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Paleolithic and Mediterranean Diet Scores and Risk of Colorectal Adenoma

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Paleolithic and Mediterranean Diet Scores and Risk of Colorectal Adenoma

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Abstract

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By Kristine Valenzuela

Background: A Westernized diet and lifestyle is associated with risk for colorectal cancer and adenomas. Evolutionary discordance could explain this association.

Objective: We investigated associations of scores for two proposed healthy diet patterns, the "Paleolithic" and Mediterranean diets, with risk for incident, sporadic colorectal adenomas.

Methods: In the Minnesota Cancer Prevention Research Unit case-control study of colorectal polyps, 1,248 participants with no history of colorectal neoplasms completed extensive questionnaires, including a Willett food frequency questionnaire, prior to an elective, outpatient colonoscopy. Of these participants 564 were identified as cases and 684 as colonoscopy-negative controls. An additional group of 535 frequency-matched population controls were also recruited. Paleolithic and the Mediterranean diet scores were calculated and categorized into quintiles, and associations were estimated using unconditional logistic regression.

Results: The Paleolithic and the Mediterranean diet patterns were similarly inversely associated with colorectal adenomas when comparing the cases to the population controls: the multivariable-adjusted odds ratios [OR] were 0.66 (95% confidence interval [CI] 0.45 - 0.96, p_{trend} = 0.03) and 0.65 (95% CI 0.44 - 0.96, p_{trend} = 0.03) for those in the highest relative to the lowest quintiles of the Paleolithic and Mediterranean diet scores, respectively. The associations tended to be stronger in men (OR 0.51 [95% CI 0.31 - 0.85, p_{trend} = 0.01] for the Paleolithic diet score, and OR 0.60 [95% CI 0.37 - 0.99, p_{trend} = 0.03] for the Mediterranean diet score) and those who were overweight or obese (OR 0.45 [95% CI 0.25 - 0.82, p_{trend} < 0.01] for the Paleolithic diet score, and OR 0.41 [95% CI 0.22 - 0.78, p_{trend} < 0.01] for the Mediterranean diet score). However, there was no evidence for an association of either dietary pattern with risk for adenoma in the comparisons involving the colonoscopy-negative controls.

Conclusion: These findings suggest that higher adherence to the Paleolithic or Mediterranean diet patterns may be similarly associated with lower risk for incident, sporadic colorectal adenomas; however, especially considering the discrepant findings from the comparisons of the cases with the two different control groups, further study is needed.

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LITERATURE REVIEW

Introduction—Colorectal cancer is the third most commonly diagnosed cancer and the second leading cause of cancer mortality in the United States, with approximately 5% of the U.S. population expected to develop colon cancer in their lifetime [1]. Colon cancer is a disease that is highly correlated with a westernized lifestyle and diet. Rapidly increasing incidence rates documented in Italy, urban China, Japan, and in male Polynesians in Hawaii coincided with those populations adopting a more westernized lifestyle [2]. With globalization, this pattern has been repeated worldwide, and there has been a corresponding increase in the global incidence of colon cancer [3]. This, in conjunction with data on colon cancer incidence in migrant populations, show that while there is a genetic component to colon cancer, risk for most individuals is extremely sensitive to changes in lifestyle[2].

Genetic, Diet & Lifestyle Factors and Colon Cancer—These international differences in colon cancer incidence rates and migrant population studies have informed a plethora of case-control and cohort studies examining dietary and lifestyle exposures and colon cancer risk. Yet no single dietary or lifestyle factor has emerged as a major determinate of colon cancer risk, though there are several characteristics that influence a person's risk of colon cancer moderately.

Family History—There are two predominant types of genetic mutations associated with increased risk of colorectal cancer. The first is *familial adenomatous polyposis* (FAP), which is a rare syndrome where the individual develops multiple, sometimes thousands of colorectal adenomas in late childhood or early adulthood. This condition and several other, closely related conditions are caused by autosomal dominantly inherited mutations in the APC gene, which is a tumor suppressor gene. The second genetic mutation associated with an increased risk of colon cancer is *hereditary nonpolyposis colorectal cancer* (HNPCC), another inherited autosomal dominant syndrome characterized by early onset of colon cancer and a specific pattern of other cancers, including endometrial, urinary, stomach, and bile tract cancers. Two mutations in genes

that code for proteins in the mismatch repair system, MSH2 and MLH1, account for most of the mutations associated with this condition[4].

Alcohol & Folate—Several case-control studies and prospective cohort studies found an association of high intakes of alcohol (greater than 2 drinks a day or 30g/day) and increased incidence of colon cancer. It is thought that alcohol consumption interferes with the absorption and function of folate as they are in the same biochemical pathway. Since a high intake of alcohol effectively lowers an individuals' circulating levels of folate, a greater intake of folate-rich foods and supplements are necessary to attain the same beneficial effect. Examined individually, neither alcohol or folate consumption seems to have a strong association with colon cancer, but alcohol is a potent antagonist of folate metabolism. Comparing individuals with high intakes of alcohol and low intakes of folate, there is generally a two to five fold elevation in colon cancer or colorectal adenoma risk[5].

Fat and Meat—One of the dominant hypotheses regarding the impact of diet on colon cancer risk has been that increased dietary intake of meat or fat increases risk for colon cancer, since increased meat and dietary fat intake are hallmarks of a Westernized diet. While some case-control study results supported the hypothesis of a direct association between meat intake and colon cancer incidence, only one of several large prospective studies found a positive association for overall meat consumption. However, a direct association with red meat or processed meat has been somewhat more consistently found[2, 6]. Similar ambiguous results regarding the association between colon cancer and fat intake have been found[2]. Some of the ambiguity regarding fat intake may be residual confounding from the known association between positive energy balance and colon cancer, to be discussed later.

Fiber and Fruit & Vegetable Intake—Another leading dietary hypothesis for increased colon cancer risk has been low dietary fiber, or low fruit and vegetable intake. In general, the epidemiological studies examining the association between colon cancer incidence and fiber have been mixed, though generally positive [2]. Several large prospective cohort studies found an inverse

association between fiber intake and colon cancer, though that association was not statistically significant. High fruit and vegetable consumption has also been a popular association to examine, and has been somewhat consistently inversely associated with colon cancer incidence[7]. Several biologically plausible mechanisms have been suggested by which dietary fruit and vegetable intake could decrease colon cancer risk, including oxidative balance, increased fiber intake, increased folate consumption, and others [2]. Translating these findings into prevention studies has proved difficult. Several dietary intervention trials failed to find any beneficial effect of increased fruit and vegetable intake, or specific vitamin or mineral intake on colon cancer incidence [8].

Calcium Supplementation and Dairy Foods—Higher intakes of calcium or dairy have been consistently inversely associated with colorectal adenoma reoccurrence in several randomized trials[9],[10]. Calcium supplementation reduced cell proliferation in colon crypts[11], the microstructures of the colon that generate new colon epithelial cell lining as well as on 8-hydroxy-2′-deoxyguanosine (8-OH-dG), a marker of oxidative DNA damage[11]. Another double-blind randomized trial comparing 1200 mg of elemental calcium daily compared to a placebo showed a 15-20% reduction in the incidence of metachronous colorectal adenomas. [4].

Energy Balance (Physical Activity/BMI)—Consistent epidemiological evidence has pointed towards a direct association between a positive energy balance (i.e. excess total energy intake relative to energy expenditure) and colorectal cancer. Low physical activity and high body mass index (BMI) have both been consistently associated with a higher risk of colorectal cancer[7]. There is also some evidence that a diet with a high glycemic index may be associated with higher risk of colon cancer[12]. Interventions to change individual behavior in favor of losing excess weight or increasing physical activity have had limited success in randomized intervention trials.

Nonsteroidal Anti-Inflammatory Drugs (COX-2 Inhibitors)—Nonsteroidal anti-inflammatory drugs (NSAIDs) include medications such as aspirin, and are consistently associated with a decreased risk of colon cancer. Most case-control and cohort studies found lower risk of both colon cancer and adenomatous polyps. The results from clinical trials have also yielded results,

showing that metachronous adenomas occur at lower frequencies with aspirin use, though the most effective dosage is still uncertain. Chemoprevention trials for those with FAP have shown that stronger drugs such as celecoxib reduce polyposis occurrence [13], [14]. NSAIDs suppress the enzyme COX-2, which in turn reduces the production of arachidonic acid, decreases epithelial cell proliferation, and increases apoptosis. NSAIDs also impact chronic inflammation levels in the body, which may also lower colon cancer or adenoma risk [4].

The Mediterranean/DASH Diet—High intakes of fruit, vegetables, fish, and whole grains; moderate amounts of alcohol and dairy products; and low amounts of red or processed meats and sweets characterize the traditional Mediterranean diet. The Dietary Approaches to Stop Hypertension (DASH) diet features high intakes of fruit, vegetables, legumes, and nuts; moderate amounts of animal protein and sweets; and a low sodium intake. Both of these diets have been examined in relation to risk of colorectal cancer in a pooled analysis of the Nurses health study (NHS) and Health Professionals Follow-up Study (HPFS), where a modified Mediterranean diet score (aMed) and DASH dietary scores were calculated for each participant. While there was no association seen between the aMed score and colon cancer, the DASH score was statistically associated with lower risk of colorectal cancer with each quintile of the DASH score (0.80 0.70,0.91; P for trend=0.0001) [15]. The scoring method may account for some of difference between the results for the aMed score and the DASH score, with the aMed score generated out of a series of dietary elements, where intake above the median received a 1 and intake below the median received a 0. In contrast, the DASH score was created based on quintiles of intake, with the hypothesized unhealthiest level of intake receiving a 1 and the hypothesized healthiest receiving a 5. This quintile-intake scoring creates a greater separation between participant intakes, leading to a greater range of possible scores.

