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Associations of Evolutionary-Concordance Diet and Lifestyle Pattern Scores with Incident, Sporadic Adenoma in a Pooled Case-Control Study

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By

McKenna J. Penley

B.A., Indiana University, 2012

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

An abstract of
A thesis submitted to the Faculty of the
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2020

Abstract

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By McKenna J. Penley

The evolutionary-concordance hypothesis posits that differences in diet and lifestyle, relative to those of our Paleolithic-era ancestors, may explain the high incidence of major chronic diseases, including colorectal cancer (CRC), in modern Westernized countries. To address this, we previously reported evolutionary-concordance diet and lifestyle pattern scores to reflect closeness of diet and lifestyle patterns to those of Paleolithic-era humans, and found them to be associated with lower CRC incidence in women. Separate and joint associations of the scores with colorectal adenoma among men and women are unknown.

We pooled data from three case-control studies of incident, sporadic colorectal adenomas (N = 771 cases, 1,990 controls), and used participants' responses to food frequency and lifestyle questionnaires to calculate evolutionary-concordance diet (comprising 14 components) and lifestyle (comprising smoking status, body mass index, and physical activity) pattern scores, such that higher scores indicated higher evolutionary-concordance. We estimated associations of the scores with adenomas using multivariable unconditional logistic regression.

The multivariable-adjusted odds ratios comparing those in the highest relative to the lowest quintiles of the diet and lifestyle scores were 0.84 (95% confidence interval [CI]: 0.62-1.12, P_{trend}: 0.04) and 0.41 (95% CI: 0.29-0.59, P_{trend}: <0.0001), respectively. The inverse associations were stronger for adenomas with higher risk characteristics, and among those with both high a diet and lifestyle score relative to those with both a low diet and lifestyle score.

These results suggest that more evolutionary concordant diet and lifestyle patterns, separately and jointly, may be associated with lower risk for incident, sporadic colorectal adenoma.

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Associations of Evolutionary-Concordance Diet and Lifestyle Pattern Scores with Incident, Sporadic Adenoma in a Pooled Case-Control Study

By, McKenna J. Penley

Chapter 1: Background

Globally, colorectal cancer (CRC) is the third most common cancer among men, and the second most common cancer among women (1). There are 1.4 million newly diagnosed cases and 690,000 deaths annually, representing 9.7% of all cancer cases (excluding non-melanoma skin cancers), and 8.5% of all cancer deaths (1,2). The global CRC burden is expected to increase 60% over the next 15 years (1).

A family history of CRC in at least one first-degree relative is found in 15-20% of CRC cases (1,2). Approximately 80% of CRC cases occur after age 55, and therefore screening is recommended for average-risk individuals beginning at age 50 (2). Globally, CRC is more common among men – the incidence rate for men is 1.44 times that of women (2). In the United States, incidence is different by race; the highest annual incidence rates occur among African Americans (men: 63.8/100,000 people; women: 47.6/100,000 people) and the lowest occur among Asian/Pacific Islanders (men: 40.8/100,000; women: 31/100,000 people) (2). African Americans also have the highest CRC mortality rate (men: 29.4/100,000 people; women: 19.4/100,000 people), which may be related to lower socioeconomic status (SES) (2). SES is associated with CRC incidence; in the US, lower SES is associated with higher CRC risk, which may be due to a higher prevalence of obesity, poor diet, smoking, leisure time inactivity, and reduced screening among low SES groups (2). However, in European and Nordic countries SES is inversely associated with CRC risk, and this may be due to higher adherence to the Mediterranean and Nordic diet patterns (2).

Overall, there is wide international variation in CRC incidence–the highest CRC rates are observed in Australia, New Zealand, Europe, and North America, and the lowest rates are observed in African and South-central Asian countries–with ten-fold difference in incidence from the least- to most-affected countries (1,2). International

incidence rates are associated with economic development and uptake of the Western diet and physical inactivity (2). For example, approximately two-thirds of CRC cases, and ~60% of CRC deaths, occur in countries categorized as high or very high in development indices, and increasing trends in risk are observed among economically-transitioning regions, such as in Asia, Eastern Europe, and Latin American (1,2). Further, migration studies found that individuals who moved from low- to high-incidence countries initially had CRC incidence rates intermediate between those in their home and host countries, becoming more like those in the host country with longer duration of residence (2). Taken together, this suggests a role of environmental factors in the development of CRC.

CRC can occur anywhere along the large bowel, from the cecum to the rectum (2). Most CRCs develop from adenomatous polyps, or adenomas, which are pre-malignant, neoplastic growths arising from the wall of the large intestine (2). However, fewer than 10% of adenomas will progress into CRC, and this process will typically take at least 10 years (2). Adenomas occur as three histologic types: tubular (which account for 75-90% of adenomas), tubulo-villous, and villous (2). Adenoma characteristics considered high-risk for progression to CRC include villous histology, larger size (≥1.0 cm in diameter), multiplicity, and a higher degree of dysplasia (2). Once CRC develops, the five-year survival ranges from 90% for stage I to 13% for stage IV (1).

Most CRC cases are considered sporadic; however, about 5% of cases are due to recognized high-penetrance inherited mutations (1,2). There are three major CRC molecular subtypes, with different pathways of development—the most common being the chromosomal instability (CIN) pathway (2). The CIN pathway involves mutation of the tumor suppressor gene *APC*, and is involved in about 85% of sporadic CRC cases (3). When the inactivating mutation of the *APC* gene is inherited, familial adenomatous polyposis (FAP) results (accounting for less the 1% of CRC cases) and causes hundreds

to thousands of polyps by the ages of 20-30 years, and most often the development of CRC by the age of 40 years (2,3). The second major molecular pathway is the CpG island methylator pathway (CIMP), which involves aberrant DNA methylation, causing epigenetic silencing of tumor suppressor genes (2,3). Finally, the third major pathway is the microsatellite instability (MSI) pathway, which involves inactivation of DNA mismatch repair genes, such as *MLH1* and *MLH2* (2). When a mutated allele of a mismatch repair gene is inherited, and later accompanied by a somatic inactivation the other allele, hereditary non-polyposis colon cancer (HNPCC) results (responsible for 1-5% of CRC cases), leading to the development of CRC at an early age (mid-forties) (2,3). It is generally understood that sporadic CRC results from interactions of multiple modifiable risk factors in combination with low-penetrance susceptibility genes, and chance (2).

Some lifestyle factors have been identified as important risk factors for CRC, including physical activity, body-mass index (BMI), and cigarette smoking. Physical activity has been consistently inversely associated with CRC incidence. In a meta-analysis of 12 studies (n = 8,396 cases) the relative risk of colon cancer for those in the highest relative to the lowest levels of physical activity was 0.80 (95% confidence interval [CI]: 0.72-0.88) (1). BMI has been found to be positively associated with CRC incidence. In a dose-response meta-analysis of 57 studies (n = 71,089 cases), the relative risk of CRC for each 5 kg/m_2 increase in body weight was 1.05 (95% CI: 1.03-1.07) (1). Cigarette smoking has been found to be positively associated with CRC incidence. In a meta-analysis of 22 studies, the relative risks for CRC among current and former smokers were 1.15 (95% CI: 1.00-1.32) and 1.20 (95% CI: 1.04-1.38), respectively (4). Each of these individual lifestyle factors is weakly associated with CRC risk; therefore, it may be useful to use a lifestyle pattern score in order to account for the combined and interacting effects of these individual lifestyle factors.

In previous work, a combined lifestyle pattern score, termed the evolutionary-concordance lifestyle score (a higher score reflects higher concordance, hypothesized to be lower risk), that included physical activity, BMI, and smoking status, was statistically significantly inversely associated with incident CRC risk (5). The relative risk for those in the highest (i.e., high physical activity, normal BMI, and never smoker) relative to those in the lowest lifestyle (i.e., low physical activity, obese, current smoker) pattern score quintiles was 0.66 (95% CI: 0.56-0.78) (5).

