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Higher Dietary Quality Protects against Colorectal Cancer among Normal Weight and Overweight Men and Women but not among Obese Adults

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Title: Higher Dietary Quality Protects against Colorectal Cancer among Normal Weight and Overweight Men and Women but not among Obese Adults

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Key Words: colorectal cancer, diet, food, and nutrition, body mass index

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ABSTRACT

Objective: Lower body mass index (BMI) and higher dietary quality lowers colorectal cancer (CRC) risk, but the association between diet and (CRC) risk according to BMI for men and women is not well-known.

Methods: We used NIH-AARP Diet and Health Study data on 398,458 persons who were 50-71 years old in 1995-1996 and followed through 2006. The exposures were the Mediterranean Diet, Healthy Eating Index-2010, and Dietary Approaches to Stop Hypertension scores; and BMI. The outcome was CRC diagnosis using cancer registry data. Cox Regression models adjusted for disease risk factors.

Results: Among normal-weight or overweight men, CRC risk was 25-30% lower with high as compared with low adherence to each dietary measure. The association was of borderline significance and inconsistent across the three dietary measures for obese men and women in all BMI categories.

Conclusion: Health benefits of consuming a higher dietary quality may include reduction of CRC risk. More research is needed for other groups defined by sex and weight.

Public Health Implications: The findings accentuate the need to establish a healthy food environment to reduce obesity as a cancer prevention strategy.

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Article Summary
Strengths and Limitations

- To our knowledge, this is the first study to examine the potential benefits of healthy eating patterns in reducing colorectal cancer risk among men and women across normal weight, overweight and obese adults.
- In this longitudinal national study of almost 400,00 adults, we found that among normal weight and overweight men, colorectal cancer risk was 25-30% lower with high adherence to each dietary measure.
- Health benefits of consuming a high-quality diet may include reduction of colorectal cancer risk.
- The findings accentuate the need to establish a health food environment to reduce obesity as a cancer prevention strategy.
- There are limitations to our study. Dietary intake was self-reported and assessed using a single baseline Food Frequency Questionnaire, thus, there is potential for non-differential measurement error. Over 90% of the sample was non-Hispanic white. Research is needed to examine whether associations are similar in other racial/ethnic groups.

Contributors

All authors read and approved the final version of the manuscript. Rosalie A. Torres Stone drafted the original manuscript and interpreted the findings, Chyke A. Doubeni conceived of the study and participated in the analyses and interpretation of the data. Jeroan Allison and Molly E. Waring conducted the analyses and interpreted the data. Sarah L. Cutrona and Catarina I. Kiefe contributed to the interpretation of the findings and critically revised the manuscript.

Extra data is available:

Extra data is available by submitting a proposal for each project/manuscript for review by the NIH AARP Steering Committee prior to accessing NIH AARP data and to developing an associated manuscript. A proposal must be submitted through the public website, NIH-AARP Diet & Health Study Tracking and Review System (STaRS, https://www.nihaarpstars.com).

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No additional data is available.

Ethical approval:

Not required. The data is de-identified.

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INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the United States, claiming over 49,700 lives in 2016.(1) Modifiable risk factors such as excess body weight and unhealthy behaviors (sedentary lifestyles, unhealthy dietary patterns, and smoking) increase the risk of CRC.(2-15) Most colorectal cancers are preventable through screening, detection and removal of precancerous lesions, or healthy behaviors.(16, 17) More specifically, it has been estimated that up to 70% of colorectal cancers could be avoided by risk factor modification.(18)

Obesity is a particularly concerning risk factor, as 37% of U.S. adults are obese.(19) A recent meta-analysis found a 30% higher risk of colon cancer in men and a 12% higher risk in women for every 5-kg/m^2 higher body mass index (BMI).(9) Another meta-analysis found that obese adults were at roughly 20% greater risk of developing CRC compared with those of normal weight, and risk of CRC increased 7% for every 2-kg/m^2 higher BMI.(10)

Despite steady improvements in healthy eating patterns among US adults the overall dietary quality remains poor particularly in low income populations.(20, 21) Like obesity, diet is estimated to be one of the most important modifiable risk factors for CRC.(13-15) A dietary pattern that is rich in whole grains, vegetables, fruit, fish, legumes, and nuts and low in red and processed meat and alcohol has been linked to a substantial reduction in the risk of CRC.(2-7, 13, 14) A recent narrative review of publications using the Nurses' Health Study (1976-2016) identified red and processed meat, alcohol, smoking and obesity as factors that increase the risk of CRC.(15) An ecological study suggested that 76% of the inter-country variation in colorectal cancer incidence was explained by meat, fish, and olive oil intake, with olive oil intake being associated with reduced risk.(2) Therefore, the World Health Organization recommends improving dietary quality by increasing consumption of fruit and vegetables, as well as legumes, whole grains, and nuts.(22) These recommendations are similar to those defined in the Dietary Guidelines, studied in the Dietary Approaches to Stop Hypertension trial,(23) and are also similar to recommendations found in the alternate Mediterranean Diet examined in the Seven Countries Study.(24) However, it is not known whether the potential benefits of dietary interventions are similar across varying weight categories and among men and women.

Despite the potential benefits of a healthy BMI, many overweight and obese adults are not motivated or able to lose weight,(25) raising important questions. In the absence of weight loss, can a healthy diet still reduce CRC risk among overweight or obese adults? If so, does the protective effect of a healthy dietary pattern vary by weight category? To our knowledge, these questions have not been answered previously. Our study examined the association between dietary quality and the risk of CRC and studied the variation in this association between normal weight, overweight, and obese adults. Because dietary patterns and their effects have been observed to be different for men and women analyses were stratified by gender.(13)

METHODS

We used data from the National Institutes of Health-AARP (formerly the American Association of Retired Persons) Diet and Health Study. The NIH-AARP cohort was established in 1995-1996. AARP members who were contacted, returned questionnaires eliciting information on demographic and anthropometric characteristics, dietary intake, and health-related behaviors. Initial response rate was 18%. Eligible participants were 50 to 71 years old and resided in six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan).

Outcome

The outcome for this analysis was diagnosis with incident adenocarcinoma of the colon/rectum ascertained from tumor registries through December 31, 2006. Cancer diagnosis in participants was determined through probabilistic linkage with 8 state cancer registries. A validation study found that this approach captured approximately 90% of all cancers.(26) Cancer type and histologic characteristics were obtained from tumor registry data using International Classification of Diseases – Oncology codes [8000, 8010, 8020, 8140-43, 8210-8211, 8221, 8255, 8261-3, 8480-1, 8490, 8510, and 8574].

Determinants

The main determinants for this analysis were three indices of dietary quality. At baseline in 1995-1996, dietary intake during the past 12 months were assessed using a 124-item Food Frequency Questionnaire. The NIH-AARP Food Frequency Questionnaire was previously validated against 24-hour dietary recall in this cohort.(26) The Diet History Questionnaire has been calibrated,(26, 27) and further validation was performed by using two 24-h recalls within a subset of the NIH-AARP Diet and Health Study.(28) By using the guidance-based food group equivalents and other nutrient variables, we calculated component and index scores for the Healthy Eating Index-2010 (HEI-2010).(29) alternate Mediterranean Diet Score,(30) and the Dietary Approaches to Stop Hypertension (DASH)(30), adjusting(30) on the basis of published descriptions of the indices, making appropriate adjustments for energy intake as described by Reedy et. al.(31)

The alternate Mediterranean Diet Score ranges from 0 to 9 with higher scores corresponding to diets more consistent with a Mediterranean diet (healthier). The score was energy adjusted by multiplying by 2,500 calories for men and 2,000 calories for women and dividing by reported energy intake.(13, 30, 32) One point each is given for: intake at or greater than the sex-specific median for whole grains, vegetables, fruit, fish, legumes, and nuts; intake less than the sex-specific median for red and processed meat; and the monounsaturated: saturated fat ratio. Alcohol intake was scored by predetermined cut points for moderate intake (men: 10-25 grams per day, women: 5-15 grams per day);(13) participants with moderate alcohol intake received 1 point; other intakes (none, occasional, excessive) received 0 points.

The Healthy Eating Index 2010 was developed for measuring dietary quality based on federal guidelines.(29) It awards points based on the adequacy of intake in nine categories (total fruit, whole fruit, total vegetables, greens and beans, whole grains, dairy, total protein foods, and seafood and plant proteins, and fatty acids) and moderation of intake in three categories (refined grains, sodium, and empty calories). The Healthy Eating Index 2010 ranges from 0 to 100 with higher scores indicating better dietary quality.

DASH scores capture the diet tested in 2 DASH randomized controlled feeding trials,(23, 33) which examined the role of dietary patterns on blood pressure. Several versions of the DASH score exist, and we used the one most commonly found in the literature with U.S. populations.(30) To derive the score for the DASH Diet, intake was classified into quintiles for the following categories: fruits, vegetables, nuts and legumes, whole grains, low-fat dairy (higher intake indicated by higher quintile) and sodium, red and processed meats, and sweetened beverages (higher intake indicated by lower quintiles).(31) Based on these eight categories, the DASH Score ranged from 8 to 40, with higher scores indicating better dietary quality.

BMI was calculated from height and weight self-reported at baseline and categorized based on WHO criteria (normal: 18.5 to < 25 kg/m^2, overweight: 25 to < 30 kg/m^2, and obese: ≥ 30 kg/m^2).

Covariates

Characteristics self-reported at baseline included gender, age (50-54 years, 55-59 years, 60-64 years, 65-69 years, ≥ 70 years), educational level (high school or less, some college, or college degree), and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian/Pacific Islander, American Indian/Alaskan Native). Self-reported health status was based on a single item by which respondents classified their current state of general health as excellent, very good, good, fair, or poor. Other risk factors for CRC included: smoking status (never smoked, former smoker, current smoker) and physical activity. Participants were asked how often (in the previous 12 months) they engaged in physical activity that lasted ≥ 20 minutes and caused increases in breathing or heart rate, or made the participant sweat (never, rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, ≥ 5 more times per week).

Construction of the analytic sample

Of the 566,398 adults enrolled in the Diet-AARP Health Study, we excluded those who: (1) completed questionnaires by proxy (n=15,760); (2) reported a history of end-stage renal disease (1,299); (3) reported a history of cancer (8,902) or had registry confirmed prevalent cancer (50,591); (4) reported a history of colonic or rectal polyps (57,179); (5) reported any first-degree relatives with colon cancer (50,552); (6) were underweight (BMI < 18.5 kg/m$^{2)}$ (5,912); (7) were missing height or weight (13,944), and participants who reported implausibly high or low energy intake based on Box-Cox transformation procedures designed for this dataset (n=3,534),(28) resulting in an analytic sample of 398,458 adults.

Statistical Analysis

Univariate characteristics were examined for all variables. Chi-square tests were used to compare characteristics of participants who did and did not develop CRC over the follow-up period for categorical variables, and the ANOVA was used for continuous variables. We examined the multivariable association of participant characteristics with dietary adherence using a linear regression model treating the dietary measures as continuous. Based on known risk factors for CRC, covariates in these models included age, gender, race/ethnicity, education, smoking status, physical activity, and weight category.

Next, we examined the association of dietary patterns with incident CRC stratified by BMI category (normal, overweight, and obese) separately for men and women. Two-level dietary pattern comparisons were based on the highest and lowest tertiles of adherence. Bivariate associations were based on the log-rank test.

Cox regression with person-years as the underlying time metric was used to calculate the hazard of developing CRC, within BMI category and gender groups. Separate models were constructed for each dietary index and all models were adjusted for age, race/ethnicity, smoking, and physical activity. A second set of Cox regression models was also created across weight categories that included interaction terms for weight category and dietary adherence. From this second set of models, we predicted the probability of incident CRC at 10 years for each level of dietary quality and weight by raising the baseline hazard at 10 years to the power of the exponentiated linear predictor. Confidence intervals for the predicted probabilities were constructed with the delta method for approximation of complex variance estimates using Taylor linearization.(34) We found no evidence to suggest that proportional hazards assumptions were violated.(35) All analyses were performed with Stata 14.1 (StataCorp LP, College Station, TX).

RESULTS

At baseline, most participants were ≥60 years old (61%) and non-Hispanic white (91%); 59% were men (Table 1).

Table 1. Baseline Characteristics of Sample by Subsequent Diagnosis of Colorectal Cancer over 10 Years of Follow Up, NIH-AARP Diet and Health Study, 1995-2006

	Overall	Did Not Develop Colorectal Cancer	Developed Colorectal Cancer	P-value
N	398,458	391,943	6,515	
Age (years), %				
<55	17.28	17.42	7.97	
55-59	22.04	22.15	15.25	
60-64	26.29	26.28	27.50	<0.001
65-69	30.33	30.12	43.29	
> 69	4.06	4.03	5.99	
Gender				
Female, %	40.60	40.76	31.19	<0.001
Race/Ethnicity, %				
Non-Hispanic White	92.31	92.30	92.84	
Non-Hispanic-Black	3.99	3.98	4.16	
Hispanic	1.99	2.00	1.65	0.031
Asian/Pacific Islander	1.42	1.43	1.06	
American Indian/ Alaska Native	0.29	0.29	0.30	
Education, %				
High School	26.38	26.31	30.40	
Some College	34.24	34.23	34.86	<0.001
College Degree	39.38	39.45	34.74	
Smoking Status, %				
Never	37.00	37.11	30.71	
Former	50.60	50.50	56.68	<0.001
Current	12.40	12.39	12.61	
Physical Activity (≥20 minutes in past 12 months) , %				
Never	4.41	4.40	5.32	
Rarely	13.63	13.61	15.03	
1-2 times/month	13.74	13.74	13.93	<0.001
1-2 times/week	21.78	21.78	21.51	
2-4 times/week	26.99	27.01	25.99	
3-5 times/week	19.45	19.47	18.23	
Baseline weight status, %				
Normal	35.09	35.18	29.98	
Overweight	42.81	42.77	44.88	<0.001
Obese	22.10	22.05	25.14	

Weight status was based on BMI (normal weight: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).

About 35% of the sample were normal weight, 43% were overweight, and 22% were obese.

Mean (sd; range) scores for dietary quality were 4.2 (1.7; 0 - 9) for the alternate Mediterranean

Diet, 65.9 (10.7; 18.2 - 98.4) for the Healthy Eating Index 2010, and 23.8 (4.1; 8 – 37) for the DASH Diet.

During 10 years of follow-up, 6,515 participants (1.64%) were diagnosed with colorectal cancer. The percent of those diagnosed with colorectal cancer was higher moving across BMI categories from normal to obese (1.4%, 1.8%, 1.9%; p-value from log-rank trend test < 0.001). Older age, being male, having lower levels of physical activity, smoking, having less education, being overweight or obese, and poorer diet quality were associated with an increased risk of colorectal cancer ($p < 0.001$) (Table 1). Compared to non-Hispanic whites, the incidence of colorectal cancer was higher for non-Hispanic blacks and lower for Asians/Pacific Islanders ($p = 0.031$).

Results from the linear regression models predicting dietary adherence and the measures of dietary quality are presented in Table 2.

Table 2. Association of Participant Characteristics with Dietary Patterns, NIH-AARP Diet and Health Study, 1996-2006*						
	Mediterranean Diet		Healthy Eating Index		DASH Diet	
	β	95% CI	β	95% CI	β	95% CI
Age (years)						
<55	---	---				
55-59	0.16	0.14 – 0.18	1.17	1.05 – 1.28	0.32	0.28 – 0.37
60-64	0.26	0.25 – 0.28	2.03	1.92 – 2.14	0.63	0.59 – 0.68
65-69	0.31	0.30 – 0.33	2.62	2.51 – 2.73	0.89	0.85 – 0.93
> 69	0.37	0.34 – 0.41	3.10	2.90 – 3.29	1.18	1.10 – 1.25
Gender						
Male	---	---				
Female	0.10	0.08 – 0.10	3.80	3.72 – 3.87	0.39	0.36 – 0.41
Race/Ethnicity						
Non-Hispanic White	---	---				
Non-Hispanic-Black	0.31	0.28 – 0.34	0.78	0.59 – 0.97	-0.25	-0.32 – -0.18
Hispanic	0.05	0.01 – 0.10	0.77	0.51 – 1.03	0.09	-0.01 – 0.19
Asian/Pacific Islander	0.01	-0.04 – 0.06	-0.36	-0.67 – -0.06	-0.64	-0.76 – -0.52
American Indian/ Alaska Native	0.07	-0.04 – 0.18	0.10	-0.57 – 0.77	-0.08	-0.34 – 0.18
Education						
High School	---	---	---	---	---	---
Some College	0.28	0.26 – 0.29	1.97	1.87 – 2.06	0.59	0.55 – 0.63
College Degree	0.59	0.58 – 0.61	3.80	3.70 – 3.89	1.29	1.26 – 1.33
Smoking Status						
Never	---	---				
Former	0.02	0.00 – 0.03	-0.28	-0.36 – -0.20	-0.18	0.55 – 0.63
Current	-0.71	-0.73 – 0.69	-5.89	-6.01 – -5.77	-1.90	1.26 – 1.33
Physical Activity (≥20 minutes in past 12 months)						
Never	---	---				
Rarely	0.14	0.11 – 0.17	1.26	1.07 – 1.46	0.09	0.01 – 0.16
1-2 times/month	0.30	0.27 – 0.33	2.71	2.52 – 2.92	0.37	0.29 – 0.45
1-2 times/week	0.52	0.48 – 0.55	4.17	3.98 – 4.36	0.91	0.84 – 0.99
2-4 times/week	0.79	0.76 – 0.82	6.05	5.86 – 6.24	1.72	1.64 – 1.79
3-5 times/week	0.88	0.84 – 0.91	6.52	6.33 – 6.71	2.30	2.22 – 2.37
Weight Category†						
Normal	---	---				
Overweight	-0.16	-0.17 – -0.15	-0.39	-0.47 – -0.31	-0.33	-0.36 – -0.30
Obese	-0.31	-0.32 – -0.29	-0.88	-0.98 – -0.78	-0.38	-0.42 – -0.35

*From separate linear regression models for each dietary measure.
†Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).

