Examining the Role of Adiposity in Racial and Ethnic Disparities in Prostate Cancer

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God is good…all the time.

This work is dedicated foremost to my mother, Carolynne E. Martin, and the Martin Clan from whom she descended. I will be forever grateful for her sacrifice, faith, and encouragement.

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ACS	American Cancer Society
AIM	Ancestry informative marker
BDNF	Brain-derived neurotrophic factor gene
BMI	Body Mass Index
BMR	Basal metabolism
CDC	Centers for Disease Control and Prevention
d.f.	Degrees of freedom
DRE	Digital rectal exam
DXA	Dual-emission X-ray absorptiometry
EBRT	Electron beam radiation therapy
FA	Fatty acid
FASN	Fatty acid synthase gene
FTO	Fat mass and obesity-associated (aka alpha-ketoglutarate-dependent dioxygenase)
GLST	Generalized lease squares trend
HC	Hip Circumference
IGF	Insulin-like growth factor
IGFBP	Insulin-like growth factor binding protein
IL-6	Interluken-6
KCTD15	Potassium channel tetramerisation domain containing 15 gene
LBM	Lean body mass
MC4R	Melanocortin receptor 4 is a protein
MeSH	Medical subject headings
MLXIPL	MLX Interacting Protein Like Protein
MTCH2	Mitochondrial carrier homolog 2

LIST OF ABBREVIATIONS (continued)

NCOA	National Change of Address
NDI	National death index
NEGR1	Neuronal growth regulator 1
NF-kB	Nuclear Factor-Kappa Beta
NLM	National Library of Medicine
PCa	Prostate Cancer
PiK3	Phosphatidylinositol 3-kinase
PSA	Prostate-specific antigen
REE	Resting energy expenditure
RMR	Resting metabolic rate
SAT	Subcutaneous adipose tissue
SCD-1	Stearoyl-CoA desaturase 1
SNP	Single nucleotide polymorphism
SREBPF1	Sterol regulatory element binding protein
SSA DMF	Social Security Administration Death Master File
TEE	Total energy expenditure
TNF-α	Tumor necrosis factor-alpha
TRUS	Transrectal ultrasound
US	United States
USPS	United States postal service
VAT	Visceral adipose tissue
VEGF	Vascular endothelial growth factor
WC	Waist Circumference
WHO	World Health Organization

LIST OF ABBREVIATIONS (continued)

WHR	Waist to Hip Ratio
WLS	weighted least squares

SUMMARY

Black men have the highest prostate cancer rates of any racial group. Recent United States (US) statistics show that the incidence of prostate cancer in Black men is 1.5 times the incidence in all other races combined, and 1.6 times that of their White counterparts. The death rate in Black men is 2.3 times the rate in all other races, and 2.4 times that of White men. Prostate cancer is the most commonly diagnosed cancer in US Black men, accounting for 40% of their cancer diagnoses across all sites in 2011.Various biologic, behavioral, demographic, contextual, and environmental factors are suggested components of persisting prostate cancer disparities. The contribution of body composition to these racial and ethnic disparities in occurrence and course remains unclear. The overarching objective of this work is to use available data to clarify the role of adiposity in prostate cancer outcomes, with special consideration of its role in disparities observed in Black men.

In light of the objective, two specific aims were put forth for this dissertation. Aim1 was to conduct a systematic review, with meta-analysis, to empirically synthesize the current literature to elucidate the association between adiposity (defined as body mass index (BMI), waist circumference (WC), and waist-hip ratio (WHR) and observed racial disparities in prostate cancer outcomes (incidence, progression, and mortality). Aim2 used national-level prospective cohort data to examine the association between central adiposity and prostate cancer outcomes, exploring possible confounders and effect modifiers, particularly race.

Data for Aim1 was obtained by searching the US National Library of Medicine National Institutes of Health PubMed database for English articles published through October 1, 2011. Criteria for selection were: 1) An adiposity related factor (BMI, WHR, etc.) was the exposure of interest associated with a prostate cancer outcome (i.e. diagnosis, progression, mortality); 2) The participant sample included men of predominant African ancestry (AA) (e.g. Black, African American, Jamaican); and 3) Race or ethnicity-specific effect estimates for prostate cancer occurrence, mortality, or

progression were reported in the manuscript, particularly AA-specific estimates. Adjustment for race in a multivariate model alone was not sufficient for inclusion in the review analysis. No reviews, editorials, or comments were included in the review results, although they were cited for background content.

Current prostate cancer reviews do not adequately address the role of adiposity in observed racial and ethnic disparities. Reviews which considered adiposity, particularly BMI, while also addressing racial disparities in prostate cancer, primarily focused on racial disparities in screening relative to incidence, progression, or mortality. Occurrence and outcomes articles often did not present race-specific effect estimates. Most studies treated race as a confounder, and adjusted for it in multivariate models, without reporting stratified analyses.

The available literature suggests a unique role for adiposity related factors (i.e. body size, and body fat distribution) in observed racial differences in prostate cancer occurrence, progression, treatment efficacy, aggression, and cause-specific mortality. The literature was lacking in studies robust with AA participants, prohibiting the reporting of race or ethnicity-specific estimates for these men. This was especially apparent in the basic, molecular, biologic, and genetics literature dedicated to the role of lipids, body fat, and body size in prostate cancer.

The cohort analysis for Aim2 explored associations of WC, HC, and WHR with risks of incident prostate cancer and prostate cancer-specific mortality. Estimates for central adiposity associated overall prostate cancer risk, as well as separately for localized and advanced disease, were based on 142,003 male participants, ages 50-71, from the NIH-AARP Diet and Health Study. At baseline, participants completed dietary, lifestyle, and medical history questionnaires, which ascertained information on height, weight, HC, and WC. During up to 11 years of incidence follow-up time, 12,165 prostate cancer cases (including 1,128 advanced cases) were identified. Four hundred and fourteen deaths, with prostate cancer as the underlying cause, were identified during a maximum of 13 years of mortality follow-up.

Cox models were fit, with age as the underlying time metric, to estimate associations between WC, HC, WHR, and incident and fatal prostate cancer risks. Adjusted models included variables for race, educational attainment, physical activity, personal history of diabetes, family history of prostate cancer, and prostate cancer screening history.

Waist circumference was inversely associated with prostate cancer incidence (overall and localized disease, specifically) and positively linked to prostate cancer-specific mortality in these men. Larger hip circumference was inversely associated with prostate cancer occurrence incidence (overall and localized disease, specifically), and positively associated with mortality. However, WHR was unrelated to any of the endpoints. Adjustment for BMI attenuated the significance of many WC and WHR findings; HC estimates tended to maintain their significance in the presence of BMI adjustment. We were unable to detect a significant association between WC and prostate cancer when the analytic sample was limited to Black participants (n = 2722; 373 cases; and 18 deaths).

Worldwide, prostate cancer-specific incidence, morbidity, and mortality are highest in AA men. The distinct contributions of central adiposity to prostate cancer etiology in general, and persisting prostate cancer racial disparities, in particular, are unclear in the literature. Our results highlight the need for further research on apparent WC and HC associations with prostate cancer occurrence and mortality. Ensuring racial and ethnic diversity among research participants will be crucial to enable disparities research, which could illuminate mechanisms for further study, and identify targets for intervention.

I. INTRODUCTION

A. Background and Significance

Prostate cancer is of great public health concern. The highest incidence rates occur in Western Europe and the Americas (1). The probability of developing an invasive prostate cancer among men of all races in the United States (US) from birth to death is 1 in 6(2). According to the American Cancer Society (ACS), prostate cancer comprises 29% of all incident cancer cases and 11% of all cancer deaths in US men, second only to lung cancers (2). Prostate cancer-specific death rates have been declining (2). In US data spanning 1990 to 2006, death rates declined by 39% (15.01 absolute difference in rates) (3). Between 1992 and 2006, the incidence declined an average of 3.9% per year (3).

For all cancer sites combined, Black men have a 19% higher incidence rate and a 37% higher death rate than White men (3). Black men have the highest incidence and mortality rates compared to all other races (146.3 per 100,000 and 56.3 per 100,000, respectively) (3). The death rate for Black men is on average 20% higher than that of White men, despite overall declines in national rates in both groups since the early 1990's (2). Incidence of prostate cancer in Black men is 1.5 times the incidence in all other races combined, and 1.6 times that of their White counterparts (3). Death due to prostate cancer in Black men is 2.2 times the death rate in all other races, and 2.4 times that of White men(2). Black men have more distant stage tumors at diagnosis, and have lower 5-year survival rates compared to all other races irrespective of tumor stage (3). Various demographic, behavioral, socio-contextual, and environmental factors have been put forth as components of the persisting racial disparities in prostate cancer outcomes (1). Studies have found higher rates of recurrence, and aggressive (high grade) disease in Black men as compared to White men (4, 5). Explanations for racial and ethnic disparities in incidence, morbidity, and mortality span socio-demographic, behavioral, nutrition, genetic, and differences in approach to treatment (6, 7).

Many researchers have called for multifactorial approaches to explore and explain these disparities, which focus on the interactions between biologic and social factors (8, 9). In order to elucidate causes of clearly observed racial and ethnic disparities in prostate cancer, a paradigm shift must occur. Effective epidemiologic studies on these disparities must collect anthropometric, environmental, and occupational exposure, genetic, socio-demographic, cognitive, behavioral, dietary, and medical history data from the individuals involved. Traditional studies pick a few of the aforementioned factors to explore alongside the outcome (10), but a "cells to society" approach, which incorporates methods from molecular, genetic, social, and classical epidemiology, can provide critical new insights into the causes of disparities.

1. Physiology and measurement of energy balance and adiposity

Adiposity is the state of having excess body fat. This excess fat is a manifestation of energy imbalance, or the net effect of diet, physical activity, metabolic function, and genetics on body size. Obesity, defined as a body mass index (BMI) $\geq$30 kg/m^2, is a growing public health issue (11, 12). As of 2007, 66% of US adults were overweight or obese, with racial and ethnic minorities having the highest rates of obesity compared to their White counterparts irrespective of age, gender, or socio-economic status (12). Non-Hispanic Black women have the highest prevalence of obesity, followed by Black men (12).

The primary causes of obesity are sedentary lifestyle and diet (12). Energy taken in exceeds energy expended, resulting in weight gain in the form of excess fat. Basal metabolism (BMR), resting energy expenditure (REE), and resting metabolic rate (RMR), the energy expended to maintain life supporting bodily functions, account for the majority of daily energy expenditure (13). The greatest source of variation in energy balance comes from the interplay of dietary intake and physical activity patterns (13). One's BMR itself varies by age, height, sex, stress, pregnancy or lactation, hormonal status, illness, injury, and smoking among other factors. In addition to BMR, RMR, and REE, duration,

frequency and intensity of physical activity determines total energy expenditure (TEE), and thus body composition (muscle mass versus body fatness) (13). Lean body mass (LBM) is an important component of energy balance. Lean or non-adipose material, like bone, muscle tissue, and water, may have lower metabolic activity than organs, but they consume much more oxygen (have higher metabolic rates) than adipose tissue (13). Thus, LBM determines one's RMR. Resting metabolic rate is a crucial component of TEE as it is the major determinant of body composition, thyroid function, sympathetic nervous system function, and thus body size.

a. Body mass index has limitations as an adiposity measure

Body weight is the net result of the complex physiologic balance between energy intake and output, or the sum of RMR, thermic effect of food, and activity energy expenditure (13). Body weight is often measured in kilograms (kg) or pounds (lbs.), which are scientific units of mass; weight is mass per gravity. BMI, the most widely used body size measure, uses the Quetelet Index (kg/m^2) to provide an easy to calculate, statistical proxy, for adiposity (13). It does not measure body fatness in any way. Rather, it assumes that any excess mass, given ones height, is due to the presence of fat instead of muscle (13). According to the US Centers for Disease Control and Prevention: an underweight BMI is below 18.5 kg/m^2; a healthy weight falls between 18.5 and 24.9 kg/m^2; 25.0 to 29.9 kg/m^2 is overweight, and 30 or greater is obese (12). Outside of the US, classifications of BMI vary (14).

b. Other measures of adiposity

There are other, more direct, methods of assessing body fatness. Hydrodensitometry Weighing or 'Underwater Weighing' estimates whole body density by measuring body volume (15). Skinfold measurements use calipers at various points on the body to estimate fatness (often combined with Hydrodensitometry) (16). Dual Energy X-ray Absorptiometry (DXA) uses the abruption rate of low-dose x-rays to distinguish total body mass, lean mass components, and fat tissue (17). Other methods include: Near Infrared Interactance; Magnetic Resonance Imaging, Total Body

Electrical Conductivity, Computed Tomography; Air Displacement ("Bod Pod"); and Bio Electrical Impedance (18). Although the aforementioned techniques provide more precise insight into the amount of adipose versus lean body mass, relative to BMI, these methods may not be pragmatic for large population-based studies, due to some of their cost, methodologic assumptions, as well as time and technology requirements (18).

2. Waist circumference: Estimating visceral adiposity

Waist circumference (WC), hip circumference (HC), and waist-to hip ratio (WHR) provide estimation tools for body fat distribution and assessing body shape (15). While waist-based measures do not provide insight into body weight, they have low error in estimating body fat in most body types, and provide insight into the type of obesity at hand (i.e. visceral android or gynecoid obesity) (19). Visceral fat or central adiposity, often apple shaped in men (upper body or abdomen), and pear shaped in women (hips or thighs), has been associated with inflammation, metabolic syndrome, cardiovascular disease, and cancers, independent of total body fatness (18, 20). Intra-abdominal fat surrounds our most crucial organs, having a strong effect on endocrine function in those tissues, and thus disease risk (18, 20).

Studies have suggested that WC and WHR provide DXA-comparable estimates of intra-abdominal fat in non-obese men; DXA is often considered the gold standard (18). Waist circumference has been shown to predict total abdominal fat and average visceral fat better than WHR, providing average visceral fat estimates comparable to DXA in large population based surveys (18). Waist circumference was also found to be the best predictor of central adiposity in adult men. Studies have found that WC and WHR were better predictors of morbidity and mortality in older men, than BMI, while BMI was a better predictor in men under 65, providing evidence that measuring both BMI and WC is beneficial in large population-based studies (18, 21). The demonstrated tendency for underreporting (attenuated measurement) of WC by self-report, did not statistically significantly reduce

the correlation between self-reported measures and technician reported measures in two large population-based studies (18). This bodes well for the utility of WC as a reliable self-report measure of adiposity and body shape in addition to BMI.

3. Visceral adiposity in prostate cancer disparities

Visceral adipose tissue associates with all-cause morbidity and mortality, independent of body mass (21). Despite having higher BMI's compared to their White counterparts, several studies suggest similar or lower visceral adipose tissue deposition among Black men and women compared to their White counterparts (20, 22, 23). Racial differences in visceral adiposity are not completely explained by differences in diet and physical activity (19).

Difference in subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) (24) across race are inversely related to current BMI associations with race, suggesting a complex interplay between adiposity and disease not completely captured by measuring BMI alone. Subcutaneous adipose tissue was found to be higher in White men before adjustment for age, total fat mass, and smoking, after which, SAT was higher in Black men (25). The pathophysiology of obesity and disease may vary within and across race and gender groups. Careful consideration for mechanisms unique to those with high levels of African ancestry should be made when exploring the role of adiposity in etiology of disease.

4. Pathways for the involvement of adiposity in prostate cancer disparities

Adiposity, may contribute to tumorgenesis by increasing free fatty acids and cytokines like tumor necrosis factor-alpha, while suppressing adiponectin (26, 27). The ensuing insulin resistance promotes insulin-like growth factor bioavailability, creating a commensal environment for cell proliferation, and down regulating apoptotic signaling, and thus tumor development (27). Obesity upregulates the pro-cancer effects of androgens, leptin, interleukin-6, Vascular endothelial growth factor, insulin, and IGF-1, while down regulating anti-cancer adipokines (i.e. IGFBP-3 and adiponectin)(28). The IGF-1 axis hypothesis fails to consider paracrine mechanisms (29). The paradoxical directionality of

free IGF with body fatness and weight loss may explain some of the inconsistency in observed cancer-adiposity association studies(29); insulin mediated pathways (i.e. metabolic syndrome) are clearly associated to prostate cancer progression(30, 31). Other probable mechanisms underlying observed associations between adiposity and cancer include the adipose tissue hypoxia hypothesis, migration of adipose derived stromal cells, obesity induced inflammation, and oxidative stress and obesity-cancer related genetic co-expression and epistasis (29, 32-38).

Results from studies of body mass index (BMI) and prostate cancer risk have been mixed. Obesity has been shown to be both inversely and directly associated with prostate cancer incidence, progression (30, 39-41). On the other hand, a clearer relationship has emerged between BMI and prostate cancer mortality (42) . In their 2007, analysis of the National Institutes of Health-AARP (NIH-AARP) Diet and Health Study cohort, for example, Wright et al. demonstrated that morbid obesity ($\geq$40kg/m^2), and weight change from age 18 to baseline, were positively associated with fatal prostate cancer (43).

Most studies on the prostate cancer – adiposity association have relied on BMI, without consideration of other important measures related to body composition: actual adiposity, energy balance, or body fat distribution. Studies have noted differential all-cause mortality being associated with measures of body fat distribution (i.e. WC and WHR) (21, 44, 45). In 2000, Hsing et al. noted an association between prostate cancer risk and high WHR (18, 46). Zilli et al. recently found that greater central adiposity was "strongly associated with adverse pathologic features in patients with localized prostate cancer"; they observed a direct association between WC and Gleason sum (47). High levels of VAT were also associated with risk for secondary malignancies (47).

5. The relationship between adiposity and prostate cancer disparities

Very few papers have looked at prostate cancer-specific mortality (or risk) accounting for: dietary patterns, levels of physical activity, metabolic comorbidities (i.e. diabetes), smoking, drinking,

socio-demographic risk factors, anthropometric measures, and molecular markers (i.e. fatty acids, adipokines) (4). Even fewer have attempted to explore the combined contribution of molecular, socio-demographic, and anthropometric factors to racial disparities in prostate cancer risk, progression, and outcomes.

a. Fatty acid intake

Although only one half of the energy balance equation, the other being physical energy expenditure, excess fat intake is an important source of adiposity and a likely component of the contribution that adiposity makes to racial and ethnic disparities in prostate cancer (48, 49). Dietary fat intake varies by race for socio-cultural reasons (50, 51). There are structural determinants of access to low-fat foods, and cultural patterns in dietary fat consumption (52). Just as built environment may mediate associations between race and obesity; the availability safe open or recreational space may limit physical activity (53-55). Neighborhoods may systematically be unsafe, and perceived to be of low-profit potential by grocery stores and food corporations, limiting distribution of fresh foods to these areas (56). Race and neighborhoods cluster, thus food, particularly, fat intake cluster around race (53-55). Research suggests that low nutritional quality higher fat foods are strategically marketed to ethnic minorities (57, 58). Increased consumption of fat heightens the possibility that one may not be able to balance the energy equation; not expending enough energy to avoid storage of the excess fat consumed. High fat diet is associated with PCa risk and progression (51, 59, 60). Further understanding of the diets of Black men is a crucial aspect of the role of adiposity disentangling PCa racial disparities.

b. Molecular-level factors

Social, behavioral, and contextual determinants of health make a well-established contribution to observed disparities in prostate cancer outcomes in men of predominant African ancestry as compared to men with ancestries of other origins, particularly European (4). A biopsychosocial paradigm of the determinants of health disparities acknowledge those contributing

factors, including access to and patronage of screening, differences in treatments offered and accepted, while incorporating the possible role of biologic factors such as genetics (8). Ideally, studies would have robust genetic information to accompany socio-demographic, clinical, behavioral, and cultural information of participants in cancer disparities research.

Adiposity contributes functionally to disparities in detection, treatment efficacy tumor progression, and fatality (61). Numerous studies have noted the attenuating impact of excess mass (high BMI) on the sensitivity of PSA testing (62). Naturally occurring molecular markers of lipid metabolism and insulin regulation, such as HbA1c, C-peptide, leptin, and adiponectin, have been shown to have an inverse relationship with PSA levels (63). The higher these blood borne metabolic molecules, the lower PSA levels; the effect was particularly pronounced in Black men (63). These disparities findings speak to the need to understand the activity and interactions of molecules involved in metabolism. Particularly, how they affect our ability to detect early stage tumors in Black men, as they have the highest prostate cancer incidence rates. Spangler et al. recently reported a statistically significant association between obesity and treatment failure in Black men, but not in white men (64).

6. Genetics, energy balance, and adiposity

Thousands of single nucleotide polymorphisms (SNPs) on various genes including FTO, MC4R, FASN, NEGR1, SCD-1, KCTD15, MTCH2, and BDNF (65), have been found to be associated with obesity, insulin regulation and or lipid metabolism using linkage, candidate gene, and genome-wide methods (66). The functional significance of these SNPs remains unclear, as they are involved in various pathways associated with various contributing components of adiposity, including complex hormonal and neural networks (66). Genes involved in the manifestation of adiposity may regulate not only energy expenditure, but intake, and partitioning (storage as fat versus protein or carbohydrate). The FTO gene was the first with common association with BMI, and obesity, in particular (67). In human and animal studies, FTO has been shown to regulate appetite, lipolytic activity (decreased) in adipocytes, and

interact with physical activity (risk allele association with obesity had an inverse relationship with activity) (67-69).

Increased biogenesis of fatty acid (FA) synthase, key for termination of FA synthesis, has been observed in tumors and precursor lesions (70). This increase in lipogenesis confers a proliferative, and thus survival, advantage in tumor cells (27). Genetic variations in FA synthesis genes, including FASN, SREBPF1, and MLXIPL have been associated with BMI (71). Although not consistently or directly associated with cancer risk, their strong association with BMI renders them important in disentangling the complex relationship between adiposity and pathobiology of prostate cancer (70, 72, 73). Recent findings suggest that SNPs on the FASN gene interact with BMI to confer increased risk for aggressive and or lethal prostate cancer (34).

The FASN gene regulates energy metabolism, appetite, insulin sensitivity, and body weight by way of the hypothalamic neuron system, hepatocytes, and adipose tissues (34). This enzyme is involved in the metabolic activity of tumors via *de novo* lipogenesis (34). Both pathways influence prostate cancer progression and fatal outcome in men with elevated BMI ≥25 kg/m2 (74). Single nucleotide polymorphism on FASN had significant joint effects with high BMI associated with prostate cancer risk and fatality (74). Its expression is mediated by BMI, as overweight men are impacted by the presence of the variant differently than lean men (74). This interaction is evidence of a plausible biologic mechanism linking obesity to prostate cancer outcomes.

7. <u>Variation in adiposity genes by ancestry</u>

There are findings, which suggest differences across levels of BMI and race racial in expression of genes which moderate the metabolic molecules (i.e. adipokines and fatty acids [FA]) crucial for energy balance (75, 76). Much of the genome wide association (GWA) research to identify genes and SNPs associated with BMI, appetite, and lipid metabolism has been conducted in exclusively European ancestry populations (69). The loci identified in these studies have been the loci of focus for

investigations into the associations between adiposity genes and prostate cancer occurrence and progression, but research suggests that loci of importance for prostate cancer and BMI may vary by ancestral origin (77-79). For example, the association between *FTO* and weight and hip circumference found in people with predominantly European ancestry replicated in Hispanic Americans, but not African-Americans (69).

