DIETARY PREDICTORS OF COLORECTAL ADENOMA IN DIFFERENT RACIAL SUBGROUPS USING THREE DIFFERENT METHODS OF DIETARY EVALUATION

by

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(Under the Direction of Mark H Ebell)

ABSTRACT

Background: A colorectal adenoma (CRA) is a benign tumor of the inner lining of the colon or rectum that may progress to cancer. A serious concern is that there are notable racial disparities in the incidence of colorectal cancer and likely in the incidence of colorectal adenomas. It is estimated that between 40-70% of colorectal cancer cases can be attributed to diet. Considering the similarities between colorectal cancer and CRA, it seems likely that diet has an important role in the development of CRA, and differences in diet may be a contributing factor to racial disparities in CRA prevalence.

Methods: Several approaches to determining the healthiness of diet (alternate Mediterranean diet index (altMED), Dietary Inflammatory Index (DII), and data-driven methods, such as factor analysis and classification and regression tree (CART) analysis) were used to determine whether or not differences in dietary intake were associated with colorectal adenoma prevalence in the different racial subgroups in the screening arm participants enrolled in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Baseline dietary questionnaires were used to characterize diet.

Results: Results from logistic regression indicate that higher (more favorable) scores on the altMED index were associated with lower odds of CRA in men. In stratified analysis, black and white men had significantly lower odds of CRA with a more Mediterranean-like diet. Lower (less inflammatory) DII scores were associated with lower odds of CRA in men, compared to those with higher (more inflammatory) scores, specifically in white men. The odds of CRA was lower in men who had lower scores on the "Western" diet (consisting of meats and processed grains). This was true for all races but was only significant among white men. Higher scores on the "Fruits and vegetable" diet were not associated with CRA prevalence.

Conclusion: In racially-stratified models, the altMED diet was most strongly associated with CRA prevalence in black men. Future work should focus on ways to increase the access and availability of healthy foods to high-risk populations as a primary preventive measure for reducing CRA disparities.

INDEX WORDS: Mediterranean diet, Dietary Inflammatory Index, colorectal adenoma, racial disparities

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DEDICATION

I would like to dedicate this dissertation to my husband and son, Brett and Will, who were there by my side the whole way. Thank you both for your examples and encouragement. Truly I could not have gone through this process without your love and support.

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CHAPTER 1

INTRODUCTION

Statement of the Problem

A colorectal adenoma (CRA) is a benign tumor of the inner lining of the colon or rectum. It is estimated that at least 50% of the Western population will develop a CRA by the time they reach 70 years of age (1). While not all adenomas become cancerous, almost all colorectal cancers develop from adenomas. The lifetime risk of developing colorectal cancer is 1 in 20 (5%), and is higher in men than in women (2). Colorectal cancer is the third leading cause of cancer and the third leading cause of cancer-related death in both men and women (2). It is expected that more than 130,000 people will be diagnosed with colorectal cancer in 2014 (2). Because adenomas are almost always, if not always, precursors to colorectal cancers, preventing colorectal adenomas is a key way to reduce the incidence of this common cancer. An important concern is that there are notable racial disparities in the incidence of colorectal cancer. However, results from previous studies are not consistent regarding whether or not there are racial disparities in CRA incidence, although many of the studies support the presence of such disparities (3-6). Considering the similarities between colorectal cancer and CRA, it seems likely that diet has an important role in the development of CRA. While some estimate that 70-80% of colorectal cancer cases can be attributed to diet (7, 8), more conservative estimates for lifestyle factors, including diet, are between 40-55% (9).

Similar to colorectal cancer, several nutrients are associated with the development of CRAs, including calcium, vitamin D, fiber and folate (10-12). However, the results from these

studies have been inconsistent and inconclusive, perhaps because these studies have focused on individual nutrients and food components rather than the sum effects of diet. These conflicting results highlight the need for consistent and conclusive evidence that furthers our understanding of nutrition's role in CRA development, and the need for better characterization of diet as a whole. The examination of specific nutrients on the development of CRA is limited in application because people usually do not consume individual nutrients; rather, a whole diet with multiple nutrients and food components are consumed. The interactive effects with other nutrients, food/nutrient colinearity, and the biological form in which the nutrient is consumed, are considerations that may influence the association between a food component and CRA incidence. Therefore, a focus should be placed on understanding the role of eating habits and diet as a whole in the development of CRAs.

There have been a few studies looking at diet as a whole with regards to its relationship with CRAs. These studies have generally found that diets with more fruits, vegetables, and whole grains are associated with a lower occurrence of CRAs than diets with less of these food items. But again, the studies that have examined the effect of the whole diet and the incidence or prevalence of CRA are limited and have not resulted in consistent results, and none of them have examined racial differences (13-15).

Studies have also shown an association between diet and systemic inflammation (16). Oxidative stress, which promotes inflammation, occurs when a high-fat and/or high-carbohydrate meal is consumed (17). Conversely, foods high in anti-oxidants and flavonoids, such as fruits and vegetables, reduce inflammation by scavenging for free radicals, inhibiting pro-oxidant enzymes, binding the free radicals, and possibly modulating the expression of pro-inflammatory molecules (18). An increase in systemic inflammation, from either excess oxidative stress or a

lack of anti-oxidants, appears to contribute to colorectal cancer development (19). Inflammation appears to promote an environment that increases genetic mutations, while inactivating the body's ability to repair mutations (20). There is also evidence that inflammation may promote growth factors that enhance tumor growth, particularly through enhanced angiogenesis (20). Further, a vicious cycle is created in that tumor cells produce cytokines that attract leukocytes, which further promote inflammation (21). Despite these findings, it is unknown whether or not an inflammatory diet increases the incidence of CRA through the mechanism of systemic inflammation, particularly in sub-populations with a potentially higher risk of developing CRAs, such as those of black race.

Multiple methods of evaluating the "healthiness" of diet have been proposed, and several of them have been associated with systemic inflammation. Two of these indexes will be used to describe potential differences in diet quality between racial groups – the Dietary Inflammatory Index and the Mediterranean diet score (22, 23). These indexes were developed in a way that was investigator driven, in that the components of these indexes are determined *a priori* by the investigator based on previous literature or expert opinion, rather than on a multivariate analysis of a dataset. The primary difference between the two is that the Dietary Inflammatory Index was specifically designed to evaluate the inflammatory nature of diet, whereas the Mediterranean diet was developed because of the observation that people living in the Mediterranean region have better than expected cardiovascular health (24).

Alternatively, methods such as factor analysis and classification and regression tree analysis (CART) can identify more general dietary patterns or predictors that are specific for CRA. Factor analysis can be used to identify dietary patterns when there is the collinearity between multiple variables that is often observed in diet analysis. CART analysis examines the

independent association between dietary predictors of CRA and the likelihood of adenoma, is a model-free estimator, and is effective at studying multiple predictors when there is interaction between multiple variables.

Purpose and Objectives

Factors that contribute to CRA incidence are not well understood, and racial differences in dietary factors that may contribute to disparities CRA are even less well understood. Further research is needed to elucidate the differences in diet quality between racial groups, which could contribute to these disparities.

The overarching goal of these analyses is to reduce the racial disparities that occur in the prevalence and incidence of colorectal adenomas, and, consequently, invasive colorectal cancer, through preventable dietary approaches. An examination of differences in dietary intake and an evaluation of whether these potential differences are associated with prevalent or incident adenoma are steps to accomplish this overarching goal.

Three methods for assessing diet quality are used. The first two methods are investigator-driven methods (i.e., the investigator determines the dietary scoring) that score the general "healthiness" (e.g. inflammatory nature) of diets, while the third method is a data driven method (i.e., patterns in the data determines the outcome). The first method uses the patented Dietary Inflammatory Index, which is a research-developed method of scoring the inflammatory nature of diet using 45 food items identified as pro- or anti-inflammatory, based on previously published studies (22). Scores between +1 and -1 are calculated for each food item, where +1 is maximally pro-inflammatory and -1 is maximally anti-inflammatory. The scores for each food item are then summed for an overall dietary inflammatory score. The second method uses the alternative variant of the Mediterranean diet index, which is based upon the consumption of

fruits, vegetables, nuts, whole grains, legumes, fish, a high ratio of mono-saturated fats/saturated fats, limited alcohol, and limited meat (23). Diets for each individual are scored between 0 and 9, where 9 is optimally Mediterranean-like and 0 is poorly Mediterranean-like. Finally, the third method uses principle component analysis, or factor analysis, to determine dietary patterns in the PLCO cohort. Factor scores for identified dietary patterns were subsequently calculated for each individual and then examined for potential associations with adenoma outcomes.

For the first two methods (Dietary Inflammatory Index and Mediterranean diet score), baseline dietary data were analyzed and compared between the different races to see if there were racial differences in the intake of these diets. The association between diet score and prevalent CRA was examined, adjusted for important lifestyle factors such as non-steroidal anti-inflammatory use, physical activity, age, smoking, and socioeconomic status. For the third method, the independent dietary predictors of adenomas were determined using two approaches, factor analysis and CART analysis. Factor analysis is a way to minimize the number of variables from a large set of variables. Factor analysis is advantageous in that it is able to identify a few dietary patterns from a large number of dietary variables. Alternatively, CART uses a series of separate logistic regressions to sequentially divide the dataset into smaller and smaller subgroups, at each point stratifying the group using the predictor variable that is most strongly associated with the outcome. These analyses are stratified by race to identify independent dietary predictors specific for each racial subgroup.

Specific Aims

Aim 1: To determine whether or not there are racial differences in the consumption of inflammatory diets, as measured by a validated Dietary Inflammatory Index, in a group of men and women, between the ages of 55 and 74 enrolled in the screening arm of the Prostate, Lung,

Colorectal, and Ovarian (PLCO) Screening Trial. To determine whether or not an inflammatory diet at baseline is associated with the prevalence, incidence, or recurrence of colorectal adenomatous polyps, and whether or not this association is modified by race.

Hypothesis: We hypothesize that there are racial differences in Dietary Inflammatory Index scores. We further hypothesize that people who have a higher Dietary Inflammatory Index at baseline are more likely to have a prevalent colorectal adenoma or incident adenoma during follow-up than those with a lower Dietary Inflammatory Index, and that this association is modified by race.

Aim 2: To determine whether or not there are racial differences in the consumption of the Mediterranean diet, assessed using a validated dietary index, in a group of men and women between the ages of 55 and 74 enrolled in the screening arm of the PLCO Screening Trial. To determine whether or not a lower score on the Mediterranean diet at baseline is associated with the prevalence, incidence, or recurrence of colorectal adenomatous polyps, and whether or not this association is modified by race.

Hypothesis: We hypothesize that there are racial differences in Mediterranean diet scores. We further hypothesize that people who have a lower Mediterranean diet score at baseline have a higher prevalence of colorectal adenoma or incident adenoma during follow-up than those with a higher Mediterranean diet score, and that this association is modified by race.

Aim 3: To determine whether or not there are racial differences in food intake patterns, identified through factor analysis, and to determine whether or not the identified patterns are associated with colorectal adenoma in a group of men and women between the ages of 55 and 74 enrolled in the screening arm of the PLCO Screening Trial.

Hypothesis: We hypothesize that there will be differences in the identified dietary predictors of colorectal adenoma between the different races.

Significance of Research

There are several salient points that make this proposed research significant and needed. First, few studies have examined differences in specific dietary nutrients or foods between different races. And, no studies have examined racial differences in diet as a whole in regards to CRA incidence or prevalence. These analyses explore racial differences in diet in an attempt to identify factors that contribute to racial disparities in the prevalence, incidence, and recurrence of CRAs. Second, because systemic inflammation is a predictor of many chronic diseases, including colorectal cancer and CRAs, identifying external factors that give rise to systemic inflammation may be a key to reducing the risk of these diseases. The Dietary Inflammatory Index is a novel way to characterize the pro- or anti-inflammatory nature of diet. The effects of an inflammatory diet, as measured by the Dietary Inflammatory Index, are largely unknown, because of the novelty of the index. These analyses use the Dietary Inflammatory Index to explore the under-researched areas of an inflammatory diet and the risk of health outcomes such as CRAs. Third, no studies have been done to examine the racial differences in dietary intake using the alternative Mediterranean diet index, which is a simpler method of diet analysis than the Dietary Inflammatory Index. Fourth, no studies have used CART analysis to explore the specific independent predictors of colorectal adenomas. This method is advantageous in that it is a model-free approach that considers the interactive effects of all variables, which can be common in epidemiological studies, whereas, traditional methods that have been used previously are limited in their ability to fully examine interactive effects.

Study Outline

Chapter 2 is a thorough review of what is known about inflammation and diet, and how these variables relate to the incidence and development of CRAs. It begins with an overview of the general epidemiology of CRA, with a focus on racial distribution. This is then followed by a discussion about what is known about nutrition and CRA, followed by what is known about inflammation and CRA, and then what is known about the relationship between diet and inflammation. The discussion will then turn to the methods used to evaluate dietary quality, including the Dietary Inflammatory Index and the Mediterranean diet. A discussion of factor analysis and the novel method of CART analysis will be presented, along with the advantages, disadvantages, and application of these methods. And finally, the discussion concludes with gaps in what is known about these subjects.

Chapter 3 is a complete discussion of the methods used in the analyses. It discusses the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial participants, recruitment methods, and screening protocol. It also discusses the methods used to calculate the Dietary Inflammatory Index and the Mediterranean diet, as well as the variables that were used in data-driven methods, such as factor analysis and CART analysis. Chapter 3 concludes with a discussion of the statistical methods used in the analyses.

Chapter 4 is the first of three manuscript style research chapters. It investigates potential racial differences in Mediterranean diet scores in a group of men and women between the ages of 55 and 74 enrolled in the PLCO Cancer Screening Trial. Racial differences in the alternative Mediterranean diet may partially explain the racial disparities in CRA incidence. Testing was done to determine whether there is an association between a lower Mediterranean diet score (indicating a more unhealthy diet) and the prevalence, incidence, and recurrence of colorectal

adenomatous polyps, and whether or not race modifies this association. The findings from these analyses are presented and discussed.

Chapter 5 discusses the effects of an anti-inflammatory diet on CRAs in a group of adult men and women aged 55 to 74 years enrolled in the PLCO Cancer Screening Trial. First, a validated Dietary Inflammatory Index was used to assess the inflammatory nature of diet among people of different races. Testing was done to determine whether there is an association between higher Dietary Inflammatory Index scores (indicating a more inflammatory diet) and the prevalence, incidence, and recurrence of colorectal adenomatous polyps, and whether or not race modifies this association. Results from these analyses are presented and discussed.

Chapter 6 discusses the findings of factor analysis, and the dietary patterns in the different racial subgroups. It also includes findings of a recursive partitioning or classification and regression tree (CART) analysis, which is a model-free estimator that is used to determine independent predictors of an outcome, and considers interactive effects of all variables. This method was used to determine the association between specific dietary predictors of CRAs and the likelihood of adenoma occurrence in the different racial subgroups.

Finally, Chapter 7 is the concluding chapter presented as part of this dissertation. In this chapter, the findings are summarized, and an overall conclusion is provided, as well as discussion of future research.

CHAPTER 2

LITERATURE REVIEW

Introduction

Colorectal adenomas (CRAs) are prevalent and, in spite of their preventable nature (through diet and lifestyle), notable racial differences in the incidence of this condition have been demonstrated (3). Because diet is so influential on colorectal cancer incidence and, therefore, possibly colorectal adenomas, the research proposed here will focus on racial differences in diets that may contribute to racial disparities in CRA incidence. A review of the literature will be presented in regards to "Dietary predictors of colorectal adenoma in different racial subgroups using three different methods of dietary evaluation". To begin, an overview of CRAs will be presented along with the current epidemiological statistics of CRA. Current knowledge about the association between diet and CRAs will then be discussed, followed by current knowledge about inflammation, another risk factor for CRAs. Two methods for evaluating dietary quality and one method of determining independent predictors of CRA will be discussed. Finally, after presenting what is known about CRAs, gaps in the research will be discussed.

Colorectal Adenomas

CRAs are small, benign tumors that occur in the lining of the large intestine. CRAs are a type of polyp, but are more serious due to the increased risk of progression to colorectal cancer with which they are associated. Genetic mutations in the suppressor genes (1) can lead to adenomas developing into colorectal cancer in a span of about 10-15 years (25). While most, if

not all, colorectal cancers arise from CRAs, fewer than 10% of people with adenomas will develop colorectal neoplasia (2, 26).

Polyps can form in the mucosal lining of the colon; polyps are often considered hyperplastic and have a low probability of becoming cancerous. Adenomas are specific types of polyps that can have tubular or villous characteristics and have a higher probability of becoming cancerous, compared to small, nonadenomatous hyperplastic polyps. Histologically, most (81%) of adenomas are tubular (adenomatous), but villous or tubulovillous adenomas comprise about 16% of the adenomas and have the highest likelihood of developing into a colorectal cancer (27). Large adenomas (> 9 mm) are more likely to become cancerous than smaller adenomas (28). The degree of dysplasia in polyps is an indicator of the likelihood of the polyp becoming cancerous (29). Inactivation of the adenomatous polyposis coli (APC) gene can initiate tumor development; activation of the K-RAS oncogene often initiates progression of the early adenoma to the intermediate adenoma. Loss of chromosome 18 and loss of deleted in colon cancer (DCC) loci have been observed in intermediate to advanced adenoma. Genomic changes to other oncogenes, such as tumor suppressor p53, are associated with the progression of late adenoma to carcinoma (30).

It is estimated that at least 50% of the Western population will develop a CRA by the time they reach 70 years of age (1, 31), and generally one individual out of 20 will develop colorectal cancer (2). While cases of colorectal cancer are far less common than cases of colorectal adenoma, colorectal cancer still affects many people. Colorectal cancer is the third leading cause of cancer and the third leading cause of cancer-related death in both men and women. In 2014, it is expected that almost 140,000 people will develop colorectal cancer (2).

Preventing colorectal adenomas is a key way to reduce the incidence of this common cancer type.

Because there are no registries that collect data on adenomas, the incidence and prevalence of adenomas are less well known. In an employer-based screening-colonoscopy program with 906 participants (32), 10% of individuals aged 40-49 years had hyperplastic polyps, 8.7% had tubular adenomas, and 3.5% had advanced neoplasms (large tubular adenoma at least 1 cm in maximal diameter, a polyp with villous features, a polyp with high-grade dysplasia, or a cancer), but no polyps or adenomas were cancerous (32). Other researchers have reported that colorectal polyps are found in about 14% of screening cohort participants over 50 years of age in the United States, while small (6-9 mm) and large (≥10 mm) polyps were found in about 8% and 6%, respectively, of the screening participants (33).

High-risk subgroups are similar for both CRA and colorectal cancer. Males consistently have a higher prevalence of adenomas than females, with a ratio of adenomas in males to females between 1.5 and 2.0 to 1 (34). Older individuals have a higher prevalence than younger individuals (35). Racial differences in colorectal cancer are very clear – blacks are about 25% more likely to develop colorectal cancer and about 50% more likely to die from colorectal cancer than whites or Asian/Pacific Islanders (2). Additionally, blacks are more likely to present with colon cancer at a younger age, have cancer in the proximal (right-sided) colon, and have colon cancer diagnosed at a more advanced stage than whites (36-38). Racial differences in CRA prevalence are also apparent.

Multiple studies have provided estimates on the prevalence of adenomas by race, and most have found racial disparities. In a larger population of U.S. residents undergoing screening (N=85,525), blacks were significantly more likely to have an adenoma than whites, while

Hispanics had a similar prevalence compared to whites (19%, 22%, and 26% for whites, Hispanics, and blacks, respectively) (3). However, one small study found that there were no differences in the prevalence of polyps or adenomas in a population of 1,230 Philadelphia residents undergoing screening between blacks 45-49 years old, blacks ≥50 years old, and whites ≥50 years old, although it cannot be ruled out that the null findings in this study were due to small sample size. The prevalence of adenomas for each group was, respectively, 37.8%, 42.9%, and 38.5%. In this same study there were no racial differences in anatomical location. Another study found that among those over 60 years, there were significant differences between blacks and whites. This was true for both males (5.29% vs. 2.84%) and females (6.40% vs 4.79%)(40) . Although more studies suggest racial differences in overall adenoma prevalence than not, the inconsistency in findings may have to do with the anatomic location of the adenoma.

Differences in Anatomical Location and Severity of Polyps and Adenomas

Racial differences are especially pronounced when considering the location of polyp or adenoma formation. Generally, studies show that blacks are more likely than whites to develop adenomas in proximal sites (3), whereas blacks were either about as likely or less likely to develop adenomas or polyps in distal sites (41, 42). Additionally, some of these studies demonstrated racial differences in the size of the adenoma or the degree of differentiation between adenomas, but these differences were dependent upon the location of the polyp or tumor. For example, one study found that the odds of adenoma were greater for blacks than whites in proximal colon sites, but not in distal sites (6). Another study (N=46,726) found that, in adjusted analysis, the prevalence of benign polyps was lower in blacks than whites, but this study also noted that blacks were more likely to develop more serious tumors than whites (5).

Conversely, in a population of blacks, larger polyps were more common on the left side (distal) than the right side of the colon, but villous histology was similar between the two sides (43). In a smaller study (N=3,321), the prevalence of advanced neoplasia (tubulovillous >1 cm, villous, or high dysplasia) was higher in whites than blacks, although blacks were more likely than whites to have proximal advanced neoplasia (42). Another study found that the prevalence of distal adenomas (both any adenoma or adenoma <5 mm) was no different between blacks and whites who were screened using flexible sigmoidoscopy, but when those with a positive flexible sigmoidoscopy returned for a colonoscopy, blacks had a higher prevalence of large (≥10 mm) proximal adenomas and a lower prevalence of small adenomas (<5 mm) than whites (44). This study also found that Asians were more likely to have distal adenomas but less likely to have proximal adenomas on follow-up, compared to whites, although the sample size for Asians was small (N=77) (44). In one study comparing whites, blacks, and Hispanics, the investigators found that both Hispanics and blacks were more likely than whites to have an isolated proximal adenoma, which is defined as an adenoma in the proximal colon but no adenoma in the distal colon (3). Although another study found that Hispanics had a similar risk of large (≥10 mm) adenomas as whites in both proximal sites and any site (45). Blacks were also more likely than whites to have ≥3 adenomas, and both Hispanics and blacks were more likely than whites to have advanced features to their adenomas (3).

Finally, one study found that among colon cancer cases reported to the Surveillance and End Results (SEER) program, blacks were 63% more likely to have in situ cancers and about 10% more likely to have invasive cancer proximal to the splenic flexure, compared to non-Hispanic whites (38).The author conclude that racial/ethnic differences in the anatomic

distribution of colon cancers are likely because a higher screening rate in whites, as previous studies have indicated, should result in a higher, not lower, proportion of less-invasive lesions.

Taken together, the results from these studies suggest that colorectal cancer screening in blacks is more effective and complete when performed with colonoscopy, rather than flexible sigmoidoscopy. This is in contrast to findings that indicate that low-income blacks are more likely to be screened using flexible sigmoidoscopy, but less likely to be screened with colonoscopy, when compared to low-income whites (46). Further, it has been reported that blacks are less likely to receive any type of colon cancer screening but were more likely to receive a colonoscopy for diagnostic purposes (37).

Studies consistently show that adenoma prevalence increases with age, but results from one study indicate that this association is not linear (6). In this study, the risk of adenoma was about 25% greater in those 55-59 years old compared to those 50-54 years of age. The risk was about double in those older than 70 years of age when compared to those 50-54 years of age. Adenomas in the proximal location may be primarily responsible for the increase in adenoma occurrence. It has been reported that the differences in the occurrence of adenomas between those 50-54 years of age and those older than 70 years of age was greatest for proximally-located adenomas, when compared to adenomas located in the distal colon (6).

Racial Access to Care

Notable disparities in CRA may be attributed, in part, to health care utilization and screening, although results from studies looking into race and screening are equivocal. It has been estimated that black Medicare beneficiaries are, respectively, 18% and 39% less likely to receive a colonoscopy or flexible sigmoidoscopy than white Medicare beneficiaries (47). Conversely, one study found that among respondents in the National Health Interview Survey

(2010), blacks were more likely than whites to report not having a colonoscopy but when adjusting for other covariates such as income, insurance status, and health, the difference disappeared (48). In another study blacks were as likely as whites to have had a sigmoidoscopy but less likely to have had a colonoscopy (46). In the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, blacks who had colorectal cancer screening were 12% less likely to undergo diagnostic colonoscopy than whites (49). Interestingly, the only racial difference in adenoma prevalence in this cohort was among blacks and whites with postgraduate education. It is important to consider that the black population in the PLCO cohort may not be entirely representative of the general black population of the United States. In a study of a subsample of PLCO participants and non-participants, those who participated in the PLCO cohort were generally more educated, had a higher income, had a close relative diagnosed with cancer, and had more knowledge about some of the lifestyle preventive strategies for cancer (50).

Other studies have found that all minority subgroups were less likely than whites to be screened for colon cancer, but those with less education, less health insurance coverage, and had recently immigrated to the United States were especially likely to not be screened (51). Another study found that while access to care was effective in improving screening rates, it was insufficient in reducing racial disparities in screening (52), suggesting that other actions would need to be taken in order to reduce colorectal cancer incidence and mortality through the use of preventive screening methods. Having a primary care physician trained in colonoscopy procedures may improve screening in a typically under screened, high-risk population (53). Further, increased screening with the use of either flexible sigmoidoscopy and fecal occult blood testing every 5 years or colonoscopy every 10 years is more cost-effective in blacks compared to whites (54). Considering that screening is highly associated with education and income,

separating the effects of race and socioeconomic status is imperative considering the poverty rate is three times higher in blacks than in whites (36).

Differences in screening may account for racial or ethnic disparities in colorectal cancer and adenoma incidence or prevalence. Data from the National Health Interview Survey (2000-2004) indicate that there were no differences in colorectal cancer screening between Hispanics and whites (adjusted for socioeconomic status and insurance), but blacks were about 13% less likely to be screened by fecal occult blood testing, flexible sigmoidoscopy, or colonoscopy (55). Asians were even less likely to be screened (about 34%), compared to whites. In this same study, low education, poverty, and having no insurance were associated with a lower likelihood of being up-to-date on screening. Data from another national survey (National health Interview Survey, 1987-2003) also indicate that whites reported a higher use of endoscopic screening, followed by blacks, Hispanics, and Asians (56). In another study of Medicare enrollees, there were no racial differences in colorectal cancer screening, when adjusting for insurance, education, income, language, and other health care access variables, suggesting that education and income are more important predictors of colorectal cancer screening than race or ethnicity (57). It seems unlikely that screening, or lack thereof, could fully explain racial differences in CRA since the pattern of lower screening participation does not always follow the pattern of adenoma incidence in racial subgroups.

Considering the similarities between colorectal cancer and CRA, it seem likely that diet also has an important role in the development of CRA, since 40- 80% of colorectal cancer cases can be attributed to diet and lifestyle (58-61), likely due to the anti-oxidant properties of specific nutrients and their involvement in the regulation of DNA integrity (62, 63).

Nutrition and Colorectal Adenomas

Much research has gone into specific dietary factors that reduce the risk of CRAs. The studies have examined the effect of individual nutrients, as well as foods and dietary patterns that consist of complex interactions between individual nutrients. Folate, calcium, vitamin D, and fiber are the specific nutrients that have shown the strongest and most consistent association with CRAs in larger populations, but other nutrients, including phosphorous and beta-carotene, have also been examined in their association with CRAs (11, 64). Results from these studies, while somewhat promising, remain mostly inconclusive.

Folate/folic acid

For example, several observational studies have found an association between higher folate/folic acid consumption and a lower risk of CRA recurrence and incidence (10, 65). One of these studies found an inverse association between higher folate intake and lower recurrence of CRAs, but fiber and fat intake attenuated this finding (10). In men and women with a prior history of CRAs, not only were higher intakes of dietary folate and vitamin B-6 associated with less CRA recurrence, but so was plasma folate (66). However, clinical trials have not been supportive of the association between folate and CRA (67, 68). One such study found that participants assigned to receive 1 mg/d of folic acid did not have a lower risk of CRA, compared to those on placebo (67). Another study found similar null findings (68). It is important to note, however, that most clinical trials examining this association were performed in populations that were served by folic acid fortification programs, and the reference group was already receiving a certain amount of folic acid in their diet that may have been adequate for CRA prevention, which may partially explain the null findings. For example, in China, where there is no folic acid

fortification program, a randomized control trial demonstrated a 50% reduction in CRA incidence among adults older than 50 years taking 1 mg/d of folic acid (69).

Calcium and vitamin D

Calcium and vitamin D, which have been shown to be preventive of colorectal cancer, have a complicated relationship with CRA development. One prospective observational study found a 20% lower risk of CRA in those with the highest quartile of calcium intake, compared to those with the lowest quartile of calcium intake (11). Phosphorous was also shown to be protective of adenoma incidence, but there was no association between vitamin D intake and CRA (11). In another prospective observational study, calcium and vitamin D were shown to have no effect in the risk of CRA in men and women health professionals, although vitamin D from supplements was shown to have small protective effect on CRA occurrence in women (70). In a meta-analysis of epidemiologic studies, higher serum 25(OH)D was associated with an 30% lower risk of CRA, although vitamin D intake was not associated with a significantly lower risk (71).

Clinical trials on calcium and CRA have mainly focused on CRA recurrence, whereas, few trials have been conducted examining the relationship between vitamin D and CRA incidence or recurrence. One clinical trial found that adults (mean age 61 years) taking 3 grams of calcium carbonate had about a 25% lower risk of colorectal adenoma recurrence compared to placebo (72). Another clinical trial found an almost 30% reduction in CRA recurrence among those assigned to the calcium arm, but only found an association between vitamin D and CRA among those assigned to the calcium group, suggesting a protective effect from the combination of the two nutrients (73). Alternatively, one clinical trial found no reduction in CRA occurrence in those assigned to the calcium treatment arm (74).

Fiber

Higher fiber intake, which has been shown to have a protective effect on colorectal cancer development, was associated with a lower prevalence of CRA in a group of men and women (75). Fiber from grains, cereals, and fruits had the strongest effect. However, other studies have not found fiber to be protective. One study found that a diet low in fat and high in fiber, fruits and vegetables was no more effective in preventing adenoma recurrence than a usual diet (76). Similar null findings were found in a group of healthy women enrolled in the Nurses' Health Study (77). One clinical trial even found a higher risk of CRAs among those assigned to the ispaghula fiber treatment group (74). The inconsistency in findings between observational and randomized controlled trials is likely due to unaccounted bias and confounding in the observational studies.

Individual foods

Studies on individual foods have also resulted in equivocal findings. An early study demonstrated that intake of vegetables (including green-yellow, raw, and pickled vegetables), beans, fish, and meats was associated with a lower risk of colorectal adenoma (78). This study did not find an association between fruit intake and CRA prevalence, although this particular study also did not adjust for other important covariates, such as smoking status, physical activity, or non-steroidal anti-inflammatory use (NSAID). Later studies have shown that, in female nurses, higher fruit and legume intake was associated with a lower incidence of CRAs when compared to those with lower intakes (79). Total fruit intake, but not total vegetable intake, was also associated with a lower prevalence of CRA in a prospective study (80). In the study by Millen et al., fruit juice, melons/berries and yellow vegetables were specific foods identified as being associated with a lower prevalence of CRA, but dry beans were not found to be associated

with a lower prevalence of CRA. Dairy has been shown to be protective of adenoma occurrence in one observational study (11), but was found to be unrelated to adenoma occurrence in another observational study (70).

Dietary patterns

Studies looking at the association between dietary patterns as a whole and CRA are limited. One study using cluster analysis found that a low-energy diet consisting of a low intake of high-fat processed meat, bread, pork, and wine was associated with a lower odds of CRAs, compared to those who had a high intake of bread, pork, oils, and high-fat processed meat (81). Another study found that in black women, the intake of a Western-type diet high in fats, refined grains, processed meats, butter, and snacks, was associated with a higher incidence of CRAs, while a diet high in vegetables, fruits, whole grains, beans, low fat dairy, fish, and poultry was associated with a lower incidence of CRA (13).

Another study found that in Japanese men, there was a reduced odds of colorectal adenoma in those who had a high consumption of fermented dairy products, confectionaries, fruits, bread, and vegetables, but more interesting was the lack of association between a more Japanese-style diet (low in bread, high in soybean products vegetables, seaweed, and green tea) and the prevalence of CRA (82). Further, another study found that a high vegetable, moderate meat diet was associated with a higher risk of CRA, while a diet high in fruits and low in meat was associated with a lower odds of CRAs (83). But, similar to the results analyzing the relationship between individual nutrients/food items and colorectal cancer, these studies have resulted in limited and inconsistent results. Furthermore, these studies did not examine racial differences, in spite of potential racial disparities in CRA prevalence, thus strengthening the

argument that a better understanding of the effects of diet on the incidence of CRA in specific racial groups is needed.

Inflammation and Colorectal Growths

An alternative to researching the association between specific foods and CRA prevalence is to examine the effects of inflammation on CRA prevalence. Researchers have broadly found that chronic systemic inflammation is associated with many chronic health conditions, including cancer (84, 85).

Acute inflammation is beneficial in the body's healing process. When healthy tissue in our bodies is injured (e.g., cuts, bruises, or breaks), the body's normal healthy response in dealing with these injuries results redness, swelling, heat and pain. This allows for the vessels in the area to open, and allows immune cells to enter the area and fight off any infection and/or repair damage that has been done. Initially, chemotactic cytokines are released that signal the recruitment of neutrophils (84). Monocytes, which may eventually become macrophages, and mast cells follow the arrival of neutrophils. These cell lines are important in the release of growth factors, histamines, prostaglandins, and proteases, which help orchestrate the healing and inflammatory processes (84). Inflammation can be measured by circulating proteins, cells, and cytokines in the blood such as C-reactive protein (CRP), interleukin-6, interleukin-8, fibrinogen, and total white blood cell count.

Unfortunately, if left unchecked, inflammation can also lead to other problems including abnormal cellular growth. During the healing process, the action of neutrophils and macrophages results in the release of reactive nitrogen species, which can lead to additional damage (63). Many studies have found associations between colorectal cancer and inflammatory proteins, such as CRP (86-89). It seems logical that inflammation would also be associated with

the development of CRAs, given the natural history of adenoma to carcinoma. Further supporting the association between inflammation and CRA, one study found a higher expression of myofibroblasts (present only in pathological states such as inflammation) in CRAs when compared with normal mucosal tissue (90). There have been few epidemiological studies conducted that examine the relationship between systemic inflammatory markers and CRAs, but they have mostly resulted in equivocal findings (91-93). One such study found that high plasma or serum concentrations of the inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were more likely to be associated with the development of CRAs (91). However, other studies have not found any associations between inflammatory cytokines and CRA prevalence (92, 93), yet several studies have shown that inflammatory-regulating genes are associated with CRAs (92, 94). One such study found no association between either serum CRP or IL-6 and CRA prevalence, but these researchers did find an association between polymorphisms in CRP alleles and CRA prevalence (92). Another study found an association between CRA prevalence and polymorphisms in the IL1B-31 and IL8-251A alleles (94).

Further supporting the association between inflammation and CRAs is the finding of a lower incidence of CRA among individuals receiving non-steroidal anti-inflammatory drugs in clinical studies (95). There may be two possible explanations for these findings: 1) higher inflammation leads to an increased incidence of CRA, which then leads to a higher risk of colorectal cancer, and 2) inflammation creates an environment in which the progression from adenoma to carcinoma is more likely to occur. Research is needed to elucidate the exact mechanism, but is out of the scope of these proposed analyses.

It is believed that inflammation appears to promote an environment that increases genetic mutations, as well as disabling the mechanisms that repair these errors (96). There is also

evidence that inflammation may promote growth factors that enhance tumor growth, particularly through enhanced angiogenisis (96). Further, a vicious cycle is created in that tumor cells produce cytokines that attract leukocytes, which further promote inflammation (84).

Thus, it appears that the mediation of the inflammatory process is one crucial avenue of reducing CRA incidence. Anti-inflammatory drugs such as aspirin may be one way to combat inflammation-induced cancers, as they have been shown to prevent CRA incidence (95) and colorectal cancer mortality (97). However, in addition to the benefits of cancer prevention, these drugs can also have unpleasant and harmful side effects, such as gastrointestinal bleeding, hospitalization, nausea, and dyspepsia (98). Other ways to reduce inflammation and prevent resultant pathological states without harmful side-effects (such as diet) therefore warrant further investigation.

Diet and Inflammation

The biologic effects of diet are complex and there are several main reasons why diet can affect inflammation. Oxidative stress, which promotes inflammation, occurs when a high-fat and/or high-carbohydrate meal is consumed, resulting in the production and release of free radicals and reactive oxygen species into the tissues (99, 100). Conversely, foods high in anti-oxidants and flavonoids, such as fruits and vegetables, reduce inflammation by scavenging for the free radicals, inhibiting pro-oxidant enzymes, binding the free radicals, and possibly modulating the expression of pro-inflammatory molecules (62, 63).

Studies have shown an association between diet and systemic inflammation, as measured by leukocyte count and inflammatory proteins such as CRP and interleukin-6 (101, 102). These studies have focused on a diversity of dietary components, from micro-nutrients such as carotenoids (103), flavonoids (104, 105), and magnesium(106) to macronutrients such as omega-

3 fatty acids (107), carbohydrates (108, 109), and saturated fats (110); to whole foods such as fruits and vegetables (111).

Each nutrient or food component has unique ways to reduce or promote inflammation. Carotenoids have important anti-oxidant activities by trapping reactive oxygen species, but they also appear to engage in anti-proliferative and pro-differentiation activities, have hypocholesterolemic effects, and perhaps engage in the modulation of cyclooxygenase pathways (112). Flavonoids, like carotenoids, are important scavengers of reactive oxygen species and they can also interfere with nitric-oxide synthase activity, which is important in minimizing damage done by ischemia during injury (113). The mechanism for magnesium's role in the inflammatory process is that a higher intracellular ratio of calcium to magnesium leads to the activation of calcium ion dependent signaling events, which can result in the over-activation of pro-inflammatory proteases and nitric oxide synthase (114).