We found "dose-response" associations for older age, higher education, and more frequent physical activity with higher quality diet. Women had better adherence for all three dietary patterns. For the alternate Mediterranean Diet and Health Eating Index-2010, Non-Hispanic Black and Hispanic individuals exhibited small yet statistically significantly higher scores compared to those white adults. Separate models for men and women revealed no important differences (data not shown).

Based on the multivariable models, which included adjustment for age, gender, race/ethnicity, smoking, and physical activity, the hazards of incident CRC were 25-30% lower for men with high dietary adherence who were of normal weight or who were overweight (Table 3a). Smaller differences that were not statistically significant were observed for men who were obese. In general, similar differences in the risk of incident CRC were also observed for women across all dietary quality measures (Table 3b), but these associations were not statistically significant. Women of normal weight with high adherence to the DASH diet and women who were overweight with high adherence to the Healthy Eating Index-2010 had statistically lower incidence of CRC than those with low diet quality on these measures.

Table 3a. Hazard Ratios and 95% Confidence Intervals for Incidence of Colorectal Cancer by Baseline Dietary Pattern and Weight Category, NIH-AARP Diet and Health Study, 1996-2006, n=238,754 for men

	Normal Weight		Overweight		Obese	
Dietary Score	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Mediterranean Diet						
Low Adherence	---	---	---	---	---	---
High Adherence	0.73	0.60 – 0.89	0.73	0.63 – 0.84	0.85	0.69 – 1.05
Healthy Eating Index						
Low Adherence	---	---	---	---	---	---
High Adherence	0.70	0.58 – 0.84	0.74	0.65 - 0.84	0.84	0.70 – 1.02
Dietary Approaches to Stop Hypertension						
Low Adherence	---	---	---	---	---	---
High Adherence	0.73	0.61 – 0.88	0.75	0.66 - 0.85	0.88	0.73 – 1.06

Cox proportional hazard models adjusted for age, gender, race/ethnicity, smoking, and physical activity and include interaction terms for baseline dietary scores and weight category. Separate models were developed for each dietary pattern. Dietary categories (low, high) are based on tertiles of native score. The lowest tertile is the reference group. Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).

Table 3b. Hazard Ratios and 95% Confidence Intervals for Incidence of Colorectal Cancer by Baseline Dietary Pattern and Weight Category, NIH-AARP Diet and Health Study, 1996-2006, n=163,238 for women						
	Normal Weight		Overweight		Obese	
Dietary Score	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Mediterranean Diet						
Low Adherence	---	---	---	---	---	---
High Adherence	0.97	0.77 – 1.22	0.99	0.77 – 1.27	0.76	0.56 – 1.04
Healthy Eating Index						
Low Adherence	---	---	---	---	---	---
High Adherence	0.84	0.68 – 1.04	0.70	0.55 – 0.89	0.80	0.62 – 1.03
Dietary Approaches to Stop Hypertension						
Low Adherence	---	---	---	---	---	---
High Adherence	0.80	0.64 – 0.98	0.81	0.64 – 1.03	0.82	0.63 – 1.08
Cox proportional hazard models adjusted for age, gender, race/ethnicity, smoking, and physical activity and include interaction terms for baseline dietary scores and weight category. Separate models were developed for each dietary pattern. Dietary adherence categories are based on lowest and highest tertiles. Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).						

High dietary adherence was associated with a statistically significant decrease in the probability of incident CRC of about 0.6% for men who were of normal weight or overweight (Table 4a). Smaller differences that were not statistically significant were found for men who were obese and for women from all weight categories (Tables 4a and 4b).

Table 4a. Probability and 95% Confidence Interval of Colorectal Cancer at 10 Years by Baseline Dietary Pattern and Weight Category, NIH-AARP Diet and Health Study, 1996-2006, n=238,754 for men

	Mediterranean Diet		Healthy Eating Index		Dietary Approaches to Stop Hypertension	
Dietary Score	Probability	95% CI	Probability	95% CI	Probability	95% CI
Normal Weight						
Low	0.018	0.008 – 0.028	0.019	0.009 – 0.029	0.018	0.008 – 0.028
High	0.012	0.005 – 0.019	0.012	0.005 – 0.020	0.012	0.005 – 0.020
Difference	0.006	0.002 – 0.010	0.006	0.002 – 0.010	0.006	0.002 – 0.009
Overweight						
Low	0.020	0.009 – 0.031	0.021	0.001 – 0.032	0.020	0.008 – 0.032
High	0.014	0.006 – 0.022	0.015	0.007 – 0.024	0.015	0.006 – 0.024
Difference	0.006	0.002 – 0.010	0.005	0.002 – 0.009	0.005	0.001 – 0.008
Obese						
Low	0.021	0.009 – 0.032	0.021	0.009 – 0.033	0.021	0.009 – 0.033
High	0.018	0.008 – 0.028	0.018	0.008 – 0.028	0.019	0.007 – 0.030
Difference	0.003	-0.001 – 0.007	0.003	-0.001 – 0.007	0.002	-0.001 – 0.006

Probabilities are based on a Cox model that adjusts for age, gender, race/ethnicity, smoking, and physical activity and include interaction terms for baseline dietary scores and weight category. Separate models were developed for each dietary pattern. Dietary adherence categories are based on lowest and highest tertiles. Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2). Differences at last decimal place may not be exact because of rounding.

Table 4b. Probability and 95% Confidence Interval of Colorectal Cancer at 10 Years by Baseline Dietary Pattern and Weight Category, NIH-AARP Diet and Health Study, 1996-2006, n=163,238 for women

	Mediterranean Diet		Healthy Eating Index		Dietary Approaches to Stop Hypertension	
Dietary Score	Probability	95% CI	Probability	95% CI	Probability	95% CI
Normal Weight						
Low	0.011	-0.000 – 0.022	0.012	-0.000 – 0.024	0.012	-0.000 – 0.024
High	0.010	-0.001 – 0.021	0.010	-0.000 – 0.021	0.010	-0.000 – 0.020
Difference	0.000	-0.001 – 0.003	0.002	-0.001 – 0.004	0.002	-0.001 – 0.005
Overweight						
Low	0.012	-0.001 – 0.025	0.013	-0.001 – 0.027	0.013	-0.001 – 0.028
High	0.012	-0.001 – 0.024	0.009	-0.000 – 0.019	0.011	-0.001 – 0.023
Difference	0.000	-0.003 – 0.003	0.004	-0.001 – 0.009	0.002	-0.001 – 0.006
Obese						
Low	0.014	-0.001 – 0.029	0.014	-0.001 – 0.029	0.014	-0.001 – 0.028
High	0.012	-0.001 – 0.024	0.012	-0.001 – 0.025	0.012	-0.001 – 0.024
Difference	0.003	-0.001 – 0.007	0.002	-0.002 – 0.006	0.002	-0.002 – 0.006

Probabilities are based on a Cox model that adjusts for age, gender, race/ethnicity, smoking, and physical activity and include interaction terms for baseline dietary scores and weight category. Separate models were developed for each dietary pattern. Dietary categories (low, high) are based on tertiles of native score.
Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).
Differences at last decimal place may not be exact because of rounding.

DISCUSSION

In this large national study of nearly 400,000 older adults, we found that high quality diets as measured by three diet quality indices (alternate Mediterranean Diet Score, the Healthy Eating Index 2010, and the Dietary Approaches to Stop Hypertension Score) were each associated with lower risk of CRC among normal weight and overweight men. Additionally, high quality diets as measured by the DASH were associated with lower incidence of CRC among normal weight women, and high diet quality measured by the Healthy Eating Index was associated with lower risk among overweight women. Diet quality was not associated with risk of CRC among either obese men or obese women.

Although previous studies have not examined differences according to baseline weight status, our findings are consistent with previous studies that demonstrate that higher dietary quality is associated with reduced risk of colorectal adenoma in general.(13) A review of epidemiological studies investigating the associations between dietary patterns including the DASH, the Mediterranean Diet, and the Healthy Eating Index has also shown a consistently protective effect against colorectal adenoma and cancer incidence of higher scores on all of the dietary indexes for men, but was less conclusive for women.(13, 36) Results from a large prospective examination of four established DASH indexes found that greater compliance with the DASH dietary pattern is protective against CRC for both men and women.(37) This consistency across the three dietary patterns is not surprising because each of these dietary approaches is built on a similar foundation of fresh fruits and vegetables, whole grains, and low saturated fat.

There are physiologic mechanisms through which diet may be protective against CRC and also through which this protective effect may differ for men and for women. For example, studies focused on individual nutrients suggest that olive oil may exert a protective effect by influencing secondary bile acid patterns in the colon. This may in turn affect polyamine metabolism in colonic enterocytes, reducing progression from normal mucosa to adenoma and carcinoma.(3) Fiber intake may reduce the contact between carcinogens and the lining of the colon/rectum and increase stool bulk which dilutes fecal carcinogens and decreases transit time.(2, 7) Red and processed meat may exert a carcinogenic effect due to heme iron, N-nitro compounds and heterocyclic amines generated during cooking at high temperatures as well as a pro-neoplastic effect due to increased adiposity and insulin. Other studies suggest that dietary patterns that include a high consumption of high saturated fatty acid intake may increase CRC risk via their effects on serum insulin concentrations and on the bioavailability of insulin-like growth factor-I (IGF-I).(38) Whole grain intake has been associated with decreased fasting insulin level and improved insulin sensitivity.(7, 39) The differential response of dietary intake to risk of CRC incidence by sex in our study could be explained by differences in the etiology of CRC between men and women.(13) Studies have indicated that women are more likely to develop proximal CRC compared to men.(40) Because proximal and distal CRC appear to arise from different pathways it is possible that the response to dietary intake varies by proximal and distal location type.(40)

These results support initiatives to establish a healthy food environment to support whole grains, vegetables, fruit and plant based proteins to reduce obesity as a cancer prevention strategy.(31, 41) There is growing evidence that local food environments influence access and availability to health eating patterns.(42) A study investigating the associations of supermarket availability and healthy dietary patterns found that participants who have no supermarkets near their homes were 25-46 percent less likely to have a healthy diet.(7, 41) Fostering a food environment that makes it easier for US adults to consume a high-quality diet would provide health benefits to the population, both in terms of potential prevention of CRC and also other chronic diseases linked to dietary intake such as diabetes and cardiovascular disease.(31, 32, 42-44)

Our study has some limitations. Dietary intake was self-reported and assessed using a single baseline Food Frequency Questionnaire, thus, there is potential for non-differential measurement error.(45) With only a single measure, we could not examine changes in dietary intake over time. It is possible that the observed differences between men and women are artifacts from how the data were collected. For example, it has been suggested that differential bias could be introduced by the way women and men complete the Food Frequency Questionnaire.(45, 46) It is also possible that women in the AARP (as a group) have more variation in diet patterns and perception of dietary intake (and weight status) over time than men.(26) Additionally, there is evidence that difference in dietary patterns may vary for men and women who respond in a similar manner to the same survey.(13) Over 90% of the sample was non-Hispanic white. The research consistently shows that incident rates of CRC and obesity prevalence are higher in African Americans compared to whites.(47, 48) Research is needed to examine whether associations are similar in other racial/ethnic groups.

This longitudinal national study of almost 400,000 adults found that among normal-weight and overweight men, CRC risk was 25-30% lower with high adherence to each dietary measure. High adherence to the DASH diet was associated with lower risk among normal weight women, and high adherence to the Healthy Eating Index was associated with lower risk among overweight women. Diet quality was not associated with cancer risk among obese adults. Health benefits of consuming a high-quality diet may include reduction of CRC risk.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract ***see pg.1***
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ***see pg. 2***
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ***see pgs. 4-5***
Objectives	3	State specific objectives, including any prespecified hypotheses ***see pgs. 4-5***
Methods		
Study design	4	Present key elements of study design early in the paper ***see pg. 5***
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants ***see pg. 5***
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable ***see pgs. 6-8***
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy ***see pgs. 8-9***
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ***see pg. 8***
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ***see pgs. 9-11***
		(b) Indicate number of participants with missing data for each variable of interest ***see pg. 8***
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures ***see pg. 6***
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ***see pgs. 11-15***
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives ***see pgs. 16-19***
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ***see pg. 18***
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ***see pgs. 16-18***
Generalisability	21	Discuss the generalisability (external validity) of the study results ***see pgs. 16-18***
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ***see pgs. 19-20***

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The Association of Dietary Quality with Colorectal Cancer among Normal Weight, Overweight, and Obese Men and Women: A Prospective Longitudinal Study

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Title: The Association of Dietary Quality with Colorectal Cancer among Normal Weight, Overweight, and Obese Men and Women: A Prospective Longitudinal Study

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Key Words: colorectal cancer, diet, food, and nutrition, body mass index

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ABSTRACT

Objective: Lower body mass index (BMI) and higher dietary quality reduces the risk of colorectal cancer (CRC) risk, but we lack a full understanding of how this association varies according to BMI for men and women.

Methods: We used data from the NIH-AARP Diet and Health Study consisting of 398,458 persons who were 50-71 years old in 1995-1996 and followed through 2006. Exposures were dietary quality as reflected by the Mediterranean Diet, the Healthy Eating Index-2010, and the Dietary Approaches to Stop Hypertension score, stratified by BMI category. The outcome was CRC diagnosis from cancer registry data. Cox Regression models adjusted for disease risk factors.

Results: Over a mean duration of 123 months of follow-up, there were 6,515 new diagnoses of colorectal cancer (1,953 among the normal weight, 2,924 among the overweight, and 1,638 among the obese; 4,483 among men and 2,032 among women). For normal-weight and overweight men, dietary adherence in the highest tertile (versus the lowest tertile) was associated with 25-30% lower CRC risk for each of the three measures. In addition, a gradient effect linked increasing dietary adherence with decreasing CRC risk. The associations were of borderline significance and inconsistent across the three dietary measures for obese men and women in all BMI categories.

Conclusion: These findings illustrate the value of healthy eating habits among men who normal weight and provide evidence to inform new strategies for cancer prevention.

Public Health Implications: The findings accentuate the need to establish strategies to improve diet quality and prevent obesity as a cancer prevention strategy.

Word Count: 255

Key Words: colorectal cancer, diet, food, and nutrition, body mass index

Article Summary

Strengths and Limitations

- To our knowledge, this is the first study to examine the potential benefits of healthy eating patterns in reducing colorectal cancer risk among men and women who are at normal weight, overweight and obese adults.
- In this longitudinal national study of 398,458 adults, we found that among normal weight and overweight men, colorectal cancer risk was 25-30% lower with high adherence to each dietary measure (Mediterranean Diet, Healthy Eating Index-2010, and the Dietary Approaches to Stop Hypertension). Findings were inconsistent among obese men and women of all weight categories.
- Dietary intake was self-reported and assessed using a single baseline Food Frequency Questionnaire, thus, there is potential for non-differential measurement error. With only a single measure, we could not examine changes in dietary intake over time. Over 90% of the sample was non-Hispanic white. Research is needed to examine whether associations are similar in other racial/ethnic groups and to better understand the inconsistency in the results for women.

Contributors

All authors read and approved the final version of the manuscript. Rosalie A. Torres Stone drafted the original manuscript and interpreted the findings, Chyke A. Doubeni conceived of the study and participated in the analyses and interpretation of the data. Jeroan Allison and Molly E. Waring conducted the analyses and interpreted the data. Sarah L. Cutrona and Catarina I. Kiefe contributed to the interpretation of the findings and critically revised the manuscript.

Extra data is available:

Extra data is available by submitting a proposal for each project/manuscript for review by the NIH AARP Steering Committee prior to accessing NIH AARP data and to developing an associated manuscript. A proposal must be submitted through the public website, NIH-AARP Diet & Health Study Tracking and Review System (STaRS, https://www.nihaarpstars.com).

Data sharing:

No additional data is available.

Ethical approval:

Not required. The data is de-identified.

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INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer-related deaths in the United States, claiming over 49,190 lives in 2016.[1] Modifiable risk factors such as excess body weight and unhealthy behaviors (sedentary lifestyles, unhealthy dietary patterns, and smoking) increase the risk of CRC.[2-15] Most colorectal cancers are preventable through screening, detection and removal of precancerous lesions, or by engaging in healthful behaviors.[16 17] More specifically, it has been estimated that up to 70% of colorectal cancers could be avoided by risk factor modification.[18]

Obesity is a particularly concerning risk factor, as 37% of U.S. adults are obese.[19] A recent meta-analysis found a 30% higher risk of colon cancer in men and a 12% higher risk in women for every 5-kg/m^2 increase in body mass index (BMI).[9] Another meta-analysis found that obese adults were at roughly 20% greater risk of developing CRC compared with those of normal weight, and the risk of CRC increased 7% for every 2-kg/m^2 higher BMI.[10]

Like obesity, diet is estimated to be one of the most important modifiable risk factors for CRC.[13-15] A dietary pattern that is rich in whole grains, vegetables, fruit, fish, legumes, and nuts and low in red and processed meat and alcohol has been linked to a substantial reduction in the risk of CRC.[2-7 13 14] Therefore, the World Health Organization recommends improving dietary quality by increasing consumption of fruit and vegetables, as well as legumes, whole grains, and nuts.[20] These recommendations are similar to those studied in the Dietary Approaches to Stop Hypertension trial,[21 22] and are also similar to recommendations found in the alternate Mediterranean Diet examined in the Seven Countries Study.[13 23]

Despite the potential benefits of a healthy BMI, many overweight and obese adults are not motivated or able to lose weight,[24] raising important questions. In the absence of weight loss, can a healthy diet still reduce CRC risk among overweight or obese adults? Likewise, because diet is emphasized as a means for weight loss, those who may be of normal weight may also lack the motivation to engage in health eating. These considerations raise unanswered questions about how the association of health eating patterns varies by weight categories. Therefore, our study examined the association between dietary quality and the risk of CRC and studied the variation in this association among normal weight, overweight, and obese adults. Because dietary patterns have been observed to be different for men and women analyses were stratified by gender.[13]

METHODS

We used data from the National Institutes of Health-AARP (formerly the American Association of Retired Persons) Diet and Health Study. The NIH-AARP cohort was established in 1995-1996. AARP members who were contacted, returned questionnaires eliciting information on demographic and anthropometric characteristics, dietary intake, and health-related behaviors. The initial response rate was 18%. Eligible participants were 50 to 71 years old and resided in six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan).