Ancestry is theoretically independent of the socially constructed racial groups that we often use to discuss health disparities. It is a crucial conceptual component of disparities research hoping to identify molecular targets for intervention (80, 81). Markers of import in individuals with ancestral predominance of European or Asian origin may be systematically different than individuals with predominantly African ancestry, for anthropologic and genetic reasons independent of the racial construct (81-83). The social institutions, social networks, and experiences structured by ascription to the racial paradigm inherently structure biology, by influencing mating patterns and exposures (likely environmental) uniquely tied to particular racial and social position. Ancestry informative markers (AIMs) are polymorphisms that occur in significantly different frequencies between populations which come from different geographical areas (83, 84).Three factors, which contribute to ancestral informativeness of these markers include: 1.) allele frequency differences between the parental populations (δ), 2.) the respective genetic contribution of each founding population to the admixed population (m), and 3.) Parental population allele frequencies, p, (irrespective of δ) (85).

a. Racial and ancestral variation in 8q24

The intermediary role of energy balance in prostate cancer racial and ethnic disparities could be best understood by clearly capturing the potential diversity of biologic phenomena along racial and ancestral lines, rather than assuming ubiquity of scientific findings based solely on research participants of racial predominance. Gathering information and specimens from racial and ethnic minorities may take concerted and unique research recruitment efforts. Examples of the

importance of sensitivity to diversity in research are findings relating to the prostate susceptibility locus 8q24 (78, 86-88). Initial prostate cancer risk associations with associations with 8q24 identified associations with risk variants in the region (e.g. rs1447295 and rs6983267), which did not hold in analyses looking at prostate cancer risk in AA men (89). Robins et al. confirmed the importance of the 8q24 region as a susceptibility loci, but revealed that there were regions, likely novel to men of predominant African ancestry (rs7008482 and rs16901979), which significantly predicted risk in addition to the regions reported in studies using Asian and European samples (89). Recently Murphy et al. reported ethnic and geographic variation in 8q24 risk associations between Caribbean and West African men of predominant African ancestry, suggesting the importance of considering the ethnic diversity of men who may comprise the Black racial group when exploring prostate cancer susceptibility loci (77).

b. Racial and ancestral variation in prostate cancer susceptibility loci

In a recent GWAS of prostate cancer associated variants, which included variants previously identified in European and Asian samples, Haiman et al. reported that only one-half of the 30 previously identified variants replicated in their large AA sample (3425 cases and 3290 controls). They identified 6 additional variants in previously reported regions, which better associated with risk in AA men, but not in European or Asian men (79). Taken together, these findings suggest that there may be unique constellation of susceptibility variants associated with African ancestry, and that the diversity of African ancestral groups may lead prostate cancer researchers to novel regions for exploration. It is imperative that these findings are extended to explore the lipid, and adiposity related loci. Detailed explorations of previously reported adiposity gene findings must be examined in AA men, and considering body size in (or adiposity associated loci) in prostate susceptibility research at this level will assist in disentangling mechanisms underlying observed disparities.

8. Significance

It has been shown that prostate cancer outcomes vary across BMI. Thus far, excess fat likely plays more of a role in progression than occurrence (39, 90-92). It is unclear how adiposity contributes to prostate cancer racial and ethnic disparities in the context of established prostate cancer risk factors.

B. Objectives and Aims

The overarching objective of this work is to use available data to clarify the role of adiposity in prostate cancer outcomes, with special consideration of its role in disparities observed in Black men when compared to White men. In light of the objective, two specific aims were put forth for this dissertation:

1. Specific aim 1

Conduct a systematic review, with meta-analysis, to empirically synthesize the current literature regarding the association between adiposity (as defined by BMI, waist circumference, waist/hip ratio, and adipose tissue) and observed racial disparities in prostate cancer occurrence, progression, and prostate cancer-specific mortality.

a. Research question 1

What does the existing literature say about how adiposity contributes to prostate cancer racial and ethnic disparities in the context of established prostate cancer risk factors?

b. Research question 1a

Will the summary estimates for the association between prostate cancer and adiposity differ across Black and White racial groups?

2. Specific aim 2

Use the National Institutes of Health-AARP Diet and Health Study (NIH-AARP Diet and Health Study) prospective cohort male survey respondent data to analyze the association between

central adiposity and prostate cancer incidence, stage at presentation, and prostate- cancer specific mortality.

a. Research question 2a

Is high central adiposity (WC) associated with increased prostate cancer incidence, advanced disease, or cause-specific death, after adjustment for age, race, education, physical activity, smoking status, family history of prostate cancer, diabetes status, screening history, and dietary factors?

b. Research question 2b

Does the association of high central adiposity with prostate cancer risk (overall, local, advanced, and cause-specific mortality) differ between Non-Hispanic Blacks and Non-Hispanic Whites after adjustment for the education, age, physical activity, smoking status, family history of prostate cancer, diabetes status, screening history, and dietary intake pattern?

c. Research question 2c

Does the joint effect of central adiposity and body mass (WC*BMI) have a significant positive association with prostate cancer risk (overall, local, advanced, and prostate cancer-specific death), independent of the main effect of WC?

The effect of central adiposity, independent of, and in addition to, BMI on the risk of prostate cancer occurrence, high stage, and eventual prostate cancer-specific mortality remains unclear. A significant joint effect between central adiposity and race would suggest unique mechanisms for the impact of central adiposity for Blacks, and may help explain their differential rates of prostate cancer occurrence and poor prognoses.

This work was intended to contribute a unique perspective on the role of adiposity in racial disparities in prostate cancer risk by addressing body fat distribution, in addition to mass, taking into account possible modifying and confounding effects using self-reported measurements of dietary,

lifestyle, and family history. Given the increasing prevalence of obesity (especially among Blacks), the excess morbidity and mortality from prostate cancer observed by Black men, and the strength of the previously established associations between high BMI and prostate cancer morbidity and mortality, it is imperative that the role of adiposity, and body fat distribution in the observed racial and ethnic prostate cancer disparities are clarified to inform further research on the mechanistic underpinnings of this phenomena.

II. CONCEPTUAL MODEL AND RELATED LITERATURE

A. The Role of Adiposity in Prostate Cancer Racial Disparities

Men of predominant African ancestry (AA) have the greatest incidence and poorest prostate cancer-specific outcomes (3, 60). Warnecke et al. called researchers to approach disparities research considering a robust interdisciplinary 'cells-society' paradigm (8). Their paradigm considers the spectrum of distal, intermediary, and proximal factors when exploring health disparities. This broader scope allows researchers to gain more applicable insight into the underlying mechanisms of racial disparities. Figure 1 shows where Aims 1 and 2 are situated in the conceptual continuum of racial and ethnic disparities research. This dissertation is situated at the proximal end of the conceptual scale.

Race is the most commonly measured proxy for the complex relationship between culture and biology. One is assigned, or ascribes to, a race due to socio-cultural normative constructs, which cluster pigmentation phenotypes and ethnically derived allegiances (93, 94) Race manifests as a social experience that, whether assigned or ascribed, effects health (94). Thus, Figure 2 opens the conceptual framework for these aims with the constructs of anthro-historical origin, capturing the socially structured population biology underlying ancestry and race the demographic construct measured in most research studies. The social construct of race often plays a determinate role in ones lived social experience (93, 94). The model continues from ancestry and race to a row of various known prostate cancer risk factors, which span the distal to proximal scale of health determinants. These determinants converge at an arrow that runs the full course of the model, reflecting the presence of the racial disparities throughout the adiposity-prostate cancer relationship.

Age, educational, attainment, and socioeconomic position may be determinants in one's access to care, health knowledge, attitudes, beliefs, and practices (8, 9, 53). Dietary patterns, smoking, and screening patronage may indeed be influenced by social position and perspective. General health status, and IGF-axis morbidities (i.e. insulin resistance), and cardiovascular diseases are, in part, a result of

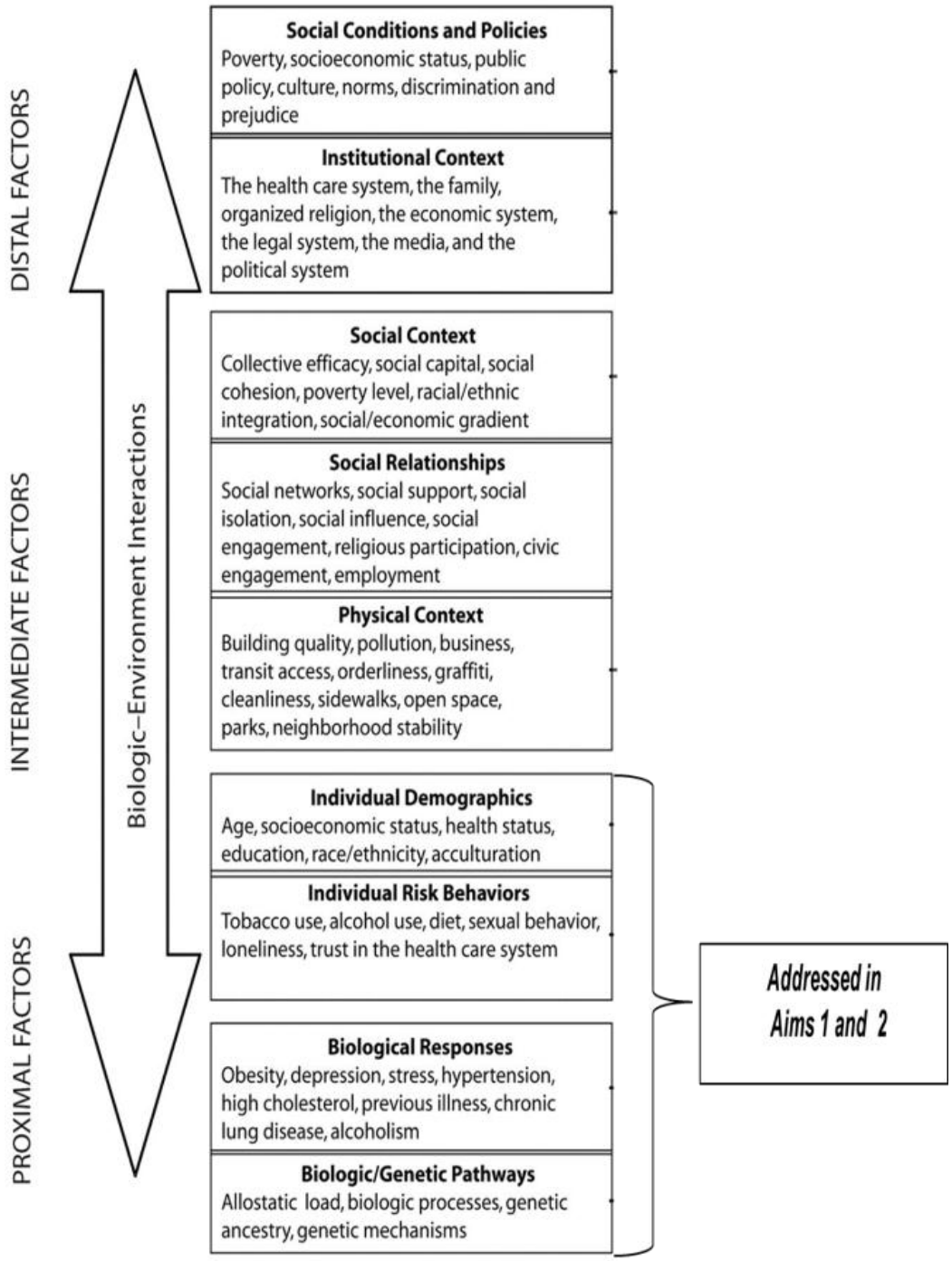

Figure 1. Dissertation aims within a biopsychosocial paradigm for health disparities (8).

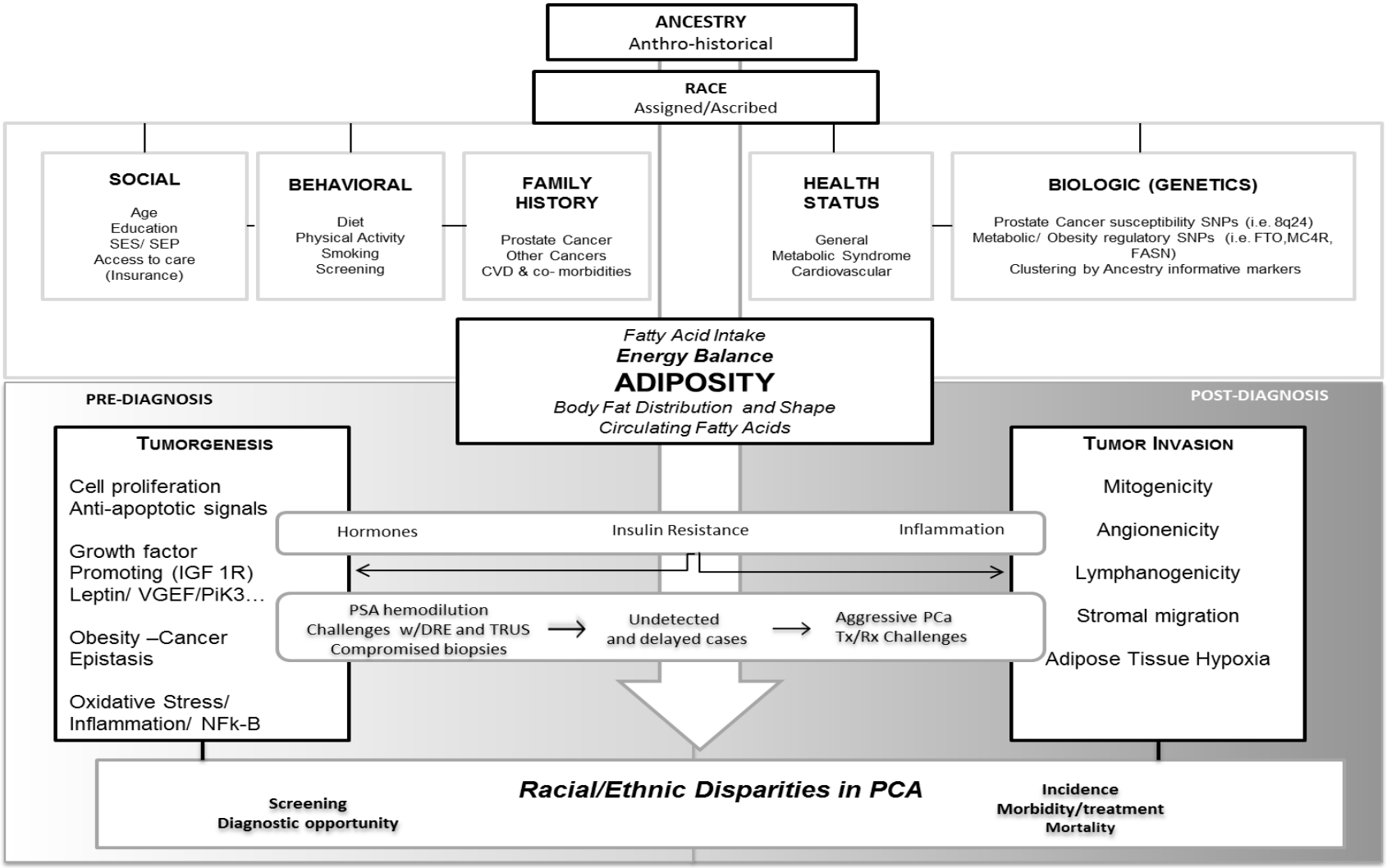

Figure 2. Conceptual model for the contribution of adiposity to racial and ethnic disparities in prostate cancer.

behaviors (95). Metabolic syndrome has been associated with prostate cancer incidence and outcomes (96, 97). Biologic and molecular level risk factors for prostate cancer range from inherited or somatic to epigenetic changes in DNA conducive to carcinogenesis or aggression (98). Epigenetic changes may be related to stress-induced chronic inflammation and oxidation (98, 99).

Molecular susceptibility markers for prostate cancer aggression and obesity vary across race categories (61). A plethora of bio-socio-behavioral factors may contribute to one's adiposity (lean versus fat mass) as well as fat deposition patterning (100). Excess adipocytes encourage hormone synthesis (estrogen), and increase free fatty acids, inducing a state of low-grade chronic inflammation resulting in higher levels of pro-cancer inflammation markers (leptin IL-6,VEGF, and TNF-α, while suppressing anti-cancer adipokines (i.e. IGFBP-3 and adiponectin) (26, 27). Obesity has been shown to induce insulin resistance and subsequently promotes insulin like growth factor -1 (IGF-1) bioavailability, creating a commensal environment for cell proliferation, and down regulating apoptotic signaling, and thus promoting tumor development (28).

Obesity lessens the sensitivity of PSA testing, creating challenges for clinical screening, diagnostic, and treatment practices (i.e. DRE, TRUS, biopsy and EBRT)(90). This results in reduced detection rates, delayed case diagnosis, or compromise in treatment efficacy (90). Obese men may have more aggressive tumor phenotypes in addition to the impaired detection and treatment resulting from their size, rendering poor prognostic outlook for them upon diagnosis (90).

Currently, 33.8% of adults in the US are obese (defined as a BMI ≥30 kg/m2) (12). There has also been a striking increase in the prevalence of obesity among adolescents (12). Furthermore, Blacks are disproportionately affected by both the obesity epidemic, and prostate cancer (12, 60). Despite declining prostate cancer death rates since the 1990's, the gap between the White and Black rates persist (2). The rising prevalence of obesity, coupled with apparent racial disparities, presents a unique concern for health in general, and prostate cancer risk, progression, and mortality, specifically.

B. Previous Studies

1. Current reviews on the association between adiposity and observed racial and ethnic disparities in prostate cancer

The US National Library of Medicine (NLM) National Institutes of Health PubMed database was searched for articles in English published through October 1, 2011. Medical Subject Headings (MeSH) indexing the following terms were used: Race, African ancestry (Black; African American, African, Ancestry Informative Markers [AIMs]); Adiposity (Obesity, energy balance, visceral fat, visceral adiposity, waist or hip circumference, WHR, dual energy X-ray absorptiometry [DXA], BMI, fatty acid, lipids, leptin, adiponectin); health status disparities (disparities, racial and ethnic disparities, minority health, Black men's health); and prostatic neoplasm (prostate cancer). The search produced 31 articles, of which 8 were reviews. All of the articles comment on the importance of anthropometric and molecular measures in deconstructing adiposity related mechanisms contributing to prostate cancer disparities; five mention genomics or genes playing a role (35, 61, 62, 101-104). One meta-analysis on metabolic genes in African ancestry populations and cancers, including prostate cancer, but did not relate the findings to anthropometry (35). None of the disparities reviews included sections on body fat distribution (e.g. waist circumference), obesity genetics, ancestry markers, prostate tumor markers, clinical factors, and comorbities simultaneously, and they do not generate mechanistic hypotheses on the role of adiposity in prostate cancer racial and ethnic disparities. This search suggests the need for further synthesis of literature relating adiposity to prostate cancer disparities.

2. The National Institutes of Health AARP Diet and Health Study

The National Institutes of Health-AARP Diet and Health Study (NIH-AARP) began in 1995 when an extensive questionnaire capturing information on diet, height and weight, and other risk factors was mailed to 3.5 million AARP members between the ages of 50 and 71 years who resided in California, Pennsylvania, Florida, New Jersey, North Carolina, Louisiana, Atlanta, Georgia, or Detroit,

Michigan. After the initial mailing, 617,119 people returned the questionnaire and 567,169 people remained after data quality exclusions. In 1996, a supplementary questionnaire measuring cancer screening practices, including prostate specific antigen (PSA) testing and digital rectal examination (DRE) 3 years prior to baseline, as well as recalled weight and height at age 18, was completed by 334,910 participants who had returned the baseline questionnaire. Table I describes the characteristics of the NIH-AARP cohort at baseline. Several publications have reported on specific characteristics of the cohort: three percent of men were self-identified as not Hispanic Black, (~10,204 men); the mean age of men was 62.3 years at baseline (105) (12.4% were < 55 years; 21.8% 55-59 years; 28% 60-64 years; 33.8% 65-69 years; and 3.9% ≥70 years)(106). According to CDC BMI classifications, 29% of men were classified as normal weight (< 25 kg/m^2), 48.2% were classified as overweight (25-29.9 kg/m^2), and 20.9% were classified as obese (≥30kg/m^2) at baseline (12).

In 1995, the baseline cohort was expected to see 10,746 incident prostate cancers after 5 years of follow-up and 22,752 after 10 years of follow up. Currently, of the approximately 339,000 male respondents at baseline, ~196,000 responded to the more detailed risk factor questionnaire (106). In the baseline cohort, without any exclusion, there are approximately 26,000 incident prostate cancer cases, including ~2500 advanced prostate cancer cases; ~17,300 of the prostate cancer cases have both the detailed and baseline survey data.[1]

3. Previous work on prostate cancer and adiposity in the National Institutes of Health AARP Diet and Health Study

Body size is believed to influence prostate cancer risk outcomes, but most studies have only focused on BMI, without simultaneously considering the independent and joint effects of other

[1] Prostate case data on the full cohort is not published. Park, Yikyung, (NIH/NCI), 2011, Personal communication).

TABLE I

CHARACTERISTICS OF MALE PARTICIPANTS IN NATIONAL INSTITUTES OF HEALTH AARP COHORT AT BASELINE[a]

Characteristic	Value
Age (mean)	62.3
Mean height in cm (inches)	178.3 (70.2)
Mean weight in kg (pounds)	86.6 (191.0)
Mean BMI* (weight (kg)/height (m)^2)	27.2
Race/ethnicity (%)	
White, not Hispanic	93.7
Black, Hispanic, Asian, other	6.4
Education (%)	
≤11 years	6.6
12 years/high school	16.5
Vocational/technical	9.6
Some college	22.5
College graduate	21.9
Postgraduate	23.0
Family history of cancer (participant or first-degree relative) (%)	31.4
Currently smoking (%)	10.7
Former smoker (%)	59.2
Physical activity (%)	
Never/rarely	15.8
1–3/month	13.1
1–2/week	21.9
3–4/week	27.9
≥5/week	21.3
Currently using HRT	
Median kcal/day	1,895.1
Alcohol intake (≥15 g/day)	28.0

[a] *N* = 340,148. Men who remained after customary caloric exclusion of participants whose reported energy intake was extreme (men, <800 or ≥4,200 kcal.) (105).

important measures related to body fat distribution (i.e. WC), dietary pattern, lifestyle factors (i.e. physical activity), and metabolic syndrome. The NIH-AARP cohort presents a special opportunity to examine complex questions.

a. Obesity and risk prostate cancer occurrence and death in the National Institutes of Health AARP Cohort

In 2007, Wright et al. demonstrated that BMI and weight change are positively associated with fatal prostate cancer (43), and Koster et al. showed that higher waist circumference predicted total mortality, independent of BMI (21). The analysis by Wright et al. was based on 287,760 male participants, including 172,961 who had completed the aforementioned supplementary questionnaire on prostate cancer screening practices (43). During up to 5 years of follow-up time, 9,986 incident cases of prostate cancer (including 1,445 that were classified as advanced) and 173 prostate cancer deaths were identified. In the analytic cohort, 29% of the men were normal weight, 50% were overweight, and 21% were obese by WHO classification at baseline. Men with higher baseline BMI were younger, less physically active, more likely to be Black, more likely to not currently smoke, and less educated than leaner individuals. After adjusting for age, race, smoking status, education, personal history of diabetes, and family history of prostate cancer, the relative risks (RR) for total prostate cancer among men in the highest BMI category, $\geq$40 kg/m^2 , compared to men in the lowest BMI category, <25 kg/m^2 was 0.65 [0.50-0.85], p = .0008. In contrast, significantly increased risk of prostate cancer mortality was observed at higher BMI levels (for BMI <25 kg/m^2: RR, 1.0 [referent group]; BMI 25-29.9 kg/m^2: RR 1.25[0.87-1.80]; BMI 30-34.9 kg/m^2: RR 1.46[0.92-2.33] and BMI >or = 35 kg/m^2: RR 2.12[1.08-4.15], p = .02). Weight gain between the ages of 18 and baseline was also associated with a higher risk of fatal disease (RR 2.98 [0.99-9.04], p = .009), but not with incident prostate cancer. There was no evidence of effect modification by race in this analysis.(43)

Wright et al. note that their non-significant finding BMI and prostate cancer incidence may be due to one or more of the following: 1.) PSA and DRE screening being lower among obese men as compared to lean men, although adjustment for screening practices did not mediate nor modify the effect estimates. The information on screening may not have been complete enough to fully capture the impact of screening on the BMI effect. 2.) Abnormal DRE and PSA levels are attenuated in obese men. Hemodilution of the detected protein renders PSA testing less sensitive in obese men, making it less likely to detect a cancer if one is present. DRE is more difficult in practice on an obese man and may result in a lower detection rates using DRE in obese men. This detection bias may have attenuated the estimate of BMI's effect on prostate cancer incidence. 3.) Survival bias might have explained the strong association with mortality as compared to incidence in obese men; obesity has been associated with more aggressive tumors. They did not observe differences in survival across levels of BMI, among men diagnosed with prostate cancer. (43)

b. Waist circumference and all-cause mortality in the National Institutes of Health AARP Cohort

In 2008, Koster et al. followed the baseline survey participants with waist circumference data prospectively between 1996 and 2005 and found that elevated WC (5^{th} quintile v. second) conferred a risk of all-cause mortality (male hazard ratio (HR) = 1.22; 95% CI, 1.15-1.29; women: HR = 1.28, 95% CI, 1.16-1.41) even after adjusting for smoking, race, BMI, and prevalent disease status (21). There seemed to be effect modification by race. In Blacks, no significant association with WC and mortality was observed, while associations were seen in at least one gender from every other racial group. Asian men had a significant positive association in the 4^{th} quintile of WC. The product term between WC and race was not found to be significant in the sample (44). Among Blacks, those with a normal BMI [18.5 -≤24.9 kg/m^2] and high WC had an elevated risk of all-cause mortality , as compared to those with normal BMI and normal WC (men: HR = 1.23, 95% CI; 1.08-1.39; women:

HR = 1.22, 95% CI; 1.09-1.36)(21). In a subsequent analysis, Koster et al. found among people who were inactive, those with high WC had twice the risk for mortality compared to those with normal WC (45). In this analysis physical activity reduced the excess risk for all-cause mortality associated with adiposity (high BMI and high WC) (45). Race was not included in the joint association analysis.

