The Effects of Metabolic Disturbances on Prostate Cancer Risk and Detection

by

Lauren Patricia Wallner

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Doctoral Committee:

Professor Hal Morgenstern, Co-Chair
Research Assistant Professor, Aruna V. Sarma, Co-Chair
Professor Jeremy M. G. Taylor
Assistant Professor, Lynda Diane Lisabeth
Assistant Professor, Jennifer L. St. Sauver, Mayo Clinic College of Medicine
Assistant Professor, Debra J. Jacobson, Mayo Clinic College of Medicine

Dedication

To my parents, who instilled in me the value of an education and inspired a lifetime love of learning for which I will always be grateful.

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Abstract

Prostate cancer is the most common non-cutaneous cancer and the second leading cause of cancer death among US men. Findings from previous studies suggest that metabolic conditions, including type 2 diabetes, hypertension and obesity may be associated with prostate cancer risk. As these conditions become increasingly prevalent, it is crucial to gain a better understanding how these conditions influence the risk of prostate cancer over time and how they influence prostate cancer detection. Therefore, the goal of this dissertation was to estimate the effects of type 2 diabetes, hypertension, and obesity on prostate-cancer risk and detection over 15 years of follow-up, utilizing the resources of The Olmsted County Study of Urinary Symptoms and Health Status among Men (OCS). In 1990, a randomly selected cohort of Caucasian men ages 40-79 was recruited; 2,445 completed a questionnaire that included physician-diagnosed diabetes and hypertension. Anthropometric measures were collected during clinical examination. Biopsy-confirmed prostate cancer was identified from medical records. A 25% random subset was invited to participate in a urologic exam, during which serum prostate specific antigen levels were measured. Proportional hazards (Cox) regression was used to estimate the effects of these metabolic conditions, both individually and in combination, on the incidence rate of prostate cancer and likelihood of prostate cancer biopsy. Mixed effects linear regression was used to estimate the effects of these metabolic conditions on changes in prostate specific antigen levels and prostate volume. Type 2 diabetes, obesity

and hypertension, alone and in combinations with each other were differentially associated with prostate cancer risk. Men with diabetes experienced greater age-adjusted reductions in PSA levels than did non-diabetic men. Baseline body mass index was inversely associated with the annual percent change in PSA and positively associated with the annual percent change in prostate volume. These results suggest that the presence of these metabolic conditions influences both the risk and detection of prostate cancer. Findings from these studies will set the direction for the next set of investigations to elucidate these associations and provide clues to understanding the etiology, as well as shape detection strategies in men with these metabolic conditions.

Chapter 1

Introduction

Significance

Prostate cancer is the most common non-cutaneous cancer among American men and is the second leading cause of cancer death in the United States (1, 2). The incidence of this disease is estimated to have exceeded 192,280 cases and 27,360 deaths in 2009 alone (2). Extensive literature has been published investigating various factors that may influence prostate cancer risk, currently focusing on the role of the metabolic syndrome and its components, specifically, type 2 diabetes mellitus (T2DM) and obesity. Type 2 diabetes, hypertension and obesity are all highly prevalent conditions in the elderly US population with an estimated 68% of US adults described as overweight and/or obese (3),1 in 3 US adults are hypertensive, and 11% of US men diagnosed with diabetes (4). Metabolic syndrome is also becoming increasingly prevalent, affecting approximately a quarter of US adults (5). These conditions have arguably reached epidemic proportions and are thought, in part, to explain the increase in chronic disease seen in this country (6). Although previous literature has implicated these metabolic disturbances in prostate cancer development, the literature in this field is both inconsistent and methodologically limited. To date, the majority of findings suggest that obesity is inversely associated with the incidence of prostate cancer, and this association may differ by stage of disease at diagnosis. Although the relation of T2DM with prostate cancer remains somewhat unclear, the metabolic syndrome has been found to be positively associated with the risk

of prostate cancer. Not only are the interpretations of these results controversial, but the impact of the increasing prevalence of these conditions on prostate specific antigen (PSA) levels is only beginning to be investigated. This is particularly relevant as Freedland et al. (7) suggested that PSA testing, currently our most utilized prostate cancer screening tool, is less predictive in obese men. This has been attributed to overweight men having decreased PSA levels (8, 9) and to increased prostate volumes, which make cancer detection by biopsy and digital rectal examination more difficult. Furthermore, lower PSA levels in obese men with prostate cancer have been attributed to plasma hemodilution (10). Others have argued that the inverse association between obesity and prostate cancer is due to detection bias, resulting from the association of obesity with PSA level or prostate volume among men at risk of prostate cancer (7, 11). Other explanations for the inverse association seen between obesity and prostate cancer include the use of varying measures of obesity, heterogeneity of study populations, heterogeneity across disease stage at diagnosis, as well as hormone levels.

Similar conflicting observations have been reported for T2DM with time since diagnoses having varying associations with prostate cancer risk. These inconsistent findings have been attributed to changes in insulin concentration during the course of diabetes development and progression. Given the gap in our clear understanding of these relations, investigating the possible effects of metabolic disturbances on both prostate cancer risk and detection in a prospective, longitudinal study that allows for the careful consideration of potential confounders and effect modifiers is crucial for our understanding of these complex associations. Thus, the focus of this dissertation was to investigate the role of the metabolic syndrome and its components in prostate cancer

development and determine how these factors impact prostate cancer detection in a population-based sample of men aged 40-79.

I utilized *The Olmsted County Study of Urinary Symptoms and Health Status among Men (OCS)* to complete this dissertation. This ongoing NIH-funded, longitudinal, population-based study of Caucasian men provides a unique opportunity in that it contains clinical data with extensive covariate measurements collected through comprehensive physical examinations and reliable, well-tested questionnaires over 15 years of follow-up thus far. Findings from this dissertation will help to inform future studies as these metabolic conditions and prostate cancer continue to become increasingly prevalent. Determining the impact of metabolic disturbances on prostate cancer risk and detection may also help to shape better prevention strategies in the future for prostate cancer among men with these conditions.

Background

Prostate Cancer

Prostate cancer is the second most common non-cutaneous cancer and leading cause of cancer deaths in US men (1). While only 15% of men diagnosed with prostate cancer will die from it, the prevalence of clinically diagnosed disease remains high. Currently, prostate specific antigen (PSA) testing and digital rectal examination (DRE) are used in conjunction with prostate needle-biopsy to detect prostate cancer. PSA is the most common screening test for prostate cancer with 58% of Caucasian men receiving an annual test (12). Recently, the specificity of the test and impact on mortality has been questioned as most men who are subjected to biopsy after an abnormal PSA test are found not to have prostate cancer (13). The low specificity of PSA testing and questionable benefit of PSA screening on prostate cancer mortality highlight the need for better detection strategies for prostate cancer (14, 15). Knowledge of the influence of concomitant comorbidities on serum PSA concentrations may improve the discriminant value of this test and reduce the number of unnecessary biopsies and subsequent overdiagnosis of indolent cancers.

Metabolic Syndrome

Metabolic syndrome, defined as a cluster of metabolic disturbances, including diabetes, hypertension, abdominal obesity, lipid disorders and disturbances in glucose metabolism related to hyperinsulinemia and insulin resistance (IR), has become a world-wide epidemic with significant consequences for the aging population. Not only has it been estimated that a quarter of US adults are suffering from metabolic syndrome (5, 16),

but metabolic syndrome has also been found to be positively associated with the risk of many common chronic diseases, including cardiovascular disease (ischemic heart disease and stroke), type 2 diabetes mellitus (T2DM), and multiple types of cancer (17). The clustering of these conditions is often referred to as a syndrome because it is thought that these conditions share an underlying pathophysiological component, insulin resistance (18). Currently, three definitions are used to describe this syndrome with two of the most widely used presented below (Table 1.1). The definitions of the World Health Organization (WHO), the National Cholesterol Education Program's Adult Treatment Panel III (ATP III), and the European Group on Insulin Resistance agree that dyslipidemia, glucose intolerance, obesity, insulin resistance and hypertension all contribute to the syndrome.

Table 1-1: Definitions of the Metabolic Syndrome (17)

Risk factors	National Cholesterol Education Program's Adult Treatment Panel III (ATP III) (≥3 of 5 criteria necessary)	World Health Organization (WHO) 1999 (impaired glucose regulation or hyperinsulinemia and ≥2 of criteria necessary)	European Group on Insulin Resistance (EGIR) 2002 (hyperinsulinemia and ≥2 of criteria necessary)
Impaired glucose regulation	110 to 126 mg/dl (6.1 to 7.0 mmol/L)	Plasma glucose: fasting ≥6.1 mmol/L or 2-hour postglucose load ≥7.8 mmol/L or capillary whole blood glucose: fasting ≥5.6 mmol/L or 2-hour postglucose load ≥7.8 mmol/L	Fasting plasma ≥6.1 mmol/L or capillary whole blood ≥5.6 mmol/L
Hyperinsulinemia	Not included	Fasting serum insulin ≥ third quartile for control group	Fasting serum insulin ≥ third quartile for nondiabetic control group
Abdominal obesity	Men: waist circumference ≥40 inches (102 cm); women: waist circumference ≥35 inches (89 cm)	Waist-to-hip ratio >0.85 or BMI >30 kg/m^2	Waist circumference >80 cm
Triglycerides	≥150 mg/dl (1.7 mmol/L)	Fasting serum triglyceride ≥1.7 mmol/L	Fasting serum triglyceride >2.0 mmol/L and/or HDLc <1.0 mmol/L and/or treatment for dyslipidemia
HDLc	Men: ≤40 mg/dl (1.04 mmol/L); women: ≤50 mg/dl (1.3 mmol/L)	Not included	Included with triglycerides
Hypertension	≥130/≥80 mm Hg	≥140/90 mm Hg	Systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or treatment for hypertension
Microalbuminuria	Not included	Albumin/creatinine ratio ≥30 mg/g	Not included

Obesity

Obesity is a growing global epidemic, with more than half of the world's adults categorized as being overweight and up to 30% categorized as obese (body mass index [BMI] >30 kg/m^2) (19). In the US alone, 68% of adults are either overweight or obese (3). Furthermore, obesity has been found to be associated with a number of medical conditions including hypertension, dyslipidemia, diabetes, hypertriglyceridemia (20), and more recently several types of cancer (17).

Hypertension

Hypertension, or high blood pressure, is one of the most prevalent chronic diseases in the United States, with one in three Americans afflicted (21). Not only is this condition prevalent, but it is also a very costly with an estimated 77 billion dollars expected to be spent on it in 2010 alone (22). Furthermore, hypertension is a risk factor for kidney disease, congestive heart failure, myocardial infarction, and stroke, which are the first and third most common causes of mortality in the United States (21).

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus, a chronic disorder of carbohydrate, fat and protein metabolism, is a important cause of morbidity and mortality in the U.S (23). The Centers for Disease Control and Prevention (CDC) estimate that diabetes mellitus affects 18 million American adults (6). Using data from the Behavioral Risk Factor Surveillance System, Mokdad et al. (24) found that the prevalence of diabetes increased from 4.9% in

1990 to 7.3% in the U.S. in 2000, representing an increase of 49%. This change is striking as it is estimated that 5.9 million Americans are still unaware that they have the disease, thus greatly increasing the potential prevalence in the community (23). Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease. In addition, hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes. The morbidity associated with long-standing diabetes results from these complications. Although there is some literature suggesting that complications are a genetic concomitant unrelated to metabolic abnormalities, most of the available evidence suggests that the complications of diabetes mellitus are a consequence of the metabolic derangements associated with the disease (25). The role of circulating insulin concentration in the development of type 2 diabetes has been controversial with both insulin excess and insulin deficiency having been postulated as important antecedents. Prospective epidemiologic studies of type 2 diabetes incidence in which insulin levels were measured suggest that the initial event leading to diabetes is peripheral resistance to insulin action, known as insulin resistance.

Metabolic conditions and Prostate Cancer Overview

Recent literature has suggested that features of the metabolic syndrome may be predictive of prostate cancer risk. The presence of multiple components of metabolic syndrome has been shown to increase the risk of prostate cancer development as well as play a role in disease progression. Specifically, in a prospective study of 16,209 men, those with more than three components of the metabolic syndrome were 1.5 times more likely to be diagnosed with prostate cancer in the 27 years of follow-up than were men

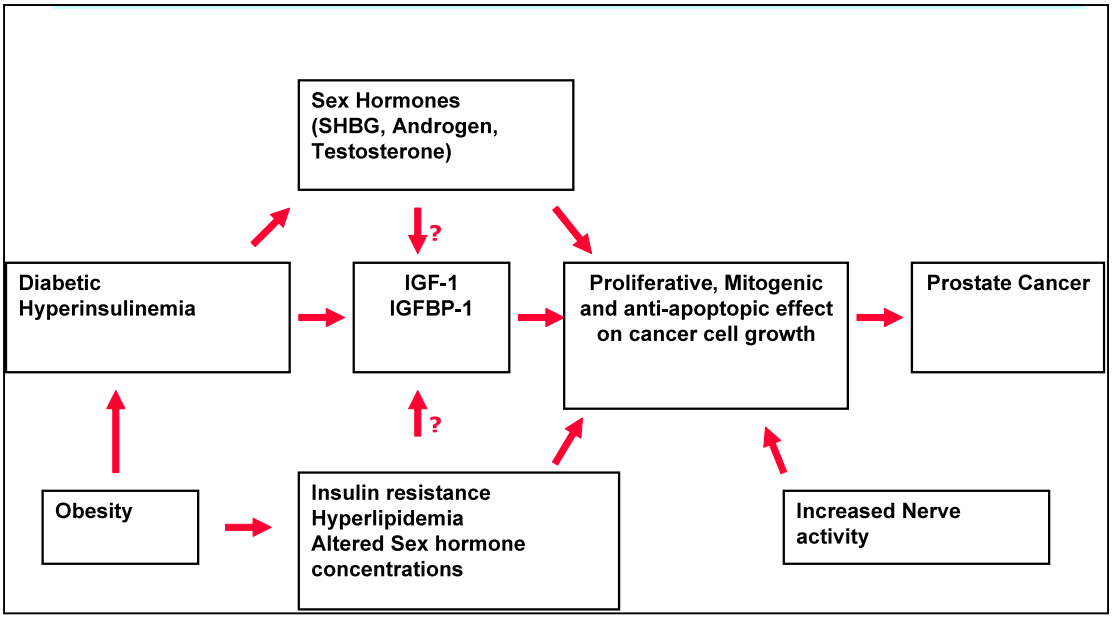
with no metabolic syndrome components (26). Hammarstan et al. (27) found that men with disseminated (T3) prostate cancer were more likely to have 3 components of the metabolic syndrome compared to men with localized (T2) disease. Furthermore, a prospective study of Finnish men found that men with the metabolic syndrome have a 2-fold increased risk of developing prostate cancer and that the risk is greater in men with a BMI greater than 27 kg/m^2 than in men with a BMI less than 27 kg/m^2 (28). In addition to the overall cluster of conditions known as the metabolic syndrome being related to prostate cancer development, the main metabolic components of the syndrome, obesity and T2DM, have also been shown to be influence PSA levels (8, 29).