Outcome

The outcome for this analysis was diagnosis with incident adenocarcinoma of the colon/rectum ascertained from tumor registries through December 31, 2006. Cancer diagnosis in participants was determined through probabilistic linkage with 8 state cancer registries. A validation study found that this approach captured approximately 90% of all cancers.[25] Cancer type and histologic characteristics were obtained from tumor registry data using International Classification of Diseases – Oncology codes [8000, 8010, 8020, 8140-43, 8210-8211, 8221, 8255, 8261-3, 8480-1, 8490, 8510, and 8574].

Determinants

The main determinants for this analysis were three indices of dietary quality. At baseline in 1995-1996, dietary intake during the past 12 months were assessed using a 124-item Food Frequency Questionnaire. The NIH-AARP Food Frequency Questionnaire was previously validated against 24-hour dietary recall in this cohort.[25] The Diet History Questionnaire has been calibrated,[25 26] and further validation was performed by using two 24-h recalls within a subset of the NIH-AARP Diet and Health Study.[27] By using the guidance-based food group equivalents and other nutrient variables, we calculated component and index scores for the Healthy Eating Index-2010 (HEI-2010),[28] the alternate Mediterranean Diet Score,[29] and the Dietary Approaches to Stop Hypertension (DASH),[29] according to algorithms described by Reedy et. al.[30]

The alternate Mediterranean Diet Score ranges from 0 to 9 with higher scores corresponding to diets more consistent with a Mediterranean diet. The score was energy adjusted by multiplying by 2,500 calories for men and 2,000 calories for women and dividing by reported energy intake.[13 29 31] One point each is given for: intake at or greater than the sex-specific median for whole grains, vegetables, fruit, fish, legumes, and nuts; intake less than the sex-specific median for red and processed meat; and the monounsaturated: saturated fat ratio. Alcohol intake was scored by predetermined cut points for moderate intake (men: 10-25 grams per day, women: 5-15 grams per day);[13] participants with moderate alcohol intake received 1 point; other intakes (none, occasional, excessive) received 0 points. Mediterranean Diet Scores were energy adjusted.

The Healthy Eating Index 2010 was developed for measuring dietary quality based on federal guidelines.[28] It awards points based on the adequacy of intake in nine categories (total fruit, whole fruit, total vegetables, greens and beans, whole grains, dairy, total protein foods, and seafood and plant proteins, and fatty acids) and moderation of intake in three categories (refined grains, sodium, and empty calories). The Healthy Eating Index 2010 ranges from 0 to 100 with higher scores indicating better dietary quality. HEIX scores were not energy adjusted.

DASH scores capture the diet tested in two DASH randomized controlled feeding trials,[21, 32] which examined the role of dietary patterns on blood pressure. Several versions of the DASH score exist, and we used the one most commonly found in the literature with U.S. populations.[29] To derive the score for the DASH Diet, intake was classified into quintiles for the following categories: fruits, vegetables, nuts and legumes, whole grains, low-fat dairy (higher intake indicated by higher quintile) and sodium, red and processed meats, and sweetened beverages (higher intake indicated by lower quintiles).[30] Based on these eight categories, the DASH Score ranged from 8 to 40, with higher scores indicating better dietary quality. DASH score were energy adjusted.

BMI was calculated from height and weight self-reported at baseline and categorized based on WHO criteria (normal: 18.5 to < 25 kg/m^2, overweight: 25 to < 30 kg/m^2, and obese: ≥ 30 kg/m^2).

Covariates

Characteristics self-reported at baseline included gender, age (50-54 years, 55-59 years, 60-64 years, 65-69 years, ≥ 70 years), educational level (high school or less, some college, or college degree), and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian/Pacific Islander, American Indian/Alaskan Native). Other risk factors for CRC included: smoking status (never smoked, former smoker, current smoker) and physical activity. Participants were asked how often (in the previous 12 months) they engaged in physical activity that lasted ≥ 20 minutes and caused increases in breathing or heart rate, or made the participant sweat (never, rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, ≥ 5 more times per week).

Construction of the analytic sample

Of the 566,398 adults enrolled in the Diet-AARP Health Study, we excluded those who: (1) completed questionnaires by proxy (n=15,760); (2) reported a history of end-stage renal disease (1,299); (3) reported a history of cancer (8,902) or had registry confirmed prevalent cancer (50,591); (4) reported a history of colonic or rectal polyps (57,179); (5) reported any first-degree relatives with colon cancer (50,552); (6) were underweight (BMI < 18.5 $kg/m^{2)}$ (5,912); (7) were missing height or weight (13,944); or (8) reported implausibly high or low energy intake based on Box-Cox transformation procedures designed for this dataset (n=3,534),[27] resulting in an analytic sample of 398,458 adults.

Statistical Analysis

Univariate characteristics were examined for all variables. Chi-square tests were used to compare characteristics of participants who did and did not develop CRC over the follow-up period for categorical variables, and the ANOVA was used for continuous variables. We examined the multivariable association of participant characteristics with dietary adherence using a linear regression model treating the dietary measures as continuous. Based on known risk factors for CRC, covariates in these models included age, gender, race/ethnicity, education, smoking status, physical activity, and weight category.

Next, we examined the association of dietary patterns with incident CRC stratified by BMI category (normal, overweight, and obese) separately for men and women. Two-level dietary pattern comparisons were based on the highest and lowest tertiles of adherence. Bivariate associations were based on the log-rank test.

Cox regression with duration of observation as the underlying time metric was used to calculate the hazard of developing CRC, within BMI category and gender groups. Separate models were constructed for each dietary index and all models were adjusted for age, race/ethnicity, smoking, and physical activity. A first set of Cox models took dietary exposure as a dichotomous measure stratifying on gender and weight categories. A second set of Cox regression models was also created across all weight categories that included interaction terms for weight category and dietary adherence. From this second set of models, we predicted the probability of incident CRC at 10 years for each level of dietary quality and weight by raising the baseline hazard at 10 years to the power of the exponentiated linear predictor. Confidence intervals for the predicted probabilities were constructed with the delta method for approximation of complex variance estimates using Taylor linearization.[33] We found no evidence to suggest that proportional hazards assumptions were violated.[34] All analyses were performed with Stata 14.1 (StataCorp LP, College Station, TX).

RESULTS

At baseline, most participants were ≥60 years old (61%) and non-Hispanic white (91%); 59% were men (Table 1).

Table 1. Baseline Characteristics of Sample by Subsequent Diagnosis of Colorectal Cancer over 10 Years of Follow Up, NIH-AARP Diet and Health Study, 1995-2006				
	Overall	Did Not Develop Colorectal Cancer	Developed Colorectal Cancer	P-value
N	398,458	391,943	6,515	
Age (years), %				
<55	17.28	17.42	7.97	<0.001
55-59	22.04	22.15	15.25	
60-64	26.29	26.28	27.50	
65-69	30.33	30.12	43.29	
> 69	4.06	4.03	5.99	
Gender				
Female, %	40.60	40.76	31.19	<0.001
Race/Ethnicity, %				
Non-Hispanic White	92.31	92.30	92.84	0.031
Non-Hispanic-Black	3.99	3.98	4.16	
Hispanic	1.99	2.00	1.65	
Asian/Pacific Islander	1.42	1.43	1.06	
American Indian/ Alaska Native	0.29	0.29	0.30	
Education, %				
High School	26.38	26.31	30.40	<0.001
Some College	34.24	34.23	34.86	
College Degree	39.38	39.45	34.74	
Smoking Status, %				
Never	37.00	37.11	30.71	<0.001
Former	50.60	50.50	56.68	
Current	12.40	12.39	12.61	
Physical Activity (≥20 minutes in past 12 months) , %				
Never	4.41	4.40	5.32	<0.001
Rarely	13.63	13.61	15.03	
1-2 times/month	13.74	13.74	13.93	
1-2 times/week	21.78	21.78	21.51	
2-4 times/week	26.99	27.01	25.99	
3-5 times/week	19.45	19.47	18.23	
Baseline weight status, %				
Normal	35.09	35.18	29.98	<0.001
Overweight	42.81	42.77	44.88	
Obese	22.10	22.05	25.14	
Dietary Scores (mean ± sd)				
Mediterranean Diet	4.16 ± 1.71	4.15 ± 1.71	3.99 ± 1.72	< 0.001
Health Eating Index	65.94 ± 10.75	65.97 ± 10.74	64.42 ± 11.01	<0.001
Dietary Approaches to Stop HTN	23.85 ± 4.10	23.85 ± 4.11	23.41 ± 4.11	<0.001

Weight status was based on BMI (normal weight: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).

About 35% of the sample were normal weight, 43% were overweight, and 22% were obese.

Mean (sd; range) scores for dietary quality were 4.2 (1.7; 0 - 9) for the alternate Mediterranean

Diet, 65.9 (10.7; 18.2 - 98.4) for the Healthy Eating Index 2010, and 23.8 (4.1; 8 – 37) for the DASH Diet.

Over a mean follow-up duration of 123 months, 6,515 participants (1.64%) were diagnosed with colorectal cancer. There were 6,515 new diagnoses of colorectal cancer (1,953 among the normal weight, 2,924 among the overweight, and 1,638 among the obese; 4,483 among men and 2,032 among women). Of all new diagnoses, 9.7% were Stage 0; 38.4% were Stage 1; 14.0% were Stage 2; 22.7% were Stage 3; and 15.3% were Stage 4. The percent of those diagnosed with colorectal cancer increased moving across BMI categories from normal to overweight to obese (1.4%, 1.8%, 1.9%; p-value from log-rank trend test < 0.001). Older age, being male, having lower levels of physical activity, smoking, having less education, being overweight or obese, and lower diet quality were associated with an increased risk of colorectal cancer ($p < 0.001$) (Table 1). Compared to non-Hispanic whites, the incidence of colorectal cancer was higher for non-Hispanic blacks and lower for Asians/Pacific Islanders ($p = 0.031$).

For the overall population, the hazard of incident colorectal cancer diagnosis was 33.3% less for women compared to men. Compared to those who had normal weight, the hazard of incident colorectal cancer diagnosis was 13.1% greater for those who were overweight and 30.6% greater for those who were obese.

Results from the linear regression models predicting dietary adherence and the measures of dietary quality are presented in Table 2.

Table 2. Multivariable Association of Participant Characteristics with Dietary Patterns, NIH-AARP Diet and Health Study, 1996-2006*						
	Mediterranean Diet		Healthy Eating Index		DASH Diet	
	β	95% CI	β	95% CI	β	95% CI
Age (years)						
<55	---	---				
55-59	0.16	0.14 – 0.18	1.17	1.05 – 1.28	0.32	0.28 – 0.37
60-64	0.26	0.25 – 0.28	2.03	1.92 – 2.14	0.63	0.59 – 0.68
65-69	0.31	0.30 – 0.33	2.62	2.51 – 2.73	0.89	0.85 – 0.93
> 69	0.37	0.34 – 0.41	3.10	2.90 – 3.29	1.18	1.10 – 1.25
Gender						
Male	---	---				
Female	0.10	0.08 – 0.10	3.80	3.72 – 3.87	0.39	0.36 – 0.41
Race/Ethnicity						
Non-Hispanic White	---	---				
Non-Hispanic-Black	0.31	0.28 – 0.34	0.78	0.59 – 0.97	-0.25	-0.32 – -0.18
Hispanic	0.05	0.01 – 0.10	0.77	0.51 – 1.03	0.09	-0.01 – 0.19
Asian/Pacific Islander	0.01	-0.04 – 0.06	-0.36	-0.67 – -0.06	-0.64	-0.76 – -0.52
American Indian/ Alaska Native	0.07	-0.04 – 0.18	0.10	-0.57 – 0.77	-0.08	-0.34 – 0.18
Education						
High School	---	---	---	---	---	---
Some College	0.28	0.26 – 0.29	1.97	1.87 – 2.06	0.59	0.55 – 0.63
College Degree	0.59	0.58 – 0.61	3.80	3.70 – 3.89	1.29	1.26 – 1.33
Smoking Status						
Never	---	---				
Former	0.02	0.00 – 0.03	-0.28	-0.36 – -0.20	-0.18	0.55 – 0.63
Current	-0.71	-0.73 – 0.69	-5.89	-6.01 – -5.77	-1.90	1.26 – 1.33
Physical Activity (≥20 minutes in past 12 months)						
Never	---	---				
Rarely	0.14	0.11 – 0.17	1.26	1.07 – 1.46	0.09	0.01 – 0.16
1-2 times/month	0.30	0.27 – 0.33	2.71	2.52 – 2.92	0.37	0.29 – 0.45
1-2 times/week	0.52	0.48 – 0.55	4.17	3.98 – 4.36	0.91	0.84 – 0.99
2-4 times/week	0.79	0.76 – 0.82	6.05	5.86 – 6.24	1.72	1.64 – 1.79
3-5 times/week	0.88	0.84 – 0.91	6.52	6.33 – 6.71	2.30	2.22 – 2.37
Weight Category†						
Normal	---	---				
Overweight	-0.16	-0.17 – -0.15	-0.39	-0.47 – -0.31	-0.33	-0.36 – -0.30
Obese	-0.31	-0.32 – -0.29	-0.88	-0.98 – -0.78	-0.38	-0.42 – -0.35

*From separate linear regression models for each dietary measure.
†Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).

We found "dose-response" associations for older age, higher education, and more frequent physical activity with higher quality diet. Women had better adherence for all three dietary patterns. For the alternate Mediterranean Diet and Health Eating Index-2010, Non-Hispanic Black and Hispanic individuals exhibited small yet statistically significantly higher scores compared to those white adults. Separate models for men and women revealed no important differences (data not shown).

The first set of multivariable models examined the association of being in the top (versus bottom) tertile of dietary adherence with the outcome of CRC. Based on these models, which included adjustment for age, gender, race/ethnicity, smoking, and physical activity, the hazards of incident CRC were 25-30% lower for men with high dietary adherence who were of normal weight or who were overweight (Table 3a). Smaller and inconsistent associations were found for men who were obese and for women of all weight categories (Table 3b).

Table 3a. Hazard Ratios and 95% Confidence Intervals for Incidence of Colorectal Cancer by Baseline Dietary Pattern and Weight Category, NIH-AARP Diet and Health Study for Men, 1996-2006 (n=182,762)

	Normal Weight		Overweight		Obese	
Dietary Score	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Mediterranean Diet						
Low Adherence	---	---	---	---	---	---
High Adherence	0.73	0.60 – 0.89	0.73	0.63 – 0.84	0.85	0.69 – 1.05
Healthy Eating Index						
Low Adherence	---	---	---	---	---	---
High Adherence	0.70	0.58 – 0.84	0.74	0.65 - 0.84	0.84	0.70 – 1.02
Dietary Approaches to Stop Hypertension						
Low Adherence	---	---	---	---	---	---
High Adherence	0.73	0.61 – 0.88	0.75	0.66 - 0.85	0.88	0.73 – 1.06

Cox proportional hazard models adjusted for age, gender, race/ethnicity, smoking, and physical activity. Separate models were developed for each dietary pattern and weight category. Dietary categories (low, high) are based on tertiles of native score. The lowest tertile is the reference group.
Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).

Table 3b. Hazard Ratios and 95% Confidence Intervals for Incidence of Colorectal Cancer by Baseline Dietary Pattern and Weight Category, NIH-AARP Diet and Health Study for Women, 1996-2006 (n=125,281)						
	Normal Weight		Overweight		Obese	
Dietary Score	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Mediterranean Diet						
Low Adherence	---	---	---	---	---	---
High Adherence	0.97	0.77 – 1.22	0.99	0.77 – 1.27	0.76	0.56 – 1.04
Healthy Eating Index						
Low Adherence	---	---	---	---	---	---
High Adherence	0.84	0.68 – 1.04	0.70	0.55 – 0.89	0.80	0.62 – 1.03
Dietary Approaches to Stop Hypertension						
Low Adherence	---	---	---	---	---	---
High Adherence	0.80	0.64 – 0.98	0.81	0.64 – 1.03	0.82	0.63 – 1.08

Cox proportional hazard models adjusted for age, gender, race/ethnicity, smoking, and physical activity.. Separate models were developed for each dietary pattern and weight category. Dietary adherence categories are based on lowest and highest tertiles. Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).

Finally, based on the multivariable model Cox regression models, we predicted incidence of new colorectal cancer at 10 years. For this set of models, dietary quality was entered in quintiles. As shown in Table 4a, we found statistically significant linear trends, suggesting a gradient affect associating increasing adherence to high-quality dietary patterns with decreasing incidence of colorectal cancer at 10 years. Gradient effects were strongest for men who were of normal weight or overweight, and less strong for men who were obese. The findings were more mixed for women (Table 4b). For both men and women, the absolute predicted rates of colorectal cancer were consistently less than 2.5%.