Evolutionary Discordance & the Paleolithic Diet—The increasing discrepancy between a modern diet and the lifestyle under which *Homo sapiens* evolved has been suggested as a guiding theory to investigate the increase in chronic diseases in the 20th and 21st centuries. Evolutionary

discordance can range over a variety of possible exposures, from overarching dietary patterns to increasing light exposure and sleep patterns. In order to examine possible dietary discrepancy, anthropologists have developed a "Paleolithic Diet" which is the hypothetical diet *Homo sapiens* would have eaten prior to the development of agriculture. Constructed from a combination of fossil evidence and anthropological studies of modern hunter-gather groups, the overall Paleolithic diet pattern consists of lean meat, fish, shellfish, fruits, vegetables, roots, eggs, and nuts, but excludes grains, dairy products, salt, refined fats, and sugar.

Several pilot randomized clinical trials have been conducted with a Paleolithic dietary intervention arm. One outpatient, calorie-controlled crossover study of nine non-obese sedentary volunteers measured arterial blood pressure, 24-hour urine sodium and potassium excretion, plasma glucose concentrations, and brachial artery reactivity in response to ischemia. Compared with the usual diet, there were significant reductions in blood pressure, plasma insulin vs. time areas under the curve during the oral glucose tolerance test, and large significant reductions in total cholesterol, low-density lipoproteins, and triglycerides [16]. In a second randomized crossover study, 13 patients with Type 2 diabetes were instructed to eat a Paleolithic diet and then a Diabetes diet during two-consecutive three-month periods. Compared to the diabetes diet, the Paleolithic diet resulted in lower mean values of HbA1c, triacylglycerol, diastolic blood pressure, weight, BMI, and waist circumference, as well as higher mean values of high-density lipoprotein cholesterol [17]. Given the significant estimated health benefits in these pilot studies of a Paleolithic dietary intervention, examining existing study food frequency questionnaires to determine potential beneficial health effects in other areas such as cancer prevention would be useful before funding a full-scale dietary intervention trial.

ABSTRACT

Background: A Westernized diet and lifestyle is associated with risk for colorectal cancer and adenomas. Evolutionary discordance could explain this association.

Objective: We investigated associations of scores for two proposed healthy diet patterns, the "Paleolithic" and Mediterranean diets, with risk for incident, sporadic colorectal adenomas.

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Conclusion: These findings suggest that higher adherence to the Paleolithic or Mediterranean diet patterns may be similarly associated with lower risk for incident, sporadic colorectal

adenomas; however, especially considering the discrepant findings from the comparisons of the cases with the two different control groups, further study is needed.

INTRODUCTION

Colorectal cancer is the third most commonly diagnosed cancer and the second leading cause of cancer mortality in the United States[1]. Rapidly increasing incidence rates documented in urban China, Japan, and in male Polynesians in Hawaii coincided with those populations adopting a more westernized lifestyle [2]. Migration studies also point to a strong influence of diet and other lifestyle factors on colon cancer risk.

Many, but not all, epidemiological studies have found diets high in fruits and vegetables to be associated with a decreased risk of colon cancer[2,4]. Epidemiological studies on high fat and meat consumption have found inconsistent, weak evidence of an increased risk of colon cancer[2, 6]. Yet human intervention trials of low-fat diets, fiber or antioxidant supplements have had negligible success in reducing colorectal adenomatous polyp recurrence [8].

Rather than examine individual dietary exposures and their associations with colorectal cancer, it may be more useful to characterize the entire dietary pattern. Several studies have done this previously by scoring food frequency questionnaire (FFQ) responses and comparing associations of various hypothesized high and low risk dietary patterns with risk for breast cancer, colon cancer, and colorectal adenomas[15,18 19 20 21 22]. Most healthy diet models have focused on intakes of fat, carbohydrate, fiber, fruits, and vegetables. A diet commonly used for such studies is the Mediterranean diet, consisting of a high intakes of fruit, vegetables, fish, and whole grains; moderate amounts of alcohol and dairy products; and low quantities of red or processed meats and sweets [23]. While the Mediterranean dietary pattern has several aspects that are hypothesized to be consistent with a healthy diet, it has been proposed that a dietary pattern more comparable to those available during late human evolution may be ideal for the prevention of modern chronic diseases.

The evolutionary discordance hypothesis posits that the rapid increase in many chronic conditions or diseases is a result of the recent changes to the diet and lifestyle patterns of modern humans compared to those of our evolutionary ancestors. Anthropologists have constructed a "Paleolithic Diet" which is the model diet *Homo sapiens* would have eaten prior to the development of agriculture [24]. The Paleolithic diet is characterized by lean meats, fish, shellfish, fruits, vegetables, eggs and nuts, and excludes grains, dairy products, salt, refined fats, and sugar. Few studies of the Paleolithic diet and health outcomes have been reported to date[16,17]. In one small (n=29), randomized dietary intervention trial, after 12 weeks, on average there was a 26% a decrease in mean glucose response during a 120 min. oral glucose tolerance test in the Paleolithic group compared to only a 7% decrease in the Mediterranean diet group. There was also a larger drop in waist circumference in the Paleolithic group (-5.6cm Paleolithic group, -2.9cm Mediterranean group, p=0.03). Taken together the findings from this trial suggested that an ancestral diet may provide greater health benefits than a conventional healthy diet[25].

Examining dietary patterns, rather than specific food groups, may more realistically and robustly account for the effects of multiple weak, likely interacting, foods on disease risk.

MATERIALS AND METHODS

Study Population and Data Collection

This case-control study was conducted between April 1991 and April 1994 as part of the Minnesota Cancer Prevention Research Unit, a joint project between the University of Minnesota and a large, multi-clinic private gastroenterology practice. The gastroenterology practice performed colonoscopies in 10 hospitals, and at the time of the study, was responsible for ~60% of all colonoscopies in the Minneapolis metropolitan area.

The gastroenterology practice staff initiated study recruitment at the time of scheduling elective, outpatient colonoscopies. The initial eligibility for study participation was that patients be between 30 and 74 years old, residents of the Minneapolis-St. Paul metropolitan area, English speaking, free of known genetic syndromes associated with a predisposition to colonic neoplasia,

and with no individual history of ulcerative colitis, Crohn's disease, adenomatous polyps, and cancers except for non-melanoma skin cancer. Patients were recruited at all 10 of the practice's endoscopy sites.

Consent and completed questionnaire forms were collected at the colonoscopy visit, and blood samples drawn. The colonoscopists recorded adenoma locations, *in vivo* size, and shape on standardized forms. All polyps were removed and examined histologically by a single index study pathologist using the National Polyp Study diagnostic criteria. If polyps had been removed during a sigmoidoscopy performed prior to the colonoscopy, the study pathologist also evaluated the relevant slides.

On the basis of the colonoscopy 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 had a complete colonoscopy reaching the cecum, had all polyps removed, not have a new diagnosis of ulcerative colitis or Crohn's disease, and have no polyps with invasive carcinoma. Adenoma cases had at least one adenomatous polyp (defined as either adenomatous or mixed pathology). Controls were free of both adenomatous and hyperplastic polyps at colonoscopy.

Potential community controls were randomly selected from the 1991 Minnesota State Driver's License Registry and frequency matched on age, sex, and zip code, and were included only of the met the same eligibility criteria as the colonoscopy-based participants except that they did not undergo colonoscopy to confirm their current polyp status.

Study participants provided detailed information on demographic characteristics, personal medical history, smoking history, diet, usual physical activity, anthropometrics, reproductive history and hormone use (women only), and family history of cancer. The frequency of current aspirin and non-aspirin NSAID use was assessed as number of pills per week.

A total of 1,783 participants completed the study, including 564 cases, 684 colonoscopy-negative controls, and 535 population controls. Participants missing more than 10% of the FFQ

data or had implausible total energy intakes (<600kcal/day or > 5000kcal/day) (10 cases, 23 colonoscopy-controls, and 15 population controls) were excluded from the analyses.

Dietary Scores

Dietary scores were created for both the Paleolithic diet and the Mediterranean diet, the latter based loosely on the aMed scoring system presented in Fung et al 2006 and Fung et al 2010 [15,18]. For both men and women, the distributions of food intakes in the population controls were used to create cutpoint values for quintiles.

For the Paleolithic diet score, foods were determined to be either consistent or discordant with a Paleolithic diet based on the dietary guidelines outlined in Eaton and Konner.[24] Using this scheme, the Paleolithic diet score was constructed by giving each food component a quintile ranking based on the sex-specific distribution of consumption in the population controls, and assigning a code from 0-5 points. Vegetables and fruits were given 5 points for the highest level of intake. Another, unique, variable, a fruit and vegetable diversity score, was created by summing the total number of responses in the FFQ fruit and vegetable sections that indicated that the participant ate a given food item "Never or less than once per month" or "1-3 servings per month". Those in the lowest quintile with the fewest such responses received 5 points, and so on as above. To consider the separate effects of dietary calcium and dairy products, we ran a linear regression of the two variables and used the residuals to represent the effect of dairy foods independent from calcium. The residuals were ranked, and the lowest "dairy" score received 5 points, whereas the highest intake of dietary calcium received 5 points. Low intakes of grains and red meat and high intakes of lean meat, fish, and nuts each received 5 points. Low intakes of sodium, baked goods, sugar-sweetened beverages, and alcohol consumption all received the maximum score of 5. Together, the Paleolithic diet score was composed of 14 components, which could yield a total score from 14 to 70, with an average score of 42 among all participants.

