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Dietary Patterns and Prostate Cancer Aggressiveness in African-American and European-American Men

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DIETARY PATTERNS AND PROSTATE CANCER AGGRESSIVENESS IN AFRICAN-AMERICAN AND EUROPEAN-AMERICAN MEN

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For Donald and Joricia Schneider, for their continued love and support.

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ABSTRACT

Several foods and nutrients have been linked to prostate cancer risk, but the effect of overall diet on prostate cancer outcomes is not well understood. Previous research has primarily examined *a posteriori* dietary patterns in relation to prostate cancer; studies that have used *a priori* dietary patterns and their relationship with prostate cancer have been inconclusive. Furthermore, racial differences in prostate cancer incidence and aggressiveness are not well understood. Data from the case-only North Carolina-Louisiana Prostate Cancer Project (PCaP) was used to examine the association between overall dietary pattern, as measured by the Mediterranean Diet (MED) score and the Dietary Approaches to Stop Hypertension (DASH) score, and prostate cancer aggressiveness in African-American (AA) and European-American (EA) men. Dietary patterns were assessed using a modified NCI Diet History Questionnaire for a final sample of 1,899 participants. Higher MED scores were found to be inversely associated with high aggressive prostate cancer overall (OR: 92; 95% CI: 0.84-0.99; p trend: 0.03); and results were similar for AA men and EA men. DASH scores were not significantly associated with prostate cancer aggressiveness. These results suggest that following a Mediterranean diet may decrease the risk of developing high aggressive prostate cancer.

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CHAPTER 1

INTRODUCTION

1. Statement of problem

General

Prostate cancer is the most commonly diagnosed cancer in American men and is the second leading cause of cancer mortality. There were an estimated 233,000 new prostate cancer cases diagnosed in the United States (U.S.) in 2014, accounting for 27% of all male cancer diagnoses; in the same year, 29,480 estimated deaths were attributed to prostate cancer, or 10% of all cancer-related deaths in American men (Siegel, Ma et al. 2014). Between the years 1975-1988, incident rates of prostate cancer showed small increases; a sharp increase in the number of prostate cancer diagnoses in the years 1988-1992 reflects the introduction of the prostate-specific antigen (PSA) blood test for screening, with the number of new cases declining in subsequent years (Edwards, Noone, et al. 2014; Siegel, Ma et al. 2014).

Several risk factors for prostate cancer are known, including age, race/ethnicity, and family history. The majority of new cases are diagnosed between the ages of 65-74 years (36.6%), and less than 11% of all diagnoses occur in men younger than 55 years of age. Incidence rates differ by race: African Americans (AA) are more likely than any other race or ethnicity to be diagnosed with prostate cancer (223.9 new cases per 100,000). American Indian and Alaskan natives have the lowest prostate cancer incidence (71.5 and 79.3 new cases per 100,000, respectively), while whites (139.9 new cases per

100,000) and Hispanics (121.8 new cases per 100,000) fall between the two extremes (Howlander, Noone et al. 2014). Family history has been shown to increase the risk of developing prostate cancer, with Grönberg finding a positive correlation between the number of affected family members and the risk of disease (2003).

Although prostate cancer is the most common cancer in men, the high 5-year survival rate (98.9%) and slow growth of prostate cancers has led to recent changes in the U.S. Preventive Services Task Force screening recommendations. In May 2012, they released a report that recommended against PSA screening tests for adult males without symptoms, citing the asymptomatic nature of most cases, high false-positive rates for the PSA screening test, and the potentially harmful side effects of treatment options (Moyer 2012). Other cancer-related organizations advocate for screening only among high-risk individuals (older, AA men, and/or those with a family history). An alternative to the PSA blood test is the digital rectal exam (DRE), or the tactile examination of the prostate by a physician. Both methods are widely accepted, and the decision to perform either test is at the discretion of the primary care physician and patient. If prostate cancer is detected, treatment plans may be as mild as no action to as invasive as radical prostatectomy (Bill-Axelson, Holmberg et al. 2005).

Survival rates for prostate cancer remain high, even when measured at 10 (96.9%) and 15 (94%) years. These rates best reflect local and regional stage diagnoses; distant stage prostate cancers only have a 28% 5-year survival rate. Mortality rates also vary by race: AA men are almost twice as likely as European American (EA) or Hispanic men to die of prostate cancer (Howlander, Noone et al. 2014). Often, prostate cancer does not cause death: other health complications result in death before the metastasis of the tumor.

Given that the majority of diagnosed prostate cancers are indolent and not likely to cause clinical symptoms or death, there has been a recent shift in the focus on studying risk factors for overall prostate cancer to investigating risk factors for aggressive prostate cancer.

Regional Disparities

The data for this population-based study were collected from men residing in Louisiana and North Carolina; these states exhibit distinctive prostate cancer statistics and trends. Louisiana had an estimated 3,720 new prostate cancer cases diagnosed in 2014; the age-adjusted prostate cancer incidence rate in the state between 2006 and 2010 was 169.3 new cases per 100,000 men. In North Carolina, an estimated 7,580 new cases were diagnosed, though the 2006-2010 incidence rate was lower, with only 151.9 new cases per 100,000 men. Both state's incidence rates are higher than the national average (146.6 per 100,000 men) over the same time period. In 2014, approximately 920 deaths in men living in North Carolina were attributed to prostate cancer, while less than half that number (n=400) of deaths in Louisiana men were caused by prostate cancer. However, the prostate cancer mortality rate in Louisiana is slightly higher than in North Carolina (26.6 versus 25.8 deaths per 100,000), after adjusting for age (Siegel, Ma et al. 2014).

Racial Disparities

Incidence and Mortality

AA men have the greatest prostate cancer risk of any racial or ethnic group in the United States (Gann 2002). Between 2005 and 2009, prostate cancer incidence rates for AA men (228.8 per 100,000) and EA men (140.3 per 100,000) indicate that AA men are 1.63 times more likely to develop prostate cancer than EA men. This disparity is more

pronounced when comparing mortality rates: AA men are 2.44 times more likely to die from prostate cancer than EA men (DeSantis, Naishadham et al. 2013). Several reasons that may account for this discrepancy are discussed further here.

Screening and PSA

AA men are less likely than EA men to be screened for prostate cancer. In a study by Jones et al., EA men were significantly more likely to have received a DRE prostate cancer screening (OR=2.08, 95% CI: 1.03-4.21) than AA men; PSA screening tests also occur more frequently in EA men than in AA men (Jones, Liu et al. 2008; Carpenter, Howard et al. 2009; Carpenter, Godley et al. 2010). In a biracial sample of North Carolina men diagnosed with prostate cancer, Conlisk et al. found that having a recent PSA screening test was significantly ($p=0.01$) and inversely correlated with stage at diagnosis for AA men, but not for EA men ($p=0.20$) (Conlisk, Lengerich et al. 1999). A family history of prostate cancer was positively associated with having a recent PSA test (OR=3.03, 95% CI: 1.13-8.10), but not a DRE, in AA men (Bloom, Stewart et al. 2006).

Disease Diagnosis and Treatment

The stage and grade of prostate cancer at time of diagnosis differs between AA men and EA men. Race is an independent predictor of prostate cancer stage at diagnosis, with AA men consistently presenting more advanced stage cancer than EA men (Schwartz, Crossley-May et al. 2003; Ward, Jemal et al. 2004). AA men are almost twice as likely to present with late stage prostate cancer then EA men; the likelihood of early-stage diagnosis remains lower for AA men than EA men across socioeconomic status, clinical factors, and pathologic factors (Bennett, Ferreira et al. 1998; Ward, Jemal et al. 2004; Hoffman, Gilliland et al. 2001; Jones, Liu et al. 2008). Measures of disease grade

(i.e., Gleason grade) tend to be higher in AA men: multiple studies have found that a higher proportion of AA men than EA men (20% versus 12%) will present with high-grade tumors (Fowler & Bigler 1999; Reddy, Shapiro et al. 2003; Gaines, Turner et al. 2014).

Despite their higher rates of diagnosis for distant stage prostate cancer, AA men are less likely to receive aggressive treatment therapies, namely radical prostatectomy (Klabunde, Potosky et al. 1998; Underwood, De Monner et al. 2004; Harlan, Potosky et al. 2001; Shavers, Brown et al. 2004). They are also more likely than their EA counterparts to remain untreated (Tewari, Horninger et al. 2005). Across all treatment options, mortality rates for AA men remain higher than for EA men (Godley, Schneck, et al. 2003); when access to care is adjusted for, disparities in outcome are attenuated across treatment arms (Optenberg, Thompson et al. 1995).

Genetics

Family history is a long established risk factor for prostate cancer; a portion of the hereditary nature of prostate cancer occurrence has been attributed to genetic variants and gene-environment interactions (Schaid 2004; Stephenson 2008; Alvarez-Cubero, Saiz 2013). Genes that have been linked with increased prostate cancer risk include: *ELAC2 (HPC2), MSR1*, and *RNASEL (HPC1)* for familial cases; *AR, ATBF1, EPHB2 (ERK),* and *KLF6* for sporadic cases; and *AR, BRCA1, BRCA2, CHEK2 (RAD53), CYP17, CYP1B1, CYP3A4, GSTM1, GSTP1, GSTT1, PON1, SRD5A2,* and *VDR* with both familial and sporadic cases (Dong 2006). Most of these genes are associated with tumor suppression, cell regulation, or androgen reception (Barbieri, Tomlins 2014). Racial differences in the frequency of allele presentation have been found and may explain part of the prostate

cancer disparities between AA and EA men (Ziegler-Johnson, Spangler et al. 2008; Freedland, Isaacs 2005).

Socioeconomic factors

Socioeconomic status (SES) has been found to explain some of the prostate cancer disparities between AA and EA men. In a study conducted by Du, et al., lower SES was associated with decreased survival in all prostate cancer cases (HR: 1.31; 95% CI: 1.25-1.36); when comparing mortality between AA and EA men, socioeconomic status was found to be a significant factor in the survival disparities between the two groups (Du, Fang et al. 2006). SES has been found to have a greater impact on prostate cancer outcomes in AA men than EA men, both in terms of stage at diagnosis and mortality (Conlisk, Lengerich et al. 1999; Steenland, Rodriguez et al. 2004). Education, a common proxy for SES, has been shown to have a significant effect on mortality rates in AA men: those who completed 12 or less years of education had a prostate cancer mortality rate double that of men completing 12 or more years of education (RR: 2.17; 95% CI: 1.82-2.58) (Albano, Ward et al. 2007). AA men have historically lower levels of SES and educational attainment than EA men; this likely has contributed to disparities in prostate cancer (U.S. Census Bureau 2012).

Diet

Several individual components of dietary intake have been associated with prostate cancer occurrence, and differing levels of intake by race may account for some of the disparities in disease incidence. Increased intakes of fat, particularly animal fats, have been shown to be associated with increased prostate cancer incidence and fatality, with intake differences accounting for approximately 10% of AA-EA incidence

disparities (Gann 2002; Pelser, Mondul et al. 2013; Whittemore, Kolonel et al. 1995). Intake of dairy and dairy products above recommended levels has also been shown to modestly increase the risk of prostate cancer (Rodriguez, McCullough et al. 2003). Conversely, high intakes of soy, fiber, fruits and vegetables, and vitamins D & E, selenium, and lycopene (tomatoes) have been inversely associated with prostate cancer (Hardin, Cheng et al. 2011; Cheung, Wadhera et al. 2008; Hurst, Hooper et al. 2012). However, supplemental vitamin intake does not appear to be protective in reducing prostate cancer risk, and there is some suggestion that certain supplements (e.g., vitamin E) may be harmful under certain conditions, as seen in the Selenium and Vitamin E Cancer Prevention Trial (SELECT) (400 IU/day vitamin E intervention: HR: 1.13; 95% CI: 0.95-1.35; P = 0.06) (Lippman, Klein et al. 2009). Variations in intakes between AA and EA men, due to cultural eating habits, food availability, or gene-diet interaction may explain racial differences in prostate cancer (Reedy, Shapiro et al. 2003; Discacciati, Wolk 2014), and it is likely the combination of dietary factors, rather than single foods or nutrients alone, that will have the largest impact.

2. Proposal and Specific Aims

The purpose of this case-only study was to examine the association between overall dietary pattern and prostate cancer aggressiveness, particularly in relation to racial disparities in prostate cancer between AA and EA men. Two dietary indexes, the Mediterranean Diet Score (MED), and the Dietary Approaches to Stop Hypertension (DASH), evaluate diet quality based on intakes of specific foods and food groups; the association between overall diet quality and prostate cancer aggressiveness, as determined by PSA count, stage and Gleason sum, in the large, case-only North Carolina-

Louisiana Prostate Cancer Project (PCaP) was evaluated using these two dietary measures. ***My specific aim was*** to examine the relationship between diet quality and prostate cancer aggressiveness among AA and EA men using two different dietary indexes: 1) the MED diet score, as a measure of conformity to a Mediterranean diet; and the 2) DASH diet score as a measure of conformity to the Dietary Approaches to Stop Hypertension (DASH) diet.

3. Significance of Research

Prostate cancer is the most commonly diagnosed malignancy and the second most common cause of cancer mortality in American men (Siegel, Ma et al. 2014). Age, race, and family history are established risk factors for increased risk of prostate cancer; diet has been proposed as possible risk factor, yet evidence of the influence of overall dietary patterns remains inconclusive. To date, five studies have examined overall diet according to the MED or alternate MED (aMED) in relation to prostate cancer (Ax, Garmo et al. 2014; Bosire, Stampfer et al. 2013; Kenfield, DuPre et al. 2014; Möller, Galeone et al. 2013; Muller, Severi et al. 2009). None have used DASH to evaluate prostate cancer outcomes. The remaining body of evidence for total diet and prostate cancer is based on study-specific dietary patterns (Ambrosini, Fritschi et al. 2008; Askari, Parizi et al. 2014; De Stefani, Ronco et al. 2010; Jackson, Walker et al. 2009; Jackson, Tulloch-Reid et al. 2013; Tseng, Breslow et al. 2004; Walker, Aronson et al. 2005; Wu, Hu et al. 2006). While there is a large body of literature on the association between individual dietary factors and prostate cancer, much of this evidence is contradictory and does not account for effects of other foods consumed. The lack of consistent measures of both individual diet components and overall dietary patterns hinders comparability across studies, and

impedes the formulation of dietary recommendations for prostate cancer prevention and treatment.

This study utilized widely-accepted, standardized dietary indexes to evaluate overall diet; therefore, results are easy to interpret in the context of overall diet recommendations. Results from this study may support the adoption of the dietary pattern recommendations as a prostate cancer prevention strategy.