Table 4a. Probability and 95% Confidence Interval of Colorectal Cancer at 10 Years by Baseline Dietary Pattern and Weight Category, NIH-AARP Diet and Health Study for Men, 1996-2006 (n=182,762)						
	Mediterranean Diet		Healthy Eating Index		Dietary Approaches to Stop Hypertension	
Dietary Score	Probability	95% CI	Probability	95% CI	Probability	95% CI
Normal Weight						
Quintile 1	0.018	0.010 - 0.259	0.019	0.011 - 0.027	0.019	0.011 - 0.027
Quintile 2	0.016	0.001 - 0.024	0.017	0.009 - 0.025	0.017	0.009 - 0.025
Quintile 3	0.014	0.007 - 0.021	0.015	0.008 - 0.021	0.015	0.008 - 0.022
Quintile 4	0.014	0.007 - 0.020	0.013	0.007 - 0.191	0.015	0.008 - 0.022
Quintile 5	0.011	0.005 - 0.157	0.012	0.006 - 0.018	0.012	0.006 - 0.018
p-for-trend	0.0001		<0.0001		0.0001	
Overweight						
Quintile 1	0.200	0.011 - 0.029	0.022	0.012 - 0.032	0.021	0.001 - 0.031
Quintile 2	0.017	0.009 - 0.025	0.017	0.009 - 0.025	0.018	0.010 - 0.026
Quintile 3	0.017	0.009 - 0.025	0.016	0.009 - 0.024	0.016	0.009 - 0.024
Quintile 4	0.014	0.008 - 0.021	0.018	0.009 - 0.026	0.016	0.008 - 0.023
Quintile 5	0.015	0.008 - 0.022	0.014	0.007 - 0.020	0.016	0.008 - 0.023
p-for-trend	0.0003		<0.0001		<0.0000	
Obese						
Quintile 1	0.021	0.011 - 0.031	0.022	0.012 - 0.032	0.024	0.013 - 0.035
Quintile 2	0.018	0.010 - 0.027	0.021	0.011 - 0.030	0.017	0.009 - 0.026
Quintile 3	0.021	0.011 - 0.031	0.018	0.001 - 0.027	0.019	0.010 - 0.028
Quintile 4	0.020	0.010 - 0.029	0.020	0.010 - 0.029	0.020	0.010 - 0.029
Quintile 5	0.015	0.007 - 0.024	0.017	0.009 - 0.026	0.019	0.010 - 0.028
p-for-trend	0.0944		<0.0184		0.1150	

Probabilities are based on a Cox model that adjusts for age, gender, race/ethnicity, smoking, and physical activity and include interaction terms for baseline dietary scores and weight category. Separate models were developed for each dietary pattern. Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).

Table 4b. Probability and 95% Confidence Interval of Colorectal Cancer at 10 Years by Baseline Dietary Pattern and Weight Category, NIH-AARP Diet and Health Study for Women, 1996-2006 (n=125,281)						
	Mediterranean Diet		Healthy Eating Index		Dietary Approaches to Stop Hypertension	
Dietary Score	Probability	95% CI	Probability	95% CI	Probability	95% CI
Normal Weight						
Quintile 1	0.011	0.001 - 0.021	0.013	0.001 - 0.024	0.012	0.001 - 0.023
Quintile 2	0.009	0.006 - 0.017	0.010	0.001 - 0.019	0.011	0.001 - 0.020
Quintile 3	0.010	0.001 - 0.020	0.009	0.000 - 0.018	0.009	0.000 - 0.017
Quintile 4	0.011	0.001 - 0.209	0.010	0.001 - 0.018	0.011	0.001 - 0.021
Quintile 5	0.010	0.000 - 0.020	0.011	0.001 - 0.022	0.009	0.001 - 0.018
p-for-trend	0.7829		0.1574		0.0585	
Overweight						
Quintile 1	0.012	0.001 - 0. 323	0.014	0.001 - 0.027	0.013	0.001 - 0.026
Quintile 2	0.012	0.001 - 0.023	0.012	0.001 - 0.024	0.012	0.001 - 0.023
Quintile 3	0.011	0.001 - 0.021	0.013	0.001 - 0.026	0.012	0.001 - 0.024
Quintile 4	0.012	0.001 - 0.023	0.011	0.001 - 0.020	0.010	0.000 - 0.019
Quintile 5	0.012	0.000 - 0.023	0.010	0.000 - 0.019	0.011	0.001 - 0.021
p-for-trend	0.8314		0.0015		0.0343	
Obese						
Quintile 1	0.014	0.001 - 0.028	0.016	0.001 - 0.030	0.014	0.001 - 0.028
Quintile 2	0.015	0.001 - 0.029	0.014	0.001 - 0.026	0.015	0.001 - 0.030
Quintile 3	0.011	0.001 - 0.022	0.014	0.001 - 0.028	0.012	0.001 - 0.024
Quintile 4	0.011	0.000 - 0.021	0.013	0.001 - 0.026	0.012	0.000 - 0.023
Quintile 5	0.014	0.000 - 0.028	0.012	0.001 - 0.232	0.013	0.001 - 0.025
p-for-trend	0.2932		0.0378		0.0569	
Probabilities are based on a Cox model that adjusts for age, gender, race/ethnicity, smoking, and physical activity and include interaction terms for baseline dietary scores and weight category. Separate models were developed for each dietary pattern. Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).						

DISCUSSION

In this large national study of nearly 400,000 of middle aged and older adults, we found that high quality diets as measured by three diet quality indices (alternate Mediterranean Diet Score, the Healthy Eating Index 2010, and the Dietary Approaches to Stop Hypertension Score) were each associated with lower risk of CRC among normal weight and overweight men. We also found an important gradient effect linking improving dietary quality with lower incident colorectal cancer for men. Associations were inconsistent and of smaller magnitude among obese men and women of all weight categories.

Although previous studies have not examined differences according to baseline weight status, our findings are consistent with other studies demonstrating that higher dietary quality is associated with reduced risk of colorectal adenoma in general.[13] For example, a recent narrative review of publications using the Nurses' Health Study (1976-2016) identified red and processed meat, alcohol, smoking and obesity as factors that increase the risk of CRC.[15] Likewise, an ecological study suggested that 76% of the inter-country variation in colorectal cancer incidence was explained by meat, fish, and olive oil intake, with olive oil intake being associated with reduced risk.[2]

A review of epidemiological studies investigating the associations between dietary patterns including the DASH, the Mediterranean Diet, and the Healthy Eating Index has also shown a consistently reduced risk of colorectal adenoma and cancer incidence of higher scores on all of the dietary indexes for men, but was less conclusive for women.[13 35] Another large prospective examination of four established DASH indexes found that greater compliance with the DASH dietary pattern was associated with a reduced risk of CRC for both men and women.[36] This consistency across the three dietary patterns is not surprising because each of these dietary approaches is built on a similar foundation of fresh fruits and vegetables, whole grains, and low saturated fat.

There are physiologic mechanisms through which diet may be associated with a reduced risk of CRC and through which this association may differ for men and for women. For example, studies focused on individual nutrients suggest that olive oil may exert a reduced risk of CRC by influencing secondary bile acid patterns in the colon. This may in turn affect polyamine metabolism in colonic enterocytes, reducing progression from normal mucosa to adenoma and carcinoma.[3] Fiber intake may reduce the contact between carcinogens and the lining of the colon/rectum and increase stool bulk, which dilutes fecal carcinogens and decreases transit time.[2 7] Red and processed meat may exert a carcinogenic effect due to heme iron, N-nitro compounds and heterocyclic amines generated during cooking at high temperatures as well as a pro-neoplastic effect due to increased adiposity and insulin. Other studies suggest that dietary patterns that include a high consumption of high saturated fatty acid intake may increase CRC risk via their effects on serum insulin concentrations and on the bioavailability of insulin-like growth factor-I (IGF-I).[37] Whole grain intake has been associated with decreased fasting insulin level and improved insulin sensitivity.[7 38]

The differential response of dietary intake to risk of CRC incidence by sex in our study could be explained by differences in the etiology of CRC between men and women.[13] Studies have indicated that women are more likely to develop proximal CRC compared to men.[39] Because proximal and distal CRC appear to arise from different pathways it is possible that the response to dietary intake varies by proximal and distal location type.[39] Hormonal factors may also be responsible for sex differences CRC etiology. Studies of postmenopausal hormone therapy and colorectal cancer report a reduction in risk of colon cancer and a decrease in the risk of rectal cancer for postmenopausal women who had ever taken hormone therapy compared with women who never used hormones. The CRC risk reduction appears to be stronger for current and long-term hormone users.[40 41]

The association was of borderline significance and inconsistent across the three dietary measures for obese men and women. It is plausible that the beneficial effects of a healthy diet are attenuated by the inflammatory, hormonal, and other metabolic changes induced by obesity that promote colorectal carcinogenesis.[42] For example, the gut microbiome that provides important metabolic capabilities, is responsive to alterations of diet,[43] and has been shown in obese people to be different from, and less diverse than, those of the non-obese.[44]

Our study has some limitations. Our analytic dataset excluded those with family history of colorectal cancer and are therefore only generalize to those who are of average risk. Medical co-morbidity was not included as a covariate in the multivariable models. Our study population was relatively homogenous with upper-to-middle class Americans in urban centers: non-whites comprised a relatively small proportion of our sample. Dietary intake was self-reported and assessed using a single baseline Food Frequency Questionnaire, thus, there is potential for non-differential measurement error.[45] With only a single measure, we could not examine changes in dietary intake over time. It is possible that the observed differences between men and women are artifacts from how the data were collected. For example, it has been suggested that differential bias could be introduced by the way women and men complete the Food Frequency Questionnaire.[45 46] Women in the AARP (as a group) may have more variation in diet patterns and perception of dietary intake (and weight status) over time than men.[25] Additionally, there is evidence that difference in dietary patterns may vary for men and women who respond in a similar manner to the same survey.[13] Over 90% of the sample was non-Hispanic white. The research consistently shows that incident rates of CRC and obesity prevalence are higher in African Americans compared to whites.[47 48] Although our sample was drawn from a nationally representative sample, it is not representative of adults in that age group because individuals from low socioeconomic status were not included. This is important because despite steady improvements in healthy eating patterns among US adults the overall dietary quality remains poor particularly in low income populations.[49 50]

CONCLUSION

This longitudinal national study of 398,458 middle aged and older adults found that among normal-weight and overweight men, CRC risk was 25-30% lower with high adherence to each dietary measure. Diet quality was not associated with cancer risk among obese adults. Health benefits of consuming a high-quality diet extend to normal weight men, offering potential insights about approaches to cancer prevention. Additional research is needed to understand the inconsistent results for women.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract ***see pg.1***
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ***see pg. 2***
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ***see pgs. 4-5***
Objectives	3	State specific objectives, including any prespecified hypotheses ***see pgs. 4-5***
Methods		
Study design	4	Present key elements of study design early in the paper ***see pg. 5***
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants ***see pg. 5***
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable ***see pgs. 6-8***
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy ***see pgs. 8-9***
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ***see pg. 8***
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ***see pgs. 9-11***
		(b) Indicate number of participants with missing data for each variable of interest ***see pg. 8***
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures ***see pg. 6***
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ***see pgs. 11-15***
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives ***see pgs. 16-19***
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ***see pg. 18***
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ***see pgs. 16-18***
Generalisability	21	Discuss the generalisability (external validity) of the study results ***see pgs. 16-18***
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ***see pgs. 19-20***

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The Association of Dietary Quality with Colorectal Cancer among Normal Weight, Overweight, and Obese Men and Women: A Prospective Longitudinal Study

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Keywords:	EPIDEMIOLOGY, Gastroenterology < INTERNAL MEDICINE, NUTRITION & DIETETICS

Title: The Association of Dietary Quality with Colorectal Cancer among Normal Weight, Overweight, and Obese Men and Women: A Prospective Longitudinal Study

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Key Words: colorectal cancer, diet, food, and nutrition, body mass index

Manuscript Word Count: 3,302

ABSTRACT

Objective: Lower body mass index (BMI) and higher dietary quality reduce the risk of colorectal cancer (CRC). A full understanding of how these associations vary by sex and weight is lacking.

Methods: We used data from the NIH-AARP Diet and Health Study for 398,458 persons who were 50-71 years old in 1995-1996 and followed through 2006. Exposures were dietary quality as reflected by the Mediterranean Diet, the Healthy Eating Index-2010, and the Dietary Approaches to Stop Hypertension score, stratified by BMI category. The outcome was CRC diagnosis from cancer registry data. Cox Regression models adjusted for disease risk factors.

Results: Over a mean duration of 123 months of follow-up, there were 6,515 new diagnoses of colorectal cancer (1,953 among the normal weight, 2,924 among the overweight, and 1,638 among the obese; 4,483 among men and 2,032 among women). For normal weight and overweight men, we found a strong dose-response pattern for the association of increasing quintile of dietary quality with decreasing risk of CRC; this pattern was observed for obese men as well, but less consistently across the three measures of dietary quality. The findings were of smaller magnitude and less consistent for women, but still suggesting associations of similar direction.

Conclusion: We observed that increased dietary quality was associated with lower risk of incident CRC up to 10 years later for men regardless of baseline weight category.

Public Health Implications: The findings accentuate the need to establish strategies to improve diet quality and prevent obesity as a cancer prevention strategy.

Word Count: 252

Key Words: colorectal cancer, diet, food, and nutrition, body mass index

Article Summary

Strengths and Limitations

- To our knowledge, this is the first study to examine the potential benefits of healthy eating patterns in reducing colorectal cancer risk among men and women who are at normal weight, overweight and obese adults.
- In this longitudinal national study of 398,458 adults, we found that the incidence of colorectal cancer decreased in a generally consistent dose-response manner with increasing adherence to three dietary measures (Mediterranean Diet, Healthy Eating Index-2010, and Dietary Approaches to Stop Hypertension) for men who were of normal weight or overweight. Similar findings were of smaller magnitude and more inconsistent among men who were obese and among women of all weight categories.
- Dietary intake was self-reported and assessed using a single baseline Food Frequency Questionnaire, thus, there is potential for non-differential measurement error. With only a single measure, we could not examine changes in dietary intake over time. Over 90% of the sample was non-Hispanic white. Research is needed to examine whether associations are similar in other racial/ethnic groups and to better understand the inconsistency in the results for women.

Contributors

All authors read and approved the final version of the manuscript. Rosalie A. Torres Stone drafted the original manuscript and interpreted the findings, Chyke A. Doubeni conceived of the study and participated in the analyses and interpretation of the data. Jeroan Allison and Molly E. Waring conducted the analyses and interpreted the data. Sarah L. Cutrona and Catarina I. Kiefe contributed to the interpretation of the findings and critically revised the manuscript.

Extra data is available:

Extra data is available by submitting a proposal for each project/manuscript for review by the NIH AARP Steering Committee prior to accessing NIH AARP data and to developing an associated manuscript. A proposal must be submitted through the public website, NIH-AARP Diet & Health Study Tracking and Review System (STaRS, https://www.nihaarpstars.com).

Conflict of Interest:

None declared

Data sharing:

No additional data is available.

Ethical approval:

Not required. The data is de-identified.

Word Count: 3,209

INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer-related deaths in the United States, resulting in an estimated more than 49,000 deaths in 2016.[1] Modifiable risk factors such as excess body weight and unhealthy behaviors (sedentary lifestyles, unhealthy dietary patterns, and smoking) increase the risk of CRC.[2-15] Most colorectal cancers are preventable through screening, detection and removal of precancerous lesions, or by engaging in healthful behaviors.[16 17] More specifically, it has been estimated that up to 70% of colorectal cancers could be avoided by risk factor modification.[18]

Obesity is a particularly concerning risk factor, as 37% of U.S. adults are obese.[19] A recent meta-analysis found a 30% higher risk of colon cancer in men and a 12% higher risk in women for every 5-kg/m^2 increase in body mass index (BMI).[9] Another meta-analysis found that obese adults were at roughly 20% greater risk of developing CRC compared with those of normal weight, and the risk of CRC increased 7% for every 2-kg/m^2 higher BMI.[10]

Like obesity, diet is estimated to be one of the most important modifiable risk factors for CRC.[13-15] A dietary pattern that is rich in whole grains, vegetables, fruit, fish, legumes, and nuts and low in red and processed meat and alcohol has been linked to a substantial reduction in the risk of CRC.[2-7 13 14] Therefore, the World Health Organization recommends improving dietary quality by increasing consumption of fruit and vegetables, as well as legumes, whole grains, and nuts.[20] These recommendations are similar to those studied in the Dietary Approaches to Stop Hypertension trial,[21 22] and are also similar to recommendations found in the Mediterranean Diet examined in the Seven Countries Study.[13 23]

Despite the potential benefits of a healthy BMI, many overweight and obese adults are not motivated or able to lose weight,[24] raising important questions. In the absence of weight loss, can a healthy diet still reduce CRC risk among overweight or obese adults? Likewise, because diet is emphasized as a means for weight loss, those who may be of normal weight may also lack the motivation to engage in health eating. These considerations raise unanswered questions about how the association of health eating patterns varies by weight categories. Therefore, our study examined the association between dietary quality and the risk of CRC and studied the variation in this association among normal weight, overweight, and obese adults. Because dietary patterns have been observed to be different for men and women analyses were stratified by gender.[13]

METHODS

We used data from the National Institutes of Health-AARP (formerly the American Association of Retired Persons) Diet and Health Study. The NIH-AARP cohort was established in 1995-1996. AARP members who were contacted, returned questionnaires eliciting information on demographic and anthropometric characteristics, dietary intake, and health-related behaviors. The initial response rate was 18%. Eligible participants were 50 to 71 years old and resided in six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan).

Outcome

The outcome for this analysis was diagnosis with incident adenocarcinoma of the colon/rectum ascertained from tumor registries through December 31, 2006. Cancer diagnosis in participants was determined through probabilistic linkage with 8 state cancer registries. A validation study found that this approach captured approximately 90% of all cancers.[25] Cancer type and histologic characteristics were obtained from tumor registry data using International Classification of Diseases – Oncology codes [8000, 8010, 8020, 8140-43, 8210-8211, 8221, 8255, 8261-3, 8480-1, 8490, 8510, and 8574].

Determinants

The main determinants for this analysis were three indices of dietary quality. At baseline in 1995-1996, dietary intake during the past 12 months were assessed using a 124-item Food Frequency Questionnaire. The NIH-AARP Food Frequency Questionnaire was previously validated against 24-hour dietary recall in this cohort.[25] The Diet History Questionnaire has been calibrated,[25 26] and further validation was performed by using two 24-h recalls within a subset of the NIH-AARP Diet and Health Study.[27] By using the guidance-based food group equivalents and other nutrient variables, we calculated component and index scores for the Healthy Eating Index-2010 (HEI-2010),[28] the Mediterranean Diet Score,[29] and the Dietary Approaches to Stop Hypertension (DASH),[29] according to algorithms described by Reedy et. al.[30]

The Mediterranean Diet Score ranges from 0 to 9 with higher scores corresponding to diets more consistent with a Mediterranean diet.[13 29 31] One point each is given for: intake at or greater than the sex-specific median for vegetables, fruit, nuts, legumes, fish, and whole grains; and intake less than the sex-specific median for the monounsaturated: saturated fat ratio and red and processed meat. Alcohol intake was scored by predetermined cut points for moderate intake (men: 10-25 grams per day, women: 5-15 grams per day);[13] participants with moderate alcohol intake received 1 point; other intakes (none, occasional, excessive) received 0 points.