The Continuous Update Project (CUP), managed by the World Cancer Research Fund (WCRF) in partnership with the American Institute for Cancer Research (AICR), is an ongoing program "to analyze cancer prevention and survival research related to diet, nutrition, and physical activity from all over the world" (1). The CUP collects research from around the world, performs systematic reviews of the data, and serves as a trusted and authoritative scientific resource to inform guidelines and policy for cancer prevention (1). According to the CUP, there is strong evidence of lower risk of CRC associated with consumption of whole grains (RR: 0.83, 95% CI: 0.78-0.89, per 90 g increase/day), dietary fiber (RR: 0.91, 95% CI: 0.88-0.94, per 10 g increase/day), dairy products (RR: 0.87, 95% CI: 0.83-0.90, per 400 g increase/day), and dietary calcium (RR: 0.94, 95% CI:0.93-0.96, per 200 mg increase/day) (1). While not as strong, there is some evidence of lower risk of CRC associated with higher intakes of vitamin C (RR: 0.94, 95% CI: 0.89-0.99, per 40 mg increase/day), fish (RR: 0.89, 95% CI: 0.80-0.99, per 100 g increase/day), and vitamin D (RR: 0.95, 95% CI: 0.93-0.98, per 100 IU increase/day), and with taking multivitamins (RR: 0.88, 95% CI: 0.79-0.98, users vs non-users). Additionally, there is strong evidence that red and processed meat intake (RR: 1.12 95% CI:1.04-1.21, per 100 g increase/day) and alcohol use among men (RR: 1.08, 95% CI: 1.06-1.09, per 10 g increase/day), and some evidence that low vegetable consumption (increased risk below 100 g/day), low fruit consumption (increased risk below 100

g/day), and heme iron (increased risk above 0.6 mg/day) are all associated with higher risk of CRC (1).

While these individual dietary components have been associated with CRC, none of them fully explain the 10-fold difference in risk that is observed among the highest- compared to the lowest-risk countries. Therefore, when considering the impact of diet on CRC risk, it may be useful to investigate dietary patterns, rather than individual dietary components. Dietary patterns account for the full scope of components consumed, as well as potential interactions among the components. Well-known dietary patterns include the Mediterranean diet (MD), the Dietary Approaches to Stop Hypertension (DASH) diet, and the Health Eating Index (HEI). The evolutionary concordance diet score was developed to quantify the relative closeness of a diet to a diet consumed in Paleolithic times. It addresses the evolutionary discordance hypothesis, which posits that recent changes in human diet and lifestyle, relative to those of our Paleolithic-era ancestors, may explain the sudden rises in chronic diseases, including CRC, during the 20th century (6). The Paleolithic diet is characterized as high in fruits, vegetables, and lean meats, very low in sugar and salt, and excluding grains and dairy (6,7). Previous investigations found Paleolithic diet pattern scores to be inversely associated with incident, sporadic colorectal adenomas, the precursors of most CRC, and with risk of incident colorectal cancer among older white females (5,8).

In previous work, interaction was observed between evolutionary-concordance diet and lifestyle pattern scores ($P_{interaction} < 0.01$) in relation to risk for incident colorectal cancer among older, white women (5). This finding suggested that the combination of lifestyle and diet pattern scores may be more strongly associated with CRC risk than either score alone. In fact, the lowest relative risk was among women in the joint highest tertile of the evolutionary-concordance diet pattern score and the evolutionary-concordance lifestyle score (0.72 [95% CI: 0.60-0.87]), relative to those in the lowest

joint tertile. However, these results were from a study of a mostly homogeneous group (older, white women). A lifestyle evolutionary-concordance score has not been investigated among men, and a potential interaction of the evolutionary-concordance diet and lifestyle scores in relation to colorectal neoplasms has not been investigated among men or in relation to colorectal adenoma.

Accordingly, I will investigate associations of evolutionary-concordance diet and lifestyle pattern scores, separately and jointly, with incident, sporadic adenomas in three pooled case-control studies with a large, more diverse population (n = 2,761).

Chapter 2: Manuscript for Submission for Publication in a Peer-Reviewed Journal

Student Contributions and Intended Journal

McKenna Penley's contributions to the project include secondary data analysis, data interpretation, writing, and figure/table development.

This manuscript is intended for submission to the journal *Cancer Epidemiology, Biomarkers & Prevention*.

Title: Associations of evolutionary-concordance diet and lifestyle pattern scores with incident, sporadic adenoma in a pooled case-control study

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Abbreviations: ACS, American Cancer Society; AICR, American Institute for Cancer Research; ANOVA, analysis of variance; BMI, body mass index; CI, confidence interval; CPRU, Cancer Prevention Research Unit; CRC, colorectal cancer; DASH; Dietary Approaches to Stop Hypertension; DII, dietary inflammation index; FFQ, food frequency questionnaire, HEI; Heathy Eating Index; HRT, hormone replacement therapy; IWHS, Iowa Women's Health Study; MAP, Markers of Adenomatous Polyps; MD, Mediterranean diet; MET, metabolic equivalent of task; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; RR, risk ratio; WCRF, World Cancer Research Fund

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Abstract

The evolutionary-concordance hypothesis posits that differences in diet and lifestyle, relative to those of our Paleolithic-era ancestors, may explain the high incidence of major chronic diseases, including colorectal cancer (CRC), in modern Westernized countries. To address this, we previously reported evolutionary-concordance diet and lifestyle pattern scores to reflect closeness of diet and lifestyle patterns to those of Paleolithic-era humans, and found them to be associated with lower CRC incidence in women. Separate and joint associations of the scores with colorectal adenoma among men and women are unknown.

We pooled data from three case-control studies of incident, sporadic colorectal adenomas (N = 771 cases, 1,990 controls), and used participants' responses to food frequency and lifestyle questionnaires to calculate evolutionary-concordance diet (comprising 14 components) and lifestyle (comprising smoking status, body mass index, and physical activity) pattern scores, such that higher scores indicated higher evolutionary-concordance. We estimated associations of the scores with adenomas using multivariable unconditional logistic regression.

The multivariable-adjusted odds ratios comparing those in the highest relative to the lowest quintiles of the diet and lifestyle scores were 0.84 (95% confidence interval [CI]: 0.62-1.12, P_{trend}: 0.04) and 0.41 (95% CI: 0.29-0.59, P_{trend}: <0.0001), respectively. The inverse associations were stronger for adenomas with higher risk characteristics, and among those with both high a diet and lifestyle score relative to those with both a low diet and lifestyle score.

These results suggest that more evolutionary concordant diet and lifestyle patterns, separately and jointly, may be associated with lower risk for incident, sporadic colorectal adenoma.

Introduction

Globally, colorectal cancer (CRC) is the third most common cancer among men, and the second most common cancer among women, representing 9.7% of all cancer cases (excluding non-melanoma skin cancers), and 8.5% of all cancer deaths (1,2). The global CRC burden is expected to increase 60% over the next 15 years (1). There is a ten-fold variation in international incidence rates among the highest- (e.g., New Zealand) relative to the lowest-incidence (e.g., Western Africa) countries (1,2). The global incidence rates are linked with Western lifestyles; approximately two-thirds of CRC cases and ~60% of CRC deaths occur in developed and highly developed countries, and the uptake of Western diet and physical activity patterns appear to correspond with an increase in incidence in Asia, Eastern Europe, and Latin America (1,2). Further, migration studies found incidence rates among first-generation immigrants to be intermediate between those in their home and host countries, becoming more like those in the host country with longer duration of residence (9,10). Taken together, these observations suggest a role of environmental factors, such as diet and lifestyle, in the development of CRC.

According to a consensus report from the World Cancer Research Fund/American Institute for Cancer Research, strong evidence supports lower risk of CRC with higher consumption of whole grains, dietary fiber, dairy products, and dietary calcium, and some evidence supports lower risk with higher intakes of vitamin C, vitamin D, multivitamins, and fish (1). The report also stated that strong evidence supports higher risk of CRC with higher consumption of red and processed meats and alcohol among men, and some evidence supports higher risk with lower consumption of vegetables and fruit, and higher intakes of heme iron (1). In addition, some lifestyle factors were identified as important risk factors for CRC, including physical activity, body-mass index

(BMI), and cigarette smoking (1). However, whereas most of these individual diet and lifestyle factors are weakly associated with CRC risk, their collective contributions to risk may be substantial. Diet and lifestyle pattern scores may account for the combined and interacting associations of multiple individual exposures.

Evolutionary-concordance diet and lifestyle pattern scores were developed to quantify the relative closeness of diets and lifestyles to those in Paleolithic times, and address the evolutionary discordance hypothesis, which posits that recent changes in human diet and lifestyle, relative to those of our Paleolithic-era ancestors, may explain the sudden rises in chronic diseases, including CRC, during the 20th century (6,7). The Paleolithic diet is characterized as high in fruits, vegetables, and lean meats, low in sugar and salt, and excluding grains and dairy (6,7).