A higher intake of carbohydrates and particularly foods that have a high glycemic index (the propensity of carbohydrates to increase blood sugar) appears to increase oxidative stress through an imbalance in the ratio of NADH and NAD^+ during hyperglycemic states (109). Additionally, evidence suggests that NF-kB, an important inflammation-regulating protein, is activated more with higher glycemic index foods than lower glycemic index foods, and that NF-kB concentrations mirrored blood glucose concentrations (115). The activated NF-kB may then act on genes that regulate pro-inflammatory cytokines. Fats in the diet - namely saturated and omega-3 fatty acids - can have either pro-inflammatory or anti-inflammatory mechanisms. Omega-3 fatty acids appear to be involved in the regulation of transcription factors, help to minimize the production of inflammatory cytokines, and decrease the action of NF-kB (116), whereas, saturated fats appear to stimulate inflammation through activation of NF-kB (117).

Other research has focused on dietary components that promote oxidation or inflammation. Research that focuses primarily on one food constituent is limited in its ability to conceptualize the whole diet and the interactive effects of multiple food components that can have both beneficial and detrimental health effects. Because of the limited application of focusing on individual components of diet, researchers have tried to evaluate the association between diet as a whole and inflammation (62, 118). Generally, these studies have found that diets high in fruits and vegetables, omega-3 fatty acids, but are low in saturated fats and low-glycemic foods are anti-inflammatory in nature (101).

Multiple ways of evaluating the "healthiness" of diet have been proposed, and several of them have been shown to be associated with systemic inflammation. Two of these indexes will be used to describe potential differences in diet quality between various races: the Dietary Inflammatory Index and the Mediterranean diet score. These methods are investigator driven, in that the components of these methods are determined *a priori* by the investigator. The primary difference between the two is that the Mediterranean diet score was developed based on food consumption patterns of an exceptionally healthy population, while the Dietary Inflammatory Index was developed to specifically measure the inflammatory nature of diet based on nutrients that have been found to either increase or decrease systemic inflammation in the literature.

Dietary Inflammatory Index

The Dietary Inflammatory Index is a tool developed to provide scores indicating where an individual's diet falls on a continuum of maximally inflammatory to minimally inflammatory. Recently, the Dietary Inflammatory Index was updated with an improved scoring system that represented a diverse array of diets (22). The newer method is similar to the former method, but is improved in that data are collected from a larger collection of articles, is based on food

consumption data sets from around the world, and uses a percentile scoring system that helps to make the food/nutrient scores more comparable. With the creation of the index, forty-five food/nutrient parameters were identified as being influential on the inflammatory nature of diet. Food items that were found to be pro-inflammatory include: vitamin B12, carbohydrate, cholesterol, energy, total fat, iron, protein, saturated fat, and trans fat. Foods that were found to be anti-inflammatory include: vitamin B6, beta carotene, caffeine, eugenol, fiber, folic acid, vitamins A, D, C, and E, niacin, riboflavin, thiamin, magnesium, selenium, zinc, mono-unsaturated fatty acids, omega-3 fatty acids, omega-6 fatty acids, polyunsaturated fatty acids, flavan-3-ol, flavones, flavonols, flavonones, anthocyanidins, isoflavones, turmeric, green/black tea, pepper, alcohol, thyme/oregano, rosemary, garlic, ginger, onion, and saffron.

In calculating the Dietary Inflammatory Index, articles (through December 2010) were gleaned from journal review databases (Pubmed® and Ovid®), which provided evidence for foods/nutrients being either anti-inflammatory or pro-inflammatory. The inflammatory effects (pro [+1], anti [-1], or null [0]) of foods/nutrients were then calculated by summing the number of articles that showed an effect and multiplying this by the study design weight (10=experimental; 8=prospective cohort; 7=case-control; 6=cross-sectional; 5=animal experimental; 3=cell culture experimental). The weighted score for anti-, pro-, and null effects were then divided by the overall total weighted score to derive a fractional score for the three effect types. The anti-inflammatory fractional score was then subtracted from the pro-inflammatory fractional score to calculate the food/nutrient parameter-specific overall inflammatory effect score. To account for literature robustness, scores that were ≥236 (the median score) were assigned the full value of the score, but for those foods/nutrients that were <236, and adjustment was made. This adjusted for nutrients that had a small pool of literature,

but could have contributed to the overall inflammatory nature of diet. Nutrients with little research done could be more fairly compared to nutrients with many published studies devoted to their association with inflammation.

A database was then created by calculating the means and standard deviations for each of the 45 food/nutrient parameters for eleven countries around the world (United States, Australia, Bahrain, Denmark, India, Japan, New Zealand, Taiwan, South Korea, Mexico, and United Kingdom). A z-score and centered percentiles for each food parameter could be created for each individual by subtracting the 'standard mean' from the individual's reported amount of consumed food/nutrient, and dividing this value by its standard deviation. This value is then converted to a percentile score, doubled, and then had '1' subtracted from it, resulting in a symmetrical distribution with values centered on zero (null). Positive one is maximally pro-inflammatory and negative one is maximally anti-inflammatory. This method makes the scores more comparable (e.g. food/nutrient units in mg vs µg).

The final steps in calculating the Dietary Inflammatory Index score include: multiplying the percentile value for each food/nutrient parameter by its respective overall food/nutrient parameter-specific overall inflammatory effect score to derive a food-specific dietary inflammatory score, then summing the food-specific dietary inflammatory scores to derive an overall dietary inflammatory score. The score is then energy adjusted (per 1,000 calories) to account for differences in food intake. This index has been shown in multiple studies to predict several circulating inflammatory proteins, including CRP (22) and interleukin-6 (119). Previously published work has shown the Dietary Inflammatory Index to be associated with a higher prevalence of asthma, an inflammatory condition (119), higher risk of pancreatic cancer (120), and prostate cancer (121). The index also differs by work status in a sample of U.S.

workers, with night workers having a more inflammatory diet (122). Most recently, higher scores on this index (indicating a more inflammatory diet) have been shown to be associated with a higher incidence of colorectal cancer in the Women's Health Initiative and the Iowa Women's Health Study (123, 124). The few studies that have been done on the Dietary Inflammatory Index and CRC show that the effect of the Dietary Inflammatory Index are most associated with colon cancer and less with rectal cancer. Another recent study showed a correlation between dietary inflammatory index scores and IL-4 polymorphisms (rs2243250) (125). This study also showed an interactive effect from the Dietary Inflammatory Index scores on the association between the IL-4 polymorphism and colorectal cancer, suggesting that individuals with a more inflammatory diet and the IL-4 polymorphism have a higher risk of colorectal cancer than those with the polymorphism and consuming a less inflammatory diet.

This list of food items provides a comprehensive tool for evaluating the inflammatory nature of diet, however an abbreviated dietary index has been developed because not all food frequency questionnaires ascertain information for all of the 45 food/nutrient parameters. In this case, using twenty-five of the more common foods/nutrients associated with inflammation has also been shown to predict inflammation (119).

The Mediterranean Diet

"Mediterranean diet" refers to the general dietary patterns of those residing in Greece and southern Italy in the early 1960s. This type of diet has garnered considerable interest in recent years due to the exceptionally high life expectancy and notably low rates of coronary heart disease, cancer, and other diet-related chronic disease of those residing in the area (126). The diet can be described in general terms as one that is high in plant foods, including fruit, vegetables, breads, potatoes, beans, nuts, and seeds, uses olive oil as the primary source of fat, is

low in processed foods, is low to moderate in the amount of dairy products, fish, eggs, and poultry, is low in red meats, and with a low to moderate amount of wine (one to two glasses per day) (126).

Previous researchers have scored the Mediterranean nature of diets by assigning points based on the dietary intake of the study population. For example, points are assigned (1-5) to an individual based upon the quintile rank of food group (vegetables, fruits, lean meats, fish, nuts, and monounsaturated: saturated fat ratio, red and processed meats, sodium, dairy foods, grains and starches, and alcohol) that was consumed in relation to the sex-specific distribution of study population intake (127). Another set of researchers has used a scoring system based on median intake of key food groups in the study population (128). Participants who had intakes above the median for "healthy" foods (vegetables, legumes, fruits and nuts, cereal, fish, and a high monounsaturated: saturate fat ratio) received 1 point, while those below the median intake received a "0"; participants with food intakes below the median for "unhealthy" foods (meat, poultry, and dairy) received 1 point, while those above the median intake received a "0". Men who consumed between 10 and 50 grams of alcohol per day, and women who consumed between 5 and 25 grams of alcohol per day received 1 point; this results in a score between 0 (minimal adherence to the Mediterranean diet) and 9 (maximal adherence to the Mediterranean diet).

Numerous studies have demonstrated the benefits of a Mediterranean diet on reduced inflammation (129), longer telomere length (130), and longer survival (128). Compared to individuals that had a low Mediterranean diet score, individuals with a higher Mediterranean diet score were shown to have lower systemic inflammation when using several types of inflammatory markers, including white blood cell counts, CRP, fibrinogen, interleukin-6, and homocysteine (129). Similarly, in a randomized trial, people who were assigned to the

Mediterranean diet arm, compared to the control arm (given information about healthy food choices, in general), had greater weight loss and lower levels of several inflammatory proteins, including interleukin-6, interleukin-7, and interleukin-8, and CRP after 2 years follow-up (131). In another randomized trial, participants with high cardiovascular disease risk on a Mediterranean diet were about 30% less likely to experience a cardiovascular event (another type of condition that is related to inflammation), compared to individuals who only received information on a low-fat diet (132). While evidence exists of the positive health benefits of a Mediterranean diet, implementing this type of diet into populations of other cultures has not always resulted in the hoped-for benefits. In a randomized trial, patients who were assigned to the Mediterranean diet group did not have a significant decline in body mass index, nor did they have lower concentrations of CRP, fibrinogen, or homocysteine after follow-up, compared to those in the control arm (133). In this study where no benefit was seen, the participants were from a German population, whereas the studies that showed an improvement in inflammatory markers used people who were indigenous to Mediterranean countries (Italy and Greece).

Several studies have been conducted that examined the relationship between the Mediterranean diet, colorectal cancer and CRAs. One study found that the association between the intake of a more highly Mediterranean diet and colorectal cancer was insignificant, although there was a trend in women ($p=0.06$) (23). Conversely, two other studies found that intake of a more highly Mediterranean diet was associated with CRAs only in men (134). All of these studies used a Mediterranean diet score that was based on the study population intake, which may affect associations between diet and health outcomes. The first of the three studies used a group of health professionals, and even though dietary intake was broken down into quintiles,

even those in the lowest quintile may have been consuming quantities of foods that were adequate for protective benefits, thus explaining the null findings.

It is important to note that none of these studies compared diet scores between the different races, even though racial disparities in CRAs have been demonstrated. It would seem logical that to truly understand the etiology of racial disparities in CRA incidence and recurrence, one would need to investigate the differences in dietary intake in a condition that is so strongly associated with nutrition.

Similarities and Differences between the Dietary Inflammatory Index and the Mediterranean Diet

The Mediterranean Diet index was created because of the exceptional health of the people living around the Mediterranean Sea, particularly those residing in Greece and southern Italy. The index was not created with a specific health outcome in mind, but rather, it was to measure how similarly others eat to those residing in the Mediterranean region (126) Alternatively, the Dietary Inflammatory Index (DII) was specifically created to examine the inflammatory potential of diet, regardless of the cultural or geographical foods that are consumed (135). Another distinction between the two indexes is that the Mediterranean diet index measures the consumption of whole foods, whereas the DII is composed of food components (and spices) and individual nutrients. The Mediterranean diet does not distinguish between high- and low-quality, nutrient-dense fruits and vegetables, whereas, the DII is more dependent on individual nutrients and food components that can be found in multiple food groups. For example, beta-carotene is a nutrient that has been shown to modify the inflammatory process (112). The Mediterranean diet index does not distinguish between foods that are high or low in this nutrient, but the DII takes into account the intake of this nutrient.

One similarity between the two is that studies have shown both these indices to have anti-inflammatory properties. A diet with a high consumption of nutrient-dense fruits and vegetables, monounsaturated fats, and low in red meat, trans fats, and saturated fats would most likely receive high scores on both diet indices. Further, both have been found to be associated with systemic inflammation, where more favorable scores were associated with lower concentrations of inflammatory proteins and cytokines (22, 129). Indeed, one study found an association between higher Mediterranean diet scores and lower scores on the DII (136), suggesting some overlap in what the two indices measure.

However, even with the similarities between the two indices, there are differences in what they actually measure, and depending on the outcome, potential differences in the associations between each index and outcome could exist. It is possible that the association between colorectal adenoma occurrence and diet could be different, depending on the index used (either Mediterranean diet or DII). Because the DII was developed to characterize the inflammatory nature of diet, a stronger positive association between the DII and colorectal adenoma than the association between the Mediterranean diet and colorectal adenoma would suggest a reduction in adenoma occurrence due to inflammatory mechanisms rather than other mechanisms. An example of this type of effect was demonstrated in a clinical trial where people assigned to one of two Mediterranean diets (one supplemented with nuts and the other supplemented with olive oil) or a low-fat non-Mediterranean diet (136). The results showed that even after controlling for the effect of a Mediterranean diet, higher DII scores were associated with higher adiposity indices; obesity being an inflammatory condition. Alternatively, a stronger association between the Mediterranean diet and colorectal adenoma than the association between the DII and colorectal adenoma would suggest a mechanism other than inflammatory in nature,

perhaps due to the action of fiber in the colon (affecting the rate of gastrointestinal absorption, colonic flora, or sterol metabolism(137)) or strengthened cell membrane structure or regulation of genes involved in cell proliferation from beneficial fatty acids (138).

Differences in results between the two methods could be due to the differences in the foods that are measured. A person could conceivably receive a high (good) score on the Mediterranean diet because of eating a high quantity, but low-variety, of foods, thus consuming a narrow range of nutrients and food components; whereas, this same person would have only a moderate score on the DII because they are consuming only a few of the food components and nutrients that are anti-inflammatory. An example of this type of diet would include a high intake of low-nutrient fruits and vegetables, calories, and carbohydrates, and low intake of spices. Conversely, another person could consume a diet with lots of food components and nutrients that are anti-inflammatory and thus receive a low (good) score on the DII but receive only a moderate score on the Mediterranean diet. An example of this type of diet would include a high intake of spices, nutrient-rich fruits and vegetables, fiber from non-carbohydrate sources, and a low intake of calories.

By using foods rather than food components in an analysis, the inflammatory action of a food component may be obscured because it could be present in multiple food groups. For example, zinc is an anti-inflammatory component of the DII and it is present in a wide variety of food items, such as red meat, seafood, nuts, peas and beans, oatmeal, and cheese. In an analysis of health outcomes using food items, the anti-inflammatory contribution of zinc would be missed. Also, anti-inflammatory items such as ginger, turmeric, and saffron are very anti-inflammatory but amounts of these food items typically are eaten in relatively small amounts. These food items would not necessarily be measured with an index that relies on food groups

such as the Mediterranean diet index, but could have a materially important impact on health outcomes.

In summary, there is overlap between the two dietary indices in that they both measure a component of "healthiness", and better scores for both are associated with lower inflammatory concentrations (129, 139). However, the two indices differ in what they are specifically measuring. Differences in the association between each diet index and health outcome is possible. Associations between the DII and health outcome would suggest a mechanism that is inflammatory in nature, whereas associations between the Mediterranean diet and health outcome, with null findings between the DII and health outcome, would suggest a mechanism other than inflammatory in nature.

Data-Driven Dietary Analysis

Factor Analysis

Factor analysis is a statistical tool to reduce the number of variables in a set of data with possibly many correlated variables, which is a common occurrence in dietary analyses (140). Factor analysis uses the intercorrelations between dietary items to aggregate dietary variables to determine eating patterns among a groups of individuals (141). These factor scores can then be used in logistic regression to predict disease outcomes. Factor analysis has the advantage that the effect of multiple correlated nutrients can be examined at the same time (142). Additionally, because the effect of an individual nutrient may be inconsequential compared to the cumulative effects of multiple nutrients are examined, factor analysis has the advantage of being able to analyze these cumulative effects (142).

Classification and Regression Tree Analysis

In an alternative to the investigator-driven methods discussed previously, classification and regression tree analysis (also known as CART analysis or binary recursive partitioning) is a data-driven method that uses complex statistics to find meaningful patterns in the data that may not have been considered by the investigator (143). This method type is considered data-driven because patterns are examined *posteriori*. This is a relatively novel technique that helps to answer the question of, "What features of the diet are most strongly associated with a reduced risk of adenoma?" (144)

The basic idea for this method of analysis is that predictors are identified in the study population by splitting the group into two, multiple times, based upon the main predictors identified and the most meaningful cut-offs. A "parent node" is identified and a decision is made on what variable, and at what level, to split the parent node. The splitting then results in two child nodes, which can be further split. This process is repeated multiple times. This process is sometimes referred to as binary recursive partitioning – binary, because nodes are split into two; recursive, because this splitting can occur multiple times; and portioning, because the dataset is split into sections (145).

In addition to the novelty of this method, there are also several advantages of using CART analysis, compared to more traditional methods (e.g. logistic regression). One of the main advantages of using CART analysis is that complex interactions can be analyzed in one main analysis, using multiple comparisons that would otherwise be impractical or overly complicated using methods such as regression. A second advantage is that it is inherently non-parametric, which means that that are no assumptions about the underlying distribution of the variables (145). A third advantage is that CART analysis is able to use observations with missing

data points because it uses best available information (145). Another advantage of CART analysis is that it is both easy to use (i.e., relatively little input is required from the analyst), from the perspective of the analyst, and relatively simple to interpret, from the perspective of the clinician or policymaker (145).

There are also several limitations of this approach. The main disadvantage is that because it is so novel, there are relatively few people, including statisticians, who are familiar with this method (145). Also, little has been published about the full utility of this method.

There are four basic steps in CART analysis – tree building, stopping the building process, "pruning" the tree, and finding the optimal tree. Tree building is the recursive, or repeated, process of creating branches from split nodes. At each parent node split, the most predictive variable of the outcome is selected and the most predictive value for partitioning the group is determined. Once the parent node is split, the process is repeated again for each child node. These two child nodes are both split into two, using the next best predictor variable at the best possible cut-point. Optimal splitting is based on the impurity criterion, which is the reduction in the residual sum of squares because of a binary split of the data at that tree node (146). Maximal impurity function is 0.5, where $p_{i/j}$ is the probability that the dependent variable is equal to *i* in node *j*, where *i* can take values 0 or 1 (147). The impurity function is calculated by determining the Gini diversity index for the parent node ($\Sigma 1- p_{i/j}^2=2p_{1/j}(1-p_{1/j})$ and then for the two child nodes. Then, the weighted diversity index is calculated ($[(p_1)(\text{diversity index}_1)] + [(p_2)(\text{diversity index}_2)]$) where p_1 and p_2 refer to the proportions of the parent node that are included in the respective child nodes (147). Finally, the splitting criterion is based upon where the greatest difference is between the diversity index of the parent node and the weighted average of the diversity index of the two child nodes.

The process of node splitting (branching) is repeated until one of three things happen: there is only one observation in each of the child nodes; all observations within each child node have identical distribution of predictor variables; or after a number of iterations that was pre-specified by the programmer. Tree pruning cuts away branches (starting with the terminal nodes) in order to create a simpler tree. A balance between tree simplicity and accuracy needs to be maintained. Finally, optimal tree selection is one that fits the data, as well as other data sets, but is not so overly fit that the tree will not generalize to other datasets (145).

CART analysis has been used for various purposes. One study used CART analysis to determine post-surgical survival prognosis of colorectal cancer patients (148), and it has also been used to determine appropriate cut-offs for predicting high-risk and low-risk survival groups in patients with advanced colon and rectal cancer (149).

There have only been a few studies that have used the CART method to analyze dietary data. For example, one study analyzed nationally representative Irish food frequency data to determine what foods were most likely to predict overall dietary quality (150). Similarly, one study used CART analysis to determine demographic and socioeconomic characteristics that predicted who was most likely to consume at least four servings of fruits and vegetables per day (151). Another study used this type of analysis to identify variables most likely to predict esophageal and gastric cancers (152). Among those with esophageal squamous cell carcinoma and noncardia gastric adenocarcinoma, the intake of vegetables, citrus and other non-citrus fruits, and meats were notable predictors of these conditions. Finally, one team of researchers has used this methodological tool to determine main predictors of colorectal cancer. This group found that while non-steroidal anti-inflammatory drug (NSAID) use was the best predictor of colorectal cancer, a more "Western" diet was a secondary predictor of colorectal cancer among those taking

NSAIDs (153). This study was particularly useful for describing the dietary, lifestyle, and genetic interactions that occur in a multifactorial disease, like colorectal cancer.

Racial Differences in Dietary Intake

Numerous studies have shown that diet is influential in CRA development, but there are conflicting results as to which specific foods and nutrients influence the risk of CRA, and even less is known about differences in the association between food/nutrient intake and CRA incidence by race, in spite of previous research showing racial disparities in both food/nutrient intakes and CRA. These differences in food/nutrient intakes may contribute to differences in CRA incidence between different race/ethnicities.

Previous studies have examined racial differences in food and nutrient intake and the development of CRA. Some of these differences are among nutrients that have been shown to be associated with CRA. For instance, data from NHANES indicate that non-Hispanic blacks had total folate intakes lower than non-Hispanic whites and Mexican Americans (154). Further, non-Hispanic black women were more likely to not meet the recommendations for folate intake (23.2%) than non-Hispanic white and Mexican American women (13.0% and 12.6%, respectively). Men showed similar patterns.

National data also show that African Americans have calcium intakes that are less than that of non-African Americans (155). However, national data indicate that vitamin D intake from foods does not differ by race or ethnicity in American adults (156) .

Other studies suggest that there are differences in food intake between races/ethnicities. One such study found that among white individuals in North Carolina, having intakes of beta-carotene, vitamin C, and calcium in the highest quartiles was associated with a reduction of about 50% of developing colorectal cancer, as compared to the lowest quartile (157). Among

African American individuals, having intakes of beta-carotene, vitamin C, and vitamin E in the highest quartiles was associated with a 40-70% reduction in the development of colorectal cancer, compared to those with intakes in the lowest quartile. In another study, it was shown that among white individuals, mean daily intake of dark green or deep yellow vegetables and dairy foods was higher among controls than among cancer cases (158). However, among African American individuals, only mean daily vegetable intake was significantly different between cases and controls. Results from these previously reported studies suggest that there are differences in the association between colorectal cancer risk and nutrient/food intake between different ethnic/racial groups. However, no studies have been done looking at the dietary differences between racial subgroups and the risk of CRA. Also, these previous studies only examined blacks and whites, and did not include Hispanics or Asians because of low numbers of study participants, and the study population was limited in geographic region. Further investigation into the differences in dietary and nutrient intake may help further explain the disparities that occur in CRA, a very common condition.

Gaps in Knowledge

It is clear that diet plays an important role in CRA incidence and prevalence, but results from studies have been largely inconclusive in identifying the specific elements of diet that contribute to these associations (67, 68, 74, 76). Inflammation appears to be associated strongly with CRA prevalence (91), but it also related to diet (101, 102). Another unknown is whether or not an inflammatory diet is related to incident CRA. The Dietary Inflammatory Index is a useful tool to help quantify the inflammatory nature of diet (22), but because of its novelty, little research has been done on the utility of this index in predicting disease outcomes, specifically

colorectal adenoma. Further, the interactive effects of race in the association between CRA and inflammatory diet are largely unexplored.

There are potential racial disparities in CRA incidence that may be explained, at least partially, by differences in dietary intake. Previous research has shown dietary intake differences by race in certain foods and nutrients (154, 155, 157), but it is unknown whether or not there are differences in the overall quality of diets between black and white individuals. These proposed analysis aim to evaluate racial differences in dietary intake that could lead to potential disparities in the incidence of abnormal colorectal growths by using three different methods. Specifically, questions that are addressed throughout chapters 4-6 include:

1. Are there racial differences in the intake of a Mediterranean diet, and if so, could these explain disparities in colorectal adenoma prevalence, incidence, and recurrence?
2. Are there racial differences in the intake of an inflammatory diet, as measured by the DII, and if so, could these explain disparities in colorectal adenoma prevalence, incidence, and recurrence?
3. Are there differences in dietary patterns between racial subgroups, and are dietary factors associated with CRA in the different racial subgroups?

CHAPTER 3

METHODS

Data

Population

Data for these secondary analyses were collected as part of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. The primary purpose of the PLCO Screening Trial was to determine whether disease-specific mortality could be reduced by cancer screening, using the most promising screening methods available at the time. Secondary analyses have evaluated cancer stage, screening test operating characteristics, survival, costs, risks, etiology, and the natural history of cancers. Methods for this trial have been previously described (159-161). Study participants were recruited with mailed informational brochures and letters of invitation to age-eligible individuals identified on public, commercial, or screening center-specific mailing lists. Ten screening centers began enrolling and obtaining informed consent from men and women across the United States in 1993 and completed enrollment in 2001. Efforts were made to recruit a study population that had a similar racial profile to that of the United States. The PLCO Screening Trial was designed to randomly assign 148,000 men and women to either an intervention arm or a control arm and to span 23 years of time.

Men assigned to the treatment (screening) arm received a prostate specific antigen (PSA) test and digital rectal examination (DRE) to screen for prostate cancer, a postero-anterior chest x-ray (CXR; discontinued April 1999 for those who never smoked) to screen for lung cancer, and a flexible sigmoidoscopy (FS) to screen for colorectal cancer. Screening occurred at regular

intervals during the first 6 years of participation. Women assigned to the intervention (screening) arm received a CXR, FS, cancer antigen 125 (CA-125), modified CA-125, transvaginal ultrasound (TVU), and bimanual palpation of the ovaries (BPO; discontinued in April 1999) for the first 6 years of participation. Screening schedules are presented in Table 3.1. In total, 38,340 men and 39,105 women were assigned to the treatment (screening) arm. The 38,345 men and 38,111 women assigned to the control arm received their usual medical care. It was anticipated that participants would be followed for at least 13 years from randomization, (with completion in 2014) to be able to ascertain whether or not the screening resulted in reduced disease-specific mortality. Randomization was done using blocks of random permutations of varying lengths, stratified by screening center, gender, and age.

Screening centers include: University of Colorado Health Sciences Center (Hispanic recruitment), Lombardi Cancer Research Center of Georgetown University, Pacific Health Research Institute (Asian recruitment), Henry Ford Health System (black recruitment), University of Minnesota School of Public Health/Virginia L. Piper Cancer Institute, Washington University School of Medicine, University of Pittsburgh/Pittsburgh Cancer Institute/Magee-Women's Hospital, University of Utah School of Medicine, Marshfield (Wisconsin) Medical Research and Education Foundation, and the University of Alabama at Birmingham (black recruitment). All participants signed informed consent documents approved by both the National Cancer Institute and their local institutional review board.

Eligibility

Men and women ages 55-74 years were eligible for the primary study. The age minimum was originally 60 years but because of the high incidence rates of prostate cancer at age 60 (160), the age was lowered to 55 years in 1996. Participants were ineligible if they 1) were younger

than 55 years or older than 74 years of age; 2) were currently undergoing treatment for cancer (except basal cell and squamous cell skin cancer); 3) had a known prior diagnosis of prostate, lung, colon, rectal, or ovarian cancer; 4) previous removal of the entire prostate, one lung, or entire colon; 5) were participating in another cancer screening or cancer primary prevention trial at the time; 6) were taking Proscar; 7) had more than one PSA test in the prior 3 years; 8) had a colonoscopy, sigmoidoscopy, or barium enema in the three years prior to enrollment; or 9) were unable or unwilling to sign the consent form. Before October 1996, women with surgical removal of both ovaries were excluded, but after October 1996, these women were not excluded.

For these presently proposed analyses, only those enrolled in the screening arm were included due to more complete follow-up and adenoma ascertainment of these individuals. Participants were excluded if they developed any type of cancer (except for melanoma) between study entry and completion of the dietary questionnaire.

Several questionnaires were administered by the individual screening centers to the study participants. The baseline questionnaire asked about demographics, body build, history of selected medical conditions and treatments, cancer screening history, family history of cancer, tobacco use, and occupation. In a separate questionnaire, baseline diet history was asked about, but only to those in the screening arms. Five years into the trial (1998), the dietary history questionnaire (DHQ) was administered to all new study participants in the control arm at trial entry and to all existing study participants at the anniversary of their randomization. For those who were randomized to the screening arm after 1998, the DHQ was administered at the third year anniversary of their randomization. Details of the dietary history questionnaire are discussed later.

Introduced in 2006, the supplemental questionnaire was a follow-up to the original questionnaire, and contained questions regarding demographics, family history, BMI and physical activity, health history and medication, smoking, and gender-specific health information. An annual study update was also mailed to each study participant, asking about any diagnosis of cancer, the type of cancer diagnosed, date of diagnosis, hospital or clinic of diagnosis, physician contact information, and the ingestion of finasteride (Proscar or Propecia) for men.

Ascertainment of Adenomas

Detection of prevalent colorectal polyps in the distal colon was the primary outcome for this part of the analyses, which were restricted to those in the screening arm. Incident or recurrent adenoma were secondary outcomes for these analyses. Adenomas in the distal colon (from splenic flexure to the rectum) were detected during screening with a 60-cm flexible sigmoidoscopy. CRA in the proximal colon could not detected using this method, but polyps in the distal colon are of greater concern since they are more likely to develop into advanced neoplasia (162). Data on proximal polyps were collected on individuals who had an abnormal FS screen and had a follow-up examination. FS was shown in one small study to reach 48% of adenomas, compared to colonoscopy (163). This suggests that fewer polyps were detected but because everyone is screened similarly, this would result in non-differential misclassification and perhaps a loss in power to detect differences if they exist. A result was positive if there was any evidence of a mass or polyp; negative if there was not a mass or polyp detected; or inadequate if the scope was not able to reach at least 50 cm or if less than 90% of mucosal surface could be observed due to inadequate bowel preparation (35). Subjects with inadequate bowel preparation were allowed to return at a later date for a second procedure. Adenoma screening was performed

via flexible sigmoidoscopy at baseline and then again at year 3 or 5. Initially, follow-up FS was scheduled for year 3 but a change in protocol was implemented in 1998 that changed the follow-up interval to 5 years. Patients and their physicians received communication of their FS results afterwards. PLCO protocol did not preclude colonic biopsy or polypectomy during screening, but individuals with abnormal screenings were referred to their physician for follow-up care. Screening center consultants were available for doctors and study participants who had questions about results and diagnostic approach. Subjects were followed for at least 12 months after their screening to ascertain relevant information about diagnostic work-ups (including colonoscopy). Fecal occult blood tests were not used in the screening because previous clinical trials had already proven that they were an effective screening method (164), but participants were asked about a history of having had this test.

Adenomas were considered advanced if they were of villous or tubulovillous nature, large (≥1.0 cm), or exhibited high-grade dysplasia. *In situ* and borderline malignant carcinomas were also considered advanced adenomas. Incident adenomas were adenomas that were detected at follow-up, after having a negative baseline screening. Recurrent adenomas were adenomas that occurred during follow-up, after having a positive baseline screening with polyp removal. Table 3.2 lists the number of abnormal findings on the initial FS that were reported in the PLCO trial, by racial subgroups.

Dietary Data

Dietary questionnaire

Nutritional data were collected by using a food frequency questionnaire, the Diet History Questionnaire (DQX), developed by the National Cancer Institute (165). The DQX is a 16-page questionnaire that asked about the frequencies, portion sizes, and in some cases, the seasonal

intake or food type, for 137 different foods. The questionnaire asked about diet during the year prior to enrollment. Additionally, there are six questions that asked about the use of low-fat foods, four summary questions, and ten dietary supplement questions. This method has been shown to perform at least as well as the Block and Willett food frequency questionnaires, which are validated and reliable measures of dietary intake used in research (165). Responses were used to estimate daily individual nutrients intake, based on the Continuing Survey of Food Intakes by Individuals (CSFII) data (165). The CSFII created 182 food groups from 5,261 individual food codes. Food usage and nutrient content of the individual foods were similar within food groups. The list of food groups to include in the food/nutrient database was narrowed by excluding those that contributed little to the nutrient intake in the United States, often because of infrequent consumption (165).

These calculated responses were then used to score the overall quality of the diet, based on several dietary indexes/methods. These methods include the Dietary Inflammatory Index and the Mediterranean diet. For the third specific aim (factor analysis), the responses were kept in the original form (grams of food or nutrient consumed).

Dietary Inflammatory Index

The Dietary Inflammatory Index is a tool to score the inflammatory nature of an overall diet (135). Recently, the Dietary Inflammatory Index was updated with an improved scoring system that better represented a diverse range of diets (22). The updated index was created in an effort to create a more universal index that could be used in a broad spectrum of cultures and to make food items more comparable within the index. Forty-five food/nutrient parameters were identified as being influential on the inflammatory nature of diet. Food items that were found to be pro-inflammatory included: vitamin B12, carbohydrate, cholesterol, energy, total fat, iron,

protein, saturated fat, and trans fat. Foods that were found to be anti-inflammatory included: vitamin B6, beta carotene, caffeine, eugenol, fiber, folic acid, vitamins A, D, C, and E, niacin, riboflavin, thiamin, magnesium, selenium, zinc, mono-unsaturated fatty acids, omega-3 fatty acids, omega-6 fatty acids, polyunsaturated fatty acids, flavan-3-ol, flavones, flavonols, flavonones, anthocyanidins, isoflavones, turmeric, green/black tea, pepper, alcohol, thyme/oregano, rosemary, garlic, ginger, onion, and saffron.

In calculating the Dietary Inflammatory Index, articles through December 2010 were gleaned from journal review databases (Pubmed® and Ovid®), which provided evidence for foods or nutrients that were either shown to be anti-inflammatory or pro-inflammatory. The inflammatory effects (pro [+1], anti [-1], or null [0]) of foods/nutrients were then calculated by summing the number of articles that showed an effect and multiplying this by the study design weight (10=experimental; 8=prospective cohort; 7=case-control; 6=cross-sectional; 5=animal experimental; 3=cell culture experimental). The weighted score for anti-, pro-, and null effects were then divided by the overall total weighted score to derive a fractional score for the three effect types. The anti-inflammatory fractional score was then subtracted from the pro-inflammatory fractional score to calculate the food/nutrient parameter-specific overall inflammatory effect score (overall inflammatory effect score). To account for literature robustness, scores that were ≥236 (the median score) were assigned the full value of the score, but for those foods/nutrients that were <236, an adjustment was made by dividing the number of weighted articles by 236 and multiplying by the food parameter-specific raw inflammatory effect score (Table 3.3).

A database was previously created, which calculated the means and standard deviations for each of the 45 food/nutrient parameters for eleven countries around the world (United States,

Australia, Bahrain, Denmark, India, Japan, New Zealand, Taiwan, South Korea, Mexico, and United Kingdom; Table 3.3). A z-score and centered percentiles for each food parameter was then created for each individual in the PLCO by subtracting the 'standard mean' from the individual's reported amount of consumed food/nutrient, and dividing this value by its standard deviation. This value was then converted to a percentile score, doubled, and then had '1' subtracted from it, resulting in a symmetrical distribution with values centered on zero (null), and making the scores more comparable (e.g. food/nutrient units in mg vs µg). Positive one is maximally pro-inflammatory and negative one is maximally anti-inflammatory.

The final steps in calculating the Dietary Inflammatory Index score included: multiplying the percentile value for each food/nutrient parameter by its respective 'overall food parameter-specific inflammatory effect score' to derive a 'food-specific dietary inflammatory score', then summing all the 'food-specific dietary inflammatory score's' to derive an overall dietary inflammatory score. This index has been shown in multiple studies, to predict several circulating inflammatory proteins, including CRP (22) and interleukin-6 (119). Previously published work has shown that the Dietary Inflammatory Index is associated with a higher prevalence of asthma, an inflammatory condition (119) and that US night-shift workers having a more inflammatory diet (122).

This list of food items provides a comprehensive tool for evaluating the inflammatory nature of diet, but not all food frequency questionnaires ascertain information for all of these food/nutrient parameters. In this case, using twenty-five common foods/nutrients has also been shown to predict inflammation (119). The shortened list of inflammatory food components/nutrients include: vitamins A, B1, B2, B6, B12, C, and E, niacin, iron, magnesium, zinc, selenium, folic acid, beta-carotene, and caffeine, total calories, carbohydrates, proteins, fats,

alcohol, fiber, cholesterol, fats (saturated, mono-unsaturated, and poly-unsaturated), and omega-3 and omega-6 fatty acids (119).

For the present analyses, a z-score and centered percentiles for each food parameter were calculated for each individual in the PLCO by subtracting the 'standard global mean' from the individual's reported amount of consumed food/nutrient, and dividing this value by its standard deviation (reference values and global means and standard deviation (SD) were calculated previously and are presented in Table 3.3). This value was then converted to a percentile score, doubled, and had '1' subtracted from it, resulting in a more symmetrical distribution with values centered on zero (null).

The final steps in calculating the Dietary Inflammatory Index score were to multiply the percentile value for each food/nutrient parameter by its respective 'overall food/nutrient parameter-specific inflammatory effect score' to derive a 'food-specific dietary inflammatory score', and then summing all of the 'food-specific dietary inflammatory scores' to derive an overall dietary inflammatory score. The score was then energy adjusted (per 1,000 calories) to account for differences in food intake. Higher scores indicate a more inflammatory diet, whereas, negative scores indicate an anti-inflammatory diet. For regression analyses, the Dietary Inflammatory Index scores were categorized into quartiles, based upon the values in the PLCO cohort.

Mediterranean diet

The Mediterranean diet score is based upon the original index proposed by Trichopoulou and colleagues (128), but for these analyses a modified version proposed by Fung and colleagues (23) was used. Categories for the original index included, vegetables, legumes, fruit and nuts, dairy, cereals, meat and meat products, fish, alcohol, and the ratio of monounsaturated to

saturated fat. The modified version excludes potatoes from the total vegetable group; splits the fruit and nut group into two separate groups; eliminates the dairy group; includes only whole grains in the cereal group; including only red and processed meats for the meat group; and restricts the alcohol group to intakes of between 5 and 15 g/day.

Table 3.4 lists the food groups, foods included in each food group, and the criteria for assigning points to each group. For "healthy" foods a point was given if the intake of a particular food item was above the sex-specific median intake (vegetables, legumes, fruits, nuts, whole grains, fish, high ratio of monounsaturated to saturated fat, ethanol between 5-25 g/day). For "unhealthy" foods, a point was given if the intake of a particular food item was below the sex-specific median intake (red and processed meats).