III. THE CONTRIBUTION OF ADIPOSITY TO RACIAL DISPARITIES IN PROSTATE CANCER OCCURANCE AND PROGESSION: A REVIEW

A. Introduction

1. Racial disparities in prostate cancer

Prostate cancer (PCa) is of great public health concern. The highest incidence rates occur in Western Europe and the Americas (1). The probability of developing an invasive prostate cancer among men of all races in the United States (US) from birth to death is 1 in 6 (2). According to the American Cancer Society (ACS), prostate cancer comprises 29% of all incident cancer cases and 11% of all cancer deaths in US men, second only to lung cancers (2). Prostate cancer-specific death rates have been declining (2). In US data spanning 1990 – 2006, death rates declined by 39%, an absolute difference of 15 percentage points (3). Between 1992 and 2006, the incidence declined an average of 3.9% per year (3).

For all cancer sites combined, Black men have a 19% higher incidence rate and a 37% higher death rate than White men (3). Black men have the highest incidence and mortality rates compared to all other races (146.3 per 100,000 and 56.3 per 100,000, respectively) (3). The death rate for Black men remains, on average, 20% higher than that of White men, despite overall declines in national rates in both groups since the early 1990's (2). Incidence of prostate cancer in Black men is currently 1.5 times the incidence in all other races combined, and 1.6 times that of their White counterparts (3). Death due to prostate cancer in Black men is 2.2 times the death rate in all other races, and 2.4 times that of White men (2). Black men have more distant stage tumors at diagnosis, and lower 5-year survival estimates compared to all other races, irrespective of tumor stage at diagnosis (3). Studies have seen the highest rates of recurrence, and aggressive (high grade) disease in Black men (4, 5). Explanations for racial and

ethnic disparities in incidence, morbidity, and mortality span socio-demographic, behavioral, nutrition/diet, genetic, and differences in approach to treatment (6, 7).

Many researchers have called for multifactorial approaches to explore and explain these disparities, which focus on the interactions between biologic and social factors (8, 9). In order to elucidate causes of clearly observed racial and ethnic disparities in prostate cancer, a paradigm shift must occur. Effective epidemiologic studies of these disparities must collect anthropometric, environmental and occupational exposure, genetic, socio-demographic, cognitive, behavioral, dietary, and medical history data from the individuals involved. In traditional studies, only a few of the aforementioned factors were explored alongside the outcome (10), but a "cells to society" approach, which incorporates methods from molecular, genetic, social, and classical epidemiology, can provide critical new insights into the causes of disparities. Further development of multi-factor indices may assist in effectively addressing the breath of likely component causes of prostate cancer disparities. This would encourage further distillation of the conceptual construct underlying each component.

2. Racial disparities in obesity

According to the most recently available National Health and Nutrition Examination Survey (NHANES) data, 33% of adult US men (age 20-74 years) are obese (Body Mass Index (BMI > 30)(2). Among men, 37% of Black men are obese (BMI > 30) compared to 32% of White men. Although an inverse disparity is seen when considering overweight category alone (BMI >25-29.9); 73% of White men are overweight compared to 69% of Black men. The combination of high rates of obesity and higher incidence, as well as death rates, for PCa among Black men compared to all other racial groups, makes these men the ideal population to explore the relationship between adiposity and PCa occurrence, progression, and mortality. Our review is an effort to synthesize the existing literature on role of adiposity in the perpetuation of racial and ethnic disparities in PCa occurrence and outcomes, comparing men of predominant African ancestry to men of other groups.

B. Methods

1. Study overview

This systematic review examines the current literature elucidating the association between adiposity (as defined by anthropometric measures BMI, waist circumference (WC), Hip circumference (HC), and waist to hip ratio (WHR)), and observed racial disparities in PCa occurrence, progression, and mortality. Subsequently, articles with race-specific effect estimates available were used to conduct a brief meta-analysis of the effect of adiposity on PCa occurrence.

2. Search methodology

The US National Library of Medicine (NLM) National Institutes of Health PubMed database was searched for articles in English published through October 1, 2011. Medical Subject Headings (MeSH) indexing the following terms were used: Race, African ancestry (Black; African American, African, Ancestry Informative Markers [AIMs]); Adiposity (Obesity, energy balance, visceral fat, visceral adiposity, waist or hip circumference, WHR, dual energy X-ray absorptiometry [DXA], BMI, fatty acid, lipids, leptin, adiponectin); health status disparities (disparities, racial and ethnic disparities, minority health, Black men's health); and prostatic neoplasm (prostate, cancer). Abstracts of all articles returned by the NLM PubMed database after entering all of the terms were read. References of potentially qualifying and related articles were also examined for potential manuscripts. Two of the authors independently, searched, reviewed the articles, and abstracted the data; disagreements were resolved by consultation with a third review working group member.

3. Inclusion and exclusion criteria

Papers selected had to include the following characteristics: 1.) An adiposity related factor (BMI, WHR, etc.) as the exposure of interest associated with a PCa outcome (i.e. occurrence, progression, mortality); 2.) a participant sample which included men of predominant African ancestry [AA] (e.g. Black, African American, Jamaican, Ghanaian etc.); and 3.) reported race-stratified,

particularly AA-specific, effect estimates for PCa occurrence, mortality, or progression. Adjustment for race in a multivariate model alone was not sufficient for inclusion in the review analysis. We did not consider articles focused on screening behaviors, or screening PSA disparities due to obesity related hemodilution, as these associations are well established (62). No reviews, editorials, or comments were included in the review results, although they were cited for background content and mined for potentially qualifying manuscripts. After selection for the review, articles were considered for meta-analysis. Inclusion in the meta-analysis was contingent upon having complete estimate information for PCa occurrence, progression, or mortality by at least a White and Black racial or ethnic group. Estimations were based on reported continuous RRs; categorical RR's supported by information on the number cases and non-cases in each category of an explicitly defined exposure. Confidence intervals (95%CI) or standard errors for each estimate produced, within each category of exposure explored. Exposure distribution and categorizations were, ideally, defined by upper or lower bounds, or presented by way of mean and standard deviation. Articles which had no other article for comparison due to design, or anthropometric measure of interest were excluded from meta-analysis.

4. Statistical analyses

The following information was recorded into a database for each study: date of retrieval, first author, journal, location, publication year, outcome of interest, study type, study period, study population characteristics (i.e. age, anthropometric, and race distributions), sample size, measure of effect, confidence interval, and adjustment variables. The rate and odds ratios of qualifying articles were used to calculate a RR per 5 kg/m^2 increase in BMI estimate for ease of qualitative comparison, and statistical calculation. Generalized least squares for trend (GLST) estimates were calculated when person-time data were provided, and weighted least squares (WLS) estimation was used with count data (107). Using previously described methods (39, 107, 108), we calculated the midpoints of BMI categories, or assumed that the larger of 2-category BMI estimates were similar to the per 5 kg/m^2

estimate (39). These per 5 kg/m^2 article estimates contributed to the DerSimonian and Laird method meta-analysis (109). All analyses were conducted in STATA® version 12.

C. Results

Our systematic review resulted in 9 distinct studies (4 case-control, 2 cross-sectional and 3 cohort studies) which met our inclusion criteria (see Figure 3). Six of those articles examined the association between BMI and PCa occurrence (total and aggressive, see Table II) (41, 97, 110-113). BMI was the sole anthropometric predictor of the two articles addressing adiposity associations with progression (64, 114). Only one article looked at hip circumference (111); 4 considered waist-based measures (112, 115-117). Two of the studies included in our review were conducted with African, African American, or Black Caribbean men only (97, 111, 117). No articles fit our criterion for the risk of PCa-specific mortality.

Articles with a primary focus on screening disparities were outside the scope of our research question. We excluded articles (Figure 3) which did not provide an effect estimate specifically for prostate cancer risk, progression, or mortality (n = 88). Also excluded, were articles in which adiposity was not a main exposure (n = 22), and those which did not provide race-specific estimates for the association between adiposity and the prostate cancer outcome of interest (n = 49), or include men of predominant African ancestry in their sample (n = 43). Many manuscripts were from cohorts with multi-ethnic participants, but did not publish the race-specific estimates necessary to qualify for this review.

1. Study design and reporting

Tables II and III present the characteristics of all the articles included in the review of anthropometric associations with PCa disparities. All of the studies included in this review provided robust descriptions of study design recruitment and case definition. Follow-up time and response rates were provided. Control recruitment varied from population random selection to hospital based, and the time of control selection in relation to timing of the case was not always clear. The study populations

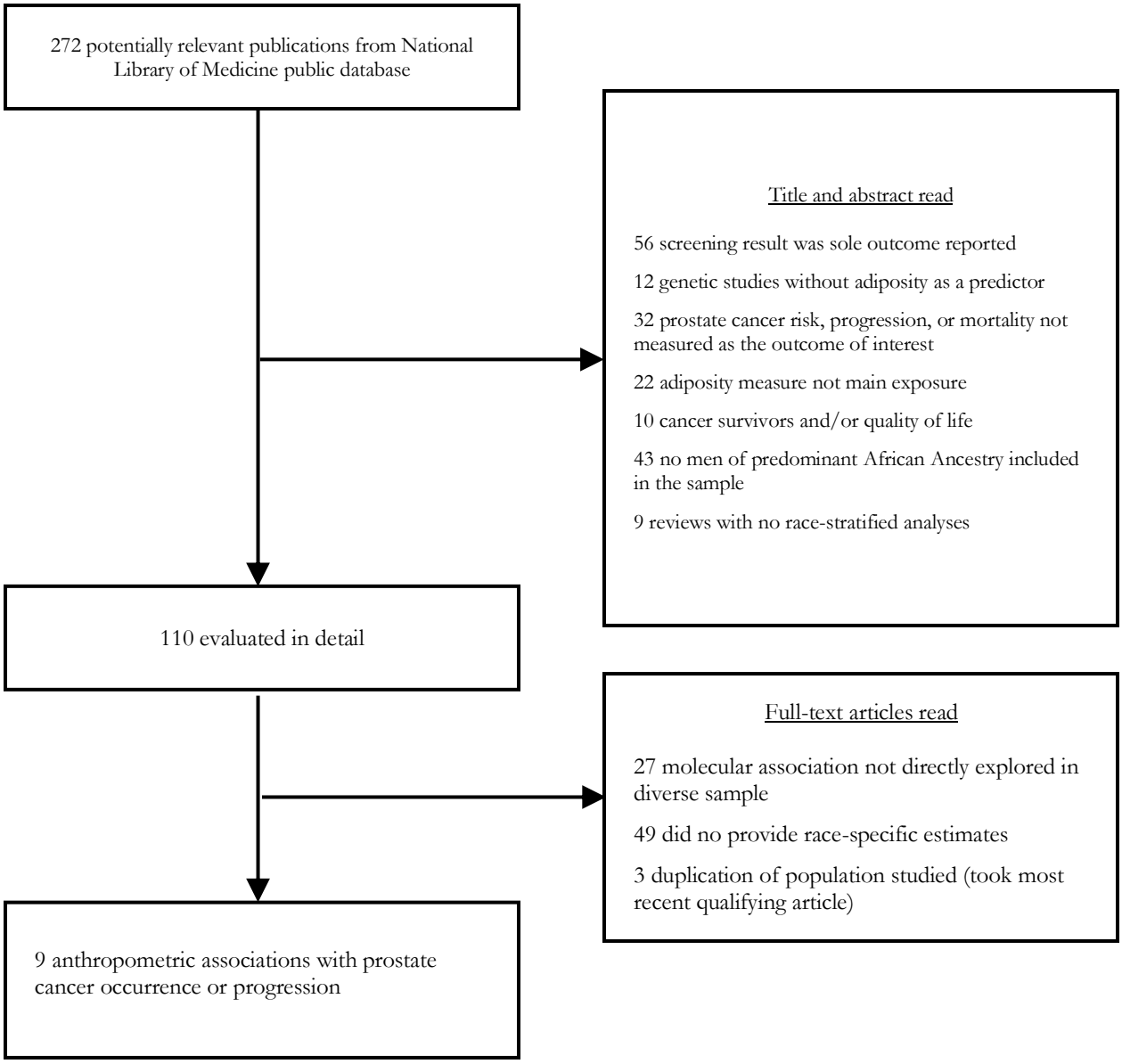

Figure 3. Flow of inclusion and exclusion.

TABLE II

CHARACTERISTICS OF STUDIES PRESENTING RACE-STRATIFIED ESTIMATES OF BODY MASS INDEX ASSOCIATIONS WITH TOTAL PROSTATE CANCER RISK[a]

Study	Study characteristics	Sample size	No. of cases	BMI categories published	AA estimates		WH estimates		Adjustments
					RR (95% CI)	RR per 5 kg increase in BMI (95% CI)	RR (95% CI)	RR per 5 kg increase in BMI (95% CI)	
				Case-control studies (n = 3)					
Beebe-Dimmer, Urology, 2009	Period : 1999-2002 Setting: Flint Men's Health Study	881 AA 378	637	BMI kg/m² <30 ≥30	 1.15 (0.70-1.89)	 1.15 (0.70-1.89)	 0.51 (0.33- 0.80)	 0.51 (0.33-0.80)	Age, PSA screening history
Hayes, Cancer Epidemiology, Biomarkers & Prevention, 1999	Period 1986-1989 Setting: Population-based cancer registries	2,133 AA 992	932	Median BMI kg/m² 21.9 24.3 25.8 28.9 ptrend	 1.00 (ref) 0.8 (0.60-1.10) 0.8 (0.50-1.20) 0.8 (0.60-1.20) 0.32	0.98 (0.73-1.32 p = .90	 1.00 (ref) 0.9 (0.70-1.30) 0.8 (0.50- 1.10) 1.2 (0.90-1.70) 0.43	0.98 (0.71-1.35) p = 0.91	Age, study site
Jackson, Cancer Causes Control. 2010	Period: 2005-2007 Setting: tertiary hospitals, private practices, Kingston, Jamaica	AA only 518	243	BMI kg/m² ≤ 24.9 25.0-29.9 ≥30 ptrend	 1.00 (ref) 0.80 (0.49-1.29) 1.36 (0.66-2.81) 0.69	1.10 (0.73-1.65) p = 0.64	N/A	N/A	Age, height, education, current smoking, physical activity
Habel, The Prostate, 2000	Period: 1964-1973 Kaiser Permanente Medical Care Group Median follow-up: 19.5 years	70,712 AA 8,696	2,079	BMI kg/m² Quintile 1 Quintile 2 Quintile 3 Quintile 4 Quintile 5	 1.00 (ref) 1.27 (0.88-1.83) 1.28 (0.90-1.82) 1.05 (0.74-1.50) 1.03 (0.72-1.48)	0.99 (0.67-1.47) p = 0.99	 1.00 (ref) 1.03 (0.87-1.23) 1.03 (0.87-1.22) 1.00 (0.44-1.19) 0.98 (0.82-1.16)	0.99 (0.73-1.35) p = 0.99	Age, birth year

TABLE II (continued)

CHARACTERISTICS OF STUDIES PRESENTING RACE-STRATIFIED ESTIMATES OF BODY MASS INDEX ASSOCIATIONS WITH TOTAL PROSTATE CANCER RISK

Study	Study characteristics	Sample size	No. of events	BMI categories published	AA estimates RR (95% CI)	AA estimates RR per 5 kg increase in BMI (95% CI)	WH estimates RR (95% CI)	WH estimates RR per 5 kg increase in BMI (95% CI)	Adjustments
				Cohort Studies (n = 3)					
Habel, The Prostate, 2000	Period: 1964-1973 Kaiser Permanente Medical Care Group Median follow-up: 19.5 years	70,712 AA 8,696	2,079	BMI kg/m² Quintile 1 Quintile 2 Quintile 3 Quintile 4 Quintile 5	 1.00 (ref) 1.27 (0.88-1.83) 1.28 (0.90-1.82) 1.05 (0.74-1.50) 1.03 (0.72-1.48)	0.99 (0.67-1.47) p = 0.99	 1.00 (ref) 1.03 (0.87-1.23) 1.03 (0.87-1.22) 1.00 (0.44-1.19) 0.98 (0.82-1.16)	0.99 (0.73-1.35) p = 0.99	Age, birth year
Samanic, Cancer Causes and Control, 2004	Period 1969-1996 Setting: Inpatients at VA hospital across US Follow-up: 27 years	4,500,700 AA 832,214	65,194	BMI ICD8/ICD9 BMI kg/m² <30 ≥30	 1.00 (ref) 1.12 (1.04-1.20)	 1.12 (1.04-1.20)	 1.00 (ref) 1.19 (1.15-1.24)	 1.19 (1.15-1.24)	Age and calendar year
Hernandez, Cancer Epidemiology, Biomarkers & Prevention, 2009	Period 1993-2004 Setting: Multiethnic Cohort Average follow-up: 9.6 years	83,879 AA 10,934	5,554	BMI kg/m² <18.5 18.5-24.9 25.0-29.9 ≥30 ptrend	 0.62 (0.30-1.28) 1.00 (ref) 1.15 (1.01-1.32) 0.99 (0.83-1.19) 0.62	0.99 (0.76-1.29) p = 0.94	 0.59 (0.26-1.34) 1.00 (ref) 1.06 (0.93-1.21) 0.94 (0.76-1.17) 0.90	0.98 (0.76-1.26) p = 0.90	Age, family history of PCa, marital status, education, birthplace, and smoking

[a] N = 6. N/A = not applicable; population not examined. Total prostate cancer displayed only; low and high-grade estimates available.

TABLE III

CHARACTERISTICS OF STUDIES PRESENTING RACE-STRATIFIED ESTIMATES OF BODY MASS INDEX ASSOCIATIONS WITH RISK OF AGGRESSIVE PROSTATE CANCER AND PROGRESSION[a]

					AA estimates		WH estimates		
Study	Study characteristics	Sample size	No. of events	BMI categories published	RR (95% CI)	RR per 5 kg increase in BMI (95% CI)	RR (95% CI)	RR per 5 kg increase in BMI (95% CI)	Adjustments
				Aggressive prostate cancer risk (n = 4)					
Jackson, Cancer Causes Control. 2010[b]	Period: 2005-2007 Setting: tertiary hospitals, private practices, Kingston, Jamaica	AA only 518	Cases 243	BMI kg/m² ≤24.9 25.0-29.9 ≥30 ptrend	 1.00 (ref) 0.80 (0.46-1.29) 1.36 (0.66-2.88) 0.69	0.97 (0.64-1.45) p = 0.88	N/A	N/A	Age and height as, education, current smoking, physical activity
Su, Cancer Epidemiology, Biomarkers & Prevention, 2011[c]	Period 2004-2009 Setting: North Carolina-Louisiana PCa Project Treatment: RP Median follow-up: 2 years	2,173 AA 1,049	Cases 377	BMI kg/m² 18-25 >25-30 30-35 >35 ptrend	 1.00 (ref) 1.13 (0.74-1.74) 1.38 (0.85-2.23) 1.71 (1.00-2.90) 0.032	1.04 (0.63-1.71) p = 0.88	 1.00 (ref) 1.27 (0.73-2.19) 2.00 (1.13-3.54) 2.09 (1.06-4.14) 0.004	1.06 (0.52-2.12) p = 0.87	Age at diagnosis, education, site, smoking, 1st degree family history, screening history, screening frequency, treatment initiation, Charlson comorbidity index
Beebe-Dimmer, Urology, 2009[d]	Period : 1999-2002 Setting: Flint Men's Health Study	881 AA 378	Cases 637	BMI kg/m² <30 ≥30	 1.00 (ref) 1.75 (0.92-3.31)	1.75 (0.92-3.31)	 1.00 (ref) 0.30 (0.15-0.59)	0.30 (0.15-0.59)	Age, PSA screening history
Hayes, Cancer Epi, Biomarkers & Prev, 1999[e]	Period 1986-1989 Setting: Population-based cancer registries	2,133 AA 992	Cases 932	Median BMI kg/m² 21.9 24.3 25.8 28.9 ptrend	 1.00 (ref) 0.80 (0.50-1.20) 0.60 (0.30-1.00) 0.90 (0.50-1.40) 0.58	0.93 (0.96-1.26) p = 0.66	 1.00 (ref) 1.00 (0.50-1.70) 1.03 (0.70-2.20) 1.03 (0.80-2.30) 0.20	1.02 (0.59-1.78) p = 0.94	

TABLE III (continued)

CHARACTERISTICS OF STUDIES PRESENTING RACE-STRATIFIED ESTIMATES OF BODY MASS INDEX ASSOCIATIONS WITH RISK OF AGGRESSIVE PROSTATE CANCER AND PROGRESSION[a]

					AA estimates		WH estimates		
Study	Study characteristics	Sample size	No. of events	BMI categories published	RR (95% CI)	RR per 5 kg increase in BMI (95% CI)	RR (95% CI)	RR per 5 kg increase in BMI (95% CI)	Adjustments
				Prostate cancer progression (n = 2)					
Jayachandran Cancer, 2009[f]	Period 1989-2008 Setting: SEARCH database multi-centers Treatment: RP Median follow-up: 3.3 years	1,415 AA 662	Recurrences 452	BMI kg/m² <30.0 ≥ 30.0 Continuous	 0.75 (0.45-1.25) 0.89 (0.52-1.54) 1.04 (1.01-1.07)	1.22 (1.05-1.40) p = 0.01	 0.69 (0.36-1.32) 2.52 (1.40-4.54) 1.06 (1.03-1.10)	1.34 (1.16-1.61) p<0.001	Age, year of surgery, clinical stage, biopsy, Gleason score, center, pre-op PSA
Spangler, J Urology, 2007[g]	Period 1995-2004 Setting: Univ. of Pennsylvania Health System Urology Treatment: RP Follow-up: 3 years	924 AA 140	Recurrences 153	BMI kg/m² <30 ≥30	 1.00 (ref) 5.49 (2.16-13.9)	5.49 (2.16-13.9)	 1.00 (ref) 1.14 (0.96-2.08)	1.14 (0.96-2.08)	Age, Stage, Path Gleason grade, SVI

[a] N/A = Not applicable, adequate numbers to estimate not provided in manuscript or population not examined.

[b] For risk of aggressive high-grade cancer defined as Gleason Sum ≥ 7

[c] High grade defined as Gleason sum ≥ 8, or PSA>20ng/mL, or Gleason sum ≥7 and Clinical Stage T3-T4 and PSA< 10ng/mL

[d] Aggressive disease was defined as having either a Gleason Sum ≥7 and or a T3a or higher clinical stage

[e] Single PSA greater than 0.2 ng/mL

[f] Two successive post-treatment PSA > 0.2 ng/dL

[g] Advanced disease determined by clinical stage "regional / distant"

were diverse and large, ranging from N = 498 to 4,500,700. Two of the studies were comprised of AA men only, while others were larger multiethnic cohorts. The outcomes for occurrence and progression were clearly defined and tended to follow clinical standards, varying as the clinical standards definitions did at the time of their publication. Anthropometric exposure was defined using distributional categories (i.e. dicot, quartiles, and quintiles) and the definition of adiposity (total or central) followed CDC or WHO standards in most of the studies (12, 118). Model adjustment varied greatly; from age only adjustments to inclusion of other anthropometric measures, education, lifestyle (i.e. smoking, and marital status) family history, screening history, birthplace, clinical and treatment characteristics (i.e. seminal vesicle involvement (SVI), and date of treatment initiation). This was due primarily to differences in the underlying research question prompting the study. Estimate reporting in the studies consistently included 95% confidence intervals and overall counts. Exposure-level counts of cases and controls in race-stratified analyses were not as consistently reported. Interaction p-values were reported in some studies looking at effects across race, but not all. Many of the qualitative differences in reporting were due, in part, to differences in individual study objective.

