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Paleolithic and Mediterranean Diet Pattern Scores and Risk of Incident Colorectal Cancer in Iowa Women, 1986-2012

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Epidemiology

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BMED, B.Ec., Peking University, 2015

Thesis Committee Chair: Roberd M. Bostick, MD, MPH

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

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Whereas diet is strongly implicated in the etiology of colorectal cancer (CRC), single dietary constituents tend to be weakly and inconsistently associated with the disease. Dietary patterns may be more helpful for investigating associations of diet with colorectal cancer. Paleolithic and Mediterranean diet pattern scores were previously found to be inversely associated with incident, sporadic colorectal adenoma. To investigate associations of these dietary pattern scores with incident colorectal cancer, we analyzed data from the prospective Iowa Women's Health Study (IWHS). Of the 35,221 56-64 years old women who were cancer-free at baseline, 1,731 developed incident CRC during follow-up. Both diet scores were calculated for each participant and categorized into quintiles, and associations were estimated using Cox proportional hazards models. The multivariable-adjusted hazard ratios comparing persons in the highest quintiles of the Paleolithic and Mediterranean diet scores relative to those in the lowest were 0.99 (95% confidence interval (CI) 0.85, 1.19; $P_{trend} = 0.85$) and 1.01 (95% CI 0.86, 1.18; $P_{trend} = 0.98$), respectively. Our findings suggest that diet patterns that are more Paleolithic- or Mediterranean-like may not be associated with risk for colorectal cancer among older, white women.

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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer deaths and the third most commonly diagnosed cancer in the US(1). CRC mortality remains high despite advances in screening, prevention, and treatment. International ecologic and migration studies clearly point out the importance of environmental exposures—especially diet and physical activity—in the etiology of the disease(2). However, the evidence for specific dietary factors remains weak and inconsistent. Many, but not all(3, 4), epidemiologic studies found that fruits and vegetables were associated with lower risk of CRC(2). Whereas high-fat diets and high meat consumption overall have been weakly, inconsistently directly associated with CRC risk(5), processed meats, and to a lesser extent red meats (which in the US tends to equate with high fat meats), have been somewhat consistently associated with higher risk(6). The efficacy of several dietary supplements and one dietary pattern in reducing the recurrence of colorectal adenoma (the precursor to most CRCs) were tested in various trials. Among supplemental calcium, vitamin D, folic acid, limited numbers of antioxidant micronutrients, and fiber, as well as a low-fat/high-fiber/high fruits and vegetables diet, evidence for efficacy was found only for calcium, whereas folic acid increased the recurrence of advanced adenomas(7-10).

Since diet is strongly implicated in the etiology of colorectal cancer CRC, but single dietary constituents tend to be only weakly and inconsistently associated with the disease(7), there is renewed interest in associations of diet patterns with CRC. Dietary patterns are helpful in studying the associations of total diet with health outcomes, including cancer, cardiovascular disease, and mortality(11). Existing databases and published food frequency questionnaires can be used to construct many different theoretical diet patterns to investigate associations of diet with CRC(12-15). The Mediterranean diet pattern is a commonly examined diet pattern; another, the Paleolithic-like diet pattern has received little study.

The Mediterranean diet is the historically traditional diet in the Mediterranean region, where life expectancy was among the highest in the world(16). Characteristics of the Mediterranean diet pattern include high intakes of fruits, vegetables, nuts, fish, and whole grains; moderate intakes of alcohol and dairy products; and low intakes of red or processed meats and sweets. An intervention trial found the Mediterranean diet pattern may reduce the recurrence of colorectal adenomas, at least in women(17). A review concluded that up to 25% of the incidence of colorectal cancer could be prevented if the populations of highly developed Western countries shifted to the traditional healthy Mediterranean diet(18). A European cohort study found that a more Mediterranean-like diet may be modestly inversely associated with CRC risk(13).