Previous investigations found evolutionary concordance lifestyle pattern scores, which included physical activity, BMI, and smoking status, to be statistically significantly, strongly inversely associated with incident CRC risk (5). Also, evolutionary-concordance diet pattern scores were inversely associated with incident, sporadic colorectal adenomas, the precursors of most CRC, and with risk of incident colorectal cancer among older white females (5,8). Further, women in the joint-highest quantile of both evolutionary concordance diet and lifestyle score had the lowest risk of incident CRC relative to those in the joint-lowest tertiles ($P_{interaction} < 0.01$) (5). Here, we present an investigation of associations of evolutionary-concordance diet and lifestyle pattern scores, separately and jointly, with incident, sporadic adenoma among men and women in three pooled-case control studies.

Methods

Study population

For this secondary analysis of de-identified data, we pooled data from three case-control studies of incident, sporadic colorectal adenomas. The three studies, the Cancer Prevention Research Unit study of colorectal polyps (CPRU), and the Markers of Adenomatous Polyps studies I and II (MAP I and MAP II), were conducted in Minnesota 1991 – 1994, North Carolina 1994 – 1997, and South Carolina in 2002, respectively. All three studies, CPRU (11), MAPI (12,13) and MAPII (14,15), used nearly identical study methods that were described in detail elsewhere. Analyses of the pooled studies were also published (16,17). As described below, most study participants were recruited from patients scheduled to receive elective, outpatient colonoscopies at local gastroenterology practices; in the CPRU study, two additional groups of controls who were not scheduled for colonoscopies were recruited. Participation was similar across the three studies and ranged from 62% to 76%.

Initial eligibility criteria included ages 30 – 74 years, English-speaking, no genetic predisposition to colonic neoplasia, no personal history of adenomatous polyps, inflammatory bowel disease, or previous cancer diagnosis (except non-melanoma skin cancer). During colonoscopies, the presence of polyps and their locations and *in vivo* shapes and sizes were documented. All polyps were removed and examined histologically by an index study pathologist using National Polyp Study diagnostic criteria (18). Cases were defined as those who received a complete, clean colonoscopy reaching the cecum and had one or more index pathologist-confirmed adenomatous polyps, whereas colonoscopy-negative controls were those who received a complete,

clean colonoscopy reaching the cecum, and lacked any adenomatous or hyperplastic polyps. The CPRU study included two additional control groups: 1) sigmoidoscopy-negative controls, who met the same eligibility criteria as colonoscopy-negative controls, but only received flexible sigmoidoscopy, and 2) community controls, who were randomly selected from the 1991 Minnesota driver's license registry, and frequency-matched on age (in 5-year intervals), sex, and zip code, and met all the requirement of the endoscoped controls, except they did not receive an endoscopy to confirm their polyp status. The cases and the endoscoped controls had all polyps removed, and were not discovered to have incident inflammatory bowel disease or polyps with invasive carcinoma. For the current analysis, we pooled all case groups and all control groups from the three case-control studies.

Data collection

Prior to endoscopy, participants completed self-administered questionnaires to provide detailed information about their demographic characteristics, personal medical history, anthropometrics, usual physical activity, smoking habits, alcohol use, non-steroidal anti-inflammatory drug (NSAID) use, reproductive history, and family history of CRC. In addition, participants completed Willett food frequency questionnaires (FFQs) concerning their usual dietary and nutritional supplement intakes over the previous 12 months (19). The questionnaires allowed for nine possible frequency of consumption responses that ranged from "never or less than once per month" to "6 or more times per day". Total daily energy and nutrient intakes were calculated by summing energy and nutrients, respectively, from all food and supplement sources using the dietary database developed by Willett (20). Physical activity was assessed using modified Paffenbarger questionnaires (21).

Patients were excluded from analysis if they were over 74 years old (n = 8), skipped 10% or more of the food frequency questionnaire items (n = 3), indicated an improbable total energy intake (< 500 or > 5,000 kcal/day) (n = 11), or were missing data on alcohol consumption or lifestyle characteristics (n = 55). The final analytic sample size was 771 cases and 1,990 controls.

Constructing evolutionary-concordance scores in the pooled case-control studies

We used participants' responses to the food-frequency and lifestyle questionnaires to construct the evolutionary-concordance diet (8,22,23) and lifestyle (5) scores similar to as previously described. The evolutionary-concordance diet score comprised 14 equally-weighted components (see Table 1). All dietary components initially were continuous variables, and most were then categorized into quintiles based on the study- and sex-specific distributions among the controls as shown in Table 1. For alcohol, sugar-sweetened beverage, and fish consumption we used alternative cut points because their distributions were not conducive to quintile categorization (see Table 1). A maximum of 5 points were assigned for the highest intake, and 1 point was assigned for the lowest intake of components for which higher exposures were considered more evolutionary concordant. The point assignments were reversed for components considered less evolutionary concordant (i.e., 5 was assigned for lowest and 1 for highest intake). Two unique score components were created: 1) a fruit and vegetable diversity score that was the sum of the total number of different fruits and vegetables that were consumed more than 1 – 3 times per month, and 2) because there is evidence that Paleolithic diets were high in calcium but also low in dairy foods, a calcium residual score from the regression of total calcium intake on total dairy intake to account for

calcium intake fully adjusted for dairy intake (1). The point values for each person's dietary components were then summed to constitute their evolutionary-concordance diet pattern score. The total evolutionary-concordance diet pattern score could range from 14 to 70 points, with a higher score indicating higher evolutionary concordance.

The evolutionary-concordance lifestyle score comprised three equally-weighted components: smoking status, body-mass index (BMI), and physical activity (metabolic equivalents of task for moderate and vigorous activities), as shown in Table 1. To be consistent across lifestyle components, we categorized all components into three categories: smoking was categorized as current, former, and never; BMI was categorized according to World Health Organization criteria for underweight/normal (≤ 24.99 kg/m_2), overweight (25 – 29.99 kg/m_2), and obese (30+ kg/m_2); and physical activity was categorized according to study-specific tertiles among the controls. Then, to be consistent with the scoring scale for the 5-category dietary components, we assigned point values of 1, 3, or 5 to the categories as shown in Table 1. The point values for each person's lifestyle components were then summed to constitute their evolutionary concordance lifestyle score. The total evolutionary-concordance lifestyle pattern score could range from 3 to 15 points, with a higher score indicating higher evolutionary concordance.

Statistical analyses

Cases and controls were assessed for differences in selected characteristics using analysis of variance (ANOVA) tests for continuous variables (transformed by the natural logarithm to meet the normality assumption, when indicated) and chi-square tests for categorical variables. Participants were categorized into evolutionary-concordance diet

and lifestyle score quintiles based on the distributions among the controls. To estimate associations of the evolutionary concordance dietary and lifestyle scores with adenoma, we used multivariable unconditional logistic regression models to calculate odds ratios (OR) and their 95% confidence intervals (95% CI). Covariates were selected based on biological plausibility, previous literature, and the magnitude of change in the OR when included/excluded from the model. Covariates considered in the models for both scores included age, sex, family history of CRC in a first-degree relative, total energy intake, hormone replacement therapy among women, regular (once a week or more) aspirin and/or other NSAID use, education, and current multivitamin use. In the diet score model, additional covariates included smoking status, body-mass index, and physical activity; in the lifestyle model, the diet score was also included as a covariate. We calculated *P*-values for trend using the median values for each score quintile as a continuous variable in the models. To assess potential interaction between the diet and lifestyle score, we conducted a joint-combined (cross-classification) analysis in which the lowest quintiles of both scores served as the reference group, and calculated a *P* for interaction using the likelihood ratio test.

To assess potential differences in the associations of the scores with adenoma according to selected participant characteristics, we repeated the above analyses stratified by sex, study, age (<65/65+ years), family history of CRC in a first-degree relative (yes/no), and regular (once a week or more) aspirin and or other NSAID use (yes/no). For the diet pattern score we also stratified by BMI (<30/30+ kg/m_2), physical activity (high/low), and ever smoking (yes/no). We assessed interaction via comparing the stratum-specific associations and calculating *P* for interaction using the likelihood ratio test.

We also assessed associations of the diet and lifestyle pattern scores with adenomas of different characteristics, including adenoma location (right colon, left colon, or rectum), number (1 or > 1), size (< 1 cm or 1+ cm), subtype (tubular or tubulovillous/villous), and degree of dysplasia (mild or > mild) of the "worst" adenoma. "Worst" adenoma was determined by assigning each adenoma a score ranging from 0 – 3, with one point given for each of the following characteristics: ≥ 1 cm, villous histology, > mild dysplasia; the adenoma with the highest score was identified as the worst.

Finally, we assessed the sensitivity of the lifestyle pattern score-adenoma association to removal of any one component from the score. To do this, we repeated the analyses, removing (and replacing) each of the three individual components of the lifestyle score (BMI, smoking status, physical activity) one at a time, and included the removed component as an independent covariate in the logistic regression model with the modified score.