Obesity and Prostate Cancer

While large population-based studies have shown that BMI is associated with an increased risk of prostate cancer (30-33), other studies have found either no association or an inverse association between obesity and prostate cancer incidence (34-36). In a recent meta-analysis of 22 prospective studies, MacInnis and English (37) concluded that obesity was weakly associated with an increased risk of prostate cancer, and the association varied appreciably across studies (37). Possible explanations for conflicting results include variations in the measurements of obesity between studies and at different times in the life course, differences in study design, insufficient control of confounders, different distributions of effect modifiers and obesity in the study populations. Three recent large prospective cohort studies found that obesity was differentially associated with aggressive and non-aggressive forms of prostate cancers; a reduced risk of low-stage disease and an increased risk of high-stage disease was observed for obese men (38-

40). It is not clear if these findings are the result of obesity affecting the type of prostate cancer, if obesity is a prognostic marker for prostate cancer progression, or if obesity simply affects the detection of prostate cancer. A biologically plausible explanation for this finding is that obese men have lower levels of testosterone that may prevent prostate cancer or delay detection (7, 41). Obesity is known to alter serum concentrations of hormones such as testosterone, estrogen, insulin, IGF-1, and leptin, all of which are associated with prostate cancer (7). Finally, an increase in the production of inflammatory markers, thought to underlie prostate cancer pathogenesis, has been recently observed to be associated with obesity. A conceptualized and plausible biological pathway through which obesity in conjunction with T2DM influences prostate-cancer risk is shown in Figure 1.1.

Figure 1-1: Conceptualized model of pathogenesis of prostate cancer and metabolic disturbances



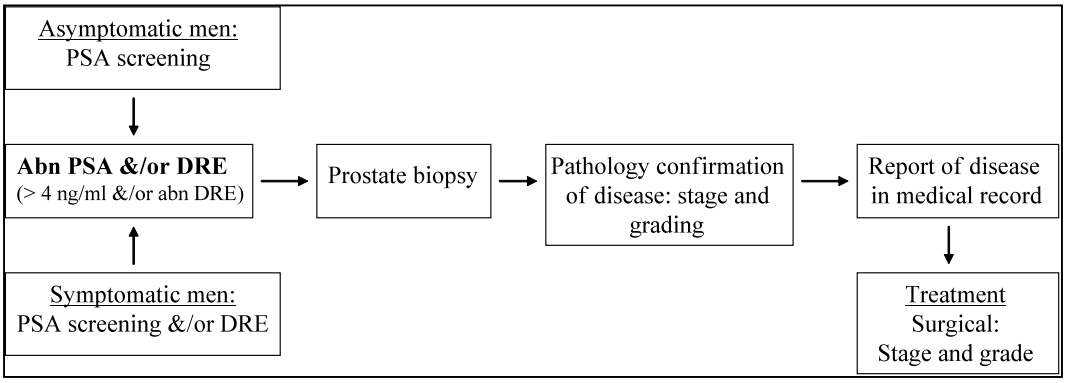
IGF-1: Insulin growth factor 1, IGFBP-1: Insulin growth factors binding protein 1, SHBG: Sex hormone binding globulin

Obesity and PSA

In addition to its effect on prostate cancer pathogenesis, obesity may also influence the detection of prostate cancer through its impact on prostate-cancer screening, PSA level, difficulty in performing DREs (affecting their results), and prostate volume (affecting biopsy results). In fact, several recent studies have suggested that detection bias associated with obesity may partly explain the inverse association between obesity and prostate cancer incidence (7, 11, 42). Digital rectal examinations known to be more difficult to perform in obese men may lead to an increased number of missed diagnoses (11). Additionally, elevated PSA levels are considered a marker for prostate cancer presence; however, needle-biopsy is necessary for confirmation. Obese men have lower PSA levels than do non-obese men (8, 11, 41), and PSA decreases with increasing concomitant BMI levels (9, 43, 44). These inverse associations are possibly due to decreased testosterone concentrations and resulting PSA (7) or to lower PSA levels as a result of plasma hemodilution in obese men (10). As a result, it is possible that obese men are less likely to be recommended for biopsy, thereby lowering the number of cancers detected in this group. Finally, obese men tend to present with larger prostates than do non-obese men (7, 45, 46). Larger prostate volumes make prostate needle-biopsy more difficult and, as a result, may result in a lower probability of cancer detection. The combined effects of obesity on performance of DREs, PSA level, and prostate volume may lead to appreciable detection bias when estimating the effect of obesity on prostate cancer. Prostate cancer detection begins with a physical exam that includes a DRE and PSA test due to symptoms, or a PSA in asymptomatic men as part of screening. The results of these tests define the process of cancer detection, which is illustrated in Figure

1.2. Determining how these tests are affected by obesity and what role prostate volume plays in influencing its impact may lead to a better-suited screening program for obese men.

Figure 1-2: The path to prostate cancer detection



Diabetes and Prostate Cancer

The association between diabetes and prostate cancer risk has been studied in several epidemiologic studies, and the consensus is that a reduction in risk is associated with type 2 diabetes. In their recent meta-analysis, Kasper and Giovannucci (47) found that the majority of the evidence supports a reduction in prostate-cancer risk associated with type 2 diabetes. Two of the largest studies found reductions in risk ranging from approximately 10-47 percent (38, 48). Results from several smaller studies, however, have been mixed with some reporting positive associations. These inconsistencies may be attributable to changes in insulin action over the course of diabetes. As noted above, type 2 diabetes is a complex metabolic disease characterized initially by insulin resistance and hyperinsulinemia. However, with increasing duration of the disease, the pancreas loses its ability to create insulin because of damage to the pancreatic B cells and circulating levels

of insulin decrease. Risk of prostate cancer has been associated with high circulating levels of insulin and insulin resistance. Consequently, it has been hypothesized that the incidence rate of prostate cancer increases among men recently diagnosed with diabetes, but then subsequently declines when insulin levels decrease (ignoring the effect of aging). In support of this hypothesis, investigators from the Cancer Prevention Study Nutrition Cohort, a prospective study of cancer incidence and mortality among 184,192 US men and women, reported that prostate-cancer incidence was higher among men recently diagnosed with diabetes than among men of the same age with diabetes diagnosed several years earlier (49). Furthermore, diabetic men have been found to have a 20% lower mean PSA level than do non-diabetic men (50, 51). As shown in figure 1.1, it is plausible, based on this evidence, that hyperinsulinemia influences sex-hormone signaling, which proliferates changes in the cell cycle that perpetuate prostate cancer cell growth. Taken together, these data provide compelling evidence that associations between diabetes duration and insulin resistance and prostate cancer biology exist. However, further research is necessary to understand what role diabetes plays in prostate cancer development as a comorbid condition in the metabolic syndrome.

Hypertension and Prostate Cancer

Research investigating the role hypertension plays in prostate cancer etiology is sparse. Hypertension was positively associated with prostate cancer diagnosis in the Flint Men's Health Study, a population-based study of African American men, which was modeled after the OCS (52). Furthermore, a prospective cohort study of 29,364 Norwegian men found that every 12 mm increase in blood pressure resulted in an 8%

increase in the incidence or prostate cancer (30). It is plausible that hypertension increases the risk of prostate cancer through sympathetic nervous system activity that can result in androgen-mediated stimulation of prostate cancer growth (53).

Specific Aims and Hypotheses

Prostate cancer and metabolic syndrome and its components, T2DM and obesity, are common comorbid conditions that bring millions of older American men to medical attention each year. Although results from epidemiologic studies have suggested that metabolic syndrome, diabetes and obesity may be risk factors for prostate cancer, no clear consensus has been reached. As these conditions become more prevalent, it is crucial not only to gain a better understanding as to how metabolic syndrome and its components affect prostate cancer risk, but also to understand the extent to which those factors influence disease detection. Furthermore, the majority of the conclusions in this field, to date, have been drawn from cross-sectional studies of prevalent cases and case-control studies that rely on recall of past weight ; and most have neglected the role of prostate volume on outcome. Therefore, the goal of this dissertation was estimate the effects of metabolic syndrome, T2DM, hypertension, and obesity on prostate-cancer risk and detection, while accounting for the influence of prostate volume, disease stage, PSA levels, and hormone levels. I accomplished this research goal by addressing five specific aims.

Specific Aims

1. To test the hypothesis that the metabolic syndrome and its components (type 2 diabetes, hypertension and obesity) affect the risk of prostate cancer in middle-aged and older Caucasian men. **(Chapter 2)**

2. To test the hypothesis that diabetes and hypertension lower PSA levels in men at risk of prostate cancer. **(Chapter 3)**

3. To test the hypothesis that obesity or increases in obesity lower PSA levels in men at risk of prostate cancer. **(Chapter 4)**

4. To test the hypothesis that the obesity and PSA association is influenced by detection issues involving the plasma hemodilution of PSA and increasing prostate volumes. **(Chapter 4)**

5. To test the hypothesis that the metabolic components decrease the risk of prostate biopsy in men at risk of prostate cancer and decrease the risk of a positive prostate biopsy among 519 men who received biopsies during follow-up. **(Chapter 5)**

With the incidence of metabolic diseases reaching epidemic proportions in the United States, elucidating the associations between metabolic syndrome and its components with prostate cancer risk and detection would have striking implications for the health of the aging male population. Findings from this study will set the direction for the next set of investigations to elucidate these associations and provide clues to understanding the etiology, as well as shape detection strategies for prostate cancer in men with these metabolic conditions.

Chapter 2

The Effects of Metabolic Conditions on Prostate Cancer Incidence over 15 Years of Follow-up: Results from the Olmsted County Study

Abstract

Objective: Research on the possible role of the metabolic syndrome in the etiology of prostate cancer has yielded inconsistent results. Combining multiple components of the syndrome into a single variable may obscure the separate and combined effects of these metabolic components on prostate cancer risk. The goal of this study was to determine if combinations of obesity, hypertension, and diabetes influence the development of prostate cancer over 15 years of follow-up.

Methods: In 1990, a randomly selected cohort of Caucasian men from Olmsted County, Minnesota, ages 40-79, was recruited; 2,445 completed a questionnaire that included physician-diagnosed diabetes and hypertension. Anthropometric measures were collected during clinical examination. Biopsy-confirmed prostate cancer was identified from medical records. Proportional hazards regression was used to estimate the effects of these metabolic conditions, both individually and in combination, on the incidence rate of prostate cancer.

Results: Men with hypertension alone or in combination with diabetes were more likely to develop prostate cancer than were men without any of the metabolic conditions. The metabolic syndrome—the presence of all three conditions compared to men with no

metabolic components—was only minimally and inversely associated with prostate cancer (HR: 0.81; 95% CI: 0.20, 3.3) and no monotonic association between the number of metabolic components and prostate cancer was observed.

Conclusions: Our results suggest that it may not be sufficient to treat metabolic conditions as one variable when investigating the etiology of prostate cancer in Caucasian men. Further research should focus on the separate and combined effects of these metabolic conditions in large samples**.**

Introduction

Prostate cancer is the most common non-cutaneous cancer among American men and the second leading cause of cancer death among men in the United States (54). The incidence of this disease is estimated to exceed 192,000 cases among American men in 2009 (2).

The metabolic syndrome, a cluster of conditions including type 2 diabetes, dyslipidemia, hypertension and obesity, is also a highly prevalent condition in the aging US population with overall prevalence in US adults estimated to be 25% (6). The main components of the metabolic syndrome, type 2 diabetes, hypertension, and obesity are arguably reaching epidemic proportions in the United States, resulting in significant morbidity and bringing millions of men to medical attention each year. Currently, 34% of US adults, age 20 and over, are described as obese (55); 31% suffer from high blood pressure (4); and 18 million adults are reported to currently have type 2 diabetes (23, 56).

Recently, several groups of investigators have suggested that features of the metabolic syndrome may be predictive of prostate cancer risk. Specifically, men with more than three components of the metabolic syndrome in a prospective study of 16,209 men were 1.5 times more likely to be diagnosed with prostate cancer in the 27 years of follow-up than were men with no metabolic syndrome components (26). Hammarstan et al. found that men with disseminated (T3) prostate cancer were more likely than men with localized (T2) disease to have multiple components of the metabolic syndrome (27). Furthermore, a prospective study of Finnish men found that men with the metabolic syndrome have a 2-fold increased risk of prostate cancer, and that the risk was greater in men with a body mass index (BMI) greater than or equal to 27 kg/m^2 compared to the

risk in men with a BMI less than 27 kg/m^2 (28). These results are in conflict with a recent prospective study that found little to no evidence that metabolic syndrome or its components were associated with prostate cancer in 29,364 Norwegian men followed for an average 9.3 years (30).

Each of the primary components of the syndrome--diabetes, obesity and hypertension--have been found to be associated with prostate cancer. While large population-based studies have shown that body mass index is positively associated with the incidence of prostate cancer (31-33, 36), more recent studies have found either no association or an inverse association between obesity and prostate cancer incidence (35, 47, 57). It is unclear, however, whether these findings reflect the effect of obesity on the risk of prostate cancer, the prognostic effect of obesity on prostate cancer progression, or the effect of obesity on detection of the disease.

Evidence of the association between type 2 diabetes and prostate cancer yields conflicting findings; results may reflect the changing action of insulin over the course of diabetes progression. A recent meta-analysis found that the majority of the evidence to date supports a reduction in prostate cancer risk associated with type 2 diabetes (52). Previous work assessing the association between hypertension and prostate cancer is sparse; however, the presence of hypertension may increase the risk of prostate cancer (30).

It is unclear, however, whether combining these conditions into one syndrome is an appropriate approach when investigating the etiology of prostate cancer. Specifically, combining multiple components of the syndrome into a single variable may confound or obscure the separate effects and interactions of these metabolic components on prostate

cancer risk. Therefore, the goal of this study was to determine whether obesity, hypertension, and diabetes alone and in combination, influence the incidence of prostate cancer over 15 years of follow-up.

Materials and Methods

Subject Selection

The Olmsted County Study (OCS) of Urinary Symptoms and Health Status among Men is a longitudinal, population-based investigation of Caucasian men, residing in Olmsted County, MN (58, 59). In 1990, a random sample of men 40-79 years old, as enumerated by the Rochester Epidemiology Project, was screened for inclusion (60). Men with a history of prostate or bladder surgery, urethral surgery or stricture, or medical or neurological conditions that affect normal urinary function were excluded. Eligible men (n=3,874) were invited to take part in the study, and 2,115 (55%) agreed to participate. Participants completed a previously validated baseline questionnaire that ascertained information on urinary symptoms, medical histories, and various demographic and behavioral characteristics. A 25% random subset of the total cohort was invited to participate in a detailed urologic clinical examination. Of the 537 randomly selected men, 475 (88%) agreed to participate in the clinical portion of the study.

Since 1990, the cohort has been followed biennially using a similar questionnaire to that used at baseline. During the second and third rounds of visits, men who did not participate in the follow-up were replaced by randomly selected eligible men from the community (n=332 total cohort; n=159 clinic cohort). After the third round, the study has been maintained as a fixed cohort.

Measurements

Biopsy-confirmed cases of prostate cancer were identified through detailed review of medical records, yielding a total of 206 cases. Information on self-reported

physician-diagnosed type 2 diabetes, and high blood pressure was collected at baseline. Men who reported using antihypertensive medication prior to baseline or who reported a physician diagnosis of hypertension at baseline were considered hypertensive for this analysis. Men that reported diabetes at baseline were considered diabetic. A trained research assistant measured height and weight, and BMI was calculated by dividing the weight in kilograms by the height in meters squared. Men with a BMI greater than or equal to 30 kg/m^2 were considered obese, based on the definition established by the World Health Organization (WHO) (55).