Using the Mayo Clinic's guidelines for a Mediterranean diet[23], food categories were categorized as being either beneficial and deleterious. A score of 5 was given to the highest level

of intake of presumed beneficial food groups, the fruits, vegetables, fish, nuts, and lean meats; a score of 1 was given to the highest intake of deleterious foods, red meat and salt. Dairy and grain or starch intakes were scored on a "moderate" scale, with 3 points assigned to the medium intake level, 2 points assigned to the second or fourth quintiles of intake, and 1 to the extreme quintiles of intake. There was no distinction made in the FFQ between whole grains and refined grains, hence the moderate level of intake being scored as the best. Daily alcohol intakes between 5g and 15g received 1 point, while higher or lower levels of intake received 0 points. Last, a monosaturated to saturated fat ratio was computed and ranked by quintiles in the population controls. The scores for the quintiles ranged from 0 for the lowest quintile to 5 for the highest quintile. Each of these eleven components were then added together to create a Mediterranean diet score, which could range from a total of 10 to 47 points, with an average score of 27 among all the participants in the CPRU study.

Statistical Analyses

The characteristics of the cases and controls were summarized and compared using chi-square tests for categorical variables and two-sample t-tests for continuous variables. Unconditional logistic regression models were used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for associations between the two dietary scores and colorectal adenomas. The Paleolithic and Mediterranean diet scores were analyzed as both continuous and categorical (as quintiles) variables.

Based on previous literature and biological plausibility, potential confounding variables were considered to be sex, age, race, BMI, family history of colon cancer in a first-degree relative, hormone replacement therapy use, education level (yrs.), regular (≥ once/week) NSAID use, supplemental calcium intake (g/day), kilocalories consumed daily, physical activity (METs), and smoking (current/former/never). Inclusion in the final models included one or more of the following criteria: biological plausibility, statistical significance, and/or whether the inclusion/exclusion of the variable from the model changed the adjusted OR for the primary

exposure variable by more than 10%. The final adjusted model controlled for sex, hormone replacement therapy use, age, family history of colon cancer in a first-degree relative, regular (≥ once/week) NSAID use, BMI, and total energy intake.

The associations of the dietary scores with adenomas were also stratified by family history of colon cancer (yes/no), sex, age (< 56 yrs/ ≥ 56 yrs), smoking (ever/never), BMI (normal/overweight & obese), education (12 years or less/some college), regular (≥ once/week) NSAID use (yes/no), and physical activity (< 25 METs/week / ≥ 25 METs/week). In addition, the diet-adenoma associations were also analyzed according to adenoma characteristics, including number of adenomas found (1 / > 1), size (<10 cm/ ≥ 10cm), colon location (right/left), degree of atypia (mild / moderate-severe), and histologic subtype (tubular / tubulovillous & villous).

All analyses were conducted using SAS statistical software (SAS ver. 9.3, SAS Statistical Institute, Cary, NC). Two-sided tests were statistically significant if $p < 0.05$.

RESULTS

Selected characteristics of the cases and controls are summarized in Table 1. Compared to the cases, the colonoscopy controls, on average, were younger and had lower intakes of alcohol, dietary fiber, meat, and supplemental calcium, and were more likely to be female, have a family history of colon cancer in a first-degree relative, not smoke, and, if a woman, be on hormone replacement therapy. Also compared to the cases, on average, the population controls had a lower BMI, were more likely to be female, have no family history of colon cancer in a first-degree relative, and not smoke.

Table 2 summarizes the overall associations of the dietary scores with colorectal adenoma. In the multivariable-adjusted analyses involving the community controls, when the diet scores were treated as continuous variables, risk for adenoma was estimated to be borderline statistically significantly lower by 2% and 3% with each one point increase in the Paleolithic and Mediterranean diet scores, respectively. When the diet scores were treated as categorical variables based on quintiles of their distributions, risk was statistically significantly (both the

point estimate and p for trend) approximately 35% lower for those in the upper quintiles compared to the lower quintiles of either diet score. In the corresponding analyses involving the colonoscopy-negative controls, there was no evidence for diet score-adenoma associations.

Multivariable-adjusted analyses stratified by selected participant characteristics are shown in Table 3. In the comparisons involving the community controls, for both dietary scores, the inverse associations tended to be stronger among men, those who were older, non-smokers, overweight/obese, less educated, and did not take a NSAID. The inverse association of the Paleolithic diet score with adenomas tended to be a little stronger among those with higher levels of physical activity, whereas the inverse association of the Mediterranean diet score with adenomas tended to be a little stronger among those with lower levels of physical activity. Of these various findings in the stratified analyses, the OR for the upper quintiles compared to the lower quintiles and/or the p for trend was statistically significant or borderline statistically significant only among men (both diet scores), those who were older (both diet scores), non-smokers (Paleolithic diet), overweight/obese (both diet scores), less educated (Paleolithic diet), did not take a NSAID (both diet scores), and those who were more or less physically active (Paleolithic and Mediterranean diet scores, respectively). However, none of the multiplicative interaction terms were statistically significant in the multivariable-adjusted logistic regression models.

Multivariable-adjusted associations of the diet scores with adenomas according to adenoma characteristics are shown in Table 4. The inverse association of the Paleolithic diet score with adenomas tended to be stronger for multiple adenomas (OR 0.51, 95% CI 0.28 – 0.92) than for single adenomas, and the inverse association of the Mediterranean diet score with adenomas tended to be stronger for multiple adenomas (OR 0.47, 95% CI 0.26 – 0.87), adenomas with moderate/severe dysplasia (OR 0.55, 95% CI 0.34 – 0.89), and adenomas with a villous component (OR 0.48, 95% CI 0.28 – 0.84).

DISCUSSION

Both the Paleolithic and Mediterranean diet patterns were similarly inversely associated with colorectal adenomas when comparing the cases to the population controls but not to the colonoscopy-negative controls. The reasons for the discrepant findings in the comparisons involving the two control groups are unclear. Possibilities include chance and that the community control group may have been more representative of a normal population than were the colonoscopy-negative controls. The MN CPRU case-control study was conducted at a time when Medicare and most major insurance companies had not begun to cover colonoscopies for screening purposes beyond screening among those with a strong family history for colon cancer. Thus, the colonoscopy-negative controls may have been higher risk than the community controls. In support of this was that a higher proportion of the colonoscopy-negative controls had a history of colorectal cancer in a first degree relative than was found among the cases, a well-known bias in colonoscopy-based case-control studies conducted prior to the late 1990s. Also limited to the comparisons involving the community controls were that the findings of inverse associations of the two dietary scores tended to be stronger 1) among men and those who were overweight or obese as well as perhaps among those who were older and did not regularly take a NSAID, and 2) for multiple adenomas and adenomas with more advanced characteristics. If the comparisons involving the community control group are closer to the truth, then our findings would suggest that either a more Paleolithic- or Mediterranean-like diet may reduce risk for colorectal adenoma, especially advanced adenoma among those who may have higher levels of inflammation for other reasons.

As both the dietary scores we investigated placed heavy importance on high intakes of fruits and vegetables and a low intakes of fatty meats, the inverse associations of the Paleolithic and Mediterranean diet scores is consistent with earlier findings[2, 3, 7, 8]. Both the Paleolithic and Mediterranean diet have several biologically plausible mechanisms through which they could reduce the risk of colorectal adenomas. Both diets emphasize a high intake of vegetables, which

have high folate content. Folate has been consistently, though weakly associated with lower risk of colorectal adenomas, although supplementation with relatively high doses of folic acid increased the recurrence of multiple and advanced adenoma in a large clinical trial[26]. The Paleolithic diet in particular gives those individuals with the highest intake of alcohol the lowest score, and as alcohol is a potent antagonist of folate metabolism, folate-alcohol balance may account for the inverse association seen in these data[5]. High vegetable and vegetable intake also can also serve as proxy for a high fiber diet, which is hypothesized to reduce the risk of colorectal cancer through multiple mechanisms, including decreased stool transit time and diluting fecal mutagens contact with the colon mucosa[2]. Chronic inflammation is also associated with increased risk of colorectal cancer, which a diet high in fruit and vegetables might combat with a large and varied antioxidant content[22]. In addition to a large intake of fruits and vegetables in both diets, the fruit and vegetable diversity component present in the Paleolithic diet score may represent antioxidant diversity in the diet, and thereby account for some portion of the inverse association seen in the data.

High intakes of calcium or dairy have been consistently inversely associated with colorectal adenoma reoccurrence in several randomized trials[4, 9, 10]. Calcium supplementation has been shown to reduce cell proliferation in colon crypts[11], the microstructures of the colon that generate new colon epithelial cell lining as well as reducing 8-hydroxy-2′-deoxyguanosine (8-OH-dG), a marker of oxidative DNA damage[11]. The Mediterranean diet allows for moderate intake of dairy, thereby providing dietary calcium and thereby possibly reducing the risk of colorectal adenoma. The Paleolithic diet does not include dairy, but would ideally include high intakes of calcium through wild-grown leafy greens, which have been shown to have high calcium content [27]. The Paleolithic diet could then reduce colorectal adenoma risk via high levels of dietary calcium without the usual recommendation of dairy consumption.

