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Original Contribution

Paleolithic and Mediterranean Diet Pattern Scores and Risk of Incident, Sporadic Colorectal Adenomas

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The Western dietary pattern is associated with higher risk of colorectal neoplasms. Evolutionary discordance could explain this association. We investigated associations of scores for 2 proposed diet patterns, the "Paleolithic" and the Mediterranean, with incident, sporadic colorectal adenomas in a case-control study of colorectal polyps conducted in Minnesota (1991–1994). Persons with no prior history of colorectal neoplasms completed comprehensive questionnaires prior to elective, outpatient endoscopy; of these individuals, 564 were identified as cases and 1,202 as endoscopy-negative controls. An additional group of community controls frequency-matched on age and sex ($n = 535$) was also recruited. Both diet scores were calculated for each participant and categorized into quintiles, and associations were estimated using unconditional logistic regression. The multivariable-adjusted odds ratios comparing persons in the highest quintiles of the Paleolithic and Mediterranean diet scores relative to the lowest quintiles were, respectively, 0.71 (95% confidence interval (CI): 0.50, 1.02; $P_{trend} = 0.02$) and 0.74 (95% CI: 0.54, 1.03; $P_{trend} = 0.05$) when comparing cases with endoscopy-negative controls and 0.84 (95% CI: 0.56, 1.26; $P_{trend} = 0.14$) and 0.77 (95% CI: 0.53, 1.11; $P_{trend} = 0.13$) when comparing cases with community controls. These findings suggest that greater adherence to the Paleolithic diet pattern and greater adherence to the Mediterranean diet pattern may be similarly associated with lower risk of incident, sporadic colorectal adenomas.

case-control studies; colorectal neoplasms; diet; dietary pattern; Mediterranean diet; Paleolithic diet

Abbreviations: CI, confidence interval; CRC, colorectal cancer; EPIC, European Prospective Investigation into Cancer and Nutrition; MET, metabolic equivalent of task; NSAID, nonsteroidal antiinflammatory drug.

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second-leading cause of cancer mortality in the United States (1). Rapidly increasing incidence rates in previously low-incidence populations in urban China and Japan and among male Polynesians in Hawaii have coincided with the adoption of a more westernized lifestyle by those populations (2). These changing incidence rates, along with studies of immigrant populations (2), point to a strong influence of diet and other lifestyle factors on CRC risk. Many epidemiologic studies, but not all, have found diets high in fruits and vegetables to be associated with lower risk of CRC (2, 3). Epidemiologic studies on high-fat diets and high meat consumption have generally found weak, inconsistent evidence of higher risk of CRC (2, 4), with consumption of red and processed meats being more convincingly associated with higher CRC risk (4). However, several trials that tested interventions with low-fat diets, fiber supplements, or antioxidant supplements were unsuccessful in reducing the recurrence of colorectal adenomatous polyps (5, 6)—the precursors of most CRCs (6–8).

Because no single dietary constituent appears responsible for the majority of CRC risk, it may be more useful for future public health recommendations to characterize diet patterns and their relationships to risk of CRC. Dietary patterns are helpful in studying the associations of total diet with health outcomes, and they can be data-driven and flexible enough to examine many different theoretical diets. Several published studies used food frequency questionnaire responses to create various dietary patterns either by using purely data-driven methods (e.g., principal component, factor, and cluster analyses) or

Table 1. Constituents and Construction of the Paleolithic and Mediterranean Diet Pattern Scores in a Case-Control Study of 2 Diet Pattern Scores and Risk of Incident, Sporadic Colorectal Adenomas, Minneapolis-St. Paul, Minnesota, 1991–1994[a]

Intake Category	Scoring	Paleolithic Diet Score[b]	Mediterranean Diet Score[c]
Highest intake "best"	No. of points assigned to each quintile = quintile rank (e.g., highest and lowest quintiles scored +5 and +1 points, respectively)	Vegetables	Vegetables
		Fruits	Fruits
		Fruit and vegetable diversity[d]	Lean meats[e]
		Lean meats[e]	Fish
		Fish	Nuts
		Nuts	Monounsaturated:saturated fat ratio
		Calcium[f]	
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)	Red and processed meats[g]	Red and processed meats[g]
		Sodium	Sodium, mg
		Dairy foods	
		Grains and starches	
		Baked goods[h]	
		Sugar-sweetened beverages	
		Alcohol, drinks/week	
Moderate intake "best"	Third quintile scored +5 points, second and fourth quintiles scored +3 points, and first and fifth quintiles scored +1 point		Dairy foods
			Grains and starches
Other			Alcohol—
			Women: 5–15 g/day (+5 points)
			Men: 10–25 g/day (+5 points)
			Outside of sex-specific range (+1 point)

[a] All constituents were measured in servings/week unless otherwise indicated.
[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] Fruit and vegetable diversity was calculated by summing the total number of responses in the food frequency questionnaire fruit and vegetable sections that indicated that the participant consumed more than 1–3 servings of a given food item per month.
[e] Lean meats included skinless chicken or turkey and lean beef.
[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 nonlean red meat combined.
[h] Baked goods included items such as cake, pie, and other pastry-type foods.