The evolutionary discordance hypothesis is that the rapid increases in many chronic diseases (including cancer) during the 20th century may be a result of recent changes in diet and lifestyle relative to those of our pre-historic ancestors(19). 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(20). 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. Chronic low-grade inflammation or oxidative stress is hypothesized to increase risk for colorectal neoplasms, hypotheses supported by basic science studies and a growing body of epidemiologic literature. In a cross-sectional study of two adult, outpatient, elective colonoscopy populations, a Paleolithic diet pattern score was inversely associated with circulating biomarkers of oxidative balance and inflammation(21). In a case-control study it was found that a more Paleolithic-like diet pattern was associated with lower risk of incident, sporadic colorectal adenomas(22). To the best of our knowledge, there are no reported studies of an association of the Paleolithic diet pattern with risk of incident colorectal cancer. Accordingly, herein we report the results of an investigation of an association of a Paleolithic diet score with incident colorectal cancer in the prospective Iowa Women's Health Study (IWHS), and contrast those findings with those of a Mediterranean diet- CRC association.

METHODS

Study population and data collection

The Iowa Women's Health Study (IWHS), established in 1986, is a long-running, population-, geographically-based prospective cohort study. As described previously, a total of 195,294 women from Iowa ages 55 to 69 years were identified using the 1985 Iowa Driver's License List. A total of 99,826 women were randomly selected and 41,836 were enrolled. In addition to the original survey, six follow-up surveys were sent to study participants, in 1987, 1989, 1992, 1997, 2004, and 2012. The University of Minnesota Institutional Review Board (IRB) approved the study, and written informed consent was obtained from each study participant. Through a data use agreement, with Emory University IRB approval, Emory University maintains a limited dataset for data analyses, including the present analysis.

Cancer incidence and deaths among IWHS participants were obtained annually via linkage to the State Health Registry of Iowa, which is a part of the National Cancer Institute's Surveillance, Epidemiology, and End Results program. For IWHS women diagnosed with cancer, standardized information on cancer sequence number, primary site, morphology, diagnostic confirmation, extent of disease, initial therapy, and vital status were obtained; ascertainment was nearly 100%.

At baseline, study participants provided detailed information on demographics, self-measured anthropometrics, lifestyle, medical history, hormone replacement therapy (HRT), diet, family history, physical activity, and other factors. A self-administered, 166-item modified semi-quantitative Willett food frequency questionnaire was used to assess food and nutritional supplement intakes over the previous 12 months. For each food, a commonly used portion size was specified and 9 possible frequency-of-consumption responses ranged from "never or less than once per month" to "6 or more times per day". Total energy and nutrient intakes were calculated by adding energy and nutrients from all food sources using the dietary database developed by Willett, *et al*. Aspirin and other nonsteroidal anti-inflammatory drug (NSAID) use was not collected until the 1992 follow up.

A total of 38,006 participants were cancer free at baseline. Participants who left more than 10% the food frequency questionnaire questions blank (2,499 participants) or had implausible total energy intakes (< 600 or > 5,000 kcal/day; 286 participants) were excluded from the analysis, leaving an analytic cohort of 35,221 participants.

Dietary scores

The Paleolithic and Mediterranean diet pattern scores were constructed in a similar manner, as summarized in Table 1 and described previously(21, 22). The foods and associated point values were determined before analysis. For the most part, 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' intakes at baseline. Higher scores were given for higher intakes of foods that were considered characteristic of the diet pattern, and lower scores were given for lower-to-no consumption of foods that were not considered characteristic of the diet pattern.

For the Paleolithic diet score, we created two unique variables. The first was a fruit and vegetable diversity score, which was created by summing the total number of responses in the fruit and vegetable section of the food frequency questionnaire to which participants reported consuming more than 1-3 servings of a given food item per 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 scores were calculated according to previous literature. However, although Mediterranean diet scores are most often constructed using two categories of intake (high vs. low, based on median intake), in this study, we constructed Mediterranean diet scores based on quintiles of intake to facilitate a more direct comparison of the two diet scores.

The final scores could range from 11 to 55 for the 11-component Mediterranean diet score and from 14 to 70 for the 14-component Paleolithic diet score.

Statistical analysis

The characteristics of the participants were summarized and compared using the χ^2 test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. Cox proportional hazards models were used to calculate hazards ratios (HR) and 95% confidence intervals (CI) for associations of the two dietary scores with incident colorectal cancer. The Paleolithic and Mediterranean diet pattern scores were analyzed as both 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.