Covariate Data

Several variables were evaluated as confounders in specific aims 1 and 2 (Table 3.5), including smoking, age, gender, race, physical activity, and non-steroidal anti-inflammatory use, as indicated by manual model selection procedures, which will be discussed in the statistical methods section. Obesity was defined by a high body mass index (BMI; >30), which is a measurement of relative weight, as compared to height. BMI can be calculated by either dividing the mass (kg) by height (m^2), or by dividing mass (lb.) by height (in^2) and then multiplying by 703. Height and weight were self-reported at baseline and follow-up.

Numerous studies have shown that these variables are associated with diet, but especially CRA development. For instance, many studies have shown that smoking is associated with the development of CRA (166), especially smaller polyps. Another study found that a high BMI and low physical activity are associated with the development of CRA. Anti-inflammatory drugs, including aspirin, have been shown to be associated with a lower incidence of CRA (95).

Alcohol has been shown to significantly increase the incidence of developing CRA (10). Higher fiber intake, which has been shown to have a protective effect on colorectal cancer, was shown to be associated with a lower risk of CRAs in a group of men and women (75). Fiber from grains, cereals, and fruits had the strongest effect. However, other studies have not found fiber to be protective.

Data Justification

The PLCO Cancer Screening Trial is a large, national longitudinal cohort, assembled with the specific purpose of evaluating the impact of screening on cancer morbidity and mortality. The sample size (almost 155,000 subjects) is large enough to collect counts for even relatively rare outcomes, such as CRA and cancer, and study subjects are followed for a relatively long period of time (for at least 13 years), thus allowing for adequate time for adenoma development after baseline and initial enrollment. A great effort was made to recruit subjects from a diverse racial background, including two centers that had special recruitment efforts for blacks and Hispanics (167). Multiple questionnaires were administered to each study participant to collect a broad range of information, not only at baseline, but at different time points throughout the study, including a validated dietary questionnaire (165), which asks about the intake of 137 foods. From these reported intakes, the intake of several dozen nutrients and food components were estimated for each individual. The lengthy follow-up of a large, but diverse, cohort, coupled with an impressive array of nutritional data makes this an ideal data set to use for this analysis.

Data Analysis

Specific Aim 1

To determine whether or not there are racial differences in the consumption of the Mediterranean diet, assessed using a validated dietary index, in a group of men and women between the ages of 55 and 74 enrolled in the screening arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial. To determine whether or not a lower score on the Mediterranean diet at baseline is associated with the prevalence of colorectal adenomatous polyps, and whether or not this association is modified by race.

Means (standard deviations) and frequencies were calculated for continuous and categorical descriptive and demographic characteristics, stratified by race/ethnicity. Chi-square and t-tests were used to determine differences, if any, in descriptive characteristics and Mediterranean diet scores between those who develop CRA during follow-up and those who do not. Alternatively, chi-square and t-tests were used to determine differences, if any, in descriptive characteristics and Mediterranean diet scores between the various racial subgroups. For continuous variables not normally distributed, Wilcoxon-rank sum tests were used. Normal distribution was assessed with histograms (QQ plot or Shaprio-Wilk test) for each variable.

Mediterranean diet scores were categorized into low (<3), medium (3-5), and high (>5), based on previous work [169]. Multivariable logistic regression models were used to calculate the prevalence odds of CRA for different categories of Mediterranean diet scores, using baseline data. Logistic regression models (Equation 2) were used to derive odds ratios and 95% confidence intervals for the association between the prevalence of CRA and the Mediterranean diet score categories, stratified by race and ethnicity (white, black, Asian, and other). Other models examined the association between the Mediterranean diet and either incident or recurrent

adenoma as the outcome of interest. This method was used to quantify the race-specific risk of CRA for different categories of the Mediterranean diet, when adjusting for potential confounders.

Regression models were adjusted for smoking, age, physical activity, body mass index, hormone status (females), education, and non-steroidal anti-inflammatory use, and folate intake as indicated by model selection procedures. All potential covariates were included in the initial model and then variables were removed one at a time using the backward selection method. The AIC statistic for each potential model was compared. The most parsimonious model that retained predictive accuracy, as indicated by a lower AIC value, was the model selected.

Equation 1, for each race: $OR_{\text{colorectal adenomatous polyps (prevalent, incident, or recurrent)}} = h0(t) * \exp$ [β1 Mediterranean diet score + β2 age + β3 gender + β4 physical activity + β5 anti-inflammatory use + β6 education + β7 body mass index+ β8 dietary variables].

Specific Aim 2

To determine whether or not there are racial differences in the consumption of inflammatory diets, as measured by a validated Dietary Inflammatory Index, in a group of men and women, between the ages of 55 and 74 enrolled in the screening arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial. To determine whether or not an inflammatory diet at baseline is associated with the prevalence of colorectal adenomatous polyps, and whether or not this association is modified by race.

Means and standard deviations for normally distributed continuous variables, medians and ranges for not-normally distributed variables, and frequencies for categorical variables were calculated for descriptive and demographic characteristics, stratified by race. Differences in means, medians, and frequencies between cases and controls, by race, were calculated. Chi-

square and t-tests were used to determine differences, if any, in descriptive characteristics and Dietary Inflammatory Index scores between the cases and controls. Chi-square and t-tests were also used to determine differences, if any, in descriptive characteristics and Dietary Inflammatory Index scores between the different racial subgroups. For continuous variables not normally distributed, Wilcoxon-rank sum tests were used to determine differences between cases and controls. Normal distribution was assessed with histograms (QQ plot or Shapiro-Wilk test) for each variable.

Dietary Inflammatory Index scores were stratified into quartiles. Univariate and multivariable logistic regression was used to calculate the unadjusted and adjusted odds of CRA prevalence for different quartiles of Dietary Inflammatory Index scores, using baseline data. Logistic regression models were also used to derive odds ratios and 95% confidence intervals for the association between both the prevalence of colorectal adenomatous polyps and the Dietary Inflammation Index score quartiles, stratified by race/ethnicity (white, black, Asian, and other). Logistic regression models were used to derive the odds of both incident and recurrent adenoma (in separate models) by Dietary Inflammatory Index quartiles. This method was used to quantify the race-specific odds of colorectal adenomatous polyps from an inflammatory diet, when adjusting for potential confounders.

Regression models were adjusted for smoking, age, physical activity, income, body mass index, education, calcium, alcohol, fiber, hormone status (females), and non-steroidal anti-inflammatory use, as indicated by model selection procedures. All potential covariates were included in the initial model and then variables were removed one at a time using backward selection method. The Akaike information criterion (AIC) statistic for each potential model was compared to identify the most parsimonious model that retained predictive accuracy (168). The

model with better fit, as indicated by a lower AIC value was the model selected. The AIC is advantageous over traditional likelihood function in that it takes model complexity into account and penalizes overparameterization (169), thus keeping a balance between model parsimony and added information. AIC values are relative and it is the difference between AIC values and not the actual AIC value that determines the model with highest predictive accuracy. The AIC assumes that the sample size is large enough to ensure the likelihood function will approximate its asymptotic properties and that the distribution of parameter estimates follow a multivariate normal distribution (170). AIC values are calculated as such: $N \ln (SS_{error}/N) + 2k$; where N = the number of observations and k = number of parameters + 1.

Equation 2, for each race: $OR_{\text{colorectal adenomatous polyps (prevalent, incident, or recurrent)}} = h_0(t) * \exp$ [β_1 Dietary Inflammatory Index score + β_2 age + β_3 gender + β_4 physical activity + β_5 anti-inflammatory use + β_6 education + β_7 body mass index + β_8 calcium supplements]

Specific Aim 3

To identify food intake patterns in the different racial subgroups through factor analysis, and to determine whether or not the identified patterns are predictors of colorectal adenoma in a group of men and women between the ages of 55 and 74 enrolled in the screening arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial.

Several methods were used to determine the dietary predictors of CRA for racial subgroups. Logistic regression was the primary method of determining the dietary predictors of CRA prevalence. One option was to create a fully saturated model with all of the potential independent dietary predictors and potential interaction terms, adjusted for other important covariates (age, gender, education, anti-inflammatory use, and body mass index). However, this would have resulted in an inordinate number of variables, so to minimize the number of variables

and create a more parsimonious model, principal factor analysis was used. Table 3.6 lists the dietary variables that was included in the factor analysis and are based off of lists used by other studies (171). Food quantities were not energy adjusted during the principal factor analysis. Rather, energy adjustment occurred during the logistic regression analysis. Previous studies have shown no notable difference in results between using either energy-adjusted variables in factor analysis or unadjusted variables in factor analysis but energy-adjusting during regression analysis (172).

For factor analysis, PROC FACTOR in SAS with option METHOD = PRINCIPAL was used. The ROTATE = VARIMAX function was used for the rotation of the factors by an orthogonal transformation, which helps in the interpretability of the factors. The determination of what factors that were retained from each food classification method was determined by inspection of the scree plots. The point where the rate of change in the magnitude of the eigenvalues for the factors begins to level off was used determine the number of factors included in the analysis. Individual factor scores from the identified factors were categorized into quintiles and then used in subsequent logistic regression to analyze the association between dietary factors and colorectal adenoma. Food components that were not included in any of the identified factors, but have been shown to be associated with the prevalence of CRA in previous studies, as well as other potentially confounding variables, were also included in the logistic model.

For the logistic regression, all potential covariates were included in the initial model and then variables were removed one at a time using the backward selection method. The AIC statistic for each potential model were compared. The most parsimonious model that retained predictive accuracy, as indicated by a lower AIC value, was the model selected. Interaction terms

(gender*dietary factor(s) identified in factor analysis) were entered into the model to asses interaction.

Secondarily, CART analysis was used to determine what foods are associated with colorectal adenoma prevalence, and at what levels of intake are most protective. CART analysis is advantageous over more traditional statistical methods, such as logistic regression, because it allows for the examination of complex interactions between variables, and does not make any assumptions about the distribution of the data. In addition to identifying specific predictors, CART analysis is also useful in determining the most appropriate cut-off for these predictors.

There are four basic steps in CART analysis – tree building, stopping the building process, "pruning" the tree, and finding the optimal tree. The tree building process was used to predict the incidence of CRA. The factors identified previously were used for this analysis, but also included variables included in Table 3.7. Binary recursive portioning was used to split the entire population (at a parent node) into two daughter nodes, based upon the predictor variable that best stratifies the population into two - those with CRA and those without. This process was repeated until a pre-specified branching point was reached or there were no other predictor variables identified. The splitting, based on homogeneity, occurs at a point that makes the data more "pure", or where there is the least "noise". Optimal splitting is often based on the impurity criterion, which is the reduction in the Gini Index because of a binary split of the data at that tree node (146). For these analyses, the LogWorth value was used (173). For each possible split, a likelihood ratio chi-square statistic for a test of independence is calculated. A LogWorth value is then calculated for each of these Chi-square values (X^2). The LogWorth statistic is the negative log of adjusted p-values for the Chi-square statistic. Finally, the splitting criterion for the variable is based on the cutoff that maximizes the LogWorth value. This gives rise to the term

purity criterion. Missing values were dealt with by imputation, based upon non-missing data. Once the tree was constructed, it was "manually" pruned to minimize the number of branches without significantly affecting goodness-of-fit. An important distinction between the logistic regression method and CART analysis is that CART analysis is easier to interpret and is non-parametric.

All data analysis was performed using SAS v. 9.3 (SAS Institute), with the exception of the CART analysis, which was performed using JMP 9.0.2 (SAS Institute). Where applicable, an alpha of 0.05 and power of 80% were used, unless otherwise indicated.

Strengths and Limitations

One of the major strengths of these analyses is the prospective collection of data that measures the exposure before the outcome occurs. This helps to establish temporality and reduce recall bias of the main exposure. There is still a risk that respondents may not fully remember their diet from the previous year, but the dietary recall used in these data has been shown to perform at least as well, and sometimes better, than other well-accepted food frequency questionnaires (165). Further, any potential misclassification due to dietary assessment is likely be non-differential since the exposure occurred before the outcome. Another strength is that the PLCO cohort is a very large national study that includes a diverse racial make-up. Because of stratification, the number of individuals in each group become small, thus minimizing power to adequately detect differences, but the numbers for black race are second in size to white race. This was the comparison of interest when considering the disparities between these two races.

Other strengths of these analyses are the novel methods used to characterized exposure and identify predictors. The Dietary Inflammatory Index is a validated, research-based method of characterizing the inflammatory nature of diet, while the CART analysis allows for analysis of

complex interaction between dietary and non-dietary factors to identify specific predictive factors of colorectal adenomas.

One limitation is that FS only reaches 60 cm into the colon. While it is likely that CRAs were missed, because all participants in the PLCO cohort were exposed to the same screening methods, this would likely have resulted in non-differential misclassification of adenoma status. Also, because distal CRAs are more likely to develop into advanced neoplasia, this method is considered adequate for detecting colorectal adenomas and cancers. (162).

Table 3.1: Screening design for treatment arm of the Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial

	Cancer Type	**Tests and screening**
Men	Prostate	PSA: annual T0-T5
		DRE: annual T0-T3
	Lung	CXR: annual T0-T3
	Colorectal	FS: T0 plus T3 or T5
Women	Ovarian	CA-125: annual T0-T5
		TVU: annual T0-T3
		OVR: annual T0-T3
	Lung	CXR: annual T0-T3
	Colorectal	FS: T0 plus T3 or T5

T0 = the initial baseline screening examination; T3, T5 = the third and fifth annual screening re-examinations; PSA = prostate-specific antigen (Hybritech Tandem R); FS = digital rectal examination; CXR = posteroantero chest X-ray (T3 exam discontinued April 1999 for all who "never smoked"); FS = 60-cm flexible sigmoidoscopy (changed from T3 to T5 in April 1999); CA125 = cancer antigen 125 modified (Centocor CA125 II); TVU = transvaginal ultrasound; BPO = palpation of the ovaries (discontinued in April 1999).

Table 3.2: Number of total participants and number of people with abnormal findings on the initial flexible sigmoidoscopy (FS) screening for each racial subgroups in Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial participants

White	**Black**	**Hispanic**	**Asian**	**Pacific Islander or American Indian**
Total number of participants				
66,874	3,883	1,421	2793	605
Total number of abnormal findings on initial FS screen				
13,743	767	Not indicated	Not indicated	Not indicated

Table 3.3: Values used in determining Dietary Inflammatory Index Score[1]

Food parameter	Weighted number of articles	Raw inflammatory effect score[2]	Overall inflammatory effect score[3]	Global daily mean intake (units/d)	SD[4]
Alcohol (g)	417	-0.278	-0.278	13.98	3.72
Vitamin B12 (mg)	122	0.205	0.106	5.15	2.70
Vitamin B6 (mg)	227	-0.379	-0.365	1.47	0.74
b-Carotene (mg)	401	-0.584	-0.584	3718	1720
Caffeine (g)	209	-0.124	-0.110	8.05	6.67
Carbohydrate (g)	211	0.109	0.097	272.2	40.0
Cholesterol (mg)	75	0.347	0.110	279.4	51.2
Energy (kcal)	245	0.180	0.180	2056	338
Eugenol (mg)	38	-0.868	-0.140	0.01	0.08
Total fat (g)	443	0.298	0.298	71.4	19.4
Fiber (g)	261	-0.663	-0.663	18.8	4.9
Folic acid (mg)	217	-0.207	-0.190	273.0	70.7
Garlic (g)	277	-0.412	-0.412	4.35	2.90
Ginger (g)	182	-0.588	-0.453	59.0	63.2
Fe (mg)	619	0.032	0.032	13.35	3.71
Mg (mg)	351	-0.484	-0.484	310.1	139.4
MUFA (g)	106	-0.019	-0.009	27.0	6.1
Niacin (mg)	58	-1.000	-0.426	25.90	11.77
n-3 Fatty acids (g)	2588	-0.436	-0.436	1.06	1.06
Onion (g)	145	-0.4910	-0.301	35.9	18.4
Protein (g)	102	0.049	0.021	79.4	13.9
PUFA (g)	4002	-0.337	-0.337	13.88	3.76
Riboflavin (mg)	22	-0.727	-0.068	1.70	0.79
Saffron (g)	33	-1.000	-0.140	0.37	1.78
Saturated fat (g)	205	0.429	0.373	28.6	8.0
Selenium (mg)	372	-0.191	-0.191	67.0	25.1
Thiamin (mg)	65	-0.354	-0.098	1.70	0.66
Trans fat (g)	125	0.432	0.229	3.15	3.75
Turmeric (mg)	814	-0.785	-0.785	533.6	754.3
Vitamin A (RE[5])	663	-0.401	-0.401	983.9	518.6
Vitamin C (mg)	733	-0.424	-0.424	118.2	43.46
Vitamin D (mg)	996	-0.446	-0.446	6.26	2.21
Vitamin E (mg)	1495	-0.419	-0.419	8.73	1.49
Zn (mg)	1036	-0.313	-0.419	8.73	1.49
Green/black tea (g)	735	-0.536	-0.536	1.69	1.53
Flavan-3-ol (mg)	521	-0.415	-0.415	95.8	85.9
Flavones (mg)	318	-0.616	-0.616	1.55	0.07
Flavonols (mg)	887	-0.467	-0.467	17.70	6.79
Flavonones (mg)	65	-0.908	-0.250	11.70	3.82
Anthocyanidins (mg)	69	-0.449	-0.131	18.05	21.14
Isoflavones (mg)	484	-0.593	-0.593	1.20	0.20
Pepper (g)	78	-0.397	-0.131	10.00	7.07

Food parameter	Weighted number of articles	Raw inflammatory effect score[2]	Overall inflammatory effect score[3]	Global daily mean intake (units/d)	SD[4]
Thyme/oregano (mg)	24	-1.000	-0.102	0.33	0.99
Rosemary (mg)	9	-0.333	-0.013	1.00	15.00

1. Shivappa et al., 2014
2. This is referred to as the 'food parameter-specific raw inflammatory effect score' in the text and is abbreviated here for ease of presentation. Note that the effect is per unit amount noted for each food parameter.
3. This refers to the 'food parameter-specific overall inflammatory effect score' accounting for the robustness of the literature, which is considered optimal at the median of 236 articles, and is computed as described in the text.
4. From the world composite database, as described in the text.
5. RE, retinol equivalents.

Table 3.4: Foods and point values for food groups included in the alternate Mediterranean Diet Score (aMED; Total score range: 0-9)

Food group	**Foods in each food group**	**Criteria for assigning points[1]**	**Sex-specific median intake for each food group**
Vegetables	All vegetables except white/red potatoes	Greater than the median intake (grams/day)	Male: 250.5 Female: 250.7
Legumes	Tofu, string beans, peas, beans	Greater than the median intake (grams/day)	Male:35.0 Female: 28.6
Fruit	All fruit and fruit juices	Greater than the median intake (grams/day)	Male: 350.7 Female: 367.0
Nuts	Nuts, peanut butter	Greater than the median intake (grams/day)	Male: 2.6 Female: 1.2
Whole grains	Whole-grain ready-to-eat cereals, cooked cereals, crackers, dark breads, brown rice, wheat germ, bran, popcorn	Greater than the median intake (grams/day)	Male: 43.0 Female: 44.6
Red and processed meats	Hot dogs, deli meat, bacon, hamburger, beef	Less than the median intake (servings/day)	Male: 50.0 Female: 22.0
Fish	Fish and shrimp	Greater than the median intake (grams/day)	Male: 13.3 Female: 12.7
Ratio of monounsaturated to saturated fat		Greater than the median intake (grams/day)	Male: 1.1 Female: 1.1
Ethanol	Wine, beer, liquor	5-25 g/day for males 5-15 g/day for females	

1. Median intake is based upon population intake for the screening arm population of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. For scoring, for "healthy" items 1 point was given for above the median and 0 point for below the median, and for "unhealthy" items 1 point was given for below the median and 0 point for above the median.

Table 3.5: Covariates and confounders and how they will be operationalized

Covariate/Confounder	**Operationalized**	**Categories (if applicable)**
Smoking	Categorical	Never smokers Current smokers Former smokers (haven't smoked for at least 6 months)
Age (years)	Continuous	
Race	Categorical	White, non-Hispanic Black, non-Hispanic Asian Other
Body mass index (BMI)	Categorical	Underweight (<18.5) Normal (18.5-24.9) Overweight (25-30.0) Obese (>30)
Physical activity	Dichotomous	2 or more hours of vigorous activities per week vs. less than 2 hours of vigorous activities per week
Non-steroidal anti-inflammatory use (aspirin/aspirin containing or ibuprofen/ibuprofen-containing products)	Dichotomous	3-4 per week vs. less than 3 per week
Education	Categorical	<12 years High school diploma Some college or post high school training other than college College degree Graduate degree
Hormone replacement therapy	Categorical	Current, former, or never using hormone replacement therapy, or unknown
Calcium	Continuous	Total calcium from diet and supplements (mg/day)
Alcohol	Continuous	Total alcohol intake(g/day)
Fiber	Continuous	Total fiber from diet and supplements (g/day)
Total energy intake	Continuous	kcal/day

Table 3.6: Description of food groups used in a factor analysis, in addition to the food items for each food group

Food group	Description[1]
Fruit	Apples, applesauce, apricot, banana, cantaloupe, grapefruit, grapes, oranges, peaches, pear, pineapple, plum, prune, raisin, strawberry, watermelon
Tomatoes	Tomatoes (cooked or raw), tomato juice, tomato sauce
Cruciferous vegetables	Broccoli, cabbage, cauliflower, Brussel sprouts,
Deep yellow/orange vegetables	Carrots, winter squash, sweet potatoes
Dark green vegetables	Leafy greens (spinach, lettuce), green beans
Potatoes	White potatoes
'Other' vegetables	Beets, celery, corn, cucumber, green pepper, iceberg lettuce, onion, summer squash, vegetable medley, vegetable soup
Dry beans and peas (legumes)	Dry beans, peas, tofu
Nuts and nut butter	Peanuts, peanut butter
Whole grain bread, rice and pasta	Dark, whole-grain breads or rolls, bran muffins, brown rice, oatmeal, high-fiber cold cereal
Refined grain bread, rice, and pasta	White bread and rolls, white rice, flour or corn tortillas, other hot cereal, noodles or pasta, refined-grain cold cereal
Eggs	Eggs
Lean fish	Fish, shellfish, tuna
Lean poultry	Roasted, broiled, baked, or ground chicken
High-nitrate or processed meats	Hot dogs, lunch meat, ham, bacon, sausage
Red meats	Hamburger, cheeseburger, meatloaf, beef, pork, or lamb steaks, roasts, barbeque or ribs
Added fats	Margarine, butter, or salad dressing

Pasta dishes	Lasagna, pizza, macaroni and cheese
Salty snacks	Potato, corn, or tortilla chips, crackers, pretzels, popcorn
Desserts	Pies doughnuts, cookies, cakes, pastries, brownies
Ice cream	Regular ice cream
Frozen yogurt	Plain yogurt (unflavored), flavored yogurt
Cottage and ricotta cheese	Cottage or ricotta cheese
Regular dairy	Whole milk, cheese
Low-fat dairy	Skim, 1%, and 2% milk; yogurt
Candy	Chocolates, candy
Tea	Black or green tea, hot or iced
Alcohol	Wine, liquor, beer

1. g/day

Table 3.7: Description of predictor variables used in Classification and regression tree analysis

Variable name	**Variable type**	**Description**
Mediterranean diet	Continuous	Overall score
Factor 1 scores: "Fruits and vegetables"	Continuous	
Factor 2 scores: "Western"	Continuous	
Factor 3 scores: "Sweet and salty"	Continuous	
Dietary fiber	Continuous	Total dietary fiber from diet (g/day)
Energy intake	Continuous	Food energy from diet (kcal/day)
Calcium	Continuous	Total calcium from diet and supplements (mg/day)
Total fat intake	Continuous	Total fat form diet (g/day)
Total protein intake	Continuous	Total protein from diet (g/day)
Alcohol	Continuous	Total alcohol from diet (g/day)
Physical activity	Dichotomous	2 or more hours of vigorous activities per week vs. less than 2 hours of vigorous activities per week
Hormone replacement therapy	Categorical	Current, former, or never using hormone replacement therapy, or unknown
Smoking	Categorical	Never smokers Current smokers Former smokers (haven't smoked for at least 6 months)
Age	Continuous	Age (years)
Body mass index (BMI)	Continuous	BMI at baseline (kg/m^2)
Non-steroidal anti-inflammatory use (aspirin/aspirin containing or ibuprofen/ibuprofen-containing products)	Dichotomous	3-4 per week vs. less than 3 per week
Education	Categorical	High school or less Some college or college graduate Postgraduate
Sex	Categorical	Male vs. female

CHAPTER 4

IMPACT OF RACE ON THE ASSOCIATION BETWEEN MEDITERRANEAN DIET SCORES AND THE PREVALENCE, INCIDENCE, AND RECURRENCE OF COLORECTAL ADENOMA[1]

[1] Alyson Haslam, Sara Wagner Robb, James R Hébert, Hanwen Huang, Mark H Ebell. To be submitted to the journal, "Public Health Nutrition"

Abstract

Objective: To examine potential racial differences in Mediterranean diet intake and whether these differences are associated with the prevalence, incidence, or recurrence of colorectal adenoma (CRA).

Design: Cross-sectional analysis of data from a large, population-based screening trial. Flexible sigmoidoscopy was used to determine the presence of colorectal adenoma. Mediterranean diet scores were calculated from food frequency questionnaire responses. Logistic regression was used to determine the association between Mediterranean diet scores and the odds of prevalent, incident, or recurrent CRA, stratified by sex. Models for prevalent CRA were also stratified by race.

Setting: Ten cancer screening centers across the United States

Subjects: Adults ages 50-74 years in the screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

Results: Asians, followed by blacks, had higher Mediterranean diet scores than whites. Asian males had significantly lower adjusted odds of colorectal adenomas (adjusted odds ratio [aOR]=0.63; 95% CI=0.48-0.82), compared to white males. Black males also had lower odds of colorectal adenoma (aOR=0.79; 95%CI=0.61-1.02) compared to white males, although the significance was borderline. Stratifying by race, lower Mediterranean diet scores were associated with higher odds of colorectal adenoma in white (aOR=1.39; 95% CI=1.20-1.60) and black males (aOR=2.62; 95% CI=1.14-6.00) but not in women. Mediterranean diet scores were not associated with recurrent adenoma.

Conclusions: In this study population, blacks, who had higher (more favorable) Mediterranean diet scores than whites, also had a lower adjusted odds of prevalent distal colorectal adenoma than whites. Reducing or eliminating inequalities in diet intake in the broader black population that has historically poor health outcomes may be an effective primary preventive measure to reduce racial disparities in colorectal adenoma prevalence and colorectal cancer.

Introduction

The prevalence of colorectal adenomas (CRA) differs by race and ethnicity (3-6, 42). Previous studies have reported a higher prevalence of CRA in blacks than in whites, with Hispanics having a prevalence either similar to that of whites or somewhere between that of blacks and whites (3, 42). Studies examining the prevalence of adenomas in Asians are few, but one small study demonstrated a higher risk of distal adenomas but a lower risk of proximal adenomas, compared to whites (41). Disparities in CRA may lead to disparities in colorectal cancer, as adenomas are precursors to cancer. Screening is an effective secondary preventive measure for colorectal cancer (3, 4), but it is unknown whether diet could also be used as a primary preventive measure in minimizing disparities in CRA.

Several dietary indices have been developed to characterize the healthiness of diet, including the Mediterranean diet, which has been shown to reduce cardiovascular events and breast cancer incidence in randomized trials (174, 175). Moreover, in a meta-analysis of observational studies, a more Mediterranean-like diet was associated with lower overall cancer mortality and lower incidences of breast, colorectal, and liver cancers (176).

Only a few studies have examined the relationship between Mediterranean diet scores and CRA prevalence (134, 177). In the Prostate, Lung, Colorectal, Ovarian (PLCO) Cancer Screening Trial cohort, an intake of a more Mediterranean-like diet was associated with a lower prevalence of CRA, but only among men (134). Similar results were found in a case-control study (177). However, neither of these studies examined the effect of race on the association between the Mediterranean diet and CRA prevalence, even though racial disparities in CRA prevalence have been demonstrated (e.g. blacks having a higher prevalence than whites; (3, 4)).

Given what is known about the generally inverse association between a more Mediterranean-like diet and lower risk of CRA, it seems likely that dietary differences by racial subgroup could be contributing to the racial differences in adenoma incidence or prevalence. However, studies that examine racial differences in dietary intake and its relationship with the development of CRA are lacking. Therefore, the purpose of this study is to examine potential racial differences in Mediterranean diet scores and whether these differences are associated with the prevalence, incidence, or recurrence of CRA.

Subjects and Methods

Study population

Data for these secondary analyses were collected as part of the PLCO Cancer Screening Trial. Methods for this trial have been previously described in detail (159, 161, 178). Briefly, 148,000 men and women aged 55-74 years were recruited between 1993 and 2000 at one of 10 centers across the US, and were randomized to either a screening arm or a control arm (usual care). Individuals assigned to the screening arm underwent flexible sigmoidoscopy (FS) at baseline and at either year 3 (if enrolled before April, 1999) or year 5 (if enrolled after April, 1999). Patients who had an abnormal finding on FS examination were referred for endoscopic follow-up, usually with colonoscopy. Trained medical abstractors reviewed all available medical records and obtained data on all lesions removed during the diagnostic endoscopy and related surgical procedures. Participants were asked to complete a detailed questionnaire at baseline that asked about sociodemographic characteristics, diet, physical activity, personal and family cancer history and other diseases, smoking history, and use of selected drugs. Institutional review boards at the National Cancer Institute and the 10 screening centers provided approval of the study, and informed consent was provided by all study participants.

We included participants if they were assigned to the screening arm and had returned the baseline questionnaire (N=75,611). Participants were excluded in this order if: they had extreme calories reported on the dietary questionnaire (top or bottom 1% of sex-specific energy intake; n=1,264); had eight or more missing responses on the dietary questionnaire (N=545); did not complete the dietary questionnaire (n=12,415); had a personal history of any cancer (except basal-cell skin cancer) or did not know their personal history of cancer before the dietary questionnaire (n=2,800); FS examination was inadequate (defined as insertion to at least 50 cm with >90% of mucosa visible or suspect lesion found) or not done (n=10,021); race not identified (n=12); had ulcerative colitis, Crohn's disease, Gardner's syndrome, or familial polyposis (n=604); or had a positive FS but had either no follow-up or ambiguous follow-up (n=3,064). These exclusions left 44,886 participants. Further, participants with missing information for key variables (body mass index (BMI), education, physical activity, smoking status, and dietary components specific to these analyses) were also excluded, resulting in a total sample size of 41,973 for analyses.

Definitions

Prevalent adenoma: Prevalent adenomas were defined as those found distally (rectum to the splenic flexure) at the baseline screening.

Incident Adenomas: Incident adenomas were those that were found distally at subsequent sigmoidoscopic screening (at year 3 or 5) in individuals who did not have an adenoma at baseline. Study participants included in the prevalent analyses were excluded from the incident analyses if they did not complete or have an adequate subsequent sigmoidoscopic screening, resulting in a sample size of 18,609.

Recurrent adenomas: Participants for recurrent analyses were a selected set of individuals from the PLCO screening trial who were invited to take part in the Study of Colonoscopy Utilization (SCU), which is an ancillary study nested within PLCO study (179) (Pinsky et al., 2009). These participants had a positive screen on the baseline FS and no cancer findings on follow-up colonoscopy within 18 months. They were then followed to ascertain results of surveillance or other colonoscopy procedures by local health care providers and findings that occurred more than six months and less than ten years after a positive screen at baseline. The sample size for these analyses was 1,618.

Dietary data

Questionnaire: Nutritional data were collected by using a food frequency questionnaire, the Diet History Questionnaire (DQX), developed by the National Cancer Institute (165). The DQX is a 16-page questionnaire that asked about the frequencies, portion sizes, and in some cases, the seasonal intake or food type, for 137 different foods during the year prior to enrollment. Additionally, there are six questions that asked about the use of low-fat foods, four summary questions, and ten dietary supplement questions. This method has been shown to perform at least as well as the Block and Willett food frequency questionnaires, which are validated and reliable measures of dietary intake used in research (165). Responses were used to estimate daily individual nutrients intake, based on the Continuing Survey of Food Intakes by Individuals data (165).

Mediterranean diet: The exposure of interest was the Mediterranean diet index that was based on an original index proposed by Trichopoulou and colleagues, and was then modified by Fung and colleagues (23). This index captures how closely people eat in accordance with a general Mediterranean dietary prescription, regardless of whether or not they are eating an actual

Mediterranean diet. Components for the original index included, vegetables, legumes, fruit and nuts, dairy, cereals, meat and meat products, fish, alcohol, and the ratio of monounsaturated to saturated fat. The alternate version proposed by Fung excludes potatoes from the total vegetable group; splits the fruit and nut group into two distinct groups; eliminates the dairy group; includes only whole grains in the cereal group; includes only red and processed meats for the meat group; and reduced the optimal intake for alcohol. Therefore, the Mediterranean diet will hereafter be referred to as the alternate Mediterranean diet (altMED).

For "healthy" foods, a point was given if the intake of a particular food item was above the sex-specific median intake (vegetables, legumes, fruits, nuts, whole grains, fish, high ratio of monounsaturated to saturated fat; Table 4.1). For "unhealthy" foods, a point was given if the intake of a particular food item was below the sex-specific median intake (red and processed meats; Table 4.1). One point was given for alcohol if intakes were between 5 and 15 g/day for women and 5 and 25 g/day for men. Points were summed for a range of 0 to 9, with higher scores indicating a more Mediterranean-like diet. The altMED diet scores were categorized into low (<3), medium (3-5), and high (>5), based on previous work (180).

Covariate Data

The dataset included information regarding the following covariates: smoking (never, current, or former), sex (male or female), self-report of race/ethnicity (black, white, Asian, or other), physical activity (less than 2 hours of vigorous activities per week vs. 2 or more hours of vigorous activities per week; (181)), and non-steroidal anti-inflammatory use (regular use of aspirin/aspirin-containing or ibuprofen/ibuprofen-containing products or not). BMI (kg/m^2) was categorized as underweight (<18.5); normal (18.5-24.9); overweight (25-30.0); and obese (>30). Height and weight were self-reported at baseline. Education was categorized into less than high

school; high school degree; some college or post high school training; and college or graduate degree. Hormone status, in regards to taking female hormones, was categorized as never, current, former, or unknown. Age at randomization (years), calcium intake (food and supplements; mg/day), folic acid (food and supplements; mcg/day), and energy intake (kcal/day) were left as continuous variables.

Statistical analysis

Means and frequencies with their respective standard deviations and percentages were calculated for continuous and categorical descriptive and demographic characteristics, stratified by race/ethnicity. Chi-square tests for categorical variables and analysis of variance for continuous variables were used to determine significant differences, if any, in descriptive characteristics and altMED diet scores between racial subgroups. Further, chi-square tests were used for determining racial differences in points awarded for each altMED diet index component. Normal distribution was assessed with histograms (QQ plot or Shapiro-Wilk test) for each variable.

Univariate and multivariable logistic regression models were used to calculate the odds of CRA for different categories of Mediterranean diet scores. Models were run using prevalent CRA as the outcome and the altMED diet score as the primary independent variable, but other models were run using recurrent CRA or incident CRA as main outcomes. Regression models initially included race, smoking, age, physical activity, education, hormone status, non-steroidal anti-inflammatory use, calcium intake, and daily energy. To test for racial differences in the association between altMED diet scores and prevalent distal CRA, models were stratified by race. This was done because of the a priori hypothesis that there would be racial differences in regards to the association between altMED diet scores and prevalent CRA. An interaction term

for sex and altMED diet score was included in the model and considered significant if the p-value was <0.20. Covariates were evaluated for model inclusion if they were not significant in the model ($p<0.20$) and then removed if their exclusion did not result in a lower Akaike information criterion (AIC) statistic (182). The most parsimonious model that retained predictive accuracy, as indicated by a lower AIC value, was selected. All analyses were performed using SAS software (version 9.4; SAS Institute, Cary, North Carolina) using a p-value of 0.05, unless otherwise indicated.

Results

Prevalent adenomas

Compared to whites, blacks were less likely to report high physical activity (43% vs. 57%; $p<0.0001$), whereas Asians more likely to report high activity (61% vs. 57%; $p=0.0004$; Table 4.2). Compared to whites, blacks and those of other races were less likely to have never smoked (42% ($p<0.0001$) and 41% ($p=0.0006$), respectively, vs. 48%), while Asians were more likely to have never smoked (55% vs. 48%; $p<0.0001$; Table 4.2). Blacks and Asians had higher scores than whites on the altMED diet index (4.5 and 5.1 points, respectively, vs. 4.1 points; $p<0.0001$ for both comparisons; Table 4.2).

There were significant differences between race/ethnicities regarding point distributions for the altMED diet score (Table 4.3). Compared to whites, blacks were more likely to receive a point for fruits, whole grains, monounsaturated to saturated fat ratio, and alcohol, but they were less likely to receive a point for vegetables, nuts, red and processed meats, and fish. Asians were more likely than whites to receive a point for legumes, red and processed meats, fish, and monounsaturated to saturated fat ratio, but less likely to receive a point for nuts or alcohol.

Those of other race or ethnicities were more likely to receive a point for legumes and a high monounsaturated to saturated fat ratio but less likely to receive a point for nuts.

There was a significant interaction between sex and altMED diet score ($p<0.0001$), so models were stratified by sex. Among males, having an altMED score in the low (adjusted odds ratio (aOR)=1.39; 95% confidence intervals (CI)=1.21-1.59; Table 4.4) or moderate (aOR=1.16; 95% CI=1.04-1.30) category was associated with a higher odds of having a prevalent distal adenoma, compared to those with an altMED score in the high category when adjusted for physical activity, body mass index, education, smoking, calorie intake (kcal/day), calcium intake (mg/day), folic acid (mcg/day), and age. Also, Asian males had a lower odds (aOR=0.63; 95% CI=0.48-0.82; Table 4.4) of having a prevalent adenoma in the fully adjusted model, compared to white males. Among females, the altMED diet was not associated with having a prevalent adenoma in the fully adjusted model, but being Asian was associated with a lower odds of having a prevalent adenoma compared to whites (aOR=0.57; 95% CI=0.38-0.85; Table 4.4).