Metabolic syndrome was defined using a modified version of the WHO definition (17) and focused on the three components measured at baseline: self-reported type 2 diabetes, self-reported diagnosis of hypertension and/or use of antihypertensive medication prior to baseline, and measured obesity at baseline.

Potential confounders and effect modifiers included in these analyses were family history of prostate cancer based on self-reported first degree relative with physician-diagnosed prostate cancer, non-steroidal anti-inflammatory drug (NSAID), 5-alpha reductase inhibitor (5-ARI) or statin use prior to baseline, household income, years of education, and age at baseline.

Statistical Analysis

Incidence rates of prostate cancer were estimated for the total cohort and by category of selected demographic, medical history and metabolic component status by dividing the number of incident prostate cancer cases by the amount of person-time at risk. Participants' person-time contribution began on the date they completed their baseline questionnaires and ended at the diagnosis of prostate cancer or the last date of

passive surveillance chart review, whichever came first. The associations of sociodemographic characteristics and baseline metabolic conditions with prostate cancer were described using crude incidence rates. Age-adjusted hazard (incidence rate) ratios and 95% confidence intervals measuring the associations between the metabolic characteristics and prostate cancer incidence were estimated using Cox proportional hazards regression (SAS procedure proc phreg). The proportional hazards assumption was assessed using Schoenfeld residuals as well as an interaction term with time and not found to be violated for the three metabolic components. The effects of the various combinations of the metabolic conditions, as well as their interactions, on prostate cancer risk were assessed using multivariable Cox models adjusting for age. Equations used in this analysis are displayed in Appendix 1. All statistical analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC).

Results

Among this cohort of Caucasian men, 206 cases of prostate cancer were detected, and the estimated incidence rate was 6.88 per 1,000 per year. Prostate cancer was positively associated with age (Table 2-1; p for trend <0.001). The incidence rate of prostate cancer was greater in men with a family history of prostate cancer than in men without a family history of prostate cancer (p<0.001). Also, men who achieved more education and earned more income had lower incidence rates of prostate cancer when compared to men with less education (p for trend=0.0005) and income (p for trend=0.0008) (Table 2-1).

Table 2-2 displays the crude and age-adjusted hazard ratios for each metabolic variable, unadjusted for the others. Men with a history of diabetes did not have an elevated rate of prostate cancer (Table 2-2). Hypertensive men were 1.5 times more likely to develop prostate cancer than were non-hypertensive men (hazard ratio (HR): 1.5; 95% confidence interval (CI): 1.1, 2.0), although this association was attenuated when adjusted for age (HR: 1.1; 95% CI: 0.79, 1.4). An increasing number of metabolic components were not consistently associated with prostate cancer incidence, adjusting for age (Table 2-2). Those with one component had a slightly increased rate, while those with two or three components had a slightly decreased rate of prostate cancer. Adjustment for age, family history of prostate cancer and baseline statin use did not change these results, nor did adjustment for age, family history of prostate cancer, baseline statin use, education and income (data not shown).

Despite small numbers of cases, the combined categories of the three conditions were also examined. Figure 2-1 displays the unadjusted hazard ratios and age-adjusted

hazard ratios of prostate cancer for all eight combinations of the three components of the metabolic syndrome. Compared to men with no components of the syndrome, men with all three--the metabolic syndrome--did not have an elevated rate of prostate cancer, adjusting for age (HR: 0.81; 95% CI: 0.20, 3.3); however, this estimate is imprecise because there were only two cases diagnosed in the group with all three conditions. The presence of diabetes alone was inversely associated with prostate cancer (age-adjusted HR: 0.62; 95% CI: 0.15, 2.5), but men who were hypertensive, diabetic and not obese were more likely to develop prostate cancer compared to men who did not have any of the three conditions (age-adjusted HR: 1.3; 95% CI: 0.53, 3.2). Obesity and hypertension alone were associated with an increased risk of prostate cancer; however, the combination of the two was associated with a decreased risk of prostate cancer compared to men with none of the conditions (age-adjusted HR: 0.50; 95% CI: 0.23, 1.1) (Figure 2-1).

In further examination of the interaction between obesity and hypertension, the only notable departure from multiplicative effects in the proportional hazards model was the interaction between obesity and hypertension ($p = 0.013$) (Table 2-3). The estimated hazard ratio, comparing men with both conditions to men with neither condition, was 0.69 (95% CI: 0.35, 1.4). In contrast, the estimated hazard ratio for men with only hypertension was 1.8 (95% CI: 1.3, 2.5).

Discussion

In this prospective study of 2,445 Caucasian men ages 40-79, the metabolic syndrome, defined as the presence of obesity, hypertension and type 2 diabetes, was minimally and inversely associated with the development of prostate cancer over 15 years of follow-up. However, the components of the metabolic syndrome alone were differentially associated with the rate of prostate cancer. After adjustment for age, the presence of only hypertension was associated with an increased rate of prostate cancer. The combinations of components were also found to influence the rate of prostate cancer differently, as men who were hypertensive and obese were less likely to develop prostate cancer and men who were diabetic and hypertensive were more likely to develop prostate cancer, adjusting for age. Obesity modified the association between hypertension and prostate cancer, as men who were obese and hypertensive were less likely to develop prostate cancer, while men who were hypertensive alone were more likely to develop prostate cancer compared to men who did not have either condition.

The association between diabetes and prostate cancer risk has been studied in several epidemiologic studies. In their recent meta-analysis, Kasper and Giovannucci found that the majority of the evidence supports a reduction in prostate cancer risk associated with type 2 diabetes (47). A weak inverse association between diabetes and prostate cancer was also observed in the current study, but it may have been a chance finding. Alternatively, our findings may obscure the changing association between insulin level and prostate cancer risk over the course of diabetes progression. Insulin levels are initially high in type 2 diabetes but fall over time due to the damage to the pancreatic ß cells. Therefore, the relation between diabetes and prostate cancer may change from

positive to inverse as diabetes progresses. This explanation is supported by research suggesting that men with early-stage diabetes have an increased risk of prostate cancer while men with later stage disease have a decreased risk (49, 61). Unfortunately, we did not have information on insulin levels or the duration of diabetes in our database, and we observed only 9 cases of prostate cancer among diabetics.

Obesity (BMI ≥30 kg/m^2) was minimally and inversely associated with prostate cancer in this cohort when compared to a BMI of less than 30 kg/m^2. Our results are consistent with previous studies, suggesting either no association or an inverse association between obesity and prostate cancer incidence (35, 47, 57). In addition, obesity has been differentially associated with aggressive versus non-aggressive prostate cancers; a reduced risk of low-grade disease and an increased risk of high-grade disease have been observed for obese men (40, 62, 63). Our results, however, did not change when stratified by grade and stage of prostate cancer (data not shown).

While other large, population-based studies have found obesity to be associated with an increased risk of prostate cancer, the current literature as a whole has yielded inconsistent results (31-33, 36). Several recent studies have suggested that detection bias associated with obesity may partly explain the inverse association between obesity and prostate cancer incidence (7). Obese men have lower prostate specific antigen (PSA) levels than do non-obese men, (8, 11) possibly due to decreased testosterone concentrations or a hemodilution effect as a result of increased prostate volumes (10). As a result, obese men are less likely to be recommended for biopsy based on their PSA levels. Furthermore, the difficulty of detecting cancer upon biopsy is increased due to the larger prostate volumes (10, 11), thereby lowering the number of cancers detected in this

group. While it is plausible that obesity can influence the growth of prostate cancer through the action of adipocytes, it is unclear if the associations seen in this study and in previous work are biased due to detection issues that occur among obese men.

Research investigating the role hypertension plays in prostate cancer etiology is very sparse. Hypertension was positively associated with the rate of prostate cancer in this study, which is similar to results found in the Flint Men's Health Study, a population-based study of African American men that was modeled after the OCS (52). Also, a prospective cohort study of 29,364 Norwegian men found that every 12 mm increase in blood pressure resulted in an 8% increase in the incidence or prostate cancer (30). It is plausible that hypertension could increase the risk of prostate cancer through sympathetic nervous system activity that can result in androgen-mediated stimulation of prostate cancer growth (53). Men with both hypertension and obesity had a lower rate of prostate cancer in our study compared to men with neither condition, and men with hypertension who were not obese were at increased risk. This apparent heterogeneity of effects may be influenced by the likelihood of these men receiving biopsies. Specifically, it is possible that men with both comorbidities are less likely to be biopsied, as a result of physician perception that these comorbidities are more life threatening than prostate cancer.

In the current study, little association was seen between the presence of all three components of metabolic syndrome and prostate cancer. While we did observe an association between the presence of one component and an increase in the rate of prostate cancer adjusting for age, an increasing number of components was not found to be positively and consistently associated with prostate cancer. These results seem to conflict with previous population-based studies that found more than three components of the

metabolic syndrome were associated with an increased risk of prostate cancer (26-28). The discrepancy in results may in part be due to the varying definitions of metabolic syndrome used in the current and previous investigations (i.e., three vs. more than three components of the metabolic syndrome) or to the small number of cases detected among men with all three components. Additionally, the definitions of metabolic syndrome recommended by the WHO and Adult Treatment Panel III were used in previous investigations, but our study focused on the combination of the components rather than the syndrome alone. It is also possible that the differing results are due to the unaccounted influence of dyslipidemia on prostate cancer risk in the OCS.

Our results, however, are consistent with those of Tande et al. (25), who found men with at least three out of the five metabolic syndrome components were approximately 25% less likely to develop prostate cancer. Men who had two or three components had a slightly decreased risk of prostate cancer compared to those who had no components of the metabolic syndrome. It is possible that the metabolic syndrome reduces the risk of prostate cancer through the action of sex hormones. The cross-talk between androgens, sex hormone-binding globulin and insulin is thought to influence prostate cancer (26), and men with metabolic syndrome exhibit decreased testosterone levels (64), thus potentially decreasing their risk of prostate cancer. It is also possible that these results are explained in part by a detection bias that results in a lower rate of prostate cancer among obese men.

The current study utilized a large, ongoing cohort of Caucasian men, which included 15 years of follow-up to date. However, there are several limitations that must be considered. First, the baseline measures of diabetes and hypertension do not account

for changes in these conditions over time. Furthermore, ages at diagnosis of diabetes and hypertension are not available in this cohort and thus limit our ability to make inferences about the progression of these conditions. Finally, while we are limited in our reliance on self-report of several metabolic conditions, diabetes diagnosis was validated among self-reported cases in a larger cohort study of diabetes in Olmsted County from 1950 to 2000 (65).

Although the long follow-up period lends itself to problems associated with attrition, previous work in this cohort found that participant dropout was not associated with diabetes, hypertension, or PSA level after adjustment for age, thus suggesting the potential impact of this bias may be limited (66). Also, because this is a Caucasian sample of men, generalizing these findings to other racial groups may not be appropriate. The incidence rate of prostate cancer as well as the prevalence of the components of metabolic syndrome are thought to differ by race (9, 67); therefore, our effect estimates in Caucasians may not be applicable to other racial groups with different incidences of these conditions. However, the methods used in this study to estimate the effects of metabolic conditions on the incidence of prostate cancer can be applied to other populations from diverse settings. Finally, it is possible that our results were influenced by the detection bias that is thought to exist in obese men.

In summary, we assessed whether different combinations of metabolic conditions confer different risks of prostate cancer. Men who were hypertensive and obese had a lower incidence rate of prostate cancer than did men without either condition, though this association was imprecisely estimated and may have been influenced by detection bias, as noted earlier. However, men with hypertension alone were at increased risk of disease,

suggesting that the different combinations of these metabolic conditions may affect prostate cancer incidence differently. Explanations as to why these conditions may differentially influence prostate cancer risk remain unclear. Previous work dealing with the influence of the overall metabolic syndrome on prostate cancer etiology may have obscured the separate and combined effects of the conditions it includes. Future studies, therefore, should examine the individual components of the metabolic syndrome in addition to combining them into a single variable; however, large samples will be needed to achieve sufficient precision and power.

Table 2-1: Crude incidence rate (IR), hazard ratio (HR) and age-adjusted HR, by category of selected baseline demographic variables

Variable Category	Prostate Cancer Cases	Person-years	Crude IR (per 1000/year)	p-value (Association /trend)	Crude HR (95%CI)	Age-adjusted HR (95%CI)
Age at baseline				<0.01/<0.01		
40-49	33	13743	2.40		1	--
50-59	63	8076	7.80		3.2(2.1, 4.9)	--
60-69	71	5511	12.88		5.4(3.6, 8.1)	--
70+	39	2633	14.81		6.3(4.0, 10.1)	--
Family history of prostate cancer				<0.01		
No	169	27224	6.21		1	1
Yes	37	2739	13.51		2.2(1.5, 3.1)	2.0(1.4, 2.9)
5-ARI use				0.58		
No	205	29882	6.86		1	1
Yes	1	81	12.38		1.8(0.26, 13.1)	1.5(0.21, 10.8)
NSAID use				0.55		
No	158	23505	6.72		1	1
Yes	48	6458	7.43		1.1(0.80, 1.5)	0.79(0.57, 1.1)
Statin use				0.82		
No	199	28756	6.92		1	1
Yes	7	1206	5.80		0.83(0.39, 1.8)	0.67(0.32, 1.4)
Education				<0.01/<0.01		
Less than high school graduate	36	2604	13.83		1	1
Finished high school/some college	101	15364	6.57		0.47(0.32, 0.69)	0.78(0.52, 1.2)
College degree and beyond	68	11698	5.81		0.42(0.28, 0.62)	0.84(0.55, 1.3)
Marital status				0.90		
Single, divorced, widowed, separated	23	3038	7.57		1	1
Married/living together	183	26833	6.82		0.89(0.58, 1.4)	0.79(0.51, 1.2)
Salary				<0.01/<0.01		
<$25,000	58	5148	11.27		1	1
$25,000-$44,999	62	8786	7.06		0.62(0.43, 0.88)	0.82(0.57, 1.2)
$45,000-$64,999	31	7573	4.09		0.36(0.23, 0.55)	0.65(0.41, 1.0)
$65,000+	47	7226	6.51		0.57(0.39, 0.84)	1.1(0.74, 1.7)

Table 2-2: Crude incidence rate (IR), hazard ratio (HR), and age-adjusted HR, by category of selected baseline metabolic characteristics