CHAPTER 2

BACKGROUND & LITERATURE REVIEW

1. Primary Hypothesis - Dietary Pattern and Prostate Cancer

Dietary Patterns

A dietary pattern is defined as "the quantities, proportions, variety or combination of different foods, drinks, and nutrients in diets, and the frequency with which they are habitually consumed" (Krebs-Smith 2014). Rather than examining individual food or nutrient consumption, dietary pattern analysis attempts to examine disease outcomes in terms of habitual intakes of all foods, beverages, and supplements. The benefit of looking at overall intake patterns, as opposed to individual nutrient or food intakes, is that patterns attempt to account for "the highly interrelated nature of dietary exposures…. It is often difficult to separate out the specific effect of nutrients or foods… in relation to disease risk" (Jacques, Tucker 2001). The reductionist approach, or emphasizing the role of single nutrients or foods, is useful for identifying individual foods that have substantial health effects; however, using dietary pattern as a measure of nutritional exposure allows for study of the health effects of food combinations, often culturally specific, on disease prevention and outcomes (Jacobs, Steffen 2003).

Past research on the effect of dietary patterns on prostate cancer has relied on reported food intakes of the study population to determine the dietary patterns of analysis; the heterogeneity of diet quality assessment makes comparison and consensus of results difficult (see Table 2.1). The earliest study to examine the relationship between

patterns of dietary intake and prostate cancer was a cohort study conducted by Tseng, et al. using data from the National Health and Nutrition Examination Survey Epidemiological Follow-up Study cohort. The pattern, characterized by high intakes of fruits, vegetables, fish, and shellfish; a "red meat-starch" pattern, characterized by high intakes of red meats, potatoes, salty snacks, cheese, sweets, and desserts; and a "Southern" pattern, characterized by high intakes of beans, rice, cornbread, grits, sweet potatoes, and okra; none of the diets were found to be significantly associated with an increased risk of prostate cancer (Tseng, Breslow, et al. 2004). However, there was a non-significant inverse association for both the "red meat-starch" (highest tertile vs. lowest tertile RR: 0.8; 95% CI: 0.4-1.4) and "Southern" (RR: 0.6; 95% CI: 0.4-1.1) seen within the American men sampled. The protective effect seen with the "red meat-starch" pattern, given the similarity of the "red meat-starch" dietary pattern to the "Western" diet, is counterintuitive. The "Western" diet, characterized by high intakes of fatty meats, dairy products, refined cereals, salt, refined sugars, and refined vegetable oils, has been shown to be associated with the high rates of chronic disease in developed nations (Cordain, Boyd Eaton et al. 2005). Others have examined the association between the Western diet and prostate cancer: the majority of these studies have found a significant, positive association between a Western pattern of consumption and prostate cancer (Ambrosini, Fritschi et al. 2008; Askari, Parizi et al. 2014; De Stafani, Ronco et al. 2010; Walker, Aronson et al. 2005; Wu, Hu et al. 2006).

Patterns characterized by high intakes of fruit and vegetables have been shown to offer protection against prostate cancer incidence and aggressive forms of prostate cancer, but these associations were not statistically significant (Ambrosini, Fritschi et al.

2008; Askari, Parizi et al. 2014; De Stafani, Ronco et al. 2010; Jackson, Tulloch-Reid et al. 2013; Jackson, Walker et al. 2009; Muller, Severi et al. 2009; Walker, Aronson et al. 2005; Wu, Hu et al. 2006).

Few studies have used *a priori* dietary pattern indexes in prostate cancer research. The index most commonly used to assess diet in relation to prostate cancer is the MED, or the closely related aMED. A cohort study of Swedish men did not find a significant association between high conformity to MED and odds of prostate cancer (OR: 1.01; 95% CI: 0.75-1.37); they did find a significant, inverse relationship between eating a low-carbohydrate, high-protein diet and prostate cancer (OR: 0.77; 95% CI: 0.61-0.96) (Ax, Garmo et al. 2014). Bosire et al. found in a cohort of American men that a high aMED score did not translate into a decreased risk of advanced prostate cancer diagnosis (HR: 1.00; 95% CI: 0.87-1.15); and there was no association with risk of death from prostate cancer (HR: 0.80: 95% CI: 0.59-1.10) (Bosire, Stampfer et al. 2013). Other studies using MED or aMED measures, including a cohort, a case-only cohort, and case-control, also found no significant association with prostate cancer outcomes (Kenfield, Du Pre et al. 2014; Möller, Galeone et al. 2013; Muller, Severi, et al. 2009).

Only one study has used the HEI-2010 to assess diet quality when exploring prostate cancer cases: HEI-2010 score was not significantly associated with the stage of diagnosis (HR: 1.10; 95% CI: 0.96-1.26) or with mortality (HR: 0.96; 95% CI: 0.71-1.30) of prostate cancer though there was an inverse association with total prostate cancer risk for those with high adherence to the HEI-2010 dietary guidelines (HR: 0.92; 95% CI: 0.86-0.98) (Bosire, Stampfer et al. 2013). To our knowledge, the DASH index has not been used in any prostate cancer study to date.

Dietary Indices

Mediterranean Diet Score

The Mediterranean diet specifically refers to food patterns typically seen in 1960s throughout Greece, Crete, and southern Italy: diets of people residing in these areas during the time period were characterized by high intakes of plant-based foods (fruits vegetables, whole grains, nuts, seeds, beans, and potatoes); seasonally fresh and locally grown foods; dessert and sweet consumption limited to a few times a week; olive oil as the primary source of fat; low-to-moderate daily consumption of dairy products, fish, and poultry; low consumption of red meat; and moderate wine consumption. (Willett, Sacks et al. 1995). In the now-famous Seven Countries Study, Ansel Keys found that people adhering to what is now known as the Mediterranean diet had greatly reduced rates of coronary heart disease (Keys 1980). Trichopoulou et al. began scoring diets on their adherence to traditional Mediterranean diets in their 1995 study "Diet and overall survival in elderly people." Median values of intakes for eight component characteristics (vegetables, legumes, fruits and nuts, dairy products, cereals, meat and meat products, ethanol, and monounsaturated:saturated fat ratio) were calculated: those with intakes above the median for positive components (vegetables, legumes, fruits and nuts, cereals, ethanol, and monounsaturated:saturated fat ratio, were given a score of 1 for that component, and those below the median were given a score of 0; meat and meat products and dairy products were scored in reverse. High scores (highest possible = 8) were found to be associated with improved survival in the elderly (Trichopoulou, Kouris-Blazos et al. 1995). More recent versions have included scores for fish and poultry, increasing the maximum score to 9, with other scoring variations being used while maintaining similar

food groups (Trichopoulou, Costacou wt al. 2003; Panagiotakos, Pitsavos et al. 2006; Rumawas, Dwyer et al. 2009). Further applications have linked high MED scores to decreased incidence of colorectal, breast, and prostate cancers (Trichopoulou, Lagiou et al. 2000).

Dietary Approaches to Stop Hypertension Score

The Dietary Approaches to Stop Hypertension (DASH) originated in a clinical trial of the same name: the multicenter, randomized feeding trial was designed to test the combined effects of food on blood pressure and found that certain dietary patterns could help control hypertension (Appel, Moore, et al. 1997). The diet emphasizes fruit, vegetable, low-fat dairy, whole grains, poultry, fish, and nut consumption while minimizing red meat, sweets, sugar-sweetened beverages, total fat, saturated fat, and cholesterol intakes (Sacks, Svetkey et al. 2001). A systematic review of cohort studies using the DASH score as a measure of dietary quality found a significant risk reduction in cancer incidence and mortality (RR: 0.85; 95% CI: 0.82-0.88) (Schwingshackl, Hoffmann 2015).

Mechanisms

There are several ways that diet may influence prostate cancer risk. There is evidence to suggest that consuming certain foods may increase inflammation within the body, while other foods decrease inflammation (Cui, Jin et al. 2012; Cavicchia, Steck et al. 2009; Giugliano, Ceriello et al. 2006). Chronic inflammation has been linked with certain types of cancer, including prostate cancer: inflammatory markers, specifically C-reactive protein (CRP) are high in men with metastases, and elevated CRP is associated with poor prognosis in men diagnosed with prostate cancer (Lehrer, Diamond et al. 2006;

Trautner, Cooper, et al. 1980; Latif, McMillan et al. 2002). Dietary fat may produce DNA damage through fatty acid oxidation into lipid radicals, increasing circulating androgen concentrations, inhibiting healthy cell communication and transduction, and negatively impacting the immune system (Kolonel 2001). Food preparation methods, especially charring meat, may also introduce carcinogens into the body, elevating cancer risk (De Marzo, Nakai et al. 2007; John, Stern et al. 2011). Fruits and vegetables contain a number of anticarcinogenic substances (such as carotenoids, flavonoids, isoflavones, among others), which can decrease cell proliferation, regulate DNA methylation, and increase apoptosis of cancer cells (Steinmetz, Potter 1996). Fiber, which increases sex-hormone-binding globulin and improves insulin sensitivity, may decrease prostate cancer risk by reducing androgen levels in the blood and controlling antiapoptotic effects of circulating insulin (Tabung, Steck et al. 2012; Chan, Stampfer et al. 1998). Alcohol consumption, regardless of type, increases serum estrogen while decreasing androgens; it also weakens cell defenses against carcinogens (Dennis, Hayes 2001).

Potential Confounders

Age

Age is a known risk factor of prostate cancer: prostate cancer incidence is positively correlated with increasing age, peaking in the 65-74 age group (Howlander, Noone et al. 2014). In men under the age of 60, prostate cancer prevalence is much lower than other cancer types (Jemal, Siegel et al. 2009). Screening frequency decreases as age increases, and prostate cancer prognoses worsen with age (Zeliadt, Penson et al. 2003; Grönberg, Damber et al. 1994).

Family History

Another known risk factor for prostate cancer is family history. A diagnosis of a first-degree relation (father or brother) with prostate cancer approximately doubles a man's prostate cancer risk; risk increases with the number of affected relatives (Crawford 2003; Grönberg 2003). Genetics and common environment both play a role, though heritable genetic variations are estimated to contribute to 43% of cases diagnosed in the aged 55 and younger; genetics confer less risk as age of diagnosis increases (Carter, Beaty et la. 1992). Men with a familial history also tend to be diagnosed before the age of 60, due in part to a greater propensity to receive prostate cancer screening (Bratt, Garmo et al., 2010; Crawford 2003).

Screening

Previously, prostate cancer screening was recommended for all men beginning at age 50; with the release of the U.S. Preventive Task Force report on prostate cancer screening recommendations, only men with known risk factors or who are exhibiting symptoms are recommended to be tested. Current screening methods include the PSA test and the DRE: the PSA tests measures the level of PSA in blood serum (higher levels are associated with prostate cancer), while the DRE requires a physician to digitally feel the prostate for lumps, tenderness, hard areas, or general enlargement (Barrett 2002). AA men are less likely than EA men to be screened for prostate cancer, and screening is less likely to improve stage at diagnosis for AA men than EA men (Jones, Liu et al. 2008; Carpenter, Howard et al. 2009; Carpenter, Godley et al. 2010; Conlisk, Lengerich et al. 1999). The high rates of survival associated with early stage prostate cancer have been

partially attributed to proactive screening programs in the last 20 years (Howlander, Noone 2014).

Stage and Grade at Diagnosis

Prostate cancer progression is measured in four intervals according to the American Joint Committee on Cancer (AJCC) Tumor, Nodes, Metastases (TNM) system. In first stage prostate cancer, T1, the physician is unable to feel or see the tumor; often cancer in this stage is found incidentally or as a result of increased PSA levels. Progression to the next stage, T2, is characterized by tumor(s) that are able to be felt (with a DRE) or seen by ultrasound. T2 prostate cancer is still confined to the prostate. When the cancer has grown outside of the prostate, particularly the seminal vesicles, T3 cancer is diagnosed; further spreading of the cancer cells from the prostate to the rectum and bladder tissues or bone marrow is classified as T4, or late stage prostate cancer (American Cancer Society 2015).

The Gleason system grades cancer tissues by appearance (as viewed under a microscope) and is the most common grading system for prostate cancers. Possible Gleason scores range from 2 (indicating well-differentiated cells in both primary and secondary patterns) to 10 (indicating poorly-differentiated cells in both primary and secondary patterns). Both cancer stage and grade are associated with prostate cancer outcomes, with later stage and higher grade cancers displaying higher mortality rates and shorter survival times (Drake, Keane et al. 2006; Gandaglia, Karakiewicz et al. 2014).

Comorbidities

Comorbid conditions that are often found with prostate cancer include cardiovascular disease, hypertension, and diabetes; the Charlson Index uses a weighted

impact score to estimate the impact of these conditions on mortality (Charlson, Pompei et al. 1987). A greater Charlson score in prostate cancer cases increases the risk of non-prostate cancer mortality, and this effect is greater in EA men than AA men (Chamie, Daskivich et al 2011; Putt, Long et al. 2009). In prostate cancer cases where comorbidity is high, non-aggressive treatments are recommended because of the greater risk of death from other causes (Daskivich, Chamie et al. 2011).

Socioeconomic Status

Lower socioeconomic status has been shown to be associated with higher cancer risk and mortality rates, yet for prostate cancer, higher SES is associated with increased risk of prostate cancer diagnosis (Clegg, Reichman et al. 2009; Major, Norman Oliver et al. 2012). This phenomenon is often attributed to regular prostate cancer screenings in more affluent men, and is reflected in lower mortality rates for men of higher SES (Clegg, Reichman et al. 2009; Byers, Wolf et la. 2008). Education level, a common proxy for SES, is also associated with increased prostate cancer incidence, likely due to increased awareness of prostate cancer screening (Clegg, Reichman et al. 2009). Increased rates of insurance and access to health care, along with better quality health care likely account for better prostate cancer outcomes in those with greater SES (Du, Fang et al. 2006; Major, Norman Oliver et al. 2012).

Body Mass Index

Higher body mass index (BMI) has been found to be associated with increased risk of aggressive forms of prostate cancer and prostate cancer mortality (Su, Arab et al. 2011; Rodriguez et al. 2001; Hague, Van Den Eeden et al. 2014; Stacewicz-Sapuntzakis, Borthakur et al. 2008). Interestingly, one study found that high BMI increased the risk of

aggressive prostate cancer but offered protection for less-aggressive forms of the disease (Giovannucci, Liu et al. 2007). Excess weight may increase androgen production, leading to increased risk of prostate cancer by loss of tumor control (Stacewicz-Sapuntzakis, Borthakur et al. 2008).

Physical Activity

Physical activity may lower risk of prostate cancer (Whittemore, Kolonel et al. 1995; Giovannucci, Liu et al. 2007). A meta-analysis found consistent, protective effects of occupational, recreational, and total physical activity (Liu, Hu et al. 2011). The mechanisms of physical activity's effect on prostate cancer are unclear, but proposed causes include enhanced immune systems, decreased hormone levels, and lower BMI (Lee, Sesso et al. 2001).