High fat and meat consumption, especially red and processed meats, have long been hypothesized to increase the risk of colorectal cancer, through either the increased production of

bile acids in response to fat intake, increased oxidative damage from fat or meat consumption, carcinogenic heterocyclic amines produced from cooking meat at high temperatures, or red-meat intake increasing endogenous production of potentially mutagenic *N*-nitroso compounds[2, 6]. Both the Paleolithic and the Mediterranean diets allow for regular meat consumption, but prefer lean meats and fish to red and processed meats, which is consistent with the hypothesized biological mechanisms of fat and meat intake increasing the risk for colorectal adenoma.

Diets with a high glycemic index and glycemic load have also been hypothesized to contribute to the etiology of colorectal cancer by possibly increasing glucose and insulin levels, though the evidence for this has been inconsistent and weak[28]. The Paleolithic diet minimizes the intake of grains and baked goods in general, and the Mediterranean diet emphasizes only whole grains, thereby minimizing both diets' use of high glycemic index foods and possibly contributing to an inverse association with colorectal adenomas. Though, given the improved oral glucose tolerance test results of the Paleolithic group compared to the Mediterranean diet group in the Lindberg et al. 2007 intervention trial[25], if high glycemic index and glycemic load were a strong risk factor for colorectal adenoma, likely a greater difference between the associations of the two dietary scores with adenomas would have been seen in our. This does not mean that the glycemic load of the Paleolithic and Mediterranean diets did not contribute to the inverse association, but rather that our study's observational nature may make it difficult to distinguish between the potential effects of the two dietary patterns on risk for adenoma. Unlike a dietary intervention trial, in which the intervention diet can be designed to mimic the desired dietary pattern exactly, in an observational study in a US population it is likely that even among those in the highest quintiles of the dietary scores there would be few, if any participants whose dietary patterns would be sufficiently similar to an ideal Paleolithic or Mediterranean dietary pattern to see strong associations with colorectal adenomas. Those individuals with a high Paleolithic diet score likely had a similarly high Mediterranean diet score, and further study is needed to differentiate the two.

Systemic inflammation is a common mechanism through which each of these dietary

components can contribute to the association of diet and colorectal adenoma. In one clinical trial a combination of antioxidant-related micronutrients were found to reduce biomarkers of oxidative stress and inflammation in patients with a history of colorectal adenoma [22]. Intervention studies of high-dose antioxidant vitamins (typically as single or small combinations of agents in supraphysiologic doses) to prevent colorectal adenoma recurrence have not been successful [8, 29], but an oxidative balance score, which combines multiple pro- and anti-oxidant components of diet, has been inversely associated with colorectal adenomas[30]. These seemingly conflicting results lend credence to the idea that supplementation of a single antioxidant in high doses may not prevent colorectal adenomas as well as a spectrum of antioxidants, as is found in a diet high in fruits and vegetables like in the Paleolithic and Mediterranean diets.

The stronger associations of both diets with more advanced adenomas and among men and overweight and obese individuals also supports the idea that individuals with higher levels of inflammation may benefit more from a more Paleolithic- or Mediterranean- like diet. COX-2 expression in adenomas increases with adenoma progression[31]. Systemic oxidative stress levels differ by sex. Men have a higher fasting oxidative stress levels, and may also experience a higher oxidative stress response to a high-fat meal compared to women [32]. Similarly, overweight and obese individuals have higher chronic inflammation levels compared to their normal weight counterparts, due to adipose tissue secreting a variety of adipokines, some of which are potent pro-inflammatory cytokines[33]. If the dietary components of both the Paleolithic and the Mediterranean diets reduce risk of colorectal adenoma by their higher antioxidant content, it would be expected to see stronger, more inverse associations in men compared to women, in overweight and obese participants compared to normal weight individuals, and in those cases with more advanced adenomas, which is consistent with our data.

The study has several limitations and strengths that should be considered in interpreting its results. Although our sample size was among one of the largest for observational studies of colorectal adenoma, it was still limited for stratified analyses. As noted above, there was a family

history bias in relation to the colonoscopy-negative control group, which may have also been at higher risk for other reasons. Persons with a family history of colon cancer may be more likely to have a screening colonoscopy, and to do so at an earlier age, before adenomas have formed. This may have attenuated the associations seen with the colonoscopy-negative controls. On the other hand, the current adenoma status of the population control group was not known, making it likely that there was some case/control group misclassification which could have attenuated the associations seen in the comparisons involving this control group. There are also known limitations to dietary assessment using food frequency questionnaires, including recall error and bias; however, the use of the food frequency questionnaires in large, population-based studies is well validated.

The study also has several important strengths, including the use of both a confirmed adenoma-free control group and a more general population-representative control group; that all self-report information was obtained prior to colonoscopy, thus minimizing the potential for recall bias; and detailed information on current medications and supplements and other potential confounding and modifying factors, such as medical and reproductive history, was collected.

In conclusion, our findings suggest that higher adherence to the Paleolithic or Mediterranean diet patterns may be similarly associated with lower risk for incident, sporadic colorectal adenomas, especially for multiple and advanced adenomas and among persons who may have higher levels of inflammation. However, especially considering the discrepant findings from the comparisons of the cases with the two different control groups, further study is needed.

Public Health Implications, Possible Future Directions

The primary goal of this study was to assess associations of two different hypothesized healthy dietary patterns with risk for colorectal adenomas and whether these associations differed from each other. We found that both of the dietary scores were inversely associated with risk for adenomas in the comparisons involving the community control group, but not the colonoscopy negative control group, and that the associations for each of the two scores with adenomas were virtually the same.

There are several possible reasons for the similar the findings for the two scores. The food frequency questionnaire used was created to investigate general macronutrient and micronutrient intakes rather than assess general dietary patterns. The Paleolithic diet in particular places great importance on food quality. For example, the nutrient profile of grass-fed meats differs greatly in fat composition [34]. Two different cultivars of beans can also have vastly different nutritional compositions [35], and farming practices, location, and storage can also influence the resulting quality of vegetables. Without a better way to characterize a Paleolithic diet's quality, many of the hypothesized health benefits may not be apparent even if present. Given the similar results for the Paleolithic diet and the Mediterranean diet, no specific health recommendations can be made on the basis of this study, but opportunities to further explore dietary patterns and colorectal cancer development can be generated.

The first step to furthering the analysis presented here is to examine dietary component weighting within each of the dietary scoring systems. For each dietary component (e.g., grains) the point value assigned for the rank of intake was consistent with the recommendations for either diet. Yet the relative importance of two different dietary components to the overall score was not assessed. One possible opportunity to calibrate the weights for dietary components would be to use the results from the cardiovascular and diabetes pilot studies as expected endpoints for a case-control study on heart disease that uses FFQs. Another possibility is to a priori assess the relative macronutrient intakes expected for the given dietary scheme and reassess scoring weights.

Once recalibrating the score is complete, there are several opportunities for further analysis. A larger case-control study or a prospective cohort study of adenoma occurrence or colon cancer development may provide the sample size needed to determine differences in these two dietary scoring systems.

Last, the ideal study design to examine the differences between two diets and risk for colorectal cancer would be controlled-feeding trials. Such an approach could be to first conduct short-term feeding trials with biomarkers of risk for colorectal neoplasms as the study endpoints. Then, depending on the results of these studies, possible trials with adenoma reoccurrence or cancer development as the endpoints could be designed.

Table 1: Selected characteristics of participants in the Minnesota CPRU case-control study of incident, sporadic colorectal adenomas (N=1,783).

Characteristics	Cases (n=564)		Colonoscopy-Negative Controls (N=684)			Population Controls (N=535)		
	% or Mean	SD	% or Mean	SD	p value	% or Mean	SD	p value
Demographics								
Age (yrs.)	58.1	(9.7)	52.8	(11.0)	<0.01	57.7	(10.4)	0.46
Male (%)	61.7		37.6		<0.01	55.1		0.03
White (%)	97.9		97.2		0.22	97.2		0.43
Family History								
First-degree relative with colon cancer (%)	16.3		27.5		<0.01	6.9		<0.01
Lifestyle Factors								
Never Smoker (%)	32.5		46.9		<0.01	44.1		<0.01
Physical Activity (MET-hours/week)	37.4	(39.4)	33.5	(31.1)	0.06	38.2	(39.2)	0.72
Body Mass Index (kg/m^2)	27.4	(4.7)	26.9	(5.0)	0.07	26.4	(4.5)	0.05
Current ethanol intake (g/day)	5.2	(7.6)	3.6	(8.4)	<0.01	4.5	(4.5)	0.22
Taking NSAID (%)	36.4		45.2		<0.01	39.4		0.29
Education (yrs.)	14.0	(3.3)	14.2	(3.0)	0.16	14.1	(2.9)	0.36
Hormone Replacement Therapy (%) (in Women, N=883)	38.8		49.7		0.01	44.2		0.25
Dietary Factors								
Calcium Intake (mg/day)	959.4	(531.1)	985.2	(526.3)	0.39	987.7	(552.4)	0.39
Dietary calcium	860.4	(455.0)	845.8	(437.2)	0.57	882.8	(470.1)	0.42
Supplemental Calcium	99.0	(269.2)	139.4	(328.8)	0.02	104.9	(262.5)	0.71
Dietary Fiber intake (g/day)	13.7	(7.9)	12.7	(6.8)	0.02	13.1	(7.3)	0.19
Total fat intake (g/day)	73.1	(34.4)	68.9	(30.8)	0.02	70.2	(70.2)	0.15
Total Red meat intake (servings/week)	4.7	(4.7)	4.6	(3.6)	0.59	4.4	(3.2)	0.07
Total Vegetable intake (servings/week)	25.5	(25.5)	26.1	(17.6)	0.50	26.0	(14.8)	0.57
Total energy intake (kcal/day)	2,090.7	(775.7)	2,017.2	(720.6)	0.09	2,054.5	(2054.5)	0.42

Table 2: Associations of Paleolithic and Mediterranean Diet scores with incident, sporadic, colorectal adenomas; Minnesota CPRU case-control study.