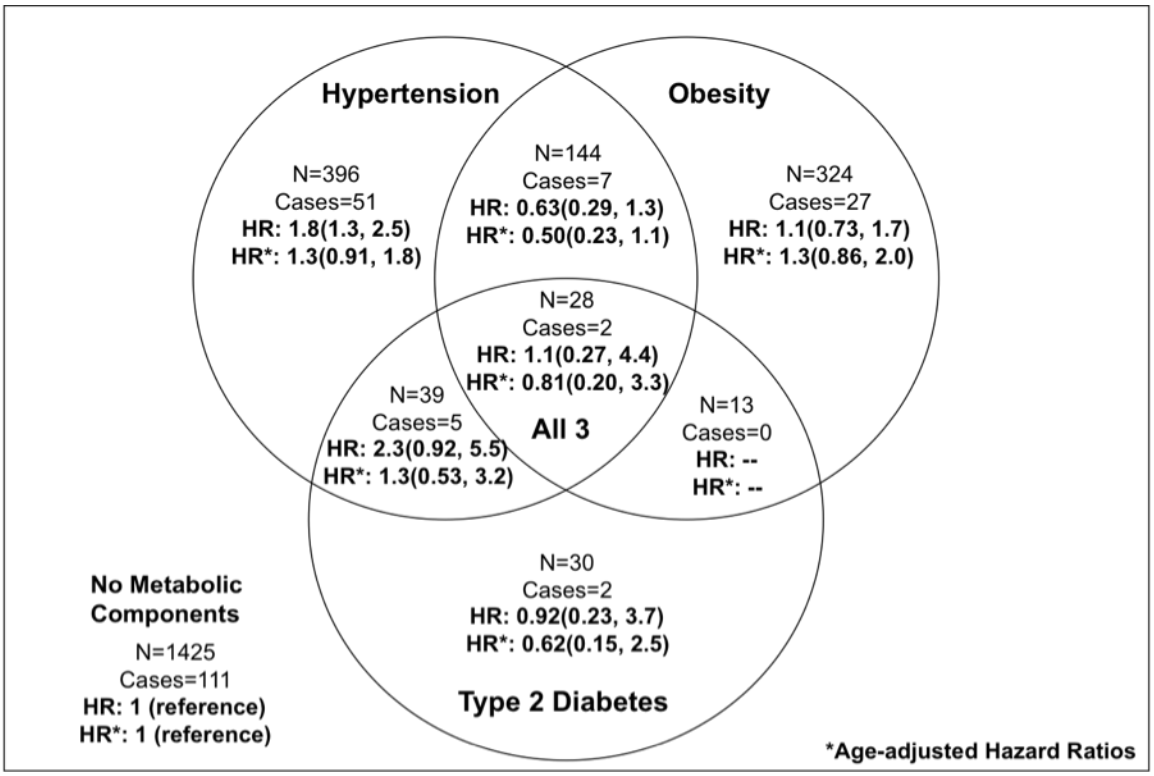
Characteristic Category	Prostate Cancer Cases	Person-years	Crude IR (per 1000/year)	Crude HR (95%CI)	Age-adjusted HR (95%CI)
Diabetes diagnosis at baseline					
No	197	28764	6.85	1	1
Yes	9	1198	7.51	1.1(0.57, 2.2)	0.77(0.39, 1.5)
Hypertensive at baseline					
No	140	22832	6.13	1	1
Yes	66	7130	9.26	1.5(1.1, 2.0)	1.1(0.79, 1.4)
Obesity					
Not Obese (<30 kg/m^2)	169	23316	7.25	1	1
Obese (≥30 kg/m^2)	36	6228	5.78	0.80(0.56, 1.1)	0.88(0.61, 1.3)
Number of metabolic syndrome components					
0	111	18348	6.05	1	1
1	81	8974	9.03	1.5(1.1, 2.0)	1.3(0.96, 1.7)
2 or 3	14	2641	5.30	0.88(0.50, 1.5)	0.65(0.37, 1.1)

Table 2-3: Estimated crude hazard ratios (HR) for combined categories of hypertension and obesity

	Hypertension	No Hypertension	
	HR (95% CI)	**HR (95% CI)**	**p-value***
Obese	0.69(0.35, 1.4)	1.1(0.70, 1.6)	0.013
Not Obese	1.8(1.3, 2.5)	1	

*Corresponds to a two-sided test of the null hypothesis that the effects of hypertension and obesity are multiplicative on the rate scale.

Figure 2-1: Comparison of prostate cancer incidence among all 8 combined categories of three metabolic syndrome components, shown as a Venn diagram



-Diabetes is defined as self-reported physician-diagnosed diabetes at baseline.
-Obesity was calculated using the measured height and weight from the clinic examination, with those ≥30 kg/m^2 classified as obese.
-Hypertension was defined as those with high blood pressure at baseline or who reported using anti-hypertensive medication prior to baseline.
-Note: 46 patients are missing from the above Venn diagram due to missing data on metabolic components.

Chapter 3

The Effects of Type 2 Diabetes and Hypertension on Changes in Serum Prostate Specific Antigen Levels: Results from the Olmsted County Study

Abstract

Objective: Men with type 2 diabetes have lower concomitant prostate-specific antigen (PSA) levels; however, the influence of metabolic conditions on PSA changes over time remains unknown. Therefore, the goal of this study was to assess associations between type 2 diabetes and hypertension and changes in serum PSA levels.

Methods: In 1990, a randomly selected cohort of Caucasian men, ages 40-79, from Olmsted County, MN completed questionnaires ascertaining demographic characteristics, current medical conditions and medications biennially, with a subset undergoing blood draws. Men with a physician diagnosis of diabetes or hypertension at baseline, or who reported using medications to treat these conditions prior to baseline were considered exposed. Men with at least two serum PSA measurements (n=569) and no history of prostate cancer were included in this analysis. Linear mixed models were used to estimate the annual percent change in serum PSA levels associated with diabetes and hypertension, adjusting for baseline age.

Results: The overall mean change in serum PSA levels was 3.6% per year and increased with age (p=0.009). Men with diabetes experienced less annual change in serum PSA

levels (1.1%) than did non-diabetic men (3.7%), adjusting for age (p=0.02). Age-adjusted change in serum PSA levels differed little by hypertension status (3.7% vs. 3.6%; p=0.49).

Conclusions: Our results suggest that Caucasian men with type 2 diabetes experience smaller increases in serum PSA levels as they age compared to men without diabetes. Additional research is needed to elucidate whether this difference results in a relatively lower incidence of prostate cancer or less cancer detection among diabetic men.

Introduction

Prostate cancer is the most common non-cutaneous cancer in U.S. men, with an estimated 192,280 new cases diagnosed in 2009 (68). While only 15% of men diagnosed with prostate cancer will ultimately die from it, the prevalence of clinically diagnosed disease remains high. Currently, prostate-specific antigen (PSA) is the most common screening test for prostate cancer with 58% of Caucasian men receiving an annual test (12). The low specificity of PSA testing and questionable benefit of PSA screening on prostate cancer mortality highlight the need for better detection strategies for prostate cancer ((15). Knowledge about the influence of concomitant comorbidities on serum PSA concentrations may improve the discriminant value of this test and reduce the number of unnecessary biopsies and subsequent overdiagnosis of indolent cancers.

Type 2 diabetes and hypertension, two increasingly prevalent chronic diseases in the U.S., are arguably reaching epidemic proportions. It is estimated that 1 in 3 U.S. adults suffer from high blood pressure and 11% of U.S. men have type 2 diabetes (4, 55). Many studies have investigated the association between type 2 diabetes and prostate cancer, with the majority of evidence supporting an inverse association; the reported reduction in risk ranges from 10-40% in diabetics (47, 69). Previous findings also suggest that the effect of diabetes on prostate-cancer risk varies with the duration of diabetes; men with newly diagnosed diabetes have an increased risk, but as their diabetes progresses, their risk of prostate cancer declines (49). Furthermore, diabetes is associated with serum PSA levels; men with diabetes have approximately 10 to 20% lower concurrent serum PSA levels than do men without diabetes (50, 51). Similarly, elevated hemoglobin A1C levels are also inversely associated with serum PSA levels, and men

who use insulin and oral glucose medications have lower serum PSA levels than do men who do not use medications to treat diabetes (70). Taken together, these findings suggest that diabetes influences prostate-cancer risk and concurrent serum PSA levels.

Studies evaluating the relationship between hypertension and prostate-cancer risk are more limited, with previous results suggesting that men with hypertension are more likely than men without hypertension to be diagnosed with prostate cancer (52). Research by Han and colleagues[12] suggests that high blood pressure is positively associated with concurrent serum PSA levels.

Although the results from these epidemiologic studies suggest that diabetes and hypertension may be associated with prostate cancer and concurrently influence serum PSA concentrations, they are limited by their cross-sectional designs. The effect of these conditions on serum PSA levels over time has yet to be characterized. This is important as the change in serum PSA levels has been demonstrated to be more reliable in the detection of prostate cancer than single serum PSA measurements (71, 72). The increasing prevalence of hypertension and diabetes coupled with the increasing speculation regarding the reliable detection of prostate cancer with serum PSA levels make it crucial to gain a better understanding as to how these metabolic conditions influence prostate cancer detection. Therefore, the goal of this study was to determine the associations between type 2 diabetes and hypertension and longitudinal changes in serum PSA levels over 15 years of follow-up, using data from The Olmsted County Study (OCS) of Urinary Symptoms and Health Status among Men.

Materials and Methods

The OCS of Urinary Symptoms and Health Status among Men is a longitudinal study of Caucasian men, residing in Olmsted County, MN ((58, 59). In 1990, a random sample of men 40-79 years old, as enumerated by the Rochester Epidemiology Project, was screened for inclusion (60). Men with a history of prostate or bladder surgery, urethral surgery or stricture, or medical or neurological conditions that affect normal urinary function were excluded. Also, men with diabetes who suffered from end-organ damage were excluded at baseline. Eligible men (n=3,874) were invited to take part in the study, and 2,115 (55%) agreed to participate. Participants completed a previously validated baseline questionnaire that ascertained information on urinary symptoms, medical histories, and various demographic and behavioral characteristics. A 25% random subset of the total cohort was invited to participate in a detailed urologic clinical examination, which included transrectal ultrasonography to determine prostate volume and serum PSA measurements. Of the 537 randomly selected men, 475 (88%) agreed to participate in the clinical portion of the study.

Since 1990, the cohort has been actively followed biennially using a questionnaire similar to the one used at baseline. During the second and third rounds of visits, men who did not participate in the follow-up were replaced by randomly selected eligible men from the community (n=332 total cohort; n=158 clinic cohort). After the third round, the study has been maintained as a fixed cohort. Of the 633 men in the clinic cohort, men with at least two serum PSA measurements were included, and only serum PSA measurements obtained before prostate cancer diagnosis, BPH medication use or prostate

surgery/procedure were included. As a result, 569 men with 2,891 observations were included in this analysis (Figure 3-1).

Measurements

Information on self-reported physician-diagnosed type 2 diabetes, and high blood pressure was collected at baseline via questionnaire. Men who reported using antihypertensive medication prior to baseline or who reported a physician diagnosis of hypertension at baseline were considered hypertensive for this analysis. In addition, men who reported a physician diagnosis of diabetes at baseline or who used medication to treat diabetes prior to baseline were considered diabetic. Prostate volume, measured via transrectal ultrasonographic imaging, and serum PSA measurements were collected at each round of follow-up during the clinic examination.

Potential confounders and effect modifiers assessed in these analyses include family history of prostate cancer based on a self-reported first-degree relative with physician-diagnosed prostate cancer, household income, years of education, age at baseline blood draw, prostate volume, and body mass index (BMI). Height and weight were measured by a trained research assistant, and BMI was calculated by dividing the weight in kilograms by the height in meters squared. Men with a BMI greater than or equal to 30 kg/m^2 were considered obese, based on the definition established by the World Health Organization (WHO) (55).

Statistical Analysis

Linear mixed effects regression models were used to estimate the annual percent change in serum PSA levels by regressing each measure on time from initial blood draw and adjusting for 10-year baseline age groups. Interaction terms with time were included

to allow for different slopes across these age groups. An overall annual change in serum PSA levels for each man was estimated by combining the average longitudinal change (fixed effects) with the individual changes (random effects). Additional models included terms for diagnosis of diabetes or hypertension and interaction terms to compare intercepts and slopes among those with and without a diagnosis. The mixed models used to estimate these parameters is shown in Appendix 2. Because of the skewed distribution, serum PSA levels were natural log-transformed, and therefore, annual changes represent percent changes per year assuming an exponential growth curve. Two-stage analysis was used to validate estimates of slopes from the mixed models. All statistical analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC).

Results

The 569 men in this sample were followed for a median of 8.4 years after baseline blood draw. The majority of men (91.2%) did not report a family history of prostate cancer. Twenty-five men (4.4%) reported type 2 diabetes at baseline, and 149 (26.2%) reported being hypertensive at baseline. The majority of men were not considered obese at baseline, as 425 (75%) men had a BMI less than 30 kg/m^2 (Table 3-1).

In general, serum PSA levels increased over time as men aged in this cohort, as displayed in the observed and predicted values of serum PSA levels shown in Figure 3-2. Table 3-2 displays the annual percent changes in serum PSA levels from the linear mixed models. Overall, serum PSA levels in this cohort increased by 3.58% per year ($p<0.001$). The annual percent change in serum PSA levels increased with age ($p=0.009$), with men ages 70 and over at baseline experiencing the greatest annual percent increase in serum PSA levels (4.66%), followed by men ages 60-69 (4.64%), ages 50-59 (3.94%), and ages 40-49 (2.59%) (Table 3-2). After adjusting for baseline age, baseline (intercept) serum PSA values were not different across diabetes status ($p=0.65$), or hypertension status ($p=0.12$) (results not shown). After adjusting for age, men with diabetes at baseline experienced less of an annual increase in serum PSA levels than did men without diabetes (1.11 vs 3.68%; $p=0.02$) (Table 3-2). Annual age-adjusted percent change in serum PSA levels did not differ by hypertension status (3.67% vs. 3.55%; $p=0.49$). Figure 3-3 displays the median predicted values in serum PSA levels during follow-up, by diabetes status. Additional results not discussed in this chapter are displayed in Appendix 2.

Discussion

In this prospective cohort study of Caucasian men, ages 40-79, serum PSA levels increased at a rate of 3.6% per year. Older men had more rapid increases in serum PSA levels compared to younger men, and men without diabetes had more rapid increases serum PSA levels compared to men with diabetes. Hypertension, however, was not associated with rate of change in serum PSA levels.

Although there are no other studies evaluating the impact of diabetes on changes in serum PSA levels over time, our finding that the change in serum PSA levels was associated with diabetes is consistent with previous cross-sectional findings suggesting that serum PSA levels are lower among diabetic men than among non-diabetic men. Specifically, Muller et al. found men with elevated and highly elevated hemoglobin A1C levels had 15% and 29% lower serum PSA levels, respectively. Men who were on insulin treatment and oral diabetic medications also had lower serum PSA concentrations (70). Using the National Health and Nutrition Examination Surveys, Werny and colleagues found 22% lower average serum PSA levels among men with type 2 diabetes ((50). These findings were further replicated by Fukui et al. (51) who observed 10 to 16% lower average serum PSA levels among male Japanese diabetics, ages 50-79 years. Our results suggest that men with diabetes have slower increases in serum PSA levels over time, and this might account for the lower serum PSA levels observed among diabetics in cross-sectional studies.

As noted in the introduction, the association between diabetes and serum PSA levels is hypothesized to vary with the duration of diabetes. Several studies have found an inverse relation between diabetes duration and serum PSA levels (49, 50). It is plausible

that as the duration of diabetes increases, the action of insulin decreases and testosterone increases, resulting in subsequent drops in serum PSA levels. This is supported by findings that later-stage diabetes is characterized by insulin resistance and lower levels of circulating insulin, which have been associated with lower prostate-cancer risk and serum PSA levels (49, 73). A lower risk in later-stage diabetes may be attributable to the androgen regulation of PSA levels. PSA cleaves insulin growth factor binding protein 3 (IGFBP-3), a major binding protein for insulin growth factor 1 (IGF-1), which is involved in insulin signaling and associated with an increase in prostate-cancer risk (74, 75). Previous findings that show use of diabetic medication is associated with serum PSA levels also support this hypothesis, as diabetic-medication use may be a proxy for diabetes severity (70).