Smoking

Smoking is a known causative agent of lung cancer, and has been shown to increase the risk of other cancers; however, evidence that smoking affects prostate cancer risk is inconclusive, as seen in Hickey et al.'s systematic review (2001). Several cohort and nested case-control studies have found positive but weak associations between smoking and prostate cancer incidence, but more have found no association at all (Hickey, Do et al. 2001; Giovannucci, Rimm et al. 1993). Smoking is known to affect male hormone levels, increase genetic mutation rates, and decrease immune function; upon this biological basis, smoking may be associated with prostate cancer, despite a lack of epidemiological evidence (Hickey, Du et al. 2001). The U.S. Surgeon General has concluded that smoking is a 'probable' contributor to prostate cancer mortality (US Department of Health and Human Services 2004).

Alcohol

There are inconsistent findings on the effect of alcohol on prostate cancer risk. One systematic review found moderate alcohol consumption (less than or equal to three drinks per day) is not associated with prostate cancer risk, but imbibing seven or more alcoholic drinks per day may increase prostate cancer risk (Dennis, Hayes 2001). A meta-analysis of alcohol dose response found no association with prostate cancer, even at high doses (Rota, Scotti et al. 2012). Alcohol may increase cell permeability and inhibit cell repair mechanisms, leading to prostate cancer susceptibility (Dennis, Hayes 2001; Garro, Lieber 1990).

Non Steroidal Anti-Inflammatory Drugs

Non steroidal anti-inflammatory drugs (NSAIDs) help decrease inflammation and reduce pain and fever. Common NSAID medications include aspirin, ibuprofen, and naproxen; regular use of these medications may confer a reduced risk of prostate cancer by reducing the damaging effects of chronic inflammation and inhibiting cyclooxygenase (COX) enzymes (Bosetti, Rosato et al. 2014; Wagenlehner et al. 2007). COX inhibitors have shown pro-apoptotic properties thought to regulate cell proliferation (Fleshner, Zlotta 2007). However, long-term use of some NSAIDs causes increased risk of cardiovascular problems and gastrointestinal bleeding, and severe side effects must be considered.

Fats and Animal Meats

There is strong evidence that higher intakes of dietary fat and animal meats increase prostate cancer risk. Several ecologic studies have found a positive association between fat consumption and prostate cancer mortality and incidence (Stacewicz-

Sapuntzakis, Borthakor et al. 2008; Rose, Boyar et al. 1986; Kolonel 2001). Cohort studies have consistently found strong, positive associations between saturated fat, animal fat, and meat consumption and prostate cancer (Stacewicz-Sapuntzakis, Borthakor et al. 2008; Whittemore, Kolonel et al. 1991; Kolonel 2001; Hayes, Ziegler et al. 1999). In a study of Hawaii residents, high intake of saturated fats was estimated to account for 13% of prostate cancer cases (Hankin, Zhao et al. 1992); between 10-15% of the disparity in prostate cancer cases among AA, EA, and Asian American men has been attributed to differences in saturated fat intakes (Crawford 2003).

Dairy Products, Calcium, and Vitamin D

There is probable evidence that diets high in calcium increase prostate cancer risk, though evidence that dairy products themselves increase risk is more limited (World Cancer Research Fund/American Institute for Cancer Research 2007). A meta-analysis conducted by Aune, et al. found that high intakes of total dairy products, milk, cheese, total calcium, and dairy calcium were associated with increased risk of prostate cancer (2015). Pettersson et al. found that whole milk consumption after prostate cancer diagnosis was positively associated with fatal outcomes (Pettersoson, Ksperzyk et al. 2012; Song, Chavarro et al. 2013). However, calcium and dairy product intakes do not necessarily correlate, and results for one should not be interpreted for the other (Aune, Navarro Rosenblatt et al. 2015).

Vitamin D has been shown to exhibit anticancer effects on prostate cancer cells in laboratory settings (Schwartz 2009; Beer, Myrthue 2006). Studies on sunlight exposure and prostate cancer have shown generally positive benefits for increased UV exposure and prostate cancer outcomes (Schwartz 2013). It is hypothesized that “vitamin D

maintains the normal phenotype of prostatic cells and that vitamin D deficiency permit[s] the development of clinical prostate cancer from preclinical precursors," though benefits of vitamin D may vary by calcium levels (Schwartz 2013).

Fruits and Vegetables

High intakes of vegetables and fruits are the basis of most healthy diet recommendations, since the high nutrient density and low calorie density of these foods help maintain healthy weight and optimal body functions. Many antioxidants and flavonoids are found in fruits and vegetables, yet the literature does not provide convincing evidence that overall vegetable and fruit intakes affect prostate cancer outcomes in the United States (Stacewicz-Sapuntzakis, Borthakor et al. 2008; Wu, Hu et al. 2006). Cruciferous vegetables, including broccoli, cabbage, and Brussel sprouts, contain isothiocyanates which have demonstrated anticancer properties in laboratory and in vivo setting (Sing, Srivastava et al. 2005; Melchini, Traka et al 2013). Fiber is also a beneficial component of fruits and vegetables. Previously in PCaP, higher fiber intake was associated with reduced odds of high aggressive prostate cancer (Tabung, Steck et al. 2012).

Lycopene, Tomatoes, and Tomato-based products

While all vegetables are recommended for their numerous health benefits, tomatoes in particular, which contain lycopene, have been shown to offer protection against prostate cancer. Lycopene is a powerful antioxidant that may also help in DNA repair. Two meta-analyses found modest protective effects of lycopene (Etminan, Takkouche et al. 2004; Chen, Song et al. 2013). A review by the U.S. Food and Drug Administration (FDA) concluded that there is limited evidence supporting tomato and

lycopene consumption as a method of decreasing prostate cancer risk (Kavanaugh, Trumbo et al. 2007).

Fish/omega-3

Fish and fish oil (primarily omega-3 fatty acids) consumption do not have conclusive evidence of a positive or negative association with prostate cancer incidence, though a meta-analysis found a 63% percent reduction in cancer-specific mortality for men with the high levels of intake (Szymanski, Wheeler et al. 2010). Most studies, regardless of design, have found null or insignificant improvement in prostate cancer risk with increasing fish oil or omega-3 fatty acid intakes (Willett 1997).

Table 2.1: Summary table of articles concerning dietary patterns and prostate cancer outcomes								
Study Design	Lead Author	Year of Publication	Country	Number of Subjects	Dietary Assessment Technique	Patterns Examined	Confounders	Results
Case-control	Ambrosini, G.L.	2008	Australia	546 cases, 447 controls	FFQ, 10-years previous	Vegetable, Western, Health conscious[a]	BMI (current/10 year previous), family history prostate cancer, smoking, PA	[OR, (95% CI)] Q4 vs. Q1 Vegetable: All cases: 1.13 (0.72-1.78) p for trend: 0.46 Aggressive cases: 1.31 (0.77-1.24) p for trend: 0.31 Non-Aggressive cases: 1.02 (0.57-1.83) p for trend: 0.77 Western: All cases: 1.82 (1.15-2.87) p for trend: 0.02 Aggressive cases: 2.11 (1.25-3.60) p for trend: <0.01 Non-Aggressive cases: 1.41 (0.79-2.53) p for trend: 0.37 Health Conscious: All cases: 1.06 (0.72-1.58) p for

								trend: 0.97 Aggressive cases: 1.00 (0.63-1.59) p for trend: 0.89 Non-Aggressive Cases: 1.28 (0.77-2.12) p for trend: 0.90
Case-control	Askari, F.	2014	Iran	50 cases, 100 controls	FFQ	Healthy, Western[b]	BMI, smoking, history of diabetes, EI	[OR, (95% CI)] High vs. Low (median) Healthy: 0.4 (0.2-1.0) Western: 4.0 (1.5-11.0)
Cohort	Ax, E.	2014	Sweden	133 cases of 566 eligible	7-day dietary records (consecutive)	aMED, Low Carbohydrate-High Protein (LCHP)	EI, smoking status, PA, education level	[OR, (95% CI)] (ref = low adherence) aMED score Numeric: 1.01 (0.75-1.37) Medium: 1.10 (0.59-2.04) High: 1.04 (0.43-2.49) P for trend: 0.90 LCHP score Numeric: 0.77 (0.61-0.96) Medium: 0.55 (0.32-0.96) High: 0.47 (0.21-

								1.04) P for trend: 0.04
Cohort	Bosire, C.	2012	U.S.	23,453 cases of 293,464 eligible	124 pt. FFQ, over past 12 months	HEI-2005, aMED, AHEI-2010	Age, race, BMI, PA, smoking status, family history of prostate cancer, PSA screening, education level, diabetes history, EI	[HR, (95%CI)] Q5 vs. Q1 Advanced prostate cancer HEI-2005: 0.97 (0.84-1.12), p for trend: 0.88; aMED: 1.00 (0.87-1.15), p for trend: 0.82; AHEI-2010: 1.10 (0.96, 1.26), p for trend: 0.54 Fatal prostate cancer HEI-2005: 1.06 (0.76-1.48), p for trend: 0.83; aMED: 0.80 (0.59-1.10), p for trend: 0.23; AHEI-2010: 0.96 (0.71-1.30), p for trend: 0.59
Case-control	De Stefani, E.	2010	Uruguay	345 cases, 690 controls	64 pt. FFQ	Prudent, Traditional, Substituter, Drinker, Western[c]	Education, Dixon, L.B., family history (first-degree relatives), BMI, tobacco	[OR, (95% CI)] Q4 vs. Q1 Prudent: OR=0.82 (0.55-1.23), p trend=0.40; Traditional: OR=1.85 (1.16-2.94), p trend=0.01;

							smoking, EI, other patterns	Substituter: OR=1.07 (0.70-1.65), p trend=0.58; Drinker: OR=1.18 (0.78-1.78), p trend=0.42; Western: OR=2.35 (1.44-3.85), p trend<0.0001
Case-control	Jackson, M.	2009	Jamaica	204 cases, 204	FFQ	Healthy, Carbohydrate, Sugary foods & sweet baked products, Organ meat and fast food[d]	Age, family history (first-degree relatives), education, smoking, BMI, alcohol, EI, other patterns	[OR, (95% CI)] Total Prostate Cancer [T3 vs. T1] Healthy: OR=0.84 (0.43-1.58); Carbohydrate: OR=1.16 (0.55-2.47); Sugary foods & sweet baked goods: OR=0.72 (0.38-1.35); Organ meat and fast food: OR=0.88 (0.47-1.63)
Case-control	Jackson, M.	2013	Jamaica	243 cases, 275 controls	FFQ	Healthy, Fast Foods, Meat, Carbohydrate[e]	Age, family history (first-degree relatives), education, BMI, smoking, PA, EI	[OR, (95% CI)] Total Prostate Cancer T3 vs. T1 Healthy: OR=0.91 (0.50-1.67), p trend=0.766; Fast foods: OR=0.66

								(0.34-1.16), p trend=0.162; Meat: OR=1.10 (0.62-1.96), p trend=0.735; Carbohydrate: OR=2.02 (1.05-3.87), p trend=0.029
Cohort (case only)	Kenfield, S.A.	2014	U.S.	6,220 cases of 47,867 eligible	FFQ	MED	Age, time period, EI, BMI, PA, smoking status, PSA history	[HR, (95% CI)] (ref = low adherence) Gleason score 2-6 Moderate adherence: 1.01 (0.92-1.10); High adherence: 0.96 (0.88-1.06); p trend = 0.37 Gleason score ≥ 7 Moderate adherence: 0.98 (0.88-1.10) High adherence: 1.00 (0.89-1.11); P trend = 0.94
Case-control	Möller, E.	2013	Sweden	1,482 cases, 1,108 controls	FFQ	MED, aMED	Age, residential region, education, smoking, BMI, EI, PA, history of	[OR, (95% CI)] (ref=low adherence) MED Total Prostate Cancer Medium adherence: 1.08 (0.88-1.33);

							diabetes, family history	High adherence: 1.03 (0.81-1.30) Advanced Prostate Cancer Medium adherence: 1.09 (0.84-1.41); High Adherence: 1.09 (0.81-1.48) Localized Prostate Cancer Medium adherence: 1.15 (0.86-1.53); High Adherence: 1.08 (0.78-1.50) aMED Total Prostate Cancer Medium adherence: 1.02 (0.83-1.26); High adherence: 1.13 (0.90-1.41) Advanced Prostate Cancer Medium adherence: 1.20 (0.91-1.56); High Adherence: 1.24 (0.93-1.64) Localized Prostate Cancer Medium adherence: 0.94 (0.70-1.26);

								High Adherence: 1.12 (0.83-1.52)
Cohort	Muller, D.C.	2009	Australia	1,018 cases of 14,627 eligible	FFQ	MED, Vegetable, Meat & Potatoes, Fruit & Salad	Age, EI, ethnicity, BMI, PA, smoking, alcohol intake, education	No association between any dietary pattern and prostate cancer risk (overall, nonaggressive, or aggressive)
Cohort	Tseng, M.	2004	U.S.	139 cases of 3,779 eligible	FFQ	Vegetable-Fruit, Red meat-Starch, Southern[f]	Age, race, urban/rural residence, residential region, education, family history (first-degree), BMI, PA, family income, sun exposure, alcohol intake, smoking	[RR, (95% CI)] (ref=T1) Vegetable T2: 1.5 (0.9-2.3); T3: 1.2 (0.7-2.0); p trend=0.64 Red meat-Starch T2: 0.7 (0.5-1.2); T3: 0.8 (0.4-1.4); p trend=0.37 Southern T2 0.9 (0.6-1.4); T3: 0.6 (0.4-1.1); p trend=0.08
Case-Control	Walker, M.	2005	Canada	80 cases, 334 controls	FFQ	Healthy Living, Traditional Western, Processed, Beverages[g]	Age	[OR, (95% CI);] (ref=T1) Healthy Living T2: 0.99 (0.55-1.78); T3: 0.78 (0.42-1.45); p

								trend=0.45 Traditional Western T2: 1.00 (0.53-1.88); T3: 1.43 (0.79-2.59); p trend=0.22 Processed T2: 2.11 (1.06-4.22); T3: 2.75 (1.40-5.39); p trend=0.0035 Beverages T2: 0.68 (0.37-1.25); T3: 0.84 (0.47-1.51); p trend=0.54
Cohort	Wu, K.	2006	U.S.	3002 cases of 47,725 eligible	FFQ	Prudent, Western[h]	Age, height, smoking, family history (first degree), race, vasectomy, PA, alcohol intake, BMI, EI	[RR, (95% CI)] Q5 vs. Q1 Prudent Total Prostate Cancer: 0.95 (0.84-1.07); p trend=0.37 Advanced Prostate Cancer: 1.05 (0.78-1.42); p trend=0.60 Western Total Prostate Cancer: 1.02 (0.91-1.15); p trend=0.62 Advanced Prostate Cancer: 1.14 (0.85-

								1.53); p trend=0.28

Abbreviations: MED, Mediterranean diet score; aMED, alternate Mediterranean diet score; HEI, Healthy Eating Index; AHEI, alternate Healthy Eating Index; BMI, body mass index (weight (kg)/ height (m^2)); PA, physical activity; EI, energy intake (kcals); OR, odds ratio; RR, relative risk; 95% CI, 95% confidence interval; Q1, lowest quartile/quintile; Q4, highest quartile; Q5, highest quintile; T1, lowest tertile; T3, highest tertile; ref, reference level.