	Colonoscopy-Negative Controls							
	Paleolithic Diet				Mediterranean Diet			
	Crude OR	95% CI	Adjusted OR	95% CI	Crude OR	95% CI	Adjusted OR	95% CI
Continuous								
	1.01	0.99, 1.03	1.00	0.98, 1.02	1.02	1.00, 1.04	1.01	0.98, 1.03
Quintiles								
1	1.00		1.00		1.00		1.00	
2	0.93	0.65, 1.33	0.86	0.58, 1.28	1.05	0.75, 1.47	0.99	0.68, 1.43
3	1.17	0.84, 1.62	1.23	0.86, 1.77	0.94	0.67, 1.30	0.87	0.60, 1.26
4	1.11	0.77, 1.60	1.08	0.72, 1.62	1.13	0.79, 1.61	1.00	0.68, 1.49
5	1.10	0.78, 1.56	0.96	0.65, 1.40	1.32	0.92, 1.88	1.12	0.75, 1.67
p for trend	*0.37*		*0.80*		*0.16*		*0.67*	

	Population Controls							
	Paleolithic Diet				Mediterranean Diet			
	Crude OR	95% CI	Adjusted OR	95% CI	Crude OR	95% CI	Adjusted OR	95% CI
Continuous								
	0.98	0.96, 1.00	0.98	0.96, 1.00	0.98	0.96, 1.00	0.97	0.95, 1.00
Quintiles								
1	1.00		1.00		1.00		1.00	
2	0.96	0.65, 1.43	0.87	0.58, 1.32	0.84	0.58, 1.21	0.83	0.57, 1.22
3	0.98	0.69, 1.41	0.90	0.62, 1.31	0.75	0.52, 1.09	0.75	0.52, 1.10
4	0.87	0.59, 1.28	0.82	0.55, 1.23	0.80	0.54, 1.17	0.75	0.50, 1.12
5	0.68	0.47, 0.98	0.66	0.45, 0.96	0.68	0.47, 0.99	0.65	0.44, 0.96
p for trend	*0.03*		*0.03*		*0.05*		*0.03*	

Table 3: Associations of Paleolithic and Mediterranean Diet scores and incident, sporadic colorectal adenomas according to selected risk factors for colorectal neoplasms; Minnesota CPRU case-control study.

	Colonoscopy-Negative Controls				Population Controls			
	Paleolithic		Mediterranean		Paleolithic		Mediterranean	
Diet Scoring Quintiles	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Family History of Colon Cancer								
Yes								
1	1.00		1.00		1.00		1.00	
2	1.20	0.47, 3.04	0.66	0.28, 1.52	0.52	0.10, 2.86	1.09	0.20, 6.04
3	1.32	0.58, 3.01	0.70	0.28, 1.73	0.24	0.05, 1.04	0.16	0.03, 0.75
4	1.18	0.44, 3.18	1.40	0.58, 3.39	0.21	0.04, 1.07	0.38	0.09, 1.66
5	1.04	0.43, 2.55	0.91	0.36, 2.33	0.41	0.08, 2.10	0.47	0.10, 2.25
p for trend	*0.95*		*0.53*		*0.18*		*0.16*	
No								
1	1.00		1.00		1.00		1.00	
2	0.79	0.51, 1.23	1.10	0.73, 1.66	0.88	0.57, 1.36	0.83	0.56, 1.23
3	1.22	0.81, 1.84	0.94	0.63, 1.41	1.00	0.68, 1.49	0.84	0.57, 1.25
4	1.07	0.69, 1.67	0.89	0.57, 1.40	0.90	0.59, 1.38	0.80	0.52, 1.23
5	0.93	0.61, 1.43	1.17	0.75, 1.83	0.65	0.44, 0.97	0.67	0.45, 1.01
p for trend	*0.80*		*0.86*		*0.05*		*0.07*	
Sex								
Male								
1	1.00		1.00		1.00		1.00	
2	0.72	0.42, 1.25	0.78	0.47, 1.30	0.93	0.55, 1.59	0.74	0.45, 1.21
3	1.12	0.67, 1.87	0.85	0.51, 1.43	0.81	0.50, 1.30	0.85	0.52, 1.39
4	0.94	0.53, 1.68	0.55	0.31, 0.97	0.79	0.46, 1.36	0.58	0.34, 0.98
5	0.56	0.33, 0.96	0.87	0.50, 1.51	0.51	0.31, 0.85	0.60	0.37, 0.99
p for trend	*0.13*		*0.34*		*0.01*		*0.03*	
Female								
1	1.00		1.00		1.00		1.00	
2	1.02	0.57, 1.83	1.30	0.75, 2.23	0.81	0.42, 1.56	1.00	0.55, 1.84
3	1.22	0.71, 2.09	0.87	0.50, 1.51	1.02	0.55, 1.88	0.66	0.35, 1.22
4	1.18	0.67, 2.10	1.73	0.98, 3.02	0.84	0.45, 1.57	1.10	0.58, 2.07

5	1.65	0.96, 2.83	1.55	0.85, 2.81	0.91	0.51, 1.63	0.75	0.39, 1.43
p for trend	*0.06*		*0.10*		*0.82*		*0.49*	
Age*								
<56 yrs.								
1	1.00		1.00		1.00		1.00	
2	1.20	0.68, 2.14	1.21	0.72, 2.04	1.13	0.58, 2.22	0.71	0.39, 1.30
3	1.34	0.79, 2.26	1.22	0.73, 2.06	0.96	0.52, 1.79	0.71	0.38, 1.33
4	1.46	0.82, 2.59	1.34	0.74, 2.41	0.94	0.49, 1.80	0.60	0.31, 1.18
5	1.41	0.79, 2.51	1.00	0.55, 1.81	0.93	0.49, 1.78	0.78	0.39, 1.57
p for trend	*0.16*		*0.75*		*0.69*		*0.32*	
≥56 yrs.								
1	1.00		1.00		1.00		1.00	
2	0.72	0.42, 1.23	0.89	0.53, 1.49	0.78	0.46, 1.32	0.89	0.54, 1.46
3	1.29	0.77, 2.15	0.71	0.42, 1.18	0.84	0.53, 1.36	0.73	0.45, 1.19
4	0.94	0.54, 1.63	0.96	0.56, 1.64	0.76	0.45, 1.29	0.85	0.51, 1.41
5	0.83	0.50, 1.37	1.38	0.79, 2.41	0.55	0.34, 0.87	0.63	0.39, 1.01
p for trend	*0.76*		*0.28*		*0.01*		*0.07*	
Smoking								
Never Smoked								
1	1.00		1.00		1.00		1.00	
2	0.63	0.31, 1.29	0.98	0.52, 1.86	0.48	0.23, 1.00	0.77	0.40, 1.48
3	1.31	0.71, 2.41	1.03	0.56, 1.90	0.75	0.40, 1.40	0.82	0.43, 1.54
4	0.89	0.46, 1.71	0.61	0.31, 1.21	0.69	0.35, 1.34	0.61	0.30, 1.22
5	1.00	0.53, 1.87	1.58	0.80, 3.12	0.54	0.29, 1.01	0.62	0.32, 1.17
p for trend	*0.77*		*0.64*		*0.17*		*0.11*	
Ever Smoked								
1	1.00		1.00		1.00		1.00	
2	0.95	0.59, 1.54	0.95	0.60, 1.51	1.18	0.71, 1.98	0.84	0.52, 1.36
3	1.23	0.78, 1.95	0.80	0.50, 1.27	1.02	0.64, 1.63	0.72	0.44, 1.16
4	1.26	0.75, 2.13	1.39	0.83, 2.33	0.95	0.57, 1.60	0.82	0.49, 1.35
5	0.92	0.57, 1.49	0.90	0.55, 1.49	0.77	0.48, 1.25	0.74	0.44, 1.22

* Cutoff value based on the distribution reported in the population controls.