by constructing index-driven diet patterns in order to investigate associations of diet with CRC risk (9–17). A commonly examined pattern is the Mediterranean diet, which was characteristic of countries in the Mediterranean region circa 1960, when life expectancy there was among the highest in the world (18). The Mediterranean diet is characterized by high intake of fruits, vegetables, nuts, fish, and whole grains, moderate amounts of alcohol and dairy products, and low quantities of red or processed meats and sweets (18). One small observational study within a clinical trial cohort found that a Mediterranean diet pattern was associated with lower risk of colorectal adenoma recurrence, though only in women (19). While the Mediterranean diet is considered healthier than the Western diet, which is high in fat, sugar, and refined carbohydrates, it has also been proposed that a dietary pattern more consistent with foods that would have been available during late human evolution may be ideal for preventing modern chronic diseases, including cancer (20).

The evolutionary discordance hypothesis (21) is that the rapid increase in many chronic conditions and diseases over the past century stems from recent changes in diet and lifestyle patterns relative to those pursued by our evolutionary ancestors. Anthropologists have constructed a "Paleolithic diet" that describes the general diet *Homo sapiens* would have had prior to the development of agriculture (20). The Paleolithic diet pattern is characterized by a wide diversity of fruits and vegetables, lean meats, eggs, and nuts; it excludes grains, dairy products, refined fats, and sugar, and is very low in salt. While to our knowledge there are no reported observational studies on the Paleolithic diet pattern and risk of chronic diseases, there have been a few reported small pilot trials and 1 longer Paleolithic diet intervention study (22–25). In the pilot trials, the Paleolithic diet as compared with the Mediterranean diet appeared to provide better glucose control, increased weight loss, and reduced waist circumference after 12 weeks (25). When directed to follow a Paleolithic diet, obese postmenopausal women lost significantly more weight after 6 months than those on a conventional healthy diet, though this difference was mostly attenuated after 2 years (24).

Table 2. Selected Characteristics of Participants in a Case-Control Study of 2 Diet Pattern Scores and Risk of Incident, Sporadic Colorectal Adenomas ($n = 2,301$), Minneapolis-St. Paul, Minnesota, 1991–1994

Characteristic	Cases ($n = 564$)		Endoscopy Controls[a] ($n = 1,202$)			Community Controls ($n = 535$)		
	Mean (SD)	%	Mean (SD)	%	*P* Value[b]	Mean (SD)	%	*P* Value[b]
Age, years	58.1 (9.7)		46.5 (6.4)		<0.01	57.7 (10.4)		0.46
Male sex		61.7		38.8	<0.01		55.1	0.03
White race/ethnicity		97.7		97.2	0.44		97.2	0.47
First-degree relative with colon cancer		16.1		20.0	0.06		6.9	<0.01
Never smoker		32.5		46.3	<0.01		44.1	<0.01
Physical activity, MET-hours/week	9.5 (9.5)		8.9 (8.3)		0.13	9.9 (9.7)		0.57
Body mass index[c]	27.4 (4.7)		26.6 (4.9)		<0.01	26.8 (4.5)		0.05
Current ethanol intake, g/day	5.2 (7.6)		3.6 (7.8)		<0.01	4.5 (8.8)		0.22
Regular (≥once/week) use of NSAIDs		36.4		46.6	<0.01		39.4	0.29
Education, years	14.0 (3.3)		14.5 (3.2)		<0.01	14.1 (2.9)		0.36
Use of hormone replacement therapy[d]		14.8		66.3	<0.01		18.9	0.25
Total energy intake, kcal/day	2,090.7 (775.7)		2,002.5 (718.3)		0.02	2,054.5 (719.2)		0.42
Paleolithic diet score	41.3 (6.7)		41.8 (6.7)		0.13	42.1 (6.7)		0.05
Mediterranean diet score	29.2 (5.6)		29.3 (5.4)		0.05	29.7 (5.4)		0.13
Total calcium intake, mg/day	959.4 (531.1)		990.1 (518.3)		0.25	987.7 (552.4)		0.39
Dietary	860.4 (455.0)		837.9 (428.8)		0.31	882.8 (470.1)		0.42
Supplemental	99.0 (269.2)		152.2 (329.5)		<0.01	104.9 (262.5)		0.71
Dietary fiber intake, g/day	21.8 (9.6)		22.3 (10.2)		0.34	22.2 (9.7)		0.46
Total fat intake, g/day	73.1 (34.4)		66.8 (30.3)		<0.01	70.2 (31.3)		0.15
Total red and processed meat intake, servings/week	7.3 (6.1)		6.1 (4.9)		<0.01	6.9 (5.6)		0.16
Total fruit and vegetable intake, servings/week	42.3 (23.7)		45.6 (26.9)		0.01	44.5 (23.5)		0.12

Abbreviations: MET, metabolic equivalent of task; NSAID, nonsteroidal antiinflammatory drug; SD, standard deviation.
[a] Endoscopy controls included those who had a colonoscopy and those who had only a flexible sigmoidoscopy.
[b] *P* values were calculated using χ^2 tests for categorical variables and 2-sample *t* tests for continuous variables.
[c] Weight (kg)/height $(m)^2$.
[d] In women ($n = 883$).