All statistical tests were 2-sided, and we considered *P*-values ≤ 0.05 or 95% CIs that excluded 1.0 statistically significant. All statistical analyses were performed using SAS statistical software, version 9.3.

Results

Selected characteristics of the study population by case-control status are presented in Table 2. Cases were more likely to be male, have a higher BMI, and be heavy drinkers. On average, cases were older and had a higher total energy intake and a higher percentage of their daily energy intake from fat. Controls were more likely to have at least a bachelor's degree and never smoked. On average, controls had higher dietary

fiber and calcium intakes, and a higher percentage of their total energy intake from carbohydrates. Controls, on average, had slightly higher evolutionary-concordance diet and lifestyle scores.

Associations of the evolutionary-concordance diet and lifestyle scores with incident, sporadic adenoma are presented in Table 3. Multivariable adjustment tended to attenuate the observed associations somewhat, especially for those of the diet score. However, after multivariable adjustment, there were statistically significant trends of a decreasing odds of adenoma with increasing diet and lifestyle scores, and for each one point increase in the diet score, the odds of an adenoma was borderline statistically significantly 1% lower, and for each one point increase in the lifestyle score, the odds of an adenoma was statistically significantly 9% lower. Those in the highest relative to the lowest quintile of the diet score had an estimated 16% lower odds of having an adenoma, although the finding for the point estimate was not statistically significant, and those in the highest relative to the lowest quintile of the lifestyle score had statistically significant less than half the odds of having an adenoma (OR: 0.41, 95% CI: 0.29-0.59).

The multivariable-adjusted joint/combined (cross-classification) associations of the diet and lifestyle pattern scores with incident, sporadic adenomas are presented in Table 4. For this analysis, because of sample size constraints, we categorized the diet and lifestyle scores according to tertiles among the controls. While there were patterns of decreasing odds of having an adenoma with an increasing diet score among those in the lowest tertile of the lifestyle score, and with an increasing lifestyle score among those in the lowest tertile of the diet score, the lowest odds was among those in higher relative to the lowest (least evolutionary-concordant) joint diet and lifestyle score tertile, although the $P_{interaction}$ was not statistically significant.

Considering the limited sample size for stratified analyses, no definitive differences in the multivariable-adjusted associations of the diet and lifestyle scores with adenomas across categories of participant characteristics were noted (Tables S1 and S2). However, the inverse diet score-adenoma association appeared stronger among men and those with no family history of CRC in a first degree relative.

Considering the limited sample size for analyses of adenoma categories, no definitive differences in the multivariable-adjusted associations of the diet and lifestyle scores with adenomas were noted across adenomas of various characteristics (Table S3). However, the inverse associations tended to be stronger for adenomas with higher risk characteristics. The diet score-adenoma association appeared more inverse for multiple adenomas and adenomas that were large, or adenomas that had a villous component. The lifestyle score-adenoma association appeared more inverse for multiple adenomas and adenomas that were large or had a villous component, although the differences across adenoma categories were somewhat less than those for the diet score. Also, the inverse association of the lifestyle score, but not of the diet score, with adenoma appeared stronger for adenomas of the right side of the colon.

In sensitivity analyses, after removal of any one component from the lifestyle score, the association of the reduced lifestyle score with adenoma remained statistically significantly inverse; removal of smoking attenuated the lifestyle score-adenoma association the most (Table S4). When we assessed the association of each lifestyle score component individually with adenoma (Table S5), smoking was strongly directly associated with adenoma (current relative to never smokers had a statistically significant 2.6-fold higher odds of adenoma); BMI category was moderately associated with

adenoma (those who were obese relative to those who were normal weight had a statistically significant 31% higher odds of adenoma); and physical activity was estimated to be only minimally inversely associated with adenoma (those in the highest relative to the lowest tertile of physical activity were estimated to have non-statistically significant 4% lower odds of adenoma).

Discussion

Our findings suggest that more evolutionary-concordant diets and lifestyles, independently and jointly, may be associated with lower risk for colorectal adenoma, especially for high risk adenomas. Also, the inverse evolutionary-concordance diet-adenoma association may be stronger for men. This is the first study to report on an independent association of an evolutionary-concordance lifestyle score or on a joint association of evolutionary-concordant diet and lifestyle pattern scores with incident, sporadic colorectal adenomas among men and women.

The components of the evolutionary-concordance lifestyle score—physical activity, body mass index, and smoking—all plausibly affect CRC risk. Body fatness increases insulin resistance and inflammation (1,24). Physical activity decreases body fatness, may reduce insulin levels and inflammation, and stimulates digestion, reducing transit time through the intestine (1,24). Cigarette smoking introduces many genotoxic compounds to the colorectal mucosa (25). In a 2017 meta-analyses, the meta-relative risk for physical activity (12 studies of colon cancer) was 0.80 (95% CI: 0.72-0.88) for those in the highest relative to the lowest categories; for BMI (38 studies of CRC) the meta-relative risk was 1.05 (95% CI: 1.03-1.07) for each 5 kg/m_2 increase (1). A 2008 meta-analysis found the meta-relative risk for being a current vs never smoker (45 studies of

CRC) and for being a former vs never smoker (47 studies CRC) to be 1.07 (95% CI: 0.99-1.16) and 1.17 (95% CI: 1.11-1.22), respectively (26).

The evolutionary-concordance diet pattern score contains several components that plausibly affect CRC risk. This diet pattern emphasizes high intakes of fruits and vegetables, which contain a myriad of anti-carcinogenic agents that act through multiple mechanisms (1,27,28), and are good sources of fiber, which alters several biomarkers related to CRC risk (29). Further, this diet pattern is also characterized by low consumption of red or processed meats, which form mutagens when cooked with high heat, and contain heme iron, which can facilitate oxidative-related damage (30), and low intake of refined carbohydrates, which can increase pro-proliferative serum insulin levels (24). In one cross-sectional study, the evolutionary-concordance diet pattern score was inversely association with biomarkers of inflammation and oxidative stress, factors hypothesized to increase CRC risk (22).

The evolutionary-concordance diet pattern score, formerly referred to as the “Paleolithic diet pattern score”, was previously investigated in one case-control study of colorectal adenoma (one of the three studies included in the present pooled analysis), which found that those in the highest relative to lowest quintile of the evolutionary concordance diet pattern score had a 29% lower odds of having an adenoma when compared to endoscopy-negative controls, and a 44% lower odds of having an adenoma when compared to community controls, although neither point estimate was statistically significant (8). Additionally, both the evolutionary-concordance diet and lifestyle pattern scores were examined in one prospective cohort study of incident colorectal cancer among older, white women. In the cohort study, the Iowa Women’s Health Study (IWHS), those in the highest relative to the lowest quintile of the evolutionary-

concordance diet pattern score were not estimated to be at substantially lower CRC risk; however, those in the highest relative to the lowest evolutionary concordance lifestyle pattern score quintile had statistically significant 34% lower CRC risk (5), and those in the highest relative to the lowest joint diet and lifestyle score tertiles were at lowest CRC risk, suggesting a synergistic effect of the diet and lifestyle patterns ($P_{interaction} < 0.01$).

Several other index-based dietary patterns that share some common components with the evolutionary concordance diet pattern have been consistently inversely-associated with colorectal neoplasms in observational epidemiological studies; these include the Mediterranean diet (MD), the Healthy Eating Index (HEI), the Dietary Approaches to Stop Hypertension (DASH) diet, and others. Each of these diets emphasizes high intake of fruits, vegetables, nuts, legumes, and whole grains, and low intakes of red or processed meats (31). The MD and its subsequent iterations (32) were developed based on the diet patterns typical of Greece, Crete, and southern Italy, where during the 1960's, adult life expectancy was among the highest in the world (33). The MD comprises high intakes of vegetables, fruit, legumes, whole grains, olive oil and fish, low intakes of dairy and meat, and regular but moderate intakes of alcohol (34). The MD was investigated in 15 published reports of CRC and three published reports of colorectal adenoma (8,35,36). Among men, adherence to the MD pattern was consistently associated with lower risk of CRC and adenoma in all (8,35–43) but one published report of CRC (44), and among women it was associated with lower CRC risk in six (37–40,43,45,46) of ten published reports (37–46) (in one report, among obese women only (37)), and lower adenoma risk in one (35) of three published reports (8,35,36). A meta-analysis of eleven observational studies of the MD and colorectal neoplasms found a statistically significant inverse association (RR: 0.82, 95% CI:0.75-0.88) (32). The HEI was developed to reflect and measure adherence to federal