The Healthy Eating Index 2010 was developed for measuring dietary quality based on federal guidelines.[28] It awards points based on the adequacy of intake in nine categories (total vegetables, greens and beans, total fruit, whole fruit, whole grains, dairy, total protein foods, and seafood and plant proteins, fatty acids) and moderation of intake in three categories (sodium, refined grains, and empty calories). The Healthy Eating Index 2010 ranges from 0 to 100 with higher scores indicating better dietary quality.

DASH scores capture the diet tested in two DASH randomized controlled feeding trials,[21, 32] which examined the role of dietary patterns on blood pressure. Several versions of the DASH score exist, and we used the one most commonly found in the literature with U.S. populations.[29] To derive the score for the DASH Diet, intake was classified into quintiles for the following categories: fruits, vegetables, nuts and legumes, whole grains, low-fat dairy (higher intake indicated by higher quintile) and sodium, red and processed meats, and sweetened beverages (higher intake indicated by lower quintiles).[30] Based on these eight categories, the DASH Score ranged from 8 to 40, with higher scores indicating better dietary quality. DASH score were energy adjusted.

BMI was calculated from height and weight self-reported at baseline and categorized based on WHO criteria (normal: 18.5 to < 25 kg/m^2, overweight: 25 to < 30 kg/m^2, and obese: ≥ 30 kg/m^2).

Covariates

Characteristics self-reported at baseline included gender, age (50-54 years, 55-59 years, 60-64 years, 65-69 years, ≥ 70 years), educational level (high school or less, some college, or college degree), and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian/Pacific Islander, American Indian/Alaskan Native). Other risk factors for CRC included: smoking status (never smoked, former smoker, current smoker) and physical activity. Participants were asked how often (in the previous 12 months) they engaged in physical activity that lasted ≥ 20 minutes and caused increases in breathing or heart rate, or made the participant sweat (never, rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, ≥ 5 more times per week).

Construction of the analytic sample

Of the 566,398 adults enrolled in the Diet-AARP Health Study, we excluded those who: (1) completed questionnaires by proxy (n=15,760); (2) reported a history of end-stage renal disease (1,299); (3) reported a history of cancer (8,902) or had registry confirmed prevalent cancer (50,591); (4) reported a history of colonic or rectal polyps (57,179); (5) reported any first-degree relatives with colon cancer (50,552); (6) were underweight (BMI < 18.5 $kg/m^{2)}$ (5,912); (7) were missing height or weight (13,944); or (8) reported implausibly high or low energy intake based on Box-Cox transformation procedures designed for this dataset (n=3,534),[27] resulting in an analytic sample of 398,458 adults.

Statistical Analysis

Univariate and summary characteristics were examined for all variables. Chi-square tests were used to compare characteristics of participants who did and did not develop CRC over the follow-up period for categorical variables, and the ANOVA was used for continuous variables. Bivariate analyses also examined the association of each composite dietary measure and several sets of food groups with the incidence of colorectal cancer. Linear regression models characterized the association of participant characteristics with dietary adherence, treating the dietary measures as continuous. Based on known risk factors for CRC, covariates in all models included age, gender, race/ethnicity, education, smoking status, physical activity, and weight category. All models were also adjusted for energy intake.

Cox regression with duration of observation as the underlying time metric was used to calculate the hazard of developing CRC for a series of multivariable models. All models entered the dietary measures as quintiles and included adjustment for age, race/ethnicity, education, smoking, physical activity, and energy intake. There first set of models were based on stratified subsamples, being estimated separately for each gender-weight category and each dietary measure. A second set of Cox regression models was also created across all weight categories that included interaction terms for weight category and dietary adherence. From this second set of models, we predicted the probability of incident CRC at 10 years for each level of dietary quality and weight by raising the baseline hazard at 10 years to the power of the exponentiated linear predictor. Confidence intervals for the predicted probabilities were constructed with the delta method for approximation of complex variance estimates using Taylor linearization.[33] Statistical "trend" tests were performed with the post-regression orthogonal polynomial contrast function of Stata 14.2 We found no evidence to suggest that proportional hazards assumptions were violated.[34] All analyses were performed with Stata 14.2 (StataCorp LP, College Station, TX).

RESULTS

At baseline, most participants were ≥60 years old (61%) and non-Hispanic white (91%); 59% were men (Table 1).

Table 1. Baseline Characteristics of Sample by Subsequent Diagnosis of Colorectal Cancer over 10 Years of Follow Up, NIH-AARP Diet and Health Study, 1995-2006

	Overall	Did Not Develop Colorectal Cancer	Developed Colorectal Cancer	P-value
N	398,458	391,943	6,515	
Age (years), %				
<55	17.28	17.42	7.97	<0.001
55-59	22.04	22.15	15.25	
60-64	26.29	26.28	27.50	
65-69	30.33	30.12	43.29	
> 69	4.06	4.03	5.99	
Gender				
Female, %	40.60	40.76	31.19	<0.001
Race/Ethnicity, %				
Non-Hispanic White	92.31	92.30	92.84	0.031
Non-Hispanic-Black	3.99	3.98	4.16	
Hispanic	1.99	2.00	1.65	
Asian/Pacific Islander	1.42	1.43	1.06	
American Indian/ Alaska Native	0.29	0.29	0.30	
Education, %				
High School	26.38	26.31	30.40	<0.001
Some College	34.24	34.23	34.86	
College Degree	39.38	39.45	34.74	
Smoking Status, %				
Never	37.00	37.11	30.71	<0.001
Former	50.60	50.50	56.68	
Current	12.40	12.39	12.61	
Physical Activity (≥20 minutes in past 12 months) , %				
Never	4.41	4.40	5.32	<0.001
Rarely	13.63	13.61	15.03	
1-2 times/month	13.74	13.74	13.93	
1-2 times/week	21.78	21.78	21.51	
2-4 times/week	26.99	27.01	25.99	
3-5 times/week	19.45	19.47	18.23	
Baseline weight status, %				
Normal	35.09	35.18	29.98	<0.001
Overweight	42.81	42.77	44.88	
Obese	22.10	22.05	25.14	
Dietary Scores (mean ± sd)				
Mediterranean Diet	4.20	4.20	4.06	<0.001
Health Eating Index	65.94	65.97	64.42	<0.001
Dietary Approaches to Stop HTN	23.85	23.85	23.41	<0.001
Food Consumption				
Whole grain oz./day	0.997	0.998	0.962	0.001
Dark green vegetable cups/day	0.242	0.242	0.221	<0.001
Dry beans and peas cups/day	0.101	0.101	0.100	0.472
Fruit (excluding juice) cups/day	1.264	1.265	1.223	0.003
Chicken and poultry oz./day	0.968	0.968	0.932	0.003
Fish high in omega-3 oz./day	0.169	0.169	0.165	0.051
Franks, sausages, luncheon meats oz./day	0.564	0.563	0.628	<0.001
Beef, pork, veal, lamb oz./day	1.625	1.622	1.774	0.001

Weight status was based on BMI (normal weight: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).
Food consumption based on equivalent values from MyPyramid Equivalents Database (MPED).

About 35% of the sample were normal weight, 43% were overweight, and 22% were obese. Mean (sd; range) scores for dietary quality were 4.2 (1.8; 0 - 9) for the Mediterranean Diet, 65.9 (10.7; 18.2 - 98.4) for the Healthy Eating Index 2010, and 23.8 (4.1; 8 – 37) for the DASH Diet.

Over a mean follow-up duration of 123 months, 6,515 participants (1.64%) were diagnosed with colorectal cancer. There were 6,515 new diagnoses of colorectal cancer (1,953 among the normal weight, 2,924 among the overweight, and 1,638 among the obese; 4,483 among men and 2,032 among women). Of all new diagnoses, 9.7% were Stage 0; 38.4% were Stage 1; 14.0% were Stage 2; 22.7% were Stage 3; and 15.3% were Stage 4. The percent of those diagnosed with colorectal cancer increased moving across BMI categories from normal to overweight to obese (1.4%, 1.7%, 1.9%; p-value from log-rank trend test < 0.0001).

From bivariate analyses, older age, being male, having lower levels of physical activity, smoking, having less education, and being overweight or obese were associated with an increased risk of colorectal cancer (p < 0.001) (Table 1). Compared to non-Hispanic whites, the incidence of colorectal cancer was higher for non-Hispanic blacks and lower for Asians/Pacific Islanders (p = 0.031). Those who developed colorectal cancer had lower scores for dietary adherence and consumed more red and processed meats, less whole grains, less dark green vegetables, and less fruits.

Based on an overall multivariable model for the entire study population, the hazard of incident colorectal cancer diagnosis was 32% less for women compared to men (aOR; 95% CI: 0.68; 0.64 - 0.73). Compared to those who had normal weight, the hazard of incident colorectal cancer diagnosis was 13% greater for those who were overweight (aOR; 95% CI: 1.13; 1.05 - 1.21) and 30% greater for those who were obese (aOR; 95% CI: 1.30; 1.20 - 1.40).

Table 2. Multivariable Association of Participant Characteristics with Dietary Patterns, NIH-AARP Diet and Health Study, 1996-2006

	Mediterranean Diet		Healthy Eating Index		DASH Diet	
	β	95% CI	β	95% CI	β	95% CI
Age (years)						
<55	---	---	---	---	---	---
55-59	0.14	0.12 - 0.16	1.07	0.96 - 1.18	0.36	0.31 - 0.40
60-64	0.24	0.22 - 0.25	1.85	1.74 - 1.95	0.70	0.66 - 0.74
65-69	0.27	0.25 - 0.29	2.30	2.19 - 2.40	1.00	0.96 - 1.05
> 69	0.30	0.27 - 0.33	2.73	2.53 - 2.92	1.31	1.23 - 1.38
Gender						
Male	---	---	---	---	---	---
Female	0.49	0.47 - 0.50	2.71	2.64 - 2.79	0.77	0.74 - 0.80
Race/Ethnicity						
Non-Hispanic White	---	---				
Non-Hispanic-Black	0.25	0.22 - 0.28	1.03	0.86 - 1.22	-0.34	-0.41 - -0.27
Hispanic	0.01	-0.03 - 0.04	0.89	0.63 - 1.15	0.04	-0.06 - 0.14
Asian/Pacific Islander	-0.08	-0.12 - -0.03	-0.57	-0.87 - -0.27	-0.57	-0.68 - -0.45
American Indian/ Alaska Native	0.00	-0.11 - 0.11	0.31	-0.34 - 0.97	-0.15	-0.41 - 0.10
Education						
High School	---	---	---	---	---	---
Some College	0.25	0.24 - 0.27	1.80	1.71 - 1.90	0.65	0.62 - 0.68
College Degree	0.55	0.54 - 0.57	3.53	3.44 - 3.62	1.39	1.35 - 1.42
Smoking Status						
Never	---	---				
Former	0.01	-0.00 - 0.24	-0.30	-0.38 - -0.22	-0.17	-0.20 - -0.14
Current	-0.64	-0.67 - 0.62	-5.48	-5.61 - -5.37	-2.04	-2.08 - -1.99
Physical Activity (≥20 minutes in past 12 months)						
Never	---	---				
Rarely	0.14	0.11 - 0.17	1.15	0.96 - 1.35	0.13	0.05 - 0.20
1-2 times/month	0.30	0.26 - 0.33	2.52	2.32 - 2.71	0.44	0.37 - 0.52
1-2 times/week	0.52	0.48 - 0.55	4.09	3.90 - 4.28	0.94	0.87 - 1.01
2-4 times/week	0.77	0.75 - 0.80	5.98	5.79 - 6.16	1.74	1.76 - 1.81
3-5 times/week	0.89	0.84 - 0.90	6.68	6.49 - 6.87	2.24	2.17 - 2.31
Weight Category						
Normal	---	---	---	---	---	---
Overweight	-0.14	-0.15 - -0.13	-0.32	-0.40 - -0.24	-0.35	-0.38 - -0.32
Obese	-0.24	-0.25 - -0.22	-0.56	-0.66 - -0.47	-0.50	-0.53 - -0.46

From separate linear regression models for each dietary measure, with adjustment for energy intake. Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).

Results from the linear regression models predicting dietary adherence and the measures of dietary quality are presented in Table 2. We found “dose-response” associations for older age, higher education, and more frequent physical activity with better scores for each dietary measure. Women had better adherence for all three dietary patterns. Those who were non-Hispanic Black had better dietary scores for the Mediterranean Diet and the Health Eating Index, but had lower DASH scores. Asians/Pacific Islanders had slightly lower scores on all three dietary measures. Separate models for men and women revealed no important differences (data not shown).

Table 3a. Hazard Ratios and 95% Confidence Intervals for Incidence of Colorectal Cancer by Baseline Dietary Pattern and Weight Category, NIH-AARP Diet and Health Study for Men, 1996-2006 (n=182,762)

	Normal Weight		Overweight		Obese	
Dietary Score	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Mediterranean Diet Quintiles						
1	---	---	---	---	---	---
2	0.79	0.66 - 0.96	0.83	0.73 - 0.95	0.97	0.80 - 1.17
3	0.66	0.54 - 0.82	0.91	0.79 - 1.04	0.99	0.82 - 1.21
4	0.67	0.54 - 0.84	0.77	0.66 - 0.91	0.78	0.62 - 1.00
5	0.65	0.51 - 0.83	0.73	0.60 - 0.88	0.79	0.59 - 1.08
p for trend	0.0004		0.0013		0.0508	
Healthy Eating Index Quintiles						
1	---	---	---	---	---	---
2	0.94	0.77 - 1.14	0.80	0.69 - 0.92	0.94	0.77 - 1.14
3	0.83	0.67 - 1.03	0.73	0.63 - 0.85	0.82	0.67 - 1.02
4	0.73	0.58 - 0.91	0.81	0.70 - 0.94	0.88	0.71 - 1.10
5	0.67	0.54 - 0.84	0.63	0.53 - 0.74	0.76	0.60 - 0.99
p for trend	0.0001		<0.0001		0.0394	
Dietary Approaches to Stop Hypertension Quintiles						
1	---	---	---	---	---	---
2	0.91	0.08 - 1.11	0.82	0.72 - 0.94	0.71	0.59 - 0.87
3	0.79	0.64 - 0.99	0.73	0.63 - 0.85	0.78	0.63 - 0.96
4	0.83	0.66 - 1.04	0.69	0.59 - 0.82	0.80	0.64 - 1.00
5	0.67	0.54 - 0.84	0.70	0.60 - 0.82	0.75	0.60 - 0.94
p for trend	0.0005		<0.0001		0.0801	

Cox proportional hazard models adjusted for age, gender, race/ethnicity, education, smoking, physical activity, and energy intake. Separate models were developed for each dietary pattern and weight category. Dietary categories (low, high) are based on tertiles of native score. The lowest tertile is the reference group. Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).

The first set of multivariable models were stratified by weight category and examined the association of incident CRC by quintile of dietary score. Based on these models, which included adjustment for age, gender, race/ethnicity, smoking, and physical activity, and energy intake, increasing dietary quality was consistently associated with decreasing hazard of incident CRC for men of normal weight or were overweight (Table 3a). For obese men, the same general patterns were apparent, but the statistical significance across quintiles of dietary quality was more marginal than for the other two BMI categories. Smaller and more inconsistent associations, albeit generally in the same direction, were found for women of all three weight categories (Table 3b).

Table 3b. Hazard Ratios and 95% Confidence Intervals for Incidence of Colorectal Cancer by Baseline Dietary Pattern and Weight Category, NIH-AARP Diet and Health Study for Women, 1996-2006 (n=125,281)

	Normal Weight		Overweight		Obese	
Dietary Score	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Mediterranean Diet Quintiles						
1	---	---	---	---	---	---
2	0.95	0.76 - 1.20	1.09	0.86 - 1.38	1.35	1.04 - 1.74
3	0.88	0.69 - 1.12	1.00	0.78 - 1.30	0.86	0.64 - 1.16
4	0.90	0.68 - 1.18	0.81	0.59 - 1.11	0.89	0.63 - 1.25
5	1.02	0.75 - 1.37	0.99	0.68 - 1.41	0.95	0.63 - 1.43
p for trend	0.9384		0.4318		0.2633	
Healthy Eating Index Quintiles						
1	---	---	---	---	---	---
2	0.77	0.58 - 1.01	0.87	0.65 - 1.16	0.85	0.63 - 1.15
3	0.71	0.54 - 0.94	0.94	0.71 - 1.25	0.90	0.67 - 1.21
4	0.71	0.54 - 0.93	0.73	0.55 - 0.98	0.82	0.60 - 1.12
5	0.83	0.64 - 1.08	0.64	0.47 - 0.86	0.71	0.51 - 0.99
p for trend	0.1557		0.0018		0.0573	
Dietary Approaches to Stop Hypertension Quintiles						
1	---	---	---	---	---	---
2	0.86	0.68 - 1.09	0.86	0.67 - 1.10	1.00	0.77 - 1.30
3	0.70	0.53 - 0.93	0.92	0.70 - 1.20	0.78	0.57 - 1.06
4	0.86	0.66 - 1.13	0.74	0.54 - 1.00	0.72	0.51 - 1.00
5	0.73	0.56 - 0.95	0.83	0.62 - 1.11	0.73	0.52 - 1.02
p for trend	0.0389		0.1256		0.0128	

Cox proportional hazard models adjusted for age, gender, race/ethnicity, education, smoking, physical activity, and energy intake. Separate models were developed for each dietary pattern and weight category. Dietary adherence categories are based on lowest and highest tertiles. Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).