By examining dietary patterns rather than specific food groups, we may more realistically and robustly account for the relationships of multiple weak and probably interacting associations of foods and nutrients with colorectal adenoma risk. In this study, we evaluated associations of both the Mediterranean and Paleolithic dietary patterns with frequency of newly diagnosed, sporadic colorectal adenoma in a US case-control study of adult men and women.

METHODS

Study population and data collection

In the University of Minnesota Cancer Prevention Research Unit, a temporary, multi-institution research program, case-control study data were collected between April 1991 and April 1994 as part of a joint project between the University of Minnesota (Minneapolis, Minnesota) and a large, multiclinic private gastroenterology practice (26, 27). The gastroenterology practice performed colonoscopies and sigmoidoscopies in 10 hospitals and endoscopy units and, at the time of the study, was responsible for approximately 60% of all colonoscopies in the Minneapolis metropolitan area. The institutional review boards of the University of Minnesota and each endoscopy site approved the study. Written informed consent was obtained from each study participant.

The gastroenterology practice staff initiated study recruitment while scheduling elective, outpatient colonoscopies or flexible sigmoidoscopies ("endoscopies"). All 10 of the practices' endoscopy sites recruited patients. Initial eligibility for study participation required that patients be 30–74 years of age, residents of the Minneapolis-St. Paul metropolitan area, English-speaking, and free of known genetic syndromes associated with a predisposition to colonic neoplasia and that they have no individual history of inflammatory bowel disease, adenomatous polyps, or cancers (except for nonmelanoma skin cancer).

Mailed questionnaires were completed prior to endoscopy and returned at the endoscopy visit, and blood samples were drawn. The endoscopists recorded polyp locations and in vivo sizes and shapes on standardized forms. All polyps were removed and examined histologically by a single index study pathologist using National Polyp Study diagnostic criteria (28).

Table 3. Associations of Paleolithic and Mediterranean Diet Scores With Incident, Sporadic Colorectal Adenomas in a Case-Control Study, Minneapolis-St. Paul, Minnesota, 1991–1994

Diet Score Variable	Cases vs. Endoscopy-Negative Controls[a]								Cases vs. Community Controls							
	Paleolithic Diet Score				Mediterranean Diet Score				Paleolithic Diet Score				Mediterranean Diet Score			
	Crude OR	95% CI	Adjusted OR[b]	95% CI	Crude OR	95% CI	Adjusted OR[b]	95% CI	Crude OR	95% CI	Adjusted OR[b]	95% CI	Crude OR	95% CI	Adjusted OR[b]	95% CI
Continuous variable	0.99	0.97, 1.01	0.98	0.98, 1.01	0.99	0.98, 1.01	0.98	0.96, 1.00	0.98	0.97, 1.00	0.98	0.96, 1.00	0.98	0.96, 1.00	0.98	0.96, 1.00
Quintiles																
1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00								
2	0.96	0.71, 1.29	0.95	0.69, 1.32	0.79	0.59, 1.07	0.76	0.55, 1.05	1.12	0.78, 1.60	1.04	0.72, 1.51	0.69	0.49, 0.99	0.70	0.49, 1.02
3	0.85	0.63, 1.15	0.83	0.60, 1.15	0.87	0.65, 1.18	0.87	0.63, 1.21	0.91	0.64, 1.30	0.84	0.58, 1.22	0.79	0.55, 1.12	0.78	0.54, 1.13
4	0.80	0.58, 1.10	0.70	0.49, 0.99	0.77	0.56, 1.05	0.66	0.47, 0.94	0.73	0.50, 1.06	0.71	0.48, 1.05	0.71	0.49, 1.04	0.67	0.45, 0.99
5	0.83	0.60, 1.15	0.71	0.50, 1.02	0.88	0.65, 1.19	0.74	0.54, 1.03	0.85	0.58, 1.24	0.84	0.56, 1.26	0.79	0.55, 1.12	0.77	0.53, 1.11
P for trend	0.14		0.02		0.31		0.05		0.11		0.14		0.18		0.13	

Abbreviations: CI, confidence interval; MET, metabolic equivalent of task; OR, odds ratio.

[a] Endoscopy controls included those who had a colonoscopy and those who had only a flexible sigmoidoscopy.

[b] OR from an unconditional regression model. Covariates included age (years; continuous), sex, family history of colon cancer in a first-degree relative (yes/no), regular (≥once/week) use of nonsteroidal antiinflammatory drugs (categorical), body mass index (weight (kg)/height $(m)^2$; continuous), physical activity (MET-hours/week; continuous), total energy intake (kcal/day; continuous), and use of hormone replacement therapy (in women; categorical).