On the basis of previous literature and biological plausibility, the following variables were considered as potential confounders: age (years; continuous), family history of colorectal cancer in a first-degree relative (yes/no), smoking status (current, past, never smoker), education (less than high school, high school, more than high school), race, body mass index (weight [kg]/height [m]^2; continuous), physical activity (low, medium, high), total energy intake (kcal/day; continuous), arthritis (yes/no), and use of hormone replacement therapy (current, past, never use). Inclusion in the final models required meeting one or more of the following criteria: biological plausibility, statistical significance, and/or whether inclusion or exclusion of the variable from the model changed the adjusted hazards ratio for the primary exposure variable by ≥10%. The final adjusted models controlled for age, family history of colorectal cancer in a first-degree relative, smoking status, body mass index, physical activity, total energy intake, and use of hormone replacement therapy.

To assess potential effect modification, we conducted separate analyses within each category of the following: age (≤61/>61), family history of colorectal cancer in a first-degree relative (yes/no), smoking status (current or past/never), education (< high school or high school/>high school), body mass index (non-obese [<30 kg/m^2]/obese [≥30 kg/m^2]), physical activity (low or medium/high), total energy intake (≤1717.4 kcal/day/>1717.5 kcal/day), and use of hormone replacement therapy (current or past/never). For age and total energy intake, we used the median values as the cut-points to assess potential effect modification.

To assess the sensitivity of the associations to various factors, we repeated the analyses with the following variations: 1) excluded participants who died or were diagnosed with colorectal cancer within one or two years of follow up, and 2) censored participants when they reached the ages of 75 and 80 years. Because NSAID use is considered causally related to colon carcinogenesis, but information on it was not collected until 1992 after 6 years of follow up, we repeated the analyses using 1992 as the baseline for follow up, and compared the results from when we included or excluded aspirin and other NSAID use from the model. Finally, we investigated whether removing and replacing each component of each score one at a time strongly affected the observed associations for the scores.

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

RESULTS

Selected characteristics of the study participants according to quintiles of the Paleolithic and the Mediterranean diet scores at baseline are presented in Tables 2 and 3, respectively. Compared with participants in the lowest quintile of the Paleolithic diet score, those in the highest quintile, on average, had lower total energy and higher calcium intakes, and were more likely to be more educated, have higher physical activity, use hormone replacement therapy, and report a history of arthritis ($P < 0.01$). Compared with participants in the lowest quintile of the Mediterranean diet score, those in the highest quintile, on average, had higher total calcium intakes; were more likely to be more educated, have higher physical activity, and use hormone replacement therapy; and were less likely to report a history of chronic colitis ($P < 0.01$). The Paleolithic diet scores ranged from 19 to 68, while the Mediterranean diet scores ranged from 12 to 52. The correlation between the 2 diet scores was linear and moderately strong ($\rho = 0.68$).

The overall associations of the diet scores with incident colorectal cancer are presented in Table 4. When the diet scores were treated as continuous variables, their associations with colorectal cancer were exactly 1.0. When the scores were categorized according to quintiles, the unadjusted and adjusted associations of the Paleolithic diet scores with colorectal cancer were close to the null value. For the Mediterranean diet scores, there was a modest inverted U-shaped pattern, with the adjusted hazard ratio (HR) in the upper quintile close to the null, but that for the third quintile was 1.18 and statistically significant.

There were no consistent and clear patterns of differences in the associations of the Paleolithic and Mediterranean diet scores with incident colorectal cancer according to age, family history of colorectal cancer in a first-degree relative, smoking status, education, body mass index, physical activity, total energy intake, and use of hormone replacement therapy (Table 5). When we repeated the analyses by 1) excluding those who died or were diagnosed with colorectal cancer within one or two years of follow up, or 2) censoring participants when they reached the ages of 75 and 80 years, the overall associations of the Paleolithic and Mediterranean diet scores with incident colorectal cancer were still close to the null (Table 6). When we used 1992 as the baseline for follow up, and compared the results from when we included or excluded aspirin and other NSAID use from the model, the results (Table 7) were similar to the adjusted hazards ratios in Table 4.

Discussion

Our results do not support our hypothesis that a more Paleolithic-like dietary pattern may be associated with lower risk of incident colorectal cancer, at least in older, white, Midwestern US women. Our results also do not suggest that a Mediterranean-like dietary pattern is associated with lower risk for colorectal cancer in the same population.