It remains to be demonstrated whether or not decreases in serum PSA levels drive the lower risk of prostate cancer observed among diabetic men in previous studies (47, 76-78). If smaller increases in serum PSA levels among diabetics result in less detection of prostate cancer among asymptomatic cases, it might suggest a detection bias among diabetic men, similar to that thought to exist among obese men due to their lower serum PSA levels and increased prostate volumes (7, 42). Furthermore, if the smaller increase in serum PSA levels among diabetic men delays the diagnosis of prostate cancer, men with diabetes may be more likely to be diagnosed with later-stage disease. As such, the potential impact of diabetes on prostate-cancer detection warrants further investigation in future studies.

Hypertension was not associated with change in serum PSA levels over time in this cohort. Findings from previous studies suggest that hypertension is positively

associated cross-sectionally with serum PSA levels and longitudinally with the risk of prostate cancer (52, 73). Beebe-Dimmer et al. (52) found a positive association between hypertension and prostate cancer. Han et al. (79) found that diastolic blood pressure was positively associated with serum PSA levels in a sample of 38,356 Korean men. It is possible that androgen-mediated prostate-cancer growth is stimulated by increased sympathetic nervous-system activity subsequent to elevated blood pressure (53). The lack of an association between hypertension and change in serum PSA levels over time in our study may be in part due to the non-specificity of hypertensive medications or to hypertensive status being defined only at baseline. It is possible that some non-hypertensive men were prescribed medication because of cardiovascular disease. It is also plausible that men with hypertension in this cohort were being treated during follow-up and therefore, the effect of hypertension on serum PSA levels is attenuated, resulting in a null association when compared to men without hypertension.

While this study characterizes whether diabetes and hypertension influence change in serum PSA levels using a prospective cohort study with 15 years of follow-up, there are several potential limitations that need to be considered. First, the baseline measures of diabetes and hypertension do not account for changes in these conditions during follow-up, which might have influenced subsequent serum PSA levels. However, it is likely that not accounting for additional diabetics over time is attenuating the difference in change in serum PSA levels among this cohort. Additionally, age at diagnosis of diabetes and hypertension were not queried of men, thereby limiting our ability to make inferences about the progression of these conditions and serum PSA levels. While we are limited in our reliance on self-report of the metabolic conditions,

diabetes diagnosis was validated among self-reported cases in a larger cohort study of diabetes in Olmsted County from 1950 to 2000 (65) and most studies show a concordance between self-report and medical records for chronic conditions such as diabetes and hypertension (80, 81). Although the long follow-up period lends itself to problems associated with attrition, previous work in this cohort found that participant dropout was not associated with diabetes, hypertension, or serum PSA levels after adjustment for age, thus suggesting the potential impact of this bias on these results may be limited (66).Finally, because this is a Caucasian sample of men, generalizing these findings to other racial groups may not be appropriate.

In conclusion, our results suggest that type 2 diabetes may decrease the rate at which serum PSA levels change over time. Lower levels of serum PSA as men age potentially influences their detection of prostate cancer. Thus, it is plausible that the presence of diabetes may lead to fewer prostate cancers being detected among this group. As screening guidelines are revised for prostate cancer, it may be prudent to take into consideration the presence of metabolic conditions. Future research should investigate the longitudinal impact of these metabolic conditions on prostate-cancer detection in larger, more diverse samples.

Figure 3-1: Sample size information

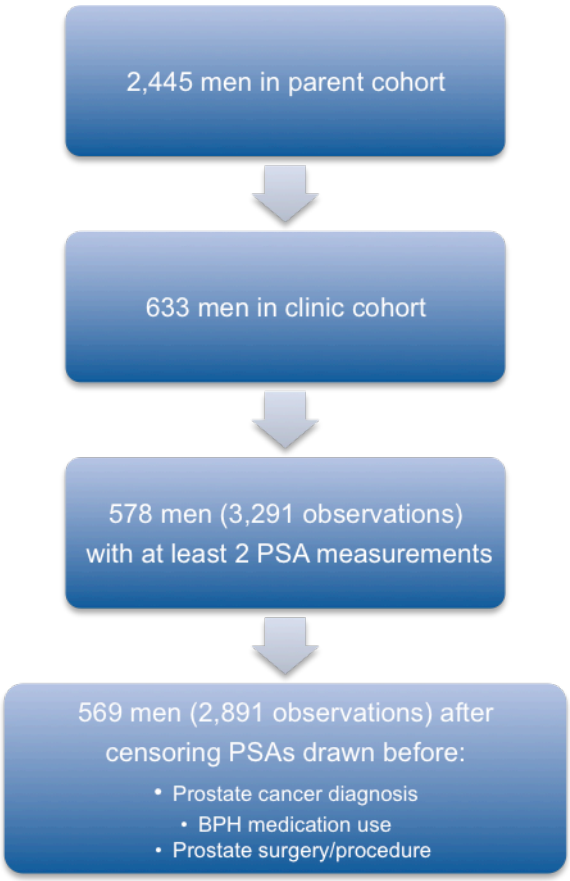


Table 3-1: Demographic and medical history characteristics of 569 men

Characteristic	N (%)
Age, years	
40-49	243(42.7)
50-59	151(26.5)
60-69	103(18.1)
70+	72(12.7)
Marital Status	
Single, divorced, widowed, separated	56(9.8)
Married/living together	511(89.8)
Education	
Less than high school graduate	60(10.5)
Finished high school/some college	267(46.9)
College degree and beyond	239(42.0)
Salary	
<$25,000	98(17.2)
$25,000-$44,999	148(26.0)
$45,000-$64,999	153(26.9)
$65,000+	143(25.1)
Family history of prostate cancer	
No	519(91.2)
Yes	50(8.8)
Diabetes at baseline	
No	544(95.6)
Yes	25(4.4)
Hypertension at baseline	
No	420(73.8)
Yes	149(26.2)
BMI at baseline, kg/m^2	
<25	151(26.5)
25-29	274(48.2)
30-34	118(20.7)
≥35	26(4.6)

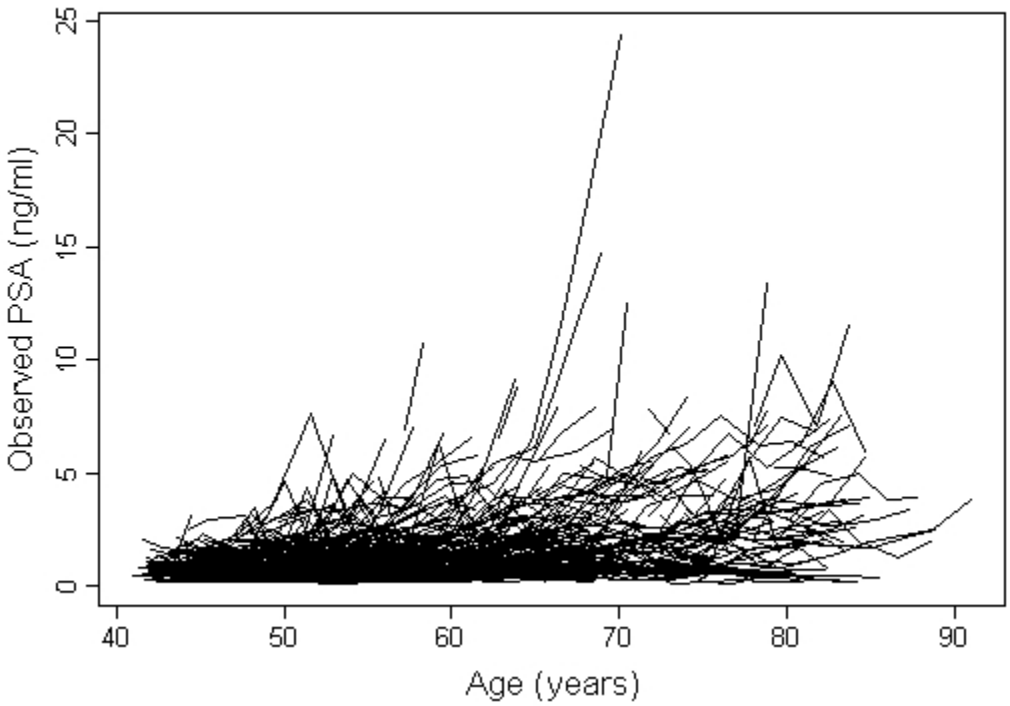
*Total N for some characteristics is less than 569 due to missing data

Table 3-2: Age-adjusted mean slopes in 569 men from mixed models

Baseline Characteristic		Annual percent change in PSA Mean, std. dev.
Overall*		3.58, 2.96
	p-value	<.0001
Age		
	40-49	2.59, 2.79
	50-59	3.94, 2.91
	60-69	4.64, 3.04
	70+	4.66, 2.46
	p-value	0.009
Diabetes*		
	No	3.68, 2.94
	Yes	1.11, 2.76
	p-value	0.02
Hypertension*		
	No	3.55, 2.96
	Yes	3.67, 2.97
	p-value	0.49

*Age-adjusted slopes from mixed models.

Figure 3-2: Observed and predicted PSA levels in 569 men from mixed model



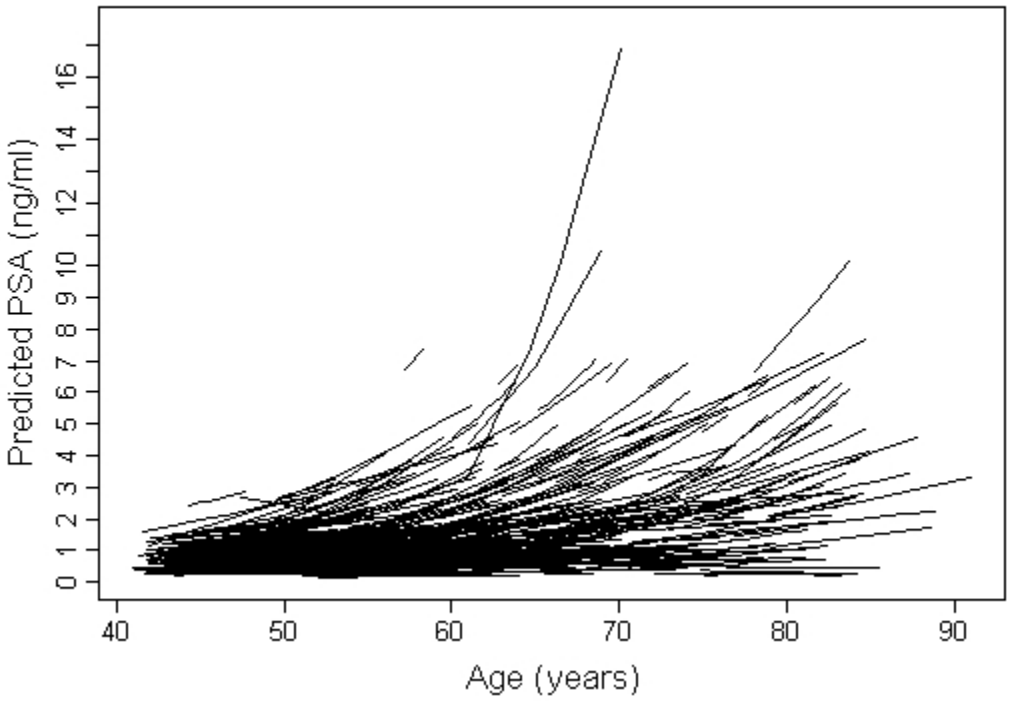
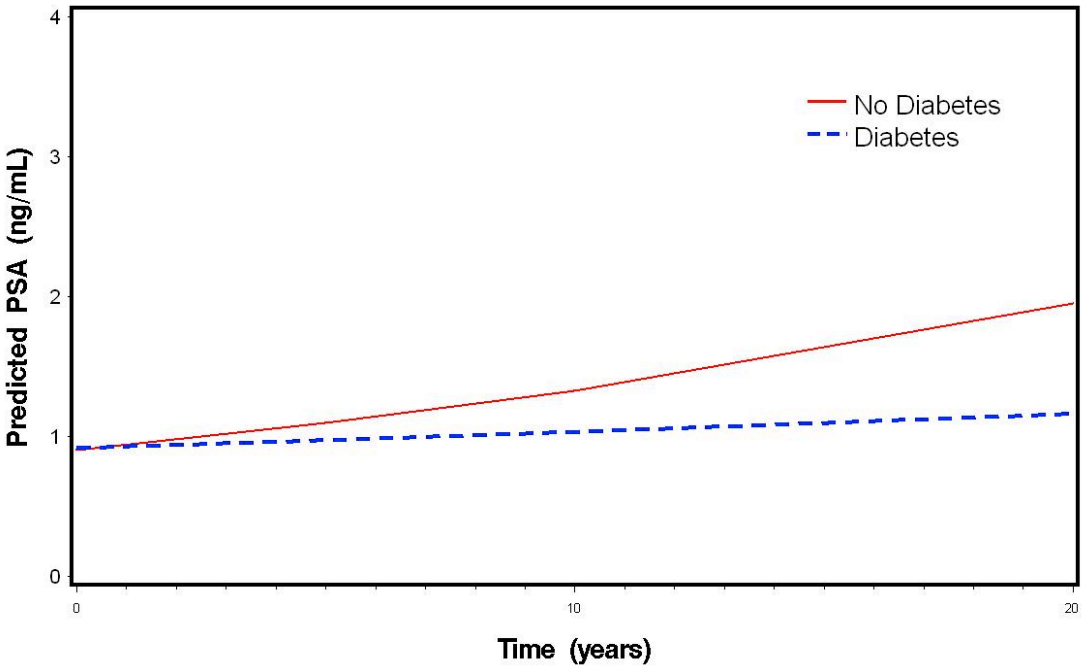


Figure 3-3: Age-adjusted median predicted PSA over time by baseline diabetes status



Chapter 4

The Effects of Body Mass Index on Longitudinal Changes in Serum Prostate Specific Antigen Levels and Prostate Volume over 15-years of Follow-up: Implications for Prostate Cancer Detection

Abstract

Objective: Body mass index (BMI) is inversely associated with prostate-specific antigen (PSA) level in cross-sectional analyses and positively, though inconsistently, associated with the diagnosis of prostate cancer. It is not clear, however, whether these findings are due to the effect of obesity on the development or progression of prostate cancer or to the greater probability of disease detection among obese men with prostate cancer (detection bias). There is little evidence about whether BMI affects change in PSA level and what other factors might explain the associations of obesity with PSA level and prostate cancer. The goal of this study was to use longitudinal data to investigate the association of BMI and BMI change with change in PSA level and to assess the possible roles of PSA hemodilution and prostate volume in explaining the associations of obesity with PSA level and prostate-cancer diagnosis.

Methods: In 1990, a randomly selected cohort of Caucasian men, ages 40-79, from Olmsted County, MN completed questionnaires ascertaining demographic characteristics, current medical conditions and medications biennially, with a subset undergoing blood draws and clinical exams during a 15-year follow-up period. Our analyses were

restricted to 545 men with at least two PSA, BMI and prostate-volume measurements. Linear mixed models were used to predict the slopes and intercepts of individual changes in BMI, PSA, prostate volume, plasma volume, and PSA mass (the product of PSA concentration and plasma volume), adjusting for age. Linear regression was then used to estimate the annual percent change in PSA associated with the predicted intercept and slope of BMI, adjusting for baseline PSA, baseline prostate volume, and rate of change in prostate volume. The mean predicted intercepts and slopes of PSA mass and plasma volume were compared across baseline BMI categories.