When the logistic regression models were stratified by race and sex, white males in the low (aOR=1.39; 95% CI=1.20-1.60; Table 4.5) and moderate (aOR=1.17; 95% CI=1.04-1.31) categories of the altMED diet had higher odds of developing CRA than white males in the high category (Table 4.5). Among black males, the odds of developing CRA were highest in those with the low category of the altMED diet score, compared to those in the high category (aOR=2.62; 95% CI=1.14-6.00; Table 4.5). altMED diet scores were not associated with CRA prevalence in any female racial subgroup.

Incident adenomas

The altMED scores were not associated with incident CRA (Table 4.6). Females were less likely to develop incident CRA than males (aOR=0.81; 95% CI=0.67-1.00; Table 4.6),

adjusted for physical activity, race, smoking BMI, hormone therapy, calcium intake, and daily calories. Blacks did not have different odds of incident CRA than whites (aOR=1.06; 95% CI=0.74-1.49), but Asians were less likely to develop an incident CRA than whites (aOR=0.74; 95% CI=0.55-0.99; Table 4.6). Males who were classified as "other" race or ethnicity were less likely to develop an incident CRA than white males (aOR=0.53; 95% CI=0.29-0.98; Table 4.6).

Recurrent adenomas

In the recurrent subgroup, cases were more likely than controls to be male (72.1% vs. 59.3%), be obese (28.4% vs. 24.0%), and be Asian or "other" race (1.6% and 1.2% vs. 0.5% and 0.3%; data not shown). Cases were also more likely to consume more daily calories than controls (2186 kcal/day vs. 2089 kcal/day; data not shown).

The altMED diet was not associated with CRA recurrence, in the fully adjusted model (Table 4.8). Females of other races were more likely to have an adenoma recurrence than white females, while adjusting for altMED diet, education, and age (aOR=3.06; 95% CI=1.55-6.04; Table 4.8).

Discussion

In this study, having a less Mediterranean-like diet was associated with higher odds of having a prevalent CRA, particularly in males. The findings of a more Mediterranean-like diet having protective effects against CRA, especially in men, are consistent with what has already been shown in the literature (134, 177). We have extended this work, by showing that this association persists after stratification by race among black and white men, but not among women.

An examination of the effects of diet on CRA occurrence may be important in helping to minimize racial disparities that may occur in CRA prevalence, thus minimizing disparities in

other more serious colorectal growths such as colon cancer. Here we show that certain populations are less likely to have prevalent CRA outcomes with the consumption of a more Mediterranean-like diet. Asians in the PLCO cohort were less likely to have a prevalent CRA than whites, and blacks had a borderline significance of being less likely to have a prevalent CRA, when adjusted for Mediterranean diet and other important covariates. Findings from previous research have been inconsistent on whether there are racial disparities in CRA prevalence, although the majority of studies show a higher overall prevalence among blacks, and a similar or higher prevalence among Asians, compared to whites (4, 6, 41). The lower prevalence of CRA among the black PLCO study participants may be due to healthy volunteer bias, with a healthier and more educated black study population in the PLCO cohort compared to the general black population of the U.S. (167). Indeed, blacks in the PLCO cohort had higher intakes of several favorable measures of the Mediterranean diet score, including fruits, legumes, whole grains, and a more favorable ratio of monounsaturated/saturated fats, compared to whites.

Consequently, blacks also had higher altMED diet scores than whites. Not surprisingly, Asians who had the lowest prevalence of CRA of all racial/ethnic groups also had the highest percentage of individuals in the "high" altMED diet category, as well as more favorable intakes of vegetables, legumes, fish and ratio of monounsaturated/saturated fats. Based upon these findings, it is likely that having a more Mediterranean-like diet could be at least partly responsible for the lower CRA findings in several of the racial/ethnic subgroups.

Higher intakes of "healthy" foods among whites, compared to those of other races or ethnicities, have been previously reported (183). In the present study it was found that whites did not have higher intakes of foods normally considered healthy, nor did they have the highest altMED diet scores. Conversely, data from the National Health and Nutrition Examination Survey

(NHANES) indicate that black males are less likely than white males to meet the dietary requirements for vegetables, but not for fruit (183). Hispanics, those of other races, and females in the NHANES did not have significantly different intakes than their counterparts (183). Similarly, in the NHANES cohort, whites had higher intakes than blacks of whole grains and vegetables, and had higher diet quality score as measured by the Healthy Eating Index (184); whites also had higher intakes of whole grains than Hispanics (184).

In the racially-stratified analysis, the benefits of the altMED diet were seen primarily among white and black males, with black males having the strongest association between altMED diet scores and prevalent CRA. One explanation for the null findings among Asians in the stratified analysis may be due to the generally high altMED diet scores among Asians. Only about nine percent of Asians were classified as having a "low" altMED diet score, compared to 15% and 20% for blacks and whites, respectively. Asians in the PLCO cohort had generally high intakes of the altMED diet. This may have limited the ability to see beneficial effects from diet because the average diet was higher than the "threshold" of adenoma formation from poor diet. It is also possible that the lack of association was due to low sample size, although there were more Asian participants than black participants, and significant results were seen in the black participants.

Interestingly, altMED diet scores were not associated with incident CRA, even though altMED diet scores were associated with prevalent CRA. It may be that a lot of diet-related adenomas were found during the baseline screening and the sample size for the incident group was smaller than the prevalent group (N=18,609 vs. N=41,973). Additionally, three or five years between baseline screen and follow-up screen may not have allowed enough time for enough adenomas to develop, which would have limited the ability to see significant differences.

Another issue that may have affected the incident analysis results is that of loss to follow-up. A high percentage of individuals (56%) were excluded because they did not return for subsequent screening. Generally those who did not receive a year 3 or 5 follow-up had lower physical activity and education status, and were more likely to smoke and have a "low" score on the Mediterranean diet index. The generally healthier cohort of individuals who received follow-up may have limited the ability to see significant associations because of the underestimation of adenomas.

Studies on the association between diet and recurrent adenomas are few, although some have focused on the effects of individual nutrients such as fiber and calcium (185, 186). Of those that studied the global effect of diet and recurrent adenoma, one found that a Mediterranean diet pattern, identified through factor analysis, was associated with a 50% reduction in recurrent adenomas (187). In considering more general diet guidelines, a low-fat, high-fiber, and high fruit and vegetable diet was no more beneficial in preventing recurrent adenomas than a usual diet (12), except for those who strictly adhered to the diet recommendations (188). In a randomized trial of a low-fat, high-fiber diet, there were no difference in adenoma recurrence between those in the intervention arm and those in the control arm (189). In the present study, we found no such reduction in recurrent adenoma incidence with a more Mediterranean-like diet. Although the studies are few, it may be that the effect of diet is smaller in recurrent adenomas than for incident adenomas; whereas, other factors, such as genetics may be a stronger predictor of recurrent adenoma than diet.

There are several strengths of this study. The large, multi-center cohort was recruited with the purpose of achieving a study population comprised of a racial makeup that was reflective of the US population (167). This goal was not achieved, but the study population does

contain a racial composition similar to other screening trials (167). Further, participants from geographically diverse locations across the US could result in a diversity of dietary intake among the individuals, thus enabling the analysis to examine adenoma status among a broad range of diets.

However, this study is limited by the small numbers of participants in non-white racial racial/ethnic strata, limiting the power to detect significant associations among those individuals. This was especially true when trying to examine the effects of diet and adenoma recurrence in racial groups. In spite of the low numbers in certain racial groups, there were significant associations found between the altMED index and distal CRA prevalence among those of black race, which was the racial group of primary interest due to health disparities that often occur among blacks. A limitation of this study is that blacks were less likely to receive follow-up to confirm the abnormal findings of their FS than were whites. Individuals who did not have their FS findings histologically confirmed were excluded, which would result in less outcome misclassification. The exclusion of those without follow-up would likely have resulted in non-differential misclassification, thus limiting the power to detect positive associations in this racial group. But even considering this, significant associations were found in the black subgroups, which was a smaller subsample of the study population. It should be noted that blacks in the PLCO were healthier and better educated than blacks in the general U.S. population (167), and therefore, the results of the current study may not be generalized to the larger U.S. population.

In conclusion, the use of a Mediterranean diet may be an effective way to reduce the prevalence of distal CRA in both black and white males. Future work should focus on ways to increase the access and availability of healthy foods to high-risk populations as a primary preventive measure for reducing CRA disparities. Interventions may have a greater effect by

being tailored toward men and toward dietary and cultural differences between blacks and whites.

Table 4.1: Foods and point values for food groups included in the alternate Mediterranean Diet Score (altMED; Total score range: 0-9)

Food group	**Foods in each food group**	**Criteria for assigning points[1]**	**Sex-specific median intake for each food group**
Vegetables	All vegetables except white/red potatoes	Greater than the median intake (grams/day)	Male: 250.5 Female: 250.7
Legumes	Tofu, string beans, peas, beans	Greater than the median intake (grams/day)	Male:35.0 Female: 28.6
Fruit	All fruit	Greater than the median intake (grams/day)	Male: 350.7 Female: 367.0
Nuts	Peanuts	Greater than the median intake (grams/day)	Male: 2.6 Female: 1.2
Whole grains	Whole-grain ready-to-eat cereals, cooked cereals, dark breads, brown rice, popcorn	Greater than the median intake (grams/day)	Male: 43.0 Female: 44.6
Red and processed meats	Hot dogs, deli meat, sausage, bacon, hamburger, beef	Less than the median intake (servings/day)	Male: 50.0 Female: 22.0
Fish	Fish and shrimp	Greater than the median intake (grams/day)	Male: 13.3 Female: 12.7
Ratio of monounsaturated to saturated fat		Greater than the median intake (grams/day)	Male: 1.1 Female: 1.1
Ethanol	Wine, beer, liquor	5-25 g/day for males 5-15 g/day for females	

1. Median intake is based upon population intake for the screening arm population of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. For scoring, for "healthy" items 1 point was given for above the median and 0 point for below the sex-specific median, and for "unhealthy" items 1 point was given for below the median and 0 point for above the sex-specific median.

Table 4.2: Descriptive characteristics of Prostate, Lung, Colorectal, and Ovarian screening arm participants in the Mediterranean diet analysis, by race (N=41,973)

Categorical Variables	**Whites (N=38,145) Reference group**	**Blacks (N=1,413)**	**Asian (N=1,550)**	**Other (N=865)**	**Overall chi-square p-value**
Sex					<0.0001
Male	20,495 (53.7)	673 (47.6)	884 (57.0)	524 (60.6)	
Female	17,650 (46.3)	740 (52.4)***	666 (43.0)*	341 (39.4)***	
Education					<0.0001
College	14,375 (37.7)	440 (31.14)	731 (47.2)	246 (28.4)	
Some college	12,858 (33.7)	524 (37.1)	498 (32.1)	334 (38.6)	
High school	8,700 (22.8)	278 (19.7)	266 (17.2)	182 (21.0)	
Less than high school	2,212 (5.8)	171 (12.1)***	55 (3.6)***	103 (11.9)***	
Physical Activity[1]					<0.0001
High	21,590 (56.6)	604 (42.8)	948 (61.2)	475 (54.9)	
Low	16,561 (43.4)	809 (57.2)***	602 (38.8)**	390 (45.1)	
Smoking					<0.0001
Never	18,320 (48.0)	598 (42.3)	847 (54.6)	358 (41.4)	
Current	3,478 (9.1)	232 (16.4)	112 (7.2)	87 (10.1)	
Former	16,347 (42.8)	583 (41.2)***	591 (38.1)***	420 (48.6)**	
Anti-inflammatory use[2]					0.01
Yes	7,653 (20.1)	293 (20.7)	283 (18.3)	210 (24.3)	
No	30,492 (79.9)	1,120 (79.3)	1,267 (81.7)	655 (75.7)*	
Hormone therapy (females only)					<0.0001
Current	9,514 (53.8)	274 (36.0)	369 (55.4)	171 (50.2)	
Former	2,710 (15.3)	163 (22.0)	100 (15.0)	56 (16.4)	
Never	5,381 (30.5)	298 (40.3)	192 (28.8)	112 (32.8)	
Unknown	45 (0.2)	5 (0.7)***	5 (0.8)	2 (0.6)	

Body Mass Index (kg/m^2)					<0.0001
0-18.5	209 (82.9)	7 (0.5)	32 (2.1)	4 (0.5)	
18.5-25	11,951 (31.3)	305 (21.6)	850 (54.8)	213 (24.6)	
25-30	16,795 (44.0)	570 (40.3)	555 (35.8)	409 (47.3)	
30+	9,190 (24.1)	531 (37.6)***	113 (7.3)***	239 (27.6)***	
Case status					<0.0001
No adenoma	34,562 (90.6)	1,298 (91.9)	1,463 (94.4)	784 (90.6)	
Adenoma	3,583 (9.4)	115 (8.1)	87 (5.6)***	81 (9.4)	
Continuous variables	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Analysis of variance p-value**
Calcium (diet and supplements; mg/day)	1,272.0 (603.9)	960.6 (536.0)***	1,001.7 (582.6)***	1,133.2 (602.0)***	<0.0001
Alternate Mediterranean diet score (altMED; 0-9)	4.2 (1.8)	4.5 (1.8)***	5.1 (1.8)***	4.2 (1.9)	<0.0001
Calories (kcal/day)	2,080.3 (793.8)	1,971.6 (536.4)***	1,859.3 (751.8)***	2,050.7 (865.0)***	<0.0001
Age (years)	62.4 (5.2)	62.1 (5.2)*	62.9 (5.6)***	61.3 (5.0)***	<0.0001

SD=standard deviation; *p-value<0.05; **p<0.001; ***p<0.0001; Chi-square for categorical and t-tests for continuous variables; comparing whites vs blacks (or Asian or other)

1. Less than 2 hours of vigorous activities per week (low) vs. 2 or more hours of vigorous activities per week (high)
2. Regular use of aspirin/aspirin-containing or ibuprofen/ibuprofen-containing products or not.

Table 4.3: Frequency (percent) of race-specific population receiving a point for each component of alternate Mediterranean diet (altMED) score, by race, in the Prostate, Lunge, Colorectal, and Ovarian Cancer screening arm

Category	**Whites (N=38,145) Reference group**	**Blacks (N=1,413)**	**Asian (N=1,550)**	**Other (N=865)**	**Overall p-value[1]**
Vegetables (excluding white potatoes)	19,136 (50.2)	578 (40.9)***	814 (52.5)	413 (47.8)	<0.0001
Fruit	18,849 (49.4)	878 (62.1)***	774 (49.9)	429 (49.6)	<0.0001
Legumes	18,723 (49.1)	720 (51.0)	1,021 (65.9)***	459 (53.1)*	<0.0001
Nuts	21,951 (57.6)	744 (52.6)**	786 (50.7)***	441 (51.0)***	<0.0001
Whole grains	18,925 (49.6)	877 (62.1)***	763 (49.2)	412 (47.6)	<0.0001
Red and processed meats	18,506 (48.5)	741 (52.4)*	1,138 (73.4)***	447 (51.7)	<0.0001
Fish	18,921 (49.6)	654 (46.3)*	1,050 (67.7)***	425 (60.4)	<0.0001
Ratio of monounsaturated to saturated fat	18,361 (48.1)	921 (65.2)***	1,274 (82.2)***	473 (54.7)***	<0.0001
Ethanol	6,539 (17.1)	298 (21.1)***	324 (20.9)***	160 (18.5)	<0.0001

1. Chi-square test; *p-value<0.05, **p<0.001, or ***p<0.0001, using Chi-square to determine significant differences between whites vs blacks (or Asian or other);

Table 4.4: Associations between prevalent colorectal adenoma and alternate Mediterranean (altMED) score categories in participants in the Prostate, Lung, Colorectal, and Ovarian screening cohort, by sex (N=22,576 males; 19,397 females)

	Males[1]	**Females[2]**
	aOR (95% CI)	**aOR (95% CI)**
Alternate Mediterranean diet score (altMED; range 0-9)[3]		
High (>5; reference)	1.00	1.00
Moderate (3-5)	**1.16 (1.04-1.30)**	1.10 (0.95-1.26)
Low (<3)	**1.39 (1.21-1.59)**	1.12 (0.94-1.33)
Race		
White (reference)	1.00	1.00
Black	0.79 (0.61-1.02)	0.75 (0.55-1.02)
Asian	**0.63 (0.48-0.82)**	**0.57 (0.38-0.85)**
Other	0.87 (0.66-1.16)	1.11 (0.74-1.66)

aOR, adjusted odds ratio; CI, confidence interval; Bolded values are significant ($p<0.05$).

1. Adjusted for race, physical activity, body mass index, education, smoking, calorie intake (kcal/day), calcium intake (food and supplements; mg/day), folic acid (food and supplements; mcg/day), and age.
2. Adjusted for race, body mass index, smoking, hormone status, calcium intake (mg/day), and age.
3. The "high" category for the alternate Mediterranean diet was used as the reference category because this was the most Mediterranean-like diet category, and therefore, thought to have the lowest risk of adenoma.

Table 4.5: Associations between prevalent colorectal adenoma and Mediterranean diet scores, by sex and race in the Prostate, Lung, Colorectal, and Ovarian Cancer screening arm participants

	Alternate Mediterranean diet (altMED) categories		
	High (>5; reference)[1]	**Moderate (3-5)**	**Low (<3)**
	aOR (95% CI)	**aOR (95% CI)**	**aOR (95% CI)**
Males[2]			
White (N=20,495)	1.00	**1.20 (1.07-1.34)**	**1.44 (1.25-1.65)**
Black (N=673)	1.00	1.17 (0.61-2.27)	**2.62 (1.14-6.00)**
Asian (N=884)	1.00	1.27 (0.69-2.33)	1.55 (0.64-3.79)
Other (N=524)	1.00	0.97 (0.47-2.01)	0.64 (0.22-1.83)
Females[3]			
White (N=17,650)	1.00	1.11 (0.96-1.29)	1.13 (0.95-1.36)
Black (N=740)	1.00	0.70 (0.34-1.44)	0.87 (0.34-1.44)
Asian (N=666)	1.00	2.00 (0.83-4.79)	**
Other (N=341)	1.00	0.77 (0.28-2.08)	1.52 (0.44-5.23)

aOR, adjusted odds ratio; CI, confidence interval; Bolded values are significant ($p<0.05$); **measure of effect could not be calculated because of few numbers in the low category.

1. The "high" category for the alternate Mediterranean diet was used as the reference category because this was the most Mediterranean-like diet category, and therefore, thought to have the lowest risk of adenoma.
2. Adjusted for physical activity, body mass index, education, smoking, calorie intake (kcal/day), calcium intake (food and supplements; mg/day), folic acid (food and supplements; mcg/day), and age.
3. Adjusted for body mass index, smoking, hormone status, calcium intake (mg/day), and age.

Table 4.6: Associations between **incident** adenoma and Mediterranean diet scores in the Prostate, Lung, Colorectal, and Ovarian cancer screening arm participants (N=18,609)

	Males	**Females**	**Males and females, combined**
Categorical variables	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
Alternate Mediterranean (altMED) score category			
High (>5; reference)	1.00	1.00	1.00
Moderate (3-5)	1.02 (0.85-1.22)	1.11 (0.86-1.44)	1.06 (0.91-1.22)
Low (<3)	0.96 (0.76-1.22)	1.11 (0.79-1.56)	1.02 (0.84-1.25)
Physical Activity[2]			
Low	1.30 (1.11-1.52)	1.22 (0.98-1.52)	1.29 (1.14-1.46)
High (reference)	1.00	1.00	1.00
Race			
White (reference)	1.00	1.00	1.00
Black	1.04 (0.67-1.64)	1.05 (0.62-1.81)	1.06 (0.75-1.49)
Asian	0.84 (0.59-1.18)	0.57 (0.32-1.03)	**0.74 (0.55-0.99)**
Other	**0.53 (0.29-0.98)**	1.01 (0.49-2.08)	0.67 (0.42-1.08)
Smoking			
Never (reference)	1.00	1.00	1.00
Current	**2.08 (1.61-2.71)**	**1.88 (1.28-2.77)**	**1.99 (1.60-2.47)**
Former	**1.24 (1.06-1.46)**	**1.43 (1.14-1.80)**	**1.31 (1.15-1.49)**
Body Mass Index (kg/m^2)			
<25 (reference)	1.00		
25-30	1.06 (0.88-1.28)		
30+	1.24 (0.99-1.54)		
Hormone therapy (females only)			
Never/unknown (reference)		1.00	1.00
Current/former		0.82 (0.65-1.02)	0.81 (0.65-1.01)

Gender			
Male			**1.00**
Female			**0.81 (0.67-1.00)**
Continuous variables	**p-value**	**p-value**	**p-value**
Calcium intake (food and supplements)	0.11	**0.02**	**0.004**
Calorie intake (kcal/day)		**0.002**	**0.008**

aOR=adjusted odds ration; CI=confidence interval; Bolded values are significant ($p<0.05$)

1. Less than 2 hours of vigorous activities per week (low) vs. 2 or more hours of vigorous activities per week (high)

Table 4.7: Associations between **recurrent** adenoma and Mediterranean diet scores in the Prostate, Lung, Colorectal, and Ovarian cancer screening arm participants (N=1,618)

	Males (N=1,052)	**Females (N=550)**
Categorical variable	**aOR (95% CI)**	**aOR (95% CI)**
Alternate Mediterranean (altMED) score category		
High (>5; reference)	1.00	1.00
Moderate (3-5)	0.96 (0.71-1.30)	0.94 (0.62-1.44)
Low (<3)	0.76 (0.52-1.10)	1.06 (0.63-1.78)
Race		
White (reference)	1.00	1.00
Other	1.52 (0.83-2.75)	**3.06 (1.55-6.04)**
Education		
College (reference)		1.00
Some college		1.32 (0.86-2.01)
High school		0.87 (0.62-1.44)
Less than high school		0.62 (0.24-1.56)
Body Mass Index (kg/m2)		
<25	1.00	
25-30	**1.92 (1.34-2.75)**	
30+	1.92 (0.84-2.75)	
Continuous variable	**p-value**	
Age (years)	1.02 (0.99-1.05)	

aOR=adjusted odds ratio; CI=confidence interval; Bolded values are significant ($p<0.05$)

CHAPTER 5

IMPACT OF RACE ON THE ASSOCIATION BETWEEN DIETARY INFLAMMATORY INDEX SCORES AND THE PREVALENCE, INCIDENCE, AND RECURRENCE OF COLORECTAL ADENOMA[2]

[2] Alyson Haslam, Sara Wagner Robb, James R Hébert, Hanwen Huang, Mark H Ebell. To be submitted to the journal, "Cancer Causes and Control"

Abstract

Background: Dietary factors such as high amounts of sugars or fats can promote inflammation, while antioxidants and flavonoids reduce inflammation. The Dietary Inflammatory Index (DII) was developed to characterize the inflammatory nature of a person's diet, which may be used to predict inflammatory conditions such as cancer. The purpose of this study was to investigate the association between the DII and colorectal adenoma (CRA), a pre-cancerous condition.

Methods: Baseline questionnaire responses (including dietary) were used calculate DII scores for participants in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. The association between DII scores and CRA prevalence, incidence, and recurrence was determined in men and women separately. Separate analyses evaluated the association between DII scores and prevalent CRA stratified by race.

Results: Men with diets in the most inflammatory quartile of DII scores had higher odds of all types of CRA (advanced, non-advanced, and multiple), compared to those with diets in the least inflammatory quartile of DII scores. Higher DII scores, representing a more inflammatory diet, were also associated with a higher prevalence of CRA in women, but not as strongly as in men. The association between DII scores and prevalent CRA is significant in whites, but no conclusions could be made about this association in the other individual races.

Conclusion: Less inflammatory diets, as measured by DII scores, are associated with lower odds of CRA in both men and women.

Introduction

The biologic effects of diet on inflammation are complex. Very simply, oxidative stress, which can occur after the ingestion of a high-fat, high-sugar meal, results in the production and release of free radicals and reactive oxygen and nitrogen species into the tissues. This in turn can lead to damaged tissues and inflammation (99, 100). Conversely, foods high in anti-oxidants and flavonoids, such as fruits and vegetables, reduce inflammation by scavenging for free radicals, inhibiting pro-oxidant enzymes, binding free radicals, and possibly modulating the expression of pro-inflammatory molecules (62, 63). Prolonged and unchecked inflammatory conditions create a microenvironment favorable for tumor growth and progression (21). Because of the interaction between diet and inflammation, identifying dietary factors that promote a less-favorable environment for inflammatory conditions may be one way to minimize the incidence of adenomas and cancer.

The Dietary Inflammatory Index (DII) was developed to characterize the inflammatory nature of a person's diet, with scores on a continuum from maximally inflammatory to maximally anti-inflammatory. This index has been shown to predict concentrations of several circulating inflammatory proteins, including C-reactive protein (CRP) (22) and interleukin-6 (119). Previously published work has shown that a more inflammatory diet, as reflected by a higher DII score, is associated with a higher prevalence of asthma (an inflammatory condition) (119), pancreatic cancer (120), and prostate cancer (121). Most recently, higher scores on this index have been found to be associated with a higher incidence of colorectal cancer in the Women's Health Initiative and the Iowa Women's Health Study (123, 124). Another recent study showed a direct correlation between DII scores and polymorphisms in the gene for the anti-inflammatory cytokine IL-4 (rs2243250) (125). In that study, individuals with a more

inflammatory diet and the IL-4 polymorphism had a higher risk of colorectal cancer than those with the polymorphism who consumed a less inflammatory diet.

While these studies have shown an association between the incidence of colorectal cancer and a more inflammatory diet, it is unknown whether colorectal adenomas (CRA), which are precursors for colorectal cancer, are associated with a more inflammatory diet. Further, racial disparities have been reported in the prevalence of both colorectal cancer (190) and CRA (3-6). To date, no one has investigated whether there are racial differences in DII scores, and it is also unknown whether differences in the intake of an anti-inflammatory diet could be contributing to disparities in CRA prevalence. The purpose of the current study is to examine whether or not a more inflammatory diet, as measured by a higher DII score, is associated with the prevalence of CRA in a large cohort of older adults. Also, because of the racial differences in CRA prevalence, the association between DII scores and CRA was examined for each race separately.

Subjects and Methods

Study population

Data were collected as part of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, and have been previously described in detail (159-161). In short, over 148,000 men and women, ages 55-74, were recruited between 1993 and 2000 at one of 10 screening centers across the US. Each participant who was randomly assigned to the screening arm was asked to complete a detailed questionnaire at baseline with questions regarding sociodemographic characteristics, diet, physical activity, personal and family cancer history, smoking history, and use of selected drugs. Individuals assigned to the screening arm received a flexible sigmoidoscopy (FS) screen at baseline and at either year 3 or year 5. Those with an abnormal finding on FS examination were referred for endoscopic follow-up. Results from

diagnostic screening and treatment, including surgical procedures, were gathered by trained medical abstractors from each participant's medical record. Institutional review board approval was obtained from the National Cancer Institute and the 10 screening centers involved with the study. Informed consent was provided by all study participants.

Data from screening arm participants who returned the baseline questionnaire, which had questions regarding sociodemographic information, health history, medications, and physical activity, were used for these secondary analyses (N=75,611). Participants were excluded in this order if FS examination was not adequate (defined as insertion to at least 50 cm with >90% of mucosa visible or suspect lesion found) or not done (n=18,148); had a positive FS but had either no follow-up or ambiguous follow-up (n=3,717); had a personal history of any cancer (except melanoma) or did not know their personal history of cancer before the dietary questionnaire (n=2,081); had ulcerative colitis, Crohn's disease, Gardner's syndrome, or familial polyposis (n=652); did not complete the dietary questionnaire (n=4,937); had 8 or more missing responses on the dietary questionnaire (n=385); had extreme calories reported on the dietary questionnaire (top or bottom 1% of sex-specific energy intake; n=796); or did not specify race (n=9). Participants were further excluded if they were missing data on key variables (Body mass index (BMI), education, physical activity, or smoking status) were also excluded, for a final sample size of 44,278.

Definitions

Prevalent distal adenoma: Prevalent adenoma in the distal region (rectum to the splenic flexure) was the main outcome of interest. Advanced adenomas were those that were villous or tubulovillous in nature, large (≥1.0 cm), or displayed severe or high-grade dysplasia.

Incident adenoma: Incident adenoma was defined as distal adenomas occurring at either year 3 or 5 screening in participants who did not have a positive screen at baseline. To be included in the incident cohort, participants had to have known findings at both baseline and years 3 or 5 screenings. The sample size for these analyses was 18,599.

Recurrent adenoma: Selected individuals from the PLCO cohort were asked to participate in the Study of Colonoscopy Utilization (SCU), a nested ancillary study to the PLCO Screening Trial (179). Participants had abnormal findings on their baseline screen but no colon cancer findings on follow-up within 18 months of their baseline screen. The participants were then followed for up to 10 years. Results of surveillance or other colonoscopy procedures from their local health care provider were gathered during this time. The sample size for these analyses was 1,601.

Dietary Data:

Questionnaire: Dietary data were collected using the Dietary Questionnaire, developed by the National Cancer Institute (165). The 16-page questionnaire asked about the usual frequency and portion size of 137 food items and 10 dietary supplements over the year prior to enrollment. The Dietary Questionnaire has been shown to have good reliability and has been validated against both the Block and Willett food frequency questionnaires (165). Values for daily nutrients and food groups were determined from the national dietary data and the Pyramid food groups servings database from the 1994-1996 Continuing Survey of Food Intakes by Individuals with a method developed by Subar and colleagues (165).

DII: The DII is a tool to score the inflammatory nature of an overall diet, and was developed using data from individuals consuming diverse diets (135). Forty-five food/nutrient

parameters were identified as being influential on the inflammatory nature of diet. The DII has been described in detail previously (22).

To calculate the DII score, dietary intake data from each participant in the PLCO cohort were linked to a previously developed world database that was created by calculating the means and standard deviations for each of the 45 food/nutrient parameters for eleven countries around the world (22). A z-score for each food parameter was created for each PLCO participant by subtracting the global standard mean from the individual's reported amount of consumed food/nutrient, and dividing this value by its respective global standard deviation. This value is then converted to a percentile score to minimize the effect of "right skewing" (fewer observations with higher intakes of food items, which often occurs with dietary data).

The 'inflammatory effect score' for each food parameter was previously calculated for 45 foods and nutrients, based on results from experimental, prospective cohort, case-control, cross-sectional, animal experimental, and cell culture studies (22). Food or nutrient percentile scores for each participant in the PLCO was multiplied by its respective 'inflammatory effect score' to derive a 'food-specific dietary inflammatory score'. Each of the 'food-specific dietary inflammatory score's' were summed to derive an overall dietary inflammatory score, where negative scores are less inflammatory and positive scores are more inflammatory. Scores are based on both food and nutrient intakes. For these analyses, 37 of the 45 foods or nutrients from the original DII were used. Pro-inflammatory food items included: vitamin B12, carbohydrate, cholesterol, energy, total fat, iron, protein, saturated fat, and trans fat. Anti-inflammatory foods included: vitamin B6, beta carotene, caffeine, fiber, folic acid, vitamins A, D, C, and E, niacin, riboflavin, thiamin, magnesium, selenium, zinc, mono-unsaturated fatty acids, omega-3 fatty acids, omega-6 fatty acids, polyunsaturated fatty acids, flavan-3-ol, flavones, flavonols,

flavonones, anthocyanidins, isoflavones, green/black tea, alcohol, and onion. DII scores for the PLCO screening arm population ranged between -5.87 (maximally anti-inflammatory) and 5.58 (maximally pro-inflammatory). The DII scores were then categorized into quartiles.

Covariate Data:

Potential covariates included: smoking (never, current, or former), sex (male or female), self-report of race (black, white, Asian, or other), and non-steroidal anti-inflammatory use (regular use of aspirin/aspirin-containing or ibuprofen/ibuprofen-containing products or not). BMI (kg/m^2) was categorized as underweight (<18.5); normal (18.5-24.9); overweight (25-30.0); and obese (>30), and was based on self-report of height and weight. Physical activity was categorized as less than 2 hours of vigorous activities per week (low) vs. 2 or more hours of vigorous activities per week (high) to stay consistent with current recommendations (181). Hormone supplement status was categorized as never, current (ever taken or currently taking female hormones), former, or unknown. Education was categorized into less than high school; high school degree; some college or post high school training; and college or graduate degree. Age at randomization, alcohol intake (g/day), fiber (g/day), calcium intake (food and supplements; mg/day), and energy intake (kcal/day) were left as continuous variables.

Statistical analysis:

Means and frequencies, with their respective standard deviations and percentages, were calculated for continuous and categorical characteristics, stratified by either race/ethnicity or DII score quartiles. Chi-square and analysis of variance tests were used to determine differences, if any, in descriptive characteristics between quartiles of DII scores or between the racial subgroups. Normal distribution was assessed with histograms (QQ plot or Shapiro-Wilk test) for each variable.

Multivariable logistic regression were used to calculate the odds of prevalent CRA for different quartiles of DII scores, as per other studies (121). Separate models were created for adenoma type (all prevalent, advanced, non-advanced, or multiple (>1) adenoma). Models were also run using incident or recurrent adenoma as the main outcome versus no CRA. Regression models were initially adjusted for sex, race smoking, age, physical activity, education, hormone status, non-steroidal anti-inflammatory use, calcium intake, daily energy, fiber intake, and alcohol intake. Additionally, an interaction term for sex and DII score category was included. All potential covariates and interaction term were included in the initial model and then were evaluated for model inclusion if they were not significant in the model ($p<0.20$) and then removed if their exclusion did not result in a lower Akaike information criterion (AIC) statistic (168). The most parsimonious model that retained predictive accuracy, as indicated by a lower AIC value, was selected. The models were stratified by sex if the interaction between sex and DII scores was significant ($p<0.20$). To more fully investigate the effects of race, models predicting prevalent distal adenoma were also run, stratified by both sex and race. The covariates identified in the sex-specific models were used for the race-specific models.

Results

Descriptive characteristics for the quartiles of the DII are presented in Table 5.1. Compared to those in quartile 4, those in quartile 1 (least inflammatory) were significantly more likely to be female (65.0% vs. 26.0%), Asian (7.4% vs. 1.6%), have a college education (45.5% vs. 27.7%), have a high amount of physical activity (68.2% vs. 42.4%), have never smoked (52.4% vs. 40.8%), and have a normal BMI (41.5% vs. 22.4%). Asians were most likely to have a diet in the lowest (least inflammatory) DII quartile (49.0%), while blacks were most likely to have a diet in the highest quartile (most inflammatory; 27.4%) Women in quartile 1 (least

inflammatory) were more likely to be current hormone users than women in quartile 4 (most inflammatory; 56.6% vs. 46.3%). Additionally, compared to those in quartile 4, those in quartile 1 were older (62.9 vs. 61.7 years), had higher intakes of calcium (1349.7 vs. 1168.4 mg/day), and lower intakes of daily calories (1836.6 vs. 2375.7 kcal/day).

In the PLCO study population, there was a higher percentage females among blacks than whites (51.9% vs. 46.3%) but Asians and those of "other" race were more likely to be male than whites (Table 5.2). Compared to whites, blacks and Asians were more likely to report "high" physical activity. Asians and those of "other" race were less likely than whites to be obese but blacks were more likely to be obese. Whites had the highest intakes of calcium, calories, and alcohol per day, compared to other racial/ethnic subgroups.

Prevalent distal adenoma

Because of the interaction with DII scores (p=0.02), models for prevalent distal adenoma were stratified by sex. In fully adjusted models (adjusted for race, education, smoking status, BMI, age, and calcium intake), compared to those with DII scores in quartile 1 (least inflammatory), males with DII scores in quartile 3 (adjusted odds ratio (aOR)=1.29; 95% confidence intervals (CI)=1.13-1.49) and quartile 4 (aOR=1.45; 95% CI=1.26-1.66; Table 5.3) were more likely to have prevalent distal CRA. Males with DII scores in quartile 3 (aOR=1.37; 95% CI=1.15-1.63) and quartile 4 (aOR=1.47; 95% CI=1.24-1.74) were also more likely to have a non-advanced adenoma, compared to those in the lowest quartile of DII scores. Males with DII scores in quartile 4 (aOR=1.31; 95% CI 1.05-1.63; Table 5.3) were more likely to have advanced CRA, compared to those with DII scores in quartile 1. Males with DII scores in quartile 3 (aOR=1.30; 95% CI=1.00-1.70) and quartile 4 (aOR=1.60; 95% CI=1.23-2.10) were more likely to have more than one distal CRA, compared to those with DII scores in quartile 1. In fully

adjusted models, the DII was not associated with the prevalence of distal CRA (advanced, non-advanced, or multiple) in females. There were no significant associations between DII scores and CRA in any racial/ethnic subgroup other than whites (Table 5.4).

Incident adenoma

There was no significant interaction between sex and DII scores (p=0.52) in models using incident adenoma as the outcome, but results are presented for men and women separately, as well as combined. Men and women with DII scores in the highest quartile (most inflammatory) were more likely to have incident adenoma, compared to those with the least inflammatory DII scores, adjusted for physical activity, race, smoking status, hormone therapy, sex, calcium intake, and daily calorie intake, although this association did not reach statistical significance (aOR=1.19; 95% CI=0.98-1.43; Table 5.5). Asians (aOR=0.76; 95% CI=0.56-1.02) and those of other races (aOR=0.67; 95% CI=0.42-1.07) had lower odds of incident CRA, compared to whites, but these results were not significant (Table 5.5).

Recurrent adenoma

There was a significant interaction between sex and DII scores (p=0.009) so models using recurrent adenoma as the outcome were stratified. In males, the odds of recurrent adenoma were higher in, but not significantly associated with, the highest quartile (most inflammatory) of DII scores, compared quartile 1 DII scores (aOR=1.32; 95% CI=0.87-1.99; Table 5.6), adjusted for race, BMI, and age. In females, the odds of recurrent adenoma were higher in, but not significantly associated with, the highest quartile (most inflammatory) of DII scores, compared to quartile 1 DII scores (aOR=1.30; 95% CI=0.78-2.22; Table 5.6), adjusted for race, education, and age.

Discussion

In this large cohort of men and women, enrolled as part of the PLCO screening arm, we sought to investigate the association between CRA and DII scores and found that a more inflammatory diet was associated with distal CRA prevalence in men, but not in women. Specifically, males who consumed a more inflammatory diet were more likely to have non-advanced adenomas, advanced adenomas, and multiple adenomas than men who consumed a less inflammatory diet. However, no conclusions could be made about the effects of the DII on CRA prevalence in any specific racial/ethnic subgroup other than whites.