2. Associations between anthropometric measurements and prostate cancer disparities

Figure 4 displays the Forrest plot of effect estimates pertaining to the association between body mass and PCa occurrence. Taken together, there was a non-significant positive relationship between BMI and PCa occurrence, RR per 5 kg/m^2 increase in BMI: 1.03 [0.94, 1.12]. The estimates included risk of total and aggressive prostate cancer, with no significant heterogeneity across the studies (I^2 = 7.9% p = 0.37).

Comparing non-Black, predominantly White, and Black estimates, the association remains insignificant, but the direction and magnitude of the estimates is opposite, RR per 5 kg/m^2: 0.95 [0.97, 1.16] and 1.07 [0.96, 1.18], respectively. There was suggestive heterogeneity in the non-Black summary

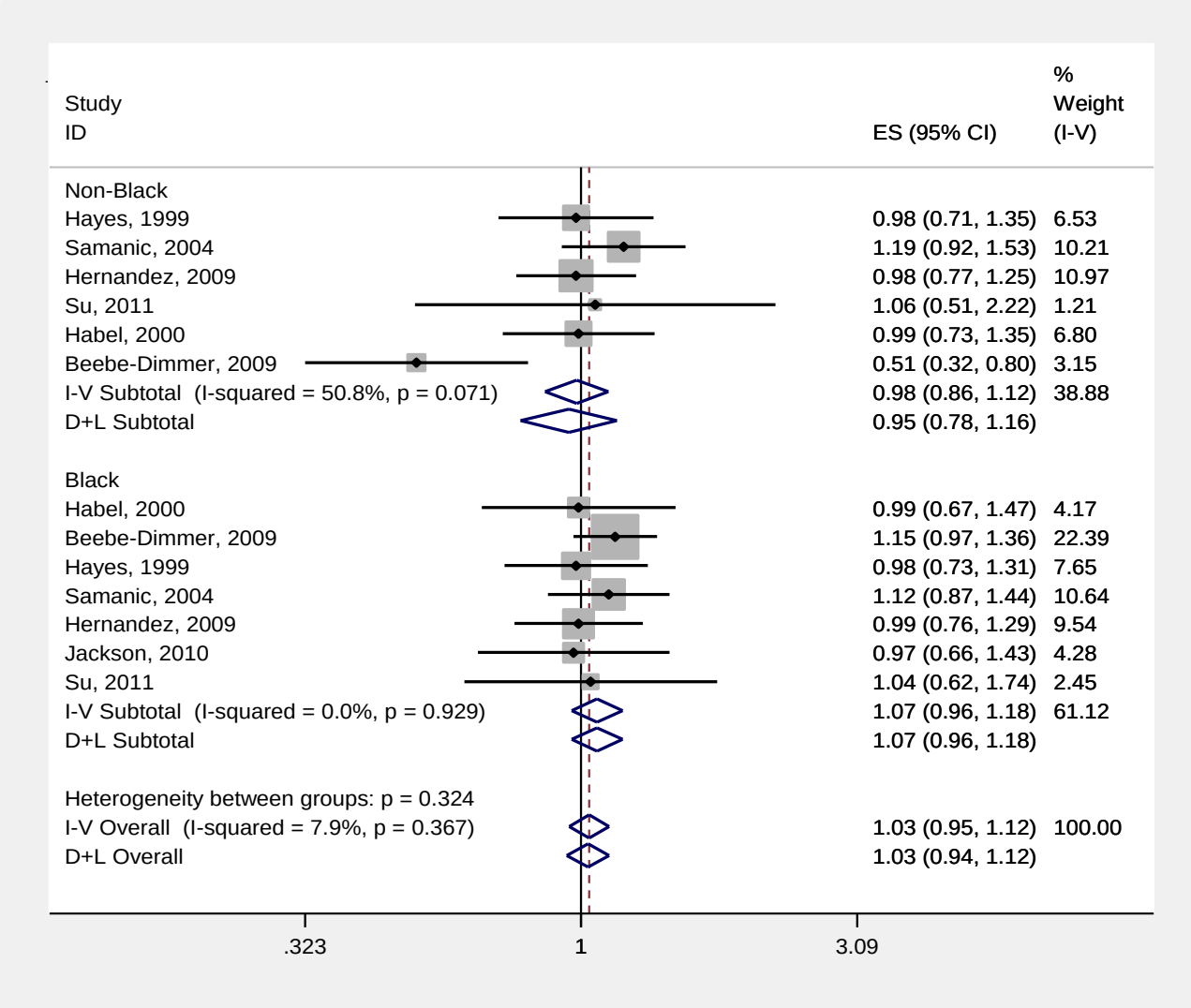

Figure 4. Relationship between body mass index (per 5 kg/m^2) and prostate occurrence calculated with adjusted rate ratios using random effects methods.

estimate ($I^2 = 50.8\%$, p = 0.07); no significant heterogeneity was detected between studies for the Black summary estimate ($I^2 = 0.06\%$ p = 0.93). Risks of aggressive prostate cancer and progression varied by race (Table III). There were 4 studies which specifically reported aggressive or advanced PCa risk estimates by race (97, 110, 111, 116), or had an estimate for AA men only (111).

Three studies focused on aggressive or advanced disease at diagnosis had estimates for non-Blacks allowing for the computation of a summary estimate RR per 5 kg/m^2 = 0.40 [0.16, 1.03]. All of the variance in the estimate was due to study heterogeneity, thus the I^2 statistic convergence was not satisfied (heterogeneity chi-squared = 1.14 (*d.f.* = 2) p = 0.57). The individual study estimates for Blacks also varied; the resulting summary statistic was 1.02 [0.25, 4.18], with a heterogeneity chi-squared = 0.03 (*df* = 3) p = 0.998. Again, the associations are non-significant and differ in direction across race.

The two studies, which explored the association between BMI and progression, had very different estimates for Blacks and non-Blacks. There was an almost five-fold difference in the RR per 5 kg/m^2 between Blacks and Whites in the Spangler et al. study; Whites had a non-significant inverse association and Blacks a significant positive risk. Jayachandran et al. saw significant positive association with obesity and risk of biochemical failure in both groups (64, 114).

Table IV presents evidence for associations between waist-based measures (*n* = 3), and hip circumference (*n* = 1). Significant positive associations were observed in Blacks for waist circumference (WC) or waist to hip ratio in 2 studies which exclusively looked at the roles of central adiposity in prostate cancer occurrence in all AA populations (111, 117). Su et al. did not observe a significant association between WHR and aggressive PCa in Blacks, but rather saw one in Whites (116). Hip circumference was only explored in Jackson et al.; they observed a non-monotonic non-significant association with total PCa risk, and irrespective of tumor grade at diagnosis (111).

TABLE IV

STUDIES PRESENTING RACE-STRATIFIED ESTIMATES OF PROSTATE CANCER RISK ASSOCIATIONS WITH WAIST-BASED MEASURES AND HIP CIRCUMFERENCE[a]

Study	Study characteristics	Sample size	No. of events	Categories published	AA estimates RR (95% CI)	WH estimates RR (95% CI)	Adjustments
Beebe-Dimmer Cancer, 2007[b]	Period : 1999-2002 Setting: Flint Men's Health Study	AA 498	Cases 139	waist circumference ≥102 (cm)	1.84 (1.17-2.91)	N/A	Age, smoking status
Jackson, Cancer Causes Control, 2010[c]	Period: 2005-2007 Setting: tertiary hospitals, private practices, Kingston Metro areas, Jamaica	AA only 518	Cases 243	WHR (cm) <0.95 ≥0.95	 1.00 (ref) 1.72 (1.01-3.00)	N/A	Age, height, education, current smoking, physical activity
				WHR (cm) <0.95 ≥0.95	 1.00 (ref) 2.02 (1.03-3.96)	N/A	
				Hip (cm) ≤92.5 92.6–97.8 97.9–103.3 ≥103.4 ptrend	 1.00 (ref) 1.28 (0.69-2.34) 0.88 (0.48-1.61) 1.05 (0.56-1.96) 0.43	N/A	
				Waist (cm) <90 90-102 ≥102 ptrend	 1.00 (ref) 1.19 (0.71-1.99) 1.56 (0.79-3.07) 0.40	N/A	
				Waist (cm) <90 90-102 ≥102 ptrend	 1.00 (ref) 1.17 (0.63-2.19) 1.61 (0.71-3.64) 0.55		

TABLE IV (continued)

STUDIES PRESENTING RACE-STRATIFIED ESTIMATES OF PROSTATE CANCER RISK ASSOCIATIONS WITH WAIST-BASED MEASURES AND HIP CIRCUMFERENCE

Study	Study characteristics	Sample size	No. of events	Categories published	AA estimates RR (95% CI)	WH estimates RR (95% CI)	Adjustments
Su Cancer Epidemiology, Biomarkers & Prevention, 2011[b]	Period 2004-2009 Setting: North Carolina-Louisiana PCa Project Treatment: RP Median follow-up: 2 years	2,173 AA 1,049	Cases 377	WHR <.0.90 0.90-0.98 >0.98 ptrend	 1.00 (ref) 0.98 (0.65-1.47) 1.18 (0.76-1.83) 0.43	 1.00 (ref) 0.84 (0.45-1.57) 2.03 (1.10-3.47) <0.0001	Age at diagnosis, education, site, smoking, 1st degree family history, screening history, screening frequency, treatment initiation, Charlson comorbidity index

[a] N/A = Not applicable, adequate numbers to estimate not provided in manuscript or population not examined.

[b] For total prostate cancer risk

[c] High grade defined as Gleason sum ≥ 8, or PSA>20ng/mL, or Gleason sum ≥7 and Clinical Stage T3-T4 and PSA< 10 ng/mL

3. Between-study variability

The number of studies comprising this review was small; with that considered, there was suggestive heterogeneity between studies detected for the non-Black pooled estimate of the relationship between BMI and prostate cancer occurrence (Figure 4). Fixed and random effects methods were employed for all pooled analyses; there are likely qualitative reasons for the observed differences. Although a meta-regression is not presented, the age distribution, relative size, design, adjustment variables (particularly, the adjustment or not of other anthropometric measures), self-report of exposure, proportion of AA men in the sample, and sources of cases or controls should be considered for their role in the observed heterogeneity of the effects.

4. Influence and publication bias

Visual inspection of Figures 5 and 6 highlight the relative influence of each study for the race stratified estimates. Beebe-Dimmer et. al 2009 had strong influence, especially in the non-Black subgroup. This study set out to investigate the effect of metabolic syndrome (MetS) risk factors on risk of prostate cancer in a robust case-control analysis of the GECAP-Genes Environment and Prostate Cancer study collaborative(97). Forty-three percent of the participants were Black men based in an extremely diverse health system (Henry Ford, Detroit Metro area, MI USA). Using ATP III guidelines, they explored the association between BMI and PCa risk, adjusting for the other four MetS features understudy (Hypertension, Diabetes, Low LDL, and High triglycerides) (97). This set of adjustments differed from all other studies in the occurrence category, in that it accounted for factors in the insulin moderated pathway.

Figure 6 displays the influence sensitivity analyses for the Black group estimates. Of note is the influence of Samanic et al. 2004 study, an extremely large prospective veteran's cohort, Table I (41). Samanic et al. estimated the obesity associated relative risks of selected cancer cites, including prostate cancer in a large prospective cohort of veterans (N = 36, 6486 White and 832,214 AA men), followed

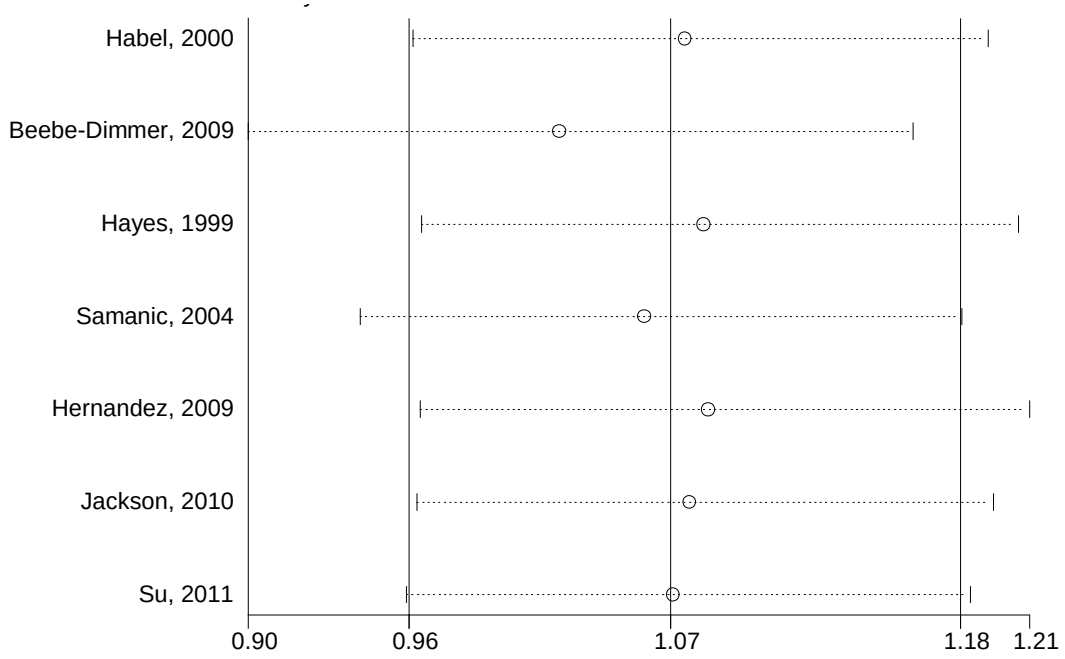

Figure 5. Influence sensitivity analyses for non-Black estimates.

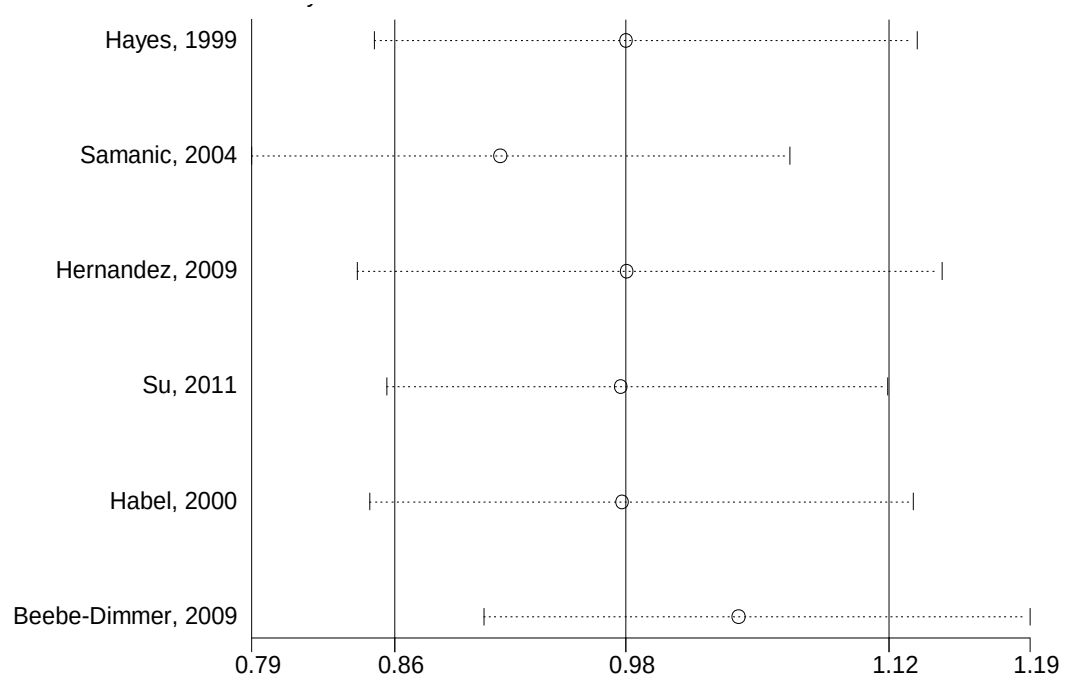

Figure 6. Influence sensitivity analyses for Black estimates.

from 1969 to 1996(41). The sheer size, diversity, and follow-up time accrued sets this study apart. Research has shown that Veteran's Administration studies provide a rare and robust opportunity to study racial disparities, because the equity of care provided by the Veteran's system relative to the civilian health care paradigm in the United States (119).

Removing both of these studies reduces heterogeneity, for both groups. With the Samanic et al. study removed, I^2 = 44.3% p = 0.13, and 0% p = 0.89 in non-Blacks and Blacks, respectively. The removal of the Beebe-Dimmer et. al study reduced I^2 to 0% p = 0.99 for both groups. Countered funnel plots for the evaluation of publication bias are presented in are presented Figure 7. Publication bias is suggested by the fact that there are very few articles in the low precision areas of the plot (120). This bias is difficult to assess confidently with a small number of manuscripts (120).

D. <u>Discussion</u>

This review explored to race-specific associations of adiposity related anthropometric measures and prostate cancer risk, progression, and mortality. Our stratified summary for the RR per 5 kg/m^2 of BMI increase reflect a non-significant inverse associations in non-Black, predominantly White, sample estimates, and a non-significant positive association for Blacks. Visual inspection of waist-based measures suggest a significant positive PCa risk association with WHR, and not WC in studies with 100% AA participants. Hip circumference was not significantly associated with PCa risk in the Black subgroup (111). Summary estimates of aggressive disease and progression in both racial groups were not significant. Despite weak associations, the directionality of the associations seen were notably opposite across racial groups; positive in Blacks and inverse among Whites. This may suggest that race has a role as an effect measure modifier of adiposity-PCa associations.

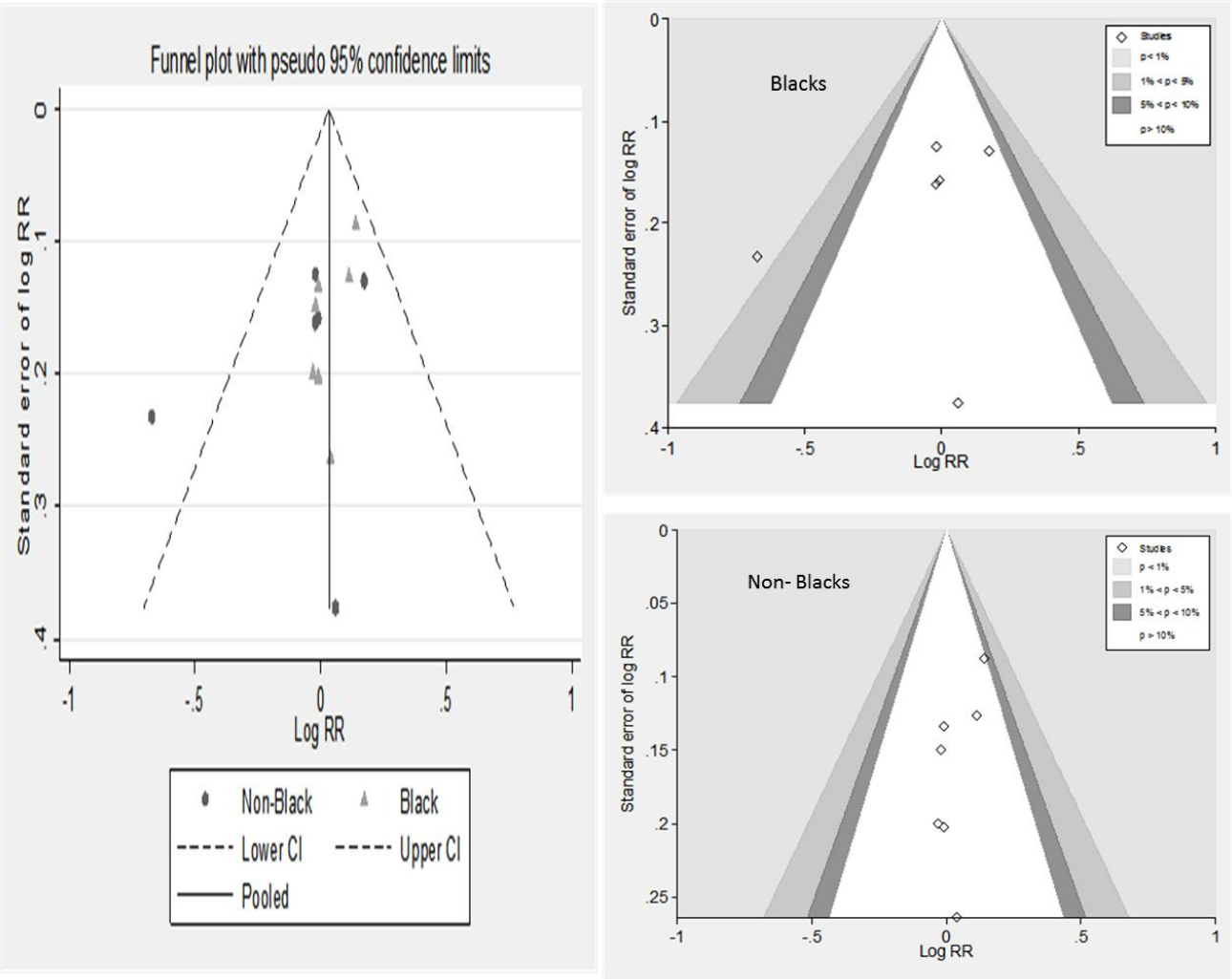

Figure 7. Publication bias for associations between body mass index and prostate cancer occurrence, by race.

1. Other reviews of general obesity and prostate cancer

a. Occurrence

Our results were similar to that of other meta-analyses in that we observed great variability in association estimates. MacInnis et al. performed an extensive meta-analysis of anthropometric associations with prostate cancer risk on studies with predominantly Caucasian participants (108). Fifty-six studies qualified for selection into the review, due to their focus on Asian and Caucasian estimates. There was a weak positive association with BMI (RR per 5 kg/m^2: 1.05[1.01, 1.08], height RR per 10cm increment: 1.05 [1.02, 1.09] (108). These results reflect the great variation in the studies contributing to the summary estimate of the BMI-PCa risk associations (108). Some studies included in this meta-analysis found no association, while others have reported a higher general PCa risk associated with elevated BMI, or higher risk for aggressive tumors (121-123). In her 2007 analysis of the NIH-AARP Diet and Health study cohort, Wright found that higher baseline BMI was significantly associated with reduced total PCa incidence (43). An earlier study had found similar inverse association between early life obesity and risk (124). We included predominantly White estimates from studies which compared Whites and Blacks; we did not include White estimates from studies without AA participants, this may have accounted for some of the difference in our summary estimate compared to previous meta-analyses. Interestingly, the Black and White estimates reported in the Samanic et al. article did not differ significantly. This Veteran's administration study population had less barriers to detection, relative to the civilian participants of the other studies in our meta-analysis. This may suggest the importance of access to care in racial differences in BMI-PCa associations.

b. Aggression and progression

The association of obesity with prostate tumor aggressiveness and progression is more consistent (125); (26, 91, 126, 127). Various studies have found positive associations between high BMI (overweight and or obese categories) and high-grade disease and or recurrence (26, 91, 126, 127).