[a] "Vegetable" pattern characterized by positive response loading to questions on vegetables listed; "Western" pattern characterized by positive response loading to questions on whole milk, white bread, eggs, refined sugar, fried potatoes, fried fish, red/processed meat including hamburgers, full-alcohol beer; "health conscious" pattern characterized by positive response loading to questions on steamed/grilled/tinned fish, chicken, rice, pasta, legumes, tofu, sprouts, nuts, yogurt, ricotta cheese, and red/white wine.

[b] "Healthy" pattern characterized by high response loading of legumes, fish, dairy products, fruits, fruit juices, vegetables, boiled potatoes, whole cereal, and eggs; "Western" pattern characterized by high response loading of sweets, desserts, organ meats, snacks, tea, coffee, French fries, salt, carbonated drinks, and red and processed meats.

[c] "Prudent" pattern characterized by high response loading of raw vegetables, citrus fruits, other fruits, and tea. "Traditional" pattern characterized by high response loading of lamb, dairy foods, cooked vegetables, and all tubers. "Substituter" pattern characterized by high response loading of fish and poultry and negative response loading for lamb. "Drinker" pattern characterized by high response loading on mate, beer, wine, and hard liquor. "Western" pattern characterized by high response loading on beef, processed meat, boiled eggs, fried eggs, and total grains.

[d] "Healthy" pattern characterized by high response loading of vegetables, peas, beans, and fruits. " Carbohydrate" pattern characterized by high response loading of white bread, refined cereals, poultry, rice/pasta, starchy roots and tubers. "Sugary foods and sweet baked products" characterized by high response loading of sugary foods, sweet baked goods, and non-diet drinks. "Organ meat and fast food" pattern characterized by high response loading of organ meat, fast food, and salty snacks.

[e] "Healthy" pattern characterized by high response loading of vegetables, nuts, peas, and beans; "fast food" pattern characterized by high response loading of fast foods, alcoholic beverages, meal replacements, and dairy dessert; "meat" pattern characterized by high response loading of processed meat, eggs, poultry, and starchy fruits, roots, and tubers; "carbohydrate" pattern characterized by high response loading of rice/pasta, sugar-sweetened beverages, sweet baked goods, and poultry.

[f] "Vegetable-Fruit" pattern characterized by positive response loading for vegetables, fruits, fish, and shellfish; "Red meat-Starch" pattern characterized by positive response loading for red meats, potatoes, salty snacks, cheese, sweets, and desserts; "Southern" pattern characterized by high response loading for beans, rice, corn bread, grits, sweet potatoes, and

okra.
[g] "Healthy Living" pattern characterized by high response loading of vegetables, fruits, whole grains, fish, and poultry; "traditional western" pattern characterized by high response loading of red meats, processed meats, milk, sweets, and hard liquor; "processed" pattern characterized by high response loading of processed meats, red meats, organ meats, refined grains, onions, tomatoes, vegetable oils, juices, bottled water, and soft drinks; "beverages" pattern was characterized by high response loading of tap water, soft drinks, fruit juices, potatoes, poultry and margarine, and inversely associated with beer, liquor, wine, and cream in coffee.
[h] "Prudent pattern characterized by high response loading of fruits, vegetables, whole grains, fish, and poultry; "Western" pattern characterized by high response loading of red and processed meats, refined grains, and high-fat dairy.

CHAPTER 3

RESEARCH METHODS

1. Background

This study utilized data from the North Carolina-Louisiana Prostate Cancer Project (PCaP), a population-based, case-only study designed to study racial differences in prostate cancer aggressiveness and survival. This research was designated as part of Project 3, nutritional modulation of prostate cancer aggressiveness, of the PCaP structure.

2. Sample Size

A total of 2,258 men were recruited for participation in the PCaP sample population: of these, 1,130 identified as AA and 1,128 identify as EA. Approximately half (52%) of the participating men were North Carolina residents; the remaining men all resided in Louisiana.

3. PCaP Methods

Study Population

As stated in paper "The North Carolina-Louisiana Prostate Cancer Project (PCaP): Methods and Design of a Multidisciplinary Population-Based Cohort Study of Racial Differences in Prostate Cancer Outcomes," by Schroeder et al., "residents of the North Carolina and Louisiana study areas with a first diagnosis of histologically confirmed adenocarcinoma of the prostate [were] eligible to participate if they [were] 40-79 years old at diagnosis, [could] complete the study interview in English, [did] not live in an institution (nursing home), [were] not cognitively impaired or in a severe debilitated

physical state, and [were] not under the influence of alcohol, severely medicated, or apparently psychotic at the time of the interview.

"Eligible men also must self-identify as at least part African American/Black or Caucasian American/White in response to the open-ended interview question, 'what is your race?' Participants who indicated more than one group [were] asked if one best describes them; if not, multiple groups [were] recorded. This classification may be used as a proxy measure of race/ethnicity as a social construct or as a proxy measure of race as a biologic construct, as deemed appropriate for the individual PCaP Consortium projects. Participants [were] asked if they consider themselves to be Cajun, Creole, or Hispanic/Latino prior to the question about race, so that these ethnic groups [were] defined independent of African American or Caucasian American race/ethnicity.

"North Carolina enrollment of patients diagnosed on or after July 1, 2004, began in September 2004. At present, the North Carolina study area consists of 42 counties Louisiana enrollment began in 13 parishes surrounding New Orleans in September 2004, but was discontinued because of Hurricane Katrina (August 29, 2005). This period of data collection (referred to as 'Louisiana Phase I') included study visits with 122 African American and 95 Caucasian American participants." A second phase of Louisiana enrollment includes an expanded study area (including at least eight additional parishes in southern Louisiana. "Louisiana data and samples collected during Phase I will be analyzed separately from data and samples collected during Phase II and will be used primarily to compare pre- and post-Katrina experiences (Schroeder, Bensen et al. 2006)."

Rapid Case Ascertainment

"Eligible North Carolina patients [were] identified by the Rapid Case Ascertainment Core Facility, a collaborative effort of the UNC-Lineberger Comprehensive Cancer Center and the North Carolina Central Cancer Registry (NCCCR). North Carolina state law mandates regular reporting of all newly diagnosed cancers (excluding non-melanoma skin cancers), and the NCCCR is authorized to release contact and eligibility information to PCaP by the North Carolina Advisory Committee on Cancer Coordination and Control. In Louisiana, eligible patients [were] identified by the Louisiana Tumor Registry (LTR) in the School of Public Health at LSUHSC. LTR operations are mandated by Louisiana law, which directs all hospitals, pathology laboratories, health care facilities, and medical care providers to report cancer cases or provide LTR staff with access to this information. Case ascertainment field representatives abstract[ed] pathology reports, review[ed] information used to screen eligibility and ensure[d] that ascertainment in hospitals and local urology clinics [was] as complete and rapid as possible.\ These data [were] entered into a relational database that [was] regularly downloaded into the PCaP Subject Tracking Database (Schroeder, Bensen et al. 2006)."

Randomized Recruitment

"Caucasian Americans account[ed] for a greater proportion of North Carolina patients than African Americans; therefore, a randomized recruitment procedure [was] used to generate comparable ascertainment and enrollment rates by race and state over the entire enrollment period. This sampling method improve[d] efficiency without compromising estimation of main effects and risk difference modification (additive scale

interactions) by race, and appropriate analysis requires only that the sampling probabilities are included as stratum-specific offset terms in some analytic models. To apply randomized recruitment, each ascertained case [was] assigned a random number and recruited only if that number [was] less than or equal to its race specific sampling probability, which is 100% for African Americans and 44% for Caucasian Americans (Schroeder, Bensen et al. 2006)."

Physician Notification

"Recruitment [began] with a mailed request to the diagnosing physician for permission to contact their patient, as mandated by the North Carolina and Louisiana cancer registries. Written physician permission [was] not required; instead, physicians [were] given 3 weeks to notify PCaP if a patient should not be contacted for any reason, including ineligibility due to mental illness or impairment, nursing home residence, or severe physical debilitation. Passive physician permission, and access to patient information under a limited waiver of consent to identify and contact potential PCaP participants, was approved by the UNC and LSUHSC IRBs and DoD HSRRB (Schroeder, Bensen et al. 2006)."

Enrollment

"Patients with active or passive physician consent [were] sent an introductory letter and brochure describing PCaP. One week later an experienced enrollment specialist [called] to confirm eligibility, explain the study, answer questions, solicit participation, and schedule an in home visit. Demographic and pathology report data (without personally identifiable information) [were] retained for cases who could not be contacted or who decline[d] participation, so that characteristics of non-participants could be

compared with those of participants to assess potential selection bias. Reasons for declining participation [were] recorded when known. Enrollment specialists [were] required to make multiple attempts to contact each potential participant. If a valid phone number could not be identified, the patient's urologist [was] asked to provide the patient with the PCaP introductory letter at his next appointment. Patients who could not be contacted within 90 days [were] sent a letter asking them to contact the study directly. If no contact [was] made within the next 30 days, the patient [was] classified as 'unable to contact.'(Schroeder, Bensen et al. 2006) "

Study Visit

"Participants [were] visited in their home (or other location of their choosing) by a trained Registered Nurse. Participants [were] asked to fast for 6 hr prior to the study visit, which [was] scheduled in the morning whenever possible, and to gather all medications and supplements used in the 2 weeks prior to the visit. Study nurses [began] each visit by explaining the study and obtaining HIPAA authorization and formal written informed consent to: (1) conduct the questionnaire interview, (2) make anthropometric measurements, (3) obtain samples of adipose tissue, blood, urine, and toenails, (4) allow temporary release of paraffin embedded prostate tissue blocks, and (5) allow retrieval and abstraction of medical records. Study consent forms [were] read aloud to illiterate participants in the presence of a witness not associated with PCaP. After consent forms [were] signed, the study nurse collect[ed] biologic samples, [made] anthropometric measurements and administer[ed] the questionnaire. Study visits [took] approximately 4 hr to complete, including two 15-min breaks. Participants [were] partially compensated for their time with a payment of up to $75 for completing the entire PCaP study visit.

"All study visit protocols [were] documented in a manual of procedures. To ensure consistency, patient safety, and confidentiality, study nurses must be certified and periodically re-certified to conduct all aspects of the visit. Interview and biologic sample collection data [were] reviewed on an ongoing basis to identify variation among study nurses or between study sites that cannot be explained by acceptable or expected trends. In addition, project managers at each site call randomly selected study participants after study visits [were] completed to assess nurse performance and solicit feedback (Schroeder, Bensen et al. 2006)."

Anthropometric Measures

"Weight (to the nearest 0.1 kg), height, and waist and hip circumferences (in cm) [were] measured after biologic sample collection using standardized instruments. Participants [were] asked their usual weight and height at age 25 and their weight 1 year prior to the visit (Schroeder, Bensen et al. 2006)."

Study Questionnaires

"Study nurses administer[ed] a series of structured questionnaires that solicit[ed] information regarding:

Background characteristics: self-described race and ethnicity, marital status, religion, education, income, tobacco use, physical activity.

Occupation: current employment, occupation and industry, longest and second occupation and industry, military service, occupations associated with pesticide use.

Family history: prostate cancer in first- and second-degree relatives.

Health status: general health and comorbid conditions.

Health care: usual sources of care, health insurance, traditional health beliefs, perceived access, and quality of care.

Prostate cancer diagnosis and screening history: PSA tests, digital rectal exams, urinary and sexual symptoms, previous prostate biopsies.

Medication survey: all prescription and over-the-counter medications and supplements used in the prior 2 weeks (transcribed by study nurses).

Non-steroidal anti-inflammatory drugs (NSAIDs): frequency and duration of use for prescription and over-the-counter NSAIDs taken during the past 5 years at least once a month for 1 week or longer, with product name show cards to aid recall.

Vitamins and supplements (including herbal products).

Diet History Questionnaire (DHQ): The DHQ was developed by the National Cancer Institute and modified by PCaP Project 3 investigators to include Southern foods. The DHQ asks about intake frequency and usual portion size for 124 food items, as well as food preparation methods. Participants are asked to recall their usual diet for the year prior to diagnosis. Questionnaire responses are linked to the updated DHQ Nutrient Database through the NCI-developed Diet*Calc software to estimate intake of fatty acid and antioxidant micronutrients, including omega-3 and omega-6 polyunsaturated fatty acids, carotenoids, and tocopherols (Schroeder, Bensen et al. 2006)."

Medical Records Retrieval and Abstraction

"Medical records [were] requested from the diagnosing physician of consenting participants. Trained staff use[d] a relational database designed specifically for PCaP to abstract information concerning comorbid conditions, family history of prostate cancer, urologic symptoms, indications for diagnostic examinations and biopsies, prostate cancer

screening examinations, and laboratory assays at or near diagnosis, imaging examinations used in staging, clinical stage and grade (as recorded), and initial treatment information. In addition, abstractors independently derive[d] clinical stage according to a standardized protocol. Pathologic stage, grade, and other prostatectomy data [were] recorded separately, when available. Approximately 10% of medical records [were] selected at random and abstracted to assess consistency between abstractors (Schroeder, Bensen et al. 2006)."

4. Variables

Primary Outcome

Cases were classified in three categories based on clinical grade (Gleason grade), clinical stage, and PSA at diagnosis. High aggressive cases were defined as having a Gleason sum ≥8 OR PSA>20 ng/ml OR Gleason sum=7 and stage T3-T4; low aggressive cases were defined as having a Gleason sum<7 AND stageT1-T2 AND PSA<10 ng/ml; all other cases were classified as intermediate aggressive. For the purposes of this study and all included analyses, cases were dichotomized into high aggressive (as defined above) and low-intermediate aggressive (all other cases). This dichotomization will allow for the calculation of the odds of high aggressive prostate cancer, and analyses to be conducted similarly to a case-control study where men with high aggressive prostate cancer will serve as "cases" and men with low or intermediate aggressive prostate cancer will serve as the comparison group, or "controls."

Main Exposures: Dietary Pattern Score

Mediterranean Diet Score

The MED scores followed the scoring scheme outlined by Trichopoulou, et al. (2003). A total of nine dietary components were evaluated: grains and cereals, refined grains, fatty acids, vegetables, legumes, fruits and nuts, fish, and alcohol. The median intake value (in grams per day) for each component was calculated from the sample scores for the nine components reflect if intake was above or below the median. For grains and cereals, fatty acids (calculated as the ratio of monounsaturated fatty acids to saturated fatty acids in g/day), vegetables, legumes, fruits and nuts, and fish, intakes above the median were scored 1 and intakes below the median were scored 0. Refined grains and meat and poultry were scored 1 for intake values below the median, 0 for values above the median. An alcohol score of 1 was given to men consuming 10-50 g alcohol/day; all other alcohol intake ranges were scored 0 (see Table 3.1).