Based on the multivariable model Cox regression models, we predicted the incidence of new colorectal cancer at 10 years separately for men (Table 4a) and women (Table 4b). We found almost no statistical significance for the interaction of dietary measures with weight category for both men and women, providing no basis for refuting the hypothesis that the association of diet with incidence CRC differs by weight category. As shown in Table 4a, we found statistically significant linear trends for men who were of normal weight and who were overweight, suggesting a gradient affect for increasing dietary quality with decreasing incidence of colorectal cancer at 10 years. Likewise, among obese men we found generally similar trends, which were of more marginal statistical significance. Consistent with the previously described hazard ratios, the findings were also more mixed for women (Table 4b). For both men and women, the absolute predicted rates of colorectal cancer were consistently less than 2.5%.

Table 4a. Probability and 95% Confidence Interval of Colorectal Cancer at 10 Years by Baseline Dietary Pattern and Weight Category, NIH-AARP Diet and Health Study for Men, 1996-2006 (n=182,762)

	Mediterranean Diet		Healthy Eating Index		Dietary Approaches to Stop Hypertension	
Dietary Score	Probability	95% CI	Probability	95% CI	Probability	95% CI
Normal Weight						
Quintile 1	0.019	0.011 - 0.028	0.019	0.011 - 0.028	0.019	0.010 - 0.027
Quintile 2	0.015	0.008 - 0.003	0.017	0.009 - 0.025	0.017	0.009 - 0.025
Quintile 3	0.013	0.007 - 0.019	0.015	0.008 - 0.022	0.015	0.007 - 0.022
Quintile 4	0.013	0.007 - 0.019	0.013	0.007 - 0.019	0.015	0.008 - 0.022
Quintile 5	0.012	0.006 - 0.019	0.012	0.006 - 0.018	0.012	0.006 - 0.018
p-for-trend	0.0002		<0.0001		0.0001	
Overweight						
Quintile 1	0.019	0.011 - 0.028	0.022	0.011 - 0.032	0.021	0.011 - 0.031
Quintile 2	0.016	0.009 - 0.024	0.017	0.009 - 0.025	0.018	0.010 - 0.026
Quintile 3	0.018	0.010 - 0.027	0.016	0.008 - 0.023	0.016	0.008 - 0.024
Quintile 4	0.016	0.009 0.023	0.018	0.009 - 0.026	0.016	0.008 - 0.023
Quintile 5	0.015	0.008 - 0.022	0.014	0.007 - 0.020	0.016	0.008 - 0.023
p-for-trend	0.0017		< 0.0001		<0.0001	
Obese						
Quintile 1	0.021	0.011 - 0.030	0.022	0.012 - 0.032	0.024	0.012 - 0.035
Quintile 2	0.020	0.011 - 0.030	0.021	0.011 - 0.031	0.017	0.009 - 0.026
Quintile 3	0.021	0.011 - 0.031	0.019	0.009 - 0.027	0.019	0.010 - 0.029
Quintile 4	0.017	0.009 - 0.026	0.020	0.011 - 0.029	0.020	0.010 - 0.030
Quintile 5	0.017	0.008 - 0.026	0.017	0.009 - 0.026	0.019	0.010 - 0.028
p-for-trend	0.0212		0.0304		0.0502	

Probabilities are based on a Cox model that adjusts for age, gender, race/ethnicity, education, smoking, physical activity, and energy intake. Models include interaction terms for baseline dietary scores and weight category. Separate models were developed for each dietary pattern. Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).

P-values for interaction terms for quintiles of Mediterranean Diet and weight category are: Q2-overweight, 0.626; Q2-obese 0.159; Q3-overweight, 0.008; Q3-obese, 0.006; Q4-overweight, 0.250; Q4-obsese, 0.408; Q5-overweight, 0.367; Q5-obese, 0.366. P-values for interaction terms for quintiles of Healthy Eating Index and weight category are: Q2-overweight, 0.227; Q2-obese 0.961; Q3-overweight, 0.411; Q3-obese, 0.974; Q4-overweight, 0.304; Q4-obsese, 0.164; Q5-overweight, 0.726; Q5-obese, 0.381. P-values for interaction terms for quintiles of Dietary Approaches to Stop Hypertension and weight category are: Q2-overweight, 0.486; Q2-obese 0.090; Q3-overweight, 0.733; Q3-obese, 0.974; Q4-overweight, 0.344; Q4-obsese, 0.920; Q5-overweight, 0.482; Q5-obese, 0.411.

Table 4b. Probability and 95% Confidence Interval of Colorectal Cancer at 10 Years by Baseline Dietary Pattern and Weight Category, NIH-AARP Diet and Health Study for Women, 1996-2006 (n=125,281)

	Mediterranean Diet		Healthy Eating Index		Dietary Approaches to Stop Hypertension	
Dietary Score	Probability	95% CI	Probability	95% CI	Probability	95% CI
Normal Weight						
Quintile 1	0.011	0.001 - 0.021	0.013	0.001 - 0.025	0.012	0.001 - 0.023
Quintile 2	0.010	0.001 - 0.020	0.010	0.000 - 0.019	0.011	0.001 - 0.021
Quintile 3	0.009	0.000 - 0.018	0.009	0.000 - 0.018	0.009	0.000 - 0.017
Quintile 4	0.010	0.000 - 0.019	0.009	0.000 - 0.018	0.011	0.001 - 0.021
Quintile 5	0.011	0.000 - 0.021	0.011	0.001 - 0.022	0.009	0.000 - 0.018
p-for-trend	0.9396		0.1547		0.0426	
Overweight						
Quintile 1	0.012	0.001 - 0.024	0.014	0.001 - 0.028	0.013	0.001 - 0.026
Quintile 2	0.013	0.007 - 0.025	0.012	0.001 - 0.024	0.012	0.001 - 0.023
Quintile 3	0.012	0.001 - 0.023	0.014	0.001 - 0.026	0.012	0.001 - 0.024
Quintile 4	0.009	0.000 - 0.018	0.011	0.000 - 0.021	0.010	0.000 - 0.019
Quintile 5	0.011	0.000 - 0.022	0.010	0.000 - 0.019	0.011	0.000 - 0.022
p-for-trend	0.1391		0.0015		0.0242	
Obese						
Quintile 1	0.013	0.001 - 0.024	0.015	0.001 - 0.030	0.014	0.001 - 0.028
Quintile 2	0.018	0.001 - 0.034	0.013	0.001 - 0.026	0.015	0.001 - 0.030
Quintile 3	0.012	0.001 - 0.023	0.014	0.001 - 0.028	0.012	0.000 - 0.024
Quintile 4	0.013	0.000 - 0.025	0.013	0.001 - 0.026	0.012	0.000 - 0.023
Quintile 5	0.014	0.000 - 0.027	0.011	0.000 - 0.023	0.013	0.000 - 0.025
p-for-trend	0.5725		0.0370		0.0399	

Probabilities are based on a Cox model that adjusts for age, gender, race/ethnicity, education, smoking, physical activity, and energy intake. Models include interaction terms for baseline dietary scores and weight category. Separate models were developed for each dietary pattern. Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).

P-values for interaction terms for quintiles of Mediterranean Diet and weight category are: Q2-overweight, 0.524; Q2-obese 0.024; Q3-overweight, 0.651; Q3-obese, 0.826; Q4-overweight, 0.354; Q4-obsese, 0.660; Q5-overweight, 0.547; Q5-obese, 0.881. P-values for interaction terms for quintiles of Healthy Eating Index and weight category are: Q2-overweight, 0.554; Q2-obese 0.664; Q3-overweight, 0.154; Q3-obese, 0.290; Q4-overweight, 0.880; Q4-obsese, 0.542; Q5-overweight, 0.156; Q5-obese, 0.358. P-values for interaction terms for quintiles of Dietary Approaches to Stop Hypertension and weight category are: Q2-overweight, 0.902; Q2-obese 0.328; Q3-overweight, 0.254; Q3-obese, 0.530; Q4-overweight, 0.256 Q4-obsese, 0.525; Q5-overweight, 0.866; Q5-obese, 0.714.

DISCUSSION

In this large national study of nearly 400,000 of middle aged and older adults, we found that baseline high quality diets as measured by three diet quality indices (Mediterranean Diet Score, the Healthy Eating Index 2010, and the Dietary Approaches to Stop Hypertension Score) were each associated with lower risk of CRC over a subsequent 10-year period among men who were of normal weight and overweight in a generally consistent “dose-response” effect. Trends were less consistent and of smaller magnitude among men who were obese and women in all three weight categories.

Although previous studies have not examined differences according to baseline weight status, our findings are consistent with other studies demonstrating that higher dietary quality is associated with reduced risk of colorectal adenoma in general.[13] For example, a recent narrative review of publications using the Nurses’ Health Study (1976-2016) identified red and processed meat, alcohol, smoking and obesity as factors that increase the risk of CRC.[15] Likewise, an ecological study suggested that 76% of the inter-country variation in colorectal cancer incidence was explained by meat, fish, and olive oil intake, with olive oil intake being associated with reduced risk.[2]

A review of epidemiological studies investigating the associations between dietary patterns including the DASH, the Mediterranean Diet, and the Healthy Eating Index has also shown a consistently reduced risk of colorectal adenoma and cancer incidence of higher scores on all of the dietary indexes for men, but was less conclusive for women.[13,35] Another large prospective examination of four established DASH indexes found that greater compliance with the DASH dietary pattern was associated with a reduced risk of CRC for both men and women.[36] This consistency across the three dietary patterns is not surprising because each of these dietary approaches is built on a similar foundation of fresh fruits and vegetables, whole grains, and low saturated fat.

There are physiologic mechanisms through which diet may be associated with a reduced risk of CRC and through which this association may differ for men and for women. For example, studies focused on individual nutrients suggest that olive oil may exert a reduced risk of CRC by influencing secondary bile acid patterns in the colon. This may in turn affect polyamine metabolism in colonic enterocytes, reducing progression from normal mucosa to adenoma and carcinoma.[3] Fiber intake may reduce the contact between carcinogens and the lining of the colon/rectum and increase stool bulk, which dilutes fecal carcinogens and decreases transit time.[2 7] Red and processed meat may exert a carcinogenic effect due to heme iron, N-nitro compounds and heterocyclic amines generated during cooking at high temperatures as well as a pro-neoplastic effect due to increased adiposity and insulin. Other studies suggest that dietary patterns that include a high consumption of high saturated fatty acid intake may increase CRC risk via their effects on serum insulin concentrations and on the bioavailability of insulin-like growth factor-I (IGF-I).[37] Whole grain intake has been associated with decreased fasting insulin level and improved insulin sensitivity.[7 38]

The differential response of dietary intake to risk of CRC incidence by sex in our study could be explained by differences in the etiology of CRC between men and women.[13] Studies have indicated that women are more likely to develop proximal CRC compared to men.[39] Because proximal and distal CRC appear to arise from different pathways it is possible that the response to dietary intake varies by proximal and distal location type.[39] Hormonal factors may also be responsible for sex differences CRC etiology. Studies of postmenopausal hormone therapy and colorectal cancer report a reduction in risk of colon cancer and a decrease in the risk of rectal cancer for postmenopausal women who had ever taken hormone therapy compared with women who never used hormones. The CRC risk reduction appears to be stronger for current and long-term hormone users.[40 41]

The association was of borderline significance and inconsistent across the three dietary measures for obese men and women. It is plausible that the beneficial effects of a healthy diet are attenuated by the inflammatory, hormonal, and other metabolic changes induced by obesity that promote colorectal carcinogenesis.[42] For example, the gut microbiome that provides important metabolic capabilities, is responsive to alterations of diet,[43] and has been shown in obese people to be different from, and less diverse than, those of the non-obese.[44]

Our study has some limitations. Our analytic dataset excluded those with family history of colorectal cancer and are therefore only generalize to those who are of average risk. Medical co-morbidity was not included as a covariate in the multivariable models. Our study population was relatively homogenous with upper-to-middle class Americans in urban centers: non-whites comprised a relatively small proportion of our sample. Dietary intake was self-reported and assessed using a single baseline Food Frequency Questionnaire, thus, there is potential for non-differential measurement error.[45] With only a single measure, we could not examine changes in dietary intake over time. It is possible that the observed differences between men and women are artifacts from how the data were collected. For example, it has been suggested that differential bias could be introduced by the way women and men complete the Food Frequency Questionnaire.[45 46] Women in the AARP (as a group) may have more variation in diet patterns and perception of dietary intake (and weight status) over time than men.[25] Additionally, there is evidence that difference in dietary patterns may vary for men and women who respond in a similar manner to the same survey.[13] Over 90% of the sample was non-Hispanic white. The research consistently shows that incident rates of CRC and obesity prevalence are higher in African Americans compared to whites.[47 48] Although our sample was drawn from a nationally representative sample, it is not representative of adults in that age group because individuals from low socioeconomic status were not included. This is important because despite steady improvements in healthy eating patterns among US adults the overall dietary quality remains poor particularly in low income populations.[49 50]

CONCLUSION

This longitudinal national study of 398,458 middle aged and older adults found that among normal-weight and overweight men, CRC risk was 25-30% lower with high adherence to each dietary measure. Health benefits of consuming a high-quality diet extend to normal weight men, offering potential insights about approaches to cancer prevention. Additional research is needed to understand the weaker and less consistent results for women.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract ***see pg.1***
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ***see pg. 2***
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ***see pgs. 4-5***
Objectives	3	State specific objectives, including any prespecified hypotheses ***see pgs. 4-5***
Methods		
Study design	4	Present key elements of study design early in the paper ***see pg. 5***
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants ***see pg. 5***
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable ***see pgs. 6-8***
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy ***see pgs. 8-9***
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ***see pg. 8***
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ***see pgs. 9-11***
		(b) Indicate number of participants with missing data for each variable of interest ***see pg. 8***
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures ***see pg. 6***
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ***see pgs. 11-15***
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives ***see pgs. 16-19***
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ***see pg. 18***
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ***see pgs. 16-18***
Generalisability	21	Discuss the generalisability (external validity) of the study results ***see pgs. 16-18***
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ***see pgs. 19-20***

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The Association of Dietary Quality with Colorectal Cancer among Normal Weight, Overweight, and Obese Men and Women: A Prospective Longitudinal Study in the United States

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Title: The Association of Dietary Quality with Colorectal Cancer among Normal Weight, Overweight, and Obese Men and Women: A Prospective Longitudinal Study in the United States

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ABSTRACT

Objective: Lower body mass index (BMI) and higher dietary quality reduce the risk of colorectal cancer (CRC). A full understanding of how these associations vary by sex and weight is lacking.

Methods: We used data from the NIH-AARP Diet and Health Study for 398,458 persons who were 50-71 years old in 1995-1996 and followed through 2006. Exposures were dietary quality as reflected by the Mediterranean Diet, the Healthy Eating Index-2010, and the Dietary Approaches to Stop Hypertension score, stratified by BMI category. The outcome was CRC diagnosis from cancer registry data. Cox Regression models adjusted for disease risk factors.

Results: Over a mean duration of 123 months of follow-up, there were 6,515 new diagnoses of colorectal cancer (1,953 among the normal weight, 2,924 among the overweight, and 1,638 among the obese; 4,483 among men and 2,032 among women). For normal weight and overweight men, we found a strong dose-response pattern for the association of increasing quintile of dietary quality with decreasing risk of CRC; this pattern was observed for obese men as well, but less consistently across the three measures of dietary quality. The findings were of smaller magnitude and less consistent for women, but still suggesting associations of similar direction.

Conclusion: We observed that increased dietary quality was associated with lower risk of incident CRC up to 10 years later for men regardless of baseline weight category.

Word Count: 228

Key Words: colorectal cancer, diet, food, and nutrition, body mass index

Strengths and Limitations of this Study:

- To our knowledge, this is the first study to examine the potential benefits of healthy eating patterns in reducing colorectal cancer risk among men and women who are at normal weight, overweight and obese adults.
- Key strengths of this study include a large US national study of 398,458 middle aged and older adults with a prospective design, use of three indices of dietary patterns to assess association of high quality diet with outcomes rather than individual dietary components, careful ascertainment of dietary exposures using Food Frequency Questionnaire and cancer outcome, and the long follow-up interval.
- Our study has some limitations. We did not have information on family history of colorectal cancer, although the impact of family history is likely small given the age of the cohort. Dietary intake was self-reported and assessed using a single baseline measurement. Therefore, there is a potential for non-differential classification of dietary exposures and we could not examine changes in dietary intake over time. Our study population was relatively homogeneous with upper to middle class U.S. Americans in urban centers and over 90% of the sample was non-Hispanic white limiting generalizability to diverse population groups

Contributors

All authors read and approved the final version of the manuscript. Rosalie A. Torres Stone drafted the original manuscript and interpreted the findings, Chyke A. Doubeni conceived of the study and participated in the analyses and interpretation of the data. Jeroan Allison and Molly E. Waring conducted the analyses and interpreted the data. Sarah L. Cutrona and Catarina I. Kiefe contributed to the interpretation of the findings and critically revised the manuscript.

Extra data is available:

Extra data is available by submitting a proposal for each project/manuscript for review by the NIH AARP Steering Committee prior to accessing NIH AARP data and to developing an associated manuscript. A proposal must be submitted through the public website, NIH-AARP Diet & Health Study Tracking and Review System (STaRS, https://www.nihaarpstars.com).

Conflict of Interest:

None declared

Data sharing:

No additional data is available.

Ethical approval:

Not required. The data is de-identified. It was submitted as an amendment to the National Cancer Institute Special Studies Institutional Review Board (SSIRB) for review and was approved.