It is believed that inflammation promotes an environment that increases genetic mutations, and disables the mechanisms that repair these errors (96). There is also evidence that inflammation may promote growth factors that enhance tumor growth, particularly through enhanced angiogenisis (96). Further, a vicious cycle is created in that tumor cells produce cytokines that attract leukocytes, which further promote inflammation (84). Higher systemic concentrations of inflammatory cytokines may then lead to the development of colorectal adenomas (191). Diet can affect systemic inflammation, both positively and negatively. A high intake of calories and certain types of fat (e.g. trans-fats) may lead to pro-inflammatory states (192, 193), while fruits and vegetables contain antioxidants that counteract inflammation (194). The DII has recently been developed as a way for researchers to characterize the overall inflammatory nature of diet (22). This index has been shown to be associated with inflammatory conditions, such as colon, prostate, and pancreatic cancers, and asthma (121, 124, 125, 195, 196), as well as circulating inflammatory proteins (22, 196, 197).

Findings of the present study are generally consistent with other studies that have found lower odds of prevalent CRA among those who consume a "healthy" diet (134, 177). For

example, men with higher scores on several dietary indices (Healthy Eating Index, Mediterranean diet, Dietary Approach to Stop Hypertension) were less likely to have a prevalent CRA, compared to men with a less healthy diet (134). These results suggest that there may be a common element, such as an anti-inflammatory dimension, among the dietary indices, which confers adenoma-protective effects, and that the specific type of diet may be less important than this common beneficial element (e.g. anti-inflammatory dimension). Indeed, for several of the mentioned dietary indices, better scores have been associated with lower concentrations of inflammatory markers (23, 198, 199).

It is interesting that lower DII scores, indicating a less-inflammatory diet, were not strongly associated with distal CRA prevalence in women, although there was a trend across quartiles of higher odds of CRA with higher DII scores. Previous studies have shown that women with more inflammatory diets, as reflected by higher DII scores, were more likely to have developed colorectal cancer, compared to those with less inflammatory diets (123, 124). Since adenomas are precursors to cancer we expected to find a positive association between DII scores and CRA prevalence in women. However, dietary predictors for adenomas may not be the same as dietary predictors for colon cancer in women. It has been estimated that only half of studies on the association between diet indices (e.g. Mediterranean diet and Healthy Eating Index) and colorectal cancers report sex-specific risks (200), suggesting that the current literature may not fully capture the effects of diet on adenoma prevalence or cancer incidence in males and females, individually. Of those that have reported on dietary predictors for CRA in men and women separately, several did not find a protective effect of diet in women (134, 177, 201). Another explanation for the discrepancy in findings between the current study and previous studies may have to do with lower (less inflammatory) DII scores in the present study (-2.1

(standard deviation: 1.6) vs. -0.9 (standard deviation: 2.0); $p<0.0001$; (124)). The generally lower scores in the present study may have restricted the ability to see beneficial dietary effects because the diets were generally "adequate" for adenoma prevention.

Conclusions about the effectiveness of the DII on CRA prevalence in the different racial/ethnic subgroups cannot be fully determined since it is unknown whether the null findings in racial/ethnic subgroups other than whites are actually true or because of the small numbers of participants in each strata. However, it is likely that the null findings are primarily from lack of sample size. Sample size calculations indicate that, assuming a 32% exposure of the most inflammatory diet among cases, a 10:1 ratio of controls to cases, and a 1.45 odds of adenoma among cases, there would need to be at least 266 cases in each racial subgroup to detect significant differences. However, another explanation for the null findings may have to do with unaccounted factors, such as way that food is prepared (e.g. fried or grilled vs. steamed) or other avenues of inflammation (e.g. physical or emotional stress). Previous literature suggests that, in black men, chronic inflammation from "biological weathering", produced by cumulative and multi-dimensional stress is common (202).

The odds of adenoma recurrence were higher among those who consumed the most inflammatory diets, compared to those consuming the least inflammatory diets, although this difference was not significant. The use of the DII is unique in that it is based on dietary intake, but it also characterizes an aspect of inflammation. Distinguishing between inflammatory and other characteristics of diet may be especially important in regards to adenoma recurrence. Previous studies examining the effect of diet on CRA recurrence have been equivocal on whether there are associations between a healthier diet and lower adenoma recurrence (187, 188). Participants who were assigned to a low-fat, high-fiber, high-fruit and –vegetable diet did not

have a lower risk of recurrent adenoma, compared to those with a usual diet (203), although those who strictly adhered to a low-fat, high-fiber, high-fruit and –vegetable diet did have lower odds of recurrent CRA after 4 years (188). Another study found that women, but not men, who adhered to a "Mediterranean" diet pattern had lower odds of recurrent CRA, although a "Western" dietary pattern was not associated with recurrent CRA in either men or women (187). However, studies are quite consistent in finding a reduced CRA recurrence among those taking aspirin and other anti-inflammatories (204-206). The discrepancy in findings between dietary and anti-inflammatory studies suggest that CRA recurrence may be more dependent on inflammation and less on nutritional status. Even with a small sample size in the recurrent cohort, the odds of recurrent CRA were higher for those who consumed the most inflammatory diets. These findings highlight the ability of the DII to discriminate between diets of high and low inflammation, and consequently be used as a tool in characterizing inflammation.

One of the strengths of this study is the large, diverse cohort of individuals with diverse dietary habits, enabling the analysis of adenoma outcomes across a broad spectrum of food intakes. Another strength of the study is the novel way to characterize the inflammatory nature of diet. Inflammation is an important factor in disease occurrence, and the DII is the first index to be developed for specifically measuring how inflammatory a diet is. A limitation of this study is the relatively small numbers of participants in the racial/ethnic subgroups other than whites, limiting the ability to detect significant associations. Finally, the DII was not able to fully determine the inflammatory nature of the diets due to some of the DII variables not being included in the dietary questionnaire (e.g. eugenol, garlic, ginger, saffron, turmeric, pepper, rosemary, and thyme/oregano). However, most items for the DII were included in the calculations, and represented the most commonly consumed foods/nutrients.

In conclusion, a more inflammatory diet is associated with a reduced risk of CRA, particularly in men. The results for women or for those of a race/ethnicity other than white were less conclusive, and future research should focus on determining more specific dietary preventive measures for these subgroups. Results from this study support an inflammatory mechanism for the development of CRA. From a public health perspective, future work should focus on helping individuals understand and incorporate anti-inflammatory elements into their diet.

Table 5.1: Baseline characteristics of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (screening arm participants), by Dietary Inflammatory Index quartiles (N=44,278)

Characteristic	**Quartile 1 DII scores (least inflammatory) <-2.93**	**Quartile 2 DII scores -2.93 to -1.80**	**Quartile 3 DII scores -1.81 to -0.45**	**Quartile 4 DII scores (most inflammatory) >-0.45**
Categorical variables	**Number (%)**	**Number (%)**	**Number (%)**	**Number (%)**
Sex				
Male	3,879 (16.3)	5,273 (22.2)	6,444 (27.1)	8,192 (34.4)
Female	7,190 (35.1)	5,797 (28.3)	4,625 (22.6)	2,878 (14.0)***
Race				
White	9,625 (24.0)	10,107 (25.2	10,141 (25.3)	10,195 (25.4)
Black	400 (24.9)	364 (22.7)	402 (25.0)	442 (27.4)
Asian	815 (49.0)	381 (22.9)	284 (17.1)	183 (11.0)
Other	229 (24.4)	218(23.2)	242 (25.8)	250 (26.6)***
Education				
College	5,034 (30.5)	4,389 (26.6)	4,012 (24.3)	3,067 (18.6)
Some college	3,616 (24.1)	3,815 (25.5)	3,732 (24.9)	3,820 (25.5)
High school	2,034 (20.3)	2,290 (22.9)	2,644 (26.4)	3,042 (30.4)
Less than high school	385 (13.8)	576 (20.7)	681 (24.4)	1,141 (41.0)***
Physical Activity[1]				
High	7,545 (30.3)	6,678 (26.8)	5,957 (24.0)	4,6949 (18.9)
Low	3,524 (18.2)	4,392 (22.6)	5,112 (26.4)	6,367 (32.8)***
Smoking				
Never	5,801 (27.3)	5,703 (26.8)	5,214 (24.6)	4,512 (21.2)
Current	569 (13.7)	759 (18.3)	1,068 (25.8)	1,746 (42.2)
Former	4694 (24.8)	4,608 (24.4)	4,787 (25.3)	4,812 (25.4)***
Anti-inflammatory use				
Yes	2,272 (25.4)	2,187 (24.5)	2,254 (25.3)	2,216 (24.8)
No	8,797 (24.9)	8,883 (25.1)	8,815 (24.9)	8,854 (24.8)
Hormone therapy (females)				
Current	4,069 (37.5)	3,083 (28.4)	2,377 (21.9)	1,331 (12.3)

Former	1,115 (34.8)	908 (28.3)	715 (22.3)	468 (14.6)
Never	1,976 (31.2)	1,779 (28.1)	1,513 (23.9)	1,064 (16.8)
Unknown	23 (33.3)	20 (29.0)	17 (24.6)	9 (13.0)***
Body Mass Index (kg/m^2)				
0-18.5	100 (37.2)	70 (26.0)	59 (21.9)	40 (14.9)
18.5-25	4,592 (32.8)	3,725 (26.6)	3,223 (23.0)	2,478 (17.7)
25-30	4,318 (22.4)	4,819 (25.0)	4,973 (25.8)	5,194 (26.9)
30+	2,059 (19.3)	2,453 (23.0)	2,814 (26.4)	3,358 (31.4)***
Missing (n=430)				
Continuous variables	**Mean (standard deviation)**	**Mean (standard deviation)**	**Mean (standard deviation)**	**Mean (standard deviation)**
Age (years; continuous)	62.9 (5.4)	62.8 (5.3)	62.4 (5.2)	61.7 (5.1)***
Calcium intake (supplements and food; mg/day)	1,349.7 (578.6)	1,256.2 (587.9)	1,212.1 (601.5)	1,168.4 (641.6)***
Calories (kcal/day)	1,836.6 (649.6)	1,960.6 (723.4)	2,093.4 (782.3)	2,375.7 (911.0)***
Alcohol (g/day)	8.4 (14.1)	9.0 (17.0)	10.9 (21.0)	15.9 (34.9)***
Fiber (g/day)	26.8 (10.8)	24.7 (10.1)	22.6 (9.3)	19.9 (8.1)***

***p<0.0001; Chi-square test for categorical and analysis of variance for continuous variables.

3. Less than 2 hours of vigorous activities per week (low) vs. 2 or more hours of vigorous activities per week (high)

Table 5.2: Descriptive characteristics of Prostate, Lung, Colorectal, and Ovarian screening arm participants in the Dietary Inflammatory Index analysis, by race (N=44,255)

Categorical Variables	**Whites (N=40,049) Reference group**	**Blacks (N=1,604)**	**Asian (N=1,663)**	**Other (N=939)**	**Overall chi-square p-value**
Sex					<0.0001
Male	21,503 (53.7)	771 (48.1)	943 (56.7)	571 (60.8)	
Female	18,546 (46.3)	833 (51.9)***	720 (43.3)*	368 (39.2)***	
Education					<0.0001
College	14,974 (37.4)	483 (30.1)	776 (46.7)	262 (27.9)	
Some college	13,493 (33.7)	596 (37.2)	527 (31.7)	357 (38.0)	
High school	9,198 (23.0)	322 (20.0)	289 (17.4)	196 (20.9)	
Less than high school	2,384 (6.0)	203 (12.7)***	71 (4.3)***	124 (13.2)***	
Physical Activity[1]					<0.0001
High	22,661 (56.6)	927 (57.8)	1,016 (61.1)	509 (54.2)	
Low	17,388 (43.4)	677 (42.2)***	647 (38.9)**	430 (45.8)	
Smoking					<0.0001
Never	19,243 (48.0)	672 (41.9)	912 (54.8)	394 (42.0)	
Current	3,653 (9.1)	274 (17.1)	121 (7.3)	92 (9.8)	
Former	17,153 (42.8)	658 (41.0)***	630 (37.9)***	453 (28.2)*	
Anti-inflammatory use					0.0009
Yes	8,039 (20.1)	349 (21.8)	306 (18.4)	229 (24.4)	
No	32,010 (79.9)	1,255 (78.2)	1,357 (81.6	710 (75.6)*	
Hormone therapy (females)					<0.0001
Current	9,963 (53.7)	308 (37.0)	403 (56.0)	186 (50.5)	
Former	2,863 (15.4)	180 (21.6)	103 (14.3)	60 (16.3)	
Never	5,668 (30.6)	336 (40.3)	208 (28.9)	120 (32.6)	
Unknown	52 (0.3)	9 (1.1)***	3 (0.8)*	2 (0.5)	
Body Mass Index (kg/m^2)					<0.00001
0-18.5	219 (0.6)	9 (0.6)	36 (2.2)	5 (0.5)	
18.5-25	12,535 (31.3)	338 (21.0)	910 (54.7)	231 (24.6)	
25-30	17,618 (44.0)	646 (40.3)	594 (25.7)	440 (46.9)	

30+	9,677 (24.2)	611 (38.1)***	123 (7.4)***	263 (28.0)***	
Case status					<0.0001
No adenoma	36,292 (90.6)	1,474(91.9)	1,572 (94.5)	856 (91.2)	
Adenoma	3,757 (9.4)	130 (8.1)	91 (5.5)***	83 (8.8)	
Dietary Inflammatory Index					<0.0001
Quartile 1 (lowest; reference)	9,619 (24.0)	399 (24.9)	815 (49.0)	229 (24.4)	
Quartile 2	10,100 (25.2)	364 (22.7)	381 (22.9)	218 (23.2)	
Quartile 3	10,139 (25.3)	401 (25.0)	284 (17.1)	242 (25.8)	
Quartile 4 (highest)	10,191 (25.5)	440 (27.4)	183 (11.0)***	250 (26.6)	
Continuous variables	**Means (SD)**	**Means (SD)**	**Means (SD)**	**Means (SD)**	**Analysis of variance p-value**
Calcium (diet and supplements; mg/day)	1,270.7 (605.2)	962.5 (533.1)	1,000.4 (577.2)	1,140.0 (603.9)	<0.0001
Calories (kcal/day)	2,078.3 (798.8)	1,987.3 (872.2)	1,865.2 (754.1)	2,058.4 (863.5)	<0.0001
Age (years)	62.5 (5.3)	62.2 (5.3)	63.01 (5.6)	61.4 (5.0)	<0.0001
Alcohol (g/day)	11.4 (23.4)	7.5 (22.6)	8.1 (25.1)	8.2 (19.2)	<0.0001
Fiber (g/day)	25.5 (9.8)	23.1 (11.6)	23.0 (10.8)	23.8 (11.8)	<0.0001

*p-value<0.05; **p<0.001; ***p<0.0001; Chi-square for categorical and t-tests for continuous variables; comparing whites vs blacks (or Asian or other)

1. Less than 2 hours of vigorous activities per week (low) vs. 2 or more hours of vigorous activities per week (high)

Table 5.3: Associations between colorectal adenoma and Dietary Inflammatory Index score quartiles[1] in the Prostate, Lung, colorectal, and Ovarian cancer screening arm participants, by sex (N=44,255)

	Quartile 1 (least inflammatory; reference)	**Quartile 2**	**Quartile 3**	**Quartile 4 (most inflammatory)**	**Wald Chi-square P-trend**
Men (N=23,788)					
All distal adenoma[2]	1.00	1.07 (0.92-1.24)	**1.29 (1.13-1.49)**	**1.45 (1.26-1.66)**	<0.0001
Non-advanced adenoma[3]	1.00	1.16 (0.96-1.40)	**1.37 (1.15-1.63)**	**1.47 (1.24-1.74)**	<0.0001
Advanced adenoma[4]	1.00	0.96 (0.76-1.21)	1.18 (0.95-1.47)	**1.31 (1.05-1.63)**	0.0001
Multiple adenomas (≥2)[5]	1.00	1.18 (0.89-1.56)	**1.30 (1.00-1.70)**	**1.60 (1.23-2.10)**	0.001
Women (N=20,467)					
All distal adenoma[6]	1.00	0.90 (0.78-1.04)	1.13 (0.98-1.31)	1.08 (0.91-1.29)	0.03
Non-advanced adenoma[7]	1.00	0.92 (0.77-1.10)	1.15 (0.96-1.39)	1.19 (0.96-1.47)	0.05
Advanced adenoma[8]	1.00	0.86 (0.68-1.08)	1.09 (0.87-1.38)	0.96 (0.73-1.27)	0.27
Multiple adenomas (≥2)[9]	1.00	0.77 (0.55-1.07)	1.08 (0.79-1.49)	1.28 (0.90-1.82)	0.04

Bolded values are significant ($p<0.05$).

1. Quartile 1: DII <-2.93; Quartile 2: DII -2.93 to -1.80; Quartile 3: DII -1.81 to -0.45; Quartile 4: DII >-0.45;
2. Adjusted for body mass index, education smoking status, race, total daily calories, calcium intake, and age; number of cases=2,654
3. Adjusted for physical activity, smoking, race, total daily calories, calcium intake, alcohol, and age; number of cases=1,582

4. Adjusted for physical activity, education, smoking, race, total daily calories, calcium intake, fiber intake, alcohol, and age; number of cases=1,038
5. Adjusted for physical activity, education, smoking, race, total daily calories, calcium intake, alcohol, and age; number of cases=736
6. Adjusted for body mass index, smoking race, hormone status, total daily calories, alcohol, and age; number of cases=1,407
7. Adjusted for body mass index, education, smoking status, race, hormone status, total daily calories, calcium intake, and age; number of cases=872
8. Adjusted for body mass index, smoking status, race, total daily calories, alcohol, and age; number of cases=526
9. Adjusted for body mass index, smoking, race total daily calories, calcium intake, alcohol, and age; number of cases=276

Table 5.4: Associations between prevalent distal colorectal adenoma and Dietary Inflammatory Index score quartiles in the Prostate, Lung, Colorectal, and Ovarian cancer screening arm participants, by race and sex (N=44,255)

	White		**Black**		**Asian**		**Other**	
	aOR (95% CI)		**aOR (95% CI)**		**aOR (95% CI)**		**aOR (95% CI)**	
Categorical variables	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
	(N=21,503)	**(N=18,546)**	**(N=771)**	**(N=833)**	**(N=943)**	**(N=720)**	**(N=571)**	**(N=368)**
Dietary Inflammatory Index quartiles[1]								
Quartile 1 (least inflammatory; reference)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Quartile 2	1.07 (0.91-1.25)	0.89 (0.77-1.03)	0.84 (0.37-1.90)	1.67 (0.77-3.63)	1.07 (0.54-2.13)	1.35 (0.53-3.45)	0.85 (0.33-2.22)	0.46 (0.14-1.55)
Quartile 3	**1.32 (1.13-1.55)**	1.12 (0.96-1.30)	0.60 (0.26-1.34)	0.96 (0.39-2.37)	0.81 (0.37-1.77)	2.33 (0.84-6.43)	0.57 (0.22-1.49)	1.96 (0.67-5.71)
Quartile 4 (most inflammatory)	**1.39 (1.17-1.66)**	1.08 (0.90-1.30)	0.91 (0.42-1.98)	1.57 (0.65-3.76)	1.21 (0.51-2.85)	**	0.85 (0.34-2.12)	0.82 (0.20-3.27)
Education								
College (reference)	1.00		1.00		1.00		1.00	
Some college	**1.16 (1.04-1.28)**		1.08 (0.58-2.01)		0.67 (0.36-1.27)		1.39 (0.65-2.95)	
High school	**1.21 (1.07-1.36)**		1.29 (0.65-2.56)		0.55 (0.22-1.37)		0.91 (0.34-2.44)	
Less than high school	**1.24 (1.05-1.46)**		1.10 (0.51-2.38)		1.20 (0.37-3.91)		**3.21 (1.38-7.48)**	
Smoking								
Never (reference)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Current	**1.94 (1.68-2.23)**	**2.36 (1.98-2.82)**	1.80 (0.94-3.45)	**3.03 (1.36-6.74)**	1.94 (0.78-4.88)	1.62 (0.34-7.77)	0.98 (0.36-2.66)	**5.25 (1.65-16.87)**
Former	**1.29 (1.17-1.42)**	**1.19 (1.05-1.35)**	1.00 (0.56-1.80)	1.54 (0.79-2.99)	1.21 (0.70-2.18)	0.52 (0.17-1.59)	0.85 (0.46-1.58)	1.20 (0.47-3.10)
Body Mass Index (kg/m^2)								
<25 (reference)	1.00	**1.00**	1.00	1.00	1.00	1.00	1.00	1.00

25-30	1.08 (0.97-1.21)	1.13 (0.99-1.30)	1.56 (0.80-3.05)	1.21 (0.49-2.98)	1.37 (0.79-2.37)	1.30 (0.58-2.93)	1.07(0.52-2.20)	0.98 (0.38-2.58)
30+	**1.23 (1.08-1.40)**	**1.27 (1.10-1.48)**	0.97 (0.54-1.75)	1.52 (0.65-3.53)	0.87 (0.29-2.65)	**	0.70 (0.29-1.71)	0.80 (0.27-2.35)
Hormone therapy								
Current		**0.82 (0.72-0.94)**		1.54 (0.78-3.06)		0.86 (0.37-1.97)		0.66 (0.24-1.79)
Former		0.94 (0.79-1.11)		0.96 (0.43-2.14)		0.38 (0.08-1.80)		1.21 (0.39-3.76)
Never/unknown (reference)		1.00		1.00		1.00		1.00
Continuous variables	**p-value**	**p-value**	**p-value**	**p-value**	**p-value**	**p-value**	**p-value**	**p-value**
Age (continuous)	**<0.0001**	**<0.0001**	0.39	**0.006**	0.75	**0.04**	0.44	0.07
Calcium intake (food and supplements; mg/day)	**0.005**	0.06	0.16	0.64	0.30	0.72	0.41	0.58
Calories (kcal/day)		0.08		0.96		0.29		0.69
Fiber (g/day)	0.41		0.16		0.29		0.27	
Alcohol (g/day)	**0.0005**	0.16	0.15	0.99	0.16	0.60	0.33	0.12

aOR=adjusted odds ratio; CI=confidence interval; bolded values are significant (p<0.05); **not able to be calculated due to small numbers

1. Quartile 1: DII <-2.93; Quartile 2: DII -2.93 to -1.80; Quartile 3: DII -1.81 to -0.45; Quartile 4: DII >-0.45;

Table 5.5: Associations between **incident** adenoma and Dietary Inflammatory Index score quartiles the Prostate, Lung, Colorectal, and Ovarian cancer screening arm participants (N=18,599)

	Males (N=10,529)	**Female (N=8,070)**	**Males and females, combined (N=18,599)***
Categorical variables	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
Dietary Inflammatory Index quartiles[1]			
Quartile 1 (least inflammatory; reference)	1.00	1.00	1.00
Quartile 2	0.97 (0.76-1.24)	1.09 (0.82-1.44)	1.03 (0.85-1.23)
Quartile 3	1.00 (0.78-1.26)	1.26 (0.94-1.68)	1.09 (0.91-1.31)
Quartile 4 (most inflammatory)	1.13 (0.90-1.42)	1.30 (0.92-1.82)	1.19 (0.98-1.43)
Physical Activity			
Low	1.30 (1.12-1.52)	1.19 (0.96-1.48)	1.27 (1.12-1.44)
High (reference)	1.00	1.00	1.00
Race			
White (reference)	1.00	1.00	1.00
Black	1.07 (0.68-1.67)	1.06 (0.62-1.83)	1.06 (0.75-1.50)
Asian	0.83 (0.59-1.18)	0.59 (0.33-1.06)	0.76 (0.56-1.02)
Other	0.54 (0.29-0.99)	1.02 (0.49-2.09)	0.67 (0.42-1.07)
Smoking			
Never (reference)	1.00	1.00	1.00
Current	**2.00 (1.54-2.59)**	**1.88 (1.28-2.77)**	1.97 (1.59-2.44)
Former	**1.26 (1.07-1.48)**	**1.46 (1.16-1.83)**	1.32 (1.16-1.50)
Hormone therapy (females only			
Never/unknown (reference)		1.00	**1.00**
Current/former		0.82 (0.66-1.02)	**0.82 (0.65-1.02)**
Sex			
Male			**1.00**

Female			**0.83 (0.68-1.01)**
Continuous variables	**p-value**	**p-value**	**p-value**
Calcium intake (food and supplements; mg/day)	0.12	0.06	**0.01**
Calories (kcal/day)		**0.01**	**0.04**

aOR=adjusted odds ratio; CI=confidence interval; Bolded values are significant ($p<0.05$); Interaction between sex and Dietary Inflammatory Index categories was not significant ($p=0.52$)

1. Quartile 1:<-2.93; Quartile 2: -2.93 to -1.80; Quartile 3: -1.81 to -0.45; Quartile 4: >-0.45; Bolded values are significant ($p<0.05$); not able to be calculated due to small numbers;

Table 5.6: Associations between **recurrent** adenoma and Dietary Inflammatory Index score quartiles the Prostate Lung, Colorectal, and Ovarian Cancer Screening Trial (N=1,601)*

	Males (N=1,052)	**Females (N=549)**
Categorical variables	**aOR (95% CI)**	**aOR (95% CI)**
Dietary Inflammatory Index quartiles[1]		
Quartile 1 (least inflammatory; reference)	1.00	1.00
Quartile 2	1.37 (0.87-2.16)	1.49 (0.94-2.37)
Quartile 3	1.07 (0.70-1.64)	0.78 (0.48-1.26)
Quartile 4 (most inflammatory)	1.32 (0.87-1.99)	1.30 (0.78-2.22)
Race		
White	1.00	1.00
Black	0.84 (0.38-1.90)	2.96 (1.05-8.29)
Asian	2.72 (0.71-10.48)	7.37 (0.84-64.38)
Other	3.33 (0.90-12.30)	2.58 (0.95-7.01)
Education		
College (reference)		1.00
Some college		1.30 (0.84-2.01)
High school		0.89 (0.56-1.42)
Less than high school		0..53 (0.21-1.36)
Body Mass Index (kg/m^2)		
<-25	1.00	
25-30	1.45 (1.06-1.98)	
30+	1.88 (1.31-2.69)	
Continuous variable	p-value	p-value
Age (years)	0.13	0.17

aOR=adjusted odds ratio; CI=confidence interval; Bolded values are significant (p<0.05); *Significant interaction between Dietary Inflammatory Index score and sex (p=0.009), therefore, no values are reported for sex combined

1. Quartile 1:<-2.93; Quartile 2: -2.93 to -1.80; Quartile 3: -1.81 to -0.45; Quartile 4: >-0.45

CHAPTER 6

IMPACT OF RACE ON THE ASSOCIATION BETWEEN DIETARY PATTERN SCORES AND THE PREVALENCE OF COLORECTAL ADENOMA[3]

[3] Alyson Haslam, Sara Wagner Robb, Hanwen Huang, James R Hébert, Mark H Ebell. To be submitted to the journal, "Public Health Nutrition"

Abstract

Background: Diet is associated with both colorectal cancer and colorectal adenomas. Factor analysis is a data-driven method to determine patterns in people's diet, which can then be evaluated for their association with CRA. Examining differences in dietary intake may be one avenue for addressing racial disparities in colorectal adenoma prevalence.

Methods: Factor analysis was used to derive both sex- and race-specific dietary patterns in the screening arm population of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Logistic regression was used to assess associations between identified factor scores and colorectal adenoma in sex- and race-specific subgroups. Classification and regression tree analysis was used to further explore dietary predictors for each race.

Results: Three diet patterns were observed in this cohort: "Fruits and vegetables", "Western", and "Sweet and salty". In men, having higher scores on the "Western" diet was associated with higher odds of any, advanced, or multiple (>1) adenoma. In women, having a "Fruits and vegetable" score in the highest quintile was associated with lower odds of multiple adenoma (>1). Men of all racial subgroups had higher odds of adenoma with higher intakes of a "Western" diet, but black men and men of other race had higher odds of adenoma with higher intakes of a "Fruits and vegetables" pattern.

Conclusion: Of the three dietary factors, the "Western" diet pattern was most strongly associated with prevalent colorectal adenoma. Further research is needed to examine the association between fruits and vegetables and adenoma in the different racial subgroups, and why the direction of the association appears to differ for different subgroups.

Introduction

Colorectal adenomas (CRA) are small, benign tumors that occur in the lining of the large intestine and are precursors to colorectal cancer. Adenomas are more common in men, and results from several studies suggest that there are racial differences in adenoma prevalence (3-6). The incidence of colorectal cancer can be influenced to a great extent by diet (8, 9). Therefore, it seems logical that diet would also be very influential in the development of CRA. The difficulty lies in being able to characterize a diet that decreases the incidence of CRA.

Multiple studies have been conducted to evaluate the association between CRA and diet using index-based assessments (134) that are often based on dietary recommendations of researchers. An alternative way to examine diet is by capturing real-world patterns of eating. A few studies have examined this association using dietary patterns (14, 207, 208), but the results from these studies are difficult to compare and are somewhat inconsistent, making it difficult to determine risky or beneficial dietary patterns. One study found that French women who had high scores for "Western" (comprised of foods such as pizza, rice, pasta, and sweets) and "Drinking" (comprised of alcohol, coffee, and snacks) patterns were at increased risk for the development of colorectal adenoma, compared to women with low scores for these patterns (207). In a cohort of Japanese men, diets high in fermented dairy products, fruits, vegetables, sweets, and low in alcohol were associated with approximately 40% lower odds of prevalent CRA, compared to those with low intakes of these foods (14). In the Health Professional Follow-Up Study, men who consumed a more "Western" diet were more likely to have colorectal adenoma, while those consuming a more "Prudent" diet (high in fruits, vegetables, whole grains, and poultry) were less likely to have colorectal adenoma, although results of the "Prudent" diet analysis were not significant (208). Black women with a more "Prudent" dietary pattern were at lower risk of

incident CRA than those with less "Prudent" dietary pattern, while black women with a more "Western" dietary pattern were more likely to have CRA compared to those with a less "Western" dietary pattern (13). In a small European intervention trial, none of the identified dietary patterns (Mediterranean, Western, or Snacks) were associated positively or negatively with CRA recurrence (187).

The subjects of these previous studies differ in their racial make-up and likely in their dietary intake as well. It is unknown whether differences in the results of these studies are due to differences in dietary intake between races, methodological differences (e.g. collection of dietary data), or both, which may limit the ability to compare study results. The purpose of the current study is to examine the dietary patterns in a diverse cohort of individuals to see if there are racial differences in identified dietary patterns, and to see if the identified dietary patterns predict the prevalence of adenoma, including when stratified by race.

Subjects and Methods

Study population

Data for these secondary analyses were collected as part of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (159-161). Between 1993 and 2000, men and women ages 55-74 were recruited to enroll in one of 10 screening trials across the US. Over 148,000 men and women were asked to complete a baseline questionnaire, with questions regarding sociodemographic characteristics, personal and family medical history, and used of selected factors, and were randomized to either a screening arm or a control arm (usual care). Individuals assigned to the screening arm received a flexible sigmoidoscopy (FS) screen at baseline and at either year 3 or year 5, depending on when they were enrolled. Patients who had an abnormal finding on FS examination were referred for endoscopic follow-up. Available

medical records and data on all lesions removed during the diagnostic endoscopy and related surgical procedures were obtained and reviewed by trained medical abstractors. Institutional review boards at the National Cancer Institute and the 10 screening centers provided approval of the study, and informed consent was provided by all study participants.

For these secondary analyses, participants were included if they were assigned to the screening arm and had returned the baseline questionnaire (N=75,611). Participants were excluded in this order if the FS examination was inadequate (defined as insertion to at least 50 cm with >90% of mucosa visible or suspect lesion found) or not done (n=18,148); had a personal history of any cancer (except melanoma) or did not know their personal history of cancer before the dietary questionnaire (n=2,202); had ulcerative colitis, Crohn's disease, Gardner's syndrome, or familial polyposis (n=712); did not complete the dietary questionnaire (n=5,726); had 8 or more missing responses on the dietary questionnaire (n=417); they had extreme calories reported on the dietary questionnaire (top or bottom 1% of sex-specific energy intake; n=896); had a positive FS but had either no follow-up or ambiguous follow-up (n=3,065); or race not identified (n=9), leaving 44,886 participants. Further, participants with missing information for key variables (body mass index (BMI), education, physical activity, and smoking status) were also excluded, resulting in a total sample size of 44,278.

Dietary questionnaire

Nutritional data were collected by using the Dietary Questionnaire that was developed by the National Cancer Institute (165). Each screening arm participant was asked to complete the 16-page Dietary Questionnaire and report the frequencies, portion sizes, and in some cases, the seasonal intake or food type for 137 different foods during the year prior to enrollment. This method has been shown to perform at least as well as the Block and Willett food frequency

questionnaires, which are validated and reliable measures of dietary intake used in research (165). Responses were used to estimate daily individual nutrients intake, based on the Continuing Survey of Food Intakes by Individuals (CSFII) data (165). The CSFII created 182 food groups from 5,261 individual food codes. The list of food groups included in the food/nutrient database was narrowed by excluding those that contributed little to the nutrient intake in the United States, often because of infrequent consumption. For these analyses, food and groups were then further collapsed into 28 food groups (Appendix 6.1).

Prevalent adenoma

Prevalent adenoma in the distal region of the colon or rectum was the main outcome of interest. Advanced adenomas were those that were villous or tubulovillous in nature, large (≥1.0 cm), or displayed severe or high-grade dysplasia.

Factor Analysis

Eating patterns were identified using factor analysis, and were based on daily intake (in grams) of each food item. For this, PROC FACTOR in SAS with option METHOD = PRINCIPAL was used. The ROTATE = VARIMAX function was used for the rotation of the factors by an orthogonal transformation, which improves the interpretability of the factors by minimizing the loading on multiple factors. Food components that loaded at <0.30 were removed from the factor analysis. The identification of retained items from each factor was determined by inspection of the scree plots and eigenvalues greater than one. A standardized factor score was calculated for each subject for each of the three factors. Individual factor scores were categorized into quintiles and used in subsequent logistic regression to analyze the association between dietary factors and CRA events. Because of small sample sizes in the

different racial subgroups, the factor scores were also categorized into tertiles for race-specific analysis.

Covariate Data

Several variables were evaluated as possible covariates in the adjusted models. These include smoking (never, current, or former), sex (male or female), physical activity (less than 2 hours of vigorous activities per week (low) vs. 2 or more hours of vigorous activities per week (high) (181)), and non-steroidal anti-inflammatory use (regular use of aspirin/aspirin-containing or ibuprofen/ibuprofen-containing products or not). Race was self-reported and was categorized as black, white, Asian, or other (Hispanic, Pacific Islander, and American Indian). BMI (kg/m^2) was categorized as underweight (<18.5); normal (18.5-24.9); overweight (25-30.0); and obese (>30). Height and weight were self-reported at baseline and follow-up. Education was categorized into less than high school; high school degree; some college or post high school training; and college or graduate degree. Hormone status was categorized as never, current, former, or unknown. Age at randomization, calcium intake (food and supplements; mg/day), fiber intake (g/day), alcohol intake (g/day), folic acid (food and supplements; mcg/day), and energy intake (kcal/day) were left as continuous variables.

Statistical analysis

Means (standard deviations) and frequencies were calculated for continuous and categorical descriptive and demographic characteristics, stratified by factor score quintiles. Chi-square and Kruskal-Wallace tests were used to determine differences in categorical and continuous variables, if any, between factor score quintiles. Normal distribution was assessed with histograms (QQ plot or Shapiro-Wilk test) for each variable.

Multivariable logistic regression was used to calculate the odds of CRA for different quintiles of factor scores, stratified by sex. Regression models were adjusted for race, smoking, age, physical activity, exercise, education, hormone status, non-steroidal anti-inflammatory use, calcium intake, folic acid, and daily energy, as indicated by model selection procedures. All potential covariates were included in the initial model. Variables that were not significant in the model ($p<0.20$) were removed if their exclusion did not result in a lower Akaike information criterion (AIC) statistic (168). The most parsimonious model that retained predictive accuracy, as indicated by a lower AIC value, was selected. To examine the effects or race, separate models were created for each sex and racial subgroup, using the factor tertiles and the covariates identified in the sex-only stratified model. All analyses were performed using SAS software (version 9.4; SAS Institute, Cary, North Carolina) using a p-value of 0.05, unless otherwise indicated.

Classification and regression tree (CART) analysis

As a secondary method to determine the dietary predictors or CRA, CART analysis was used. CART analysis is a data-driven, model-free estimator that uses recursive partitioning to find meaningful patterns in the data (209, 210). The most predictive variable is referred to as the parent node. Once the parent node is split, the process is repeated again for each child node. The two child nodes may then be split into two, using the next best predictor variable at the best possible cut-point. The process is repeated until there is only one observation in each of the child nodes, all observations within each child node have identical distribution of predictor variables, or after a certain number of splits pre-determined by the investigator.

For these analyses, SAS JMP Pro 12 (SAS Institute) was used. All previously mentioned covariates were used in the analysis (sex, age, education, exercise, BMI, smoking status,

hormone status, calcium intake, fiber intake, alcohol intake, folate intake, and total calories), as well as the factor scores identified in factor analysis. Additionally, a Mediterranean diet (altMED) score that has previously been calculated in Specific Aim 1 was used. The parameters for growing the tree included: minimum child node size of 50 and no more than seven levels. Recursive portioning was done for each race separately to more fully examine the predictors for each specific race. Once the probability of adenoma was determined for each terminal node of the CART, branches were classified as low-, moderate-, and high-risk of adenoma (<6%, 6-13%, and >13%, respectively).

Results

Table 6.1 shows the descriptive characteristics of the cohort, by race. Among blacks, female sex was more common than in other racial subgroups and there was a higher percentage with a BMI greater than or equal to 30. Asians were more likely to have a college education, to be a never smoker, and to have high amounts of physical activity than other racial subgroups. Whites had the highest intake of calcium, calories, and fiber compared with other racial subgroups.