Obesity has been associated with increased rates of biochemical failure, unsuccessful surgical intervention, and confounds the clinical utility of PSA velocity and post-operative PSA as biomarkers for relapse (128, 129). Major et al. reported lower progression free probabilities among obese radical prostatectomy patients compared to non-obese (130). Blacks had greater BMIs, higher tumor grades, and more recurrence events in a study by Amling et al., who observed a positive obesity association with risk for recurrence and high grade tumor upon resection(126). Our results concur with the broader literature; across race, adiposity tends to be positively associated with PCa recurrence. We observed that the magnitude of this positive association was higher in Blacks; this may be due to the larger prevalence of adiposity in this racial group.

c. Mortality

We were unable to explore race-specific associations between anthropometry and mortality, due to the lack of qualifying articles. Most of the mortality articles were excluded because their analyses samples did not include AA men, or they did not present race stratified analyses. A recent meta-analysis by Cao et al. observed that BMI was associated with prostate cancer mortality (12 to 20% increases per 5 increment increase in BMI) in initially disease free persons (39). Of the 26 articles in their review, 2 presented race-specific estimates (39). Neither of them had mortality as the outcome, confirming the lack of available cause-specific articles matching our search criteria.

2. Central adiposity

Most studies on the PCa-adiposity associations have relied on BMI, without consideration of other important measures related to body composition: actual adiposity, energy balance, or body fat distribution. Hsing et al. observed an association between PCa risk and high waist-hip ratio (WHR) and suggests a possible advantage of body fat distribution measures over BMI when examining adiposity-PCa associations (46, 131). In a large review, MacInnis et al. demonstrated a non-significant positive association between WHR and PCa, particularly with advanced disease, RR per

0.1cm increment increase : 1.11 [0.95, 1.30]. The summary estimate for WC was also positive, yet weak, 1.03 [0.99, 1.07](108). Neither of these findings addressed risk in AA populations.

3. Molecular-level factors

Excess adipose tissue in the body, may contribute to tumorgenesis by increasing free fatty acids and cytokines like tumor necrosis factor-alpha, while suppressing adiponectin (26, 27). The ensuing insulin resistance promotes insulin-like growth factor bioavailability, creating a commensal environment for cell proliferation, and down regulating apoptotic signaling, and thus tumor development (27). Obesity upregulates the pro-cancer effects of androgens, leptin, IL-6, Vascular endothelial growth factor, insulin, and IGF-1, while down regulating anti-cancer adipokines (i.e. IGFBP-3 and adiponectin). The IGF-1 axis hypothesis fails to consider paracrine mechanisms (29). The paradoxical directionality of free IGF with body fatness and weight loss may explain some of the inconsistency in observed cancer-adiposity association studies (29); insulin mediated pathways (i.e. metabolic syndrome) are clearly associated to prostate cancer progression(30, 31). Other probable mechanisms underlying observed associations between adiposity and cancer include the adipose tissue hypoxia hypothesis, migration of adipose derived stromal cells, obesity induced inflammation, and oxidative stress and obesity-cancer related genetic co-expression and epistasis (29, 32-38).

Our systematic review did not retain any articles exploring associations with molecular level adiposity related biomarkers, namely due to their lack of AA participants and or not having PCa risks as the endpoint under study. There was a single Beebe-Dimmer et al. article on genetic variation in ADIPOQR1 and ADIPOQ, which reported identifying an association between rs1501299 in ADIPOQ and BMI, but not PCa risk (132). As research and technology evolve, special efforts to explore underlying mechanistic associations in the adiposity-PCa relationship must reflect the diversity of those affected. Adiponectin, for example, is a protein secreted by adipose tissue, playing a rate limiting role in lipid metabolism and an anti-cancer adipokine (133). Its role in tumorgenesis is not completely

understood (28). Lower serum adiponectin is associated with obesity, specifically central obesity (134, 135). Studies have reported lower mean adiponectin levels among AA than Whites, stratified by BMI categories (normal weight, overweight, or obese) (134, 135). Many genetic variants (i.e. I164T and G276T) are related to adiponectin concentration (136-138). The prevalence of these of genetic variants and their possible function in affecting adiponectin levels need to be explored and validated in AA men. Generally, current basic science and molecular epidemiologic research on adiposity related mechanisms in PCa, need to be replicated and independently explored in AA men.

4. Strengths and limitations

The thorough search methodology, consideration for study design and quality, and use of GLST methods for RR estimation and transformation are the primary strengths of this review. Observational study biases (including recall and selection bias) may contribute to the limitations of systematic review and meta-analyses. The various categorizations of exposure and levels of detail put forth in the original studies are hard to address as potential confounders at the study-level. Our GLST method does assume that the exposure increment is constant, which may not be the case.

E. Conclusions

There are obvious etiologic differences between AA prostatic neoplasm and those from men of other ethnic backgrounds. Worldwide, African American and Jamaican men, have the highest PCa incidence rates (2). There have been reviews of the risk factors contributing to these disparities in PCa, but most are not dedicated solely to the role of adiposity (139). All of the aforementioned studies of adiposity and PCa association find Black race to be a significant predictor of PCa risk, morbidity, or mortality. Very few report data exploring race as a modifier associations between PCa occurrence, progression, or mortality and adiposity (39, 124).

The results of this systematic review highlight the need for more studies with robustly diverse participants to enable informative race and ethnicity stratified analyses. The void of such articles is especially true for AA ethnic groups, most frequently and gravely affected by prostate cancer.

IV. PROSPECTIVE ANALYSIS OF WAIST CIRCUMFERENCE IN RELATION TO PROSTATE CANCER INCIDENCE AND MORTALITY

A. Introduction

Prostate cancer (PCa) accounts for 29% of all incident cancer cases and 11% of all cancer deaths among men in the United States *(*US), which is second only to lung cancer (2). Excess body fat may contribute to prostate tumorgenesis, unfavorable progression, and PCa-specific mortality (90, 140). Currently*,* 33.8% of adults in the United States are obese (defined as a body mass index of at least 30 kg/m^2), and there has also been a striking increase in the prevalence of obesity among adolescents (141). Racial and ethnic minorities are disproportionately affected by both the obesity epidemic, and poor PCa outcomes (24, 141).

Results from studies of body mass index (BMI) and PCa risk have been mixed. Obesity has been shown to be both inversely and directly associated with PCa incidence and progression. (30, 39-41). On the other hand, a clearer relationship has emerged between BMI and prostate cancer mortality (42). In their 2007 analysis of the National Institutes of Health-AARP (NIH-AARP) Diet and Health Study cohort, for example, Wright et al. demonstrated that morbid obesity ($\geq 40kg/m^2$) and weight change from age 18 to baseline were positively associated with fatal prostate cancer (43).

BMI does not distinguish between lean and fat mass, and therefore provides a limited picture of body fatness when used on its own (24, 121). The majority of studies on adiposity and prostate cancer have relied on this metric, without consideration of body composition (i.e. lean versus fat mass). Waist circumference (WC), hip circumference (HC), and waist-to-hip ratio (WHR) are measures or central adiposity that capture body fat distribution and body shape (15, 24). Waist-based measures, including waist-t-hip ratio, have low error in estimating body fat distribution for most body types, and provide insight into the type of obesity at hand (i.e. visceral android or gynecoid obesity) (18, 142). This is important since excess visceral fat has been associated with inflammation, metabolic syndrome,

cardiovascular disease, and cancer, independent of total body fatness (20). Hip circumference, though not a direct measure of adipose tissue, has been shown to correlate with measures obtained using Dual Energy X-ray Absorptiometry (DXA), the gold standard for measuring body fatness (18, 24). No other anthropometric measure alone had done so.

We examined associations between central adiposity (WC, HC, and WHR) and prostate cancer incidence and mortality in a large prospective cohort, and assessed whether they were independent of BMI. Particular attention was paid to variation in these associations across racial groups, as African Americans have one of the highest rates of this disease in the world (2, 60).

B. Methods

1. Study population

The NIH-AARP Study began in 1995, when an extensive questionnaire that captured information on diet, height, weight, and other risk factors was mailed to 3.5 million AARP members between the ages of 50 and 71 who resided in California, Pennsylvania, Florida, New Jersey, North Carolina, Louisiana, Atlanta, Georgia, or Detroit, Michigan. After the initial mailing, 617,119 people returned the questionnaire and 567,169 respondents remained in the analytic dataset after exclusions due to skipped responses, proxy submissions, unclear gender, and withdrawals (105).

Those who responded to the baseline questionnaire were sent a second questionnaire within six months of the initial survey. This supplementary risk factor questionnaire (RFQ) ascertained WC, HC, and PCa screening history, as well as other lifestyle and medical factors. Of the 330,120 RFQ respondents, we excluded female participants (n = 134,847), men who had cancer diagnoses or cancer-specific death on or before the RFQ return date (n = 6,826), participants whose surveys were completed by proxy (n = 10,159), and men with missing or extreme values for total calories consumed (n = 1,445 with values beyond two times the interquartile range of Box-Cox log transformed intake) and or waist circumference (n = 34,840), leaving a total of 142,003 men for the present analysis. The NIH-AARP

Diet and Health Study was approved by the Special Studies Institutional Review Board of the U.S. National Cancer Institutes. All participants provided informed consent.

2. Cohort follow-up

Members of the NIH-AARP cohort are followed annually for change of address by matching the cohort database to that of the National Change of Address (NCOA) database, maintained by the U.S. Postal Service (USPS). Information on address changes are also obtained through receipt of USPS processing of undeliverable mail, from other address changes, updated services, and directly from participants who report address changes in response to study mailings, such as questionnaires, newsletters, sample kits, etc. Vital status is ascertained by annual linkage of the cohort to the Social Security Administration Death Master File (SSA DMF) on deaths in the U.S., follow-up searches of the National Death Index (NDI) for subjects that match to the SSA DMF, cancer registry linkage, questionnaire responses, and responses to other mailings. During the follow-up period, over 95% of the cohort members either did not match any records of out-of-state moves in NCOA and other address change databases, or relocated within one of the eight states included in the study; thus, a very high percentage of the cohort remained under active follow-up for cancer outcomes during the study period.

3. Ascertainment of prostate cancer cases and deaths

Incident cases of prostate cancer were identified through December 31, 2006 via linkage between eight state cancer registry databases and the NIH-AARP cohort. Using the American Joint Committee on Cancer TNM classification system, localized PCa cases were defined as organ confined with a clinical or pathologic stage of T1a-T2b, N0M0. Men with TNM classifications of T3, T4 or N1, M1, as well as those who died of prostate cancer between 1996 and 2006, were considered to have advanced (extra-prostatic) disease (143). Information on Gleason sum was not available. Deaths occurring between 1995 and 2008 with prostate cancer listed as the underlying cause were identified through linkage to the National Death Index (NDI) Plus. Virtually complete data on first and last name,

address history, gender, date of birth, and Social Security number were available for ~85% of participants, which enabled optimal matching in the NDI. Those with PCa as the underlying cause of death defined as ICD-*9-CM* diagnosis code 185 or ICD 10 code C61 were included in this analysis. Further details on the design and maintenance of this cohort have been described elsewhere (105).

4. Measures of central adiposity

Waist and hip circumferences were self-reported by study participants. The RFQ depicted proper positioning of a tape measure using an illustration, and participants were asked to use a tape measure, while standing, without bulky clothing, to obtain the circumference of their waist at a point that was 1 inch (2.5 cm) above their navel, and hips "at the largest point" below their natural waist, reporting values to the nearest quarter inch (21, 144).

5. Statistical analyses

Follow-up accrued from return of the RFQ to PCa diagnosis, death, or end of study period (December 31, 2006 or December 31, 2008 for the incidence and mortality analyses, respectively). Multivariate Cox proportional hazards models, with age as the underlying time metric, were used to estimate relative risks (RR) and 95% confidence intervals (CI) for measures of central adiposity (WC, HC, and WHR) in relation to prostate cancer risk (total, localized, and advanced) and prostate cancer-specific mortality.

All anthropometric measures were divided into quintiles based on the distribution in the cohort, with the second quintile set as the reference category. Each of these variables was also analyzed continuously (WC and HC: per 5 cm; WHR: per 0.1 unit increment). Since clinical cut points for WC and WHR have been defined by the World Health Organization (< 102 versus ≥ 102 cm for WC;<0.95 versus ≥ 0.95 for WHR (118, 118), we additionally analyzed associations between PCa and waist-based dichotomous variables. Linear tests for trend were conducted using the median value of each quintile modeled as a continuous variable.

Variables that were evaluated as confounders included race (Black, White, Other), BMI (>30 or ≤30 kg/m^2), education level (<12 years or ≥12 years), family history of prostate cancer in a first degree relative, smoking status (current, former, never), prostate cancer screening history (prostate specific antigen (PSA) and or digital rectal exam (DRE)) in the 3 years preceding the baseline survey), personal history of diabetes, self-described health status (good, fair, poor), and physical activity (defined as ≥20 minutes of vigorous movement that increased heart rate and caused perspiration; never, rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, and 5 or more times per week). Each of these variables was examined since they have been previously linked to PCa in this, or other cohort studies (43, 45, 145). Confounding by individual dietary factors, including alcohol consumption and intakes of calories, lycopene, calcium, selenium, vitamins A, D, and E, zinc, and stearic (18:0), oleic (18:1), linoleic (18:2), and linolenic acids (18:3) was also explored.

Effect modification was explored by conducting stratified analyses, as well as adding cross-product terms to main effects models. Waist circumference was categorized into tertiles rather than quintiles in stratified analyses in order to conserve power. We explored whether associations between central adiposity and PCa varied across subgroups of race (Non-Hispanic Black versus Non-Hispanic White), smoking status (Ever versus Never smoker), PCa family history (Yes or No), prostate cancer screening practices (Yes or No PSA in Past 3 years; Yes or No DRE in past 3 years), physical activity (vigorous activity > the cohort median [1.5 days per week], vigorous activity < the cohort's median activity), personal history of diabetes (Yes or No) and selected dietary factors (all split at the median value).

All analyses were performed using SAS® 9.2 software. The proportional hazards assumption was tested using the ASSESS statement with the PH option in Proc PHREG. To ensure that our associations were not influenced by preexisting disease, we conducted a lag sensitivity analysis in which cases that were diagnosed within 1, 3, and 5 years of follow-up were excluded.

C. Results

Of the 142,003 male participants with available data, 12,165 men developed prostate cancer during the incidence follow-up period (1995-2006) and 414 men had a PCa-specific death during the mortality follow-up period (1995-2008). Of the 12,165 PCa cases, 1128 were classified as extra-prostatic (advanced) disease and 7,610 were classified as organ confined (localized) disease. Approximately 2% of the analytic cohort was African American and 3% were Hispanic, Asian, Pacific Islander, American Indian, or Alaska Native. The mean age for the sample was 63.1 years. Twenty-nine percent of study participants had large WC (≥102cm); 42% of men had a WHR above 0.95cm. 48% were overweight (BMI 25-29.9 kg/m^2), and 15% were obese (BMI≥30 kg/m^2). Men with larger WC had higher BMI, were less educated and less likely to be a current smoker, were not as physically active, and had a greater likelihood of having had diabetes than men with lower WC (Table V). With respect to diet, total energy intake and intakes of total and saturated fat, alcohol, red meat, vitamin D, and lycopene were positively associated with increasing WC. In contrast, calcium and vitamin E intakes decreased with increasing WC. See Table XIV, Appendix for anthropometic correlations. See Table XV, Appendix for univariate and bivariate statistics.

1. Associations between waist circumference and prostate cancer endpoints

There were significant inverse associations between WC and total PCa occurrence in the first and fifth quintiles of WC (Table VI). A significant trend across categories was noted in age-adjusted analyses. Associations with localized disease showed similar patterns of risk. Additional adjustment for BMI attenuated the inverse associations noted among men in the highest quintile of WC. Notably, BMI remained a significant predictor of localized PCa in these models, RR_{BMI}: 0.92 (0.85, 1.00), p = 0.04. Waist circumference was not related to advanced disease, but was significantly associated with PCa-specific mortality, with men in the highest quintile experiencing 38% increases in risk compared to the

TABLE V

DEMOGRAPHIC AND LIFESTYLE CHARACTERISTICS OF NATIONAL INSTITUTES OF HEALTH AARP DIET AND HEALTH STUDY, MALE PARTICIPANTS[a b]

	Quintiles of waist circumference (cm)				
	68.1-82.2	82.3-96.4	93.98-98.55	99.06-106.17	106.68-138.43
No. of participants	25,539	29,043	29,087	27,510	30,842
Age, years	62.0	62.5	62.7	62.9	62.5
Waist circumference, cm	84.4	91.0	95.9	101.9	113.0
BMI, kg/m²	23.3	25.0	26.4	27.7	31.4
Weight, kg	71.5	78.9	84.0	89.2	101.9
Height, m	1.8	1.8	1.8	1.8	1.8
Racial/ Ethnic group (%)					
Non-Hispanic White	89.6	93.5	94.8	94.6	95.7
Non-Hispanic Black	2.9	2.1	1.7	1.4	1.7
Other [c]	6.4	3.6	2.6	2.2	1.7
Missing	1.3	0.9	0.9	0.8	0.9
Education (%)					
<12 years	16.7	17.2	17.3	17.5	20.2
12 years	8.8	8.7	9.3	9.4	10.0
Some college	20.8	21.4	21.7	22.0	23.9
≥ College degree	53.8	52.8	51.7	51.1	45.9
Smoking Status (%)					
Never	35.6	32.8	31.8	28.7	25.2
Former	51.6	58.2	60.7	64.0	67.1
Current	12.8	9.1	8.0	7.3	7.8
Physical activity, hours per week [d]	1.71	1.54	1.43	1.31	1.08
Personal history of diabetes (% Yes)	5.3	6.7	7.6	9.5	15.4
Family history of PCa (% Yes)	9.3	9.8	9.5	10.0	9.7
Screening history (% Yes) [c]					
Digital rectal exam	84.9	87.2	87.6	87.7	86.1
Prostate specific antigen	70.0	73.9	74.4	73.9	71.2
Self-reported poor health (%)	0.96	0.79	0.89	1.01	2.16
Daily dietary intake [f]					
Total energy, kcal	1,964	1,959	1,989	2,017	2,107
Fish, g	20.6	21.0	20.9	20.6	20.8
Red meat, g	58.7	64.7	68.8	72.0	79.8
Alcohol, g	15.4	16.2	16.9	17.8	17.4
Calcium, mg**	946.0	932.0	927.0	920.0	913.0
Lycopene, μg	7,523.0	7,589.0	7,504.0	7,450.0	7,813.0
α-Tocopherol, mg**	83.6	81.0	78.5	75.1	72.5
Vitamin D, mcg **	4.8	4.9	4.9	5.0	5.0
Selenium, μg**	96.9	97.4	97.5	97.8	99.1
Zinc, mg**	18.3	18.0	18.0	18.0	18.0
Total Fat, g	62.9	64.4	66.7	68.9	75.2
Saturated fat, g	19.6	20.1	20.9	21.6	23.8
α-Linoleic acid, g	2.8	3.0	3.1	3.2	3.2

[a] N = 142,003.

[b] Means for continuous variables; Percentages for categorical variables

[c] Comprised of Hispanics, Asian, Pacific Islanders, American Indian, and Alaska Natives

TABLE V (continued)

[d] Defined as physical activity ≥ 20 minutes, which increased heart rate and caused perspiration

[e] Within 3 years prior to baseline;

[f] Adjusted for energy, alcohol exclusive

[g] Includes intake from supplements

TABLE VI

RELATIVE RISKS AND CONFIDENCE INTERVALS FOR PROSTATE CANCER INCIDENCE AND MORTALITY ACCORDING TO QUINTILES OF WAIST CIRCUMFERENCE, NATIONAL INSTITUTES OF HEALTH AARP DIET AND HEALTH STUDY, MALE PARTICIPANTS

	Waist circumference quintiles (cm)					p for trend		
	68.1-82.2	88.9-93.5	94.1-98.6	99.1-106.2	106.7-138.4		Per 5 cm	<102/≥102 cm
Total incidence								
Person years	219,670	248,519	246,756	233,170	257,278		860,446	860,446
No. of cases	2,103	2,639	2,647	2,363	2,413		12,165	8,844/3,321
Age adjusted	0.93 (0.88,0.98)***	1.0 (ref)	1.02 (0.95,1.06)	1.01 (0.95,1.07)	0.89 (0.84,0.94)***	0.03	0.99 (0.98,0.99)	0.93 (0.90,0.97)
Multivariate [a]	0.93 (0.88,0.98)***	1.0 (ref)	1.01 (0.96,107)	0.96 (0.91,1.07)	0.93 (0.88,0.98)***	0.26	0.99 (0.98,1.00)	0.96 (0.93,1.00)
Multivariate [b]	0.93 (0.88,0.98)***	1.0 (ref)	1.01 (0.96,1.07)	0.96 (0.91,1.02)	0.94 (0.88,1.01)	0.99	1.00 (0.98,101)	0.98 (0.94,1.03)
Localized disease								
No. of cases	1,349	1,643	1,684	1,463	1,411		7,609	5,582/2,028
Age adjusted	0.96 (0.89,1.03)	1.0 (ref)	1.02 (0.96,1.10)	0.94 (0.87,1.01)	0.86 (0.81,0.93)***	0.03	0.98 (0.97,0.99)	0.90 (0.86,0.95)
Multivariate [a]	0.96 (0.90,1.03)	1.0 (ref)	1.03 (0.97,1.10)	0.95 (0.89,1.02)	0.91 (0.85,0.98)***	0.03	0.99 (0.98,1.00)	0.93 (0.89,0.98)
Multivariate [b]	0.96 (0.89,1.03)	1.0 (ref)	1.03 (0.97,1.11)	0.96 (0.90,1.03)	0.95 (0.88,1.03)	0.62	1.00 (0.98,1.01)	0.97 (0.91,1.03)
Advanced disease								
No. of cases	205	232	227	216	248		1,126	799/329
Age adjusted	1.02 (0.84,1.23)	1.0 (ref)	0.98 (0.82,1.18)	0.99 (0.82,1.19)	1.03 (0.86,1.23)	0.88	1.00 (0.97,1.03)	1.02 (0.90,1.16)
Multivariate [a]	1.00 (0.83,1.21)	1.0 (ref)	0.99 (0.82,1.19)	1.00 (0.83,1.21)	1.06 (0.88,1.27)	0.53	1.00 (0.98,1.04)	1.05 (0.92,1.19)
Multivariate [b]	1.00 (0.83,1.21)	1.0 (ref)	0.99 (0.82,1.18)	1.00 (0.83,1.21)	1.03 (0.84,1.29)	0.76	1.00 (0.97,1.04)	1.03 (0.88,1.20)
Mortality								
Person years	289,104	329,686	328,699	309,505	339,731		1,140,190	1,140,190
No. of deaths	61	77	84	81	111		414	262/142
No. of cases	0.92 (0.66,1.29)	1.0 (ref)	1.08 (0.79,1 .48)	1.10 (0.80,1.50)	1.38 (1.03,1.85)**	0.005	1.09 (1.04,1.14)	1.31 (1.07,1.60)
Age adjusted	0.89 (0.64,1.25)	1.0 (ref)	1.09 (0.80,1.49)	1.11 (.81,1.52)	1.35 (1.01,1.82)**	0.006	1.08 (1.04,1.13)	1.28 (1.04,1.57)
Multivariate [a]	0.89 (0.64,1.25)	1.0 (ref)	1.09 (0.80,1.48)	1.08 (0.79,1.49)	1.24 (0.88,1.75)	0.08	1.07 (1.01,1.13)	1.14 (0.89,1.45)

[a] Adjusted for race, personal history of diabetes, DRE and or PSA within 3 years of baseline, family history of prostate cancer, education level, physical activity, and smoking status.

[b] Additionally adjusted for BMI.

*p < .10. **p < .05. ***p < .01.

reference group. Adjustment for BMI attenuated these findings. Similar results were obtained when WC was analyzed continuously and as a dichotomous variable based on clinically relevant cut points. Notably, the WC-PCa specific mortality association remained significant with further adjustment for BMI when WC was modeled continuously.