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INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer-related deaths in the United States, resulting in an estimated more than 49,000 deaths in 2016.[1] Modifiable risk factors such as excess body weight and unhealthy behaviors (sedentary lifestyles, unhealthy dietary patterns, and smoking) increase the risk of CRC.[2-15] Most colorectal cancers are preventable through screening, detection and removal of precancerous lesions, or by engaging in healthful behaviors.[16 17] More specifically, it has been estimated that up to 70% of colorectal cancers could be avoided by risk factor modification.[18]

Obesity is a particularly concerning risk factor, as 37% of U.S. adults are obese.[19] A recent meta-analysis found a 30% higher risk of colon cancer in men and a 12% higher risk in women for every 5-kg/m^2 increase in body mass index (BMI).[9] Another meta-analysis found that obese adults were at roughly 20% greater risk of developing CRC compared with those of normal weight, and the risk of CRC increased 7% for every 2-kg/m^2 higher BMI.[10]

Like obesity, diet is estimated to be one of the most important modifiable risk factors for CRC.[13-15] A dietary pattern that is rich in whole grains, vegetables, fruit, fish, legumes, and nuts and low in red and processed meat and alcohol has been linked to a substantial reduction in the risk of CRC.[2-7 13 14] Therefore, the World Health Organization recommends improving dietary quality by increasing consumption of fruit and vegetables, as well as legumes, whole grains, and nuts.[20] These recommendations are similar to those studied in the Dietary Approaches to Stop Hypertension trial,[21 22] and are also similar to recommendations found in the Mediterranean Diet examined in the Seven Countries Study.[13 23]

Despite the potential benefits of a healthy BMI, many overweight and obese adults are not motivated or able to lose weight,[24] raising important questions. In the absence of weight loss, can a healthy diet still reduce CRC risk among overweight or obese adults? Likewise, because diet is emphasized as a means for weight loss, those who may be of normal weight may also lack the motivation to engage in health eating. These considerations raise unanswered questions about how the association of health eating patterns varies by weight categories. Therefore, our study examined the association between dietary quality and the risk of CRC and studied the variation in this association among normal weight, overweight, and obese adults. Because dietary patterns have been observed to be different for men and women analyses were stratified by gender.[13]

METHODS

We used data from the National Institutes of Health-AARP (formerly the American Association of Retired Persons) Diet and Health Study. The NIH-AARP cohort was established in 1995-1996. AARP members who were contacted, returned questionnaires eliciting information on demographic and anthropometric characteristics, dietary intake, and health-related behaviors. The initial response rate was 18%. Eligible participants were 50 to 71 years old and resided in six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan).

Outcome

The outcome for this analysis was diagnosis with incident adenocarcinoma of the colon/rectum ascertained from tumor registries through December 31, 2006. Cancer diagnosis in participants was determined through probabilistic linkage with 8 state cancer registries. A validation study found that this approach captured approximately 90% of all cancers.[25] Cancer type and histologic characteristics were obtained from tumor registry data using International Classification of Diseases – Oncology codes [8000, 8010, 8020, 8140-43, 8210-8211, 8221, 8255, 8261-3, 8480-1, 8490, 8510, and 8574].

Determinants

The main determinants for this analysis were three indices of dietary quality. At baseline in 1995-1996, dietary intake during the past 12 months were assessed using a 124-item Food Frequency Questionnaire. The NIH-AARP Food Frequency Questionnaire was previously validated against 24-hour dietary recall in this cohort.[25] The Diet History Questionnaire has been calibrated,[25 26] and further validation was performed by using two 24-h recalls within a subset of the NIH-AARP Diet and Health Study.[27] By using the guidance-based food group equivalents and other nutrient variables, we calculated component and index scores for the Healthy Eating Index-2010 (HEI-2010),[28] the Mediterranean Diet Score,[29] and the Dietary Approaches to Stop Hypertension (DASH),[29] according to algorithms described by Reedy et. al.[30]

The Mediterranean Diet Score ranges from 0 to 9 with higher scores corresponding to diets more consistent with a Mediterranean diet.[13 29 31] One point each is given for: intake at or greater than the sex-specific median for vegetables, fruit, nuts, legumes, fish, and whole grains; and intake less than the sex-specific median for the monounsaturated: saturated fat ratio and red and processed meat. Alcohol intake was scored by predetermined cut points for moderate intake (men: 10-25 grams per day, women: 5-15 grams per day);[13] participants with moderate alcohol intake received 1 point; other intakes (none, occasional, excessive) received 0 points.

The Healthy Eating Index 2010 was developed for measuring dietary quality based on federal guidelines.[28] It awards points based on the adequacy of intake in nine categories (total vegetables, greens and beans, total fruit, whole fruit, whole grains, dairy, total protein foods, and seafood and plant proteins, fatty acids) and moderation of intake in three categories (sodium, refined grains, and empty calories). The Healthy Eating Index 2010 ranges from 0 to 100 with higher scores indicating better dietary quality.

DASH scores capture the diet tested in two DASH randomized controlled feeding trials,[21, 32] which examined the role of dietary patterns on blood pressure. Several versions of the DASH score exist, and we used the one most commonly found in the literature with U.S. populations.[29] To derive the score for the DASH Diet, intake was classified into quintiles for the following categories: fruits, vegetables, nuts and legumes, whole grains, low-fat dairy (higher intake indicated by higher quintile) and sodium, red and processed meats, and sweetened beverages (higher intake indicated by lower quintiles).[30] Based on these eight categories, the DASH Score ranged from 8 to 40, with higher scores indicating better dietary quality. DASH score were energy adjusted.

BMI was calculated from height and weight self-reported at baseline and categorized based on WHO criteria (normal: 18.5 to < 25 kg/m^2, overweight: 25 to < 30 kg/m^2, and obese: ≥ 30 kg/m^2).

Covariates

Characteristics self-reported at baseline included gender, age (50-54 years, 55-59 years, 60-64 years, 65-69 years, ≥ 70 years), educational level (high school or less, some college, or college degree), and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian/Pacific Islander, American Indian/Alaskan Native). Other risk factors for CRC included: smoking status (never smoked, former smoker, current smoker) and physical activity. Participants were asked how often (in the previous 12 months) they engaged in physical activity that lasted ≥ 20 minutes and caused increases in breathing or heart rate, or made the participant sweat (never, rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, ≥ 5 more times per week).

Construction of the analytic sample

Of the 566,398 adults enrolled in the Diet-AARP Health Study, we excluded those who: (1) completed questionnaires by proxy (n=15,760); (2) reported a history of end-stage renal disease (1,299); (3) reported a history of cancer (8,902) or had registry confirmed prevalent cancer (50,591); (4) reported a history of colonic or rectal polyps (57,179); (5) reported any first-degree relatives with colon cancer (50,552); (6) were underweight (BMI < 18.5 kg/$m^{2)}$ (5,912); (7) were missing height or weight (13,944); or (8) reported implausibly high or low energy intake based on Box-Cox transformation procedures designed for this dataset (n=3,534),[27] resulting in an analytic sample of 398,458 adults.

Statistical Analysis

Univariate and summary characteristics were examined for all variables. Chi-square tests were used to compare characteristics of participants who did and did not develop CRC over the follow-up period for categorical variables, and the ANOVA was used for continuous variables. Bivariate analyses also examined the association of each composite dietary measure and several sets of food groups with the incidence of colorectal cancer. Linear regression models characterized the association of participant characteristics with dietary adherence, treating the dietary measures as continuous. Based on known risk factors for CRC, covariates in all models included age, gender, race/ethnicity, education, smoking status, physical activity, and weight category. All models were also adjusted for energy intake.

Cox regression with duration of observation as the underlying time metric was used to calculate the hazard of developing CRC for a series of multivariable models. All models entered the dietary measures as quintiles and included adjustment for age, race/ethnicity, education, smoking, physical activity, and energy intake. There first set of models were based on stratified subsamples, being estimated separately for each gender-weight category and each dietary measure. A second set of Cox regression models was also created across all weight categories that included interaction terms for weight category and dietary adherence. From this second set of models, we predicted the probability of incident CRC at 10 years for each level of dietary quality and weight by raising the baseline hazard at 10 years to the power of the exponentiated linear predictor. Confidence intervals for the predicted probabilities were constructed with the delta method for approximation of complex variance estimates using Taylor linearization.[33] Statistical "trend" tests were performed with the post-regression orthogonal polynomial contrast function of Stata 14.2 We found no evidence to suggest that proportional hazards assumptions were violated.[34] All analyses were performed with Stata 14.2 (StataCorp LP, College Station, TX).

RESULTS

At baseline, most participants were ≥60 years old (61%) and non-Hispanic white (91%); 59% were men (Table 1).

Table 1. Baseline Characteristics of Sample by Subsequent Diagnosis of Colorectal Cancer over 10 Years of Follow Up, NIH-AARP Diet and Health Study, 1995-2006

	Overall	Did Not Develop Colorectal Cancer	Developed Colorectal Cancer	P-value
N	398,458	391,943	6,515	
Age (years), %				
<55	17.28	17.42	7.97	
55-59	22.04	22.15	15.25	
60-64	26.29	26.28	27.50	<0.001
65-69	30.33	30.12	43.29	
> 69	4.06	4.03	5.99	
Gender				
Female, %	40.60	40.76	31.19	<0.001
Race/Ethnicity, %				
Non-Hispanic White	92.31	92.30	92.84	
Non-Hispanic-Black	3.99	3.98	4.16	
Hispanic	1.99	2.00	1.65	0.031
Asian/Pacific Islander	1.42	1.43	1.06	
American Indian/ Alaska Native	0.29	0.29	0.30	
Education, %				
High School	26.38	26.31	30.40	
Some College	34.24	34.23	34.86	<0.001
College Degree	39.38	39.45	34.74	
Smoking Status, %				
Never	37.00	37.11	30.71	
Former	50.60	50.50	56.68	<0.001
Current	12.40	12.39	12.61	
Physical Activity (≥20 minutes in past 12 months) , %				
Never	4.41	4.40	5.32	
Rarely	13.63	13.61	15.03	
1-2 times/month	13.74	13.74	13.93	<0.001
1-2 times/week	21.78	21.78	21.51	
2-4 times/week	26.99	27.01	25.99	
3-5 times/week	19.45	19.47	18.23	
Baseline weight status, %				
Normal	35.09	35.18	29.98	
Overweight	42.81	42.77	44.88	<0.001
Obese	22.10	22.05	25.14	
Dietary Scores (mean ± sd)				
Mediterranean Diet	4.20	4.20	4.06	<0.001
Health Eating Index	65.94	65.97	64.42	<0.001
Dietary Approaches to Stop HTN	23.85	23.85	23.41	<0.001
Food Consumption				
Whole grain oz./day	0.997	0.998	0.962	0.001
Dark green vegetable cups/day	0.242	0.242	0.221	<0.001
Dry beans and peas cups/day	0.101	0.101	0.100	0.472
Fruit (excluding juice) cups/day	1.264	1.265	1.223	0.003
Chicken and poultry oz./day	0.968	0.968	0.932	0.003
Fish high in omega-3 oz./day	0.169	0.169	0.165	0.051
Franks, sausages, luncheon meats oz./day	0.564	0.563	0.628	<0.001
Beef, pork, veal, lamb oz./day	1.625	1.622	1.774	0.001

Weight status was based on BMI (normal weight: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).
Food consumption based on equivalent values from MyPyramid Equivalents Database (MPED).

About 35% of the sample were normal weight, 43% were overweight, and 22% were obese. Mean (sd; range) scores for dietary quality were 4.2 (1.8; 0 - 9) for the Mediterranean Diet, 65.9 (10.7; 18.2 - 98.4) for the Healthy Eating Index 2010, and 23.8 (4.1; 8 – 37) for the DASH Diet.

Over a mean follow-up duration of 123 months, 6,515 participants (1.64%) were diagnosed with colorectal cancer. There were 6,515 new diagnoses of colorectal cancer (1,953 among the normal weight, 2,924 among the overweight, and 1,638 among the obese; 4,483 among men and 2,032 among women). Of all new diagnoses, 9.7% were Stage 0; 38.4% were Stage 1; 14.0% were Stage 2; 22.7% were Stage 3; and 15.3% were Stage 4. The percent of those diagnosed with colorectal cancer increased moving across BMI categories from normal to overweight to obese (1.4%, 1.7%, 1.9%; p-value from log-rank trend test < 0.0001).

From bivariate analyses, older age, being male, having lower levels of physical activity, smoking, having less education, and being overweight or obese were associated with an increased risk of colorectal cancer ($p < 0.001$) (Table 1). Compared to non-Hispanic whites, the incidence of colorectal cancer was higher for non-Hispanic blacks and lower for Asians/Pacific Islanders ($p = 0.031$). Those who developed colorectal cancer had lower scores for dietary adherence and consumed more red and processed meats, less whole grains, less dark green vegetables, and less fruits.

Based on an overall multivariable model for the entire study population, the hazard of incident colorectal cancer diagnosis was 32% less for women compared to men (aOR; 95% CI: 0.68; 0.64 - 0.73). Compared to those who had normal weight, the hazard of incident colorectal cancer diagnosis was 13% greater for those who were overweight (aOR; 95% CI: 1.13; 1.05 - 1.21) and 30% greater for those who were obese (aOR; 95% CI: 1.30; 1.20 - 1.40).

Table 2. Multivariable Association of Participant Characteristics with Dietary Patterns, NIH-AARP Diet and Health Study, 1996-2006						
	Mediterranean Diet		Healthy Eating Index		DASH Diet	
	β	95% CI	β	95% CI	β	95% CI
Age (years)						
<55	---	---	---	---	---	---
55-59	0.14	0.12 - 0.16	1.07	0.96 - 1.18	0.36	0.31 - 0.40
60-64	0.24	0.22 - 0.25	1.85	1.74 - 1.95	0.70	0.66 - 0.74
65-69	0.27	0.25 - 0.29	2.30	2.19 - 2.40	1.00	0.96 - 1.05
> 69	0.30	0.27 - 0.33	2.73	2.53 - 2.92	1.31	1.23 - 1.38
Gender						
Male	---	---	---	---	---	---
Female	0.49	0.47 - 0.50	2.71	2.64 - 2.79	0.77	0.74 - 0.80
Race/Ethnicity						
Non-Hispanic White	---	---				
Non-Hispanic-Black	0.25	0.22 - 0.28	1.03	0.86 - 1.22	-0.34	-0.41 - -0.27
Hispanic	0.01	-0.03 - 0.04	0.89	0.63 - 1.15	0.04	-0.06 - 0.14
Asian/Pacific Islander	-0.08	-0.12 - -0.03	-0.57	-0.87 - -0.27	-0.57	-0.68 - -0.45
American Indian/ Alaska Native	0.00	-0.11 - 0.11	0.31	-0.34 - 0.97	-0.15	-0.41 - 0.10
Education						
High School	---	---	---	---	---	---
Some College	0.25	0.24 - 0.27	1.80	1.71 - 1.90	0.65	0.62 - 0.68
College Degree	0.55	0.54 - 0.57	3.53	3.44 - 3.62	1.39	1.35 - 1.42
Smoking Status						
Never	---	---				
Former	0.01	-0.00 - 0.24	-0.30	-0.38 - -0.22	-0.17	-0.20 - -0.14
Current	-0.64	-0.67 - 0.62	-5.48	-5.61 - -5.37	-2.04	-2.08 - -1.99
Physical Activity (≥20 minutes in past 12 months)						
Never	---	---				
Rarely	0.14	0.11 - 0.17	1.15	0.96 - 1.35	0.13	0.05 - 0.20
1-2 times/month	0.30	0.26 - 0.33	2.52	2.32 - 2.71	0.44	0.37 - 0.52
1-2 times/week	0.52	0.48 - 0.55	4.09	3.90 - 4.28	0.94	0.87 - 1.01
2-4 times/week	0.77	0.75 - 0.80	5.98	5.79 - 6.16	1.74	1.76 - 1.81
3-5 times/week	0.89	0.84 - 0.90	6.68	6.49 - 6.87	2.24	2.17 - 2.31
Weight Category						
Normal	---	---	---	---	---	---
Overweight	-0.14	-0.15 - -0.13	-0.32	-0.40 - -0.24	-0.35	-0.38 - -0.32
Obese	-0.24	-0.25 - -0.22	-0.56	-0.66 - -0.47	-0.50	-0.53 - -0.46

From separate linear regression models for each dietary measure, with adjustment for energy intake. Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).

Results from the linear regression models predicting dietary adherence and the measures of dietary quality are presented in Table 2. We found "dose-response" associations for older age, higher education, and more frequent physical activity with better scores for each dietary measure. Women had better adherence for all three dietary patterns. Those who were non-Hispanic Black had better dietary scores for the Mediterranean Diet and the Health Eating Index, but had lower DASH scores. Asians/Pacific Islanders had slightly lower scores on all three dietary measures. Separate models for men and women revealed no important differences (data not shown).

Table 3a. Hazard Ratios and 95% Confidence Intervals for Incidence of Colorectal Cancer by Baseline Dietary Pattern and Weight Category, NIH-AARP Diet and Health Study for Men, 1996-2006 (n=182,762)

	Normal Weight		Overweight		Obese	
Dietary Score	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Mediterranean Diet Quintiles						
1	---	---	---	---	---	---
2	0.79	0.66 - 0.96	0.83	0.73 - 0.95	0.97	0.80 - 1.17
3	0.66	0.54 - 0.82	0.91	0.79 - 1.04	0.99	0.82 - 1.21
4	0.67	0.54 - 0.84	0.77	0.66 - 0.91	0.78	0.62 - 1.00
5	0.65	0.51 - 0.83	0.73	0.60 - 0.88	0.79	0.59 - 1.08
p for trend	0.0004		0.0013		0.0508	
Healthy Eating Index Quintiles						
1	---	---	---	---	---	---
2	0.94	0.77 - 1.14	0.80	0.69 - 0.92	0.94	0.77 - 1.14
3	0.83	0.67 - 1.03	0.73	0.63 - 0.85	0.82	0.67 - 1.02
4	0.73	0.58 - 0.91	0.81	0.70 - 0.94	0.88	0.71 - 1.10
5	0.67	0.54 - 0.84	0.63	0.53 - 0.74	0.76	0.60 - 0.99
p for trend	0.0001		<0.0001		0.0394	
Dietary Approaches to Stop Hypertension Quintiles						
1	---	---	---	---	---	---
2	0.91	0.08 - 1.11	0.82	0.72 - 0.94	0.71	0.59 - 0.87
3	0.79	0.64 - 0.99	0.73	0.63 - 0.85	0.78	0.63 - 0.96
4	0.83	0.66 - 1.04	0.69	0.59 - 0.82	0.80	0.64 - 1.00
5	0.67	0.54 - 0.84	0.70	0.60 - 0.82	0.75	0.60 - 0.94
p for trend	0.0005		<0.0001		0.0801	

Cox proportional hazard models adjusted for age, gender, race/ethnicity, education, smoking, physical activity, and energy intake. Separate models were developed for each dietary pattern and weight category. Dietary categories (low, high) are based on tertiles of native score. The lowest tertile is the reference group. Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).