The Paleolithic and Mediterranean diet patterns both have several components that could plausibly reduce risk of incident colorectal cancer. Both dietary patterns are high in fruits and vegetables, which may help improve oxidative balance, reduce inflammation, increase dietary fiber intake, and reduce total energy intake, all of which plausibly may reduce colorectal cancer risk, although support for each in epidemiologic studies is mixed(2-4). Both diet patterns are also low in red, processed, and fatty meats, which are thought to increase CRC risk via several mechanisms(5, 6). Of possible relevance to our study is that stronger associations of dietary patterns with CRC have frequently been reported in men, not in women(23, 24); it is unclear whether this may be related to true biological differences in diet effects(25), differences in diet patterns, or differential diet measurement(26).

The Paleolithic diet pattern was examined in one case-control study of incident, sporadic colorectal adenoma, one cross-sectional study with biomarkers of inflammation and oxidative stress as outcomes, and one prospective cohort study of mortality. In the colorectal adenoma case-control study (n = 564 cases identified via outpatient colonoscopy, 1,202 colonoscopy-negative controls, and 535 community controls), which also 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 diet score was 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(22). 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) in an elective outpatient colonoscopy population, 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 C-reactive protein (CRP), a marker of inflammation, and F_2-isoprostanes, a marker of oxidative stress, were measured(21). Diet patterns that were more Paleolithic-like were inversely associated with CRP and F_2-isoprostanes. The findings for CRP 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(27). In the analytic cohort (n = 21,423), for those in the highest relative to the lowest quintiles of the Paleolithic diet score the multivariable adjusted hazard ratios (HR) for all-cause, all-cancer, and all-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.

While to the best of our knowledge there have been no previous studies of an association of a Paleolithic diet score with incident colorectal cancer, three prospective cohort studies investigated Mediterranean diet scores in relation to incident colorectal cancer, generally finding them to be associated with lower CRC risk. The European Prospective Investigation into Cancer and Nutrition (EPIC) study found a 12% lower risk among women in the highest Mediterranean diet score group relative to the lowest (HR 0.88; 95% CI 0.77, 1.01) (13). In the Nurses' Health Study, those in the highest quartile of an Alternate Mediterranean Diet Index score (MDS) were at an estimated 11% lower CRC risk relative to those in the lowest quartile (OR: 0.89; 95% CI: 0.77, 1.01) (28). In the NIH-American Association of Retired Persons (NIH-AARP) Diet and Health Study, there was an estimated 11% lower risk of CRC among women in the highest quintile of a MDS relative to those in the lowest (OR 0.89; 95% CI: 0.72, 1.11) (29). We also note that in the three studies described above in relation to the Paleolithic diet pattern, the findings for the Mediterranean diet score were very similar to those for the Paleolithic diet score.

The reasons for our null results, 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 the Paleolithic or the Mediterranean diet pattern; and limited reassessment of exposures, including diet, during the years of follow up. Other possibilities include chance and that these diet patterns may not reduce risk for colorectal cancer.

Our study had other limitations, but several strengths as well. Other limitations included the known limitations of FFQs (reliance on long-term memory, complex task of estimation and calculation of frequency of intake, etc.), and not having data on NSAID use until after 6 years of follow up. Strengths of the study included that, to our knowledge, it is the first study on an association of a Paleolithic diet score with incident colorectal cancer, the prospective design, large sample size, long follow up, and the standardized, nearly 100% complete information on cancer diagnoses.

In conclusion, our findings, which are inconsistent with previous literature, do not support that consuming a more Paleolithic- or Mediterranean-like diet may be associated with lower risk for incident colorectal cancer in older, white, Midwestern women. Given previous literature and the limitations of our study, further investigation of these dietary patterns in prospectively followed cohorts with a wide range of dietary exposures (and sufficient numbers of participants in the more extreme portions of the range), measured at intervals over the years, is needed.

Table 1. Constituents and Construction of the Paleolithic and Mediterranean Diet Pattern Scores at Baseline in the Prospective Iowa Women's Health Study (n = 35,221), 1986 – 2012[a]

Constituents	Paleolithic 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 and 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 were measured in servings/week unless otherwise indicated. Highest intake "best": No. of points assigned to each quintile = quintile rank (e.g., highest and lowest quintiles scored +5 and +1 points, respectively); Lowest intake "best": No. of 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 Paleolithic diet score had 14 components; range of possible scores, 14 – 70.