p for trend	*0.89*		*0.86*		*0.20*		*0.24*	
BMI								
Under/Normal Weight								
1	1.00		1.00		1.00		1.00	
2	0.79	0.47, 1.33	1.16	0.72, 1.86	0.93	0.54, 1.98	1.16	0.71, 1.89
3	1.13	0.71, 1.80	0.82	0.51, 1.33	1.26	0.77, 1.63	0.78	0.48, 1.27
4	1.02	0.61, 1.72	1.25	0.76, 2.05	1.11	0.65, 1.60	1.40	0.82, 2.39
5	0.98	0.59, 1.61	1.29	0.77, 2.14	0.83	0.51, 1.25	0.86	0.52, 1.42
p for trend	*0.745*		*0.353*		*0.616*		*0.750*	
Overweight/Obese								
1	1.00		1.00		1.00		1.00	
2	0.95	0.51, 1.77	0.79	0.44, 1.41	0.79	0.41, 1.54	0.50	0.27, 0.94
3	1.44	0.80, 2.59	0.93	0.52, 1.68	0.56	0.31, 1.00	0.69	0.37, 1.29
4	1.21	0.62, 2.34	0.67	0.34, 1.33	0.53	0.27, 1.01	0.31	0.16, 0.60
5	0.93	0.51, 1.69	0.90	0.47, 1.73	0.45	0.25, 0.82	0.41	0.22, 0.78
p for trend	*0.91*		*0.62*		*<0.01*		*<0.01*	
Education								
High School or Less								
1	1.00		1.00		1.00		1.00	
2	0.90	0.48, 1.69	1.02	0.58, 1.81	0.88	0.46, 1.69	1.24	0.67, 2.28
3	1.37	0.76, 2.45	0.80	0.45, 1.43	0.99	0.54, 1.82	0.67	0.37, 1.21
4	0.89	0.46, 1.72	1.36	0.69, 2.69	0.64	0.33, 1.24	0.84	0.43, 1.62
5	0.69	0.35, 1.34	1.35	0.64, 2.84	0.50	0.26, 0.97	0.58	0.30, 1.13
p for trend	*0.42*		*0.43*		*0.03*		*0.06*	
Some College								
1	1.00		1.00		1.00		1.00	
2	0.84	0.50, 1.42	0.94	0.58, 1.54	0.89	0.52, 1.52	0.63	0.38, 1.04
3	1.22	0.76, 1.95	0.94	0.58, 1.54	0.86	0.53, 1.40	0.80	0.49, 1.33
4	1.23	0.73, 2.06	0.89	0.53, 1.48	0.96	0.57, 1.63	0.70	0.42, 1.18
5	1.20	0.74, 1.94	1.07	0.65, 1.76	0.77	0.48, 1.25	0.67	0.41, 1.11
p for trend	*0.22*		*0.89*		*0.38*		*0.27*	

Regular NSAID Use								
Yes (≥ once/week)								
1	1.00		1.00		1.00		1.00	
2	1.08	0.58, 1.99	1.06	0.59, 1.91	1.43	0.72, 2.84	0.94	0.49, 1.82
3	1.40	0.78, 2.50	1.10	0.62, 1.96	1.51	0.80, 2.86	0.85	0.45, 1.59
4	1.32	0.68, 2.54	1.12	0.6, 2.09	0.94	0.47, 1.87	0.73	0.37, 1.44
5	1.16	0.64, 2.11	1.28	0.7, 2.37	0.78	0.42, 1.45	0.79	0.41, 1.51
p for trend	*0.51*		*0.43*		*0.15*		*0.34*	
No (< once/week)								
1	1.00		1.00		1.00		1.00	
2	0.91	0.56, 1.49	1.18	0.75, 1.84	0.67	0.40, 1.12	0.77	0.48, 1.23
3	1.35	0.86, 2.11	0.95	0.61, 1.49	0.69	0.43, 1.09	0.69	0.43, 1.12
4	1.13	0.70, 1.83	1.44	0.89, 2.34	0.77	0.46, 1.28	0.80	0.48, 1.31
5	1.22	0.76, 1.95	1.51	0.91, 2.51	0.63	0.39, 1.01	0.59	0.36, 0.96
p for trend	*0.28*		*0.09*		*0.12*		*0.06*	
Physical Activity*								
Low (<25 METS/week)								
1	1.00		1.00		1.00		1.00	
2	0.98	0.57, 1.69	1.11	0.69, 1.81	1.04	0.59, 1.83	0.84	0.50, 1.41
3	1.18	0.72, 1.94	0.90	0.54, 1.48	1.06	0.63, 1.76	0.62	0.37, 1.05
4	1.49	0.86, 2.61	1.18	0.69, 2.03	1.06	0.60, 1.85	0.67	0.38, 1.16
5	0.89	0.52, 1.52	1.06	0.59, 1.90	0.72	0.42, 1.21	0.53	0.30, 0.94
p for trend	*0.77*		*0.81*		*0.28*		*0.02*	
High (≥25 METS/week)								
1	1.00		1.00		1.00		1.00	
2	0.71	0.39, 1.29	0.83	0.47, 1.47	0.68	0.37, 1.25	0.82	0.46, 1.45
3	1.23	0.71, 2.13	0.83	0.48, 1.43	0.72	0.41, 1.27	0.91	0.52, 1.60
4	0.78	0.43, 1.42	0.82	0.45, 1.49	0.57	0.31, 1.05	0.84	0.47, 1.52
5	1.00	0.57, 1.76	1.12	0.63, 2.00	0.57	0.33, 0.99	0.77	0.44, 1.33
p for trend	*0.87*		*0.70*		*0.05*		*0.42*	

* Cutoff value based on the distribution reported in the population controls.

Table 4: Associations of Paleolithic and Mediterranean Diet scores and incident, sporadic colorectal adenomas according to selected adenoma characteristics; Minnesota CPRU case-control study.

	Colonoscopy Negative Controls				Population Controls			
	Paleolithic		Mediterranean		Paleolithic		Mediterranean	
Diet Scoring Quintiles	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Number of Adenomas								
1								
1	1.00		1.00		1.00		1.00	
2	0.92	0.60, 1.40	1.00	0.67, 1.49	0.95	0.61, 1.47	0.85	0.56, 1.28
3	1.04	0.70, 1.56	0.84	0.56, 1.26	0.79	0.52, 1.19	0.70	0.46, 1.06
4	1.02	0.65, 1.58	0.83	0.53, 1.30	0.77	0.49, 1.20	0.61	0.39, 0.96
5	1.01	0.67, 1.52	1.21	0.79, 1.86	0.72	0.48, 1.08	0.72	0.47, 1.10
p for trend	*0.82*		*0.72*		*0.07*		*0.05*	
> 1								
1	1.00		1.00		1.00		1.00	
2	0.61	0.32, 1.15	0.88	0.50, 1.55	0.69	0.37, 1.30	0.80	0.45, 1.39
3	1.64	0.97, 2.79	0.90	0.51, 1.57	1.07	0.63, 1.81	0.84	0.49, 1.46
4	1.08	0.59, 1.98	1.23	0.70, 2.17	0.86	0.48, 1.55	1.06	0.61, 1.84
5	0.62	0.34, 1.14	0.80	0.43, 1.52	0.51	0.28, 0.92	0.47	0.26, 0.87
p for trend	*0.55*		*0.99*		*0.07*		*0.09*	
Size of Largest Adenoma								
< 1 cm								
1	1.00		1.00		1.00		1.00	
2	0.71	0.45, 1.13	0.99	0.65, 1.50	0.81	0.51, 1.29	0.87	0.57, 1.33
3	1.35	0.90, 2.02	0.82	0.54, 1.26	1.03	0.68, 1.55	0.71	0.46, 1.08
4	1.17	0.75, 1.83	1.04	0.67, 1.63	0.92	0.59, 1.44	0.80	0.51, 1.25
5	0.91	0.59, 1.40	1.23	0.79, 1.91	0.68	0.45, 1.04	0.74	0.49, 1.14
p for trend	*0.66*		*0.40*		*0.14*		*0.17*	
>=1 cm								
1	1.00		1.00		1.00		1.00	
2	1.04	0.63, 1.71	1.11	0.69, 1.79	1.03	0.62, 1.71	0.90	0.56, 1.46
3	1.06	0.66, 1.71	1.00	0.62, 1.61	0.72	0.44, 1.17	0.89	0.55, 1.43
4	0.86	0.50, 1.48	0.95	0.56, 1.61	0.62	0.36, 1.07	0.75	0.45, 1.26

5	1.07	0.66, 1.73	1.23	0.73, 2.06	0.74	0.46, 1.19	0.67	0.41, 1.11
p for trend	*0.99*		*0.70*		*0.07*		*0.09*	
Location of Worst Adenoma								
Right Colon								
1	1.00		1.00		1.00		1.00	
2	0.83	0.42, 1.64	0.82	0.44, 1.53	0.89	0.45, 1.78	0.80	0.43, 1.50
3	1.74	0.96, 3.15	0.91	0.49, 1.69	1.10	0.61, 1.99	0.83	0.45, 1.53
4	1.25	0.64, 2.46	0.94	0.49, 1.79	0.86	0.44, 1.69	0.84	0.45, 1.60
5	0.82	0.43, 1.59	1.16	0.61, 2.21	0.69	0.37, 1.31	0.73	0.39, 1.35
p for trend	*0.96*		*0.58*		*0.25*		*0.40*	
Left Colon								
1	1.00		1.00		1.00		1.00	
2	0.83	0.55, 1.26	1.01	0.68, 1.49	0.87	0.57, 1.34	0.84	0.56, 1.25
3	1.08	0.74, 1.60	0.83	0.56, 1.24	0.82	0.55, 1.23	0.71	0.48, 1.06
4	0.99	0.65, 1.52	0.98	0.64, 1.50	0.79	0.51, 1.21	0.72	0.47, 1.11
5	0.95	0.63, 1.41	1.11	0.72, 1.70	0.66	0.44, 0.98	0.64	0.42, 0.97
p for trend	*0.94*		*0.79*		*0.04*		*0.03*	
Degree of Atypia								
Mild								
1	1.00		1.00		1.00		1.00	
2	0.81	0.49, 1.34	1.11	0.70, 1.75	0.91	0.55, 1.50	0.98	0.62, 1.56
3	1.53	0.99, 2.37	1.04	0.66, 1.63	1.15	0.74, 1.80	0.87	0.55, 1.38
4	1.12	0.68, 1.85	0.96	0.58, 1.59	0.85	0.51, 1.40	0.77	0.47, 1.26
5	0.87	0.54, 1.40	1.20	0.74, 1.96	0.67	0.42, 1.07	0.75	0.47, 1.22
p for trend	*0.99*		*0.70*		*0.09*		*0.14*	
Moderate-Severe								
1	1.00		1.00		1.00		1.00	
2	0.82	0.51, 1.32	0.83	0.53, 1.32	0.82	0.51, 1.35	0.71	0.45, 1.12
3	0.94	0.59, 1.48	0.69	0.44, 1.10	0.64	0.40, 1.01	0.64	0.40, 1.01
4	0.97	0.60, 1.58	0.92	0.57, 1.49	0.75	0.46, 1.22	0.71	0.44, 1.15
5	0.90	0.57, 1.42	1.01	0.62, 1.65	0.63	0.40, 0.99	0.55	0.34, 0.89
p for trend	*0.88*		*0.98*		*0.05*		*0.03*	