nutrition guidance set by the United States government, and is updated every five years. It generally comprises high intakes of fruits, vegetables, legumes, whole grains, milk and meat, and low intakes of saturated fat, sodium, alcohol, and added sugar (47). The HEI and its iterations were investigated among men and/or women in nine published reports of CRC (37,38,41,42,45,48–51); all but two (42,48) found inverse associations. The DASH diet, originally developed to reduce blood pressure by creating a "favorable" micro- and macronutrient profile, is characterized by higher intakes of fruits, vegetables, whole grains, nuts, legumes, low-fat dairy products, and lean meats (52). The DASH diet was investigated in six published reports of CRC (37,40–42,45,50) and one published report of colorectal adenoma (36). Among men, adherence to the DASH diet was consistently inversely associated with CRC and adenoma risk; among women it was inversely associated with CRC risk in five (37,40,41,45,53) of six published reports, but the association was null in the other CRC reports and the adenoma report (36,42) . Finally, the Dietary Inflammation Index (DII), is a primarily nutrient-based index designed to reflect the contributions of dietary factors to inflammation, such that a higher score would indicate a more pro-inflammatory diet (54). The DII was consistently directly associated with colorectal neoplasms across 14 published reports of observational studies, 12 of CRC (54–65) and two of adenoma (60,66).

Various studies investigated lifestyle scores in relation to colorectal neoplasms. The scores have similarities and differences. In general, the scores comprised several modifiable lifestyle factors, such as physical activity, smoking, BMI, and alcohol consumption, but all also included a limited number of dietary components. Collectively, the scores were consistently inversely associated with colorectal neoplasms in 18 published reports of CRC (67–84) and four of adenoma (85–88). Eight of the CRC reports constructed variants of lifestyle pattern scores to reflect adherence to some or all

of the eight specific cancer prevention recommendations of the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) (1) (the eight recommendations include those for body fatness, physical activity, and intakes of alcohol, energy density, plant foods, red meat, salt-preserved foods, and supplements). The WCRF/AICR scores were inversely associated with CRC in all eight published reports of observational studies (75–82). Two published reports of observational studies investigated lifestyle patterns formulated based on the American Cancer Society's (ACS) cancer prevention guidelines, comprising BMI, physical activity, alcohol intake, and a healthy diet with emphasis on more plant foods and less refined grains and red meat (89); both reports found statistically significant inverse associations with higher adherence to the ACS's recommended lifestyle pattern (83,84). Our evolutionary-concordance lifestyle pattern differs most from the above discussed lifestyle patterns in that it does not include dietary components. Consistent with the findings in our present study, associations of lifestyle pattern scores with colorectal neoplasms across previously reported reports were stronger than those for diet pattern scores alone.

Our study has several strengths. It is the largest study to date of the evolutionary concordance diet pattern score in relation to colorectal adenomas among men and women, and it is the first study to investigate the evolutionary concordance lifestyle score in relation to colorectal adenomas, independently and jointly with an evolutionary concordance diet score, among men and women. Additional strengths include the pooled study design; collection of food frequency and other exposure information before case/control determination, thus reducing recall bias; and standardized pathological verification of adenomas, thus reducing outcome misclassification.

Our study also has several limitations. First, inherent to case-control studies is that temporality of associations involving modifiable exposures cannot be assessed; however, dietary and lifestyle exposures tend to be relatively consistent over time (90). Second, the control group included sigmoidoscopy and community controls, possibly resulting in misclassification of some cases as controls; however, this would be expected to attenuate our results, and our findings were similar across the three component studies. Third, FFQs have known limitations (e.g., limited food choices, recall error); however, there is remarkable consistency in reported associations of several dietary factors and patterns with colorectal neoplasms from across multiple studies that used various FFQs over the years (91–93). Finally, in contrast to the extensive literature on physical activity and colorectal cancer (1), in our study population the physical activity – adenoma association was minimally inverse and did not appear to contribute to the association of the overall lifestyle score – the reason for this is unclear.

In conclusion, our results taken together with the previous literature, suggest that more evolutionary-concordant diets and lifestyles, independently and jointly, may be associated with lower risk for colorectal adenoma, especially for high risk adenomas. The inverse evolutionary-concordance diet pattern score-adenoma association may be stronger for men. Our findings support further investigation into the associations of evolutionary concordant diets and lifestyles with colorectal neoplasms.

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Table 1. Constituents and construction of the evolutionary-concordance diet and lifestyle scores

Score and constituents	Evolutionary-concordance diet and lifestyle score constituents' point assignments[a]
Diet[b]	
Calcium[c]	Highest intake "best"
Fish	Highest intake "best"
Fruit & vegetable diversity[d]	Highest intake "best"
Fruits	Highest intake "best"
Lean meats[e]	Highest intake "best"
Nuts	Highest intake "best"
Vegetables	Highest intake "best"
Alcohol[f]	Lowest intake "best"
Baked goods & sweets[g]	Lowest intake "best"
Dairy foods	Lowest intake "best"
Grains & starches	Lowest intake "best"
Red & processed meats[h]	Lowest intake "best"
Sodium[i]	Lowest intake "best"
Sugar-sweetened beverages[j]	Lowest intake "best"
Lifestyle	
Body mass index[k], kg/m^2	< 25 "best"
Physical activity[l]	Highest "best"
Smoking status[m]	Never "best"

[a] The evolutionary-concordance diet pattern score consisted of 14 components, yielding possible range of 14 – 70; the evolutionary-concordance lifestyle score consisted of 3 components, yielding a possible range of 3 – 15; higher scores indicate more evolutionary-concordance

[b] All constituents measured in servings/week and points assigned based on sex-specific quintiles among the controls, unless otherwise indicated. Highest intake "best": points assigned to each quintile corresponded to quintile ranks (e.g., +1 and +5 assigned to lowest and highest quintile ranks, respectively); Lowest intake "best": points assigned to each quintile corresponded to reverse quintile ranks (e.g., +5 and +1 assigned to lowest and highest quintile rank, respectively)

[c] Calcium intake considered independently of non-calcium components of dairy foods, calculated as the residuals of the linear regression of calcium (mg/day) on dairy food intake

[d] Fruit & vegetable diversity calculated by summing the total number of types of fruit and vegetables that were consumed > 1 – 3 times/month

[e] Lean meats include skinless chicken or turkey, lean and extra lean hamburger beef

[f] Alcohol points assigned based on five sex-specific categories; men - 0, 0 – < 14, 14, > 14 – 21, and > 21 drinks/week; women - 0, 0 – < 7, 7, > 7 – 14, and > 14 drinks/week; points assigned to each category in decreasing order (e.g. +5 and +1 assigned to lowest and highest category, respectively)

[g] Baked goods & sweets includes candy, cookies, brownies, donuts, cake, and pie

[h] Red & processed meats includes bacon, hotdogs, bologna, liver, regular hamburger beef, pork, and cold cuts

[i] Measured as mg/day

[j] Sugar-sweetened beverages measured in servings/day and points assigned based on five categories: 0, 0.5, 1, 2, > 2; points assigned to each category in decreasing order (e.g. +5 and +1 assigned to lowest category and highest category, respectively)

[k] Categories for obese, overweight, and normal/underweight (≥ 30, 25 – 29.99, and 18.5 – 24.99 kg/m^2, respectively), according to WHO guidelines scored 1, 3, and 5, respectively

[l] Low, medium, high; scored 1, 3, and 5, respectively

[m] Current, former, never; scored 1, 3, and 5, respectively

Table 2. Selected characteristics of cases and controls from three pooled case-control studies of incident, sporadic, colorectal adenoma, 1991 – 2002

Characteristics[a]	Cases (n = 771)	Controls (n = 1,990)	*P*[b]
Age, years	58.2 (9.2)	54.4 (10.8)	<0.0001
White race, %	94.8	96.2	0.11
Male, %	61.1	43.1	<0.0001
Body mass index, kg/m^2	27.6 (5.2)	26.8 (5.0)	0.001
Family history of colorectal cancer, %[c]	17.0	17.7	0.64
At least a bachelor's degree, %	28.5	31.8	0.001
Hormone replacement therapy, among women only, %	35.7	37.9	0.48
Never smoker, %	30.6	45.8	<0.0001
High physical activity, %[d]	33.6	33.4	0.29
Total energy intake, kcal/day	2,064 (771)	1,987 (715)	0.03
Heavy drinker, %	35.8	33.1	<0.0001
Protein intake, % kcal	16.4 (3.2)	16.6 (3.1)	0.19
Carbohydrate intake, % kcal	51.2 (8.8)	53.0 (8.9)	<0.0001
Total fat intake, % kcal	31.2 (6.7)	30.2 (6.8)	0.001
Dietary fiber, g/1,000 kcal/day	10.9 (3.7)	11.3 (3.9)	0.01
Total calcium intake, mg/1,000 kcal/day[e]	474 (277)	510 (272)	0.0001
Evolutionary-concordance diet score[f]	43.5 (6.2)	44.3 (6.2)	0.001
Evolutionary-concordance lifestyle score[g]	9.2 (2.6)	10.0 (2.7)	<0.0001