Results: Baseline BMI was inversely associated with the annual percent change in PSA, adjusting for age, baseline PSA, and prostate volume and the rates of change in BMI and prostate volume (β=-0.003, 95% CI: -0.006, -0.0003). A baseline BMI $\geq$ 30kg/m^2 (vs. < 30kg/m^2) was associated with a 0.09% annual increase in prostate volume after adjustment for age (β=0.09, 95% CI: 0.03, 0.015). Baseline obesity was positively associated with mean baseline levels and the rate of change in plasma volume (both p <0.001). Both the mean baseline values and the rate of change in PSA mass were similar when compared across categories of baseline BMI.

Conclusions: Baseline obesity was associated with the rate of change in both PSA and prostate volume in a cohort of white men followed for 15 years. Our results suggest that the inverse association of obesity with prostate–cancer diagnosis is at least partly due to detection bias, which is due to larger prostate volumes and PSA hemodilution in obese men. Future research should focus on further elucidating what role BMI plays in the detection of prostate cancer in other racially heterogeneous populations.

Introduction

Prostate cancer is the most common non-cutaneous cancer in U.S. men, with an estimated 192,280 new cases diagnosed in 2009 (2). Prostate specific antigen (PSA) currently is the most common screening test for prostate cancer with 58% of Caucasian men receiving an annual test (12). The low specificity of PSA testing and questionable benefits of PSA screening on prostate cancer mortality highlight the need for better detection strategies for prostate cancer (15). Knowledge of the influence of concomitant comorbidities on serum PSA concentrations may improve the discriminant value of this test for predicting prostate cancer and reduce the number of unnecessary biopsies and subsequent overdiagnoses of indolent cancers.

Obesity is a growing global epidemic, with more than half of the world's adults categorized as being overweight and up to 30% categorized as obese (body mass index [BMI] $\geq$ 30) (19). In the US alone, 68% of adults are overweight or obese (3). Previous studies have implicated obesity in the development of prostate cancer, but the findings from these studies are inconsistent; large population-based studies found an increased risk of prostate cancer associated with obesity, (30-33) while other studies found either a null or inverse association between obesity and prostate cancer incidence.(34-36). Explanations for these inconsistencies include variations in the measurements of obesity between studies and at different times in the life course, differences in study design, insufficient assessment and control of confounders and effect modifiers, and different distributions of obesity in the study populations.

Obesity is hypothesized to influence the detection of prostate cancer through its impact on prostate-cancer screening (7, 11). This hypothesis stems from the findings that

digital rectal examinations are more difficult to perform in obese men, which may lead to an increased number of missed diagnoses (11). Additionally, elevated serum PSA levels are considered a marker for prostate cancer presence; however, needle-biopsy is necessary for confirmation. Obese men have lower PSA levels than do non-obese men (8, 10, 11), which may be due to decreased testosterone concentrations (7) and/or plasma hemodilution, the phenomenon that results from the dilution of soluble tumor markers being diluted by increased plasma volumes .(10). As a result, it is possible that obese men are less likely to be recommended for biopsy, thereby lowering the number of cancers detected in this group. Finally, obese men tend to present with larger prostates than do non-obese men (7, 11). Increased prostate volumes make prostate needle-biopsy more difficult and, as a result, may be lowering the number of prostate cancers detected. Thus, the combined effects of obesity on performance of digital rectal exams (DRE), PSA level, and prostate volume may lead to appreciable detection bias when estimating the effect of obesity on prostate cancer.

Results from previous studies suggesting that obesity may be associated with serum PSA concentrations are limited by their cross-sectional designs, their failure to simultaneously account for other aspects of this potential detection bias, including prostate volume, and their inability to elucidate why this association exists. Furthermore, the estimated effects of baseline obesity and weight change on change in serum PSA level and prostate volume has yet to be characterized. Understanding these longitudinal associations is relevant because change in serum PSA level may be better than a single serum PSA measurement for prostate cancer screening (13) and therefore has important implications in terms of prostate cancer detection. The increasing prevalence of obesity

coupled with the increasing speculation regarding the reliable detection of prostate cancer with serum PSA levels make it crucial to elucidate how obesity influences the multiple facets of prostate cancer detection over time. Therefore, the goal of this study was to use longitudinal data to investigate the association of BMI and BMI change with change in PSA level and to assess the possible roles of PSA hemodilution and prostate volume in explaining the associations of obesity with PSA level and prostate-cancer diagnosis.

Materials and Methods

Study population

The Olmsted County Study (OCS) of Urinary Symptoms and Health Status among Men (OCS) is a longitudinal study of Caucasian men residing in Olmsted County, MN (58, 59). In 1990, a random sample of men 40-79 years old, as enumerated by the Rochester Epidemiology Project, was screened for inclusion (60). Men with a history of prostate or bladder surgery, urethral surgery or stricture, or medical or neurological conditions that affect normal urinary function were excluded. Eligible men (n=3,874) were invited to take part in the study, and 2,115 (55%) agreed to participate. Participants completed a previously validated baseline questionnaire that ascertained information on urinary symptoms, medical histories, and various demographic and behavioral characteristics. A 25% random subset of the total cohort was invited to participate in a detailed urologic clinical examination, which included prostate volume and serum PSA measurements. Of the 537 randomly selected men, 475 (88%) agreed to participate in the clinical portion of the study.

Since 1990, the cohort has been actively followed biennially using a questionnaire similar to the one used at baseline. During the second and third rounds of visits, men who did not participate in the follow-up were replaced by randomly selected eligible men from the community (n=332 total cohort; n=159 clinic cohort) (Figure 4-1). After the third round, the study has been maintained as a fixed cohort. Of the 2,447 men in the OCS, 634 men participated in the clinic cohort after 8 rounds of follow-up, of which 552 men with at least two PSA, body mass index and prostate volume measurements were included. Measurements of PSA level and prostate volume were censored after diagnosis

of prostate cancer, prostate surgeries and procedures, and use of any medications (prescription and herbal) for treatment of benign prostatic hyperplasia (BPH). As a result, 545 men were included in this analysis, of which 544 men (2,805 observations) had information on PSA, 545 men (2,837 observations) had BMI information, and 543 men (2,687 observations) had information on prostate volume.

Measurements

BMI, prostate volume, and PSA were collected at each round of follow-up during the clinic examination. A trained research assistant measured height and weight, and BMI was calculated by dividing the weight in kilograms by the height in meters squared. Men with a BMI greater than or equal to 30 kg/m^2 were considered obese, based on the definition established by the World Health Organization (WHO) (55). Prostate volume, was measured via transrectal sonographic imaging, and serum PSA levels were determined with the Tandem-R PSA assay (Hybritech Inc, San Diego, CA, USA). Body surface area, plasma volume and PSA mass was estimated using the following established formulas: Body Surface Area (m^2)= body weight $(kg)^{0.425}$ x height $(m)^{0.725}$ x 0.2025 (82), Plasma Volume (L) = Body Surface Area ($m^{2)}$ x 1.670 (83) and PSA mass = PSA (ng/mL) x Plasma Volume (10). Demographic information including household income, years of education and age at baseline blood draw were collected via questionnaire.

Statistical Analysis

The cross-sectional associations between baseline obesity and participant demographics at baseline were tested using chi-square tests for association and Cochran-Armitage tests for trend where appropriate. The distributions of baseline values and

predicted rates of change of PSA, BMI and prostate volume were determined overall and across 10-year age groups using medians and interquartile ranges. The associations of both the baseline values and predicted rates of change with age were tested using the test for trend from linear regression. Crude cross-sectional associations between BMI and PSA, BMI and prostate volume and prostate volume and PSA at each round of follow-up were also estimated using linear regression.

Linear mixed-effects models were used to examine the association of baseline obesity with annual percent change in PSA and annual percent change in prostate volume. These models included age and a categorical measure for obesity (BMI<30, BMI ≥30) as well as an interaction (product) term between obesity and time to compare the slope of PSA among those who were obese and not obese. The mixed model used to estimate these parameters is shown in Appendix 3 (Equation 1). Additional models were fit to assess the association of baseline BMI (treated as continuous), baseline BMI based on the WHO cut-offs, and repeated measures of BMI with the annual percent changes in PSA and prostate volume.

A longitudinal 2-step analytic approach was used to examine the associations of the individual intercepts and slopes of BMI and prostate volume with the annual percent change in PSA. First, the annual percent change in PSA, BMI and prostate volume were estimated by individually regressing each measure on time from initial blood draw and age (10-year categories) using linear mixed-effects regression models. Interaction (product) terms were included to allow for different slopes across these age groups. Fixed and random effects were included to reflect both the mean effect and allow for individual variation in the baseline intercept and change over time. An overall annual change in

each measure for each man was estimated by combining the average longitudinal change in time (fixed effects) with the individual changes (random effects). Similarly, both fixed and random effects allowed determination of an overall baseline intercept for each age decade and allowed for offsets for individual variation. The models used to conduct these analyses are included in Appendix 3 (Equations 2-4). Because of their skewed distributions, PSA level and prostate volume were log-transformed, and therefore, annual changes represent percent changes per year. The change in BMI reflects annual absolute changes.

The second step of this approach was to estimate the effects of predicted intercepts of PSA, BMI and prostate volume and the predicted slopes of BMI and prostate volume on the predicted annual percent change in PSA (all derived from the mixed model in stage 1), using linear regression models adjusting for age. (Appendix 3, Equation 5)

The adjusted predicted values of the intercepts and slopes of plasma volume and PSA mass were also estimated using linear mixed-effects regression models that individually regressed each measure on time from initial blood draw and age (10-year categories) and included a categorical measure for obesity (BMI<30, BMI ≥30), as well as an interaction term to compare the intercept and slope among those who were obese and not obese where appropriate. (Appendix 3, Equations 6-8) Because of the skewed distribution, PSA mass was log-transformed, and therefore, annual changes represent percent changes per year. The change in plasma volume reflects annual absolute changes. The means and standard deviations of the predicted slopes and intercepts of PSA mass and plasma volume from the mixed models were then compared across levels of age and

baseline obesity. All statistical analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC).

Results

In this cohort of Caucasian men, age was associated with obesity at baseline (p for trend 0.03) (Table 4-1). Marital status, education and income differed little by baseline obesity status. Obese men more often reported a history of type 2 diabetes and a history of hypertension than did non-obese men at baseline (p= 0.006, 0.008). Baseline serum PSA levels differed slightly by baseline obesity status, such that men who were obese had a lower mean PSA level (1.13 ng/mL) compared to men who were not obese at baseline (1.37 ng/mL) (p=0.06). Prostate volume was similar when comparing obese to non-obese men at baseline. (Table 4-1)

Table 4-2 displays the overall and age-specific distributions of the observed baseline values and predicted rates of change for BMI, PSA and prostate volume (derived from the mixed models). At baseline, the median BMI in the total sample was 27.03 kg/m^2 and was associated with age (p for trend = 0.07). Overall, the median serum PSA level at baseline was 0.90 ng/mL, and the median prostate volume was 25.57 grams. Both PSA and prostate volume were strongly and positively associated with age (p for trend <0.0001). The median rate of change in BMI was 0.14 kg/m^2 per year and was non-linearly associated with age (p for trend 0.001). The greatest median rate of change in BMI was seen among the youngest (40-49 years) and oldest (70+ years) men in this cohort. The median rate of change of PSA was 3.82% per year, and this change increased with age (p for trend <0.0001). The median annual percent change in prostate volume overall was 2.19%, and it was minimally associated with age. (Table 4-2)

Cross-sectional analyses determined BMI to be weakly and inversely associated with PSA at each round of follow-up except at round 2. (Table 4-3) BMI was positively

but weakly associated with prostate volume cross-sectionally at each round of follow-up. Prostate volume was strongly and positively associated with PSA at each round of follow-up. (Table 4-3)

Baseline obesity (BMI $\geq$ 30 kg/m^2) was weakly inversely associated with the annual percent change in PSA (β= -0.07, 95% CI: -0.20-0.05), adjusting for age. Similar associations were observed with continuous baseline BMI and BMI categorized according to the WHO cut-offs. (Table 4-4) Baseline obesity was positively associated with the annual percent change in prostate volume (β= 0.09, 95% CI: 0.03-0.15), and this association was similar when assessed using baseline BMI and categorical BMI based on WHO cut-offs. (Table 4-4)

Table 4-5 displays the predicted annual percent change in PSA associated with the intercepts of PSA, prostate volume and BMI and the slopes of prostate volume and BMI. Baseline BMI was inversely associated with the rate of change in PSA, with a 5 unit increase in baseline BMI corresponding to a 0.003% decrease in the annual percent change in PSA (β=-0.003, 95% CI: -0.006, -0.0003), adjusting for age, baseline PSA, baseline prostate volume, annual percent change in prostate volume and the rate of change in BMI (see Model 1 in Table 4-5). Age, baseline PSA level and change in prostate volume were also positively associated with the rate of change in PSA when mutually adjusted for the other covariates. The estimated effects of the two BMI predictors and the two prostate-volume predictors did not change appreciably when the other two predictors were excluded from the model (see Models 2 and 3 in Table 4-5).

Table 4-6 summarizes the means and standard deviations of the predicted intercepts of and rates of change in plasma volume and PSA mass, by 10-year age

category and baseline obesity status. The predicted baseline values of both plasma volume and PSA mass were strongly associated with age (both $p<0.001$); plasma volume decreased and PSA mass increased with increasing age. Men who were obese at baseline had a higher age-adjusted mean plasma volume level at baseline (3.69 L) when compared to men who were not obese (3.33 L) ($p<0.001$). The age-adjusted mean PSA mass at baseline was similar for obese and non-obese men at baseline ($p = 0.79$) (Table 4-6). The rate of change in plasma volume over time decreased with increasing age ($p< 0.001$). The annual percent change in PSA mass was associated with age, although not linearly as the annual percent change in PSA mass increased and then decreased with increasing age ($p=0.05$). Baseline obesity was inversely associated with the rate of change in plasma volume after adjustment for age. The mean annual percent change in PSA mass differed little by baseline obesity status ($p=0.23$). (Table 4-6)

Discussion

In this longitudinal study of Caucasian men ages 40-79, baseline obesity, defined as BMI $\geq$ 30 kg/m^2, was inversely associated with baseline PSA level, and inversely associated with the annual percent change in PSA over time after adjustment for age, baseline PSA, and the rates of change in BMI and prostate volume. Baseline obesity was positively associated with the annual percent change in prostate volume after adjustment for age. Baseline obesity was also associated with increased plasma volume at baseline, and the rate of change in plasma volume over time after age adjustment. Baseline obesity did not influence either the baseline value or annual percent change in PSA mass over time after adjustment for age.

The hypothesis that a detection bias for prostate cancer exists among obese men is based on the following findings: 1) Obese men have decreased cross-sectional PSA levels, due to either lower testosterone levels (7) or the hemodilution of PSA among obese men (10); and 2) BMI is associated with larger prostate volumes, impacting detection via digital rectal exams and biopsies (45, 46, 84). This study expands on these previous findings by further elucidating these detection issues. This was accomplished by assessing 1) whether BMI was associated with PSA cross-sectionally and longitudinally, 2) whether this association was due in part to hemodilution, and 3) whether BMI influences prostate volume over time.