2. Waist circumference association within strata of selected covariates

a. Incidence

Stratified analyses (Table VII) demonstrated inverse associations between tertiles of WC and total and localized risk for PCa among men who underwent DRE or PSA testing in the three years prior to baseline, men with a family history of PCa, more than 12 years of formal education. Those with no personal history of diabetes had a reduced risk for localized disease. Using WHO clinical cut points, WC <102cm compared to ≥102cm, (data not shown), confirms the tertiles analyses. A positive screening history, DRE or PSA, conferred a significant protective effect estimate for total risk RR_{DRE}: 0.96 [0.92, 0.99] and localized disease, RR_{DRE}: 0.93 [0.88, 0.98], RR_{PSA}: 0.93[0.88, 0.99]). Two-category WC analysis showed a moderate inverse association was for those with (RR_{FH}: 0.94 [0.89, 1.00]) and without (RR_{FH} 0.87 [0.75, 0.97]) a positive PCa family history. Non- monotonic trends were observed with increasing WC for incident and localized disease among those with a positive screening history, no history of diabetes, and more than 12 years of formal education. Increasing WC also demonstrated non-monotonic trends with exercising less than the median for the cohort (< 1.5 days a week), having smoked, and consuming more than 15grams of alcohol per day.

Increased risk for total and localized disease associated with increasing WC was observed among men who did not recall having a PSA test in the 3 years before baseline, did not have a family history of PCa, had less than 12 years of education, and drank more than 15g of alcohol per week. WHO category analysis confirms the finding that having less than 12 years of education was associated with WC associated increased total risk, RR: 1.28 (1.01, 1.61). A moderate association was observed for men in

TABLE VII

RELATIVE RISKS AND CONFIDENCE INTERVALS FOR PROSTATE CANCER: TOTAL INCIDENCE AND MORTALITY ACCORDING TO TERTILES OF WAIST CIRCUMFERENCE, STRATIFIED BY SELECTED FACTORS, NATIONAL INSTITUTES OF HEALTH AARP DIET AND HEALTH STUDY

		Tertiles of waist circumference			
		68.1-91.6 cm	91.7-115.2 cm	115.3-138.7 cm	
	Cases	RR (95% CI)	RR (95% CI)	RR (95% CI)	p for trend
Race†					
Non-Hispanic White					
Total incidence	11,373	1.00 (ref)	1.05 (0.99, 1.09)	0.97 (0.93, 1.02)	0.16
Localized disease	7,082	1.00 (ref)	1.06 (1.00, 1.12)	0.95 (0.90, 1.01)	1.00
Advanced disease	1,051	1.00 (ref)	0.93 (0.80, 1.08)	1.02 (0.88, 1.18)	1.00
Mortality	333	1.00 (ref)	1.01 (0.78, 1.31)	1.19 (0.93, 1.52)	0.15
Non-Hispanic Black					
Total incidence	373	1.00 (ref)	0.82 (0.64, 1.06)**	0.86 (0.67, 1.11)	0.21
Localized disease	230	1.00 (ref)	0.95 (0.69, 1.29)	0.85 (0.62, 1.18)	0.33
Advanced disease	37	1.00 (ref)	0.85 (0.38, 1.91)	1.01 (0.46, 2.20)	0.79
Mortality	18	1.00 (ref)	1.09 (0.35, 3.36)	1.06 (0.34, 3.32)	0.91
BMI<30 kg/m²					
Total incidence	10,189	1.00 (ref)	1.05 (1.00, 1.10)	0.98 (0.93, 1.03)	0.71
Localized disease	6,435	1.00 (ref)	1.06 (1.01, 1.12)	0.97 (0.92, 1.04)	0.74
Advanced disease	921	1.00 (ref)	0.96 (0.83, 1.12)	1.03 (0.87, 1.21)	0.85
Mortality	323	1.00 (ref)	1.02 (0.79, 1.32)	1.04 (0.78, 1.34)	0.79
BMI≥30 kg/m²					
Total incidence	1,976	1.00 (ref)	0.97 (0.68, 1.40)**	0.97 (0.69, 1.36)	0.83
Localized disease	1,175	1.00 (ref)	0.92 (0.58, 1.46)*	0.92 (0.60, 1.43)	0.86
Advanced disease	207	1.00 (ref)	0.61 (0.23, 1.63)	0.72 (0.29, 2.82)	0.92
Mortality	91	1.00 (ref)	0.55 (0.12, 2.67)	0.69 (0.17, 2.82)	0.90
DRE *No*					
Total incidence	1,296	1.00 (ref)	1.08 (0.93, 1.23)	1.07 (0.93, 1.22)	0.34
Localized disease	775	1.00 (ref)	1.17 (0.98, 1.39)	1.04 (0.88, 1.24)	0.68
Advanced disease	155	1.00 (ref)	1.01 (0.91, 1.58)	1.16 (0.79, 1.69)	0.45
Mortality	88	1.00 (ref)	1.15 (0.67, 1.57)	1.44 (0.87, 2.41)	0.15
DRE *Yes*					
Total incidence	10,869	1.00 (ref)	1.04 (0.99, 1.09)	0.96 (0.92, 1.01)	0.09
Localized disease	6,835	1.00 (ref)	1.04 (0.98, 1.10)	0.94 (0.88, 0.99)***	0.02
Advanced disease	973	1.00 (ref)	0.95 (0.81, 1.11)	1.03 (0.88, 1.20)	0.71
Mortality	326	1.00 (ref)	1.02 (.77, 1.35)	1.16 (0.91, 1.55)	0.20
PSA *No*					
Total incidence	2,626	1.00 (ref)	1.20 (1.09, 1.32)	1.06 (0.96, 1.16)	0.32
Localized disease	1,492	1.00 (ref)	1.23 (1.09, 1.39)	1.00 (0.88, 1.13)	0.85
Advanced disease	315	1.00 (ref)	1.20 (0.91, 1.58)	1.14 (0.86, 1.49)	0.38
Mortality	148	1.00 (ref)	1.02 (0.67, 1.57)	1.39 (0.94, 2.04)	0.09

TABLE VII (continued)

RELATIVE RISKS AND CONFIDENCE INTERVALS FOR PROSTATE CANCER: TOTAL INCIDENCE AND MORTALITY ACCORDING TO TERTILES OF WAIST CIRCUMFERENCE, STRATIFIED BY SELECTED FACTORS, NATIONAL INSTITUTES OF HEALTH AARP DIET AND HEALTH STUDY

		Tertiles of waist circumference			
	Cases	68.1-91.6 cm RR (95% CI)	91.7-115.2 cm RR (95% CI)	115.3-138.7 cm RR (95% CI)	p for trend
PSA *Yes*					
Total incidence	9,539	1.00 (ref)	1.04 (0.96, 1.06)***	0.95 (0.90, 1.00)**	0.05
Localized disease	6,118	1.00 (ref)	1.01 (0.95, 1.07)***	0.93 (0.88, 0.99)**	0.03
Advanced disease	813	1.00 (ref)	0.88 (074, 1.04)*	1.01 (0.86, 1.20)	0.85
Mortality	266	1.00 (ref)	1.06 (0.78, 1.44)	1.16 (0.86, 1.57)	0.32
Family history *No*					
Total incidence	10,420	1.00 (ref)	1.05 (1.01, 1.10)	0.99 (0.94, 1.04)	0.60
Localized disease	6,522	1.00 (ref)	1.06 (1.00, 1.13)	0.94 (0.94, 1.02)	0.17
Advanced disease	969	1.00 (ref)	0.98 (0.84, 1.15)	1.07 (0.91, 1.24)	0.41
Mortality	352	1.00 (ref)	1.07 (0.83, 1.38)	1.28 (0.99, 1.65)	0.06
Family history *Yes*					
Total incidence	1,745	1.00 (ref)	0.98 (0.88, 1.10)	0.88 (0.78, 0.98)**	0.03
Localized disease	1,088	1.00 (ref)	0.97 (0.84, 1.12)	0.85 (0.74, 0.99)	0.04
Advanced disease	159	1.00 (ref)	0.82 (0.55, 1.21)	0.92 (0.63, 1.34)	0.67
Mortality	62	1.00 (ref)	0.91 (0.48, 1.72)	1.03 (0.56, 1.88)	0.92
Diabetes *No*					
Total incidence	11,404	1.00 (ref)	1.04 (0.99, 1.09)	0.96 (0.92, 1.00)	0.11
Localized disease	7,142	1.00 (ref)	1.05 (0.99, 1.11)	0.94 (0.89, 1.00)	0.04
Advanced disease	1,064	1.00 (ref)	0.94 (0.81, 1.09)	1.03 (0.89, 1.19)	0.67
Mortality	382	1.00 (ref)	1.07 (0.83, 1.38)	1.20 (0.94, 1.54)	0.14
Diabetes *Yes*					
Total incidence	761	1.00 (ref)	1.18 (0.96, 1.45)	1.12 (0.93, 1.35)	0.38
Localized disease	468	1.00 (ref)	1.98 (0.85, 1.42)	1.01 (0.80, 1.27)*	0.91
Advanced disease	64	1.00 (ref)	1.65 (0.77, 3.56)	1.46 (0.71, 2.98)	0.44
Mortality	32	1.00 (ref)	0.78 (0.23, 2.72)	1.69 (0.63; 4.52)	0.15
Physical activity < median (1.5 days/week)					
Total incidence	5,380	1.00 (ref)	1.00 (0.93, 1.07)	0.96 (0.90, 1.03)	0.28
Localized disease	3,316	1.00 (ref)	1.01 (0.93, 1.11)	0.94 (0.86, 1.02)	0.09
Advanced disease	523	1.00 (ref)	0.90 (0.71, 1.13)	1.09 (0.88, 1.02)	0.36
Mortality	215	1.00 (ref)	0.98 (0.68, 1.41)	1.19 (0.86, 1.66)	0.32
Physical activity ≥ median (1.5 days/week)					
Total incidence	6,785	1.00 (ref)	1.07 (1.01, 1.13)	0.96 (0.91. 1.03)	0.40
Localized disease	4,294	1.00 (ref)	1.07 (1.00, 1.15)	0.95 (0.88, 1.02)	0.22
Advanced disease	605	1.00 (ref)	1.01 (0.84, 1.22)	1.00 (0.82, 1.22)	0.98
Mortality	199	1.00 (ref)	1.09 (0.77, 1.54)	1.26 (0.90, 1.77)	0.10

TABLE VII (continued)

RELATIVE RISKS AND CONFIDENCE INTERVALS FOR PROSTATE CANCER: TOTAL INCIDENCE AND MORTALITY ACCORDING TO TERTILES OF WAIST CIRCUMFERENCE, STRATIFIED BY SELECTED FACTORS, NATIONAL INSTITUTES OF HEALTH AARP DIET AND HEALTH STUDY[a]

		Tertiles of waist circumference			
	cases	68.1–91.6cm RR (95% CI)	91.7–115.2cm RR (95% CI)	115.3–138.7cm RR (95% CI)	p for trend
Education < 12 yrs.					
Total incidence	2,055	1.00 (ref)	1.10 (0.98, 1.22)	1.03 (0.92, 1.14)	0.73
Localized disease	1,168	1.00 (ref)	1.21 (1.04, 1.39)	1.06 (0.92, 1.22)	0.56
Advanced disease	181	1.00 (ref)	0.83, 0.57, 1.23)	1.07 (0.76, 1.51)	0.62
Mortality	81	1.00 (ref)	1.01 (0.57, 1.79)	1.13 (0.66, 1.91)	0.64
Education ≥12 yrs.					
Total incidence	10,110	1.00 (ref)	1.03 (0.98, 1.08)	0.96 (0.91, 1.01)	0.11
Localized disease	6,442	1.00 (ref)	1.02 (0.97, 1.09)**	0.93 (0.87, 0.99)***	0.01
Advanced disease	947	1.00 (ref)	0.98 (0.84, 1.15)	1.04 (0.89, 1.21)	0.64
Mortality	333	1.00 (ref)	1.03 (0.78, 1.35)	1.21 (0.93, 1.57)	0.06
Smoking = Never					
Total incidence	4,471	1.00 (ref)	1.08 (1.0, 1.15)	0.97 (0.90, 1.04)	0.44
Localized disease	2,744	1.00 (ref)	1.12 (1.02, 1.22)	0.99 (0.90, 1.09)	0.89
Advanced disease	402	1.00 (ref)	0.90 (0.71, 1.14)	0.99 (0.78, 1.26)	0.91
Mortality	126	1.00 (ref)	0.79 (0.51, 1.22)	0.96 (0.63, 1.46)	0.82
Smoking = current or former					
Total incidence	7,694	1.00 (ref)	1.02 (1.0, 1.15)***	0.97 (0.90, 1.04)	0.29
Localized disease	4,866	1.00 (ref)	1.01 (0.94, 1.08)*	0.92 (0.86, 0.99)	0.02
Advanced disease	726	1.00 (ref)	0.99 (0.82, 1.12)	1.08 (0.90, 1.29)	0.85
Mortality	288	1.00 (ref)	1.26 (0.93, 1.72)*	1.44 (1.07, 1.93)	0.02
Alcohol <15g/ day					
Total incidence	3,703	1.00 (ref)	1.01 (0.94, 1.10)	0.98 (0.91, 1.07)	0.67
Localized disease	2,351	1.00 (ref)	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.28
Advanced disease	348	1.00 (ref)	0.99 (0.77, 1.29)	1.05 (0.81, 1.36)	0.72
Mortality	129	1.00 (ref)	1.05 (0.66, 1.67)	1.52 (0.99, 2.33)	0.04
Alcohol ≥15g/ day					
Total incidence	8,462	1.00 (ref)	1.05 (1.00, 1.11)	0.97 (0.92, 1.02)	0.19
Localized disease	5,259	1.00 (ref)	1.08 (1.01, 1.15)**	0.94 (0.88, 1.01)*	0.08
Advanced disease	780	1.00 (ref)	0.93 (0.78, 1.12)	1.04 (0.88, 1.23)	0.63
Mortality	285	1.00 (ref)	1.09 (0.81, 1.46)	1.15 (0.86, 1.53)	0.36
Calcium[b]					
LOW (<827.57mg)					
Total incidence	6,201	1.00 (ref)	1.01 (0.94, 1.07)	0.95 (0.89, 1.01)	0.10
Localized disease	3,717	1.00 (ref)	0.99 (0.91, 1.07)	0.92 (0.85, 1.00)	0.04
Advanced disease	540	1.00 (ref)	0.89 (0.72, 1.10)	0.94 (0.77, 1.16)	0.64
Mortality	200	1.00 (ref)	0.87 (0.61, 1.25)	1.05 (0.76, 1.47)	0.71

TABLE VII (continued)

RELATIVE RISKS AND CONFIDENCE INTERVALS FOR PROSTATE CANCER: TOTAL INCIDENCE AND MORTALITY ACCORDING TO TERTILES OF WAIST CIRCUMFERENCE, STRATIFIED BY SELECTED FACTORS, NATIONAL INSTITUTES OF HEALTH AARP DIET AND HEALTH STUDY[a]

		Tertiles of waist circumference			
	cases	68.1–91.6cm RR (95% CI)	91.7–115.2cm RR (95% CI)	115.3–138.7cm RR (95% CI)	p for trend
Calcium[b]					
HIGH (≥827.57mg)					
Total incidence	5,961	1.00 (ref)	1.08 (1.02, 1.48)	1.00 (0.93, 1.06)	0.84
Localized disease	3,892	1.00 (ref)	1.11 (1.03, 1.20)	0.97 (0.89, 1.05)	0.41
Advanced disease	589	1.00 (ref)	1.03 (0.84, 1.26)	1.15 (0.94, 1.40)	0.17
Mortality	214	1.00 (ref)	1.25 (0.88, 1.77)	1.47 (1.04, 2.06)	0.03
Vitamin D[b]					
LOW (<4.37mcg)					
Total incidence	5,820	1.00 (ref)	1.06 (1.00, 1.13)	0.98 (0.92, 1.04)	0.29
Localized disease	3,670	1.00 (ref)	0.82 (0.66, 1.01)	0.88 (0.74, 1.07)	0.05
Advanced disease	547	1.00 (ref)	1.01 (0.93, 1.01)	0.92 (0.85, 1.00)	0.20
Mortality	203	1.00 (ref)	0.88 (0.62, 1.26)	1.12 (0.80, 1.55)	0.48
Vitamin D[b]					
HIGH (≥4.37mcg)					
Total incidence	6,342	1.00 (ref)	1.02 (0.98, 1.11)	0.94 (0.89, 1.00)	0.38
Localized disease	3,939	1.00 (ref)	1.09 (1.01, 1.17)	0.97 (0.89, 1.05)	0.34
Advanced disease	579	1.00 (ref)	1.12 (0.91, 1.38)	1.24 (1.01, 1.52)	0.04
Mortality	211	1.00 (ref)	1.24 (0.87, 1.77)	1.39 (0.99, 1.96)	0.06

[a] Adjusted for race, personal history of diabetes, DRE and / or PSA within 3 years of baseline, family history of prostate cancer, education level, physical activity, and smoking status.

[b] Nutrient intake values are split into high and low by creating cut points using the median intake in the cohort for that specific nutrient

*p < .10. **p < .05. ***p < .01. -p value for interaction in that specified tertile.

the 2nd tertile of WC, who had BMI≥ 30 kg/m^2; two category WC stratification of BMI did not observe a significant association RR: 1.01 (0.87, 1.17). The WC- total PCa risk association was significantly higher among those who had ever been a smoker. Yet, WHO category analysis found significant association for ever smokers in the opposite direction, RR 0.92 (0.82, 0.98). The increased risk for local disease in the 2nd tertile of WC, was significant among those with a personal history of diabetes There was a significant inverse association between WC and localized disease, as well as a positive association with PCa-specific mortality, among non-Black participants (RR: 0.93[89, 0.98]) and RR: 1.28[1.04, 1.58], respectively). No race-stratified associations reached significance in the tertile analysis, although there was a suggestive association for increased localized disease among Whites. Most of the positive associations were confirmed by stratified analysis using WHO cut points. All of the positive associations occur in the 2nd tertile of WC, making them difficult to interpret.

b. Mortality

Those with no family history of PCa, and a WC ≥102cm, had increased risk of death (RR: 1.27[1.01, 1.58]). Less than 12 years of formal education among those with a large WC conferred a positive association with mortality, RR: 1.31[1.05, 1.62]. The tertile analysis of WC associations detected an increased risk among those with no family history and a moderate (2nd tertile) WC. Positive monotonic trends for mortality risk associated with increasing WC were observed among those with no PSA, family or diabetes history ($p<0.1$), those who exercise more than the cohort median, and those who consumed more than 15grams of alcohol per day. When using WHO clinical cut points for WC (data not shown), demonstrated an increased risk for advanced PCa and mortality associated with having a large WC (≥102cm) and infrequent participation in physical activity, RR: 1.29[1.09,1.62] and 1.72[1.06, 2.77], respectively. Consumption of more than 15g of alcohol per day, and having a large WC, conferred an increased risk for PCa associated mortality as well, RR 1.35 [1.06, 1.73]. The interaction term between WC and physical activity was not statistically significant.

c. Dietary factors

Modification of the WC-PCa associations by selected dietary factors was also explored (Table VIII). The WC-PCa-specific mortality association appeared strongest among participants that consumed more than the median calcium and / or vitamin D intake levels in the cohort. Of interest, was our finding that WC was positively and significantly associated with advanced prostate cancer among those with higher vitamin D intake – a finding that was not observed among men with lower vitamin D intake. Effect modification by other nutrients that have been linked with prostate cancer was also explored (data not shown). Having a WC in the first tertile was the referent for all WC-PCa associations. Low selenium intake, data not shown, was associated with increased risk of mortality, RR: 1.68[1.16, 2.42], in the 3rd tertile of WC. The mortality associations with low selenium intake had a significant test for trend, p = 0.005. Low zinc intake showed an inverse association with advanced disease among those with WC in the 3rd tertile, (RR: 0.89[0.83, 0.97]. Test for trends of the low zinc associations were significant for total incidence (p = 0.05) and localized disease (p = 0.007). Parinaric fatty acid intake above the cohort median had an inverse association with advanced disease in the 3rd tertile of WC, RR: 0.92[0.85, 0.99], with a significant trend for the localized disease associations, p = 0.03.

3. Joint-effects analysis

Analyses of the joint effects of BMI and WC on prostate cancer endpoints revealed significant elevations in the risk of PCa-specific mortality among men in the extreme tertiles of WC who were also obese (RR_{T1}: 1.74 [1.22, 2.48]; RR_{T3}: 1.58 [1.19, 2.11], respectively). However, the p-value for interaction was not significant (Table VIII). Similar findings were obtained when the dichotomous WC variable was utilized instead of tertiles ($RR_{WC\leq102}$: 1.30 [1.02, 1.66], or $RR_{WC\geq102}$: 1.53 [1.19, 1.98]). In this analysis, there was also an inverse association for those with a large WC who were also obese with localized disease (RR: 0.93 (0.87, .98) (Table IX).

TABLE VIII

JOINT EFFECTS OF WAIST CIRCUMFERENCE TERTILES AND BODY MASS INDEX ON PROSTATE CANCER INCIDENCE AND MORTALITY, NATIONAL INSTITUTES OF HEALTH AARP DIET AND HEALTH STUDY[a]

	Tertiles of waist circumference						
	68.1-91.6cm		91.7-115.2cm		115.3-138.7cm		Interaction p value
	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	
Incidence							
BMI kg/m²							
<30	2,810	1.0 (ref)	1,198	1.08 (1.01,1.16)	244	1.01 (0.88,1.15)	0.67
≥30	1,362	1.01 (0.94,1.08)	2,809	1.03 (0.98,1.09)	3,742	0.98 (0.93,1.03)	
Localized disease							
BMI kg/m²							
<30	1,780	1.0 (ref)	761	1.08 (0.99,1.18)	149	0.97 (0.82,1.15)	0.61
≥30	843	0.99 (0.91,1.07)	1,785	1.03 (0.97,1.10)	2,292	0.94 (0.89,1.00)	
Advanced disease							
BMI kg/m²							
<30	258	1.0 (ref)	100	1.00 (0.80,1.27)	23	1.05 (0.69,1.61)	0.68
≥30	133	1.04 (0.85,1.29)	238	0.95 (0.80,1.14)	376	1.06 (0.90,1.24)	
Mortality	Deaths		Deaths		Deaths		
BMI kg/m²							
<30	72	1.0 (ref)	39	1.31 (0.88,1.93)	5	0.71 (0.29,1.76)	0.75
≥30	55	1.74 (1.22,2.48)	85	1.28 (0.93,1.75)	158	1.58 (1.19,2.11)	

[a] Adjusted for race, personal history of diabetes, DRE and / or PSA within 3 years of baseline, family history of prostate cancer, education level, physical activity, and smoking status.

TABLE IX

JOINT EFFECTS OF WAIST CIRCUMFERENCE AND BODY MASS INDEX ON PROSTATE CANCER INCIDENCE AND MORTALITY, NATIONAL INSTITUES OF HEALTH AARP DIET AND HEALTH STUDY[a]

	Waist circumference (no. of cases)			
	<102/≥102	<102	≥102	Interaction p
Incidence				
BMI < 30 kg/m²	4,077/175	Ref	1.02 (0.87, 1.18)	0.75
BMI ≥ 30 kg/m²	4,767/3146	0.99 (0.95, 1.04)	0.96 (0.91, 1.01)	
Local				
BMI < 30 kg/m²	2,581/109	Ref	1.00 (0.83, 1.22)	0.09
BMI ≥ 30 kg/m²	3,001/1919	0.99 (0.94, 1.04)	0.93 (0.87, .98)	
Advanced				
BMI < 30 kg/m²	365/16	Ref	1.05 (0.63, 1.73)	0.30
BMI ≥ 30 kg/m²	434/313	1.00 (0.87, 1.15)	1.04 (0.89, 1.22)	
Mortality	Deaths			
BMI < 30 kg/m²	112/4	Ref	0.75 (0.28, 2.03)	0.13
BMI ≥ 30 kg/m²	160/138	1.30 (1.02, 1.66)	1.53 (1.19, 1.98)	

[a] Adjusted for race, personal history of diabetes, DRE and / or PSA within 3 years of baseline, family history of prostate cancer, education level, physical activity, and smoking status.

Analyses of the joint effects of WC and physical activity Looking at tertiles of WC, (Table X), the multiplicative interaction term p-values were significant for total PCa risk ($p<0.001$) and localized disease ($p<.001$). Using WHO clinical cut points for WC, (Table XI) revealed a significant inverse association between physical activity and WC, RR: 0.93 (0.88, 0.99) and increased PCa specific mortality among men who were infrequently physical activity and had a large WC (RR: 1.32[1.05, 1.65].