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

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

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

[f] Intake of calcium from sources other than 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 Paleolithic Diet Score at Baseline in the Iowa Women's Health Study (n = 35,221), 1986 – 2012

Characteristics[a]	Paleolithic Diet Score Quintiles					P[b]
	1 (n = 7,846)	2 (n = 7,171)	3 (n = 7,695)	4 (n = 7,744)	5 (n = 6,260)	
Age, years	61.3 (4.2)	61.4 (4.2)	61.6 (4.2)	61.7 (4.2)	61.6 (4.2)	<0.01
White race, %	99.4	99.3	99.3	98.9	99.0	<0.01
Body mass index, kg/m^2	26.6 (5.0)	26.9 (5.1)	27.0 (5.0)	27.1 (5.2)	27.0 (5.0)	<0.01
First-degree relative with colorectal cancer, %	3.1	3.0	3.2	3.0	3.4	0.62
Current or past HRT use, %	35.2	37.1	39.0	40.0	43.8	<0.01
History of arthritis, %	51.0	52.6	52.9	53.9	53.5	0.01
History of rectal/colon polyps, %	6.9	6.7	6.4	7.1	6.3	0.31
History of chronic colitis, %	6.3	6.1	6.0	6.0	5.9	0.74
Current or past smoker, %	36.8	34.8	33.3	32.5	33.7	<0.01
More than a high school education, %	31.2	36.2	40.7	44.6	49.6	<0.01
High physical activity, %	15.9	20.2	24.1	29.1	38.9	<0.01
Total energy intake, kcal/day	2,021 (605)	1,837 (633)	1,770 (619)	1,718 (581)	1,590 (481)	<0.01
Total calcium intake[c], mg/day	983 (493)	1,024 (537)	1,096 (562)	1,156 (567)	1,259 (580)	<0.01
Dietary calcium intake, mg/day	839 (390)	806 (403)	806 (410)	798 (399)	763 (374)	<0.01
Total fat, gm/day	82.7 (28.7)	72.0 (28.2)	67.0 (26.6)	62.5 (24.4)	54.2 (20.0)	<0.01
Saturated fat, gm/day	30.0 (11.2)	25.5 (10.6)	23.4 (10.0)	21.5 (8.8)	18.1 (7.0)	<0.01
Dietary fiber, gm/day	17.9 (6.8)	18.6 (7.8)	19.7 (8.2)	20.9 (8.3)	22.2 (8.3)	<0.01
Alcohol, gm/day	4.8 (10.1)	4.1 (9.5)	3.6 (8.4)	3.2 (7.8)	2.9 (7.7)	<0.01
Protein, gm/day	84.9 (29.2)	80.2 (31.1)	80.0 (31.3)	80.2 (31.2)	78.6 (27.3)	<0.01
Carbohydrates, gm/day	235 (81)	220 (83)	216 (83)	214 (24)	203 (70)	<0.01

Abbreviations: SD, standard deviation; HRT, hormone replacement therapy.

[a] Continuous variables presented as mean ± SD, 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] Total = diet + supplements

Table 3. Selected Characteristics of Participants according to Quintiles of Mediterranean Diet Scores at Baseline in the Prospective Iowa Women's Health Study (n = 35,221), 1986 – 2012