Median cutoff values were calculated from the responses given in cups/ounces per day. For mixed dishes, the percentage of each relevant component were estimated using common recipes; that percentage was applied to the cup/oz. value, and summed into the total component value. All values were adjusted to reflect intake in grams/day.

Dietary Approaches to Stop Hypertension Score

DASH scores followed the scoring scheme outlined by Fung et al. (2008): eight components (whole grains, low fat dairy, vegetables, legumes and nuts, fruit and fruit juices, red and processed meats, sodium, and sweetened beverages) were scored on a 1-5 scale. For whole grains, low fat dairy, vegetables, legumes and nuts, and fruit and fruit juices, the highest intake quintiles received a score of 5, with the lowest quintile receiving

a score of 1; for red and processed meats, sodium, and sugar sweetened beverages, the scoring scheme is inverted (lowest quintiles receive scores of 5). Scores may range from 8-40, with 40 reflecting the healthiest patterns of consumption (see Table 3.1).

Values may be evaluated as reported, since evaluation is based on quintiles and/or tertiles. For mixed dishes, the percentage of each relevant component will be estimated using common recipes; that percentage will be used to calculate the serving amount and summed into the total component value. Responses were standardized across frequency to achieve a common time denominator.

Potential Confounders and/or Effect modifiers

Age: Age was included as a continuous variable.

Race: Race was dichotomized into AA and EA men.

Study Site: Site was designated as either North Carolina (University of North Carolina) or Louisiana (post-Hurricane Katrina, Louisiana State University).

Family History: Family history was dichotomized into "yes" or "no": those coded as "yes" positively indicated prior prostate cancer diagnoses in their family; all others were coded as "no."

Education: Education was defined on four levels: less than high school diploma, earned high school diploma, some college/VoTec, and college graduate (including post-graduate studies).

Screening History: Screening history was defined on four levels: PSA test only, DRE only, PSA and DRE tests, and neither PSA nor DRE test.

BMI: BMI was evaluated as both a continuous and categorical (<25 kg/m^2, ≥ 25 kg/m^2 but <30 kg/m^2, and ≥ 30 kg/m^2) variable.

Smoking Status: Smoking status was defined as current smoker, past smoker, and never smoker.

NSAID Use: NSAID use was dichotomized into "yes" for those reporting regular use and "no" for all others.

Physical Activity: MET hours per week were calculated from reported physical activity levels and frequencies.

Comorbidity: Comorbidity was assessed using Charlson's Comorbidity Index; scores were categorized into 0, 1-2, and 3 or greater.

5. Analyses

Missing Data

Any participants missing outcome, covariate, or exposure data were not included in the final analyses.

Statistical Methods

All procedures were performed using SAS, version 9.4 statistical software with the intention of determining:

1. Diet scores, evaluated as numeric variables and as categorical variables. MED scores were categorized as low (0-3), moderate (4-5) and high (6-9) conformity. DASH scores were evaluated using two categorizations, tertiles and quintiles, where cutpoints were determined based on the distribution among low-intermediate aggressive cases.
2. Univariate distributions of exposures, outcomes, and potential covariates.
3. Logistic regression (2-level outcome) simple model for each dietary score, including dietary score, age, total energy intake, and race.

4. Multivariate logistic regression models further adjusting for study site, family history, BMI, education level, screening history, smoking status, physical activity, NSAID use, and comorbidities. Decisions to include these covariates in the model were based on previous literature and the "ten percent rule." Variables were added separately one at a time to the crude model, and percent change in the beta-coefficient for the exposure was calculated. If the percent change was equal to or greater than 10%, then variables were retained in the final model.
5. P-values for linear test for trend, with the exposures evaluated as both numeric variables and categorical variables. Categorical linear trend tests were conducted using an ordered dummy variable in lieu of category.
6. Possible effect modification by race, age, smoking status, and BMI were identified by inclusion of an interaction term of dietary score*covariate in the model; interaction terms significant at the 0.10 level, and that changed the OR by more than 10%, were included in the final model. Stratification by effect modifiers was performed to estimate effects within strata of age, smoking and BMI.
7. Pearson correlation between the MED and DASH scores was calculated.
8. Average intakes for total energy, fat, saturated fat, carbohydrates, protein, polyunsaturated fatty acids, monounsaturated fatty acids, alcohol, lycopene, calcium, vitamin A, vitamin C, vitamin E, vitamin D, and fiber were calculated for the total sample and categorized dietary scores.

Full Model

Logit (P(prostate cancer aggressiveness)) = $\beta_0 + \beta_1$(dietary index score) + β_2(age) + β_3(race) + β_4(total energy intake) + β_5(education) + β_6(smoking) + β_7(BMI) + β_8(PA METs/week) + β_9(family history) + β_{10}(screening history) + β_{11}(NSAIDs) + β_{12}(comorbidities) + β_{13}(site)

Table 3.1: Components and scoring standards for the diet quality indices				
Dietary Component	MED (0-9)[a]		DASH (8-40)[b]	
	Criteria for max. score	Score Range	Criteria for max. score	Score Range
Grains/Cereals	≥median g/day	0-1		
Whole grains			Highest quintile	1-5
Dairy	≤median g/day	0-1		
Low fat dairy			Highest quintile	1-5
Fatty Acids	MUFAs/SFAs≥median g/day	0-1		
Vegetables	≥median g/day	0-1	Highest quintile	1-5
Legumes	≥median g/day	0-1		
Legumes and nuts			Highest quintile	1-5
Fruit				
Total fruit (including juice)			Highest quintile	1-5
Fruit and nuts	≥median g/day	0-1		
Protein				
Fish	≥median g/day	0-1		
Meat & Poultry	≤median g/day	0-1		
Red and processed meats			Lowest quintile	1-5
Sodium			Lowest quintile	1-5
Alcohol	10-50 g/day (men)	0-1		
Sweetened beverages			Lowest quintile	1-5

[a] Taken from "Adherence to a Mediterranean diet and survival in a Greek population" by Trichopoulou A., T. Costacou, et al., 2003.
[b] Taken from "Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women" by Fung, T.T., S.E. Chiuve, et al., 2008.

CHAPTER 4

RESULTS

Tables 4.1 - 4.2: Descriptive Statistics

The final sample size included 1,899 men, with 1,567 low-intermediate aggressive cases of prostate cancer and 332 high aggressive cases of prostate cancer. Within the sample, 908 of the men identified as AA (47.8%) and 991 identified as EA (52.2%). MED scores ranged from 0 to 9 with a mean and SD of 4.19 ± 1.65. DASH scores ranged from 11to 36 with a mean and SD of 22.01 ± 4.37; both MED and DASH scores were normally distributed.

Aggressiveness Comparisons (Table 4.1)

Participants diagnosed with high aggressive prostate cancer were significantly older, had higher body mass index, consumed more calories per day, identified as AA, were more likely to have less than a high school education, were more likely to be current or former smokers, and were less likely to have been screened for prostate cancer previously than low-intermediate cases.

Racial Differences (Table 4.2)

AA men included in this study were younger, less active, consumed more calories per day, were less educated, more likely to be a current smoker, less likely to use NSAIDs regularly or to have been previously screened for prostate cancer, and had fewer comorbidities than their EA counterparts.

Tables 4.3 - 4.4: Confounding

Previous research has indicated that BMI, physical activity, education level, smoking status, NSAIDs use, family history, screening history, and comorbidities may confound the association between dietary measures and prostate cancer (Ax, Garmo, et al 2014; Bosire, Stampfer, et al. 2012; Tseung, Breslow, et al. 2004). Therefore, all these factors were justified for inclusion in the fully adjusted logistic regression models. To determine which of these known confounders presented as such in this dataset, the "ten percent rule" was used to assess each covariate: screening history and smoking history were found to highly impact the numeric dietary scores, while BMI, education level, smoking history, family history, and screening history showed substantial changes to dietary score estimates when evaluated categorically.

Tables 4.5 - 4.8: Final Models

Numeric dietary pattern scores (Tables 4.5-4.6)

For all men, higher MED and DASH scores were significantly inversely associated with the odds of aggressive prostate cancer: for every one point increase in MED score, odds of aggressive prostate cancer diagnosis decreased by 12% (95% CI: 0.82 -0.96), while a point increase in DASH score decreased aggressive diagnosis odds by 4% (95% CI: 0.93, 0.99). After adjusting for all confounders, the statistically significant inverse associate between MED score and odds of aggressive prostate cancer remained, while the association seen for the DASH score was attenuated.

Interaction p-values for race and diet scores were not statistically significant (p interaction= 0.11 and 0.15 for numeric MED and DASH scores, respectively). However, because one of our *a priori* aims was to examine associations by race, we stratified

primary analyses by race and present those results in Table 4.6. In EA men, a decrease in aggressive prostate cancer diagnosis of 12% and 5% were observed with increasing MED and DASH scores, respectively; the inverse association remained within the sample but there is not enough evidence to detect this relationship to the population. For AA men, higher MED scores were associated with lower odds of aggressive prostate cancer diagnosis (OR: 0.89; 95% CI: 0.80-0.99), though the effect was not significant when adjusted for multiple confounders. No significant association between DASH scores and aggressiveness was observed in AA men.

Categorical dietary pattern scores (Table 4.7-4.8)

As shown in Table 4.7, men with the highest MED scores (6-9) had a 34% decreased odds of an aggressive prostate cancer diagnosis compared to men with the lowest MED scores (0-3) (p trend: 0.09). The odds of aggressive prostate cancer decreased by 35% for men in the highest tertile of DASH scores compared to men in the lowest tertile (p trend: 0.02); this association was attenuated and no longer statistically significant in the adjusted model (OR: 0.76; 95% CI: 0.55-1.06; p trend = 0.23). When comparing DASH quintiles, men in the second highest quintile were significantly less likely to be diagnosed with aggressive prostate cancer than men in the lowest quintile (OR: 0.63; 95% CI: 0.43-0.92). When AA men and EA men were evaluated separately, AA men with the highest MED scores were less likely to have aggressive prostate cancer than AA men in with the lowest MED scores (OR: 0.56; 95% CI: 0.32-0.97) (Table 4.8).

Tables 4.9 - Table 4.11: Effect Modification

The interaction term with BMI was significant in the numeric DASH models (p interaction term = 0.09), but not for any categorized DASH models or MED models.

Although the interaction terms were not significant, higher MED and DASH scores appeared to have the most beneficial effect on men classified as ‘overweight (BMI 25 or greater but less than 30). Age (‘less than 65 years’ and ‘65 years or older’) and smoking status had significant interaction terms in all MED score models and in numeric DASH models. Increased conformity to both MED and DASH dietary patterns showed larger inverse associations for men aged 65 and older than for men younger than 65 on aggressive prostate cancer diagnosis. For all models, never and former smokers were observed to have lower odds of aggressive prostate cancer than current smokers.

Tables 4.12 - Table 4.15: Sensitivity Analyses Using Categorized Age Models

Analyses re-run with age categorized into ‘less than 65 years’ and ’65 years or older’ showed no substantial deviation from results found with the continuous age variable included in the model.

Table 4.16: Spearman Correlation between MED and DASH scores

Moderate, positive linear associations were found between numeric MED and DASH scores, MED categories and DASH quintiles, and MED categories and DASH tertiles for all men, AA men, and EA men (correlation coefficients were 0.53 for numeric variables and 0.46 for categorical variables, all p values <0.0001).

Table 4.17: Means and Standard Deviations of Select Nutrients Across Total Sample and Dietary Score Categories

Table 4.17 shows the average intakes of select nutrients across the total sample and dietary score categories. For all dietary score categories, those with the highest scores also has the highest intakes of energy, fat, carbohydrates, protein, polyunsaturated fatty acids, monounsaturated fatty acids, lycopene, vitamin A, vitamin C, vitamin E, vitamin

D, and fiber; the exceptions were calcium and saturated fat, where those with moderate adherence to the MED diet had the highest calcium consumption when compared to low/ high MED adherence, and alcohol, where there was no universal trend of consumption for any of the dietary categories. For all nutrients except alcohol, participants in the highest dietary score category had an average intake above the sample average.

Tables 4.18-4.19: Comparison of Research Participants Included in Analyses to Those Excluded Due to Missing Data

Men with missing PSA screening history/Gleason scores, implausible caloric intakes (<500 kcal/day or >6000 kcal/day), and/or missing covariate information (n=359) were excluded from final analyses. Excluded men were compared to included men to determine if data was missing at random or in association with the outcome; those missing other covariates were more likely to be diagnosed with aggressive prostate cancer (p value = 0.04), indicating the missing data may be associated with the outcome. Men excluded from analyses consumed more calories each day and were less physically active; they were also more likely to identify as AA, reside in Louisiana, have less education, be a current smoker, and have never been screened for prostate cancer.

All adjusted models were rerun, including all men with aggressive data (both included in primary analysis and those excluded for missing data) for comparison with association measures of included subjects; further sensitivity analysis was conducted by artificially placing all high aggressive cases with missing variables into the highest categories of dietary scores and artificially placing all low-moderate aggressive cases with missing variables into the lowest categories of dietary scores (Table 4.19). These

sensitivity analyses revealed similar results to the main analyses, suggesting that the exclusion of subjects with missing data did not substantially bias the results.

Table 4.1: Dietary and demographic characteristics of PCaP participants by high and low-intermediate aggressiveness (after excluding participants with missing covariates)					
Characteristic	**High Aggressive (n=332)**		**Low-Intermediate Aggressive (n=1567)**		**p-value***
	Mean	SD	Mean	SD	
MED Score	4.0	1.6	4.2	1.7	0.06
DASH Score	21.6	4.2	22.1	4.4	0.06
Age	64.7	7.8	62.8	7.9	<0.0001
Body Mass Index	30.2	6.0	29.1	5.0	0.002
MET hours per week	22.3	22.9	24.2	23.6	0.18
Total energy intake (kcal)	2594.3	1121.3	2458.6	1022.6	0.04
	n	%	n	%	
Race					0.005
AA	182	54.8	726	46.3	
EA	150	45.2	841	53.7	
Site					0.35
LA	179	53.9	801	51.1	
NC	153	46.1	766	48.9	
Education					<0.0001
Less than High School	96	28.9	282	18.0	
High School Graduate/Vo-Tech school	91	27.4	483	30.8	
Some college/College Graduate	111	33.4	565	36.1	
Graduate/Professional Training or Degree	34	10.2	237	15.1	
Smoking Status					0.003
Never	93	28.0	555	35.4	
Former	173	52.1	798	50.9	
Current	66	19.9	214	13.7	
NSAIDs use					0.70

No	127	38.3	617	39.4	
Yes	205	61.8	950	60.6	
Family history in first degree relative					0.45
No	260	78.3	1144	73.0	
Yes	72	21.7	423	27.0	
Screening history					<0.0001
None	73	22.0	164	10.5	
DRE only	60	18.1	230	14.7	
PSA only	17	5.1	60	3.8	
DRE & PSA	182	54.8	1113	71.0	
Charlson's Comorbidity Index					0.33
0	155	46.7	799	51.0	
1-3	152	45.8	669	42.7	
4+	25	7.5	99	6.3	

[*]P-value for differences between cases and controls determined by t-test for numeric variables and chi-square test for categorical variables.

