	0.95–1.28
3	1.01	0.87–1.17	0.79	0.68–0.91	0.83	0.72–0.97	1.18	1.02–1.36
4	1.01	0.86–1.18	0.75	0.64–0.87	0.85	0.73–0.98	1.01	0.86–1.19
5	1.01	0.85–1.19	0.66	0.56–0.78	0.70	0.59–0.81	1.01	0.86–1.18
P for trend	*0.85*		*< 0.01*		*< 0.01*		*0.98*	

Abbreviations: CI, confidence interval; HR, hazards ratio.

[a]For score construction, see text and Table 1. HRs from Cox proportional hazards models; covariates included age (years; continuous), family history of colorectal cancer in a first-degree relative (yes/no), smoking status (current, past, never smoker), education (< high school, high school, > high school), body mass index (weight [kg]/height [m]^2; continuous), physical activity (low, medium, high), total energy intake (kcal/day; continuous), arthritis (yes/no), and hormone replacement therapy use (current, past, never).

[b]Includes smoking, physical activity, and body mass index; for score construction, see text. HRs from Cox proportional hazards models; covariates included age (years; continuous), family history of colorectal cancer in a first-degree relative (yes/no), education (less than high school, high school, more than high school), total energy intake (kcal/day; continuous), arthritis (yes/no), use of hormone replacement therapy (current, past, never use), and evolutionary-concordant diet score (quintiles).

[c]Combined score = evolutionary-concordant diet score + evolutionary-concordant lifestyle score. HRs from Cox proportional hazards models; covariates included age (years; continuous), family history of colorectal cancer in a first-degree relative (yes/no), education (less than high school, high school, more than high school), total energy intake (kcal/day; continuous), arthritis (yes/no), and use of hormone replacement therapy (current, past, never use).

Table 5.

Multivariable-adjusted joint/combined associations[a] of the evolutionary-concordance lifestyle score and the evolutionary-concordance and Mediterranean diet pattern scores with incident colorectal cancer in the Iowa Women's Health Study (n = 35,221), 1986 – 2012

		Evolutionary-concordance lifestyle score tertiles		
		1	2	3
		HR (95% CI)	HR (95% CI)	HR (95% CI)
Evolutionary-concordance diet score tertiles	1	1.00 (Ref)	0.73 (0.60–0.88)	0.81 (0.66–0.99)
	2	1.00 (0.85–1.18)	0.86 (0.71–1.04)	0.83 (0.69–1.01)
	3	1.01 (0.84–1.21)	0.89 (0.73–1.09)	0.72 (0.60–0.87)[b]
Mediterranean diet score tertiles	1	1.00 (Ref)	0.80 (0.66–0.97)	0.75 (0.61–0.93)
	2	1.07 (0.91–1.26)	0.86 (0.71–1.04)	0.86 (0.71–1.04)
	3	0.97 (0.81–1.17)	0.83 (0.68–1.01)	0.76 (0.63–0.92)[b]

Abbreviations: CI, confidence interval; HR, hazards ratio.

[a]HRs from Cox proportional hazards models; covariates included age (years; continuous), family history of colorectal cancer in a first-degree relative (yes/no), education (less than high school, high school, more than high school), total energy intake (kcal/day; continuous), arthritis (yes/no) and use of hormone replacement therapy (current, past, never use).

[b]$P_{interaction} < 0.01$; from lifestyle score*diet score interaction term in the Cox proportional hazards model.