Characteristics[a]	**Mediterranean Diet Score Quintiles**					***P***[b]
	1 (n = 8,490)	2 (n = 6,710)	3 (n = 6,999)	4 (n = 5,986)	5 (n = 7,036)	
Age, years	61.2 (4.2)	61.6 (4.2)	61.7 (4.2)	61.6 (4.2)	61.5 (4.2)	<0.01
White race, %	99.1	99.2	99.2	99.2	99.3	0.13
Body mass index, kg/m^2	27.1 (5.3)	26.9 (5.1)	27.0 (5.0)	27.0 (5.0)	26.7 (4.8)	<0.01
First-degree relative with colorectal cancer, %	3.1	3.1	2.8	3.5	3.0	0.27
Current or past HRT use, %	35.6	37.2	38.5	40.6	42.4	<0.01
History of arthritis, %	53.7	52.1	52.6	52.9	51.9	0.18
History of rectal/colon polyps, %	6.7	6.4	6.7	6.6	6.9	0.46
History of chronic colitis, %	6.4	6.1	5.9	6.4	5.5	<0.01
Current or past smoker, %	35.6	33.9	23.7	33.0	35.9	<0.01
More than a high school education, %	30.7	37.2	40.3	43.6	50.4	<0.01
High physical activity, %	16.8	21.6	24.4	28.4	35.8	<0.01
Total energy intake, kcal/day	1,778 (656)	1,764 (627)	1,794 (609)	1,832 (597)	1,784 (509)	<0.01
Total calcium intake[c], mg/day	1,026 (574)	1,055 (558)	1,086 (542)	1,138 (538)	1,154 (527)	<0.01
Dietary calcium intake, mg/day	809 (460)	787 (418)	796 (390)	819 (367)	782 (305)	<0.01
Total fat, gm/day	72.7 (30.6)	68.7 (28.5)	68.1 (27.4)	67.3 (26.6)	64.3 (23.3)	<0.01
Saturated fat, gm/day	27.1 (12.3)	24.5 (10.9)	23.7 (10.0)	22.9 (9.4)	21.0 (7.9)	<0.01
Dietary fiber, gm/day	12.6 (7.1)	18.3 (7.4)	19.9 (7.7)	21.5 (7.9)	23.7 (7.8)	<0.01
Alcohol, gm/day	3.2 (9.8)	3.4 (9.3)	3.5 (8.5)	3.9 (8.3)	4.9 (7.9)	<0.01
Protein, gm/day	78.4 (31.8)	77.6 (30.5)	80.4 (30.8)	83.6 (29.8)	85.3 (26.7)	<0.01
Carbohydrates, gm/day	205 (84)	212 (80)	219 (80)	227 (80)	232 (74)	<0.01

Abbreviations: SD, standard deviation; HRT, hormone replacement therapy.
[a] Continuous variables presented as mean ± SD, 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] Total = diet + supplements

Table 4. Associations of Paleolithic and Mediterranean Diet Scores with Incident Colorectal Cancer in the Iowa Women's Health Study (n = 35,221), 1986 – 2012

	Paleolithic Diet Score				**Mediterranean Diet Score**			
Diet Score Variable	**Crude HR**	**95% CI**	**Adjusted HR[a]**	**95% CI**	**Crude HR**	**95% CI**	**Adjusted HR[a]**	**95% CI**
Continuous variable	1.00	0.99, 1.01	1.00	0.99, 1.01	1.00	0.99, 1.01	1.00	0.99, 1.01
Quintiles								
1	1.00	-	1.00	-	1.00	-	1.00	-
2	1.02	0.88, 1.17	1.02	0.88, 1.19	1.11	0.96, 1.29	1.10	0.95, 1.28
3	1.00	0.87, 1.15	1.01	0.87, 1.17	1.19	1.03, 1.37	1.18	1.02, 1.36
4	1.01	0.87, 1.18	1.01	0.86, 1.18	1.02	0.87, 1.19	1.01	0.86, 1.19
5	0.99	0.85, 1.16	1.01	0.85, 1.19	0.97	0.83, 1.12	1.01	0.86, 1.18
P for trend	0.95		0.85		0.52		0.98	

Abbreviations: HR, hazards ratio; CI, confidence interval
[a] HR 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), race, 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).

Table 5. Associations of Paleolithic and Mediterranean Diet Scores with Incident Colorectal Cancer in the Iowa Women's Health Study (n = 35,221), According to Potential Effect Modifiers, 1986 – 2012

	Paleolithic Diet Score		**Mediterranean Diet Score**	
Diet Score Variable	**Adjusted HR[a]**	**95% CI**	**Adjusted HR[a]**	**95% CI**
Age, years				
≤61				
1	1.00	-	1.00	-
2	0.96	0.78, 1.19	1.12	0.91, 1.39
3	0.95	0.76, 1.17	1.11	0.90, 1.38
4	0.95	0.76, 1.19	0.97	0.77, 1.23
5	0.91	0.72, 1.16	1.00	0.80, 1.25
P for trend	0.47		0.56	
>61				
1	1.00	-	1.00	-
2	1.09	0.94, 1.42	1.10	0.90, 1.35
3	1.08	0.92, 1.39	1.24	1.02, 1.51
4	1.08	0.92, 1.43	1.09	0.88, 1.35
5	1.14	0.89, 1.40	1.02	0.83, 1.27
P for trend	0.30		0.63	
P for interaction	0.72		0.89	
Family history of colorectal cancer				
Yes				
1	1.00	-	1.00	-
2	0.95	0.75, 1.20	1.29	1.03, 1.62
3	1.10	0.88, 1.37	1.19	0.94, 1.50
4	0.97	0.75, 1.23	1.06	0.83, 1.36
5	0.97	0.76, 1.25	1.03	0.81, 1.32
P for trend	0.76		0.96	
No				
1	1.00	-	1.00	-
2	1.07	0.88, 1.29	0.99	0.81, 1.20
3	0.94	0.78, 1.14	1.16	0.97, 1.40
4	1.04	0.85, 1.27	1.00	0.82, 1.23
5	1.07	0.87, 1.31	0.99	0.81, 1.20
P for trend	0.57		0.90	
P for interaction	0.41		0.41	
Smoking status				
Current or former				
1	1.00	-	1.00	-
2	0.84	0.65, 1.09	1.06	0.82, 1.38
3	1.02	0.79, 1.30	1.22	0.95, 1.57
4	0.94	0.72, 1.23	1.05	0.80, 1.38
5	1.04	0.80, 1.36	0.98	0.76, 1.27