Factor Analysis

The scree plots showed that there were 3 main factors. Racial subgroups had similar dietary factor loading patterns to each other (Table 6.2). Men and women had similar dietary factor loading patterns, with the exception of potatoes and nuts not loading on any factor for women and frozen yogurt not loading on any factor for men (Table 6.3). The first factor, "Fruits and vegetables" was comprised of vegetables, fruits, and legumes. For women, the "Fruits and vegetables" category also included fish. Factor 2 was named "Western diet" because of red and processed meats, fried foods, pasta dishes, and non-whole grains that loaded heavily on this

factor. Factor 3 was named "Sweet and salty" because of sweets, baked goods, ice cream, and snacks that loaded heavily on this factor.

When examining the distribution of factor scores across the racial subgroups, Asians had the highest percentage of both men and women in the highest quintile of Factor 1 ("Fruits and vegetable") intake (data not shown). Black, Asian, and "others" had similar percentages of men in quintile 5 of Factor 2 ("Western diet"; data not shown). Black women were most likely to be categorized in quintile 5 of Factor 2 ("Western diet"; data not shown). Whites had the highest percentage of both men and women in the highest quintile of Factor 3 ("Sweet and salty"; data not shown).

For men, having a higher intake of a "Western" diet was associated with higher odds of any distal adenoma (adjusted odds ratio (aOR)=1.21; 95% confidence interval (CI)=1.03-1.42; Table 6.4). Having a higher intake of a "Western" diet was even more strongly associated with having an advanced adenoma (aOR=1.32; 95% CI=1.07-1.63) or multiple adenomas (aOR=1.51; 95% CI=1.17-1.94). There were lower odds of CRA among men with higher intakes of "Fruits and vegetable" diets but this association was not significant. However, there was an overall trend that higher intake of a "Fruits and vegetable" diet was associated with lower odds of advanced CRA in men (p=0.005). For women, having an intake of a "Fruits and vegetable" diet in the highest quintile was associated with lower odds of multiple adenomas, compared to those in the lowest quintile (aOR=0.53; 95% CI=0.28-1.00; Table 6.5). Other dietary factors were not associated with having a CRA in women.

When stratifying by race and sex, white men and women of other races with higher intakes of a "Fruits and vegetable" diet were less likely to have a CRA, compared to those with lower intakes (Table 6.6). Men of all racial subgroups had higher odds of CRA with higher

intakes of a "Western diet" but the results were not significant. "Sweet and salty" factor scores were not associated the prevalence of CRA in any group.

CART analysis

In the CART analysis, different factors predicted high, moderate, and low risk of adenoma in each of the racial subgroups (Appendix 6.2; Figures 6.1-6.4). In the total study sample, men who were current smokers or men who were former smokers, older than 57 years of age, and had an altMED diet score less than four were classified as high-risk of prevalent adenomas (Figure 6.1). Women who were former or never smokers and less than 63 years of age were classified as low-risk of prevalent adenomas (Figure 6.1).

Similar to that of the total study population, white men who were current smokers and white men who were former smokers, older than 57 years of age, and have an altMED diet score less than 4 were classified as high-risk for prevalent adenomas (Figure 6.2). White women who were never or former smokers, less than 63 years of age, and had a BMI less than 30 kg/m^2 were classified as low-risk for prevalent adenomas (Figure 6.2).

Black men with alcohol intakes 0.5 g/day or more were classified as high-risk of adenomas, whereas black men with alcohol intakes of less than 0.5 g/day were classified as low-risk of adenomas (Figure 6.3). Black women who were 65 years of age or older or black women who were younger than 65 years of age but were current smokers were classified as moderate-risk of adenomas (Figure 6.3). Black women who were younger than 65 years of age and were former or never smokers were classified as low-risk of adenomas (Figure 6.3).

Asian men who had an altMED diet score of less than 8 were classified as moderate-risk for adenomas (Figure 6.4). Asian women or Asian men who had an altMED diet score of eight

or higher were classifies as low-risk of adenomas (Figure 6.4). Because of few numbers, meaningful results on the CART analysis was not able to be generated.

The overall adenoma prevalence in the total study population was 9%, with 5%, 9%, and 16% being classified as low-, moderate-, and high-risk, respectively (Table 6.7). Similarly, whites had an overall adenoma prevalence of 9%, with 5%, 9%, and 16% being classified as low-, moderate-, and high-risk, respectively (Table 6.7). Blacks had an overall adenoma prevalence of 8%, with 3%, 10%, and 14% being classified as low-, moderate-, and high-risk, respectively (Table 6.7). Asians, with the lowest prevalence of adenomas for all racial subgroups, had an overall adenoma prevalence of 5%, with respectively 4% and 7% being classified as low-and moderate-risk of adenomas, and none being classified as high-risk (Table 6.7).

Discussion

In this study, regardless of race or sex, three dietary patterns emerged from the data: "Fruits and vegetables", "Western", and "Sweet and salty". Using those dietary factor scores, among men lower intake of a "Western" diet was associated with lower odds of CRA, while higher intakes of a "Fruits and vegetable" diet was associated with lower odds of CRA in some subgroups. Among the different racial subgroups, a higher score for the "Fruits and vegetables" dietary pattern was associated with lower odds of CRA in white men and women of other races. The odds of CRA were higher in all racial subgroups for men who consumed a more "Western" diet, although the results did not reach statistical significance.

Few studies have examined dietary predictors of CRA with the specific purpose of identifying racial differences in dietary patterns that could lead to disparities in CRA, although a few have examined the association of dietary patterns and CRA in specific racial/ethnic

subgroups (13, 14, 207, 208). However, each has had slightly different findings. It is unknown whether the inconsistent findings from these studies are due to methodological differences (e.g. collection of dietary data) or the diversity of diet between the study populations. Here we show that dietary patterns of men and women in the U.S. are fairly consistent between racial subgroups. Further, the risk of CRA in men appears to be consistently higher among those consuming a more Western-like diet compared to those with a less Western-like diet, across all racial subgroups.

The findings of a higher risk of CRA among men with higher intakes of a "Western" or "Meat and Potatoes" diet is consistent with what has been previously shown, (207, 208) as these types of diets have also been associated with an increased risk of colorectal cancer. The finding of an association between a more "Western"-like diet with high meat consumption and CRA is not surprising. In fact, the International Agency for Research on Cancer recently classified red meat as a probable carcinogens and processed meats as carcinogens, likely due to the N-Nitroso compounds that form when processed meats and meats high in heme iron are metabolized (211).

A "Western" diet was associated with CRA but the associations between "Western" diet and having advanced or multiple adenomas were even stronger. Stronger associations between a more Western-like diet and CRA have also been reported for advanced adenomas, compared to non-advanced adenomas (134). Similarly, a less Mediterranean-like diet was more strongly associated with larger adenomas than smaller adenomas (208). The association between diet and CRA and an even stronger association between diet and advanced or multiple adenomas suggest that the mechanism of diet works through multiple pathways. First, by initiating the development of additional adenomas, and second, promoting the progression of existing adenomas to more serious forms.

It was interesting that a diet high in fruits and vegetables was not strongly associated with a lower prevalence of CRA. Fruits, vegetables, and legumes contain beneficial vitamins, anti-oxidants, and fiber that, individually, have been associated with a lower prevalence of CRA (212, 213). The results from prior literature have not always been consistent regarding whether this association exists (13, 187, 208). The association between fruit and vegetable consumption and colorectal cancer is no less conclusive (214). In a large study of four European cohorts, even though dietary patterns were consistent across cohorts, the association of dietary patterns with colorectal cancer was inconclusive (215). The results from the present study suggest that a diet consisting of more fruits and vegetables is associated with a weak, but lower prevalence of CRA than those with a diet poorer in fruits and vegetables. Upon further stratification, white men and women of other races were the two subgroups where a beneficial effect was seen. The weak findings among "protective" food patterns (i.e., fruit and vegetables) but significant associations between "risky" food patterns (i.e., meat and processed foods) supports the idea that adenoma or cancer development is more dependent upon the absence of unhealthy foods rather than the presence of beneficial foods, as has been previously suggested (216).

The findings of higher odds of CRA among men, but not women, with higher intakes of a "Western" diet could be related to the red and processed meats that load heavily on this dietary factor. Men are more likely to consume higher amounts of meat and processed meats than women (217), and when sex-specific intake percentiles are calculated, "high" intakes in women may be much lower than men's intake. Further, red and processed meats contain relatively high amounts of heme iron, which has not only been shown to be carcinogenic (218, 219) but also associated with adenoma development, especially in the distal regions of the colon (220). It is believed that heme acts as a catalyst for lipid peroxidation and *N*-nitroso coumpounds (221, 222).

The higher amounts of meat intake for males, and consequently heme, put men at higher risk of having excess heme exposure. Another explanation of differences in findings between men and women may have to do with anatomical location of the adenomas. Women are more likely to have proximal adenomas (223), and with a higher consumption of a "Western" diet or a lower consumption of a "Prudent" diet, were also more likely to have colorectal cancer in proximal sites but not in distal sites (224). Because of the screening method used in the PLCO trial, data on proximal adenomas were not able to be obtained on all participants, and the association between diet and proximal adenomas was not able to be explored.

When examining the association between factor scores and CRA in the individual races, there were a few differences. For example, in white men, higher "Fruits and vegetables" factor scores were associated with lower odds of CRA, compared to those with the lowest scores. However, in black men and men of other races, there were higher odds of CRA with higher "Fruits and vegetables" factor scores, although this was not significant. It is unlikely that a diet higher in fruits and vegetables would truly be associated with higher odds of CRA. A more likely explanation might be related to unstable estimates from small samples or other unmeasured differences. One explanation may be due to qualitative differences in foods, such as anti-inflammatory properties, even though quantity of fruits and vegetables are similar. Similar to that point is that factor scores do not necessarily take into account the diversity of food groups. For example, eating many types of fruits may be more beneficial due to the diversity of nutrients than eating multiple servings of only a few types of fruits.

CART analysis was used to determine the predictive variables for CRA. Not surprisingly, variables such as sex, age, and smoking were consistently predictive of adenoma status. Of the dietary patterns examined (either investigator or data driven methods), a low

Mediterranean diet pattern was the strongest dietary predictor of CRA in Asian and white men, even though both individual dietary components and overall dietary scores were included in the analysis. This might suggests that it is not enough to simply incorporate healthy foods or minimize unhealthy foods. Rather, it appears that the net effect of both positive and negative food choices that influences the prevalence of adenomas.

CART analysis is advantageous in that multi-level interactions can be assessed. Multiple interactions can often occur in nutritional epidemiological studies, and evidence of this exists in the present study. For example, high altMED diet scores were "protective" of CRA in white men, but only in those who were older than 57 years and former smokers. This risk of adenoma is often lower in former smokers compared to current smokers, but this risk can be further diminished with a healthy diet, particularly in older men. Another example of this is in black men where the prevalence of adenoma is similar to the prevalence in the general PLCO population. However, among black men who drank, even just a little (0.5 g/day) were categorized as high risk; whereas, those who drank less than that or not at all were categorized as low risk. This association was not seen among black women.

Another advantage of CART is that it can help to identify beneficial cut-points. In white men, the altMED diet score of 4 was used as the cut-point, but in Asian men, a higher score was identified as the cut-point (<8). This may be related to Asians in the PLCO having generally healthier diets compared to those of other races, and so a higher altMED diet score would be needed to be able to discern between high and low risk groups in Asians. Age is another variable that had multiple cut-points identified. It is important to remember that all participants in the PLCO cohort were at least 55 years old, and were all consequently at higher risk of adenoma occurrence, compared to the general population. The general recommendation is that the risk of

CRA is greater as people age; rates sharply increasing after age 50 (225). Even in this older population, there were age cut-points identified, suggesting that the risk of CRA does not necessarily increase linearly as people age. In men, 58 years was the cut-point, but in women, 63 years was the cut-point. Black women had the highest age for distinguishing between risk categories (age 65 years), while white men and men of all races had the lowest age for distinguishing between risk categories (age 58 years). CART analysis is one way to further refine specific groups at even greater risk for colorectal adenoma that may not have been considered by the researcher.

It should be noted that the results from the factor score analyses should be interpreted with caution. Experiment-wise error could have occurred because of multiple hypothesis testing and multiple logistic regression models being tested. Specifically, the finding of lower odds of multiple adenoma in women consuming diets with the highest "Fruits and vegetables" scores could have been a spurious finding, given the lack of significant findings with other types of adenoma and the lack of a dose-response effect. This could also apply to the odds of advanced adenoma in men whose "Fruits and vegetables" scores were in quintile 4. The lack of a clear dose-response effect in "Fruits and vegetables" scores, particularly in men in the highest quintile of intake, could have been due to the over-reporting of fruits and vegetables actually consumed. The highest reported intakes for fruits and vegetables were, respectively, over 32 and 26 servings per day, and even though people with the top and bottom 1% of sex-specific energy intakes were excluded, this may not have fully excluded those with overestimated intakes. This overestimation of exposure could have biased the estimates towards the null, resulting in the observed estimates close to 1 for those in the highest quintile of "Fruits and vegetables" intake.

There are several strengths to these analyses, including a large, racially-diverse population with a broad range of eating habits. Also, adenoma status was confirmed, often with a follow-up colonoscopy, which greatly reduces the chance of outcome misclassification. One of the limitations to these analyses is that the dietary questionnaire is not an exhaustive list of foods that people ate. Nonetheless, dietary patterns that were identified in the present study were consistent with what has been found in populations from multiple countries (215, 226). Related to the scope of the dietary questionnaire, food items were not always specific in the quality of these food items. For example, the dietary questionnaire asked about cracker consumption, but it was not specified whether crackers were low-fat, full-fat, or whole-grain. However, food items were kept separate as best as possible, if there could be meaningful differences (e.g. white bread vs. cakes vs. crackers). Having low numbers in the different racial subgroups was also a limitation of these studies.

In conclusion, dietary patterns were fairly similar between people of different races. For all races combined, an intake of a "Western" diet was associated with higher odds of CRA in men. This appeared to be true for men of all races in race-stratified analyses. Consuming a diet low in meats and processed foods is one avenue to prevent CRA in populations that are typically at higher risk of CRA. Higher odds of CRA in men were also seen in those with a less fruit and vegetable-like diet, but this may not be true for all races. Dietary patterns were not strongly associated with having a CRA in women. Further research is needed more fully understand the association between fruit and vegetable consumption in black men and men of other races.

Table 6.1: Descriptive characteristics of Prostate, Lung, Colorectal, and Ovarian screening arm participants in the Factor analysis (N=44,278)

Categorical Variables	**Whites (N=40,068) Reference group**	**Blacks (N=1,608)**	**Asian (N=1,663)**	**Other[1] (N=939)**	**Overall chi-square p-value**
Sex					<0.0001
Men	21,053 (53.7)	771 (48.0)	943 (56.7)	571 (60.8)	
Women	18,565 (46.3)	837 (52.0)	720 (43.3)	368 (39.2)	
Education					<0.0001
College	14,980 (37.4)	484 (30.1)	776 (46.7)	262 (27.9)	
Some college	13,501 (33.7)	598 (37.2)	527 (31.7)	357 (38.0)	
High school	9,203 (23.0)	322 (20.0)	289 (17.4)	196 (20.9)	
Less than high school	2,384 (6.0)	204 (12.7)	71 (4.3)	124 (13.2)	
Physical Activity[2]					<0.0001
High	22,71 (56.6)	678 (42.2)	1,016 (61.1)	509 (54.2)	
Low	17,397 (43.4)	930 (57.8)	647 (38.9)	430 (45.8)	
Smoking					<0.0001
Never	19,251 (48.0)	673 (41.8)	912 (54.8)	394 (42.0)	
Current	3,654 (9.1)	275 (17.1)	121 (7.3)	92 (9.8)	
Former	17,163 (42.8)	660 (41.0)	630 (37.9)	453 (48.2)	
Anti-inflammatory use					0.0009
Yes	8,043 (20.1)	351 (21.8)	306 (18.4)	229 (24.4)	
No	32,025 (79.9)	1,257 (78.2)	1,357 (81.6)	710 (75.6)	
Hormone therapy (women)					<0.0001
Current	9,963 (53.7)	308 (37.0)	403 (56.0)	186 (50.5)	
Former	2,863 (15.4)	180 (21.6)	103 (14.3)	60 (16.3)	
Never	5,668 (30.6)	336 (40.3)	208 (28.9)	120 (32.6)	
Unknown	52 (0.3)	9 (1.1)	6 (0.8)	2 (0.5)	
Body Mass Index (kg/m^2)					<0.0001
0-18.5	219 (0.6)	9 (0.6)	36 (2.2)	5 (0.5)	
18.5-25	12,539 (31.3)	338 (21.0)	910 (54.7)	231 (24.6)	
25-30	17,626 (44.0)	647 (40.2)	594 (35.7)	440 (46.9)	
30+	9,684 (24.2)	614 (38.2)	123 (7.4)	263 (28.0)	
Continuous variables	**Means (SD)**	**Means (SD)**	**Means (SD)**	**Means (SD)**	**Kruskal-Wallace p-value**
Calcium (diet and supplements; mg/day)	1,270.8 (605.2)	961.8 (532.8)	1,000.4 (577.2)	1,140.0 (603.9)	<0.0001
Calories (kcal/day)	2,078.3(793.7)	1,985.2 (872.1)	1,865.2 (754.1)	2,058.4 (863.5)	<0.0001
Fiber (g/day)	11.4 (23.4)	7.5 (22.5)	8.1 (25.1)	8.2 (19.2)	<0.0001
Alcohol (g/day)	23.5 (9.8)	23.1 (11.6)	23.0 (10.8)	23.8 (11.8)	<0.0001
Age (years)	62.5 (5.3)	62.2 (5.3)	63.0 (5.6)	61.4 (5.0)	<0.0001

*p-value<0.05; **p<0.001; ***p<0.0001; Chi-square for categorical and Kruskal-Wallace tests for continuous variables;

1. Hispanic, Pacific Islander, and American Indian

2. Less than 2 hours of vigorous activities per week (low) vs. 2 or more hours of vigorous activities per week

3. Quintile 1:< -0.80; Quintile 2:-0.80 to -0.39; Quintile 3:-0.40 to 0.03; Quintile 4: 0.03 to 0.65; Quintile 5: >0.65

4. Quintile 1:< -0.80; Quintile 2:-0.80 to -0.38; Quintile 3:-0.39 to 0.04; Quintile 4: 0.04 to 0.67; Quintile 5: >0.67

5. Quintile 1:< -0.79; Quintile 2:-0.79 to -0.38; Quintile 3:-0.39 to 0.02; Quintile 4: 0.02 to 0.68; Quintile 5: >0.68

6. Quintile 1:< -0.77; Quintile 2:-0.77 to -0.38; Quintile 3:-0.39 to 0.02; Quintile 4: 0.02 to 0.63; Quintile 5: >0.63

7. Quintile 1:< -0.76; Quintile 2:-0.76 to -0.35; Quintile 3:-0.36 to 0.05; Quintile 4: 0.05 to 0.68; Quintile 5: >0.68

8. Quintile 1:< -0.71; Quintile 2:-0.71 to -0.39; Quintile 3:-0.40 to 0.04; Quintile 4: 0.04 to 0.57; Quintile 5: >0.57

Table 6.2: Dietary factor loadings for the Prostate, Lung, Colorectal, and Ovarian Cancer screening arm participants, by race (N=44,278)[1]

	Whites (N=40,068)			Blacks (N=1,608)			Asian (N=1,663)			Other (N=939)		
Food or food groups	**Factor 1 Fruits and Vegetables**	**Factor 2 Western**	**Factor 3 Sweet and Salty**	**Factor 1 Fruits and Vegetables**	**Factor 2 Western**	**Factor 3 Sweet and Salty**	**Factor 1 Fruits and Vegetables**	**Factor 2 Western**	**Factor 3 Sweet and Salty**	**Factor 1 Fruits and Vegetables**	**Factor 2 Western**	**Factor 3 Sweet and Salty**
Green vegetables	0.68			0.76			0.78			0.68		
Orange vegetables	0.72			0.67			0.73			0.74		
Cruciferous	0.69			0.75			0.76			0.71		
Tomatoes	0.42			0.48			0.42			0.44		
Other vegetables	0.74			0.80			0.73			0.78		
Fruit	0.64			0.62			0.62			0.65		
Legumes	0.58			0.57			0.68			0.57		
Whole grain	0.48			0.47			0.40			0.49		
Fish	0.33	0.33		0.34				0.62			0.61	
Poultry		0.47			0.32			0.65			0.54	
Red meat		0.68			0.67			0.55	0.51		0.39	0.50
Processed meats		0.64			0.68			0.46	0.48		0.43	0.45
Fried foods		0.63			0.68			0.73			0.69	
Pasta dishes		0.50			0.54			0.35	0.40			0.43
Added fat		0.40	0.34			0.43		0.35			0.43	
White potatoes	0.32			0.40	0.38		0.41			0.32		0.32
Baked goods			0.64			0.58			0.63			0.52
Eggs		0.52			0.54			0.34			0.45	
Ice cream			0.53			0.42			0.53			0.56
Snacks			0.46			0.65			0.46			0.52
Non-whole grain		0.44			0.52			0.44			0.51	
Nuts			0.38			0.50						0.31
Candy			0.62			0.59			0.65			0.57
Regular dairy												
Cottage cheese												
Frozen yogurt												
Low-fat dairy												
Alcohol												

1. Rounded to the nearest hundredth; Factors with values <0.30 not shown

Table 6.3: Factor-loading matrix for the major factors identified by using food consumption data from the food frequency questionnaire used in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, by sex[1]

Men				Women			
Food or food group	**Factor 1: Fruits and vegetables**	**Factor 2: Western diet**	**Factor 3: Sweet and salty**	**Food or food group**	**Factor 1: Fruits and vegetables**	**Factor 2: Western diet**	**Factor 3: Sweet and salty**
Other vegetables	0.74			Other vegetables	0.73		
Orange vegetables	0.73			Orange vegetables	0.70		
Cruciferous vegetables	0.71			Green vegetables	0.70		
Green vegetables	0.69			Cruciferous vegetables	0.69		
Fruit	0.63			Fruit	0.63		
Legumes	0.61			Legumes	0.58		
Whole grain	0.48			Whole grain	0.48		
Tomatoes	0.40			Tomatoes	0.42		
Fried foods		0.62		Fish	0.39		
Red meats		0.58	0.37	Red meat		0.67	
Processed meats		0.54	0.36	Processed meats		0.66	
Poultry		0.54		Fried food		0.58	
Non-whole grains		0.47		Eggs		0.54	
Eggs		0.46		Added fat		0.46	
Pasta dishes		0.44		Pasta dishes		0.44	0.32
Fish		0.41		Poultry		0.35	
Baked goods			0.60	Non-whole grain		0.34	
Sweets			0.54	Sweets			0.66
Ice cream			0.52	Baked goods			0.65
Snacks			0.50	Snacks			0.49
Added fats		0.31	0.44	Ice cream			0.45
Nuts			0.37	Frozen yogurt			0.37
White potatoes	0.33		0.36				

1. Values rounded to nearest one-hundredth; Absolute values <0.30 were not listed in the table for simplicity. Foods or food groups with factor loadings <0.30 for all factors were excluded.

Table 6.4: Associations between colorectal adenoma and dietary factor scores in men in the Prostate, Lung, Colorectal, and Ovarian screening arm participants

	Quintile 1 (lowest; reference) OR (95% CI)	Quintile 2 OR (95% CI)	Quintile 3 OR (95% CI)	Quintile 4 OR (95% CI)	Quintile 5 (highest) OR (95% CI)	Wald chi-square p-value for trend
Factor 1: Fruits and vegetables[1]						
All distal adenoma[2]	1.00	0.93 (0.82-1.06)	0.94 (0.82-1.08)	0.86 (0.73-1.00)	1.00 (0.82-1.23)	0.13
Non-advanced adenoma[3]	1.00	0.97 (0.83-1.14)	0.97 (0.81-1.15)	0.96 (0.79-1.18)	1.01 (0.78-1.31)	0.98
Advanced adenoma[4]	1.00	0.87 (0.72-1.06)	0.91 (0.74-1.12)	**0.69 (0.54-0.89)**	1.00 (0.72-1.37)	0.005
Multiple adenomas (≥2)[5]	1.00	0.81 (0.65-1.01)	0.81 (0.63-1.04)	0.70 (0.52-0.93)	0.81 (0.56-1.18)	0.11
Factor 2: Western diet[6]						
All distal adenoma[7]	1.00	1.04 (0.91-1.19)	1.13 (0.99-1.29)	1.06 (0.92-1.22)	**1.21 (1.03-1.42)**	0.12
Non-advanced adenoma[8]	1.00	1.04 (0.88-1.24)	1.13 (0.95-1.34)	1.09 (0.91-1.30)	1.18 (0.96-1.44)	0.51
Advanced adenoma[9]	1.00	1.06 (0.86-1.29)	1.16 (0.95-1.41)	1.04 (0.84-1.28)	**1.32 (1.07-1.63)**	0.06
Multiple adenomas (≥2)[10]	1.00	1.21 (0.95-1.54)	1.23 (0.96-1.57)	1.21 (0.94-1.56)	**1.51 (1.17-1.94)**	0.03
Factor 3: Sweet and salty[11]						
All distal adenoma[12]	1.00	1.08 (0.94-1.23)	1.02 (0.89-1.17)	1.03 (0.89-1.19)	1.00 (0.84-1.18)	0.81
Non-advanced adenoma[13]	1.00	1.10 (0.93-1.30)	1.04 (0.88-1.24)	1.04 (0.87-1.25)	1.06 (0.86-1.31)	0.86
Advanced adenoma[14]	1.00	1.07 (0.88-1.32)	0.99 (0.80-1.23)	1.02 (0.82-1.28)	0.89 (0.69-1.16)	0.63
Multiple adenomas (≥2)[15]	1.00	0.90 (0.70-1.15)	0.92 (0.72-1.19)	1.06 (0.82-1.37)	0.94 (0.70-1.28)	0.60

OR=Odds ration; CI=Confidence interval; bolded values are significant ($p<0.05$)

1. Quintile 1:<-0.79; Quintile 2: -0.79 to -0.39; Quintile 3: -0.40 to 0.02; Quintile 4: 0.03 to 0.66; Quintile 5: >0.66
2. Adjusted for exercise, body mass index, education, smoking status, race, total daily calories, calcium intake, alcohol, fiber, folate, and age; number of cases=2,654
3. Adjusted for body mass index, smoking, race, total daily calories, calcium intake, fiber, folate, and age; number of cases=1,582
4. Adjusted for exercise, education, smoking, race, total daily calories, calcium intake, alcohol, fiber, and age; number of cases=1,038
5. Adjusted for exercise, education, smoking, race, total daily calories, calcium intake, alcohol, fiber, and age; number of cases=736
6. Quintile 1:<-0.81; Quintile 2: -0.81 to -0.35; Quintile 3: -0.36 to 0.10; Quintile 4: 0.11 to 0.74; Quintile 5: >0.74

7. Adjusted for exercise, body mass index, education, smoking status, race, total daily calories, calcium intake, alcohol, fiber, folate, and age; number of cases=2,654
8. Adjusted for body mass index, smoking, race, total daily calories, calcium intake, alcohol, fiber, folate and age; number of cases=1,582
9. Adjusted for exercise, education, smoking, race, calcium intake, alcohol, fiber, and age; number of cases=1,038
10. Adjusted for exercise, education, smoking, race, calcium intake, alcohol, fiber and age; number of cases=736
11. Quintile 1:<-0.79; Quintile 2: -0.79 to -0.39; Quintile 3: -0.40 to 0.02; Quintile 4: 0.03 to 0.67; Quintile 5: >0.67;
12. Adjusted for exercise, body mass index, education, smoking status, race, total daily calories, calcium intake, alcohol, fiber, folate, and age; number of cases=2,654
13. Adjusted for body mass index, smoking, race, total daily calories, calcium intake, alcohol, fiber, folate and age; number of cases=1,582
14. Adjusted for exercise, education, smoking, race, total daily calories, calcium intake, alcohol, fiber, and age; number of cases=1,038
15. Adjusted for exercise, education, smoking, race, total daily calories, calcium intake, alcohol, fiber and age; number of cases=736

Table 6.5: Associations between colorectal adenoma and dietary factor scores in women in the Prostate, Lung, Colorectal, and Ovarian screening arm participants

	Quintile 1 (lowest; reference) OR (95% CI)	Quintile 2 OR (95% CI)	Quintile 3 OR (95% CI)	Quintile 4 OR (95% CI)	Quintile 5 (highest) OR (95% CI)	Wald chi-square p-value for trend
Factor 1: Fruits and Vegetables[1]						
All distal adenoma[2]	1.00	0.97 (0.81-1.16)	1.14 (0.94-1.37)	1.14 (0.92-1.41)	1.13 (0.86-1.49)	0.40
Non-advanced adenoma[3]	1.00	0.88 (0.71-1.11)	1.09 (0.86-1.37)	1.14 (0.88-1.47)	1.04 (0.74-1.46)	0.27
Advanced adenoma[4]	1.00	1.09 (0.83-1.44)	1.19 (0.89-1.61)	1.10 (0.78-1.55)	1.22 (0.79-1.90)	0.82
Multiple adenomas (≥2)[5]	1.00	1.00 (0.69-1.45)	0.86 (0.57-1.30)	1.01 (0.65-1.58)	**0.53 (0.28-1.00)**	0.10
Factor 2: Western diet[6]						
All distal adenoma[7]	1.00	0.90 (0.76-1.07)	0.87 (0.73-1.04)	0.97 (0.82-1.15)	0.83(0.70-1.00)	0.24
Non-advanced adenoma[8]	1.00	0.83 0.67-1.04)	0.84 (0.67-1.04)	0.93 (0.74-1.16)	0.80 (0.62-1.05)	0.29
Advanced adenoma[9]	1.00	1.02 (0.77-1.34)	0.90 (0.67-1.20)	0.97 (0.72-1.30)	0.77 (0.54-1.10)	0.48
Multiple adenomas (≥2)[10]	1.00	0.78 (0.54-1.14)	0.80 0.55-1.17)	0.86 0.59-1.26)	0.84 (0.57-1.24)	0.73
Factor 3: Sweet and Salty[11]						
All distal adenoma[12]	1.00	0.96 (0.81-1.14)	1.02 (0.86-1.21)	1.10 (0.92-1.30)	0.88 (0.74-1.06)	0.18
Non-advanced adenoma[13]	1.00	0.97 (0.78-1.21)	1.15 (0.93-1.42)	1.08 (0.87-1.35)	0.88 (0.68-1.14)	0.19
Advanced adenoma[14]	1.00	0.95 (0.73-1.24)	0.83 (0.62-1.10)	1.13 (0.87-1.48)	0.91 (0.68-1.21)	0.24
Multiple adenomas (≥2)[15]	1.00	0.85 (0.59-1.24)	0.87 (0.60-1.26)	1.10 (0.77-1.58)	0.89 (0.60-1.31)	0.60

OR=Odds ration; CI=Confidence interval; bolded values are significant (p<0.05)

1. Quintile 1:< -0.80; Quintile 2:-0.80 to -0.38; Quintile 3:-0.39 to 0.04; Quintile 4: 0.04 to 0.67; Quintile 5: >0.67
2. Adjusted for body mass index, smoking, race, hormone status, total daily calcium, fiber, and age; number of cases=1,088
3. Adjusted for body mass index, smoking status, race, hormone status, alcohol, fiber, and age; number of cases=872
4. Adjusted for body mass index, smoking status, race, total daily calcium, alcohol, fiber, and age; number of cases=526
5. Adjusted for body mass index, smoking, race, calcium intake, alcohol intake, fiber and age; number of cases=276
6. Quintile 1:< -0.71; Quintile 2:-0.71 to -0.39; Quintile 3:-0.40 to 0.04; Quintile 4: 0.04 to 0.57; Quintile 5: >0.57

7. Adjusted for body mass index, smoking, education, race, hormone status, total daily calcium, fiber, and age; number of cases=1,088
8. Adjusted for body mass index, smoking status, race, hormone status, total daily calories, fiber, and age; number of cases=872
9. Adjusted for body mass index, smoking status, race, total daily calories, alcohol, fiber, and age; number of cases=526
10. Adjusted for body mass index, smoking, race calcium intake, alcohol, fiber, and age; number of cases=276
11. Quintile 1:< -0.71; Quintile 2:-0.71 to -0.39; Quintile 3:-0.40 to 0.04; Quintile 4: 0.04 to 0.57; Quintile 5: >0.57
12. Adjusted for body mass index, smoking, education, race, hormone status, total daily calcium, fiber, and age; number of cases=1,088
13. Adjusted for body mass index, smoking status, race, hormone status, total daily calories, fiber, and age; number of cases=872
14. Adjusted for body mass index, smoking status, race, total daily calcium, alcohol, fiber, and age; number of cases=526
15. Adjusted for body mass index, smoking, race calcium intake, alcohol, fiber, and age; number of cases=276

Table 6.6: Associations between prevalent distal colorectal adenoma and dietary factor score quintiles in male and female Prostate, Lung, colorectal, and Ovarian Cancer screening arm participants, stratified by race (N=44,278)

	White		**Black**		**Asian**		**Other[1]**	
	aOR (95% CI)		**aOR (95% CI)**		**aOR (95% CI)**		**aOR (95% CI)**	
	Male (N=21,503)	**Female (N=18,565)**	**Male (N=771)**	**Female (N=837)**	**Male (N=943)**	**Female (N=720)**	**Male (N=571)**	**Female (N=368)**
Factor 1: Fruits and Vegetables[2,3]								
Tertile 1 (lowest; reference)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	**1.00**
Tertile 2	**0.89 (0.80-1.00)**	1.11 (0.96-1.29)	1.37 (0.72-2.62)	0.91 (0.42-1.97)	0.99 (0.49-2.02)	3.36 (0.86-13.17)	1.36 (0.62-2.98)	**0.34 (0.12-0.98)**
Tertile 3	**0.81 (0.70-0.95)**	1.11 (0.90-1.37)	1.29 (0.52-3.17)	0.56 (0.19-1.61)	0.91 (0.34-2.45)	4.57 (0.90-23.16)	1.53 (0.55-4.28)	**0.09 (0.02-0.50)**
Factor 2: Western[4,5]								
Tertile 1 (lowest; reference)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Tertile 2	1.04 (0.93-1.16)	1.01 (0.88-1.16)	1.23 (0.66-2.32)	0.88 (0.41-1.87)	1.86 (0.82-4.23)	1.65 (0.67-4.06)	1.41 (0.64-3.10)	0.39 (0.12-1.25)
Tertile 3	1.10 (0.97-1.25)	0.89 (0.77-1.03)	1.07 (0.53-2.14)	0.77 (0.37-1.62)	1.82 (0.72-4.64)	0.97 (0.34-2.80)	1.39 (0.56-3.45)	0.77 (0.28-2.12)
Factor 3: Sweet and Salty[6,7]								
Tertile 1 (lowest; reference)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Tertile 2	1.04 (0.93-1.16)	1.03 (0.90-1.17)	1.63 (0.92-2.89)	0.91 (0.44-1.88)	1.25 (0.56-2.78)	0.82 (0.35-1.92)	0.94 (0.47-1.88)	2.95 (1.12-7.78)
Tertile 3	0.99 (0.87-1.14)	0.93 (0.80-1.09)	1.36 (0.63-2.91)	1.06 (0.51-2.23)	0.28 (0.03-2.24)	0.69 (0.15-3.13)	1.18 (0.51-2.75)	1.81 (0.54-6.10)

aOR=adjusted odds ratio; CI=confidence interval; Bolded values are significant ($p<0.05$).