Histologic Subtype								
Tubular								
1	1.00		1.00		1.00		1.00	
2	0.77	0.49, 1.22	1.11	0.74, 1.67	0.79	0.50, 1.27	0.94	0.61, 1.42
3	1.56	1.05, 2.32	0.99	0.65, 1.49	1.12	0.75, 1.68	0.80	0.52, 1.22
4	1.29	0.83, 2.01	1.11	0.71, 1.72	0.95	0.61, 1.48	0.82	0.53, 1.29
5	0.93	0.61, 1.43	1.27	0.81, 1.97	0.67	0.44, 1.02	0.74	0.48, 1.13
p for trend	*0.55*		*0.38*		*0.13*		*0.13*	
Tubulovillous or villous								
1	1.00		1.00		1.00		1.00	
2	0.91	0.54, 1.56	0.74	0.44, 1.27	0.99	0.58, 1.70	0.68	0.40, 1.14
3	0.64	0.37, 1.12	0.63	0.37, 1.08	0.45	0.26, 0.79	0.62	0.37, 1.05
4	0.68	0.38, 1.24	0.66	0.37, 1.18	0.55	0.30, 1.00	0.58	0.33, 1.01
5	0.80	0.47, 1.37	0.82	0.46, 1.45	0.62	0.37, 1.04	0.48	0.28, 0.84
p for trend	*0.25*		*0.33*		*0.02*		*0.01*	

Table 5: Distribution of Dietary scores by case-control status; Minnesota CPRU case-control study.

Status	Quintiles of Dietary Score				
Paleolithic Diet Score	1	2	3	4	5
Case (%)	20.92	16.84	25.53	16.67	20.04
Colonoscopy-Negative Control (%)	22.22	19.3	23.25	15.94	19.3
Population Control (%)	18.5	15.51	22.99	17.01	25.98
Mediterranean Diet Score					
Case (%)	22.7	21.1	20.57	17.55	18.09
Colonoscopy-Negative Control (%)	24.12	21.35	23.39	16.52	14.62
Population Control (%)	18.32	20.37	22.06	17.76	21.5

Appendix

Table 6: Cut points used for the 19 different components of the Mediterranean and Paleolithic diet scores. The cutoffs are based on the distribution of the dietary intake in the population controls in both males and females.

Males

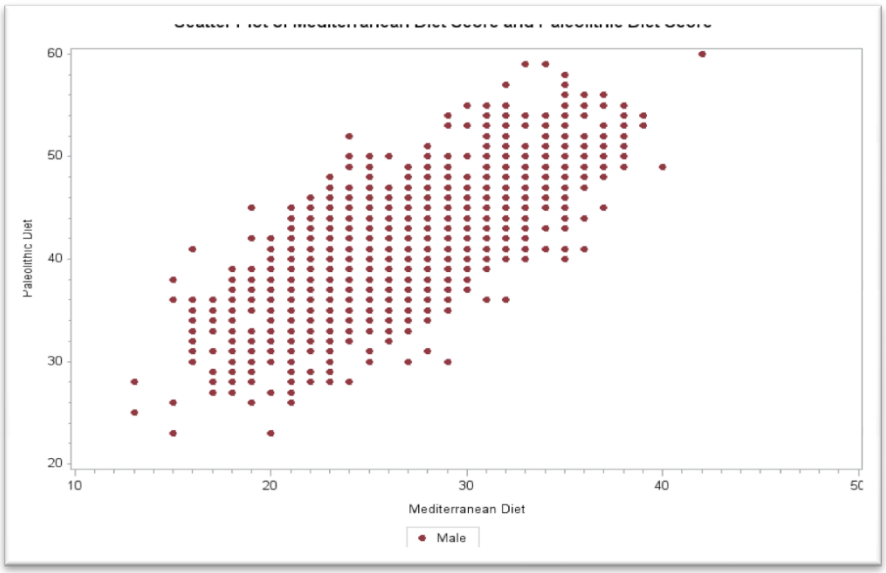
Dietary Measure	Units	20th Percentile	40th Percentile	60th Percentile	80th Percentile
Total Vegetables	Servings/Wk	13.50	19.00	25.00	35.00
High Fat Dairy	Servings/Wk	3.00	5.50	8.50	17.00
Total Dairy	Servings/Wk	9.00	13.00	21.00	28.00
Total Fruit	Servings/Wk	7.00	13.00	18.00	25.50
Total Bread, Grains, Potatoes	Servings/Wk	18.00	25.50	32.50	43.00
Red Meat	Servings/Wk	2.00	3.50	5.00	7.50
High Fat Meat	Servings/Wk	5.00	7.50	10.50	14.50
Low Fat Meat	Servings/Wk	1.00	1.50	2.50	4.00
Fish	Servings/Wk	0.50	1.00	2.00	2.50
Nuts	Servings/Wk	0.50	1.00	3.00	5.50
Alcoholic Beverages	Servings/Wk	0.00	0.50	3.50	8.00
Sodium	grams/Wk	1772.48	2274.90	2700.57	3259.82
Sweets	Servings/Wk	3.00	7.00	10.50	17.00
High Sugar Beverages	Servings/Wk	0.00	1.00	2.00	7.00
Total Calcium	grams/Wk	565.84	761.28	968.64	1328.53
Dietary Calcium	grams/Wk	542.97	731.28	916.91	1273.41
Mono:Saturated Fat Ratio		0.98	1.09	1.17	1.26
Residual Effect of Dairy and Calcium		-166.97	-42.89	80.32	220.14
Fruit and Vegetable Diversity		6.00	11.00	15.00	19.00

Females

Dietary Measure	Units	20th Percentile	40th Percentile	60th Percentile	80th Percentile
Total Vegetables	Servings/Wk	16.00	22.25	28.00	37.75
High Fat Dairy	Servings/Wk	2.50	4.50	6.50	11.00
Total Dairy	Servings/Wk	7.00	11.50	16.75	25.50
Total Fruit	Servings/Wk	9.50	14.50	21.50	28.00
Total Bread, Grains, Potatoes	Servings/Wk	16.50	21.50	28.75	39.50
Red Meat	Servings/Wk	2.00	2.50	3.50	5.00
High Fat Meat	Servings/Wk	3.00	4.50	6.00	9.00
Low Fat Meat	Servings/Wk	1.50	2.50	3.75	4.50
Fish	Servings/Wk	0.50	1.00	2.00	2.50
Nuts	Servings/Wk	0.50	1.00	1.50	3.50
Alcoholic Beverages	Servings/Wk	0.00	0.00	0.50	4.50
Sodium	grams/Wk	1505.65	2023.55	2474.51	2972.20
Sweets	Servings/Wk	2.00	4.50	7.50	12.75
High Sugar Beverages	Servings/Wk	0.00	0.00	1.00	3.00
Total Calcium	grams/Wk	517.71	768.64	1085.81	1382.11
Dietary Calcium	grams/Wk	454.33	640.65	839.84	1246.52
Mono:Saturated Fat Ratio		0.98	1.07	1.15	1.26

Residual Effect of Dairy and Calcium		-146.83	-48.73	60.98	190.04
Fruit and Vegetable Diversity		8.00	13.00	17.00	23.00

Figure 1. Scatter plot of Mediterranean diet score and Paleolithic diet score for Males and Females.



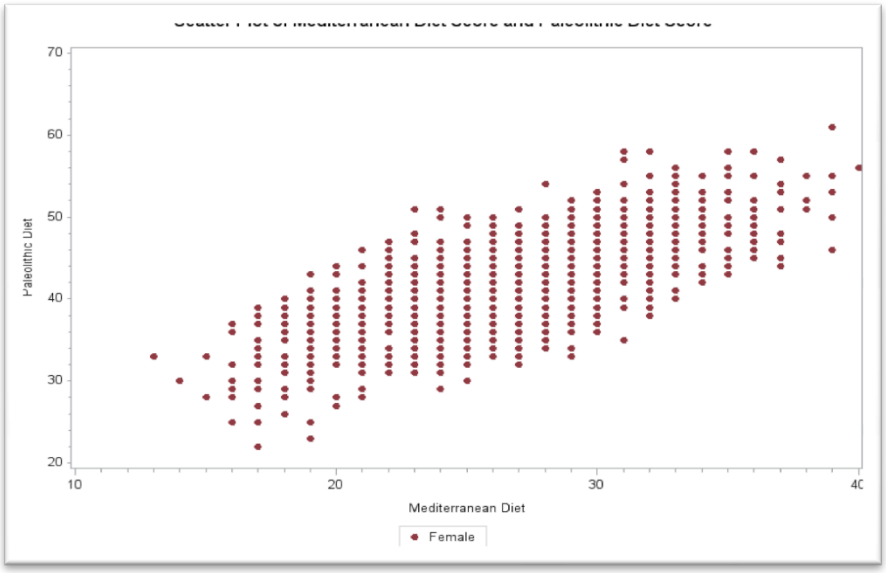


Table 7: Associations of Paleolithic and Mediterranean Diet scores and incident, sporadic colorectal adenomas according to selected female reproductive history characteristics; Minnesota CPRU case-control study.