P for trend	0.84		0.71	
Never				
1	1.00	-	1.00	-
2	1.12	0.93, 1.34	1.12	0.94, 1.34
3	1.00	0.84, 1.20	1.15	0.97, 1.37
4	1.04	0.86, 1.26	1.02	0.84, 1.23
5	1.02	0.84, 1.25	1.02	0.84, 1.23
P for trend	0.98		0.89	
P for interaction	0.31		0.96	
Education				
≤ High school				
1	1.00	-	1.00	-
2	1.02	0.85, 1.22	1.04	0.87, 1.25
3	0.97	0.81, 1.16	1.06	0.89, 1.27
4	0.92	0.76, 1.13	0.93	0.77, 1.14
5	1.06	0.87, 1.30	1.01	0.83, 1.22
P for trend	0.99		0.80	
>High school				
1	1.00	-	1.00	-
2	1.05	0.79, 1.35	1.27	0.97, 1.66
3	1.09	0.84, 1.39	1.45	1.12, 1.86
4	1.14	0.89, 1.49	1.24	0.95, 1.62
5	1.01	0.78, 1.31	1.08	0.83, 1.40
P for trend	0.74		0.85	
P for interaction	0.50		0.24	
Body mass index				
Non-obese [<30 kg/m^2]				
1	1.00	-	1.00	-
2	0.98	0.82, 1.15	1.06	0.89, 1.26
3	0.95	0.80, 1.12	1.17	0.99, 1.39
4	0.92	0.77, 1.11	1.06	0.88, 1.27
5	0.92	0.77, 1.11	0.95	0.79, 1.14
P for trend	0.30		0.51	
Obese [≥30 kg/m^2]				
1	1.00	-	1.00	-
2	1.21	0.89, 1.65	1.23	0.93, 1.63
3	1.25	0.93, 1.70	1.18	0.89, 1.56
4	1.35	0.99, 1.85	0.95	0.69, 1.30
5	1.46	1.07, 2.01	1.19	0.89, 1.60
P for trend	0.02		0.37	
P for interaction	0.12		0.41	
Total energy intake				
≤1,717.4 kcal/day				

1	1.00	-	1.00	-
2	1.09	0.86, 1.36	1.02	0.83, 1.24
3	1.00	0.80, 1.25	1.19	0.98, 1.45
4	1.02	0.81, 1.29	0.93	0.75, 1.16
5	1.07	0.86, 1.35	1.03	0.84, 1.28
P for trend	0.85		0.97	
>1,717.5 kcal/day				
1	1.00	-	1.00	-
2	0.97	0.79, 1.18	1.21	0.98, 1.50
3	1.03	0.84, 1.25	1.16	0.93, 1.43
4	1.01	0.81, 1.25	1.13	0.90, 1.41
5	0.97	0.76, 1.24	0.98	0.79, 1.23
P for trend	0.88		0.90	
P for interaction	0.86		0.38	
Use of HRT				
Current or past				
1	1.00	-	1.00	-
2	1.15	0.89, 1.48	1.17	0.91, 1.52
3	1.05	0.81, 1.35	1.24	0.97, 1.60
4	1.03	0.79, 1.35	0.99	0.75, 1.30
5	0.93	0.71, 1.22	1.04	0.80, 1.34
P for trend	0.18		0.74	
Never				
1	1.00	-	1.00	-
2	0.96	0.80, 1.15	1.07	0.89, 1.28
3	0.98	0.82, 1.17	1.14	0.96, 1.36
4	0.99	0.82, 1.20	1.05	0.87, 1.27
5	1.09	0.90, 1.33	0.99	0.82, 1.20
P for trend	0.23		0.93	
P for interaction	0.37		0.89	

Abbreviations: HR, hazards ratio; CI, confidence interval; HRT, hormone replacement therapy

[a] HR 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), race, 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 (HRT) (current, past, never).