Based on the endoscopy and pathology findings, participants were assigned final eligibility and case/control status. To be eligible as an adenoma case or a colonoscopy-negative control, the participant must have undergone a complete colonoscopy reaching the cecum, have had all polyps removed, not have a new diagnosis of inflammatory bowel disease, and have no polyps with invasive carcinoma ($n = 684$). Sigmoidoscopy-negative controls had similar eligibility requirements but completed only a flexible sigmoidoscopy ($n = 518$). Endoscopy controls were free of both adenomatous and hyperplastic polyps at endoscopy. The participation rate for all colonoscoped patients was 68%.

In addition to the endoscopy controls, a separate group of potential community controls ($n = 535$) was randomly selected from the 1991 Minnesota State Driver's License Registry and frequency-matched to the cases on age (5-year intervals), sex, and zip code. The community control participants were included in the study only if they met the same eligibility criteria as the colonoscopy patients, except that they did not undergo colonoscopy or sigmoidoscopy for confirmation of their current polyp status. The participation rate of the community controls was 65%.

Study participants provided detailed information on demographic characteristics, personal medical history, smoking history, usual physical activity, anthropometric factors, reproductive history and hormone use (women only), and family history of cancer. The frequency of nonsteroidal antiinflammatory drug (NSAID) use (aspirin and/or any other NSAID) was assessed as the number of pills taken per week. A self-administered, 166-item modified semiquantitative Willett food frequency questionnaire was used to assess food and nutritional supplement intakes over the previous 12 months. A standard portion size and 9 possible frequency-of-consumption responses, ranging from "never or less than once per month" to "6 or more times per day," were given for each food. Total energy and nutrient intakes were calculated by adding energy and nutrients from all food sources using the dietary database developed by Willett and his colleagues (29, 30).

A total of 2,301 participants completed the study and were included in this analysis, including 564 cases, 1,202 endoscopy controls, and 535 community controls. Participants who left more than 10% of the food frequency questionnaire questions blank (8 cases, 37 endoscopy-negative controls, and 14 community controls) or had implausible total energy intakes (<600 kcal/day or >5,000 kcal/day; 2 cases, 6 endoscopy-negative controls, and 1 community control) were excluded from the analyses.

Dietary scores

The Paleolithic and Mediterranean diet pattern scores were constructed in a similar manner, as summarized in Table 1. The foods and associated point values were determined before analysis using published dietary guidelines for each diet (14, 20, 31). For the most part, each study participant was assigned a quintile rank (and a score from 1 to 5) of intake for each food category, based on the sex-specific distribution of intake in the community controls. Higher scores were given for higher intakes of foods that were considered characteristic of the diet pattern and for lower-to-no consumption of foods

Table 4. Associations of Paleolithic and Mediterranean Diet Scores With Incident, Sporadic Colorectal Adenomas in a Case-Control Study, According to Selected Risk Factors for Colorectal Neoplasms, Minneapolis-St. Paul, Minnesota, 1991–1994

Risk Factor and Quintile of Diet Pattern Score	Endoscopy-Negative Controls[a]				Community Controls			
	Paleolithic Diet Score		Mediterranean Diet Score		Paleolithic Diet Score		Mediterranean Diet Score	
	Adjusted OR[b]	95% CI	Adjusted OR[b]	95% CI	Adjusted OR[b]	95% CI	Adjusted OR[b]	95% CI
Sex								
Male								
1	1.00		1.00		1.00		1.00	
2	0.86	0.57, 1.32	0.60	0.39, 0.94	0.94	0.59, 1.48	0.75	0.47, 1.20
3	0.74	0.45, 1.22	0.64	0.40, 1.04	0.60	0.35, 1.01	0.82	0.49, 1.37
4	0.68	0.40, 1.14	0.38	0.23, 0.61	0.75	0.44, 1.30	0.54	0.33, 0.89
5	0.49	0.31, 0.77	0.58	0.36, 0.95	0.73	0.44, 1.20	0.76	0.45, 1.26
P for trend	<0.01		0.01		0.11		0.13	
Female								
1	1.00		1.00		1.00		1.00	
2	1.00	0.60, 1.64	0.86	0.52, 1.42	0.98	0.54, 1.79	0.75	0.41, 1.35
3	1.08	0.68, 1.73	1.11	0.65, 1.92	1.12	0.64, 1.97	0.71	0.37, 1.34
4	0.83	0.46, 1.50	1.16	0.73, 1.84	0.86	0.44, 1.71	0.97	0.55, 1.71
5	1.20	0.70, 2.04	1.17	0.70, 1.96	0.91	0.49, 1.68	0.94	0.50, 1.74
P for trend	0.71		0.36		0.71		0.99	
P for interaction	0.07		0.16		0.15		0.66	
Body mass index[c]								
Normal weight or underweight (<25)								
1	1.00		1.00		1.00		1.00	
2	0.86	0.47, 1.56	0.98	0.56, 1.71	0.80	0.41, 1.57	0.94	0.50, 1.77
3	0.81	0.46, 1.40	0.96	0.49, 1.88	1.35	0.71, 2.58	0.78	0.36, 1.65
4	0.91	0.49, 1.70	0.93	0.54, 1.62	0.89	0.44, 1.79	1.07	0.56, 2.06
5	0.90	0.48, 1.66	1.35	0.76, 2.39	0.98	0.49, 1.96	1.22	0.63, 2.36
P for trend	0.83		0.37		0.87		0.51	
Overweight or obese (≥25)								
1	1.00		1.00		1.00		1.00	
2	1.17	0.79, 1.72	0.72	0.48, 1.08	0.95	0.61, 1.47	0.67	0.43, 1.06
3	0.92	0.59, 1.41	0.86	0.57, 1.29	0.61	0.38, 0.97	0.75	0.47, 1.18
4	0.63	0.41, 0.96	0.54	0.35, 0.81	0.59	0.37, 0.95	0.58	0.37, 0.92
5	0.65	0.42, 1.01	0.56	0.36, 0.88	0.74	0.45, 1.21	0.60	0.37, 0.99
P for trend	0.01		<0.01		0.04		0.02	
P for interaction	0.71		0.38		0.43		0.13	