4. Hip circumference and waist to hip ratio in relation to prostate cancer

Tables XII and XIII depict the age and multivariate adjusted associations for HC and WHR in relation to PCa risk and PCa-specific mortality. There was an inverse association between HC and total and localized disease, even after adjustment for BMI. The trend for the inverse associations was significant, $p = 0.02$. No significant associations were observed for risk of advanced disease. There was a suggestive increase in the risk of PCa-specific mortality among men in the highest quintile of HC, although this disappeared with further adjustment for BMI. Significant increases in risk were observed when HC was analyzed as a continuous variable although adjustment for BMI also attenuated this finding.

D. Discussion

1. Summary of findings

In this study, significant inverse associations between WC and total and localized PCa were observed. In contrast, increasing WC was linked to significant elevations in PCa-specific mortality. HC showed similar patterns of risk, whereas WHR was unrelated to any prostate cancer endpoint Examination of the WC-PCa associations within strata of selected cofactors revealed variations in risk by screening history, family history of PCa, and physical activity. Of particular note, was the finding that participating in vigorous physical activity more than the cohort median of 1.5 days per conferred an increased risk for total and localized disease, and also mortality among men with large WC. The WC-PCa association also varied across levels of calcium and vitamin D intake. Examination of the joint

TABLE X

JOINT EFFECTS OF WAIST CIRCUMFERENCE AND PHYSICAL ACTIVITY ON PROSTATE CANCER INCIDENCE AND MORTALITY, NATIONAL INSTITUTES OF HEALTH AARP DIET AND HEALTH STUDY[a]

	Tertiles of waist circumference			
	68.1-91.6 cm	91.7-115.2 cm	115.3-138.7 cm	
	RR (95% CI)	RR (95% CI)	RR (95% CI)	Interaction p
Incidence				
No. Cases	1,284	1,012	709	
none -infrequent[b]	1.0 (ref)	1.09 (1.00,1.18)	0.95 (0.86,1.04)	< 0.001
No. Cases	2,888	2995	3277	
≥once a week	1.11 (0.86,1.42)	1.14 (0.90,1.46)	1.09 (0.85,1.38)	
Localized disease				
No. Cases	817	656	449	< 0.001
none -infrequent[b]	1.0 (ref)	1.10 (0.99,1.22)	0.94 (0.83,1.05)	
No. Cases	1,806	1890	1992	
≥once a week	1.12 (0.82,1.52)	1.15 (0.85,1.57)	1.06 (0.78,1.44)	
Advanced				
No. Cases	111	82	62	0.40
none -infrequent[b]	1.0 (ref)	1.05 (0.79,1.40)	0.99 (0.73,1.35)	
No. Cases	280	256	337	
≥once a week	2.68 (0.85,8.49)	2.48 (0.78,7.87)	2.80 (0.89,8.88)	
Mortality				
No. Deaths	28	27	26	0.77
none -infrequent[b]	1.0 (ref)	1.30 (0.77,2.21)	1.51 (0.89,2.59)	
No. cases	99	97	137	
≥once a week	1.49 (0.45,4.94)	1.46 (0.44,4.86)	1.74 (0.53,5.75)	

[a] Adjusted for race, personal history of diabetes, DRE and / or PSA within 3 years of baseline, family history of prostate cancer, education level, physical activity, and smoking status.

[b] Defined as participants who reported less than 1 day a week of Physical activity.

TABLE XI

COMBINED EFFECT OF PHYSICAL ACTIVITY AND WAIST CIRCUMFERENCE ON INCIDENCE AND MORTALITY, NATIONAL INSTITUTES OF HEALTH AARP DIET AND HEALTH STUDY[a]

	Waist circumference		
	< 102	≥ 102	Interaction p
Incidence			
No. of cases	2,425	580	
None-infrequent[b]	1.0 ref	0.96 (0.92,1.01)	0.88
No. of cases	2741	6419	
≥ once a week	1.00 (0.95,1.04)	0.95 (0.87,1.04)	
Localized disease			
No. of cases	1,563	359	
None -infrequent[b]	1.0 ref	0.93 (0.88,0.99)	0.75
No. of cases	1669	4,019	
≥ once a week	1.02 (0.96,1.08)	0.93 (0.84,1.04)	
Advanced			
No. of cases	206	49	
None -infrequent[b]	1.0 ref	1.07 (0.93,1.23)	0.54
No. of cases	280	593	
≥ once a week	0.94 (0.81,1.11)	0.91 (0.68,1.21)	
Mortality			
No. deaths	61	20	
None -infrequent[b]	1.0 ref	1.32 (1.05,1.65)	0.91
No. deaths	122	211	
≥ once a week	0.78 (0.59,1.04)	0.99 (0.63,1.57)	

[a] Adjusted for race, personal history of diabetes, DRE and / or PSA within 3 years of baseline, family history of prostate cancer, education level, physical activity, and smoking status.

[b] Defined as participants who reported less than 1 day a week of Physical activity.

TABLE XII

RELATIVE RISKS AND CONFIDENCE INTERVALS FOR PROSTATE CANCER INCIDENCE AND MORTALITY ACCORDING TO QUINTILES OF HIP CIRCUMFERENCE, NATIONAL INSTITUTES OF HEALTH AARP DIET AND HEALTH STUDY, MALE PARTICIPANTS

Hip (quintiles)	25.4-95.9	96.5-99.7	100.3-104.1	104.8-109.2	109.9-175.3	p trend	Per 5 cm
Incidence							
Person years	232,993	231,007	276,913	218,725	233,585		
No. of cases	2,123	2,284	2,744	2,122	2,033		
Age adjusted RR	0.94 (0.89, 1.00)	1.0 ref	1.00 (0.95, 1.06)	0.98 (0.92, 1.04)	0.89 (0.83, 0.94)	0.02	0.99 (0.98, 1.0)
Multivariate RR [a]	0.95 (0.89,1.01)	1.0 ref	1.01 (0.95, 1.06)	1.03 (0.96, 1.08)	0.85 (079, 0.92)	0.16	0.99 (0.98, 1.00)
Multivariate RR [b]	0.95 (0.89, 1.04)	1.0 ref	1.0 (0.95, 1.06)	0.99 (0.93, 1.05)	0.92 (0.86, 0.93)	0.44	1.00 (0.90, 1.01)
Localized disease							
No. of cases	1,361	1,439	1,685	1,396	1,195		
Age adjusted RR	0.96 (0.89, 1.04)	1.0 ref	0.97 (0.91, 1.05)	1.02 (0.95,1.10)	0.83 (0.76, 0.89)	0.0005	0.98 (0.97, 0.99)
Multivariate RR [a]	0.94 (0.77, 1.14)	1.0 ref	0.97 (0.91, 1.04)	1.03 (0.86, 1.24)	0.85 (0.79, 0.92)	0.003	0.98 (0.97, 0.99)
Multivariate RR [b]	0.97 (0.91, 1.04)	1.0 ref	0.97 (0.91, 1.04)	1.03 (0.96,1.11)	0.86 (0.79, 0.95)	0.09	0.99 (0.97, 1.00)
Advanced disease							
No. of cases	190	202	247	188	220		
Age adjusted RR	0.94 (0.77, 1.15)	1.0 ref	1.02 (0.85, 1.23)	0.99 (0.81, 1.20)	1.09 (0.90, 1.32)	0.20	1.03 (1.0, 1.06)
Multivariate RR[a]	0.94 (0.77, 1.14)	1.0 ref	1.03 (0.86, 1.24)	1.00 (0.82, 1.22)	1.11 (0,92, 1.35)	0.12	1.04 (1.00, 1.07)
Multivariate RR [b]	0.94 (0.77, 1.14)	1.0 ref	1.03 (0.86, 1.24)	1.00 (0.82, 1.22)	1.11 (0.90, 1.30)	.16	1.04 (1.00, 1.08)
Mortality							
Person years	301,579	301,799	363,220	285,908	303,956		
No. of deaths	56	69	97	76	85		
Age adjusted RR	0.87 (0.61, 1.23)	1.0 ref	1.16 (0.85, 1.58)	1.17 (0.84, 1.62)	1.27 (0.92, 1.74)	0.02	1.07 (1.02, 1.13)
Multivariate RR [a]	0.81 (0.57, 1.15)	1.0 ref	1.19 (0.87, 1.62)	1.19 (0.86, 1.64)	1.23 (0.90, 1.70)	0.003	1.08 (1.02, 1.13)
Multivariate RR[b]	0.81 (0.57, 1.15)	1.0 ref	1.18 (0.86, 1.60)	1.13 (0.81,1.57)*	1.02 (0.71, 1.47)**	0.20	1.05 (0.99, 1.12)

[a] Adjusted for race, personal history of diabetes, DRE and / or PSA within 3 years of baseline, family history of prostate cancer, education level, physical activity, and smoking status.

[b] Additionally adjusted for BMI.

TABLE XIII

RELATIVE RISKS AND CONFIDENCE INTERVALS FOR PROSTATE CANCER INCIDENCE AND MORTALITY ACCORDING TO WAIST-TO-HIP RATIO, NATIONAL INSTITUTES OF HEALTH AARP DIET AND HEALTH STUDY, MALE PARTICIPANTS

WHR (Quintiles)	0.52-0.90	0.91-0.93	0.94-0.96	0.97-1.0	1.1-3.9	p trend	Per 0.1 cm	WHR[¥] < 0.95/≥0.95
Incidence								
Person years	240,281	241,430	236,706	214,948	259,858			
No. of cases	2,241	2,364	2,265	2,059	2,377			
Age adjusted RR	0.98 (0.92, 1.04)	1.0 ref	0.97 (0.92, 1.06)	0.97 (0.91, 1.03)	0.95 (0.89, 1.0)	0.11	0.98 (0.96, 1.01)	0.97 (0.94, 1.01)
Multivariate RR[a]	0.97 (0.91, 1.02)	1.0 ref	0.98 (0.93, 1.04)	0.99 (0.93,1.05)	0.98 (0.93,1.04)	0.77	1.00 (0.98, 1.03)	1.00 (0.96, 1.03)
Multivariate RR[b]	0.97 (0.91, 1.02)	1.0 ref	0.99 (0.93, 1.04)	1.00 (0.94,1.06)	0.97 (0.90, 1.05)	0.49	1.01 (0.98, 1.03)	1.00 (0.97, 1.04)
Localized disease								
No. of cases	1,386	1,505	139	1,305	1,481			
Age adjusted RR	0.95 (0.89, 1.03)	1.0 ref	0.94 (0.88, 1.02)	0.96 (0.90, 1.04)	0.93 (0.86, 1.0)	0.21	0.99 (0.96, 1.02)	0.97 (0.94, 1.03)
Multivariate RR[a]	0.94 (0.88, 1.01)	1.0 ref	0.95 (0.89, 1.03)	0.99 (0.92, 1.07)	0.97 (0.90, 1.04)	0.75	1.01 (0.98, 1.04)	1.01 (0.97, 1.06)
Multivariate RR[b]	0.94 (0.87, 1.01)	1.0 ref	0.96 (0.89, 1.03)	1.0 (0.93, 1.08)	0.99 (0.92, 1.07)	0.32	1.02 (0.99, 1.05)	1.02 (0.98, 1.07)
Advanced disease								
No. of cases	235	210	209	171	222			
Age adjusted RR	1.14 (0.94, 1.37)	1.0 ref	1.02 (0.84, 1.23)	0.91 (0.74, 1.12)	0.98 (0.81, 1.18)	0.11	0.91 (0.83,0.99)	0.92 (0.82, 1.03)
Multivariate RR[a]	1.12 (0.93, 1.35)	1.0 ref	1.02 (0.84, 1.24)	0.92 (0.75, 1.13)	0.99 (0.82, 1.20)	0.21	0.92 (0.84, 1.00)	0.93 (0.83, 1.05)
Multivariate RR[b]	1.12 (0.93, 1.36)	1.0 ref	1.02 (0.84, 1.23)	0.91 (0.75, 1.12)	0.98 (0.80, 1.18)	0.14	0.91 (0.83, 1.00)	0.92 (0.82, 1.04)
Mortality								
Person years	313,532	315,440	3,080,762	280,380	338,317			
No. of deaths	69	81	77	60	96			
Age adjusted RR	0.91 (0.66, 1.26)	1.0 ref	0,96 (0.70, 1.31)	0.81 (0.58, 1.31)	1.15 (0.85, 1.54)	0.25	1.06 (0.95,1.19)	1.04 (0.86, 1.27)
Multivariate RR[a]	0.88 (0.64, 1.22)	1.0 ref	0.94 (0.69, 1.29)	0.79 (0.57, 1.11)	1.08 (0.80, 1.45)	0.40	1.05 (0.93, 1.18)	1.03 (0.84, 1.25)
Multivariate RR[b]	0.89 (0.65, 1.20)	1.0 ref	0.93 (0.68, 1.27)	0.77 (0.55, 1.08)	1.00 (0.74, 1.36)	0.79	1.02 (0.90, 1.16)	0.99 (0.81, 1.20)

[a] Adjusted for race, personal history of diabetes, DRE and / or PSA within 3 years of baseline, family history of prostate cancer, education level, physical activity, and smoking status.

[b] Adjusted for BMI, race, personal history of diabetes, DRE and / or PSA within 3 years of baseline, family history of prostate cancer, education level, physical activity, and smoking status.

[c] WHO categories.

effects of WC and BMI showed that obesity, irrespective of WC, increased the risk for PCa-specific mortality, but not vice versa. Strong multiplicative interactions between physical activity and WC were observed for total risk and localized disease. Infrequent physical activity in combination with large WC was associated with increased risk for mortality and lowered risk of localized disease. This confirms our findings in stratified analyses. Analysis of WHR as a main effect did not render any statistically significant results. Increasing hip circumference had an inverse association with total risk of PCa and was associated with increased risk of PCa-specific mortality.

2. Previous studies of waist-based measures and prostate cancer

The literature on the association between central adiposity and prostate cancer incidence, progression, and mortality is very inconsistent (146). Few studies have focused on prostate cancer occurrence and outcomes in relation to waist-based measures, with most having only evaluated BMI (39, 146, 147). The inverse association we observed between WC and overall as well as localized PCa is consistent with the directionality and magnitude of work by Dimitropoulou et al., but their estimates did not reach significance (147). This difference may be due to our use of the second quintile as our referent rather than the lowest quintile used by most other publications (108)}}. Most publications have not seen significant associations with WC or WHR and overall PCa risk (108). A few articles have observed positive associations with advanced prostate cancer at diagnosis (148, 149), which we could not detect. Our positive association between large WC and mortality, has not been widely explored (146, 148), but the studies which have tended not to see an association (150).

Of the relatively few studies which explore central adiposity specifically, most do not observe significant associations with overall PCa risk (108). Most of the published literature finds null associations with WC, and weak positive associations with WHR (108). There are a few acceptations. Rowlands et al. reported that having a large WC is positively associated in with advanced tumors and PCa mortality (151). In their prospective European study, Pischon et al. reported a WC association with

increased risk for total, advanced, and high grade (Gleason sum ≥ 7) PCa that was only significant among men with lower BMI (152), suggesting that the cancer causing role of body fat distribution may be more pronounced in men who are not obese. We saw clear positive associations with mortality but not advanced disease, which could be due to our limited power to detect modest associations in relation to the latter endpoint. This could also be due to practical difficulties in DRE and hemodilution of PSA in obese men, resulting in lower PSA test despite the presence of disease (62, 153). Lower screening patronage among obese men has also been cited (91, 154) , although no significant difference in screening history (DRE or PSA) between the cases and those who did not become cases during the follow-up period. Our combined analysis of WC and BMI suggests that obesity itself may increase mortality risk over and above central adiposity. Pischon et al. also found that WHR increased risk of advanced PCa. WHR was positively associated with PCa mortality (152) in that cohort, agreeing with previous work by Hsing et al.(131).

Literature suggests that central adiposity may mediate pathways linked to PCa carcinogenesis, like insulin like growth factor (IGF), particularly the binding protein (IGFBP) levels (151). The mechanisms underlying the IGF-axis association with PCa risk and progression remain unclear, but inhibition of apoptosis and enhancement of cellular proliferation have been suggested (151, 155). IGFBP-2, a proposed insulin sensitivity marker, has been linked to aggressive tumors, androgen insensitive cells, metastasis, and mortality when highly expressed (151, 156). Waist circumference was significantly negatively correlated with IGFBP-2 in a recent study by Rowlands et al., (−18% change per SD increase in WC; [−20% ,−15%] ($p<0.001$) (151). In the context of this correlation finding an inverse association between total and localized makes sense; the higher the WC, the lower IGFBP-2 expression, and thus less of the aforementioned aberrant cell proliferation features associated with high levels of IGFBP-2 (151). A possible explanation in this pathway may be hyperinsulinemia, associated with excess

body fat, and lower IGFBP-2, enabling an increase in bioavailable IGF-I, leptin, or low adiponectin, creating a macro-environment conducive to carcinogenesis (157-160)

3. Race-stratified associations

Our results did not differ across race, with no statistically significant associations observed in race-stratified analyses (Table 3). Recent studies in men of predominant African ancestry (African American, and Jamaican) found significant positive associations for risk of PCa with WC and WHR (115, 153) In their analysis of all African American (N = 498) men participating in the Flint Men's Health Study, Beebe-Dimmer et al. found that abdominal adiposity, using professionally measured WC>102 cm, was statistically significantly associated with overall PCa risk OR:1.84 [1.17, 2.19](153) .Our WHR analysis did not render significant results. Jackson et al. observed that among Jamaican men with WHR ≥0.95 were at greater risk of total prostate cancer (OR: 1.72 [1.01, 3.00]) and high-grade cancer (OR: 2.02 [1.03, 3.96]) when compared to men with WHR in the normal range (115). WHR maintained significance for total prostate cancer in the Jackson analysis (OR: 1.90 [1.01, 3.53]) and high-grade disease (OR: 2.94[1.34, 6.38]) when BMI was added to their model adjustment. There was no WC-PCa association models without BMI were not significant; with BMI in the model WC ≤90 cm (OR: 2.45[1.01, 5.94]) and ≥102 cm (OR: 5.57[1.43, 18.63]) showed a monotonic association with high-grade disease ($p\ trend$ = 0.008).

4. Waist circumference and physical activity

Our interaction between WC and physical activity for incident and localized diseases has not been reported previously. Vigorous physical activity at baseline and exercise during adolescence were not statistically significantly associated with risk of total, advanced, or fatal PCa in the 2008 analysis of this cohort by Moore et al.(145) Our interaction may represent the decrease in weight observed with increasing physical activity, including reduction in central adiposity, although we did not observe significant inverse or protective associations among those who had small WCs and high levels of

vigorous physical activity at least once a week for any category of PCa risk. Stratified analyses rendered a significant association with mortality among men who did exercise more than once a week. Joint analyses found an increased risk of PCa-specific mortality associated with having a large WC in combination with exercising less than 1.5 days per week. This discrepancy, alongside the findings of Moore et al., suggests that the increase risk in PCa-specific morality is driven by WC size, irrespective of physical activity.

5. Dietary factors and waist circumference

Dietary intake is modifiable, although behavior change has proved difficult in some intervention studies (161, 162). Effect modification of the WC-PCa association by dietary factors could provide insight into underlying mechanisms of role of central adiposity in PCa occurrence and mortality. Although none of the WC-dietary factor interactions were statistically significant, literature suggests that obesity and diet vary by race (50, 51). Of particular interest is the increased risk for localized and advanced PCa associated with higher total vitamin D intake than the cohort-specific median, compared with those with intake below the median. Research on vitamin D intake and prostate cancer risk is conflicting, particularly for men of African ancestry (163-166). According to Sharhar et al. higher vitamin D levels, alongside calcium intake is associated with 'diet-induced weight loss' (167). If this is so, in the context of observed increased PCa risk and mortality with large WC, within high intake groups of both calcium and vitamin D, PCa preventive benefit of general weight loss, may not address central adiposity role in PCa.

6. Hip circumference

We found that associations between HC and prostate cancer endpoints followed a similar pattern to that observed for WC. This is not surprising as these two measures of central adiposity were highly correlated ($r = 0.75$ $p<.0001$). Our observed inverse association between HC and overall risk of PCa is consistent with that reported by Hsing et al. in Chinese men (131). The opposite of our

finding was observed among Jamaican men; Jackson et al. report a significant positive trend association with increasing HC in men with localized disease, p = 0.06(111). We are not aware of any other study to report increased risk of PCa-specific mortality associated with hip circumference. When HC association models were additionally adjusted for BMI, HC maintained its significance, suggesting that hip circumference may be a significantly distinct measure of body shape accounting for mass.

7. Strengths and limitations

Strengths of this study include its prospective design, large sample size, wide range of WC values, and the availability of a wide range of possible confounders and effect modifiers. As we did not observe significant differences in DRE or PSA screening history between cases and those who did not become cases during the follow-up period, detection bias was not likely responsible for our observations. Information on screening practices during the 11+ years follow-up would have provided more confident control for the effect of screening. No significant differences in survival were observed across WC categories, after computing a log-rank and Wilcoxon test, p>0.1. The demonstrated tendency for underreporting (attenuated measurement) or WC by self-report did not statistically significantly reduce the correlation between self-reported measures and technician reported measure in two large population-based studies (18). The central adiposity measures were significantly positively correlated with BMI; WC (r = 0.75, p<0.0001), WHR (r = 0.26, p<0.0001), and hip circumference (r = 0.65, p<0.0001) (See Table XV, Appendix) In order to examine the effects of central adiposity independent of BMI, we present BMI adjusted analyses. Adjustment of WC models with BMI took away significance of any associations seen between PCa and CW when BMI was not in the model, suggesting a lack of independence between the measures. Mediation analysis would require a clearer understanding of the temporal relationship of the mechanisms underlying body fat distribution distinct from those which govern the obesity carcinogenesis association. Although our study population included a large number of minority participants, we were still unable to explore race-specific associations with adequate power.

Another limitation is that we did not have information on Gleason sum/ grade, and therefore only relied on TNM staging as a classifier of advanced disease.

E. Conclusion

In summary, we found that WC was inversely associated with risk of total and localized prostate cancer and positively linked to PCa mortality. Additional adjustment for BMI attenuated these associations, suggesting that the relationship between body fat distribution and body mass is not independent. This moderation of the WC-PCa association has been observed in other studies (115, 131, 168-170). New measures of adiposity continue to be developed, and warrant further investigation in relation to prostate cancer. In a recent review Yang et al. note that research has shown significant correlations with composite anthropometry indices (i.e. Waist to height Ratio (WHtR) / WHR, BMI/WC and BMI/WHR) and cancer outcomes (146). None of the research on individual or composite anthropometry shows consistent results in PCa (146). The recently proposed BAI (%Adiposity = Hip (cm)/Height$^{1.5}$ (meters) – 18) (24) has yet to be thoroughly explored in PCa.

Information on body fat distribution is crucial to the full characterization of adiposity (24). Further research is needed to clarify the mechanisms that underlie anthropometric measure-PCa associations we observed, and other measures of adiposity, including waist to height ratio. In the meantime, physical activity should be encouraged as infrequent activity may perpetuate obesity and central adiposity.

V. CONCLUSION AND IMPLICATIONS FOR FUTURE RESEARCH

A. Conclusions

Prostate cancer disparities are evident and persist over time despite declines in cause specific incidence and mortality. Adiposity is increasing, particularly among ethnic minorities, with Black men being 2nd to Black women in prevalence.

Our systematic review suggests a void of research on Black men in the current literature. There is a need for more articles with the power to look at ethnicity and or race-specific associations. Molecular and mechanistic investigations are particularly lacking racial diversity. The epidemiologic literature fails to capture the nuances of Black diet and physical activity patterns, accounting for the cultural and ancestral diversity within "Blacks". Further understanding of MetS associations with PCa, as diabetes and other MetS conditions, disproportionally affect Blacks.