[b] In a first degree relative

Table 6. Associations of Paleolithic and Mediterranean Diet Scores with Incident Colorectal Cancer in the Iowa Women's Health Study (n = 35,221), after Excluding Patients Who Died or Were Diagnosed with Colorectal Cancer within One or Two Years of Follow Up, and after Censoring Participants When They Reached the Ages of 75 and 80 years, 1986 – 2012

	Paleolithic Diet Score		Mediterranean Diet Score	
Diet Score Variable	**Adjusted HR[a]**	**95% CI**	**Adjusted HR[a]**	**95% CI**
Excluding				
One Year				
1	1.00	-	1.00	-
2	1.00	0.86, 1.17	1.10	0.95, 1.28
3	1.01	0.87, 1.17	1.16	1.00, 1.34
4	1.00	0.85, 1.18	1.04	0.88, 1.22
5	1.02	0.87, 1.21	1.00	0.86, 1.17
P for trend	0.80		0.91	
Two Year				
1	1.00	-	1.00	-
2	1.01	0.87, 1.18	1.12	0.96, 1.30
3	1.01	0.87, 1.18	1.15	0.99, 1.33
4	0.99	0.84, 1.17	1.03	0.87, 1.21
5	1.04	0.88, 1.24	1.00	0.85, 1.18
P for trend	0.71		0.86	
Censoring age, years				
75				
1	1.00	-	1.00	-
2	1.02	0.88, 1.18	1.11	0.96, 1.29
3	1.00	0.86, 1.17	1.19	1.03, 1.38
4	1.00	0.86, 1.16	1.03	0.88, 1.21
5	1.02	0.86, 1.20	1.02	0.87, 1.19
P for trend	0.90		0.92	
80				
1	1.00	-	1.00	-
2	1.02	0.88, 1.18	1.11	0.96, 1.29
3	1.00	0.86, 1.16	1.18	1.02, 1.36
4	1.00	0.86, 1.18	1.03	0.88, 1.21
5	1.03	0.87, 1.21	1.02	0.87, 1.19
P for trend	0.83		1.00	

Abbreviations: HR, hazards ratio; CI, confidence interval

[a] HR 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), race, 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 (HRT) (current, past, never).

Table 7. Associations of Paleolithic and Mediterranean Diet Scores using Incident Colorectal Cancer in the Iowa Women's Health Study (n = 28,309) with 1992 as the Baseline, Stratified by Aspirin and Other NSAID Use, 1992 – 2012

	Paleolithic Diet Score		**Mediterranean Diet Score**	
Diet Score Variable	**Adjusted HR[a]**	**95% CI**	**Adjusted HR[a]**	**95% CI**
Aspirin and Other NSAID Use				
Included				
1	1.00	-	1.00	-
2	1.01	0.84, 1.22	1.07	0.88, 1.29
3	0.99	0.83, 1.19	1.25	1.04, 1.49
4	1.02	0.84, 1.24	1.05	0.87, 1.26
5	1.03	0.84, 1.26	1.00	0.82, 1.23
P for trend	0.80		0.88	
Excluded				
1	1.00	-	1.00	-
2	1.02	0.85, 1.22	1.07	0.88, 1.29
3	0.99	0.82, 1.19	1.24	1.04, 1.48
4	1.02	0.84, 1.24	1.04	0.87, 1.25
5	1.02	0.83, 1.25	1.00	0.81, 1.22
P for trend	0.85		0.95	

Abbreviation: HR, hazards ratio; CI, confidence interval; NSAID, Non-Steroidal Anti-Inflammatory Drug

[a] HR 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), race, body mass index (weight [kg]/height [m]^2; continuous), physical activity (low, medium, high), total energy intake (kcal/day; continuous), Aspirin and Other NSAIDs Use (yes/no), and hormone replacement therapy use (HRT) (current, past, never).

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