[a] Prostate cancer aggressiveness is defined as the severity of the cancer at diagnosis based on combinations of the Gleason score, morphologic stage, and PSA as follows: high aggressive, Gleason sum ≥ 8 OR PSA > 20 ng/mL OR Gleason sum ≥ 7 and stage T3-T4; low aggressive, Gleason sum < 7 and stage T1-T2 and PSA < 10 ng/mL; intermediate aggressiveness, all other cases**.**

Table 4.2: Dietary and demographic characteristics of PCaP participants by race (after excluding those with missing covariates)

Characteristic	African Americans (n = 908)		European Americans (n = 991)		p-value*
	Mean	SD	Mean	SD	
MED score	4.7	1.9	4.1	1.9	<0.0001
DASH score	23.8	4.1	24.2	4.2	0.01
Age (years)	61.9	7.8	64.2	7.9	<0.0001
Energy Intake (kcal/d)	2654.1	1165.9	2324.9	884.5	<0.0001
Body Mass Index (kg/m^2)	29.3	5.6	29.3	4.9	0.97
MET hrs/wk	21.3	22.7	26.3	23.9	<0.0001
	n	%	n	%	
Prostate cancer classification[a]					0.005
High Aggressive	182	20.0	150	15.1	
Low-Intermediate Aggressive	726	80.0	841	84.9	
Site					0.58
Louisiana	475	52.3	505	51.0	
North Carolina	433	47.7	486	49.0	
Education level					<0.0001
< 8th grade/some high school	283	31.2	95	9.6	
High school grad/vo-tech	302	33.3	272	27.4	
Some college/college grad	265	29.2	411	41.5	
Graduate school/prof. degree	58	6.3	213	21.5	
Smoking status					<0.0001
Never	282	31.1	366	36.9	
Former	432	47.6	539	54.4	
Current	194	21.3	86	8.7	
Use of NSAIDs					<0.0001
No	407	44.8	337	34.0	

Yes	501	55.2	654	66.0	
Family history (first degree relative affected)					0.11
No	656	72.2	748	75.5	
Yes	252	28.8	243	24.5	
Screening history (PSA or DRE)					<0.0001
None	171	18.8	66	6.7	
DRE	187	20.6	103	10.4	
PSA	34	3.7	43	4.3	
DRE & PSA	516	56.8	779	78.6	
Charlson's Comorbidity Index					0.03
0	427	47.0	527	53.2	
1-3	418	46.0	403	40.7	
4+	63	7.0	61	6.1	

[*] P-value for differences between AAs and EAs determined by t-test for numeric variables and chi-square test for categorical variables.

[a] Prostate cancer aggressiveness is defined as the severity of the cancer at diagnosis based on combinations of the Gleason score, morphologic stage, and PSA as follows: high aggressive, Gleason sum ≥ 8 OR PSA > 20 ng/mL OR Gleason sum ≥ 7 and stage T3-T4; low aggressive, Gleason sum < 7 and stage T1-T2 and PSA < 10 ng/mL; intermediate aggressiveness, all other cases.

Table 4.3: Assessment of confounding by 10% rules for covariates – numeric diet scores

	MED Score Beta Coefficient	% Δ	DASH Score Beta Coefficient	% Δ
Crude[1]	-0.1244		-0.0429	
BMI	-0.1172	-5.79	-0.0412	-3.96
METs/week	-0.1225	-1.53	-0.0417	-2.80
Site	-0.1256	0.96	-0.0429	0
Education	-0.1171	-5.87	-0.0390	-9.09
Smoking History	-0.1163	-6.51	-0.0371	-13.52
NSAIDs use	-0.1249	0.40	-0.0434	1.17
Affected 1st degree relative	-0.1220	-1.93	-0.0435	1.40
Screening history	-0.1014	-18.49	-0.0317	-26.11
Charlson's Comorbidity Score	-0.1240	-0.32	-0.0430	0.23

[1] Crude model includes age, total energy intake, and race

Table 4.4: Assessment of confounding by 10% rules for covariates – categorical diet scores								
MED Levels		**% Δ**	**DASH Quintiles**		**% Δ**	**DASH Tertiles**		**% Δ**
Crude[1]								
Moderate	0.0268		Q2	0.1968		T2	-0.0267	
High	-0.2963		Q3	-0.0376		T3	-0.1997	
			Q4	-0.2291				
			Q5	-0.1654				
BMI								
Moderate	0.0226	-15.67	Q2	0.2123	7.88	T2	-0.0342	28.09
High	-0.2749	-7.22	Q3	-0.0540	43.62	T3	-0.1869	-6.41
			Q4	-0.2297	0.26			
			Q5	-0.1477	-10.70			
Physical activity in METs/week								
Moderate	0.0265	-1.12	Q2	0.1946	-1.12	T2	-0.0275	3.00
High	-0.2930	-1.11	Q3	-0.0386	2.66	T3	-0.1932	-3.25
			Q4	-0.2254	-1.62			
			Q5	-0.1569	-5.14			
Site								
Moderate	0.0267	-0.37	Q2	0.1984	0.81	T2	-0.0265	-0.75
High	-0.2982	0.64	Q3	-0.0380	1.06	T3	-0.1997	0
			Q4	-0.2287	-0.17			
			Q5	-0.1653	-0.06			
Education								
Moderate	0.0295	10.07	Q2	0.2056	4.47	T2	-0.0273	2.25
High	-0.2804	-5.37	Q3	-0.0549	46.01	T3	-0.1828	-8.46
			Q4	-0.2183	-4.71			
			Q5	-0.1355	-18.08			
Smoking history								
Moderate	0.0306	14.18	Q2	0.1999	1.58	T2	-0.0255	-4.49
High	-0.2833	-4.39	Q3	-0.0422	12.23	T3	-0.1769	-11.42

			Q4	-0.2227	-2.79			
			Q5	-0.1206	-27.09			
NSAIDs use								
Moderate	0.0259	-3.36	Q2	0.1977	0.46	T2	-0.0285	6.74
High	-0.2970	0.24	Q3	-0.0389	3.46	T3	-0.2011	0.70
			Q4	-0.2295	0.17			
			Q5	-0.1673	1.15			
Affected 1st degree relative								
Moderate	0.0357	33.21	Q2	0.2099	6.66	T2	-0.0296	10.86
High	-0.2990	0.91	Q3	-0.0405	7.71	T3	-0.2043	2.30
			Q4	-0.2408	5.11			
			Q5	-0.1641	-0.79			
Screening history								
Moderate	0.0268	0	Q2	0.1632	-17.07	T2	-0.0173	-35.21
High	-0.2530	-14.61	Q3	-0.0579	53.99	T3	-0.1507	-24.54
			Q4	-0.2095	-8.56			
			Q5	-0.0799	-51.69			
Charlson's Comorbidity Score								
Moderate	0.0272	1.49	Q2	0.1986	0.91	T2	-0.0280	4.87
High	-0.2956	-0.24	Q3	-0.0383	1.86	T3	-0.1994	-0.15
			Q4	-0.2311	0.87			
			Q5	-0.1640	-0.85			

[1] Crude model includes age, total energy intake, and race

Table 4.5 Association between dietary scores (numeric) and prostate cancer aggressiveness

	OR	95% CI	P(trend)
MED			
Crude[1]	0.88	(0.82, 0.96)	0.002
Adjusted[2]	0.92	(0.84, 0.99)	0.03
DASH			
Crude[1]	0.96	(0.93, 0.99)	0.004
Adjusted[2]	0.98	(0.95, 1.01)	0.11

[1] Model includes dietary score, age, total energy intake and race

[2] Model includes dietary score, age, total energy intake, race, BMI, smoking status, family history, NSAIDs use, education, screening history, Charlson's comorbidity score, and site

Table 4.6 Association between dietary score (numeric) and prostate cancer aggressiveness, stratified by race

	AA			EA		
	OR	**95% CI**	**P (trend)**	**OR**	**95% CI**	**P (trend)**
MED						
Crude[1]	0.89	(0.80, 0.99)	0.04	0.88	(0.79, 0.98)	0.02
Adjusted[2]	0.91	(0.81, 1.02)	0.10	0.90	(0.80, 1.02)	0.10
DASH						
Crude[1]	0.96	(0.93, 1.00)	0.07	0.95	(0.91, 0.99)	0.03
Adjusted[2]	0.99	(0.94, 1.03)	0.50	0.96	(0.91, 1.00)	0.07

[1] Model includes dietary score, age, and total energy intake
[2] Model includes dietary score, age, total energy intake, BMI, smoking status, family history, NSAIDs use, education, screening history, Charlson's comorbidity score, and site

Table 4.7: Association between dietary score (categorized) and prostate cancer aggressiveness

	High/Low-Intermediate Aggressive	Crude[1]			Adjusted[2]		
MED		**OR**	**95%CI**	**P(trend)**	**OR**	**95% CI**	**P(trend)**
Low (0-3)	128/544	1.00	(ref)		1.00	(ref)	
Moderate (4-5)	144/668	0.78	(0.60, 1.03)		0.85	(0.64, 1.14)	
High (6-9)	60/355	0.57	(0.40, 0.81)	0.007	0.66	(0.46, 0.95)	0.09
DASH – quintiles							
Q1 (11-18)	80/344	1.00	(ref)		1.00	(ref)	
Q2 (19-21)	93/374	0.97	(0.69, 1.36)		1.08	(0.76, 1.53)	
Q3 (22-23)	50/247	0.76	(0.51, 1.14)		0.80	(0.53, 1.21)	
Q4 (24-26)	61/347	0.63	(0.43, 0.92)		0.71	(0.48, 1.06)	
Q5 (27-36)	48/255	0.67	(0.45, 1.01)	0.06	0.87	(0.56, 1.34)	0.22
DASH – tertiles							
T1 (<20)	142/590	1.00	(ref)		1.00	(ref)	
T2 (20-24)	105/512	0.78	(0.58, 1.03)		0.83	(0.62, 1.21)	
T3 (25+)	85/465	0.65	(0.48, 0.89)	0.02	0.76	(0.55, 1.06)	0.23

[1] Model includes dietary score, age, total energy intake and race

[2] Model includes dietary score, age, total energy intake, race, BMI, smoking status, family history, NSAIDs use, education, screening history, Charlson's comorbidity score, and site

Table 4.8 Association between dietary score (categorized) and prostate cancer aggressiveness by race

	AA							EA						
		Crude[1]			Adjusted[2]				Crude[1]			Adjusted[2]		
	High/ Low-Intermediate Aggressive	OR	95% CI	P (trend)	OR	95% CI	P (trend)	High/ Low-Intermediate Aggressive	OR	95% CI	P (trend)	OR	95% CI	P (trend)
MED														
Low (0-3)	55/191	1.00	(ref)		1.00	(ref)		73/353	1.00	(ref)		1.00	(ref)	
Moderate (4-5)	87/338	0.77	(0.52, 1.15)		0.81	(0.55, 1.19)		57/330	0.82	(0.54, 1.25)		0.86	(0.57, 1.29)	
High (6-9)	40/197	0.58	(0.36, 0.93)	0.08	0.56	(0.32, 0.97)	0.19	20/158	0.63	(0.38, 1.04)	0.11	0.65	(0.37, 1.16)	0.34
DASH - quintiles														
Q1 (11-18)	44/155	1.00	(ref)		1.00	(ref)		36/172	1.00	(ref)		1.00	(ref)	
Q2 (19-21)	53/181	1.06	(0.67, 1.67)		0.85	(0.51, 1.41)		40/193	1.25	(0.77, 2.03)		0.87	(0.51, 1.48)	
Q3 (22-23)	27/111	0.85	(0.49, 1.46)		0.69	(0.38, 1.24)		23/136	0.93	(0.53, 1.64)		0.66	(0.36, 1.23)	
Q4 (24-26)	33/151	0.68	(0.41, 1.16)		0.56	(0.32, 0.98)		28/196	0.80	(0.46, 1.39)		0.59	(0.33, 1.07)	
Q5 (27-36)	25/111	0.72	(0.41, 1.27)	0.39	0.62	(0.34, 1.13)	0.55	23/144	1.02	(0.56, 1.86)	0.26	0.66	(0.34, 1.26)	0.40
DASH - tertiles														
T1 (11-20)	80/295	1.00	(ref)		1.00	(ref)		62/295	1.00	(ref)		1.00	(ref)	

T2 (21-23)	54/223	0.79	(0.53, 1.18)		0.87	(0.57, 1.32)		51/289	0.76	(0.50, 1.16)		0.75	(0.48, 1.16)	
T3 (24-36)	48/208	0.70	(0.46, 1.07)	0.22	0.84	(0.54, 1.30)	0.69	37/257	0.61	(0.38, 96)	0.10	0.65	(0.40, 1.06)	0.20

[1] Model includes dietary score, age, and total energy intake

[2] Model includes dietary score, age, total energy intake, BMI, smoking status, family history, NSAIDs use, education, screening history, Charlson's comorbidity score, and site

Table 4.9: Stratification by potential effect modifiers, MED									
		Numeric		Low		Moderate		High	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Main Effect[1]		0.88	(0.82, 0.96)	1.00	(ref)	0.78	(0.60, 1.03)	0.57	(0.40, 0.81)
BMI	**High/Low-Intermediate Aggressive**								
<25	56/295	0.95	(0.79, 1.14)	1.00	(ref)	1.56	(0.76, 3.22)	1.06	(0.45, 2.49)
25 - <30	126/693	0.83	(0.73, 0.94)	1.00	(ref)	0.52	(0.33, 0.81)	0.41	(0.23, 0.70)
30+	150/579	0.94	(0.83, 1.06)	1.00	(ref)	0.95	(0.62, 1.44)	0.71	(0.40, 1.25)
Interaction p-value			0.31						0.11
Age[2]									
<65	159/900	0.97	(0.87, 1.08)	1.00	(ref)	0.97	(0.65, 1.45)	0.86	(0.53, 1.40)
65+	173/667	0.81	(0.72, 0.91)	1.00	(ref)	0.66	(0.45, 0.97)	0.39	(0.23, 0.67)
Interaction p-value			0.0098*						0.049*
Smoking status									
Never	93/555	0.88	(0.76, 1.02)	1.00	(ref)	0.77	(0.47, 1.26)	0.48	(0.24, 0.97)
Former	173/798	0.85	(0.76, 0.95)	1.00	(ref)	0.68	(0.46, 1.01)	0.51	(0.31, 0.82)
Current	66/214	0.95	(0.78, 1.15)	1.00	(ref)	1.24	(0.61, 2.50)	0.88	(0.37, 2.10)
Interaction p-value			0.06*						0.09*

***p-value <0.10, considered statistically significant interaction**
[1] Base model includes age, race, and total energy intake
[2] Model uses age category variable in place of age