Table continues

that were not considered characteristic of the diet pattern. For the Mediterranean diet score, this scheme was modified in relation to dairy foods, grains, and starches and alcohol intakes, as noted in Table 1. Although the Mediterranean diet score most often is constructed by simply using 2 categories of intake (high and low, based on median intake), we constructed ours based on quintiles of intake to facilitate a more direct comparison of the 2 diet scores. For the Paleolithic diet score, we created 2 unique variables. The first, a fruit and vegetable diversity score, was created by summing the total number of responses in the food frequency questionnaire fruit and vegetable sections that indicated that the participant consumed more than 1–3 servings of a given food item per month. More diversity was considered desirable. Second, because the Paleolithic diet had little dairy food but high amounts of calcium (from wild greens) (20), to consider dietary calcium separately from dairy products we used the residuals of a linear regression of total calcium intake on total dairy food intake to represent calcium intake independent of dairy consumption. The final scores could range from 11 to 55 for the 11-component Mediterranean

Table 4. Continued

Risk Factor and Quintile of Diet Pattern Score	Endoscopy-Negative Controls[a]				Community Controls			
	Paleolithic Diet Score		Mediterranean Diet Score		Paleolithic Diet Score		Mediterranean Diet Score	
	Adjusted OR[b]	95% CI	Adjusted OR[b]	95% CI	Adjusted OR[b]	95% CI	Adjusted OR[b]	95% CI
Age, years								
<56								
1	1.00		1.00		1.00		1.00	
2	1.01	0.62, 1.63	0.89	0.54, 1.45	0.98	0.53, 1.81	0.87	0.48, 1.59
3	0.86	0.52, 1.43	1.20	0.74, 1.94	0.69	0.37, 1.29	1.09	0.60, 2.00
4	0.92	0.54, 1.58	0.72	0.41, 1.26	0.83	0.43, 1.61	0.57	0.29, 1.12
5	0.78	0.45, 1.34	0.66	0.39, 1.12	1.25	0.62, 2.53	1.25	0.63, 2.48
P for trend	0.35		0.13		0.85		0.95	
≥56								
1	1.00		1.00		1.00		1.00	
2	0.94	0.60, 1.48	0.63	0.41, 0.98	1.06	0.66, 1.72	0.59	0.36, 0.94
3	0.80	0.52, 1.24	0.68	0.43, 1.06	0.89	0.55, 1.42	0.62	0.38, 1.01
4	0.59	0.37, 0.95	0.63	0.40, 0.98	0.64	0.39, 1.05	0.68	0.42, 1.11
5	0.65	0.40, 1.06	0.74	0.48, 1.14	0.69	0.42, 1.15	0.60	0.38, 0.94
P for trend	0.02		0.16		0.04		0.06	
P for interaction	0.53		0.10		0.50		0.44	

Abbreviations: CI, confidence interval; MET, metabolic equivalent of task; OR, odds ratio.

[a] Endoscopy controls included those who had a colonoscopy and those who had only a flexible sigmoidoscopy.

[b] OR from an unconditional regression model. Covariates included age (years; continuous), sex, family history of colon cancer in a first-degree relative (yes/no), regular (≥once/week) use of nonsteroidal antiinflammatory drugs (categorical), body mass index (continuous), physical activity (MET-hours/week; continuous), total energy intake (kcal/day; continuous), and use of hormone replacement therapy (in women; categorical).

[c] Weight (kg)/height $(m)^2$.

diet score and from 14 to 70 for the 14-component Paleolithic diet score.