	Colonoscopy Negative Controls				Population Controls			
	Paleolithic		Mediterranean		Paleolithic		Mediterranean	
Diet Scoring Quintiles	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Hormonal Birth Control Use								
Yes								
1	1.00		1.00		1.00		1.00	
2	1.03	0.46, 2.29	1.22	0.59, 2.51	0.85	0.33, 2.22	0.68	0.28, 1.63
3	1.03	0.50, 2.12	1.13	0.55, 2.30	1.02	0.42, 2.50	0.54	0.22, 1.31
4	1.45	0.67, 3.13	1.87	0.90, 3.91	0.86	0.36, 2.09	0.98	0.40, 2.43
5	1.70	0.81, 3.59	1.23	0.53, 2.87	1.04	0.44, 2.47	0.42	0.16, 1.11
p for trend	*0.11*		*0.28*		*0.92*		*0.25*	
No								
1	1.00		1.00		1.00		1.00	
2	1.00	0.41, 2.41	1.35	0.59, 3.10	0.90	0.35, 2.34	1.39	0.58, 3.32
3	1.52	0.67, 3.44	0.65	0.27, 1.57	1.11	0.46, 2.69	0.71	0.29, 1.77
4	0.89	0.38, 2.12	1.50	0.62, 3.61	0.83	0.33, 2.09	1.16	0.46, 2.92
5	1.66	0.75, 3.67	1.84	0.76, 4.46	0.87	0.39, 1.96	1.15	0.47, 2.78
p for trend	*0.29*		*0.19*		*0.69*		*1.00*	
Age at Menopause*								
Young (<48)								
1	1.00		1.00		1.00		1.00	
2	1.13	0.52, 2.48	1.06	0.52, 2.14	1.24	0.53, 2.94	0.91	0.41, 2.04
3	1.34	0.64, 2.78	1.07	0.54, 2.14	1.62	0.71, 3.71	0.65	0.29, 1.43
4	1.29	0.60, 2.80	1.24	0.59, 2.64	1.72	0.72, 4.10	0.78	0.32, 1.87
5	1.79	0.83, 3.84	1.24	0.55, 2.77	1.13	0.51, 2.49	0.62	0.25, 1.52
p for trend	*0.13*		*0.52*		*0.65*		*0.27*	
Old (≥48 yrs)								
1	1.00		1.00		1.00		1.00	

* Cutoff value based on the distribution reported in the population controls.

2	0.98	0.39, 2.45	1.75	0.73, 4.22	0.44	0.15, 1.27	1.13	0.45, 2.87
3	1.18	0.53, 2.66	0.62	0.25, 1.57	0.52	0.20, 1.36	0.62	0.23, 1.70
4	1.13	0.47, 2.72	2.64	1.08, 6.50	0.35	0.13, 0.89	1.51	0.58, 3.93
5	1.57	0.72, 3.43	1.92	0.76, 4.87	0.61	0.24, 1.51	0.89	0.34, 2.31
p for trend	*0.25*		*0.10*		*0.30*		*0.98*	
Age at First Birth*								
Young (<23 yrs)								
1	1.00		1.00		1.00		1.00	
2	1.54	0.49, 4.80	2.15	0.72, 6.39	1.22	0.32, 4.60	1.55	0.40, 6.00
3	0.75	0.23, 2.47	1.28	0.46, 3.56	0.83	0.19, 3.65	0.96	0.27, 3.46
4	0.98	0.28, 3.42	1.37	0.43, 4.35	1.21	0.27, 5.37	1.22	0.27, 5.56
5	1.45	0.45, 4.68	0.78	0.17, 3.64	1.12	0.27, 4.61	0.29	0.04, 2.04
p for trend	*0.84*		*0.83*		*0.92*		*0.31*	
Old (≥23 yrs)								
1	1.00		1.00		1.00		1.00	
2	0.85	0.42, 1.69	1.14	0.61, 2.14	0.75	0.34, 1.66	0.92	0.46, 1.85
3	1.33	0.72, 2.46	0.75	0.39, 1.44	1.04	0.52, 2.07	0.58	0.28, 1.20
4	1.25	0.65, 2.41	1.91	0.99, 3.69	0.77	0.38, 1.55	1.09	0.53, 2.22
5	1.70	0.92, 3.16	1.70	0.86, 3.34	0.84	0.44, 1.61	0.82	0.40, 1.67
p for trend	*0.05*		*0.04*		*0.62*		*0.80*	
Hormone Replacement Therapy								
Yes								
1	1.00		1.00		1.00		1.00	
2	1.84	0.63, 5.32	0.80	0.33, 1.92	2.19	0.66, 7.29	0.85	0.32, 2.29
3	2.42	0.93, 6.28	0.63	0.25, 1.58	3.33	1.18, 9.41	0.50	0.18, 1.40
4	2.85	1.06, 7.63	1.81	0.77, 4.28	2.56	0.90, 7.32	1.66	0.62, 4.46
5	2.31	0.84, 6.39	1.13	0.46, 2.82	1.47	0.52, 4.16	1.03	0.37, 2.82
p for trend	*0.08*		*0.24*		*0.63*		*0.49*	
No								
1	1.00		1.00		1.00		1.00	
2	0.85	0.40, 1.81	1.91	0.94, 3.91	0.48	0.21, 1.10	1.05	0.48, 2.32

* Cutoff value based on the distribution reported in the population controls.

3	0.99	0.49, 2.02	1.09	0.54, 2.19	0.54	0.24, 1.22	0.75	0.34, 1.66
4	0.75	0.34, 1.63	1.72	0.81, 3.66	0.48	0.20, 1.12	0.83	0.36, 1.94
5	1.55	0.80, 3.03	2.16	0.93, 5.00	0.71	0.34, 1.50	0.61	0.26, 1.42
p for trend	*0.28*		*0.15*		*0.53*		*0.18*	
Parity								
1-2 Live Births								
1	1.00		1.00		1.00		1.00	
2	1.24	0.46, 3.33	1.15	0.44, 3.00	2.03	0.62, 6.61	0.94	0.32, 2.78
3	1.59	0.61, 4.13	0.96	0.40, 2.32	3.08	0.97, 9.78	0.94	0.32, 2.75
4	0.86	0.30, 2.51	1.58	0.59, 4.18	0.88	0.27, 2.86	0.58	0.19, 1.81
5	1.93	0.73, 5.06	0.85	0.29, 2.49	1.64	0.54, 5.02	0.48	0.14, 1.71
p for trend	*0.33*		*0.94*		*0.93*		*0.17*	
3 or More Live Births								
1	1.00		1.00		1.00		1.00	
2	0.68	0.30, 1.55	1.04	0.50, 2.17	0.39	0.15, 0.97	0.87	0.37, 2.02
3	0.85	0.40, 1.80	0.68	0.31, 1.51	0.59	0.24, 1.41	0.43	0.18, 1.04
4	1.20	0.56, 2.60	1.53	0.71, 3.29	0.60	0.25, 1.42	1.56	0.61, 3.99
5	1.03	0.49, 2.17	1.46	0.63, 3.38	0.51	0.22, 1.19	0.59	0.24, 1.47
p for trend	*0.55*		*0.24*		*0.34*		*0.58*	
Age at First Menstruation*								
Young (<13 yrs)								
1	1.00		1.00		1.00		1.00	
2	1.81	0.65, 5.10	0.84	0.33, 2.11	1.43	0.46, 4.45	0.82	0.31, 2.17
3	2.25	0.92, 5.47	0.95	0.40, 2.25	1.71	0.64, 4.55	0.98	0.39, 2.46
4	3.27	1.29, 8.30	2.39	1.00, 5.69	2.59	0.96, 7.01	2.19	0.86, 5.57
5	3.20	1.33, 7.68	1.34	0.55, 3.24	2.25	0.89, 5.71	1.64	0.64, 4.23
p for trend	*0.01*		*0.11*		*0.05*		*0.06*	
Old (≥13 yrs)								
1	1.00		1.00		1.00		1.00	
2	0.75	0.36, 1.54	1.69	0.85, 3.34	0.58	0.25, 1.34	1.02	0.46, 2.27
3	0.89	0.44, 1.81	0.80	0.38, 1.67	0.83	0.36, 1.90	0.45	0.19, 1.06

* Cutoff value based on the distribution reported in the population controls.

4	0.60	0.28, 1.30	1.26	0.59, 2.72	0.37	0.16, 0.88	0.56	0.22, 1.38
5	1.12	0.54, 2.33	1.93	0.80, 4.66	0.50	0.22, 1.12	0.35	0.14, 0.89
p for trend	*0.97*		*0.49*		*0.05*		*0.01*	

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