Table 4.10: Stratification by potential effect modifiers, DASH quintiles													
		Numeric		Q1		Q2		Q3		Q4		Q5	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Main Effect*		0.96	(0.93, 0.99)	1.00	(ref)	0.97	(0.59, 1.36)	0.76	(0.51, 1.14)	0.63	(0.43, 0.92)	0.67	(0.45, 1.01)
Interaction p-value			0.63										0.97
BMI	**High/Low-Intermediate Aggressive**												
<25	56/295	0.99	(0.93, 1.06)	1.00	(ref)	1.70	(0.69, 4.22)	0.80	(0.26, 2.53)	1.26	(0.47, 3.38)	1.23	(0.42, 3.57)
25 - <30	126/693	0.92	(0.87, 0.96)	1.00	(ref)	0.65	(0.38, 1.10)	0.65	(0.35, 1.22)	0.36	(0.19, 0.68)	0.36	(0.19, 0.70)
30+	150/579	0.99	(0.95, 1.04)	1.00	(ref)	1.25	(0.74, 2.11)	0.90	(0.50, 1.62)	0.86	(0.48, 1.53)	1.20	(0.64, 2.25)
Interaction p-value			0.09*										0.28
Age**													
<65	159/900	0.99	(0.96, 1.03)	1.00	(ref)	1.23	(0.76, 2.01)	1.08	(0.62, 1.88)	0.80	(0.46, 1.38)	1.02	(0.59, 1.79)
65+	173/667	0.93	(0.89, 0.97)	1.00	(ref)	0.76	(0.47, 1.23)	0.60	(0.34, 1.06)	0.54	(0.32, 0.92)	0.47	(0.26, 0.86)
Interaction p-value			0.02*										0.36
Smoking status													
Never	93/555	0.93	(0.88,	1.00	(ref)	0.63	(0.36,	0.60	(0.29,	0.36	(0.17,	0.45	(0.22,

			0.98)				1.19)		1.25)		0.75)		0.92)
Former	173/798	0.96	(0.92, 1.00)	1.00	(ref)	1.12	(0.69, 1.82)	0.77	(0.44, 1.36)	0.76	(0.45, 1.30)	0.72	(0.40, 1.30)
Current	66/214	1.00	(0.93, 1.08)	1.00	(ref)	1.44	(0.66, 3.16)	1.13	(0.44, 2.87)	0.75	(0.31, 1.85)	1.66	(0.58, 4.79)
Interaction p-value			0.04*										0.20

***p-value <0.10, considered statistically significant interaction**
[1]Base model includes age, race, and total energy intake
[2]Model uses agecat variable in place of age

Table 4.11: Stratification by potential effect modifiers, DASH tertiles									
		Numeric		T1		T2		T3	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Main Effect[1]		0.96	(0.93, 0.99)	1.00	(ref)	0.78	(0.58, 1.03)	0.65	(0.48, 0.89)
BMI	**High/Low-Intermediate Aggressive**								
<25	56/295	0.99	(0.93, 1.06)	1.00	(ref)	0.78	(0.38, 1.60)	0.85	(0.41, 1.76)0.75
25 - <30	126/693	0.92	(0.87, 0.96)	1.00	(ref)	0.75	(0.48, 1.18)	0.40	(0.24, 0.67)
30+	150/579	0.99	(0.95, 1.04)	1.00	(ref)	0.81	(0.52, 1.26)	0.99	(0.62, 1.59)
Interaction p-value			0.09*						0.21
Age[2]									
<65	159/900	0.99	(0.96, 1.03)	1.00	(ref)	0.90	(0.60, 1.36)	0.88	(0.58, 1.35)
65+	173/667	0.93	(0.89, 0.97)	1.00	(ref)	0.73	(0.49, 1.08)	0.53	(0.34, 0.83)
Interaction p-value			0.02*						0.25
Smoking status									
Never	93/555	0.93	(0.88, 0.98)	1.00	(ref)	0.60	(0.35, 1.02)	0.52	(030, 0.92)
Former	173/798	0.96	(0.92, 1.00)	1.00	(ref)	0.82	(0.55, 1.21)	0.63	(0.40, 0.98)
Current	66/214	1.00	(0.93, 1.08)	1.00	(ref)	0.90	(0.45, 1.84)	1.10	(0.52, 2.33)
Interaction p-value			0.04*						0.16

[1] Base model includes age, race, and total energy intake
[2] Model uses age category variable in place of age
***p-value <0.10, considered statistically significant interaction**

Table 4.12 Association between dietary score (numeric) and prostate cancer aggressiveness, including age as categorical variable

	OR	95% CI	P(trend)
MED			
Crude[1]	0.89	(0.82, 0.96)	0.003
Adjusted[2]	0.92	(0.85, 1.00)	0.04
DASH			
Crude[1]	0.96	(0.94, 0.99)	0.01
Adjusted[2]	0.98	(0.95, 1.01)	0.22

[1] Model includes dietary score, age (categorical), total energy intake and race

[2] Model includes dietary score, age (categorical), total energy intake, race, BMI, smoking status, family history, NSAIDs use, education, screening history, Charlson's comorbidity score, and site

Table 4.13 Association between dietary score (numeric) and prostate cancer aggressiveness, stratified by race, including age as categorical variable

	AA			EA		
	OR	**95% CI**	**P (trend)**	**OR**	**95% CI**	**P (trend)**
MED						
Crude[1]	0.89	(0.80, 0.99)	0.04	0.89	(0.80, 0.99)	0.04
Adjusted[2]	0.91	(0.81, 1.02)	0.11	0.92	(0.81, 1.03)	0.15
DASH						
Crude[1]	0.97	(0.93, 1.01)	0.11	0.96	(0.92, 1.00)	0.05
Adjusted[2]	0.99	(0.94, 1.03)	0.63	0.96	(0.92, 1.01)	0.16

[1] Model includes dietary score, age (categorical), and total energy intake
[2] Model includes dietary score, age (categorical), total energy intake, BMI, smoking status, family history, NSAIDs use, education, screening history, Charlson's comorbidity score, and site

Table 4.14: Association between dietary score (categorized) and prostate cancer aggressiveness, including age as categorical variable

	High/Low-Intermediate Aggressive	Crude[1]			Adjusted[2]		
MED		**OR**	**95%CI**	**P(trend)**	**OR**	**95% CI**	**P(trend)**
Low (0-3)	128/544	1.00	(ref)		1.00	(ref)	
Moderate (4-5)	144/668	0.79	(0.60, 1.04)		0.86	(0.65, 1.14)	
High (6-9)	60/355	0.59	(0.41, 0.84)	0.01	0.68	(0.47, 0.98)	0.12
DASH – quintiles							
Q1 (11-18)	80/344	1.00	(ref)		1.00	(ref)	
Q2 (19-21)	93/374	0.98	(0.70, 1.38)		1.10	(0.77, 1.56)	
Q3 (22-23)	50/247	0.81	(0.54, 1.20)		0.85	(0.57, 1.28)	
Q4 (24-26)	61/347	0.67	(0.46, 0.97)		0.76	(0.51, 1.13)	
Q5 (27-36)	48/255	0.71	(0.47, 1.06)	0.13	0.92	(0.60, 1.42)	0.36
DASH – tertiles							
T1 (<20)	142/590	1.00	(ref)		1.00	(ref)	
T2 (20-24)	105/512	0.81	(0.61, 1.07)		0.87	(0.65, 1.17)	
T3 (25+)	85/465	0.69	(0.51, 0.94)	0.05	0.81	(0.59, 1.12)	0.40

[1] Model includes dietary score, age (categorical), total energy intake and race

[2] Model includes dietary score, age (categorical), total energy intake, race, BMI, smoking status, family history, NSAIDs use, education, screening history, Charlson's comorbidity score, and site

Table 4.15 Association between dietary score (categorized) and prostate cancer aggressiveness by race, including age as categorical variable

	AA							EA						
		Crude[1]			Adjusted[2]				Crude[1]			Adjusted[2]		
	High/Low - Intermediate Aggressive	**OR**	**95% CI**	**P (trend)**	**OR**	**95% CI**	**P (trend)**	**High/Low - Intermediate Aggressive**	**OR**	**95% CI**	**P (trend)**	**OR**	**95% CI**	**P (trend)**
MED														
Low (0-3)	55/191	1.00	(ref)		1.00	(ref)		73/353	1.00	(ref)		1.00	(ref)	
Moderate (4-5)	87/338	0.77	(0.52, 1.15)		0.83	(0.55, 1.26)		57/330	0.82	(0.56, 1.20)		0.87	(0.58, 1.29)	
High (6-9)	40/197	0.59	(0.37, 0.95)	0.09	0.65	(0.39, 1.06)	0.23	20/158	0.63	(0.38, 1.04)	0.16	0.69	(0.39, 1.22)	0.43
DASH - quintiles														
Q1 (11-18)	44/155	1.00	(ref)		1.00	(ref)		36/172	1.00	(ref)		1.00	(ref)	
Q2 (19-21)	53/181	1.06	(0.67, 1.67)		1.26	(0.78, 2.04)		40/193	0.89	(0.53, 1.47)		0.92	(0.55, 1.56)	
Q3 (22-23)	27/111	0.87	(0.51, 1.50)		0.97	(0.55, 1.70)		23/136	0.76	(0.42, 1.36)		0.75	(0.41, 1.38)	
Q4 (24-26)	33/151	0.71	(0.42, 1.20)		0.84	(0.48, 1.45)		28/196	0.61	(0.35, 1.06)		0.66	(0.37, 1.18)	
Q5 (27-36)	25/111	0.75	(0.43, 1.31)	0.49	1.06	(0.58, 1.92)	0.63	23/144	0.67	(0.37, 1.21)	0.41	0.74	(0.39, 1.41)	0.63
DASH - tertiles														

T1	80/295	1.00	(ref)		1.00	(ref)		62/295	1.00	(ref)		1.00	(ref)	
T2	54/223	0.82	(0.55, 1.21)		0.90	(0.59, 1.36)		51/289	0.80	(0.53, 1.21)		0.81	(0.52, 1.24)	
T3	48/208	0.73	(0.48, 1.11)	0.31	0.87	(0.56, 1.35)	0.80	37/257	0.65	(0.41, 1.02)	0.16	0.71	(0.43, 1.16)	0.36

[1] Model includes dietary score, age (categorical), and total energy intake

[2] Model includes dietary score, age (categorical), total energy intake, BMI, smoking status, family history, NSAIDs use, education, screening history, Charlson's comorbidity score, and site

Table 4.16: Spearman correlation between MED and DASH scores		
	DASH	
MED	Numeric	Tertiles
Numeric	0.53 (<.0001)	
Group (Low, Moderate, High)		0.46 (<.0001)

Table 4.17: Means and standard deviations of selected nutrients and dietary factors across dietary scores

	Total Sample	MED groups			DASH Quintiles					DASH Tertiles		
		Low	Moderate	High	Q1	Q2	Q3	Q4	Q5	T1	T2	T3
Energy (kcal)	2637.2 (1419.4)	2136.3 (1015.9)	2840.5 (1615.62)	3028.6 (1332.1)	2091.2 (935.5)	2485.0 (1233.2)	2575.8 (1261.5)	2973.1 (1478.2)	3197.8 (1882.7)	2253.3 (1116.5)	2613.7 (1240.1)	3150.0 (1748.4)
Protein (g)	93.5 (50.6)	76.0 (34.6)	99.7 (56.2)	109.1 (52.4)	73.2 (35.6)	83.8 (37.9)	92.6 (41.9)	106.8 (54.2)	117.9 (68.6)	77.0 (36.4)	93.1 (43.3)	114.9 (63.8)
Fat(g)	99.6 (58.7)	81.7 (40.5)	107.5 (67.5)	112.2(57.8)	81.9 (38.8)	93.6 (46.3)	98.3 (51.3)	112.0 (62.2)	116.5 (84.9)	86.4 (41.9)	99.8 (52.0)	116.1 (76.8)
Sat. Fat (g)	31.4 (19.8)	27.4 (14.8)	33.9 (23.1)	32.5 (18.6)	26.5 (13.2)	29.6 (16.1)	31.4 (18.5)	35.1 (21.0)	35.4 (28.0)	27.7 (14.4)	31.7 (18.2)	35.7 (25.5)
Carbs. (g)	322.3 (173.4)	256.9 (126.2)	345.5 (191.9)	380.0 (167.7)	241.0 (121.7)	296.1 (144.0)	311.5 (149.4)	375.0 (185.2)	408.7 (212.3)	262.3 (134.2)	321.2 (153.6)	399.7 (204.6)
PUFA (g)	22.7 (13.3)	17.2 (8.8)	24.4 (14.4)	27.9 (14.1)	17.7 (8.8)	21.2 (10.8)	22.1 (10.9)	25.7 (14.0)	27.9 (18.9)	19.0 (9.8)	22.6 (11.5)	27.4 (17.2)
MUFA (g)	38.2 (23.0)	31.1 (15.5)	41.2 (26.6)	43.4 (22.5)	31.6 (15.3)	35.9 (10.1)	37.6 (19.9)	42.8 (24.3)	44.4 (33.6)	33.3 (16.5)	38.1 (20.2)	44.3 (30.3)
Alcohol (g)	18.6 (53.6)	15.5 (48.6)	21.1 (61.1)	18.6 (44.3)	18.0 (44.3)	23.5 (71.2)	17.8 (48.3)	14.5 (44.1)	18.1 (50.0)	21.9 (64.6)	15.6 (39.8)	17.5 (50.8)
Lycopene (mcg)	6532.7 (8637.2)	4429.0 (4737.5)	7052.5 (9944.2)	8831.9 (9838.3)	3619.6 (3505.5)	5026.5 (6029.36)	7378.5 (12278.6)	8303.8 (9058.4)	9465.8 (10250.2)	4248.1 (5147.8)	6895.2 (9853.4)	9046.8 (9938.6)
Calcium (mg)	922.2 (525.0)	838.1 (500.0)	973.5 (563.9)	954.5 (465.5)	657.9 (347.4)	812.4 (461.0)	936.2 (490.5)	1076.3 (513.3)	1216.1 (629.8)	714.5 (405.4)	934.7 (483.3)	1172.8 (587.4)
Vit. A (mcg)	1541.3 (1047.0)	1123.1 (631.2)	1641.1 (1067.3)	2005.0 (1267.8)	925.3 (655.7)	1264.5 (821.0)	1559.6 (782.2)	1815.0 (977.7)	2382.4 (1351.6)	1042.6 (690.3)	1557.2 (885.8)	2157.7 (1234.6)