Statistical analysis

The characteristics of the cases, endoscopy controls, and community controls were summarized and compared using χ^2 tests for categorical variables and 2-sample *t* tests for continuous variables. Unconditional logistic regression models were used to calculate odds ratios and 95% confidence intervals for associations of the 2 dietary scores with colorectal adenoma. Separate analyses are presented for comparisons of cases with the endoscopy controls and with the community controls. The Paleolithic and Mediterranean diet pattern scores were analyzed as both continuous and categorical variables (quintiles) based on the distributions of the scores in the community controls. 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 potentially confounding variables we considered included sex, age (years; continuous), race/ethnicity, total energy intake (kcal/day), education (in years), body mass index (weight (kg)/height $(m)^2$), family history of colon cancer in a first-degree relative, history of diabetes, hormone replacement therapy (women only), regular (≥once/week) NSAID use, physical activity (metabolic equivalent of task (MET)-hours/week), and smoking (current, former, or never smoker). Inclusion in the final models required meeting 1 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 odds ratio for the primary exposure variable by ≥10%. The final adjusted models controlled for age, sex, total energy intake, use of hormone replacement therapy, family history of colon cancer in a first-degree relative, NSAID use, body mass index, and physical activity.

To assess potential effect modification, we conducted separate analyses for each category of the following: age (<56 years/≥56 years), sex, family history of colon cancer in a first-degree relative (yes/no), smoking (ever/never), body mass index (normal (<25)/overweight or obese (≥25)), regular (≥once/week) NSAID use (yes/no), and physical activity (<25 MET-hours per week/≥25 MET-hours per week). In addition, separate analyses were conducted according to the cases' adenoma characteristics, including multiplicity (1 adenomatous polyp/>1 adenomatous polyp) and, based on the largest adenoma, size (<1.0 cm/≥1.0 cm), colon site (right/left), degree of atypia (mild/moderate or severe), and histological subtype (tubular/tubulovillous or villous).

To assess the sensitivity of the associations to how the scores were defined, we removed each food component from both a priori scores one at a time to determine whether any 1 component overly influenced the diet score–adenoma associations. All analyses were conducted using SAS statistical

Table 5. Associations of Paleolithic and Mediterranean Diet Scores With Incident, Sporadic Colorectal Adenomas in a Case-Control Study, According to Selected Adenoma Characteristics, Minneapolis-St. Paul, Minnesota, 1991–1994

Adenoma Characteristic and Quintile of Diet Pattern Score	Cases vs. Endoscopy-Negative Controls[a]				Cases vs. Community Controls			
	Paleolithic Diet Score		Mediterranean Diet Score		Paleolithic Diet Score		Mediterranean Diet Score	
	Adjusted OR[b]	95% CI	Adjusted OR[b]	95% CI	Adjusted OR[b]	95% CI	Adjusted OR[b]	95% CI
No. of adenomas								
1 adenoma								
1	1.00		1.00		1.00		1.00	
2	0.93	0.65, 1.33	0.76	0.53, 1.10	1.03	0.69, 1.55	0.69	0.46, 1.04
3	0.74	0.51, 1.08	0.91	0.63, 1.30	0.76	0.50, 1.15	0.80	0.53, 1.20
4	0.66	0.44, 0.98	0.53	0.35, 0.80	0.67	0.44, 1.03	0.53	0.34, 0.82
5	0.80	0.54, 1.18	0.81	0.56, 1.16	0.97	0.63, 1.49	0.85	0.57, 1.26
P for trend	0.10		0.09		0.40		0.21	
≥2 adenomas								
1	1.00		1.00		1.00		1.00	
2	1.00	0.60, 1.68	0.71	0.42, 1.20	1.07	0.62, 1.84	0.73	0.42, 1.25
3	0.97	0.58, 1.61	0.70	0.41, 1.19	0.92	0.54, 1.57	0.66	0.38, 1.16
4	0.72	0.41, 1.25	0.88	0.53, 1.46	0.77	0.43, 1.36	0.99	0.58, 1.69
5	0.43	0.23, 0.82	0.53	0.31, 0.92	0.54	0.28, 1.05	0.55	0.31, 0.97
P for trend	0.01		0.07		0.04		0.13	
Adenoma subtype								
Tubular								
1	1.00		1.00		1.00		1.00	
2	0.93	0.64, 1.36	0.86	0.59, 1.24	1.03	0.68, 1.56	0.78	0.52, 1.17
3	0.95	0.65, 1.37	0.96	0.67, 1.40	0.92	0.61, 1.39	0.85	0.56, 1.28
4	0.77	0.52, 1.15	0.73	0.49, 1.08	0.78	0.51, 1.20	0.73	0.47, 1.13
5	0.80	0.53, 1.19	0.86	0.59, 1.24	0.95	0.61, 1.47	0.87	0.58, 1.31
P for trend	0.17		0.29		0.48		0.44	
Tubulovillous or villous								
1	1.00		1.00		1.00		1.00	
2	0.97	0.60, 1.57	0.57	0.34, 0.94	1.09	0.65, 1.81	0.58	0.34, 0.97
3	0.59	0.35, 0.98	0.63	0.38, 1.04	0.60	0.35, 1.03	0.61	0.36, 1.04
4	0.51	0.29, 0.89	0.49	0.29, 0.84	0.55	0.31, 0.98	0.54	0.31, 0.95
5	0.52	0.29, 0.91	0.52	0.31, 0.86	0.66	0.36, 1.19	0.56	0.33, 0.96
P for trend	<0.01		0.01		0.02		0.03	

Abbreviations: CI, confidence interval; MET, metabolic equivalent of task; OR, odds ratio.