Our cohort analyses suggest associations between central adiposity and PCa occurrence and mortality, while highlighting the need for sensitivity to racial disparities in the design and recruitment phases of the research process. We found that WC was inversely associated with risk of total and localized PCa, and positively linked to PCa specific-mortality. Additional adjustment for BMI attenuated the significance of many associations. Body mass index only remained a significant predictor in the localized disease- WC models, suggesting that the relationship between central adiposity and PCa is not independent of body mass for localized disease in this cohort. Further research is needed to clarify the mechanisms behind the anthropometric measure-PCa associations we observed. We understand that our cohort is more active, more highly educated, and more health conscious, less racially diverse, and older than the general population at risk for prostate cancer in the US. Despite having a large cohort, and robust follow-up time, our inability to power a race-stratified analysis, comparing Blacks and Whites,

heralds the need for diligent diversification of large cohort efforts like the NIH-AARP Diet and Health Study, at the design phase.

B. Impact and future research

The genomic era provides new tools for the exploration of the role of adiposity and racial and ethnic disparities in prostate cancer tumors. There are clear dietary, behavioral risk factors for obesity, and growing evidence for genetic involvement. Relative to the body of available research, few studies have looked at molecular mechanisms underlying possible associations between adiposity and disparate prostate cancer outcomes across race. Recently identified rare and common obesity associated loci on genes (e.g. FTO, FAS, SCD-1) can be used alongside molecular-level adiposity, ancestry informative markers, and histopathologic information to elucidate mechanisms and possibly, gene by environment interactions, where the environment could be host characteristics (dietary pattern, BMI etc.) Genetics influences adiposity, meanwhile adiposity may alter expression cancer susceptibility or aggression associated loci, which could vary by race, and or ancestry. Future research should explore the connection between anthropometric indicators of adiposity, mechanistic indicators of lipid metabolism, genetic markers, and prostate cancer outcomes. My career will be devoted to alleviating disparities observed in minority and underserved populations with prostate, and other cancers, while developing strategies to improve cancer treatment infrastructure in underserved areas.

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APPENDIX

TABLE XIV

ASSOCIATIONS OF SELECTED FACTORS WITH PROSTATE CANCER RISK AND MORTALITY, BY RACE[a]

	All men (N = 142, 003)		Non-Hispanic Black men (N = 2,722)		Non-Hispanic White men (N = 133,434)	
Factor	Incidence	Mortality	Incidence	Mortality	Incidence	Mortality
Waist Circumference (≥102cm)	0.26	0.02	0.34	0.56	0.19	0.05
WHR (≥0.95)	0.40	0.86	0.20	0.89	0.33	0.91
BMI (WHO categories)	< 0.01	0.04	0.04	0.55	< .0001	0.08**
Race (Black, Yes/No)	< .0001	< 0.01	--	--	--	--
DRE (Yes/No in Past 3 years)	< .0001	< .0001	0.23	0.64	< .0001	< .0001
PSA (Yes/No in Past 3 years)	< .0001	< .0001	0.54	0.06**	< .0001	< .0001
DIABETES (Yes/No)	< .0001	0.68	0.21	0.75	< .0001	0.52
Education (≥ 12yrs)	0.80	0.61	0.47	0.75	0.79	0.74
Smoker (Never, Current, or Former)	< 0.01	< .0001	0.95	0.28	< 0.01	< .0001
Family History of PCa (Yes/No)	< .0001	< .0001	0.01	0.06**	< .0001	< 0.01
Physical Activity[b]	0.49	0.01	0.59	0.25	0.37	0.03
Total Fat (g, Quintiles)	0.30	0.09**	0.83	0.20	0.22	0.06**
Saturated fat (g, Quintiles)	0.42	0.05	0.96	0.31	0.35	0.05
Vitamin D (mcg, Quintiles)	< 0.01	0.76	0.32	0.12	< .0001	0.90
Lycopene (g, Quintiles)	< 0.01	0.81	0.92	0.39	< 0.01	0.72
Zinc (mg, Quintiles)	0.08**	0.23	0.40	0.73	0.03	0.19
Calcium (mg, Quintiles)	0.37	0.45	0.34	0.44	0.50	0.17
α-Tocopherol (mg, Quintiles)	0.95	0.58	0.86	0.45	0.61	0.50
Selenium (μg, Quintiles)	0.06**	0.008	0.28	0.02	0.08**	0.11**

[a]Chi-square p-values

[b]Defined as physical activity ≥20 minutes, which increased heart rate and caused perspiration.

** = suggestive $\alpha \leq 0.1$

TABLE XV

PEARSON CORRELATION COEFFICIENTS

	HEIGHT	WCCM	hip	BMI_CUR	WHR
HEIGHT Height	1	0.20751 <.0001 140,833	0.24547 <.0001 130,530	-0.07685 <.0001 140,055	-0.00709 0.0104 130,530
WCCM		1	0.75294 <.0001 131,573	0.75006 <.0001 140,055	0.46377 <.0001 131,573
Hip			1	0.64727 <.0001 129,845	-0.19703 <.0001 131,573
BMI_CUR BMI at current age in kg/m²				1	0.26265 <.0001 129,845
WHR					1
N	140,833	140,833	130,530	140,055	130,530

VITA

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RESEARCH INTEREST

Biopsychosocial determinants of racial and ethnic disparities in health and wellness.

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Doctorate of Philosophy, Epidemiology, 2012
Division of Epidemiology and Biostatistics, School of Public Health
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Masters in Epidemiologic Science, 2008
University of Michigan, School of Public Health, Ann Arbor, MI
Advisor: Sharon Kardia, PhD

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New England Biolabs Workshop in Molecular Biology, 2011
Smith College, Northampton, MA

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VITA (continued)

RESEARCH EXPERIENCE

2010-present
Graduate Student Researcher, *Kittles Lab*
Institute for Human Genetics, University of Illinois at Chicago, Chicago, IL.

- Apply epidemiologic and biostatistical methods in support of ongoing ancestry genomics research conducted by senior lab members.
- Assist in grant and manuscript development.
- Design and conduct original research on available data in the Kittles laboratory.

2009-2012
Trainee, *National Cancer Institute (NCI), Cancer Education, and Career Development Program*
Institutes for Health Research and Policy, University of Illinois at Chicago, Chicago, IL.

- Selected for a three year, nationally competitive, NCI R25T program, which provides salary support and research development funds for post-candidacy interdisciplinary cancer research training.
- Attended national and international cancer conferences to gain interdisciplinary cancer research exposure, as well as weekly and monthly cancer control seminars conducted locally by nationally recognized researchers at the UIC Cancer Center.
- Presented research and academic progress, annually to external advisory board comprised of professors and researchers from cancer centers nation-wide.
- Presented two successful abstracts at the 2012 Association of Preventive Oncology annual meeting.

Summer 2009
Research Assistant, *Department of Epidemiology.*
University of Illinois at Chicago (UIC), School of Public Health, Chicago, IL.

- Aided ongoing research efforts of Dr. Bridget J. McCarthy, a Research Associate Professor of Epidemiology at the UIC School of Public Health. Dr. McCarthy's work focused on brain tumor outcomes.
- Conducted bilingual, English and Spanish, interviews at the UIC Oncology Center, Neuro-oncology clinic under the supervision of Dr. J. Lee Villano, for the ongoing Gliogene study.
- Transported samples from the clinic to the UIC department of oncology for processing.
- Utilized Surveillance, Epidemiology, and End Results (SEER), SEERSTAT® program to conduct an analysis, which resulted in a publication: "Descriptive Epidemiology of Selected Olfactory Tumors" in the *Journal of Neuro-Oncology,* under the guidance of Dr. Therese A. Dolecek.

Spring 2009
Institute for Health Research and Policy, *Research Assistant*.
University of Illinois at Chicago (UIC), School of Public Health, Chicago, IL.

- Provided grant development assistance to Dr. Garth Rauscher of the Epidemiology and Biostatistics Division in the UIC School of Public Health, for his successful P-50/60 projects, which explore breast cancer disparities using imaging, tissue, blood, and survey data.

VITA (continued)

Fall 2008
Teaching Assistant/Graduate Student Instructor, *Department of Epidemiology.*
University of Illinois at Chicago (UIC), School of Public Health, Chicago, IL.

- Lead bi-weekly computer laboratory and discussion sections for approximately fifty masters and doctoral students enrolled in EPID 406 – Introduction to Epidemiologic Computing using SAS software, alongside a second GSI, Samantha Gray.
- Taught a two-day lecture series on CRAN R software applied to epidemiologic computing.
- Graded and provided feedback on submitted assignments.
- Facilitated review and study sessions to clarify core epidemiologic analysis concepts.

Spring 2009
Teaching Assistant/Graduate Student Instructor, *Department of Epidemiology.*
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- Held weekly office hours and graded homework for masters and doctoral students enrolled in the Epidemiology department EPID 404 – Intermediate Epidemiologic Methods course, which focused on fundamental quantitative epidemiologic methods.
- Graded and provided feedback on submitted assignments.
- Facilitated review and study sessions to clarify core epidemiologic analysis concepts.

Summer-Fall 2008
Graduate Assistant, *Department of Surgical Oncology*.
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- Maintained patient billing and service data for the department.

2005- 2010
Investigator and Epidemiology Consultant*, Department of Surgical Oncology.*
University of Michigan Cancer Center, Ann Arbor, MI

- Reported directly to the principal investigator for the Michigan Multi-Ethnic Breast Registry, Dr. Lisa A. Newman, Director of the Breast Care Center of the Department of Surgical Oncology, Breast Oncology Program at the University of Michigan.
- Negotiated initial collaborative agreements between the Kumasi, Ghana Radiotherapy Center director Dr. Bafour Awuah, and the principle investigator based on my long-standing relationship with the medical community in Ghana, as a past clinical MPH resident and Rotary Scholar to the region.
- Procured and processed blood, saliva, and breast tumor specimens from Ghanaian breast cancer patients and buccal cell DNA healthy controls.
- Developed linguistically and culturally appropriate nutritional and health history survey tools for the registration pilot project.
- Created processing and transport protocols for blood and tumor tissue.
- Assisted in the processing and cataloging of samples at the department of Pathology at the Komfo-Anokye Teaching Hospital. Subsequently, packaging and transporting the samples from Kumasi, Ghana to the University of Michigan Cancer Center laboratories, per Centers for Disease Control and Prevention standards for the transport of human tissues.

VITA (continued)

2005- 2008
Graduate Research Assistant, *Kardia Lab*
Department of Epidemiology, University of Michigan, School of Public Health, Ann Arbor, MI

- Obtained genetic epidemiologic methods training from the Kardia Lab which specialized in genomic epidemiology and dissemination of genetic research to lay populations.
- Assisted ongoing grant preparation, genome wide association studies, and gene-environment interaction analyses. These analyses focused on renal and cardiovascular disease outcomes for the funded Michigan Center for Integrative Approaches to Health Disparities (CIAHD) project on the genetic and social factors in blood pressure control.
- Developed and presented short lectures for the Advanced Genetic Epidemiology Seminar lead by Dr. Kardia in 2007, as well as special presentations for the lab staff on social genomics topics, including population stratification by ancestry.

2003-2004
Ambassadorial Scholar, *Rotary International District 9100, West Africa*
Rotary International, Evanston, IL
Rotary International, a global foundation with ties to the United Nations, awards ambassadorial fellowships, with the purpose of furthering international understanding and friendly relations, through service and scholarship.

- Aiding the efforts of Ghanaian Rotarians in the district.
- Presented talks at weekly Rotary sponsored events in the greater Philadelphia and metro Accra regions.
- Administered Polio vaccinations in accordance with the Rotary Polio Plus campaign, National Immunization Days in Ghana, and Nigeria. These efforts were co-sponsored by the local health ministries and UNICEF.
- Completed masters-level coursework in public health at the Bill and Melinda Gates Malaria Center in the University of Ghana, School of Public Health, earning a degree in Epidemiology and Biostatistics.
- Participated in required country-wide field service in food and occupational safety, maternal and child health, and infectious disease surveillance, in accordance with the Ghana Health Service/ Ministry of Health rotation requirements for the practical MPH program.
- Assisted in resource fundraising for Ghanaian students in the Madamfo Paa orphanage, Accra.
- Spearheaded fundraising and solicited surgical volunteers for three emergency Oral Maxillofacial surgeries on women from the town of Obadan, Accra
- Developed an agricultural micro-credit program for disenfranchised single mothers in Obadan.
- Obtained funding, harnessing private and US Rotarian donations, for an elementary school library and community toilet for the village of Obadan, outside of Accra.
- Volunteered for the Ghana Ministry of Agriculture to implement veterinary public health immunization services in Navrongo region under the supervision of Dr. Anthony Akunzele.
- Attended Ghanaian cultural events.

2002-2003
Research Coordinator, *Neuropsychiatry, Schizophrenia Research Center (SRC), Brain Behavior Lab (BBL)*
University of Pennsylvania Medical Center, Philadelphia, PA

- Obtained informed consent and pedigrees from participants in the SRC Project among African Americans to Explore Risks for Schizophrenia (PAARTNERS).
- Administered neurocognitive assessments on affected PAARTNERS participants.
- Managed data as a part of the SRC genetics team.
- Developed a guide for cultural, artistic, and learning-level tailoring of the computerized neurocognitive profile (CNP) assessment tool as a BBL team member.
- Conducted honors thesis research as a mentored University Scholar, which explored inter and intra-racial emotion recognition using functional magnetic resonance imaging data (FMRI).

VITA (continued)

2004
MPH clinical practicum resident, *National Center for Nuclear Medicine and Radiotherapy.*
Korle-Bu Teaching Hospital, Accra, Ghana, West Africa

- Participated in a four-month field residency as a Rotary Ambassadorial Scholar MPH candidate at the University of Ghana, School of Public Health.
- Conducted the clinical research for masters thesis.
- Developed survey instruments to assess the role of spirituality and communalism in the decision making processes of Ghanaian breast cancer patients patronizing the National Center for Nuclear Medicine and Radiotherapy, under the supervision of Dr. Kwodwo Koram (Epidemiologist) and Dr. Joe Nat Clegg-Lamptey (Surgeon).
- Facilitated data collection on breast patients in the unit.
- Designed an EpiInfo® database for the unit's data.
- Created data entry training modules for the oncology nurses.
- Attended weekly multi-disciplinary breast tumor board meetings.
- Participated in clinical rotations alongside Korle-Bu surgical department residents, including shadowing of general surgical procedures, cytology and histology protocols, and daily rounds on the surgical wards, with special emphasis on cancer patients, and breast cancer related procedures.
- Initiated fundraising activities for donation of prosthesis for breast cancer patients of the Korle-Bu Teaching Hospital, Accra.

2000-2003
McNair Scholar, *Ronald E. McNair Scholars Program*
University of Pennsylvania, Philadelphia, PA

- Conducted literary research on educational attainment, income, spirituality, and communalism as cultural values impacting the health behaviors and decisions of African American women with breast cancer, under the mentorship of Clinical Psychology professor Dr. Chanita Hughes-Halbert, during the three year, PhD preparatory, McNair program.
- Obtained formal skills training in literature search at the Library of Congress, abstract writing, peer-reviewed manuscript and proposal development.
- Attended courses in writing, social sciences, and statistical methods.
- Defended my research project before a panel of peers and faculty.

Summer 2003
Student Advisor, *Ronald E. McNair Scholars Program*
University of Pennsylvania, Philadelphia, PA

- Worked as a live-in supervisor of the 2003 McNair scholars.
- Taught a research skills course.
- Conducted workshops on graduate applications and fellowships.

VITA (continued)

2000- 2003
Administrative Research Assistant, *Center for Clinical Epidemiology and Biostatistics (CCEB)*
University of Pennsylvania Medical Center, Philadelphia, PA

- Performed psychometric surveys via telephone and abstracted charts for participants enrolled in the CCEB Race and Renal Allograft Study, headed by Dr. Harold I. Feldman. This longitudinal study examined the quality of life and incidence of organ rejection among kidney transplant patients associated with the Atherosclerosis Risks and Communities Study (ARIC).
- Conducted literary research on the epidemiology of kidney diseases.
- Managed data downloaded from drug compliance monitoring devices used by study participants.

Summer 1996
Research Assistant, *National Center for Fathers and Families (NCOFF)*
University of Pennsylvania, Philadelphia, PA

- Entered data and wrote abstracts for Dr. Vivian Gadsden.

GRANTS AND FELLOWSHIPS

Principal Investigator, 2011-2014
Fiscal Year 2010 (FY10) Department of Defense (DOD) Prostate Cancer Research Program (PCRP) of the Office of the Congressionally Directed Medical Research Programs (CDMRP) Health Disparity Training Award (W81XWH-11-1-0554PI: Martin IK, Co-I: Wright ME Mentors: Kittles R, Bosland MC).

Trainee, 2009-2012
NCI Cancer Education and Career Development Program (R25T) (5 R25 CA 057699-15, PI Warnecke, RB)

Rackham Merit Fellow, 2004-2008
University of Michigan, Rackham Graduate School

Center for Research on Ethnicity, Culture, and Health (CRECH) Scholar, 2004-2008
University of Michigan, School of Public Health

Rotary Ambassadorial Scholar to District 9100 (West Africa), 2003 -2004
Rotary International

University Scholar, 2000-2003
University of Pennsylvania

Ronald E. McNair Scholar, 2000-2003
University of Pennsylvania

VITA (continued)

SELECTED PUBLICATIONS AND PRESENTATIONS

1. Murphy AB, Kelley B, Nyame YA, Martin IK, Smith DJ, Castaneda L, et al. Predictors of serum vitamin D levels in african american and european american men in chicago. Am J Mens Health. 2012 Mar 8.

2. Fitzgibbon M, Tussing-Humphreys L, Porter J, Martin I, Odoms-Young A, Sharp L. Weight loss and African–American women: A systematic review of the behavioral weight loss intervention literature. Obesity Reviews. 2012.

3. Awuah B, Martin IK, Takyi V, Kleer C, Nsiah-Asare A, Aitpillah F, et al. Implementation of a percutaneous core needle biopsy training program: Results from the university of Michigan–Komfo anokye teaching hospital breast cancer research partnership. Annals of surgical oncology. 2011;18(4):957-60.

4. Villano JL, Bressler L, Propp JM, Valyi-Nagy T, Martin IK, Dolecek TA, et al. Descriptive epidemiology of selected olfactory tumors. J Neurooncol. 2010;100(1):73-80.

5. Martin IK, Awuah B, Newman LA. Guide for investigators conducting international cancer research involving developing nations. Cancer. 2010;116(6):1396-9.

6. Stark A, Kleer CG, Martin I, Awuah B, Nsiah-Asare A, Takyi V, et al. African ancestry and higher prevalence of triple-negative breast cancer. Cancer. 2010;116(21):4926-32.

7. Newman L, Martin I, Zarbo R, Awuah B, Schultz D, Takyi V, et al. In: Frequency of estrogen receptor-negative breast cancer in women with african ancestry: Results from an international study. J clin oncol (meeting abstracts); ; 2008. p. 22015.

8. Newman LA, Martin IK. Disparities in breast cancer. Curr Probl Cancer. 2007;31(3):134-56.

SELECTED POSTER PRESENTATIONS

Iman K. Martin MPH, MS; Deborah R. Rosenberg, PHD; Vincent L. Freeman, MD MPH; Yikyung Park, Sc.D.; Arthur Schatzkin, M.D., Dr.P.H.; Margaret E. Wright, PhD. *Measures of central adiposity in relation to prostate cancer incidence and mortality: A prospective cohort study.* ASPO, 2012, March, 2012

Iman K. Martin MPH, MS, Jocelyn P. Wilder MS, Adam B. Murphy, MD MBA, Abeer M. Mahmoud, MD, Leslie T. Stayner Debora Rosenberg, PhD, Maarten C. Bosland DVSc PhD, Vincent L. Freeman. *The role of adiposity in racial and ethnic disparities in prostate cancer occurrence and progression: A systematic literature review.* AACR, Annual Meeting, March 2012, Chicago, IL

Adam B. Murphy, MD, MBA, Brian Kelley, MA, Yaw A. Nyame, MHSA**, Iman K. Martin, MPH, MSc,** Demetria J. Smith, MA, Lauren Castaneda, MA, Gregory J. Zagaja, MD, Courtney M.P. Hollowell, MD, Rick A Kittles, PhD**.** *Predictors of Serum Vitamin D Levels in African American and European American Men in Chicago.* AACR: The Science of Cancer Health Disparities in Racial and ethnic Minorities and the Medically Underserved September, 2011, Washington, DC.

VITA (continued)

Abeer M Mahmoud, **Iman K Martin**, Micheal Schilisht, Larisa Nonn, Maarten Bosland. *Differential effects of the isoflavone genistein on androgen receptor expression and cell proliferation comparing prostate cancer cells with mutant and wild type androgen receptor.* AACR 102nd Annual Meeting 2011, Orlando, FL.

Newman, Lisa A. **Martin, Iman K**. Zarbo, Richard J. Awuah, Baffour. Schultz, Daniel S. Takyi, Valerie. Darko, Angela. Stark, Azadeh. *Frequency of Estrogen Receptor-Negative Breast Cancer in Women with African Ancestry: Results from an International Study*. American Society of Clinical Oncology Annual Meeting. Chicago, Illinois. May 2008.

Braman, Maria B. Kleer, Celina G. Newman, Lisa A. **Martin, Iman K.** Takyi, Valerie. *Breast Cancer in Women from Ghana and What It May Reveal about Breast Cancer in African-American Women.* United States and Canadian Academy of Pathology Annual Meeting. Denver, Colorado. March 2008.

Martin, Iman Kalifa. *Exploring the Relationship between Spirituality, Communalism, and Breast Cancer Stage at Presentation: A Case Study Among Women Who Attend the Korle-Bu Teaching Hospital in Accra, Ghana.* 2005 Global Health Council New Investigators Program, Global Health Conference, Washington, DC.

HONORS

- American Cancer Society Calle/Rodriguez Memorial Minority Travel Award for a Top Ranked Abstract, 2012
- Selected AACORN-African American Collaborative Obesity Research Network Academic Research Affiliate, Entering Class of 2010
- Participant in the University of Michigan Presidential Global Partnerships Initiative Delegation to Ghana, 2008
- Member of the Center for Global Health Search Committee, University of Michigan, 2008
- GHRTI Global Health Research Training Initiative Scholar to Ghana, University of Michigan, 2007
- University of Michigan International Institutes Travel Fellow to Ghana, University of Michigan, 2007
- University of Michigan International Institutes Travel Fellow to Ghana, University of Michigan, 2006
- The Interuniversity Consortium for Political and Social Research (ICPSR) Program Scholar, University of Michigan, 2006
- Global Health Council New Investigators Program Scholarship winner and presenter, 2005
- Center for Research on Ethnicity, Culture and Health (CRECH) Scholar, University of Michigan, 2004-2007
- University of Michigan Rackham Merit Fellow, 2004-2008
- Rotary Ambassadorial Scholar to District 9100, University of Ghana, 2003-2004
- Astra Zeneca Woman One Scholar, Nominated by Dr. David E. Nicklin of the University of Pennsylvania Health System, 2003
- Selected for thesis work by the University of Pennsylvania African Studies Department and the World Affairs Council as the student designate to commencement keynote speaker Archbishop Desmond Tutu, 2003
- University Research Scholar Award, University of Pennsylvania, 2003
- Swain Award for Academic Excellence, University of Pennsylvania, 2003
- Onyx Senior Honors Society, University of Pennsylvania, 2003
- Ronald E. McNair Scholar, University of Pennsylvania, 2001-2003
- Benjamin A. Gilman International Scholarship Program to Ghana West Africa, Bureau of Educational and Cultural Affairs, U.S. Department of State, Institutes of International Education, 2001
- University Scholar, Accepted to the honors college at the University of Pennsylvania, 2001-2003
- African American Summer Institutes Scholar, University of Pennsylvania, 1999
- Presidential Classroom Scholar, 1998

VITA (continued)

CURRENT PROFESSIONAL SERVICE

Committee on Academic Progress, PhD student Representative University of Illinois at Chicago SPH 2008-2011
Journal Review Panel Participant. *Cancer* 2011
Journal Review Panel Participant *Obesity* 2011
Reviewer American Public Health Association Black Caucus submissions 2011
Project Brotherhood, Volunteer

PROFESSIONAL MEMBERSHIPS

AACR-American Association for Cancer Research
ASPO-American Society of Preventive Oncology
AACORN -African American Collaborative Obesity Research Network
APHA-American Public Health Association
ASCO- American Society of Clinical Oncology