Vit. C (mg)	172.3 (126.5)	113.7 (81.3)	185.6 (128.8)	238.6 (139.9)	99.9 (86.0)	137.7 (94.3)	172.9 (709.2)	214.2 (130.1)	262.9 (146.3)	113.4 (91.6)	173.9 (111.2)	245.4 (141.0)
Vit. E (mg)	12.7 (7.3)	9.4 (4.8)	13.7 (7.8)	16.1 (7.4)	8.8 (4.5)	11.4 (5.6)	12.5 (6.0	14.9 (7.5)	17.1 (9.7)	9.8 (5.2)	12.7 (6.1)	16.4 (8.9)
Vit. D (mcg)	5.3 (3.8)	4.8 (3.6)	5.6 (4.0)	5.6 (3.6)	4.1 (2.9)	4.8 (3.6)	5.4 (3.7)	6.2 (3.8)	6.4 (4.6)	4.4 (3.2)	5.4 (3.7)	6.4 (4.3)
Fiber (g)	22.2 (11.6)	15.7 (7.1)	23.6 (11.6)	29.4 (12.2)	12.9 (5.5)	18.2 (7.1)	21.7 (7.6)	26.6 (9.8)	34.7 (14.2)	14.9 (6.7)	21.9 (7.9)	31.6 (13.1)
Abbreviations: Sat. Fat, saturated fat; Carbs, carbohydrates; PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids; Vit. A, vitamin A; Vit. C, vitamin C; Vit. E, vitamin E; Vit. D, vitamin D												

Table 4.18: Comparison of men excluded for missing data to study population included in final analysis

Characteristic	Men included in analyses (n = 1899)		Men excluded due to missing data (n=359)		p-value*
	Mean	SD	Mean	SD	
MED Score	4.2	1.6	4.3	1.6	0.11
DASH Score	22.0	4.4	22.3	4.2	0.23
Age	63.1	7.9	63.1	8.2	0.92
Body Mass Index	29.3	5.2	28.9	5.9	0.31
MET hours per week	23.9	23.5	20.3	18.0	0.0069
Total energy intake (kcal)	2482.3	1041.5	3341.7	2456.8	<0.0001
	n	%	n	%	
Aggressiveness[a]					0.041
High	332	17.5	64	23.4	
Low-Intermediate	1567	82.5	210	76.6	
Race					<0.0001
AA	908	47.8	222	61.8	
EA	991	52.2	137	38.2	
Site					<0.0001
LA	980	51.6	247	68.8	
NC	919	48.4	112	31.2	
Education					<0.0001
Less than High School	378	19.9	114	32.0	
High School Graduate/Vo-Tech school	574	30.2	113	31.7	
Some college/College Graduate	676	35.6	27.53	27.5	
Graduate/ Professional Training or Degree	271	14.3	31	8.7	
Smoking Status					<0.0001
Never	648	34.1	91	25.5	
Former	971	51.1	185	51.8	
Current	280	14.7	81	22.7	
NSAIDs use					0.43
No	744	39.2	127	36.9	
Yes	1155	60.8	217	63.1	

Family history in first degree relative					0.92
No	1404	73.9	128	73.6	
Yes	495	26.1	46	26.4	
Screening history					<.0001
None	237	12.5	74	20.7	
DRE only	290	15.3	85	23.7	
PSA only	77	4.1	15	4.2	
DRE & PSA	1295	68.2	184	51.4	
Charlson's Comorbidity Index					0.57
0	954	50.2	167	47.7	
1-3	821	43.2	162	46.3	
4+	124	6.5	21	6.0	

[*] P-value for differences between included and excluded men determined by t-test for numeric variables and chi-square test for categorical variables.

[a] Prostate cancer aggressiveness is defined as the severity of the cancer at diagnosis based on combinations of the Gleason score, morphologic stage, and PSA as follows: high aggressive, Gleason sum ≥ 8 OR PSA > 20 ng/mL OR Gleason sum ≥ 7 and stage T3-T4; low aggressive, Gleason sum < 7 and stage T1-T2 and PSA < 10 ng/mL; intermediate aggressiveness, all other cases.

Table 4.19 : Sensitivity analysis for excluded men						
	All men with missing outcome data excluded		Any man with missing outcome or covariate data excluded		All excluded high aggressive cases set at highest MED/DASH category and low-moderate cases set at lowest MED/DASH category	
	OR	95% CI	OR	95% CI	OR	95% CI
MED (numeric)	0.92	(0.85, 1.00)	0.92	(0.84, 0.99)	0.92	(0.85, 1.00)
MED Low	1.00	Ref	1.00	Ref	1.00	Ref
Moderate	0.88	(0.67, 1.12)	0.85	(0.64, 1.14)	0.86	(0.66, 1.14)
High	0.67	(0.48, 0.94)	0.66	(0.46, 0.95)	0.66	(0.47, 0.93)
DASH (numeric)	0.98	(0.95, 1.00)	0.98	(0.95, 1.01)	0.98	(0.95, 1.00)
DASH Q1	1.00	Ref	1.00	Ref	1.00	Ref
Q2	1.10	(0.79, 1.54)	1.08	(0.76, 1.53)	1.10	(0.79, 1.54)
Q3	0.77	(0.52, 1.13)	0.80	(0.53, 1.21)	0.77	(0.52, 1.13)
Q4	0.73	(0.51, 1.06)	0.71	(0.48, 1.06)	0.73	(0.51, 1.06)
Q5	0.87	(0.58, 1.31)	0.87	(0.56, 1.34)	0.87	(0.58, 1.30)
DASH T1	1.00	Ref	1.00	Ref	1.00	Ref
T2	0.84	(0.63, 1.10)	0.83	(0.62, 1.21)	0.84	(0.63, 1.10)
T3	0.78	(0.57, 1.05)	0.76	(0.55, 1.06)	0.78	(0.57, 1.05)
All models include dietary score, age, total energy intake, race, BMI, smoking status, family history, NSAIDs use, education, screening history, Charlson's comorbidity score, and site						

CHAPTER 5

DISCUSSION

Summary of Results

Higher conformity to the Mediterranean diet (as measured by the MED score) and to the DASH diet (as measured by the DASH score) were associated with decreased odds of aggressive prostate cancer. The associations were statistically significant for numeric measures of dietary quality in simple models adjusted for age, total energy intake, and race. Associations were attenuated when further adjustment for BMI, smoking status, family history, NSAIDs use, education, screening history, site, and comorbidities occurred, though the inverse direction of the associations remained. Though there is not enough evidence to claim healthy dietary patterns improve prostate cancer outcomes, high diet quality is unlikely detrimental for prostate health, and the Mediterranean diet, in particular, was inversely associated with prostate cancer aggressiveness among the highest conformers. There was a significant benefit for both AA men and EA men, though the benefit was slightly greater for EA men than AA men. Age modified the association between diet quality and prostate cancer aggressiveness: men aged 65 and older were shown to have a statistically significantly greater benefit from higher MED and DASH scores than men younger than 65 years of age.

Significance of Findings

Previous research that has examined the association between Mediterranean diet adherence (measured by the MED or aMED scores) and prostate cancer outcomes have

largely found modest, statistically not significant inverse relationships (Ax, Garmo et al. 2014; Bosire, Stampfer et al. 2013; Kenfield, Du Pre et al. 2014; Möller, Galeone et al. 2013; Muller, Severi et al. 2009). However, this study found a statistically significant inverse relationship between MED score and prostate cancer aggressiveness even after adjustment for potential confounders. Men in the highest level of MED score (score=6-9) had 34% lower odds of aggressive prostate cancer compared to those with the lowest scores (score=0-3). The sample population of this study is unique in that it included AA and EA American men in equal proportion; previous research conducted with American men sampled men from the NIH-AARP and Health Professionals Follow-up Study cohorts represented mostly EA men (Bosire, Stampfer et al. 2013; Kenfield, Du Pre et al. 2014). Other research on *a priori* dietary patterns and prostate cancer outcomes was based on Australian and Swedish populations (Muller, Severi et al. 2009; Ax. Garmo et la. 2014; Möller, Galeone et al. 2013). The scoring in this study was consistent with the Kenfield study (2014) and Möller study (2013); the Kenfield sample had a greater number of participants in the 'high adherence' category (29.2% vs. 21.9%), though the average MED score in the Möller study for both cases and controls was similar to this one (4.4/4.4 vs. 4.2/4.0). Bosire, et al. (2013) and Ax, et al. (2014) used the alternative MED scoring systems, though the score distributions were similarly distributed in both studies were similar to this sample; Muller, et al (2009) compared quartiles, and the average aMED score was consistent with averages (4.4 for both cases and controls) seen in this study. The case-only sample consisting of half AA men and half EA men, combined with the NCI-modified FFQ used to assess diet, may contribute to the deviation of this study's results from previous research.

This is the first known study to evaluate conformity to the DASH diet in relation to prostate cancer aggressiveness, though previous work has examined DASH diet adherence in relation to other cancers. Anic, et al. (2015) found that greater adherence to the DASH diet reduced the risk of lung cancer in former smokers, while another study found that higher DASH scores were significantly associated with decreased risk of colorectal cancer for men (Jones-McLean, et al. 2015; Dixon, Subar et al. 2007). Americans with the highest DASH scores had lower cancer mortality than those with the lowest scores in multiple studies (Liese, Krebs-Smith et al. 2015; Harmon, Boushey et al. 2015; Schwingshackl, Hoffman 2015). The results of this study further corroborate previous research that suggests that healthy eating, in accordance with the DASH Eating Plan, reduces the risk of several cancers, including aggressive cancer of the prostate.

While both the MED and DASH scores are meant to grade healthiness of diet, the two have different criteria that define healthiness. All grains are considered beneficial in MED scoring, while DASH scoring only considers whole grains as healthy; conversely, the MED score classifies all dairy as negative, whereas low-fat dairy contributes positively to the DASH score. Fish, but no other animal protein, are positively scored for MED; fish are not considered separately for DASH, but only red and processed meats contribute (negatively) to the DASH score. The MED also considers moderate alcohol and high unsaturated- to-saturated ratio fat intakes beneficial to health; the DASH does not account for consumption of either, but does discount high sodium and sugary beverage consumption. Vegetable, fruit, nut, and bean consumption in both patterns is considered positively. The differences between the two scoring schemes are reflected in their moderate correlation (see Table 4.16).

Neither dietary pattern measure showed significant differences by race. To the best of our knowledge, no other studies have examined total dietary quality and prostate cancer outcomes stratified by race, so further research is needed to corroborate our findings. Higher scores on both dietary pattern measures were modified by age, with a significantly greater benefit seen in men aged 65 and older compared to men younger than 65 years of age. There is evidence that healthy eating and cancer mortality are not associated in older men but midlife diet may affect aging (Nobbs, Yaxley et al. 2015; Assmann, Lassale et al. 2015). The results of this study suggest that healthy diets in later life may still impact cancer aggressiveness.

Strengths and Weaknesses

This study has several strengths and weaknesses. A main weakness of this study was the recruitment process, which did not enroll equal number of research subjects based on aggressiveness of disease. Typical case-control studies recruit participants based on disease diagnosis, with the intent to maximize power to analyze the disease of interest. In the current study, as all participants had prostate cancer, the ability to detect differences by cancer aggressiveness was limited by the smaller sample size of high aggressive cases. Only 17% of the men included in analysis were diagnosed with high aggressive prostate cancer, limiting statistical power. Furthermore, a lack of healthy control group and inclusion of only AA and EA men somewhat limits the generalizability of this study's findings.

Another potential weakness of this study was the measurement of the dietary data. The NCI DHQ, modified to include regional dishes of North Carolina and Louisiana, assessed participants' diet for the year prior to diagnosis. Food frequency questionnaires

can be inaccurate, as information is forgotten, misremembered, or purposefully falsified. The quality of food frequency questionnaire data is not regarded as highly as alternative assessment methods, as complete history is impossible because the questions were closed-ended (Willett 2012). Even assuming complete accuracy of dietary information, only food intakes for the year prior to diagnosis were assessed. Due to the long latency and slow progression periods possible for prostate cancer, diet for the year before diagnosis likely has less impact on prostate cancer outcomes than mid-life or lifetime diet.

Due to missing outcome, exposure, and covariate data, 359 men were excluded from analysis. When these men were compared to the final sample, there was a significant difference in outcomes between included and excluded men, with excluded men (with diagnostic measurements) more likely to have high aggressive prostate cancer. When the excluded men with available aggressiveness scores were included in the analysis, there was no change in the association estimates; this remained the case when previously excluded men with high aggressive prostate cancer were artificially given the highest dietary scores and the men with low to intermediate aggressive prostate cancers were given the lowest dietary scores. Because the associations were unchanged by including previously missing subjects in direct opposition to the hypothesis, it is unlikely that selection bias affected the association estimates.

Despite these weaknesses, this study also had a number of strengths. Because recruitment was based on race rather than disease status, the sample population was ideal to study racial differences in prostate cancer aggressiveness. While no significant racial differences were found in this study, the study's design lends confidence to the

conclusion that the effect of overall diet quality on prostate cancer aggressiveness is similar for AA and EA men. The recruitment design also limited the recall bias commonly associated with case-control studies and dietary recalls. All participants had diagnosed prostate cancer, and it is unlikely that high aggressive cases remembered their eating habits differently than men with low or intermediate aggressive disease. Also, due to the high prevalence of indolent prostate cancer in the American population, enrolling only men with confirmed prostate cancer and utilizing low-intermediate aggressive cases as the comparison group may have reduced outcome misclassification. In traditional case-control studies, some "controls" may be erroneously assumed to be disease-free because they had not been screened previously. Another strength of PCaP is that data on a large number of potential confounders and effect modifiers were collected from research subjects and used in the analyses. However, residual or unmeasured confounding cannot be ruled out in any observational study. Results in the fully adjusted models were attenuated from those in the simple models, suggesting some confounding by the included covariates.

Recommendations for Future Research

Higher conformity to Mediterranean and DASH diets was associated with lower odds of aggressive prostate cancer. Further analyses using this dataset should examine each component of the MED and DASH diets and their associations with prostate cancer aggressiveness. The Mediterranean diet differentiates fish consumption from other protein sources, unlike the DASH Easting Plan, which does not. Since fish has been shown to decrease prostate cancer risk in several previous studies, determining if high scores in the fish component of the MED score are associated with prostate cancer

aggressiveness would further clarify the possible benefits of consuming fish and omega-3 fatty acids. Similar analyses using each pattern's components could better define the potential benefits and harms of specific food groups.

The modification of the association between dietary pattern and aggressiveness by age should be further explored. Diet was measured only in the year prior to diagnosis for all men, regardless of age, so we were unable to examine diet at other life stages or changes in diet over time. Possible effects of improving diet at various stages of life would help explain the timeline for dietary modifications on health and shape dietary recommendations for each age group.

In conclusion, it was found that men who consume diets with higher conformity to the Mediterranean diet and the DASH Eating Plan were less likely to be diagnosed with high aggressive prostate cancer than those who scored lower; this association was modified by age, with men aged 65 and older receiving greater benefit from a healthy diet in relation to prostate cancer stage than men younger than 65. This study contributes to the body of literature on overall diet and prostate cancer, particularly as it relates to aggressiveness of disease. While previous studies have been inconclusive on the association between *a priori* dietary patterns and prostate cancer risk, the results of this study suggest that an overall healthy diet may protect men from aggressive prostate cancers.

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