Our finding that baseline BMI was inversely associated with PSA levels in cross-sectional analysis is similar to previous studies that found lower PSA levels among obese men when compared to non-obese men or decreasing PSA with increasing BMI (8, 9, 43). Furthermore, our results suggest that baseline obesity has more influence on PSA

change than does the rate of change in BMI. This finding may be due to the mean rate of change in this cohort being very small, rather than the absence of an association of the rate of change in BMI with PSA over time. Baseline BMI was also inversely associated with the rate of change in PSA adjusting for age, baseline prostate volume, baseline PSA, and the rates of change in BMI and prostate volume. These results suggest that in addition to its influence on concurrent PSA level, BMI also influences the annual percent change in PSA over the 15 years of follow-up. This finding is important, as the rate of change in PSA or PSA velocity is currently the preferred measure used to diagnose prostate cancer (13, 72). It is therefore possible that the resulting detection issues related to the influence of BMI on PSA may also limit using PSA velocity to screen obese men for prostate cancer. With increasing BMI, a decreasing rate of change in PSA may influence detection by possibly delaying diagnoses in men with higher BMI or potentially missing them all together because obese men may not experience enough of a change in PSA to be recommended for biopsy.

Our findings also suggest that the association between BMI and PSA is at least in part due to the hemodilution of PSA, as baseline obesity was associated with increased plasma volume but not with PSA mass (the product of PSA concentration and plasma volume) at baseline. Similar associations were seen longitudinally as well, as baseline obesity was associated with the rate of change in plasma volume but not with the annual percent change in PSA mass over time. Our cross-sectional results are similar to previous studies that found plasma volume to increase with increasing BMI but no relation between BMI and PSA mass.(10, 85) Our study takes these findings one step further by suggesting that the hemodilution of PSA is in part, responsible for the association of

baseline BMI and changes in PSA over time. This has important implications for prostate cancer screening and detection as current prostate cancer screening practices that use cross-sectional or longitudinal measures of PSA without taking into account this metabolic condition may result in missed or delayed diagnoses due to obese men being less likely to be referred for biopsy.

Our results further support the notion that these detection issues among obese men are also in part due to the influence of BMI on prostate volume. In this cohort, baseline BMI was positively associated with the annual percent change in prostate volume. Our results are similar to several previous studies that found obese men to have larger prostates (11, 45). Most prostate cancers detected upon biopsy are very small, resulting in more difficult detection upon biopsy in men with larger prostates. It is therefore likely that fewer cancers are then detected in obese men due to their larger prostate size or that diagnoses are delayed resulting in later stage disease at diagnosis. Previous studies have shown obese men are more likely to be diagnosed with later-stage disease and less likely to be diagnosed with early-stage disease (37, 38, 40), suggesting that the consequences of prostate volume's role in this detection issue among obese men has important implications in terms of prostate-cancer aggressiveness.

Overall, the findings from our study, taken together with findings from previous studies, suggest the detection bias among obese men is in part due to the influence of BMI on both prostate volume and the hemodilution of PSA. (11, 86) This bias, coupled with the findings that obese men present with later-stage disease (38) and have worse outcomes after treatment, including greater risk of recurrence (87, 88), suggest it may be reasonable to take into consideration whether a man is overweight or obese when he

screens with PSA or is biopsied for prostate cancer. In order to minimize this detection bias, it may be prudent to lower PSA cut-offs for overweight or obese men and/or take more cores in these men at biopsy.

The strengths of this study include the use of longitudinal data with 15 years of follow-up that contained rigorously collected repeated measures of BMI, prostate volume, and serum PSA levels. Censoring outcome values collected after prostate cancer diagnosis, BPH treatment or prostate surgery yields a disease-free, asymptomatic population. However, this study also has potential limitations that need to be considered. This cohort is comprised of solely Caucasian men, limiting our inferences to other racial and ethnic groups. Longitudinal measures of testosterone were not available in this cohort; therefore, we could not assess whether testosterone levels also influence the detection of prostate cancer in obese men. The longitudinal nature of these data may lend itself to problems with attrition; however, previous work in this cohort found that participant dropout was not associated with chronic diseases or serum PSA levels adjusted for age (66), thus suggesting that bias resulting from attrition may be small. Finally, there may have been unmeasured time-dependent confounders that we were unable to account for in our analyses.

In conclusion, baseline obesity was associated with the rate of changes in both PSA and prostate volume. Our results suggest that the inverse association of obesity with prostate–cancer diagnosis is at least partly due to detection bias, which is due to larger prostate volumes and PSA hemodilution in obese men. Future research should focus on further elucidating what role BMI plays in the detection of prostate cancer in other racially heterogeneous populations.

Figure 4-1: The Olmsted County Study participation over time

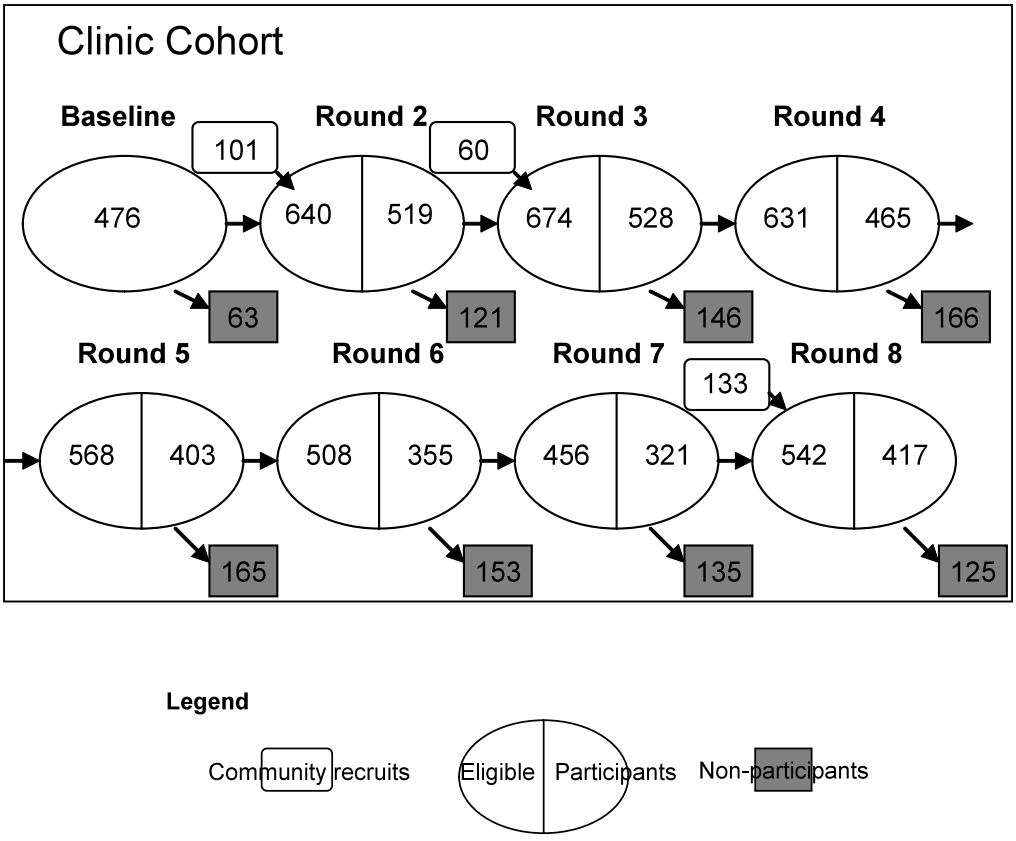


Table 4-1: Participant characteristics by baseline obesity status in 545 men

Characteristic	Not Obese (BMI < 30 kg/m^2) N=404	Obese (BMI ≥30 kg/m^2) N=141	p-value[2]
Age[1], years			
40-49	163(40.4)	69(48.9)	0.03[2]
50-59	104(25.7)	39(27.7)	
60-69	82(20.3)	19(13.5)	
70+	55(13.6)	14(9.9)	
Marital Status			
Single, divorced, widowed, separated	41(10.1)	11(7.80)	0.41
Married/living together	361(89.4)	130(92.2)	
Education			
Less than high school graduate	39(9.65)	19(13.5)	0.18
Finished high school/some college	184(45.5)	71(50.3)	
College degree and beyond	178(44.1)	51(36.2)	
Salary			
<$25,000	66(16.3)	27(19.1)	0.52
$25,000-$44,999	109(27.0)	33(23.4)	
$45,000-$64,999	109(27.0)	36(25.5)	
$65,000+	97(24.0)	42(29.8)	
Diabetes at baseline			
No	392(97.0)	129(91.5)	0.006
Yes	12(3.0)	12(8.5)	
Hypertension at baseline			
No	310(76.7)	92(65.3)	0.008
Yes	94(23.3)	49(34.8)	
PSA at baseline (ng/mL)			
Mean (SD)	1.37(1.37)	1.13(1.13)	0.06
Prostate volume at baseline (mL)			
Mean (SD)	27.8(11.8)	29.6(12.9)	0.14

[1]Age at baseline
[2] p-value from chi-square test for association
[3] p-value from 2-sided Cochran-Armitage test for trend

Table 4-2: Overall and age-stratified distributions of observed baseline and predicted rate of change for BMI, PSA and prostate volume

	Overall	**40-49 years**	**50-59 years**	**60-69 years**	**70+ years**	**p value***
Observed baseline value	Median (Q1, Q3)	Median (Q1, Q3)	Median (Q1, Q3)	Median (Q1, Q3)	Median (Q1, Q3)	
BMI (kg/m^2)	27.03 (24.97, 30.05)	27.10 (24.90, 30.35)	27.72 (25.09, 30.09)	26.56 (24.75, 28.99)	26.52 (24.99, 28.90)	0.07
PSA (ng/mL)	0.90 (0.60, 1.50)	0.70 (0.50, 1.05)	0.90 (0.60, 1.40)	1.40 (0.80, 2.60)	2.00 (1.00, 3.10)	<0.0001
Prostate volume (mL)	25.57 (20.30, 32.63)	21.27 (18.69, 26.01)	27.50 (22.32, 33.06)	31.46 (24.81, 38.20)	32.92 (25.66, 44.90)	<0.0001
Predicted rate of change						
BMI (change/year)	0.14 (0.07, 0.19)	0.16 (0.10, 0.22)	0.14 (0.08, 0.19)	0.06 (0.02, 0.09)	0.17 (0.13, 0.19)	0.001
PSA (% change/year)	3.82 (1.58, 5.64)	2.43 (0.62, 4.32)	4.39 (2.24, 6.05)	4.81 (3.16, 6.45)	5.07 (3.30, 6.08)	<0.0001
Prostate volume (% change/year)	2.19 (1.67, 2.83)	2.26 (1.72, 2.83)	2.14 (1.62, 2.74)	2.15 (1.75, 2.85)	2.17 (1.56, 2.99)	0.93

* Test for trend across age groups

Table 4-3: Cross-sectional associations between (a) BMI and PSA (b) BMI and prostate volume and (c) prostate volume and PSA from unadjusted linear regression models

	(a) Log PSA	(b) Log Prostate Volume	(c) Log PSA
	Beta (SE), p-value	**Beta (SE), p-value**	**Beta (SE), p-value**
Round 1	-0.02(0.01), 0.07	1.01(0.55), 0.07	1.15(0.09), <0.0001
Round 2	0.002(0.01), 0.84	0.69(0.52), 0.19	1.23(0.08), <0.0001
Round 3	-0.01(0.01), 0.15	0.58(0.55), 0.29	1.21(0.08), <0.0001
Round 4	-0.01(0.01), 0.37	1.07(0.59), 0.07	1.12(0.08), <0.0001
Round 5	-0.02(0.01), 0.10	0.73(0.68), 0.28	1.25(0.10), <0.0001
Round 6	-0.01(0.01), 0.20	0.66(0.76), 0.39	1.19(0.11), <0.0001
Round 7	-0.01(0.01), 0.39	1.20(0.68), 0.08	1.26(0.11), <0.0001
Round 8	-0.005(0.01), 0.72	1.04(0.74), 0.16	1.39(0.12), <0.0001

Table 4-4: Beta coefficients and 95% confidence intervals describing the association of baseline obesity with annual percent change in PSA and annual percent change in prostate volume

	PSA[1]		Prostate Volume[2]	
Baseline obesity measure	**Beta**	**95% CI**	**Beta**	**95% CI**
BMI (continuous)	-0.01	-0.02, 0.004	0.01	0.004, 0.015
Obesity				
BMI < 30 kg/m^2	0	--	0	--
BMI ≥ 30 kg/m2	-0.07	-0.20, 0.05	0.09	0.03, 0.15
BMI (WHO cut-offs)				
<25	0	--	0	--
25-29	0.06	-0.08, 0.20	0.07	0.01, 0.13
30-34	-0.01	-0.17, 0.15	0.14	0.06, 0.22
35+	-0.15	-0.42, 0.12	0.12	0.002, 0.24

*All models are adjusted for age and age*time and PSA and volume are log transformed

[1] Age in this model defined as age at baseline PSA blood draw and time defined as time since baseline blood draw

[2] Age in this model defined as age at baseline volume measurement and time defined as time since baseline volume measurement

Table 4-5: Beta coefficients and 95% confidence intervals describing the associations of the intercepts and slopes of PSA, BMI and prostate volume with the annual percent changes in PSA **

	Model 1		*Model 2*		*Model 3*	
	PSA (% change/year)		**PSA (% change/year)**		**PSA (% change/year)**	
Predictor variables	Beta	95% CI	Beta	95% CI	Beta	95% CI
Baseline age (per 10 years)	0.003	0.0002, 0.006	0.002	-0.0008, 0.004	0.003	0.0005, 0.006
PSA intercept (ng/mL)	0.017	0.012, 0.021	0.022	0.018, 0.025	0.017	0.013, 0.022
BMI intercept (per 5 kg/m^2)	-0.003	-0.006, -0.0003	-0.002	-0.005, 0.0007	--	
Change in BMI (per 5 kg/m^2/yr)	-0.04	-0.14, 0.062	-0.023	-0.12, 0.08	--	
Prostate volume intercept (mL)	-0.0004	-0.012, 0.011	--		-0.002	-0.013, 0.0092
Change in prostate volume (% change/yr)	0.67	0.40, 0.94	--		0.65	0.37, 0.92
R^2, F test p value	0.32	<0.0001	0.28	<0.0001	0.31	<0.0001
Multiple correlation (R)	0.56		0.53		0.56	

** Slopes and intercepts were obtained from models of BMI and natural log-transformed PSA and prostate volume.

Table 4-6: Mean and standard deviations of the adjusted predicted intercepts and slopes of plasma volume and PSA mass by age category and baseline obesity status (N=545)

Baseline Characteristic		Plasma volume intercept	Annual change in plasma volume	PSA mass Intercept	Annual percent change in PSA mass
Overall*		3.42 (0.27)	0.004 (0.007)	1.21 (0.67)	3.56 (2.95)
	p-value	<0.001	0.002	<0.001	<0.001
Age (years)					
	40-49	3.48 (0.29)	0.008 (0.006)	0.95 (0.49)	2.79 (2.89)
	50-59	3.45 (0.25)	0.005 (0.005)	1.14 (0.59)	4.23 (3.06)
	60-69	3.35 (0.24)	-0.002 (0.005)	1.59 (0.69)	4.38 (2.87)
	70+	3.28 (0.24)	-0.002 (0.006)	1.71 (0.83)	3.70 (2.36)
	p-value	<0.001	<0.001	<0.001	0.05
Baseline Obesity*					
	BMI <30 kg/m^2	3.33 (0.22)	-0.005 (0.007)	1.22 (0.69)	3.77 (2.83)
	BMI ≥30 kg/m^2	3.69 (0.23)	-0.001 (0.008)	1.17 (0.62)	2.95 (3.23)
	p-value	<0.001	<0.001	0.79	0.23

*Adjusted for age

Chapter 5

The Effects of Metabolic Conditions on the Likelihood and Outcomes of Prostate Biopsy

Purpose

The previous chapters of this dissertation evaluated whether metabolic conditions, specifically diabetes, hypertension and obesity were associated with prostate cancer risk and detection through their influence on PSA. The results from the previous chapters suggest that both the incidence and detection of prostate cancer through PSA testing were influenced by metabolic conditions. However, in order to better understand what role these conditions play in influencing the detection of prostate cancer, their impact on whether prostate biopsies are performed and their association with the outcomes of the biopsies need to be considered. Therefore, the goal of this additional analysis was to determine whether baseline diabetes, hypertension or obesity, alone and in combination with each other influence the likelihood of having a prostate biopsy among the 2,445 men in OCS, as well as the result of the prostate biopsy among the 519 men who received biopsies during follow-up.