[a] Endoscopy controls included those who had a colonoscopy and those who had only a flexible sigmoidoscopy.

[b] OR from an unconditional regression model. Covariates included age (years; continuous), sex, family history of colon cancer in a first-degree relative (yes/no), regular (≥once/week) use of nonsteroidal antiinflammatory drugs (categorical), body mass index (weight (kg)/height $(m)^2$; continuous), physical activity (MET-hours/week; continuous), total energy intake (kcal/day; continuous), and use of hormone replacement therapy (in women; categorical).

software, version 9.3 (SAS Institute, Inc., Cary, North Carolina). Results of the χ^2 tests and *t* tests (2-sided tests) were considered statistically significant at $P \leq 0.05$.

RESULTS

Selected characteristics of the cases and controls are presented in Table 2. Compared with the cases, the endoscopy controls, on average, were younger, had a lower body mass index, and had lower intakes of alcohol, fat, and red and processed meat and a lower total energy intake. Endoscopy controls were also more likely to be female, to have never smoked, to have a higher level of education, to be regularly taking an NSAID or supplemental calcium, to eat more fruits and vegetables, and, if female, to be on hormone replacement therapy. Compared with the cases, the community controls were more likely to be female, to have never smoked, to have a lower average body mass index, and to be less likely to have

a first-degree relative with a history of CRC. The mean Paleolithic diet score was slightly lower in the cases than in the community controls (41.3 vs. 42.1; $P = 0.03$) and minimally lower than in the endoscopy controls. Mean Mediterranean diet scores did not substantially differ by case/control status. The Paleolithic diet score ranged from 19 to 67, while the Mediterranean diet score ranged from 13 to 46. These ranges did not differ appreciably by sex. The correlation between the 2 diet scores was linear and strong ($\rho = 0.76$).

The overall associations of the diet scores with colorectal adenoma are presented in Table 3. In the multivariable-adjusted analyses, when the diet scores were treated as continuous variables, adenoma frequency was estimated to be borderline statistically significantly lower by 1%–2% per 1-point increase in the Paleolithic and Mediterranean diet scores. When the scores were treated as categorical variables (quintiles), the Paleolithic and Mediterranean diet scores were statistically significantly associated with adenoma frequency in the comparisons involving the endoscopy controls ($P_{trend} = 0.02$ and $P_{trend} = 0.05$, respectively, although the estimates for the individual quintiles were not statistically significant) but not in the comparisons involving the community controls. The odds of disease among persons in the highest quintile of each score were approximately one-fourth lower than those among persons in the lowest quintile. The magnitudes of the Mediterranean diet score–adenoma associations in the comparisons involving the 2 control groups were nearly identical to each other, but for the Paleolithic diet score, they were slightly stronger in the comparison involving the endoscopy controls.

As Table 4 illustrates, the inverse associations of both diet scores with colorectal adenoma were substantially stronger among men and persons who were overweight or obese. There were no consistent and clear patterns of differences in the associations of the scores with adenoma according to age (Table 4), family history of CRC in a first-degree relative, smoking status, physical activity, or NSAID use (data not shown). As Table 5 illustrates, the inverse associations of both scores with adenoma were substantially stronger for multiple adenomas and adenomas with a villous component, but there were no clear patterns of differences in the associations according to adenoma size, location, or degree of dysplasia (data not shown).

In the sensitivity analyses in which the components of each dietary score were removed from their respective scores one at a time, we found no substantial differences from the associations reported in the tables (data not shown).

DISCUSSION

Our results suggest that more Paleolithic- and Mediterranean-like dietary patterns may be similarly inversely associated with risk of colorectal adenoma, perhaps especially for men and persons who are overweight or obese, as well as for multiple adenomas or adenomas with a villous component.