1. Hispanic, Pacific Islander, and American Indian
2. Men: Tertile 1:<-0.53; Tertile 2: -0.53 to 0.21; Tertile 3: > 021; adjusted for exercise, body mass index, education, smoking, daily calories, total calcium intake, age, alcohol, folate, and fiber intake
3. Women: Tertile 1:<-0.54; Tertile 2: -0.54 to 0.22; Tertile 3: > 022; adjusted for body mass index, smoking, hormone status, total calcium, age, and fiber intake
4. Men: Tertile 1:<-0.53; Tertile 2: -0.53 to 0.22; Tertile 3: > 0.22; adjusted for body mass index, education, smoking, calories, total calcium, age, alcohol, folate, and fiber intake
5. Women: Tertile 1:<-0.52; Tertile 2: -0.52 to 0.20; Tertile 3: > 020; adjusted for body mass index, smoking hormone status, total calcium, age, alcohol, and fiber intake
6. Men: Tertile 1:<-0.53; Tertile 2: -0.53 to 0.21; Tertile 3: > 0.21; adjusted for body mass index, education, smoking, calories, total calcium, age, alcohol, folate, and fiber intake
7. Women: Tertile 1:<-0.50; Tertile 2: -0.50 to 0.23; Tertile 3: > 0.23; adjusted for body mass index, education, smoking, hormone status, total calcium, age, and fiber intake

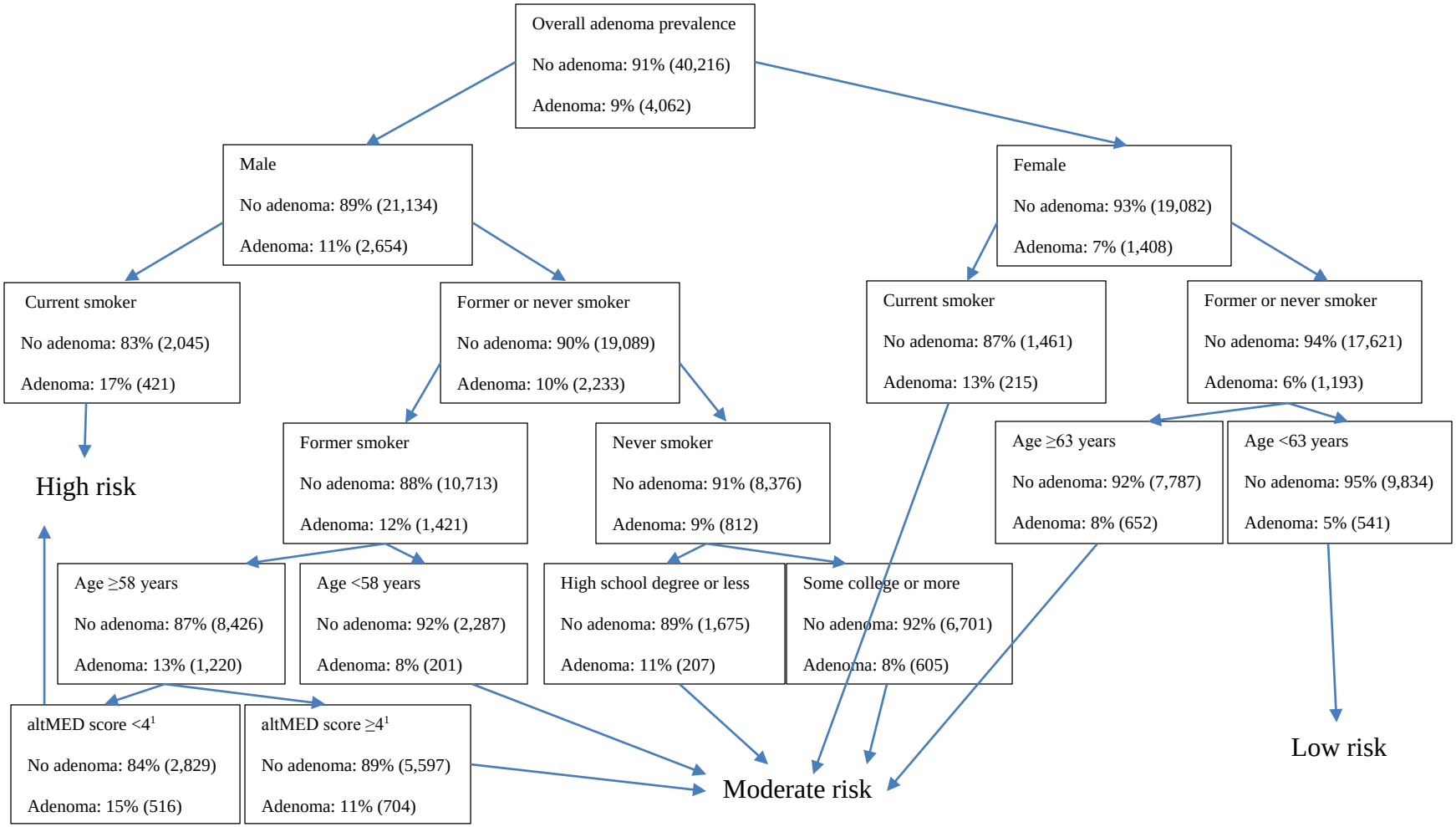

Figure 6.1: Classification and regression tree (CART) showing the variables that are associated with high risk (>13%), moderate risk (6-13%), and low risk (<6%) of prevalent colorectal adenoma in all screening arm participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

1. altMED=alternate Mediterranean diet score

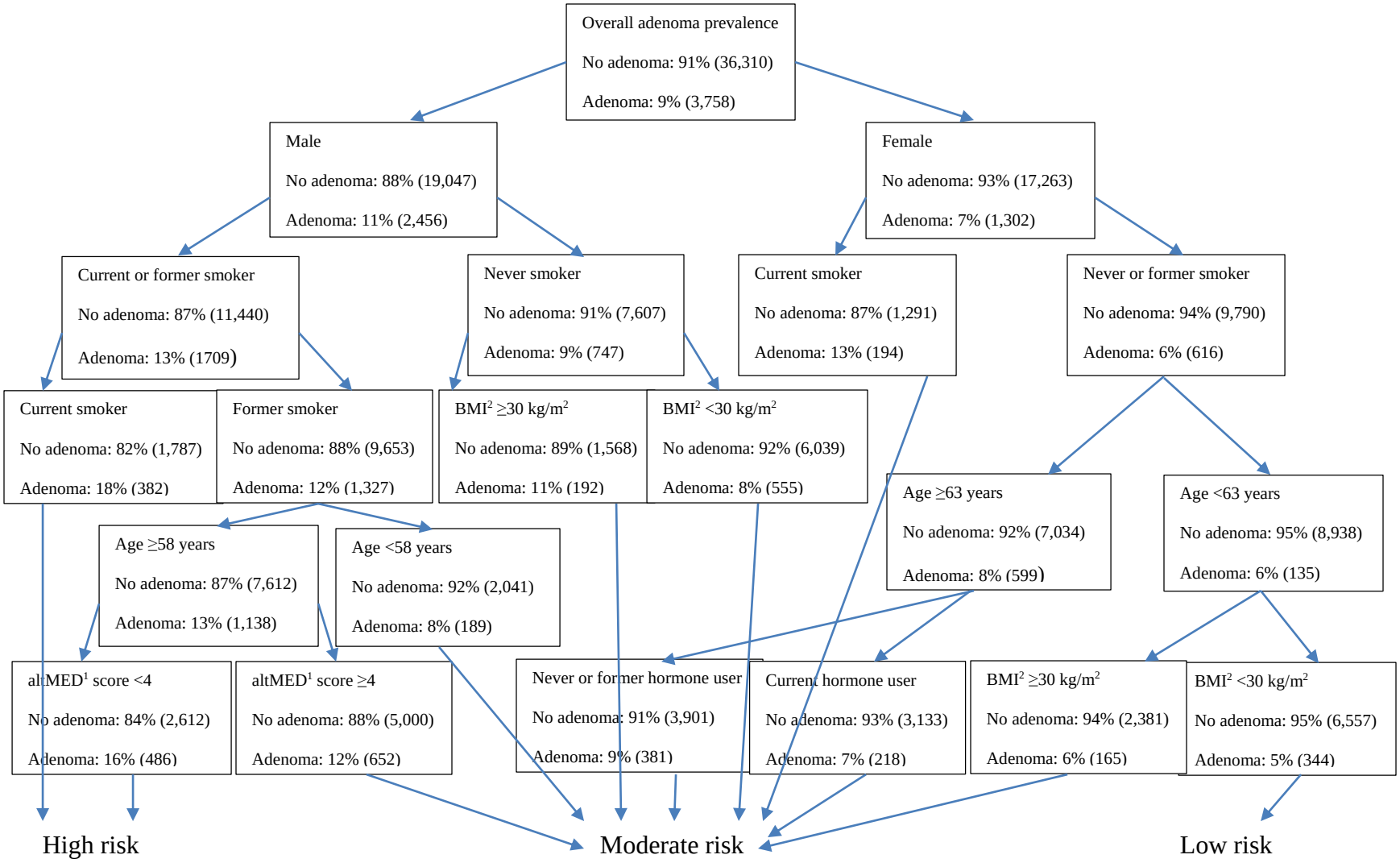

Figure 6.2: Classification and regression tree (CART) showing the variables that are associated with high risk (>13%), moderate risk (6-13%), and low risk (<6%) of prevalent colorectal adenoma in whites in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (screening arm participants only)

1. altMED=alternate Mediterranean diet score 2. BMI=Body mass index

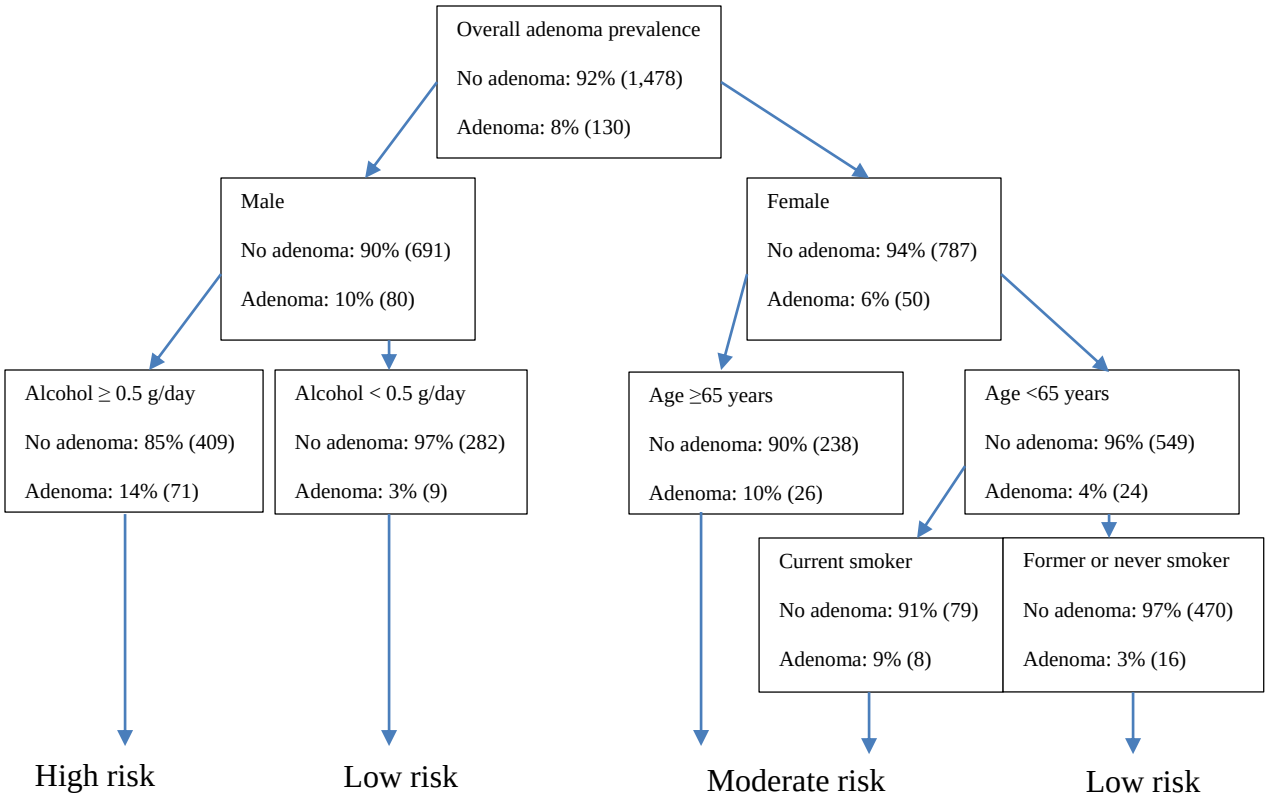

Figure 6.3: Classification and regression tree (CART) showing the variables that are associated with high risk (>13%), moderate risk (6-13%), and low risk (<6%) of prevalent colorectal adenoma in blacks in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (screening arm participants only)

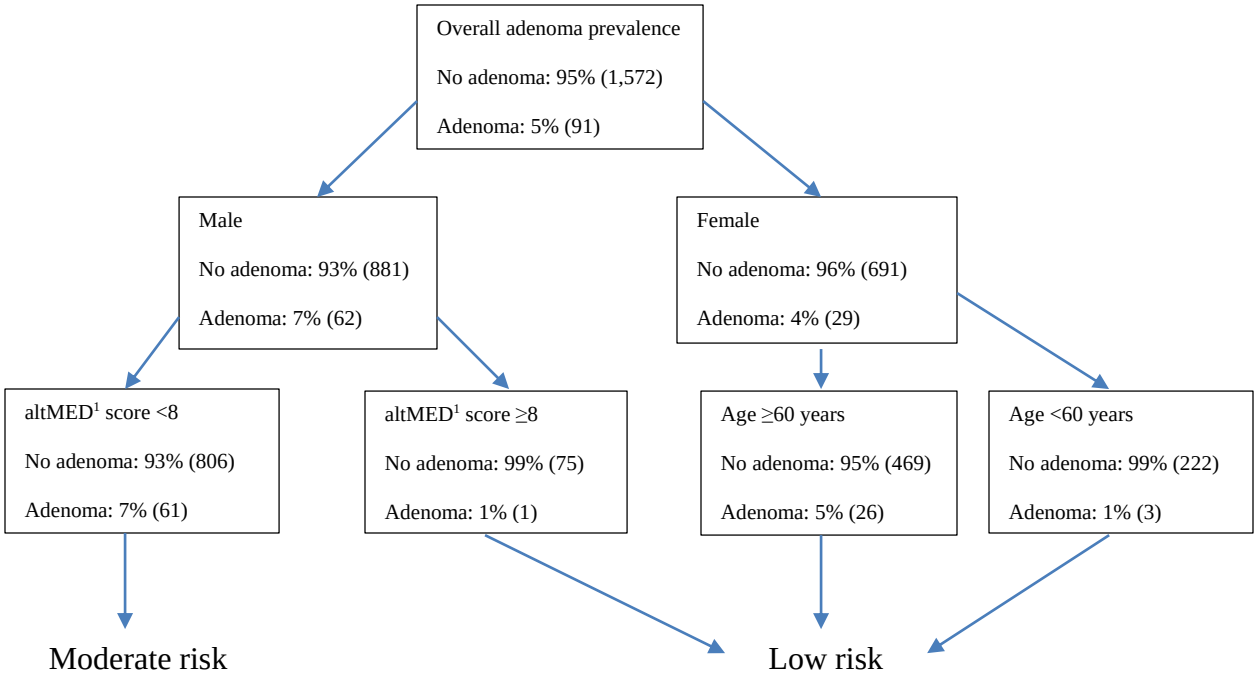

Figure 6.4: Classification and regression tree (CART) showing the variables that are associated with moderate risk (6-13%) and low risk (<6%) of prevalent colorectal adenoma in Asians in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (screening arm participants only)

1. altMED=alternate Mediterranean diet score

Table 6.7: Summary of percentages and numbers of people at low (<6%), medium (6-13%), and high risk (>13%) for prevalent colorectal adenoma in the screening arm participants enrolled in the Prostate, Lung, Colorectal, Ovarian, and Cancer Screening Trial, by race[1]

	Overall risk (adenoma/no adenoma)	**Low risk (adenoma/no adenoma)**	**Moderate risk (adenoma/no adenoma)**	**High risk (adenoma/no adenoma)**
Total population	9% (4,062/40,216)	5% (541/9,834)	9% (2,584/25,508)	16% (937/4,874)
Whites	9% (3,758/36,310)	5% (344/6,557)	9% (2,546/25,354)	16% (868/4,399)
Blacks	8% (130/1,478)	3% (25/752)	10% (34/317)	14% (71/409)
Asians	5% (91/1,572)	4% (30/766)	7% (61/806)	None

1. Numbers were too few in the "Other" category to do a meaningful analysis of adenoma risk

Appendix Table 6.1. Food groupings used in the dietary pattern analysis

Food or food groups	Food items
Other vegetables	Beets, celery, corn, cucumber, green pepper, iceberg lettuce, onion, summer squash, vegetable medley, vegetable soup
Orange vegetables	Carrots, winter squash, sweet potatoes
Cruciferous vegetables	Broccoli, Brussel sprouts, cabbage, cauliflower
Fruit	Apples, applesauce, apricot, banana, cantaloupe, grapefruit, grapes, oranges, peaches, pear, pineapple, plum, prune, raisin, strawberry, watermelon
Green vegetables	Leafy greens (spinach, lettuce), green beans
Legumes	Dry beans, peas, tofu
White potatoes	White potatoes
Whole grain	Dark breads, cooked cereal, fiber-fortified cereal, brown rice, other grains
Non-whole grain	Biscuits, cornbread, white bread, cold cereal, pancake, white rice, pasta
Low-fat dairy	Skim, 1%, and 2% milk; yogurt
Regular dairy	Whole milk, cheese
Frozen yogurt	Frozen yogurt
Added fats	Butter, margarine, salad dressing
Cottage cheese	Cottage cheese, ricotta cheese
Poultry	Chicken
Pasta dishes	Lasagna, pizza, macaroni and cheese
Tomatoes	Canned tomatoes , fresh tomatoes, tomato juice, tomato sauce
Red meats	Beef, pork
Processed meats	Bacon, cold cuts, ham, hotdog, sausage
Fish	Fish, shellfish, tuna
Egg	Eggs
Fried foods	Fried chicken, fried fish, fried potatoes
Baked goods	Cake, cookie, donut, pie

Candy	Chocolates, candy
Snacks	Chips, crackers
Added fat	Butter, margarine, salad dressing
Nuts	Peanuts
Alcohol	Beer, liquor, wine

Appendix Table 6.2: Leaf report of classification and regression tree (CART) diet and lifestyle associations with colorectal adenoma, by risk status and race

Description	**Percentage with adenoma (case/control counts) for each leaf**
All participants	
High risk (>13%)	
Individuals who are male and current smokers	17% (421/2,045)
Individuals who are male, former smokers, ≥58 years of age, and have an altMED[1] diet score <4	15% (516/2,829)
Moderate risk (6-13%)	
Individuals who are female and are current smokers	13% (215/1,461)
Individuals who are male, former smokers, ≥58 years of age, and have an altMED[1] diet score ≥4	11% (704/5,597)
Individuals who are male, never smokers, and have a high school degree or less	11% (207/1,675)
Individuals who are male, former smokers, and are <58 years of age	8% (201/1,675)
Individuals who are male, never smokers, and have at least some college education	8% (605/6,701)
Individuals who are female, are never or former smokers, and 63 years and older	8% (652/7,787)
Low risk (<6%)	
Individuals who are female, are never or former smokers, and less than 63 years of age	5% (541/9,834)
Whites	
High risk (>13%)	
Individuals who are male and current smokers	18% (382/1,787)
Individuals who are male, former smokers, ≥58 years of age, and have an altMED[1] diet score <4	16% (486/2,612)
Moderate risk (6-13%)	
Individuals who are female and currently smoke	13% (194/1,291)
Individuals who are male, former smokers, ≥58 years of age, and have an altMED[1] diet score ≥4	11% (652/5,000)
Individuals who are male, have never smoked, and a Body mass index ≥ 30 kg/m^2	11% (192/1,568)
Individuals who are female and currently smoke	13% (194/1,291)
Individuals who are female are former or never smokers, ≥63 years of age, and are a never or former female hormone user	9% (381/3,901)
Individuals who are male, a former smoker, and are <58 years of age	8% (189/2,041)
Individuals who are male, have never smoked, and a Body mass index < 30 kg/m^2	8% (555/6,039)
Individuals who are female are former or never smokers, ≥63 years of age, and are a current female hormone user	7% (218/3,133)
Individuals who are female are former or never smokers, <63 years of age, and have a Body mass index ≥ 30 kg/m^2	6% (165/2,381)
Low risk (<6%)	
Individuals who are female are former or never smokers, <63 years of age, and have a Body mass index < 30 kg/m^2	5% (344/6,557)

Blacks	
High risk (>13%)	
Individuals who are male and have an alcohol intake ≥0.5 g/day	15% (71/409)
Moderate risk (6-13%)	
Individuals who are female and are ≥65 years	10% (26/238)
Individuals who are female, are <65 years, and are current smokers	9% (8/79)
Low risk (<6%)	
Individuals who are female, are <65 years, and are never or former smokers	3% (16/470)
Individuals who are male and have an alcohol intake <0.5 g/day	3% (9/282)
Asian	
Moderate risk (6-13%)	
Individuals who are male and have an altMED[1] diet score <8	7% (61/806)
Low risk (<6%)	
Individuals who are female and ≥60 years of age	5% (26/469)
Individuals who are male and have an altMED[1] diet score greater than or equal to 8	1% (1/75)
Individuals who are female and <60 years of age	1% (3/222)

1. altMED=alternate Mediterranean diet score

CHAPTER 7

CONCLUSION

Summary of the Problem

A colorectal adenoma (CRA) is a benign tumor of the inner lining of the colon or rectum. It is estimated that at least 50% of the Western population will develop a CRA by the time they reach 70 years of age (1). While not all adenomas become cancerous, almost all colorectal cancers develop from adenomas. A serious concern is that there are notable racial disparities in the incidence of colorectal cancer and likely in the prevalence of colorectal adenomas (3-6). It is estimated that between 40-70% of colorectal cancer cases can be attributed to diet (7-9). Considering the similarities between colorectal cancer and CRA, it seems likely that diet has an important role in the development of CRA.

There have been a few studies looking at diet as a whole with regards to its relationship with CRAs. These studies have generally found that diets with more fruits, vegetables, and whole grains are associated with a lower occurrence of CRAs than diets with less of these food items. But these studies have not resulted in consistent results, and none of them have examined racial differences that may contribute to disparities in CRA incidence or prevalence (13-15).

Multiple methods of evaluating the "healthiness" of diet have been proposed, and several of them have been associated with systemic inflammation, including the DII and the altMED index (22, 23, 198). These indexes were developed in a way that was investigator driven, in that the components of these indexes are determined a priori by the investigator based on previous

literature or expert opinion, rather than on a multivariable analysis of a dataset. The primary difference between the two is that the Dietary Inflammatory Index was specifically designed to evaluate the inflammatory nature of diet, whereas the Mediterranean diet was developed because of the healthy people living in the Mediterranean region. Alternatively, data-driven methods such as factor analysis and classification and regression tree analysis (CART) can identify more general dietary patterns or predictors that are specific for CRA and do not make a priori assumptions about what is healthy or unhealthy. These methods were used to answer several key research questions, using data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. These questions included: (1) Are there racial differences in the intake of a Mediterranean diet, and if so, could these explain disparities in colorectal adenoma prevalence, incidence, and recurrence? (2) Are there racial differences in the intake of an inflammatory diet, as measured by the DII, and if so, could these explain disparities in colorectal adenoma prevalence, incidence, and recurrence? And (3) Are there differences in dietary patterns between racial subgroups, and are dietary factors associated with CRA in the different racial subgroups?

Summary of Findings

Mediterranean Diet

As discussed in Chapter 4, men who had higher alternate Mediterranean (altMED) diet scores had lower odds of prevalent CRA than those with lower altMED diet scores. This was especially true for both black and white males. Black males had higher altMED diet scores than white males, and they also had lower odds of prevalent CRA. Asians, who had the highest altMED diet scores also had the lowest odds of CRA. However, in racially stratified analyses, there was no association between altMED diet scores and prevalent adenoma, which may be due to the high diet scores, generally, in the Asian subgroup. altMED diet scores were not associated

with adenoma in women. Moreover, altMED diet scores were not associated with incident or recurrent adenoma in either men or women.

DII

As discussed in Chapter 5, Asians had the highest percentage of individuals assigned to the lowest Dietary Inflammatory Index (DII) quartile (least inflammatory). Whites, blacks, and those of other races had a similar distribution of DII scores. In the total sample, males with the most inflammatory diets were more likely to have any adenoma (any, advanced, non-advanced, or multiple, compared to those with the least inflammatory diets. There was a trend of a higher prevalence of adenoma (any, non-advanced, or multiple) with higher inflammatory diets in women. In race-stratified analyses, DII scores were only associated with adenoma in whites, which may be due to small sample sizes in the different racial subgroups but may also be due to other unmeasured factors, such as non-dietary sources of inflammation that were not able to be accounted for in the analyses. Higher DII scores were associated with a higher incidence of adenoma in men and women combined, but not with recurrent adenoma.

Factor Analysis

There were three dietary patterns ("Fruits and vegetables", "Western", and "Sweet and salty") identified in the PLCO cohort, which were consistent across racial subgroups (Chapter 6). Higher scores on the "Western" diet pattern were associated with a higher prevalence of all adenoma, advanced adenoma and multiple adenoma in men, whereas, higher scores for the "Fruits and vegetable" pattern were generally associated with a lower prevalence of advanced adenoma. "Western" diet scores were not associated with prevalent adenoma in women, but higher "Fruits and vegetables" scores were associated with a lower prevalence of multiple adenomas. Scores for the "Sweet and Salty" dietary pattern were not associated with adenoma.

When stratifying by race, there were higher odds of adenoma in those with higher scores for the "Western" diet pattern for men of all groups, but higher scores for "Fruits and vegetables" was only associated with lower odds of adenoma in white males and females of other races.

Strengths and Weaknesses

This research has several strengths. Most notably, the PLCO is a very large sample of adults in the US (over 148,000 individuals), with a diverse racial make-up and dietary intake. This allowed for the examination of adenoma outcomes across a broad spectrum of food intakes. Further, because of the prospective nature of the trial, dietary and other exposure data were collected before outcome ascertainment, thus minimizing recall bias.

Another strength of this research was the use of the DII, which is a novel way to characterize the inflammatory nature of diet (22). Research is growing on the association between inflammation and not only adenomas, but also cancers in general (191, 227). The DII allows researchers to better approximate the contribution that diet makes to the inflammatory pathway of disease.

There were several limitations in the research presented in the previous chapters. Of particular note, is that sample sizes became rather small when stratifying by the racial subgroups. The interaction between diet scores and sex further reduced sample sizes because of the need to present sex-stratified results. It is likely that the analyses were underpowered in their ability to detect significant findings. Assuming a 30% poor diet exposure in the controls, a 10 to 1 ratio of controls to cases, and a 1.44 odds of adenoma among those with a poor diet, a more desirable sample size to detect significant differences would have been around 284 cases (228), which is larger than what was in the racial subgroups other than whites. Sample size calculations were done before the research began, which indicated that there would be adequate power in detecting

differences in this cohort, although this did not take into consideration the number of people who would be excluded because of lack of complete data. Specifically, blacks, who were the primary race of interest, were less likely to have complete information for analysis than whites. However, even with that possibility, significant results were seen in the associations between prevalent adenoma and dietary scores in certain racial subgroups.

Another limitation in this research is that the dietary questionnaire was not able to fully capture all elements of a person's diet, and consequently, the actual healthiness of each person's diet was not able to be truly characterized. Unfortunately, there is no perfect way to collect dietary data, and this topic has been discussed at great lengths in the current literature (229-231). In spite of the limitations with the collection of dietary data, the dietary questionnaire in the PLCO cohort has been validated against two very common questionnaires and has been shown to have good reliability (165). Specific to this research, the DII was calculated from only those variables that were collected as part of the baseline dietary questionnaire. There were several food components that exert powerful anti-inflammatory effects that were not used in the calculation (e.g. eugenol, garlic, ginger, saffron, turmeric, pepper, rosemary, and thyme/oregano). However, data for most items for the DII were collected and included in the calculations, and these items represented the most commonly consumed foods/nutrients. Related to the limitations of a dietary questionnaire is that of limitations with using index-based methods to determine diet "healthiness". The Mediterranean diet was an estimate to how closely people ate to a prescribed index that was developed by researchers, and may not truly characterize the Mediterranean nature of diet.

Finally, it should be noted that only distal adenomas were able to be detected with the flexible sigmoidoscopy screening method. This has implications for this research that focuses on

racial differences. Studies suggest that blacks are more likely to have proximal adenomas than whites, whereas blacks were either less likely or had a similar prevalence of distal adenoma, compared to whites (6, 41, 42). Because of this, the results can only be applied to distal adenomas, and future work should determine whether diet is also associated with adenoma in the proximal sites of the colon, and whether or not this association is different between the different racial subgroups.

Public Health Implications

Overall, the results of this research suggest that diets that are anti-inflammatory in nature, low in red and processed meats, low in refined carbohydrates, and high in fruits, vegetables, and legumes are associated with lower odds of CRA. These associations are consistent in whites, but are less consistent blacks, Asians, and those of other races. Asians had the highest quality of diet, when using either the DII or altMED diet index, and they also had the lowest prevalence of CRA. The lack of association in this racial subgroup may be due to the generally high quality of diet that these individuals consume. In considering racial disparities, Asians often have better health outcomes, and would be less likely to benefit from public health interventions. However, because of the disparities that often occur in CRA prevalence among the broader black population, public health interventions may be more effective in this sub-population. Specifically, blacks in the PLCO whose diets scored more favorably on the altMED index had a lower prevalence of CRA, compared to those with lower scores. The higher altMED diet scores among blacks, compared to whites, combined with the lower prevalence of adenoma is likely from blacks in the PLCO cohort having better diets and being more educated than blacks in the general US population. However, these data suggest that diet can be an effective measure in reducing the prevalence of adenoma among blacks in the general US population because of the

positive association between better diet scores (e.g. altMED index) and lower prevalence of adenomas in blacks enrolled in the PLCO.

Simply encouraging people to consume more fruits and vegetables or less meat is not always an effective strategy. Rather, public health interventions should focus on the barriers that prevent disadvantaged populations from accessing healthy foods. It may be that people do not always understand what healthy is because of confusing advertising messages. Processed, low-quality food items are also convenient and cheap, making it difficult for busy consumers to justify the extra monetary costs and time that come with eating healthier food items.

Researchers have suggested a multi-dimensional approach is needed in order to integrate healthier eating patterns in individuals (232). This approach encompasses intrapersonal, interpersonal, organizational, community, and public policy levels in order to address personal, cultural, and environmental factors where barriers may be a factor. In a multi-approach intervention study, congregations of primarily black church-goers were successful in increasing fruit and vegetable intake when they were involved in a program that included cooking classes, gardening, church encouragement of fruit and vegetable intake, and coupon and recipe cards from local grocers to promote fruit and vegetable intake (233).

As far as messages to the general public, recommendations from the Dietary Guidelines (234) is a good starting point. These recommendations promote a variety of foods and recommend that foods be eaten in context of the broader diet. Grains, fruits, and vegetables should be the foundation of a meal, and protein sources should come from a variety of sources, including both plant and animal sources. And, while animal protein sources may provide important sources of certain nutrients (zinc, vitamin B-12, phosphorus, and iron), plant sources can also be important sources of protein and other important nutrients (fiber, calcium, and

potassium; (235)). However, recommendations should also emphasize that variety is important because of the diversity of nutrients that come with eating this way - nutrients that would likely contribute to an anti-inflammatory diet.

Future Research Needs

Future research should seek to understand the barriers to eating a healthier diet – one that would include more fruits and vegetables, fewer meat sources, and is more anti-inflammatory. Researchers should also determine more effective ways to help those of typically disadvantaged populations to achieve a healthy diet - one that would be adequate for disease prevention. This may involve social and spatial epidemiologists to determine behavioral and geographical factors involved in peoples decisions to eat the way they do.

The DII has been shown to be an effective tool in characterizing the inflammatory nature of diet (22), but it is still unknown what a clinically meaningful score would be and what an "ideal" level for adenoma prevention would be. In the current research, scores were categorized according to the distribution patterns in the PLCO cohort but it may be that there is a therapeutic cut-point that wasn't considered in this research.

Finally, future research should seek to more fully understand the specific mechanisms for CRA incidence, especially in the racial subgroups. Inflammatory mechanisms and dietary mechanisms have both been suggested from the results of the research presented here, as well as the results of other studies (134, 191). However, it is unclear whether the protective effects of diet are due to the direct action of foods and their nutrients or the indirect effect of food and nutrients through inflammatory pathways. Further, the interaction between diet and genetics should be further explored and better understood.

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APPENDIX A

SUPPLEMENTAL TABLES FOR CHAPTER 4

Supplemental Table 4.1: Baseline characteristic of the Prostate, Lung, Colorectal, and Ovarian screening arm participants, by case status (N=41,973)

Categorical Variables	**Cases N (%)**	**Controls N (%)**	**Chi-square p-value**
Gender			<0.0001
Male	2,529 (65.4)	20,047 (52.6)	
Female	1,337 (34.6)	18,060 (47.4)	
Race			<0.0001
White	3,583 (92.7)	34,562 (90.7)	
Black	115 (3.0)	1,298 (3.4)	
Hispanic	60 (1.6)	527 (1.4)	
Asian	87 (2.2)	1,463 (3.8)	
Other	21 (0.5)	257 (067)	
Education			<0.0001
College	1,306 (33.8)	14,486 (38.0)	
Some college	1,318 (34.1)	12,896 (33.8)	
High school	929 (24.0)	8497 (22.3)	
Less than high school	313 (8.1)	2,228 (5.8)	
Physical Activity[1]			<0.0001
High	2,021 (52.3)	21,596 (56.7)	
Low	1,845 (47.7)	16,511 (43.3)	
Smoking			<0.0001
Never	1,460 (37.8)	18,663 (49.0)	
Current	605 (16.6)	3,304 (8.7)	
Former	1,801 (46.6)	16,140 (42.4)	
Anti-inflammatory use			0.78
Yes	771 (19.9)	7668 (20.1)	
No	3,095 (80.1)	30439 (79.9)	
Hormone therapy (females)			<0.0001
Current	625 (46.8)	9703 (53.7)	
Former	220 (16.4)	2809 (15.6)	
Never	490 (36.6)	5493 (30.4)	
Unknown	2 (0.2)	55 (0.3)	
Body Mass Index (kg/m^2)			<0.0001
0-18.5	22 (0.6)	230 (0.6)	
18.5-25	1,047 (27.1)	12,272 (32.2)	
25-30	1,763 (45.6)	16,566 (43.5)	
30+	1,034 (26.8)	9,039 (23.7)	
Continuous variables	**Means (SD)**	**Means (SD)**	**T-test p-value**
Age (years; continuous)	63.1 (5.2)	62.34 (5.3)	<0.0001
Calcium (diet and supplements; mg/day)	1,173.6 (574.4)	1,256.31 (608.3)	<0.0001
Calories (kcal/day)	2122.0 (823.3)	2062.31 (794.4)	<0.0001

1. Less than 2 hours of vigorous activities per week (low) vs. 2 or more hours of vigorous activities per week (high)

Supplemental Table 4.2: Descriptive characteristic of the Prostate, Lung, Colorectal, and Ovarian screening arm participants in the recurrent cohort, by race and adenoma status (N=1,539; Med Diet)

Categorical Variables	**White (N=1,453)** **Cases N (%)**	**Controls N (%)**	**Black (N=40)** **Cases N (%)**	**Controls N (%)**	**Hispanic (N=19)** **Cases N (%)**	**Controls N (%)**	**Asian (N=16)** **Cases N (%)**	**Controls N (%)**	**Other (N=11)** **Cases N (%)**	**Controls N (%)**
Gender										
Male	516 (73.4)	445 (59.3)	11 (52.4)	13 (68.4)	6 (54.6)	3 (37.5)	8 (66.7)	3 (75.0)	4 (44.4)	0 (0.0)
Female	187 (26.6)	305 (40.7)***	10 (47.6)	6 (31.6)	5 (45.4)	5 (62.5)	4 (33.3)	1 (25.0)	5 (55.6)	2 (100.0)
Education										
Some college or greater	501 (71.3)	512 (68.3)	19 (90.5)	15 (79.0)	5 (45.4)	6 (75.0)	9 (75.0)	4 (100.0)	5 (55.6)	2 (100.0)
High school or less	202 (28.73)	238 (31.7)	2 (9.5)	4 (21.0)	6 (54.6)	2 (25.0)	3 (25.0)	0 (0.0)	4 (44.4)	0 (0.0)
Physical Activity										
High	379 (53.9)	416 (55.5)	8 (38.1)	12 (63.2)	5 (45.4)	5 (62.5)	5 (41.7)	3 (75.0)	6 (66.7)	1 (50.0)
Low	3324 (46.1)	334 (44.5)	13 (61.9)	7 (36.8)	6 (54.6)	3 (37.5)	7 (58.3)	1 (25.0)	3 (33.3)	1 (50.0)
Smoking										
Never	240 (34.1)	282 (37.6)	6 (28.6)	3 (15.8)	6 (54.6)	4 (50.0)	6 (50.0)	2 (50.0)	3 (33.3)	2 (100.0)
Current	89 (12.7)	100 (13.3)	7 (33.3)	6 (31.6)	2 (18.2)	1 (12.5)	4 (33.3)	1 (25.0)	3 (33.3)	0 (0.0)
Former	374 (53.2)	368 (49.1)	8 (38.1)	10 (52.6)	3 (27.3)	3 (37.5)	2 (16.7)	1 (25.0)	3(33.3)	0 (0.0)
Anti-inflammatory use										
Yes	146 (20.8)	161 (31.5)	5 (23.8)	3 (15.8)	4 (36.4)	2 (25.0)	1 (8.3)	1 (25.0)	1 (11.1)	1 (50.0)
No	557 (79.2)	589 (78.5)	16 (76.2)	16 (84.2)	7 (63.6)	63 (75.0)	11 (91.7)	3 (75.0)	8 (88.9)	1 (50.0)
Hormone therapy (females)										
Current	88 (47.1)	138 (45.2)	7 (70..0)	4 (66.7)	2 (40.0)	2 (40.0)	1 (25.0)	0 (0.0)	2 (40.0)	2 (100.0)
Former	27 (14.4)	43 (14.1)	0 (0.0)	0 (0.0)	2 (40.0)	2 (40.0)	2 (50.0)	1 (0..0)	2 (40.0)	0 (0.0)
Never	72 (38.5)	123 (40.3)	3 (30.0)	2 (33.3)	1 (20.0)	1 (20.0)	1 (25.0)	0 (0.0)	1 (20.0)	0 (0.0)
Unknown	0 (0.0)	1 (0.3)								
Body Mass Index (kg/m^2)										
<25	162 (23.0)	231 (30.8)	8 (38.1)	5 (26.3)	3 (27.3)	8 (100.0)	7 (58.3)	3 (75.0)	6 (66.7)	2 (100.0)
≥-30	541 (77.0)	519 (69.2)**	13 (61.9)	14 (73.7)	8 (72.7)	0 (0.0)	5 (41.7)	1 (25.0)	3 (33.3)	0 (0.0)
Continuous variables	**Means (standard deviation)**	**Means (standard deviation)**	**Means (standard deviation)**	**Means (standard deviation)**	**Means (standard deviation)**	**Means (standard deviation)**	**Means (standard deviation)**	**Means (standard deviation)**	**Means (standard deviation)**	**Means (standard deviation)**
Age (years)	63.0 (4.9)	62.6 (5.1)	61.7 (4.6)	64.0 (3.8)	63.0 (4.3)	62.8 (5.4)	63.9 (5.2)	63.2 (5.2)	62.3 (5.6)	61.5 (2.1)
Calcium (diet and supplements; mg/day)	1,147.1 (534.4)	1,183.7 (561.9)	851.9 (412.2)	900.2 (369.8)	1,156.7 (674.3)	1,399.2 (736.9)	725.4 (405.0)	893.7 (376.7)	847.1 (389.7)	624.4 (299.0)
Calories (kcal/day)	2,205.8 (834.4)	2,092.1 (796.8)*	2,056.1 (751.4)	2,032.5 (465.2)	2,026.7 (595.3)	2,237.5 (980.9)	1,678.2 (644.6)	1,809.5 (716.4)	1,797.9 (560.8)	1,243.5 (320.8)

*p-value<0.05; **p<0.001; ***p<0.0001; comparing cases to controls for each race; chi-square for categorical and t-tests for continuous variables

Supplemental Table 4.3: Frequency (percent) of race-specific population receiving a point for each component of the alternate Mediterranean diet (aMED) score, by race, in the Prostate, Lung, Colorectal, and Ovarian Cancer screening arm participants