[a] Continuous variables presented as mean (SD), categorical variables as percentage

[b] *P*-values from chi square test for categorical variables and ANOVA for continuous variables (transformed to meet normality assumptions when necessary)

[c] In a first degree relative

[d] Physical activity measured as metabolic equivalents of task for moderate and vigorous activities, and categorized as high, medium, or low based on study-specific tertiles of the distribution among the controls

[e] Total = diet + supplements

[f] Evolutionary-concordance diet score calculated as indicated in text and Table 1; a higher score indicates higher evolutionary-concordance

[g] Evolutionary-concordance lifestyle score calculated as indicated in text and Table 1; a higher score indicates higher evolutionary-concordance

Table 3. Multivariable-adjusted associations of the evolutionary-concordance diet and lifestyle scores with colorectal adenomas in three pooled case-control studies (n = 771 cases and 1,990 controls), 1991 – 2002

	Evolutionary-concordance scores					
	Diet[a]			Lifestyle[b]		
Score form	n (cases/controls)	Minimally-adjusted model[c] OR (95% CI)	Full model[d] OR (95% CI)	n (cases/controls)	Minimally-adjusted model[e] OR (95% CI)	Full model[f] OR (95% CI)
Quintiles						
1	164/354	1.00	1.00	89/146	1.00	1.00
2	180/402	0.97 (0.75-1.26)	1.07 (0.82-1.40)	164/316	0.83 (0.59-1.15)	0.86 (0.61-1.20)
3	147/355	0.86 (0.65-1.12)	0.93 (0.70-1.24)	200/498	0.64 (0.46-0.87)	0.67 (0.48-0.92)
4	151/471	0.63 (0.48-0.83)	0.75 (0.56-0.99)	212/544	0.62 (0.45-0.84)	0.68 (0.49-0.94)
5	129/408	0.64 (0.48-0.84)	0.84 (0.62-1.12)	106/486	0.35 (0.25-0.49)	0.41 (0.29-0.59)
P_{trend}		*<0.0001*	*0.04*		*<0.0001*	*<0.0001*
Continuous		0.97 (0.96-0.99)	0.99 (0.97-1.00)		0.89 (0.86-0.92)	0.91 (0.88-0.94)

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

[a] For diet score construction see Table 1 and text; a higher score indicates higher evolutionary-concordance

[b] For lifestyle score construction see Table 1 and text; a higher score indicates higher evolutionary-concordance

[c] ORs from unconditional logistic regression model; covariates included age (years; continuous), family history of colorectal cancer in a first-degree relative (yes/no), and total energy intake (kcal/day; continuous)

[d] ORs from unconditional logistic regression model; covariates included age (years; continuous), sex, family history of colorectal cancer in a first degree relative (yes/no), total energy intake (kcal/day; continuous), hormone replacement therapy (yes/no, if a woman), regular (once a week or more) aspirin and/or other nonsteroidal anti-inflammatory drug use (yes/no), education (high school/some college/bachelor's degree or more), current multivitamin use (yes/no), smoking status (current/former/never), body mass index (kg/m^2; continuous), physical activity (METs; continuous)

[e] ORs from unconditional logistic regression model; covariates included age (years; continuous), family history of colorectal cancer in a first degree relative (yes/no), and total energy intake (kcal/day; continuous)

[f] ORs from unconditional logistic regression model; covariates included age (years; continuous), sex, family history of colorectal cancer in a first degree relative (yes/no), total energy intake (kcal/day; continuous), hormone replacement therapy (yes/no, if a woman), regular (once a week or more) aspirin and/or other nonsteroidal anti-inflammatory drug use (yes/no), education (high school/some college/bachelor's degree or more), evolutionary-concordance diet score (quintiles), current multivitamin use (yes/no)

Table 4. Multivariable-adjusted joint/combined (cross-classification) associations[a] of the evolutionary-concordance lifestyle and diet pattern scores with incident, sporadic adenomas in three pooled case-control studies (n = 771 cases and 1,990 controls), 1991 – 2002

		Evolutionary-concordance lifestyle score[b] tertiles					
		1		2		3	
		n (cases/controls)	OR (95% CI)	n (cases/controls)	OR (95% CI)	n (cases/controls)	OR (95% CI)
Evolutionary-concordance diet score[c] tertiles	**1**	91/178	1.00 (Ref.)	77/175	0.81 (0.55-1.18)	119/303	0.78 (0.55-1.09)
	2	83/138	1.16 (0.79-1.69)	62/148	0.75 (0.50-1.12)	86/305	0.55 (0.38-0.78)
	3	73/146	0.92 (0.62-1.35)	61/175	0.67 (0.45-1.00)	114/422	0.56 (0.40-0.78)[d]

Abbreviations: CI, confidence interval; Ref., reference; OR, odds ratio

[a] ORs from multivariable unconditional logistic models; covariates included age (years; continuous), sex, family history of colorectal cancer in a first degree relative (yes/no), total energy intake (kcal/day; continuous), hormone replacement therapy (yes/no, if a woman), education (high school/some college/ bachelor's degree or more), regular (once a week or more) aspirin and/or other nonsteroidal anti-inflammatory use (yes/no), current multivitamin use (yes/no)

[b] For lifestyle score construction see Table 1 and text; a higher score indicates higher evolutionary-concordance

[c] For diet score construction see Table 1 and text; a higher score indicates higher evolutionary-concordance

[d] $P_{interaction}$ = 0.44; from lifestyle score*diet score interaction term in unconditional logistic regression model; as determined using the likelihood ratio test

Supplemental Table 1. Multivariable-adjusted associations[a] of the evolutionary-concordance diet score[b] with incident, sporadic colorectal adenomas according to categories of other risk factors in three pooled case-control studies (n = 771 cases and 1,990 controls), 1991 – 2002

Stratification variables, score quintiles	OR[a]	95% CI	*P*-trend	*P*-interaction
Sex				
Male				
1	1.00			
2	1.05	0.74-1.48		
3	0.94	0.65-1.36		
4	0.69	0.48-0.99		
5	0.71	0.47-1.05	*0.02*	
Female				
1	1.00			
2	1.14	0.73-1.77		
3	0.96	0.61-1.52		
4	0.86	0.55-1.33		
5	1.05	0.66-1.65	*0.76*	*0.46*
Study				
CPRU				
1	1.00			
2	1.20	0.88-1.64		
3	1.03	0.75-1.43		
4	0.77	0.56-1.07		
5	0.87	0.62-1.23	*0.08*	
MAP I				
1	1.00			
2	1.07	0.52-2.22		
3	0.94	0.43-2.02		
4	0.77	0.38-1.58		
5	0.87	0.39-1.91	*0.53*	
MAP II				
1	1.00			
2	0.69	0.22-2.14		
3	0.64	0.18-2.34		
4	0.76	0.23-2.53		
5	0.76	0.23-2.49	*0.73*	*0.97*
Age, years				
<65				
1	1.00			
2	1.09	0.80-1.48		
3	0.98	0.70-1.35		
4	0.79	0.57-1.09		
5	0.83	0.59-1.17	*0.09*	
65+				
1	1.00			
2	1.04	0.57-1.90		
3	0.87	0.49-1.56		
4	0.63	0.36-1.11		
5	0.86	0.48-1.56	*0.26*	*0.97*