The Paleolithic and Mediterranean diet patterns both have several components that could plausibly reduce adenoma risk. Both dietary patterns are high in fruits and vegetables, which may help improve oxidative balance, increase dietary fiber intake, and reduce total energy intake, all of which are thought to reduce colorectal adenoma and cancer risk (4, 27, 32, 33). They are also both low in red, processed, and fatty meats, which are thought to increase CRC risk via several mechanisms (2, 4, 8). The 2 diet patterns may also reduce systemic inflammation, which is associated with lower risk of CRC (34, 35). Given that overweight and obese individuals tend to have higher levels of systemic inflammation (36), our findings of stronger inverse associations of the diets with adenoma among those who are overweight or obese provide some indirect support for the hypothesis that inflammation is a key pathway by which these diet patterns act. However, women generally have a higher level of systemic inflammation than do men, yet the associations of the diet patterns with adenoma were stronger among men. Stronger associations between dietary patterns and colorectal adenoma or CRC in men have frequently been reported, and it is unclear whether this may be related to true biological differences in diet effects (37), differences in diet patterns, or differential diet measurement (38). The stronger associations for multiple adenomas and adenomas with a villous component may be related to inflammation, though the exact mechanism is unclear (39).

The Paleolithic diet pattern was examined in 3 small pilot dietary intervention studies, 1 uncontrolled (in a healthy, nonobese population) (22) and 2 with comparison groups on conventional healthy diets (in populations of type 2 diabetes or ischemic heart disease patients) (23, 25); the results from these 12-week trials suggested that the Paleolithic diet pattern may improve blood pressure, serum cholesterol level, glycemic control, and C-reactive protein level independent of any decrease in weight. A longer trial of postmenopausal obese women directed to follow a Paleolithic diet or a Nordic Nutrition Recommendations (low-fat, high-fiber) diet (40) found greater fat loss (−6.5 vs. −2.6 kg; $P < 0.001$) and lower levels of triglycerides at 6 months in the Paleolithic diet group, though much of the fat loss was attenuated after 2 years (−4.6 vs. −2.9 kg; $P = 0.095$) (24).

While to our knowledge there have been no previous epidemiologic reports on the relationship between a Paleolithic diet score and colorectal neoplasms, 6 prospective cohort studies have examined the Mediterranean diet score (1 in relation to incident adenomas, 1 in relation to adenoma recurrence, and 4 in relation to incident carcinomas), generally finding inverse associations. Among Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial participants, a higher Mediterranean diet score was inversely associated with adenoma (for the highest quintile relative to the lowest, odds ratio = 0.79 (95% confidence interval (CI): 0.68, 0.92); $P_{trend} < 0.001$) (9). A principal-components analysis conducted in the European Cancer Prevention Intervention Study identified a Mediterranean-like dietary pattern that was associated with significantly lower 3-year adenoma recurrence among women only (for the highest tertile relative to the lowest, odds ratio = 0.30 (95% CI: 0.09, 0.98); $P_{trend} = 0.04$) (19). In the 4 studies of incident CRC, the findings for the highest quantiles of the score relative to the lowest were as follows: 1) in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, the hazard ratio was 0.89 (95% CI: 0.80, 0.99; $P_{trend} = 0.02$) (11); 2) in the Italian component of EPIC, the hazard ratio was 0.50 (95% CI: 0.35,

0.71; P_{trend} =0.04) (10); 3) in the National Institutes of Health-AARP Diet and Health Study, risk ratios were 0.72 (95% CI: 0.63, 0.83) and 0.89 (95% CI: 0.72, 1.11) among men and women, respectively (13); and 4) in the Nurses' Health Study and Health Professionals Follow-up Study cohorts, risk ratios were 0.88 (95% CI: 0.71, 1.09; P_{trend} = 0.25) and 0.89 (95% CI: 0.77, 1.01; P_{trend} = 0.06) in men and women, respectively (14).

This study had several strengths and limitations. Strengths included standardized pathological verification of adenomas, thereby reducing outcome misclassification; the use of 2 control groups, each with its own strengths and limitations; assessment of exposure information prior to endoscopy, reducing opportunity for recall bias; and the collection of detailed information on potentially confounding variables. Whereas there was minimal outcome misclassification among the endoscopy controls, they may have been more similar to the cases in various respects, and whereas the community controls may have been more representative of the general population, some may have been undiagnosed cases; thus, for different reasons, the estimated associations with both control groups were probably attenuated. Although age and sex are known risk factors for colorectal neoplasms and were controlled for in the analyses, the degree to which the endoscopy controls were, on average, younger and more likely to be female raises the possibility of some selection bias. While the inverse associations between each diet and colorectal adenoma frequency were similar to each other, the point estimates for the associations with the fifth quintiles relative to the first quintiles were not statistically significant, underscoring the importance of investigating these diets in larger, preferably prospective, studies. An important limitation of our study was that, for the most part, the actual diets of the participants could not be considered to be strongly consistent with the Paleolithic or Mediterranean diet pattern. This suggests that our findings may substantially underestimate the potential of these diet patterns for reducing risk of colorectal adenoma. Finally, while our Paleolithic diet score was data-derived for the quintile cutoffs, and thus study-specific (see Reedy et al. (13) for a review of diet scores), the schema can be applied to other study populations.

In conclusion, our findings, taken in context with those from previous studies, suggest that a Paleolithic or Mediterranean diet pattern may be inversely associated with risk of incident, sporadic colorectal adenomas.

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