The first set of multivariable models were stratified by weight category and examined the association of incident CRC by quintile of dietary score. Based on these models, which included adjustment for age, gender, race/ethnicity, smoking, and physical activity, and energy intake, increasing dietary quality was consistently associated with decreasing hazard of incident CRC for men of normal weight or were overweight (Table 3a). For obese men, the same general patterns were apparent, but the statistical significance across quintiles of dietary quality was more marginal than for the other two BMI categories.   Smaller and more inconsistent associations, albeit generally in the same direction, were found for women of all three weight categories (Table 3b).

Table 3b. Hazard Ratios and 95% Confidence Intervals for Incidence of Colorectal Cancer by Baseline Dietary Pattern and Weight Category, NIH-AARP Diet and Health Study for Women, 1996-2006 (n=125,281)

	Normal Weight		Overweight		Obese	
Dietary Score	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Mediterranean Diet Quintiles						
1	---	---	---	---	---	---
2	0.95	0.76 - 1.20	1.09	0.86 - 1.38	1.35	1.04 - 1.74
3	0.88	0.69 - 1.12	1.00	0.78 - 1.30	0.86	0.64 - 1.16
4	0.90	0.68 - 1.18	0.81	0.59 - 1.11	0.89	0.63 - 1.25
5	1.02	0.75 - 1.37	0.99	0.68 - 1.41	0.95	0.63 - 1.43
p for trend	0.9384		0.4318		0.2633	
Healthy Eating Index Quintiles						
1	---	---	---	---	---	---
2	0.77	0.58 - 1.01	0.87	0.65 - 1.16	0.85	0.63 - 1.15
3	0.71	0.54 - 0.94	0.94	0.71 - 1.25	0.90	0.67 - 1.21
4	0.71	0.54 - 0.93	0.73	0.55 - 0.98	0.82	0.60 - 1.12
5	0.83	0.64 - 1.08	0.64	0.47 - 0.86	0.71	0.51 - 0.99
p for trend	0.1557		0.0018		0.0573	
Dietary Approaches to Stop Hypertension Quintiles						
1	---	---	---	---	---	---
2	0.86	0.68 - 1.09	0.86	0.67 - 1.10	1.00	0.77 - 1.30
3	0.70	0.53 - 0.93	0.92	0.70 - 1.20	0.78	0.57 - 1.06
4	0.86	0.66 - 1.13	0.74	0.54 - 1.00	0.72	0.51 - 1.00
5	0.73	0.56 - 0.95	0.83	0.62 - 1.11	0.73	0.52 - 1.02
p for trend	0.0389		0.1256		0.0128	

Cox proportional hazard models adjusted for age, gender, race/ethnicity, education, smoking, physical activity, and energy intake. Separate models were developed for each dietary pattern and weight category. Dietary adherence categories are based on lowest and highest tertiles. Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).

Based on the multivariable model Cox regression models, we predicted the incidence of new colorectal cancer at 10 years separately for men (Table 4a) and women (Table 4b). We found almost no statistical significance for the interaction of dietary measures with weight category for both men and women, providing no basis for refuting the hypothesis that the association of diet with incidence CRC differs by weight category. As shown in Table 4a, we found statistically significant linear trends for men who were of normal weight and who were overweight, suggesting a gradient affect for increasing dietary quality with decreasing incidence of colorectal cancer at 10 years. Likewise, among obese men we found generally similar trends, which were of more marginal statistical significance. Consistent with the previously described hazard ratios, the findings were also more mixed for women (Table 4b). For both men and women, the absolute predicted rates of colorectal cancer were consistently less than 2.5%.

Table 4a. Probability and 95% Confidence Interval of Colorectal Cancer at 10 Years by Baseline Dietary Pattern and Weight Category, NIH-AARP Diet and Health Study for Men, 1996-2006 (n=182,762)

	Mediterranean Diet		Healthy Eating Index		Dietary Approaches to Stop Hypertension	
Dietary Score	Probability	95% CI	Probability	95% CI	Probability	95% CI
Normal Weight						
Quintile 1	0.019	0.011 - 0.028	0.019	0.011 - 0.028	0.019	0.010 - 0.027
Quintile 2	0.015	0.008 - 0.003	0.017	0.009 - 0.025	0.017	0.009 - 0.025
Quintile 3	0.013	0.007 - 0.019	0.015	0.008 - 0.022	0.015	0.007 - 0.022
Quintile 4	0.013	0.007 - 0.019	0.013	0.007 - 0.019	0.015	0.008 - 0.022
Quintile 5	0.012	0.006 - 0.019	0.012	0.006 - 0.018	0.012	0.006 - 0.018
p-for-trend	0.0002		<0.0001		0.0001	
Overweight						
Quintile 1	0.019	0.011 - 0.028	0.022	0.011 - 0.032	0.021	0.011 - 0.031
Quintile 2	0.016	0.009 - 0.024	0.017	0.009 - 0.025	0.018	0.010 - 0.026
Quintile 3	0.018	0.010 - 0.027	0.016	0.008 - 0.023	0.016	0.008 - 0.024
Quintile 4	0.016	0.009 0.023	0.018	0.009 - 0.026	0.016	0.008 - 0.023
Quintile 5	0.015	0.008 - 0.022	0.014	0.007 - 0.020	0.016	0.008 - 0.023
p-for-trend	0.0017		< 0.0001		<0.0001	
Obese						
Quintile 1	0.021	0.011 - 0.030	0.022	0.012 - 0.032	0.024	0.012 - 0.035
Quintile 2	0.020	0.011 - 0.030	0.021	0.011 - 0.031	0.017	0.009 - 0.026
Quintile 3	0.021	0.011 - 0.031	0.019	0.009 - 0.027	0.019	0.010 - 0.029
Quintile 4	0.017	0.009 - 0.026	0.020	0.011 - 0.029	0.020	0.010 - 0.030
Quintile 5	0.017	0.008 - 0.026	0.017	0.009 - 0.026	0.019	0.010 - 0.028
p-for-trend	0.0212		0.0304		0.0502	

Probabilities are based on a Cox model that adjusts for age, gender, race/ethnicity, education, smoking, physical activity, and energy intake. Models include interaction terms for baseline dietary scores and weight category. Separate models were developed for each dietary pattern. Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥30 kg/m^2).
P-values for interaction terms for quintiles of Mediterranean Diet and weight category are: Q2-overweight, 0.626; Q2-obese 0.159; Q3-overweight, 0.008; Q3-obese, 0.006; Q4-overweight, 0.250; Q4-obsese, 0.408; Q5-overweight, 0.367; Q5-obese, 0.366. P-values for interaction terms for quintiles of Healthy Eating Index and weight category are: Q2-overweight, 0.227; Q2-obese 0.961; Q3-overweight, 0.411; Q3-obese, 0.974; Q4-overweight, 0.304; Q4-obsese, 0.164; Q5-overweight, 0.726; Q5-obese, 0.381. P-values for interaction terms for quintiles of Dietary Approaches to Stop Hypertension and weight category are: Q2-overweight, 0.486; Q2-obese 0.090; Q3-overweight, 0.733; Q3-obese, 0.974; Q4-overweight, 0.344; Q4-obsese, 0.920; Q5-overweight, 0.482; Q5-obese, 0.411.

Table 4b. Probability and 95% Confidence Interval of Colorectal Cancer at 10 Years by Baseline Dietary Pattern and Weight Category, NIH-AARP Diet and Health Study for Women, 1996-2006 (n=125,281)

	Mediterranean Diet		Healthy Eating Index		Dietary Approaches to Stop Hypertension	
Dietary Score	Probability	95% CI	Probability	95% CI	Probability	95% CI
Normal Weight						
Quintile 1	0.011	0.001 - 0.021	0.013	0.001 - 0.025	0.012	0.001 - 0.023
Quintile 2	0.010	0.001 - 0.020	0.010	0.000 - 0.019	0.011	0.001 - 0.021
Quintile 3	0.009	0.000 - 0.018	0.009	0.000 - 0.018	0.009	0.000 - 0.017
Quintile 4	0.010	0.000 - 0.019	0.009	0.000 - 0.018	0.011	0.001 - 0.021
Quintile 5	0.011	0.000 - 0.021	0.011	0.001 - 0.022	0.009	0.000 - 0.018
p-for-trend	0.9396		0.1547		0.0426	
Overweight						
Quintile 1	0.012	0.001 - 0.024	0.014	0.001 - 0.028	0.013	0.001 - 0.026
Quintile 2	0.013	0.007 - 0.025	0.012	0.001 - 0.024	0.012	0.001 - 0.023
Quintile 3	0.012	0.001 - 0.023	0.014	0.001 - 0.026	0.012	0.001 - 0.024
Quintile 4	0.009	0.000 - 0.018	0.011	0.000 - 0.021	0.010	0.000 - 0.019
Quintile 5	0.011	0.000 - 0.022	0.010	0.000 - 0.019	0.011	0.000 - 0.022
p-for-trend	0.1391		0.0015		0.0242	
Obese						
Quintile 1	0.013	0.001 - 0.024	0.015	0.001 - 0.030	0.014	0.001 - 0.028
Quintile 2	0.018	0.001 - 0.034	0.013	0.001 - 0.026	0.015	0.001 - 0.030
Quintile 3	0.012	0.001 - 0.023	0.014	0.001 - 0.028	0.012	0.000 - 0.024
Quintile 4	0.013	0.000 - 0.025	0.013	0.001 - 0.026	0.012	0.000 - 0.023
Quintile 5	0.014	0.000 - 0.027	0.011	0.000 - 0.023	0.013	0.000 - 0.025
p-for-trend	0.5725		0.0370		0.0399	

Probabilities are based on a Cox model that adjusts for age, gender, race/ethnicity, education, smoking, physical activity, and energy intake. Models include interaction terms for baseline dietary scores and weight category. Separate models were developed for each dietary pattern. Weight categories were based on BMI (normal: 18.5 to < 25 kg/m^2; overweight: 25 to < 30 kg/m^2; obese: ≥ 30 kg/m^2).

P-values for interaction terms for quintiles of Mediterranean Diet and weight category are: Q2-overweight, 0.524; Q2-obese 0.024; Q3-overweight, 0.651; Q3-obese, 0.826; Q4-overweight, 0.354; Q4-obsese, 0.660; Q5-overweight, 0.547; Q5-obese, 0.881. P-values for interaction terms for quintiles of Healthy Eating Index and weight category are: Q2-overweight, 0.554; Q2-obese 0.664; Q3-overweight, 0.154; Q3-obese, 0.290; Q4-overweight, 0.880; Q4-obsese, 0.542; Q5-overweight, 0.156; Q5-obese, 0.358. P-values for interaction terms for quintiles of Dietary Approaches to Stop Hypertension and weight category are: Q2-overweight, 0.902; Q2-obese 0.328; Q3-overweight, 0.254; Q3-obese, 0.530; Q4-overweight, 0.256 Q4-obsese, 0.525; Q5-overweight, 0.866; Q5-obese, 0.714.

DISCUSSION

In this large national study of nearly 400,000 of middle aged and older adults, we found that baseline high quality diets as measured by three diet quality indices (Mediterranean Diet Score, the Healthy Eating Index 2010, and the Dietary Approaches to Stop Hypertension Score) were each associated with lower risk of CRC over a subsequent 10-year period among men who were of normal weight and overweight in a generally consistent "dose-response" effect. Trends were less consistent and of smaller magnitude among men who were obese and women in all three weight categories.

Although previous studies have not examined differences according to baseline weight status, our findings are consistent with other studies demonstrating that higher dietary quality is associated with reduced risk of colorectal adenoma in general.[13] For example, a recent narrative review of publications using the Nurses' Health Study (1976-2016) identified red and processed meat, alcohol, smoking and obesity as factors that increase the risk of CRC.[15] Likewise, an ecological study suggested that 76% of the inter-country variation in colorectal cancer incidence was explained by meat, fish, and olive oil intake, with olive oil intake being associated with reduced risk.[2]

A review of epidemiological studies investigating the associations between dietary patterns including the DASH, the Mediterranean Diet, and the Healthy Eating Index has also shown a consistently reduced risk of colorectal adenoma and cancer incidence of higher scores on all of the dietary indexes for men, but was less conclusive for women.[13 35] Another large prospective examination of four established DASH indexes found that greater compliance with the DASH dietary pattern was associated with a reduced risk of CRC for both men and women.[36] This consistency across the three dietary patterns is not surprising because each of these dietary approaches is built on a similar foundation of fresh fruits and vegetables, whole grains, and low saturated fat.

There are physiologic mechanisms through which diet may be associated with a reduced risk of CRC and through which this association may differ for men and for women. For example, studies focused on individual nutrients suggest that olive oil may exert a reduced risk of CRC by influencing secondary bile acid patterns in the colon. This may in turn affect polyamine metabolism in colonic enterocytes, reducing progression from normal mucosa to adenoma and carcinoma.[3] Fiber intake may reduce the contact between carcinogens and the lining of the colon/rectum and increase stool bulk, which dilutes fecal carcinogens and decreases transit time.[2 7] Red and processed meat may exert a carcinogenic effect due to heme iron, N-nitro compounds and heterocyclic amines generated during cooking at high temperatures as well as a pro-neoplastic effect due to increased adiposity and insulin. Other studies suggest that dietary patterns that include a high consumption of high saturated fatty acid intake may increase CRC risk via their effects on serum insulin concentrations and on the bioavailability of insulin-like growth factor-I (IGF-I).[37] Whole grain intake has been associated with decreased fasting insulin level and improved insulin sensitivity.[7 38]

The differential response of dietary intake to risk of CRC incidence by sex in our study could be explained by differences in the etiology of CRC between men and women.[13] Studies have indicated that women are more likely to develop proximal CRC compared to men.[39] Because proximal and distal CRC appear to arise from different pathways it is possible that the response to dietary intake varies by proximal and distal location type.[39] Hormonal factors may also be responsible for sex differences CRC etiology. Studies of postmenopausal hormone therapy and colorectal cancer report a reduction in risk of colon cancer and a decrease in the risk of rectal cancer for postmenopausal women who had ever taken hormone therapy compared with women who never used hormones. The CRC risk reduction appears to be stronger for current and long-term hormone users.[40 41]

The association was of borderline significance and inconsistent across the three dietary measures for obese men and women. It is plausible that the beneficial effects of a healthy diet are attenuated by the inflammatory, hormonal, and other metabolic changes induced by obesity that promote colorectal carcinogenesis.[42] For example, the gut microbiome that provides important metabolic capabilities, is responsive to alterations of diet,[43] and has been shown in obese people to be different from, and less diverse than, those of the non-obese.[44]

Our study has some limitations. We did not have information on family history of colorectal cancer, although the impact of family history is likely small given the age of the cohort.[45] Medical co-morbidity was not included as a covariate in the multivariable models. Our study population was relatively homogenous with upper-to-middle class Americans in urban centers: non-whites comprised a relatively small proportion of our sample. Dietary intake was self-reported and assessed using a single baseline Food Frequency Questionnaire, thus, there is potential for non-differential measurement error.[46] With only a single measure, we could not examine changes in dietary intake over time. It is possible that the observed differences between men and women are artifacts from how the data were collected. For example, it has been suggested that differential bias could be introduced by the way women and men complete the Food Frequency Questionnaire.[46 47] Women in the AARP (as a group) may have more variation in diet patterns and perception of dietary intake (and weight status) over time than men.[25] Additionally, there is evidence that difference in dietary patterns may vary for men and women who respond in a similar manner to the same survey.[13] Over 90% of the sample was non-

Hispanic white. The research consistently shows that incident rates of CRC and obesity prevalence are higher in African Americans compared to whites.[48 49] Although our sample was drawn from a nationally representative sample, it is not representative of adults in that age group because individuals from low socioeconomic status were not included. This is important because despite steady improvements in healthy eating patterns among US adults the overall dietary quality remains poor particularly in low income populations.[50 51]

This is a large U.S. national study with a prospective design of 398,458 middle aged and older adults with careful ascertainment of cancer outcome and detailed exposure measure using a well-validated Food Frequency Questionnaire. We used three indices of dietary patterns to assess association of high quality diet with outcomes rather than individuals dietary components. The cohort was followed up over a subsequent 10-year period.

CONCLUSION

This longitudinal national study of 398,458 middle aged and older adults found that among normal-weight and overweight men, CRC risk was 25-30% lower with high adherence to each dietary measure. Health benefits of consuming a high-quality diet extend to normal weight men, offering potential insights about approaches to cancer prevention. Additional research is needed to understand the weaker and less consistent results for women.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract ***see pg.1***
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ***see pg. 2***
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ***see pgs. 4-5***
Objectives	3	State specific objectives, including any prespecified hypotheses ***see pgs. 4-5***
Methods		
Study design	4	Present key elements of study design early in the paper ***see pg. 5***
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants ***see pg. 5***
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable ***see pgs. 6-8***
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy ***see pgs. 8-9***
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ***see pg. 8***
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ***see pgs. 9-11***
		(b) Indicate number of participants with missing data for each variable of interest ***see pg. 8***
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures ***see pg. 6***
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ***see pgs. 11-15***
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives ***see pgs. 16-19***
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ***see pg. 18***
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ***see pgs. 16-18***
Generalisability	21	Discuss the generalisability (external validity) of the study results ***see pgs. 16-18***
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ***see pgs. 19-20***

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.