Family History of CRC[c]				
Yes				
1	1.00			
2	1.87	0.93-3.76		
3	1.25	0.61-2.60		
4	0.87	0.42-1.83		
5	1.32	0.61-2.85	*0.88*	
No				
1	1.00			
2	0.97	0.72-1.31		
3	0.91	0.67-1.24		
4	0.73	0.54-0.99		
5	0.77	0.56-1.07	*0.03*	*0.61*
BMI, kg/m^2				
<30[d]				
1	1.00			
2	1.08	0.78-1.47		
3	0.90	0.64-1.25		
4	0.72	0.52-1.00		
5	0.89	0.63-1.24	*0.12*	
30+				
1	1.00			
2	1.09	0.64-1.87		
3	1.14	0.66-1.99		
4	0.87	0.51-1.49		
5	0.76	0.41-1.41	*0.29*	*0.80*
Physical activity, MET-hrs/wk				
<41.3[e]				
1	1.00			
2	1.01	0.69-1.48		
3	1.04	0.70-1.54		
4	0.82	0.55-1.22		
5	0.84	0.54-1.29	*0.27*	
41.3+				
1	1.00			
2	1.09	0.74-1.61		
3	0.82	0.54-1.24		
4	0.65	0.44-0.97		
5	0.79	0.52-1.19	*0.04*	*0.74*
Ever smoke				
Yes				
1	1.00			
2	0.97	0.70-1.34		
3	0.91	0.64-1.29		
4	0.81	0.58-1.13		
5	0.75	0.52-1.08	*0.07*	
No				
1	1.00			
2	1.12	0.70-1.80		
3	0.90	0.55-1.47		

4	0.52	0.32-0.87		
5	0.75	0.45-1.24	*0.03*	*0.43*
Aspirin and/or NSAID use[f]				
Yes				
1	1.00			
2	1.20	0.76-1.88		
3	1.06	0.65-1.75		
4	0.84	0.53-1.34		
5	0.80	0.48-1.32	*0.15*	
No				
1	1.00			
2	0.99	0.70-1.39		
3	0.88	0.62-1.25		
4	0.68	0.48-0.96		
5	0.87	0.60-1.26	*0.13*	*0.81*

Abbreviations: BMI, body mass index; CI, confidence interval; CPRU, Cancer Prevention Research Unit case-control study of colorectal polyps; CRC, colorectal cancer; MAP, Markers of Adenomatous Polyps case-control study of colorectal adenoma; MET, metabolic equivalents of task; NSAID, nonsteroidal anti-inflammatory; OR, odds ratio

[a] From multivariable-adjusted unconditional logistic regression models; covariates included age (years; continuous), sex (except in sex-stratified analysis), total energy intake (kcal/day; continuous), family history of colorectal cancer in a first degree relative (yes/no) (except in family history-stratified analysis), hormone replacement therapy (yes/no, if a woman), regular (once a week or more) aspirin and/or other NSAID use (yes/no) (except in analysis stratified on this variable), education (high school/some college/bachelor's degree or more), current multivitamin use (yes/no), BMI (kg/m^2; continuous), smoking status (current/former/never) (except in smoking-stratified analysis), physical activity (MET-hours, continuous). P for interaction from the stratified risk factor*score interaction term in the unconditional logistic regression model

[b] For diet score construction see Table 1 and text; a higher score indicates higher evolutionary-concordance

[c] In a first degree relative

[d] World Health Organization (WHO) cutpoint for obese

[e] Median METs/wk among the controls

[f] Regularly take once a week or more

Supplemental Table 2. Multivariable-adjusted associations[a] of the evolutionary-concordance lifestyle score[b] with incident, sporadic colorectal adenomas according to categories of other risk factors in three pooled case-control studies (n = 771 cases and 1,990 controls), 1991 – 2002

Stratification variables, score quintiles	OR	95% CI	*P*-trend	*P*-interaction
Sex				
Male				
1	1.00			
2	0.92	0.60-1.40		
3	0.66	0.44-1.00		
4	0.67	0.45-1.02		
5	0.45	0.28-0.73	*0.0003*	
Female				
1	1.00			
2	0.79	0.45-1.37		
3	0.69	0.40-1.16		
4	0.69	0.41-1.16		
5	0.38	0.22-0.65	*0.0001*	*0.88*
Study				
CPRU				
1	1.00			
2	0.82	0.55-1.22		
3	0.71	0.49-1.03		
4	0.78	0.54-1.13		
5	0.43	0.28-0.65	*0.0002*	
MAP I				
1	1.00			
2	1.09	0.45-2.63		
3	0.69	0.29-1.60		
4	0.64	0.27-1.53		
5	0.37	0.15-0.91	*0.005*	
MAP II				
1	1.00			
2	0.50	0.13-1.98		
3	0.30	0.07-1.19		
4	0.22	0.05-0.88		
5	0.33	0.08-1.39	*0.08*	*0.56*
Age, years				
<65				
1	1.00			
2	0.78	0.54-1.14		
3	0.68	0.48-0.98		
4	0.69	0.48-0.99		
5	0.45	0.30-0.67	*0.0002*	
65+				
1	1.00			
2	1.26	0.57-2.76		
3	0.67	0.31-1.43		
4	0.78	0.37-1.65		
5	0.41	0.19-0.90	*0.0005*	*0.46*

Family History of CRC[c]				
Yes				
1	1.00			
2	0.85	0.35-2.08		
3	0.72	0.30-1.70		
4	0.41	0.17-0.98		
5	0.35	0.14-0.87	*0.001*	
No				
1	1.00			
2	0.86	0.60-1.24		
3	0.66	0.47-0.94		
4	0.74	0.53-1.05		
5	0.43	0.29-0.63	*<0.0001*	*0.36*
Aspirin and/or NSAID use[d]				
Yes				
1	1.00			
2	0.84	0.49-1.43		
3	0.49	0.29-0.83		
4	0.62	0.37-1.04		
5	0.46	0.26-0.81	*0.003*	
No				
1	1.00			
2	0.85	0.55-1.31		
3	0.78	0.51-1.17		
4	0.71	0.47-1.07		
5	0.38	0.24-0.60	*<0.0001*	*0.28*

Abbreviations: CI, confidence interval; CPRU, Cancer Prevention Research Unit case-control study of colorectal polyps; CRC, colorectal cancer; MAP, Markers of Adenomatous Polyps case-control study of colorectal adenoma; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio

[a] From multivariable-adjusted unconditional logistic regression models; covariates included age (years; continuous), sex (except for sex-stratified analysis), total energy intake (kcal/day; continuous), family history of colorectal cancer in a first degree relative (yes/no) (except for family history-stratified analysis), hormone replacement therapy (yes/no, if a woman), regular (once a week or more) aspirin and/or other NSAID use (yes/no) (except for analysis stratified on this variable), education (high school/some college/bachelor's degree or more), diet score (quintiles), and current multivitamin use (yes/no). *P* for interaction from the stratified risk factor*score interaction term in the unconditional logistic regression model.

[b] For diet score construction see Table 1 and text; a higher score indicates higher evolutionary-concordance

[c] In a first degree relative

[d] Regularly taken once a week or more

Supplemental Table 3. Multivariable-adjusted associations of the evolutionary-concordance diet and lifestyle scores with incident, sporadic colorectal adenomas of selected adenoma characteristics in three pooled case-control studies (n = 771 cases and 1,990 controls) 1991 – 2002

Adenoma characteristics and score quintiles	No. of cases	Evolutionary-concordance scores					
		Diet[a]			Lifestyle[b]		
		OR[c]	95% CI	*P*-trend	OR[d]	95% CI	*P*-trend
Adenoma dysplasia							
Mild	326						
1		1.00			1.00		
2		1.02	0.69-1.50		0.90	0.57-1.41	
3		1.15	0.78-1.69		0.70	0.45-1.09	
4		0.97	0.66-1.42		0.72	0.47-1.12	
5		1.00	0.66-1.51	*0.93*	0.35	0.21-0.59	*<0.0001*
> Mild							
1	431	1.00			1.00		
2		1.15	0.83-1.60		0.79	0.53-1.20	
3		0.83	0.58-1.18		0.64	0.43-0.95	
4		0.62	0.43-0.88		0.62	0.42-0.92	
5		0.75	0.52-1.09	*0.006*	0.45	0.30-0.69	*0.0001*
Adenoma location							
Right colon	183						
1		1.00			1.00		
2		0.77	0.48-1.25		0.76	0.45-1.30	
3		0.67	0.40-1.11		0.47	0.28-0.80	
4		0.64	0.39-1.03		0.49	0.29-0.82	
5		0.80	0.48-1.32	*0.24*	0.26	0.14-0.48	*<0.0001*
Left colon	450						
1		1.00			1.00		
2		1.29	0.93-1.78		0.86	0.57-1.29	
3		1.13	0.80-1.58		0.65	0.44-0.96	
4		0.68	0.48-0.97		0.74	0.50-1.08	
5		0.87	0.60-1.26	*0.04*	0.42	0.27-0.64	*<0.0001*