Category	Whites (N=38,145) Reference group	Blacks (N=1,413)	Asian (N=1,550)	Other (N=865)	Overall p-value[1]
Vegetables (excluding white potatoes)	19,136 (50.2)	578 (40.9)***	814 (52.5)	413 (47.8)	<0.0001
Fruit	18,849 (49.4)	878 (62.1)***	774 (49.9)	429 (49.6)	<0.0001
Legumes	18,723 (49.1)	720 (51.0)	1,021 (65.9)***	459 (53.1)*	<0.0001
Nuts	21,951 (57.6)	744 (52.6)**	786 (50.7)***	441 (51.0)***	<0.0001
Whole grains	18,925 (49.6)	877 (62.1)***	763 (49.2)	412 (47.6)	<0.0001
Red and processed meats	18,506 (48.5)	741 (52.4)*	1,138 (73.4)***	447 (51.7)	<0.0001
Fish	18,921 (49.6)	654 (46.3)*	1,050 (67.7)***	425 (60.4)	<0.0001
Ratio of monounsaturated to saturated fat	18,361 (48.1)	921 (65.2)***	1274 (82.2)***	473 (54.7)***	<0.0001
Ethanol	6,539 (17.1)	298 (21.1)***	324 (20.9)***	160 (18.5)	<0.0001

1. Chi-square test to determine significant differences comparing whites vs blacks (or Asian or other); *p-value<0.05; **p<0.001; ***p<0.0001;

Supplemental Table 4.4: Baseline characteristic of the Prostate, Lung, Colorectal, and Ovarian screening arm participants, by Mediterranean diet score category and adenoma status (N=41,973)

	Alternate Mediterranean (aMED) diet cut-points								
	High (N=11,291)			Moderate (N=22,845)			Low (N=7,837)		
	Cases	Controls	Total population	Cases	Controls	Total population	Cases	Controls	Total population
Gender									
Male	566 (64.83)	5,599 (53.74)	6,165 (54.57)	1,371 (64.67)	10,816 (52.17)	12,187 (53.33)	592 (67.81)	3,632 (52.15)	4,224 (53.88)
Female	307 (35.17)	4,819 (46.26)***	5,133 (45.43)	749 (35.33)	9,909 (47.83)***	10,667 (46.67)	281 (32.19)	3,332 (47.85)***	3,616 (43.12)
Education									
College	402 (46.05)	4,873 (46.74)	5,275 (46.69)	691 (32.59)	7,690 (37.10)	8,383 (36.68)	213 (24.40)	1,925 (27.64)	2,139 (27.28)
Some college	288 (32.99)	3,344 (32.12)	3,636 (32.18)	723 (34.10)	7,093 (34.23)	7,821 (34.22)	307 (35.17)	2,459 (35.31)	2,767 (35.29)
High school	134 (15.35)	1,777 (17.06)	1,912 (16.92)	540 (25.47)	4,700 (22.68)	5,242 (22.94)	255 (29.21)	2,020 (29.01)	2,276 (29.03)
Less than high school	49 (5.61)	426 (4.09)	475 (4.20)	166 (7.83)	1,242 (5.99)***	1408 (6.16)	307 (35.17)	560 (8.04)*	658 (8.39) ǂǂ
Physical Activity									
High	554 (63.46)	7,088 (68.03)	7,646 (67.68)	1,111 (52.41)	1,1476 (55.38)	12,594 (55.11)	356 (40.78)	3,032 (43.52)	3,388 (43.21)
Low	319 (36.54)	3,330 (31.97)*	3,652 (32.32)	1,009 (47.59)	9,249 (44.62)*	10,260 (44.89)	517 (59.22)	3,932 (56.48)	4,452 (56.79) ǂǂ
Smoking									
Never	391 (44.79)	5,606 (53.80)	6,000 (53.11)	803 (37.88)	9,962 (48..06)	10,767 (47.11)	266 (30.47)	3,095 (44.44)	3,362 (42.88)
Current	84 (9.62)	564 (5.41)	648 (5.74)	326 (15.38)	1,824 (8.81)	2,152 (9.42)	195 (22.34)	916 (13.15)	1,111 (14.17)
Former	398 (45.59)	4,248 (40.79)***	4,650 (41.16)	991 (16.75)	8,939 (43.14)***	9,935 (43.47)	412 (47.19)	2,953 (42.41)***	3,367 (42.95) ǂǂ
Anti-inflammatory use									
Yes	181 (20.73)	2,010 (19.30)	2,193 (19.41)	422 (19.91)	4,165 (20.10)	4,590 (20.08)	168 (19.24)	1,493 (21.44)	1,662 (21.20)
No	692 (79.27)	8,408 (80.70)	9,105 (80.59)	1,698 (80.09)	16,560 (79.90)	1,8264 (79.92)	705 (80.76)	5,471 (78.56)	6,178 (78.80) ǂ
Hormone therapy (females)									
Current	153 (49.51)	2,544 (52.79)	2,696 (52.59)	337 (44.99)	5,398 (54.48)	5,735 (53.81)	136 (48.40)	1761 (52.85)	1,897 (52.50)
Former	54 (17.59)	812 (16.85)	866 (16.89)	117 (15.62)	1,496 (15.10)	1,613 (15.13)	49 (17.44)	501 (15.04)	550 (15.22)
Never	100 (32.57)	1,451 (30.11)	1,551 (30.26)	294 (39.25)	2,985 (30.12)	3,279 (30.77)	96 (34.16)	1,057 (31.72)	1,153 (31.91)
Unknown	1 (0.33)	12 (0.25)	13 (0.25)	1 (0.13)	30 (0.30)***	31 (0.29)	0 (0.00)	13 (0.39)	13 (0.36)
Body Mass Index (kg/m^2)									
0-18.5	7 (0.80)	68 (0.65)	75 (0.66)	11 (0.52)	128 (0.62)	139 (0.61)	4 (0.46)	34 (0.49)	38 (0.48)
18.5-25	246 (28.18)	3,759 (36.09)	4,008 (35.48)	569 (26.84)	6,535 (31.52)	7,105 (31.09)	232 (26.58)	1,978 (28.39)	2,210 (28.19)
25-30	409 (46.85)	4,431 (42.52)	4,842 (42.86)	970 (45.75)	9,049 (43.66)	1,0023 (43.86)	384 (43.99)	3,086 (44.31)	3,471 (44.27)

30+	211 (24.17)	2,160 (20.74)***	2,373 (21.00)	570 (26.89)	5,013 (24.20)***	5,587 (24.45)	253 (28.98)	1,866 (26.81)	2,121 (27.05) ǂǂ
Race									
White	781 (89.46)	9,143 (87.77)	9,931 (87.90)	1,978 (93.30)	18,918 (91.28)	20,904 (91.47)	824 (94.39)	6,501 (93.35)	7,326 (93.44)
Black	34 (3.89)	408 (3.91)	442 (3.91)	55 (2.59)	701 (3.39)	757 (3.31)	26 (2.98)	189 (2.71)	217 (2.77)
Asian	37 (4.24)	667 (6.40)	704 (6.24)	41 (1.93)	667 (3.22)	708 (3.10)	9 (1.03)	129 (1.85)	138 (1.76)
Hispanic	17 (1.95)	118 (1.13)	135 (1.19)	31 (0.71)	307 (1.48)	338 (1.48)	12 (1.37)	102 (1.46)	114 (1.45)
Other	4 (0.46)	82 (0.79)*	86 (0.76)	15 (0.71)	132 (0.64)*	147 (0.64)	2 (0.23)	43 (0.62)	45 (0.57) ǂǂ

*p-value<0.05; **p<0.001; ***p<0.0001; Chi-square to compare cases and controls; łp<0.05, ǂǂp<0.0001 comparing the 3 dietary categories (high, medium, low)

APPENDIX B

SUPPLEMENTAL TABLES FOR CHAPTER 5

Supplemental Table5.1: Baseline characteristics of the PLCO screening arm participants, by adenoma status for Dietary Inflammatory Index analysis (N=44,278)

Categorical variables	**Cases N (%)**	**Controls N (%)**	**Chi-square p-value**
Gender			<0.0001
Male	2,654 (65.3)	21,134 (52.6)	
Female	1,408 (34.7)	19,082 (47.4)	
Race			<0.0001
White	3,758 (92.5)	36,310 (90.3)	
Black	130 (3.2)	1,478 (3.7)	
Hispanic	62 (1.5)	581 (1.4)	
Asian	91 (2.2)	1,572 (3.9)	
Other	21 (0.5)	275 (0.7)	
Education			<0.0001
College	1,358 (33.4)	1,514 (37.7)	
Some college	1,396 (34.4)	1,3587 (33.8)	
High school	974 (24.0)	9,036 (22.5)	
Less than high school	334 (8.2)	2,449 (6.1)	
Physical Activity[1]			<0.0001
High	2,129 (52.4)	22,745 (56.6)	
Low	1,933 (57.6)	17,471 (43.4)	
Smoking			<0.0001
Never	1,535 (37.8)	19,695 (49.0)	
Current	636 (15.7)	3,506 (8.7)	
Former	1,891 (46.6)	17,015 (42.3)	
Anti-inflammatory use[1]			1.00
Yes	819 (20.2)	8110 (20.2)	
No	3,243 (79.8)	32106 (79.8)	
Hormone therapy (females)			<0.0001
Current	652 (46.3)	10,208 (53.6)	
Former	236 (16.8)	2,970 (15.6)	
Never	517 (36.7)	5,815 (30.5)	
Unknown	2 (0.14)	67 (0.4)	
Body Mass Index (kg/m^2)			<0.0001
0-18.5	23 (0.6)	246 (0.6)	
18.5-25	1,108 (27.3)	12,910 (32.1)	
25-30	1,851 (45.6)	17,456 (43.4)	
30+	1,080 (26.6)	9,604 (23.9)	
Missing (n=430)			
Dietary Inflammatory Index			<0.0001
Quartile 1	796 (19.6)	10,273 (25.5)	
Quartile 2	854 (21.0)	10,216 (25.4)	
Quartile 3	1,097 (27.0)	9,972 (24.8)	
Quartile 4	1,315 (32.4)	9,755 (24.3)	
Continuous variables	**Means (standard deviation)**	**Means (standard deviation)**	**t-test p-value**
Age (years; continuous)	63.0 (19)	62.0 (22)	<0.0001
Calcium intake (supplements and food)	1,069.9 (4,496.3)	1,151.6 (7,012.2)	<0.0001
Energy (kcal/day)	1,978.3 (4,908.1)	1,924.6 (4,985.4)	<0.0001

*p<0.05; **p<0.01; ***p<0.0001

1. 2 or more hours of vigorous exercise per week (high) vs. less than 2 hours of vigorous exercise per week (low)
2. Anti-inflammatory use is using aspirin or ibuprofen regularly in the prior 12 months

Supplemental Table 5.2: Median (range) of select Dietary Inflammatory Index subcomponent intakes, by race

Category	Whites (N=40068) Reference group	Blacks (N=1608)	Hispanic (N=643)	Asian (N=1663)	Other (N=296)	Kruskal-Wallace p-value
DII score	-1.8 (11.4)	-1.7 (10.4)	-1.6 (9.7)	-2.9 (9.6)***	-1.9 (8.3)	<0.0001
Energy (kcal/day)	1,944.3 (4,974.4)	1,818.4 (4,973.5)	1,886.7 (4,600.3)*	1,710.2 (4,933.1)***	1,939.2 (4,867.3)	<0.0001
Carbohydrate (g/day)	260.5 (1,001.9)	250.0 (959.7)**	254.1 (647.7)	249.6 (670.3)***	262.0 (745.7)	<0.0001
Protein (g/day)	75.9 (310.5)	67.7 (213.3)***	73.7 (254.2)	66.7 (239.0)***	79.3 (215.9)	<0.0001
Fat (g/day)	61.7 (284.8)	57.8 (210.9)***	58.8 (249.3)	48.1 (186.6)***	62.2 (245.8)	<0.0001
Alcohol (g/day)	1.6 (394.9)	0.4 (380.3)***	1.2 (273.8)**	0.4 (370.2)***	0.5 (121.8)***	<0.0001
Fiber (g/day)	21.9 (106.9)	20.6 (107.8)***	21.8 (86.7)	21.0 (68.8)**	21.6 (73.1)	<0.0001
Cholesterol (mg/day)	202.2 (1391.4)	208.1 (988.6)*	216.9 (905.9)**	162.0 (1077.3)***	224.6 (822.0)*	<0.0001
Vitamin A (food and supplements; i.u./day)	14,013.5 (10,3881.6)	12,860.3 (77,066.5)***	12,770.6 (67,245.3)**	15,500.0 (78,060.9)***	14,674.5 (57,657.2)	<0.0001
Vitamin C (food and supplements; mcg/day)	250.6 (3,398.4)	235.6 (2,967.8)***	239.4 (2,500.2)	290.0 (2,989.4)*	287.5 (2,432.4)	<0.0001
Vitamin E (food and supplements; mg/day of alpha-tocopherol equivalents)	20.7 (545.1)	14.2 (511.9)***	18.4 (491.6)**	20.9 (507.9)	19.1 (519.6)	<0.0001
Folate (food and supplements; mcg/day)	536.5 (3,739.1)	445.2 (2,480.3)***	489.2 (2,983.6)	527.1 (3,016.0)*	479.4 (2,634.3)	<0.0001
Beta Carotene (food and supplements; mcg/day)	4,821.2 (32,665.0)	4,809.8 (34,797.5)*	4,466.7 (30,471.0)*	6,155.2 (3,0833.1)***	5,448.5 (24,956.4)*	<0.0001
Vitamin B12 (mcg/day)	8.8 (143.0)	6.9 (119.2)***	8.4 (132.3)	8.0 (135.7)***	8.5 (123.5)	<0.0001
Vitamin B6 (mg/day)	3.4 (35.7)	2.9 (26.2)***	3.2 (31.0)	3.4 (32.0)	3.2 (27.3)	<0.0001
Iron (mg/day)	24.4 (140.2)	20.2 (90.5)***	23.3 (111.4)***	22.9 (97.6)	22.8 (103.0)	<0.0001
Magnesium (mg/day)	416.1 (1,532.9)	350.8 (1,269.8)***	392.9 (1,090.4)*	378.3 (1,105.3)***	400.6 (1,106.6)*	<0.0001

Zinc (mg/day)	17.7 (105.7)	13.3 (62.5)***	16.6 (76.0)*	14.8 (81.7)***	17.0 (83.2)	<0.0001
Selenium (mcg/day)	95.6 (378.0)	88.9 (288.3)***	94.8 (299.3)	89.4 (308.2)***	102.8 (282.9)*	<0.0001

*p<0.05; **p<0.001; ***p<0.0001 using Wilcoxon-rank sum test was used to test for differences between race, using white as the reference group; Kruskal-Wallace test for overall test.

APPENDIX C

SUPPLEMENTAL TABLES FOR CHAPTER 6

Supplemental Table 6.1a: Descriptive characteristics of Prostate, Lung, Colorectal, and Ovarian cancer screening arm participants (N=44,278) according to quintiles of Factor 1 "Fruit and vegetables" food groupings

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Categorical Variables	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Male (N=23788)					
Race					
White	4,215 (88.6)	4,346 (91.3)	4,373 (91.9)	4,362 (91.7)	4,207 (88.4)
Black	198 (4.2)	143 (3.0)	137 (2.9)	132 (2.8)	161 (3.4)
Asian	169 (3.6)	170 (3.6)	160 (3.4)	171 (3.6)	273 (5.7)
Other	175 (3.7)	99 (2.1)	88 (1.8)	92 (1.9)	117 (2.5)***
Education					
College	1,429 (30.0)	1,822 (38.3)	2,066 (43.4)	2,219 (46.6)	2,539 (53.4)
Some college	1,671 (35.1)	1,627 (34.2)	1,511 (31.8)	1,463 (30.8)	1,365 (28.7)
High school	1,167 (24.5)	961 (20.2)	855 (18.0)	781 (16.4)	576 (12.1)
Less than high school	490 (10.3)	348 (7.3)	326 (6.8)	294 (6.2)	278 (5.8)***
Physical Activity[1]					
High	1,923 (4.04)	2,426 (51.0)	2,775 (58.3)	2,979 (62.6)	3,382 (71.1)
Low	2,834 (59.6)	2,332 (49.0)	1,983 (41.7)	1,778 (37.4)	1,376 (28.9)***
Smoking					
Never	1,487 (31.3)	1,655 (34.8)	1,853 (38.9)	2,016 (42.4)	2,177 (45.8)
Current	858 (18.0)	572 (12.0)	431 (9.1)	371 (7.8)	234 (4.9)
Former	2,412 (50.7)	2,531 (53.2)	2,474 (52.0)	2,370 (49.8)	2,347 (49.3)***
Anti-inflammatory use					
Yes	977 (20.5)	950 (20.0)	932 (19.6)	939 (19.7)	909 (19.1)
No	3,780 (79.5)	3,808 (80.0)	3,826 (80.4)	3,818 (80.3)	3,849 (80.9)
Body Mass Index (kg/m^2)					
0-18.5	12 (0.2)	13 (0.3)	7 (0.2)	10 (0.2)	20 (0.4)
18.5-25	1,020 (21.4)	1,038 (21.8)	1,176 (24.7)	1,281 (26.9)	1,491 (31.3)
25-30	2,419 (50.8)	2,475 (52.0)	2,441 (51.3)	2,412 (50.7)	2,348 (49.4)
30+	1,306 (27.4)	1,232 (25.9)	1,134 (23.8)	1,054 (22.2)	899 (18.9)***
Female (N=20490)					
Race					
White	3,763 (91.8)	3,789 (92.5)	3,791 (92.5)	3,735 (91.1)	3,487 (85.1)
Black	189 (4.6)	150 (3.7)	120 (2.9)	147 (3.6)	231 (5.6)
Asian	70 (1.7)	96 (2.3)	122 (3.0)	147 (3.6)	285 (7.0)
Other	76 (1.8)	63 (1.5)	65 (1.6)	69 (1.7)	95 (2.3)***
Education					
College	833 (20.3)	1,168 (28.5)	1,312 (32.0.)	1,499 (36.6)	1,615 (39.4)
Some college	1,443 (35.2)	1,491 (36.4)	1,489 (36.3)	1,437 (35.1)	1,486 (36.3)
High school	1,519 (37.1)	1,229 (30.0)	1,110 (27.1)	974 (23.8)	838 (20.4)
Less than high school	303 (7.4)	210 (5.1)	187 (4.6)	188 (4.6)	159 (3.9)***
Physical Activity[1]					
High	1,562 (38.1)	2,091 (51.0)	2,335 (57.0)	2,557 (62.4)	2,844 (69.4)
Low	2,536 (61.9)	2,007 (49.0)	1,763 (43.0)	1,541 (37.6)	1,254 (30.6)***
Smoking					
Never	2,233 (54.5)	2,346 (57.2)	2,430 (59.)	2,493 (60.8)	25,40 (62.0)
Current	561 (13.7)	355 (8.7)	287 (7.0)	242 (5.9)	231 (5.6)
Former	1,304 (31.8)	1,397 (34.1)	1,381 (33.7)	1,363 (33.3)	1,327 (32.4)***
Anti-inflammatory use					
Yes	912 (22.2)	874 (21.3)	820 (20.0)	825 (20.1)	791 (19.3)
No	3,186 (77.8)	3,224 (78.7)	3,278 (80.0)	3,273 (79.9)	3,307 (80.7)*
Body Mass Index (kg/m^2)					
0-18.5	43 (1.0)	32 (0.8)	32 (0.8)	40 (1.0)	60 (1.5)
18.5-25	1,415 (34.5)	1,561 (38.1)	1,640 (40.0)	1,701 (41.5)	1,695 (41.4)
25-30	1,472 (35.9)	1,472 (35.9)	1,479 (36.1)	1,392 (34.0)	1,397 (34.1)
30+	1,168 (28.5)	1,033 (25.2)	947 (23.1)	965 (23.6)	946 (23.1)***

Hormone therapy					
Current	2,097 (51.2)	2,233 (54.5)	2,212 (54.0)	2,204 (53.8)	2,114 (51.7)
Former	634 (15.5)	629 (15.4)	604 (14.8)	619 (15.1)	720 (17.6)
Never	1,345 (32.9)	1,217 (29.7)	1,268 (31.0)	1,258 (30.7)	1,244 (30.4)
Unknown	16 (0.4)	17 (0.4)	10 (0.2)	12 (0.3)	14 (0.3)*
Continuous variables	**Means (SD)**	**Means (SD)**	**Means (SD)**	**Means (SD)**	**Means (SD)**
Male					
Calcium (diet and supplements; mg/day)	,921.6 (522.3)	1,036.3 (505.7)	1,147.6 (529.1)	1,269.1 (570.5)	1,449.9 (591.8)
Calories (kcal/day)	1,927.5 (782.3)	2,113.7 (743.1)	2,319.4 (774.1)	2,497.5 (788.3)	2,823.0 (849.0)
Alcohol (g/day)	18.0 (34.6)	16.0 (29.5)	16.2 (28.2)	14.9 (26.3)	13.8 (24.7)
Fiber (g/day)	14.9 (5.2)	19.6 (5.2)	23.9 (5.9)	28.4 (6.5)	38.4 (10.5)
Age (years)	61.5 (5.1)	62.2 (5.1)	62.7 (5.2)	63.1 (5.3)	63.7 (5.4)
Female					
Calcium (diet and supplements; mg/day)	1,050.6 (560.1)	1,207.3 (574.8)	1,335.2 (584.8)	1,470.5 (602.4)	1,643.9 (644.6)
Calories (kcal/day)	1,386.8 (509.0)	1,562.5 (499.1)	1,724.7 (510.6)	1,886.3 (525.5)	2,206.0 (605.0)
Alcohol (g/day)	5.4 (12.2)	5.7 (12.8)	6.0 (13.2)	5.5 (12.6)	5.0 (11.1)
Fiber (g/day)	13.0 (4.0)	17.2 (4.0)	20.7 (4.6)	24.6 (5.1)	33.0 (8.4)
Age (years)	61.4 (5.0)	62.1 (5.3)	62.3 (5.3)	62.5 (5.3)	62.8 (5.4)

SD=standard deviation' *p-value<0.05; **p<0.001; ***p<0.0001; Chi-square for categorical and Kruskal-Wallis tests for continuous variables

1. Males: Quintile 1:< -0.80; Quintile 2:-0.80 to -0.39; Quintile 3:-0.40 to 0.03; Quintile 4: 0.03 to 0.65; Quintile 5: >0.65; Females: Quintile 1:< -0.80; Quintile 2:-0.80 to -0.38; Quintile 3:-0.39 to 0.04; Quintile 4: 0.04 to 0.67; Quintile 5: >0.67
2. Less than 2 hours of vigorous activities per week (low) vs. 2 or more hours of vigorous activities per week (high)

Supplemental Table 6.1b: Descriptive characteristics of Prostate, Lung, Colorectal, and Ovarian cancer screening arm participants (N=44,278) according to quintiles of Factor 2 "Western diet" food groupings

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Categorical Variables	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Male (N=23,788)					
Race					
White	4,413 (92.8)	4,397 (92.4)	4,319 (90.8)	4,299 (90.3)	4,075 (85.7)
Black	125 (2.6)	128 (2.7)	154 (3.2)	137 (2.9)	227 (4.8)
Asian	130 (2.7)	150 (3.2)	172 (3.6)	204 (4.3)	287 (6.0)
Other	90 (1.9)	84 (1.8)	110 (2.3)	119 (2.5)	168 (3.5)***
Education					
College	2,095 (44.0)	2,149 (45.2)	2,023 (452.5)	1,972 (41.4)	1,836 (38.6)
Some college	1,477 (31.0)	1,441 (30.3)	1,570 (33.0)	1,539 (32.3)	1,610 (33.8)
High school	814 (17.1)	831 (17.5)	835 (17.6)	932 (19.6)	928 (19.5)
Less than high school	372 (7.8)	338 (7.1)	327 (6.9)	316 (6.6)	383 (8.0)***
Physical Activity[1]					
High	2,992 (62.9)	2,806 (59.0)	2,693 (56.6)	2,596 (54.6)	2,398 (50.4)
Low	1,766 (37.1)	1,953 (41.0)	2,062 (43.4)	2,163 (45.4)	2,359 (49.6)***
Smoking					
Never	2,168 (45.6)	1,914 (40.2)	1,737 (36.5)	1,722 (16.2)	1,647 (34.6)
Current	302 (6.4)	414 (8.7)	492 (10.4)	589 (12.4)	669 (14.1)
Former	2,288 (48.1)	2,431 (51.1)	2,526 (53.1)	2,448 (51.4)	2,441 (51.3)***
Anti-inflammatory use					
Yes	794 (16.7)	890 (18.7)	952 (20.0)	1,028 (21.6)	1,043 (21.9)
No	3,964 (83.3)	3,869 (81.3)	3,803 (80.0)	3,731 (78.4)	3,714 (78.1)***
Body Mass Index (kg/m^2)					
0-18.5	12 (0.2)	12 (0.2)	13 (0.3)	12 (0.2)	13 (0.3)
18.5-25	1,686 (35.4)	1,317 (27.7)	1,153 (24.2)	992 (20.8)	858 (18.0)
25-30	2,382 (50.1)	2,519 (52.9)	2,543 (53.5)	2,448 (51.4)	2203 (46.3)
30+	678 (14.2)	911 (19.1)	1,046 (22.0)	1,307 (27.5)	1,683 (35.4)***
Female (N=20,490)					
Race					
White	3,754 (91.6)	3,748 (91.5)	3,744 (91.4)	3,732 (91.1)	3,587 (87.5)
Black	156 (3.8)	119 (2.9)	133 (3.2)	166 (4.0)	263 (6.4)
Asian	135 (3.3)	151 (6.7)	150 (3.7)	130 (3.2)	154 (3.8)
Other	53 (1.3)	80 (2.0)	71 (1.7)	70 (1.7)	94 (2.3)***
Education					
College	1,451 (35.4)	1,396 (34.1)	1,291 (31.5)	1,232 (30.1)	1,057 (25.8)
Some college	1,453 (35.5)	1,454 (35.5)	1,438 (35.1)	1,490 (36.4)	1,511 (36.9)
High school	1,038 (25.3)	1,070 (26.1)	1,188 (29.0)	1,152 (28.1)	1,222 (29.8)
Less than high school	156 (3.8)	178 (4.3)	181 (4.4)	224 (5.5)	308 (7.5)***
Physical Activity[1]					
High	2,708 (66.1)	2,462 (60.1)	2,279 (55.6)	2,141 (52.2)	1,799 (43.9)
Low	1,390 (33.9)	1,636 (39.9)	1,819 (44.4)	1,957 (57.8)	2,299 (56.1)***
Smoking					
Never	2,596 (63.4)	2,462 (60.1)	2,393 (58.4)	2,426 (59.2)	2,165 (52.8)
Current	194 (4.7)	277 (6.8)	293 (7.2)	368 (9.0)	544 (13.3)
Former	1,308 (31.9)	1,359 (33.2)	1,412 (34.5)	1,304 (31.8)	1,389 (33.9)***
Anti-inflammatory use					
Yes	758 (18.5)	835 (20.4)	818 (20.0)	900 (22.0)	911 (22.2)
No	3,340 (81.5)	3,263 (79.6)	3,280 (80.0)	3,198 (78.0)	3,187 (77.8)***
Body Mass Index (kg/m^2)					
0-18.5	61 (1.5)	45 (1.1)	37 (0.9)	36 (0.9)	28 (0.7)
18.5-25	2,195 (53.6)	1,813 (44.2)	1,636 (39.9)	1,335 (32.6)	1,033 (25.2)
25-30	1,296 (31.6)	1,478 (36.1)	1,443 (25.2)	1,525 (37.2)	1470 (35.9)
30+	546 (13.3)	762 (18.6)	982 (24.0)	1,202(29.3)	1,567 (38.2)***

Hormone therapy					
Current	2,230 (54.5)	2,241 (54.7)	2,189 (53.5)	2,149 (52.5)	2,051 (50.1)
Former	657 (16.0)	632 (15.4)	643 (15.7)	619 (15.1)	655 (16.0)
Never	1,188 (29.0)	1,211 (29.6)	1,249 (30.5)	1,309 (32.0)	1,375 (33.6)
Unknown	18 (0.4)	12 (0.3)	12 (0.3)	15 (0.4)	12 (0.3)*
Continuous variables	**Means (SD)**	**Means (SD)**	**Means (SD)**	**Means (SD)**	**Means (SD)**
Male					
Calcium (diet and supplements; mg/day)	1,080.6 (558.0)	1,044.7 (516.9)	1,113.4 (539.6)	1,205.4 (567.8)	1380.4 (622.9)
Calories (kcal/day)	1,916.5 (701.9)	1,962.6 (654.0)	2,191.5 (677.0)	2,487.7 (702.8)	3,123.0 (31.2)
Alcohol (g/day)	10.8 (23.7)	14.0 (28.2)	16.5 (29.2)	18.4 (30.6)	19.2 (31.2)
Fiber (g/day)	24.8 (11.4)	22.7 (9.9)	23.6 (9.8)	25.1(9.7)	29.1 (11.1)
Age (years)	64.6 (5.4)	63.2 (5.3)	62.6 (5.2)	61.8 (5.0)	61.0 (4.7)
Female					
Calcium (diet and supplements; mg/day)	1,356.3 (640.5)	1,294.0 (626.9)	1,302.4 (623.8)	1,339.0 (620.9)	1,415.8 (622.7)
Calories (kcal/day)	1,480.5 (515.4)	1,504.4 (484.2)	1,663.8 (484.8)	1,847.0 (507.5)	2,270.8 (625.7)
Alcohol (g/day)	3.5 (8.3)	4.9 (11.0)	5.7 (12.1)	6.5 (13.9)	6.9 (15.3)
Fiber (g/day)	22.4 (9.7)	20.1 (8.3)	20.8 (8.2)	21.5 (8.1)	23.5 (8.8)
Age (years)	63.3 (5.4)	62.6 (5.3)	62.3 (5.3)	61.8 (13.9)	61.1 (5.0)

SD=standard deviation' *p-value<0.05; **p<0.001; ***p<0.0001; Chi-square for categorical and Kruskal-Wallis tests for continuous variables

1. Males: Quintile 1:< -0.79; Quintile 2:-0.79 to -0.38; Quintile 3:-0.39 to 0.02; Quintile 4: 0.02 to 0.68; Quintile 5: >0.68;

   Females: Quintile 1:< -0.77; Quintile 2:-0.77 to -0.38; Quintile 3:-0.39 to 0.02; Quintile 4: 0.02 to 0.63; Quintile 5: >0.63

2. Less than 2 hours of vigorous activities per week (low) vs. 2 or more hours of vigorous activities per week (high)

Supplemental Table 6.1c: Descriptive characteristics of Prostate, Lung, Colorectal, and Ovarian cancer screening arm participants (N=44,278) according to quintiles of Factor 3 "Sweet and salty" food groupings

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Categorical Variables	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Male (N=23,788)					
Race					
White	3,521 (74.0)	4,353 (91.5)	4,500 (94.6)	4,549 (95.6)	4,580 (96.3)
Black	318 (6.7)	158 (3.3)	109 (2.3)	85 (1.8)	101 (2.1)
Asian	709 (14.9)	125 (2.6)	52 (1.1)	39 (0.8)	18 (0.4)
Other	210 (4.4)	121 (2.5)	96 (2.0)	85 (1.8)	59 (1.2)***
Education					
College	2,425 (51.0)	2,118 (44.5)	1,987 (41.8)	1,841 (38.7)	1,704 (35.8)
Some college	1,388 (29.2)	1,552 (32.6)	1,568 (33.0)	1,590 (33.4)	1,539 (32.4)
High school	648 (13.6)	797 (16.8)	853 (17.9)	974 (20.5)	1,068 (22.4)
Less than high school	297 (6.2)	290 (6.1)	349 (7.3)	353 (7.4)	447 (9.4)***
Physical Activity[1]					
High	2,925 (61.5)	2,756 (57.9)	2,728 (57.4)	2,615 (55.0)	2,461 (51.7)
Low	1,833 (38.5)	2,001 (42.1)	2,029 (42.6)	2,143 (45.0)	2,297 (48.3)***
Smoking					
Never	1,735 (36.5)	1,860 (39.1)	1,901 (40.0)	1,848 (38.8)	1,844 (38.8)
Current	429 (9.0)	438 (9.2)	467 (9.8)	529 (11.1)	603 (12.7)
Former	2,594 (54.5)	2,459 (51.7)	2,389 (50.2)	2,381 (50.0)	2,311 (48.6)***
Anti-inflammatory use					
Yes	924 (19.4)	922 (19.4)	929 (19.4)	929 (19.5)	101 (21.2)
No	3,834 (80.6)	3,835 (80.6)	3,836 (80.6)	3,829 (80.5)	3,747 (78.8)
Body Mass Index (kg/m^2)					
0-18.5	20 (0.4)	11 (0..2)	14 (0.3)	9 (0.2)	8 (0.2)
18.5-25	1,401 (29.4)	1,239 (26.0)	1,162 (24.4)	1,134 (23.8)	1,070 (22.5)
25-30	2,346 49.3)	2,386 (50.2)	2,465 (51.8)	2,486 (52.2)	2,412 (50.7)
30+	991 (20.8)	1,121 (23.6)	1,116 (23.5)	1,129 (23.7)	1,268 (26.6)***
Female (N=20,490)					
Race					
White	3,423 (83.5)	3,651 (89.1)	3,791 (92.5)	3,858 (94.1)	3,842 (93.8)
Black	278 (6.8)	168 (4.1)	117 (2.9)	111 (2.7)	163 (4.0)
Asian	279 (6.8)	187 (4.6)	127 (3.1)	80 (2.0)	47 (1.2)
Other	118 (2.9)	92 (2.2)	62 (1.5)	50 (1.2)	46 (1.1)***
Education					
College	1,222 (29.8)	1,302 (31.8)	1,297 (31.7)	1,339 (32.7)	1,267 (30.9)
Some college	1,528 (37.3)	1,480 (36.1)	1,432 (35.0)	1,459 (35.6)	1,447 (35.3)
High school	1,064 (26.0)	1,123 (27.4)	1,174 (28.7)	1,115 (27.2)	1,194 (29.1)
Less than high school	284 (6.9)	193 (4.7)	194 (4.7)	186 (4.5)	190 (4.6)***
Physical Activity[1]					
High	2,223 (54.2)	2,360 (57.6)	2,377 (58.0)	2,297 (56.0)	2,132 (52.0)
Low	1,875 (45.8)	1,738 (42.4)	1,720 (42.0	1,802 (44.0)	1,966 (48.0)***
Smoking					
Never	2,192 (53.5)	2,432 (59.4)	2,514 (61.4)	2,486 (60.6)	2,418 (59.0)
Current	429 (10.5)	312 (7.6)	290 (7.1)	290 (7.1)	355 (8.7)
Former	1,477 (36.0)	1,354 (33.0)	1,293 (31.6)	1,323 (32.3)	1,325 (32.3)***
Anti-inflammatory use					
Yes	847 (20.7)	828 (20.2)	841 (20.5)	877 (21.4)	829 (20.2)
No	3,251 (79.3)	3,270 (79.8)	3,256 (79.5)	3,222 (78.6)	3,269 (79.8)

Body Mass Index (kg/m^2)					
0-18.5	45 (1.1)	45 (1.1)	41 (1.0)	35 (0.8)	41 (1.0)
18.5-25	1,636 (39.9)	1,713 (41.8)	1,672 (40.8)	1,544 (37.7)	1,447 (35.3)
25-30	1,348 (32.9)	1,440 (35.1)	1,449 (35.4)	1,473 (35.9)	1,502 (36.6)
30+	1,069 (26.1)	900 (22.0)	935 (22.8)	1,047 (25.5)	1,108 (27.0)***
Hormone therapy					
Current	2,133 (51.1)	2,192 (53.5)	2,162 (52.8)	2,217 (54.1)	2,156 (52.7)
Former	654 (16.0)	616 (15.0)	645 (15.8)	636 (15.5)	655 (16.0)
Never	1,290 (31.5)	1,271 (31.0)	1,271 (31.1)	1,231 (30.0)	1,269 (31.0)
Unknown	16 (0.4)	16 (0.4)	13 (0.3)	12 (0.3)	12 (0.3)

Continuous variables	**Means (SD)**	**Means (SD)**	**Means (SD)**	**Means (SD)**	**Means (SD)**
Male					
Calcium (diet and supplements; mg/day)	984.3 (534.9)	1,036.3 (520.0)	1,115.0 (520.3)	1,245.3 (567.8)	1,443.6 (605.6)
Calories (kcal/day)	1,885.7 (738.5)	1,946.2 (656.2)	2,179.8 (632.8)	2,503.6 (675.6)	3,165.7 (810.3)
Alcohol (g/day)	17.2 (31.0)	15.9 (30.5)	14.9 (28.9)	15.9 (28.2)	14.9 (27.5)
Fiber (g/day)	22.7 (11.2)	22.6 (10.1)	24.1 (9.6)	26.2 (1.0)	29.6 (10.4)
Age (years)	62.4 (5.2)	62.7 (5.2)	62.7 (5.4)	62.9 (5.3)	62.5 (5.2)
Female					
Calcium (diet and supplements; mg/day)	1,176.6 (619.5)	1,246.9 (597.4)	1,328.4 (624.0)	1,420.7 (616.1)	1,534.8 (5.2)
Calories (kcal/day)	1,421.8 (516.4)	1,507.3 (470.5)	1,680.8 (473.7)	1,880.3 (509.0)	2,276.2 (607.1)
Alcohol (g/day)	7.4 (16.2)	5.6 (12.4)	5.1 (0.8)	5.1 (11.9)	4.3 (9.7)
Fiber (g/day)	18.8 (8.6)	20.3 (8.1)	21.8 (8.4)	22.9 (8.5)	24.6 (8.8)
Age (years)	62.4 (5.3)	62.4 (5.3)	62.3 (5.3)	62.2 (5.2)	61.8 (5.2)

SD=standard deviation' *p-value<0.05; **p<0.001; ***p<0.0001; Chi-square for categorical and Kruskal-Wallis tests for continuous variables;

1. Males: Quintile 1:< -0.76; Quintile 2:-0.76 to -0.35; Quintile 3:-0.36 to 0.05; Quintile 4: 0.05 to 0.68; Quintile 5: >0.68;

   Females: Quintile 1:< -0.71; Quintile 2:-0.71 to -0.39; Quintile 3:-0.40 to 0.04; Quintile 4: 0.04 to 0.57; Quintile 5: >0.57

2. Less than 2 hours of vigorous activities per week (low) vs. 2 or more hours of vigorous activities per week (high)