Rectum	120							
1		1.00			1.00			
2		0.93	0.51-1.70		0.96	0.44-2.13		
3		0.81	0.43-1.54		1.23	0.59-2.54		
4		1.13	0.64-1.99		0.79	0.37-1.70		
5		0.79	0.41-1.51	*0.71*	0.81	0.37-1.78	*0.31*	
No. of adenomas								
1 adenoma	507							
1		1.00			1.00			
2		1.18	0.86-1.61		0.82	0.55-1.21		
3		0.96	0.69-1.34		0.69	0.47-1.00		
4		0.82	0.60-1.14		0.73	0.50-1.05		
5		0.95	0.67-1.33	*0.26*	0.45	0.30-0.68	*0.0001*	
>1 adenoma	250							
1		1.00			1.00			
2		0.94	0.62-1.43		0.88	0.54-1.44		
3		0.95	0.62-1.45		0.63	0.39-1.01		
4		0.64	0.41-1.00		0.56	0.34-0.90		
5		0.66	0.41-1.06	*0.03*	0.34	0.19-0.59	*<0.0001*	
Adenoma size[g]								
< 1 cm	456							
1		1.00			1.00			
2		1.15	0.83-1.60		0.94	0.62-1.40		
3		0.93	0.66-1.32		0.73	0.49-1.08		
4		0.86	0.62-1.21		0.67	0.46-1.00		
5		0.85	0.59-1.22	*0.14*	0.42	0.27-0.65	*<0.0001*	
≥ 1 cm	245							
1		1.00			1.00			
2		1.07	0.72-1.60		0.61	0.38-1.00		
3		0.92	0.60-1.41		0.52	0.33-0.82		
4		0.55	0.35-0.86		0.52	0.33-0.83		
5		0.68	0.42-1.09	*0.01*	0.37	0.22-0.61	*0.0004*	

Adenoma subtype[h]							
Tubular	544						
1		1.00			1.00		
2		1.13	0.83-1.54		0.90	0.62-1.31	
3		0.98	0.71-1.35		0.71	0.49-1.01	
4		0.84	0.62-1.16		0.67	0.46-0.96	
5		0.90	0.64-1.25	*0.19*	0.42	0.28-0.63	*<0.0001*
Tubulovillous or villous	211						
1		1.00			1.00		
2		1.04	0.67-1.61		0.68	0.39-1.16	
3		0.89	0.56-1.40		0.57	0.34-0.96	
4		0.55	0.34-0.90		0.65	0.39-1.07	
5		0.73	0.45-1.21	*0.04*	0.39	0.22-0.69	*0.005*

Abbreviations: CI, confidence interval; MET, metabolic equivalents of task; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio

[a] For diet score construction see Table 1 and text; a higher score indicates higher evolutionary-concordance

[b] For lifestyle score construction see Table 1 and text; a higher score indicates higher evolutionary-concordance

[c] ORs from unconditional logistic regression model; covariates included age (years; continuous), sex, family history of colorectal cancer in a first degree relative (yes/no), total energy intake (kcal/day; continuous), hormone replacement therapy (yes/no, if a woman), regular (once a week or more) aspirin and/or other NSAID use (yes/no), education (high school/some college/bachelor's degree or more), current multivitamin use (yes/no), smoking status (current/former/never), body mass index (kg/m^2; continuous), physical activity (METs; continuous)

[d] ORs from unconditional logistic regression model; covariates included age (years; continuous), sex, family history of colorectal cancer in a first degree relative (yes/no), total energy intake (kcal/day; continuous), hormone replacement therapy (yes/no, if a woman), regular (once a week or more) aspirin and/or other NSAID use (yes/no), education (high school/some college/bachelor's degree or more), evolutionary-concordant diet score (quintiles), current multivitamin use (yes/no)

[e] Of the worst adenoma defined as a score ranging from 0 – 3, with one point given for each of the following characteristics: ≥ 1 cm, villous histology, > mild dysplasia; the adenoma with the highest score was identified as the worst

[f] Of the worst adenoma; right colon includes: cecum, ascending colon, hepatic flexure, transverse colon; left colon includes: splenic flexure, descending colon, sigmoid colon

[g] Of the largest adenoma

[h] Of the worst adenoma

Supplemental Table 4. Sensitivity of association of evolutionary-concordance lifestyle score with incident, sporadic colorectal adenomas to removal of any one score component[a]; three pooled case-control studies of incident, sporadic colorectal adenoma (n = 771 cases and 1,990 controls), 1991 – 2002

ECLS categories[c]	ECLS variable removed[b]		
	Smoking status	Body mass index	Physical activity
	OR (95% CI)	OR (95% CI)	OR (95% CI)
1	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
2	1.01 (0.81-1.26)	0.77 (0.62-0.96)	0.71 (0.56-0.89)
3	0.77 (0.61-0.98)	0.65 (0.51-0.83)	0.52 (0.40-0.67)
4	0.73 (0.54-0.98)	0.48 (0.35-0.67)	0.40 (0.29-0.55)
P for trend	*0.006*	*<0.0001*	*<0.0001*

Abbreviations: CI, confidence interval; ECLS, evolutionary-concordant lifestyle score; OR, odds ratio; Ref., reference

[a] After removal of one component, the score consisted of the remaining components, and the removed variable was included as an independent covariate in the relevant unconditional logistic regression model; a higher score indicates higher evolutionary concordance

[b] OR from multivariable-adjusted unconditional logistic regression models; covariates included age (years; continuous), sex, family history of colorectal cancer in a first degree relative (yes/no), total energy intake (kcal/day; continuous), education (high school/some college/bachelor's degree or more), hormone replacement therapy (yes/no, if a woman), regular (once a week or more) aspirin and/or nonsteroidal anti-inflammatory drug use (yes/no), current multivitamin use (yes/no), evolutionary-concordance diet score (quintiles), and the removed score component

[c] Four ECLS categories created using score cut points of 2, 4, 6, 8, and 10

Supplemental Table 5. Multivariable-adjusted associations[a] of individual evolutionary-concordance lifestyle score components with incident, sporadic colorectal adenomas in three pooled case-control studies (n = 771 cases and 1,990 controls), 1991 – 2002

Smoking status		Body mass index		Physical activity	
Categories	OR (95% CI)	Categories[b]	OR (95% CI)	Categories[c]	OR (95% CI)
Never	1.00 (Ref.)	Normal weight	1.00 (Ref.)	Low	1.00 (Ref.)
Former	1.40 (1.14-1.71)	Overweight	1.10 (0.89-1.34)	Medium	0.95 (0.76-1.17)
Current	2.66 (2.07-3.42)	Obese	1.31 (1.04-1.65)	High	0.96 (0.77-1.18)

Abbreviations: CI, confidence interval; OR, odds ratio; Ref., reference

[a] OR from unconditional logistic regression models; covariates included age (years; continuous), sex, family history of colorectal cancer in a first-degree relative (yes/no), total energy intake (kcal/day; continuous), education (high school/some college/bachelor's degree or more), hormone replacement therapy (yes/no, if a woman), aspirin and/or other nonsteroidal anti-inflammatory drug use (yes/no), current multivitamin use (yes/no), evolutionary-concordance diet score (quintiles), and the reduced lifestyle score (i.e., minus the individual component of interest) (categorical)

[b] From World Health Organization (WHO) categories: normal weight (18.5 – 24.99 kg/m^2), overweight (25 – 29.99 kg/m^2), obese (≥30 kg/m^2)

[c] Study-specific tertiles of MET-hrs./week of moderate and vigorous activity among the controls

Chapter 3: Public Health Implications and Future Research Directions

Our investigation of the evolutionary-concordance diet and lifestyle pattern scores in a pooled case-control study suggests that greater adherence to these patterns may be independently and jointly associated with lower risk for colorectal adenomas, the precursors of most CRC. Previous investigations found evolutionary-concordance diet pattern scores to be inversely associated with incident, sporadic colorectal adenomas, and with risk of incident colorectal cancer and mortality. Taken together, these findings suggest that a more evolutionary-concordant diet pattern (high in fruits, vegetables, lean meats, calcium, and nuts; low in red/processed meats, grains, dairy, sugar, and sodium) and a more evolutionary-concordant lifestyle pattern (normal BMI, high physical activity, never smoking) may reduce risk for the development and progression of colorectal neoplasms, and supports further investigation of the evolutionary concordance hypothesis in relation to colorectal neoplasia. Future work should include 1) further investigation of the evolutionary-concordance diet and lifestyle pattern scores with colorectal adenoma in other observational studies—including prospective cohort studies—in populations with diverse racial, ethnic, and geographic backgrounds; and 2) randomized controlled trials of the effects of adherence to the patterns on pre-neoplastic biomarkers of risk for colorectal neoplasia and on colorectal adenoma recurrence.