Materials and Methods

The parent cohort of the Olmsted County Study (N=2,445) was used to evaluate how the metabolic conditions influence the likelihood of having a prostate biopsy during follow-up. Men who underwent biopsies during follow-up were identified through detailed review of medical records, yielding a total of 519 biopsies. Men who reported using antihypertensive medication prior to baseline or who reported a physician diagnosis of hypertension at baseline were considered hypertensive for this analysis. Men who reported diabetes at baseline were considered diabetic. A trained research assistant measured height and weight, and BMI was calculated by dividing the weight in kilograms by the height in meters squared. Men with a BMI greater than or equal to 30 kg/m^2 were considered obese, based on the definition established by the World Health Organization (WHO) (1). PSA level as measured in the serum in ng/mL and abnormal PSA levels at baseline were defined as PSA greater than 4 ng/mL.

Participants' person-time contribution began on the date they completed their baseline questionnaires and ended at the date of first biopsy or the last date of passive surveillance chart review, whichever came first. Age-adjusted hazard (incidence rate) ratios and 95% confidence intervals measuring the associations of the demographic and metabolic characteristics with prostate cancer biopsy were estimated using Cox proportional hazards regression (SAS procedure proc phreg). The estimated effects of the metabolic conditions alone, as well as their interactions on prostate cancer biopsy risk were assessed using a single, multivariable Cox model also adjusting for age. To determine if baseline PSA level modified the associations between the metabolic conditions combinations and likelihood of biopsy, interaction (product) terms with PSA were included in the overall adjusted model.

Among the 519 men who received biopsies during follow-up, the outcome of the biopsy was classified as either positive or negative for the presence of prostate cancer, resulting in 146 positive biopsies. Age-adjusted odds ratios and 95% confidence intervals measuring the

associations of the demographic and metabolic characteristics with biopsy outcome were estimated using multivariable logistic regression. The effects of the various combinations of the metabolic conditions, as well as their interactions, on biopsy outcome was assessed using a single, multivariable logistic model adjusting for age.

Results

Among the 2,445 men in this cohort, prostate biopsy was positively associated with age (HR for 1 year: 1.05; 95% CI: 1.04, 1.06) (results not shown). The incidence rate of biopsy was greater in men with a family history of prostate cancer than in men without a family history of prostate cancer (Table 5-1: HR: 1.46; 95% CI: 1.1, 1.88). Also, men who used statins prior to baseline were approximately 25% less likely to have a prostate biopsy during follow-up when compared to men who did not use statins prior to baseline (HR: 0.77; 95% CI: 0.64, 0.94) (Table 5-1).

Table 5-1 also displays the age-adjusted hazard ratios for each metabolic variable, unadjusted for the others. Men with a history of diabetes had a slight reduced likelihood of prostate biopsy compared to men without diabetes at baseline after adjusting for age. (Table 5-1: age-adjusted HR: 0.88; 95% CI: 0.58, 1.3). Hypertensive men slightly more likely to have a prostate biopsy than were non-hypertensive men, (age-adjusted HR: 1.08; 95% CI: 0.89, 1.31), nor were obese men when compared to non-obese men at baseline after adjusting for age (age-adjusted HR: 0.92; 95% CI: 0.74, 1.15). Adjustment for age, family history of prostate cancer and baseline statin use did not change these results (results not shown).

Despite small numbers of biopsies, the combined categories of the three conditions were also examined. Figure 5-1 displays the age-adjusted hazard ratios of prostate biopsy for all eight combinations of the three components of the metabolic syndrome. Compared to men with no components of the syndrome, men with all three---the metabolic syndrome—had a reduced rate of prostate biopsy, adjusting for age (HR: 0.60; 95% CI: 0.22, 1.60); however, this estimate is imprecise because there were only 4 biopsies in the group with all three conditions. The presence of diabetes alone was nearly unassociated with prostate cancer (HR: 1.01; 95% CI: 0.50, 2.1), but men who were hypertensive, or diabetic and not obese were less likely to have a prostate biopsy compared to men who did not have any of the three conditions (Figure 5-1) Obesity and

hypertension alone were associated with a slight increased risk of prostate biopsy; however, the combination of the two was associated with a decreased risk of prostate biopsy compared to men with none of the conditions (age-adjusted HR: 0.88; 95% CI: 0.60, 1.29) (Figure 5-1).

As baseline PSA was positively associated with an increased rate of prostate biopsy, adjusting for age, (HR: 1.09; 95% CI: 1.05, 1.13) (results not shown), the interaction between the metabolic components and baseline PSA level was examined. The notable departures from multiplicative effects in the proportional hazards model that contained age, the metabolic components alone, their interactions as well as their interactions with PSA, were the interactions between diabetes and PSA ($p = 0.04$), hypertension and PSA ($p = <0.01$), hypertension, obesity and PSA ($p = 0.01$), and the four-way interaction between the components and PSA (<0.01). (data not shown).

Table 5-2 displays likelihood of biopsy associated with the baseline metabolic conditions independent of the other metabolic conditions. Among the 519 men who were biopsied in this cohort, men with diabetes were approximately 25 percent less likely to have a positive prostate biopsy compared to men without diabetes after adjustment for age (OR: 0.74; 95% CI: 0.28,1 .93). Men with hypertension were also less likely to have a positive biopsy, but men who were obese at baseline were slightly more likely to have a positive biopsy during follow-up when compared to men without these conditions. The number of metabolic components present was associated with the odds of a positive biopsy, as the presence of one component was associated with a slightly increased odds of positive biopsy and the presence of 2 or more components was associated with a 33 percent reduced odds of positive biopsy after adjustment for age.

Table 5-3 displays the age-adjusted odds ratios of prostate biopsy for the combinations of the three components of the metabolic syndrome, mutually adjusted for each other and age. Men with diabetes alone were less likely to have a positive biopsy whereas men with diabetes and hypertension were more likely to have a positive biopsy result. Men with hypertension alone or obesity alone were more likely to have a positive biopsy, but men with both of these conditions

were less likely to have a positive biopsy. Men with all three components were less likely to have a positive biopsy when compared to men without any of these conditions (age-adjusted OR: 0.72; 95% CI: 0.07, 7.09).

Discussion

In this cohort, the presence of metabolic conditions, specifically diabetes, hypertension and obesity were associated with both the rate of receiving a prostate biopsy and the probability that the prostate biopsy was positive. While the presence of any of the three components alone was associated with an increased risk of prostate biopsy, when in combination with each other such that multiple comorbidities were present, there was a reduced likelihood of prostate biopsy after adjustment for age. While men who were hypertensive and obese were less likely to have a positive biopsy, men who were hypertensive and diabetic were more likely to have a positive biopsy after adjustment for age. Furthermore, the presence of multiple metabolic components was also associated with a reduced likelihood of a positive biopsy after adjusting for age.

Overall, the findings that the presence of multiple conditions together results in a decreased risk of prostate biopsy may be indicative of a detection bias as described in previous chapters of this dissertation. Furthers supporting this hypothesis are the findings that the presence of 2 or 3 components is associated with a decreased likelihood of biopsy, while the presence of one component is associated with an increased risk. It may be that because men with multiple conditions have lower PSA levels, they are as a result less likely to be recommended for biopsy, resulting in a lower rate of biopsies among these groups when compared to men with none of these conditions. However, men with one of the metabolic conditions alone are more likely to have a biopsy, which may be a reflection that men with these conditions are more closely followed by a physician, and as such, are more likely to have a prostate biopsy when necessary, inflating the number of men receiving biopsies in these groups.

Among those who received biopsies during follow-up, men with diabetes alone, hypertension and obesity or all three of the metabolic conditions were also less likely to have a positive biopsy, suggesting that the detection of prostate cancer from biopsy tissue may be more difficult in the presence of these conditions. These results should be interpreted with caution as

only 519 men in this cohort received biopsies during follow-up, thus limiting inferences we can make regarding the influence of these metabolic conditions on biopsy outcomes. Taken together with the findings regarding the likelihood of biopsy, these findings may suggest that the influence of these conditions on prostate cancer may be in part be due to their influence on biopsy detection specifically.

In conclusion, the results from this additional analysis suggest that while the presence of the metabolic components alone is associated with a slightly increased rate of prostate biopsy, multiple conditions together are associated with a reduced rate of prostate biopsies as well as a reduced likelihood of positive biopsies. Taken together, these results suggest that these conditions do play at least a part in influencing prostate cancer incidence through their impact on prostate cancer detection. Future studies need to elucidate in larger more diverse samples how these conditions to influence detection and whether this is resulting in a lower incidence of prostate caner among these groups as a result.

Table 5-1: Age-adjusted Hazard Ratios (HR) and 95% Confidence Intervals (CI) of probability of prostate biopsy, by category of selected baseline demographic and metabolic characteristics

	Biopsies during follow-up (N=519)	Person-years (per 1000/yr)	Age-adjusted HR (95% CI)
Demographics			
Age at baseline	135	1131	
40-49	151	1140	--
50-59	150	747	--
60-69	83	182	--
70+			--
Family history of prostate cancer			
No	450	2760	1
Yes	69	441	1.46(1.1, 1.88)
Education			
Less than high school graduate	67	260	1
Finished high school/some college	247	1506	0.90(0.68, 1.19)
College degree and beyond	199	1383	1.12(0.84, 1.51)
Marital status			
Single, divorced, widowed, separated	52	268	1
Married/living together	466	2922	0.94(0.71, 1.26)
Salary			
<$25,000	111	531	1
$25,000-$44,999	160	931	1.10(0.86, 1.41)
$45,000-$64,999	103	722	1.02(0.77, 1.36)
$65,000+	126	930	1.41(1.07, 1.85)
Statin use prior to baseline			
No	377	2267	1
Yes	142	934	0.77(0.64, 0.94)
Metabolic Conditions			
Diabetes diagnosis at baseline			
No	495	3122	1
Yes	24	78	0.88(0.58, 1.33)
Hypertensive at baseline			
No	364	2459	1
Yes	155	742	1.08(0.89, 1.31)
Obesity			
Not Obese (<30 kg/m^2)	419	2573	1
Obese (≥30 kg/m^2)	98	625	0.92(0.74, 1.15)
Number of Metabolic Conditions			
0	290	1944	1
1	185	1085	1.17(0.96, 1.40)
2 or 3	44	171	0.86(0.62, 1.18)

Figure 5-1: Age-adjusted HR and 95% CI predicting the probability of prostate biopsy in 2,245 men

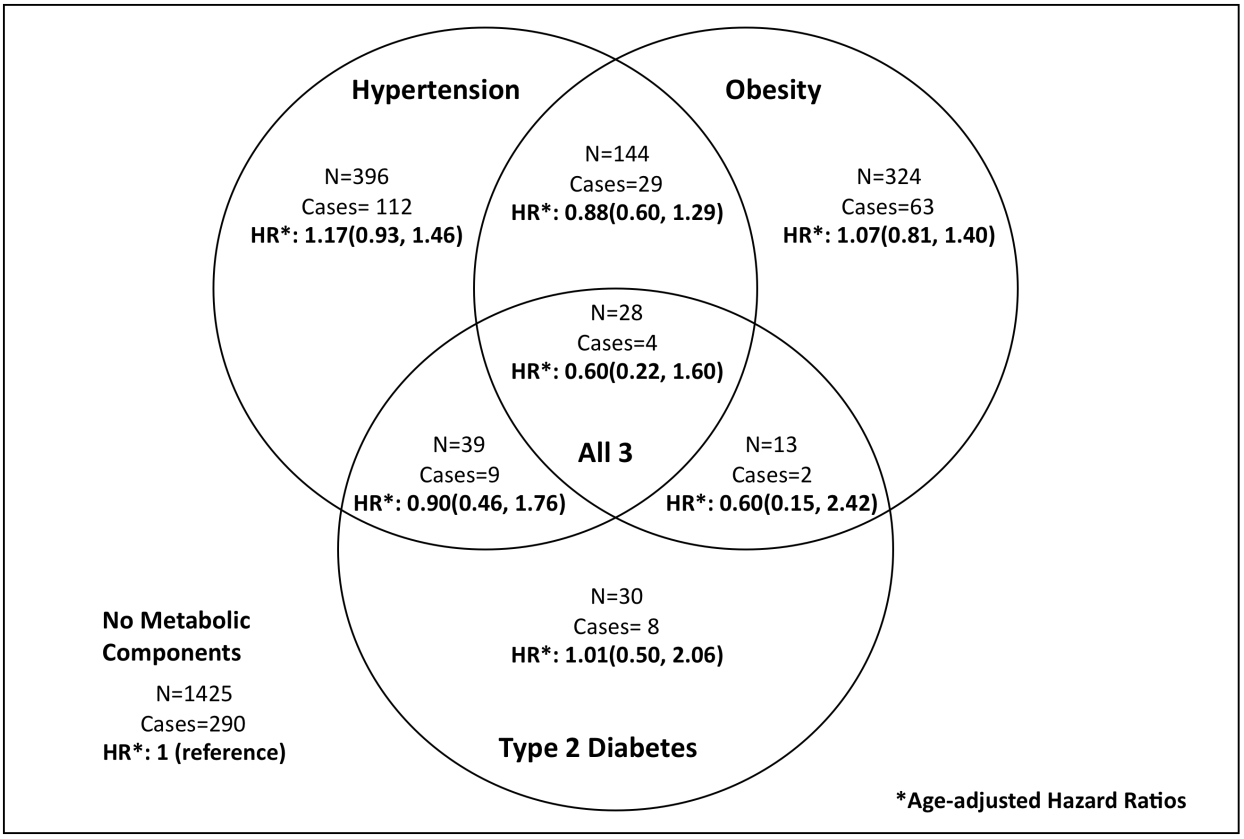


Table 5-2: Age-adjusted Odds Ratios (OR) and 95% CI of probability of having a positive biopsy among 519 men with biopsies during follow-up

	Negative Biopsy during follow-up (N=373)	Positive Biopsy during follow-up (N=146)	Age-adjusted OR (95% CI)
Metabolic Conditions			
Diabetes diagnosis at baseline			
No	355	140	1
Yes	18	6	0.74(0.28 1.93)
Hypertensive at baseline			
No	261	103	1
Yes	112	43	0.88(0.56, 1.35)
Obesity			
Not Obese (<30 kg/m^2)	301	118	1
Obese (≥30 kg/m^2)	70	28	1.04(0.64, 1.69)
Number of metabolic components			
0	301	118	1
1	70	28	1.09(0.73, 1.65)
2 or 3	70	28	0.67(0.32, 1.45)

Table 5-3: Age-adjusted ORs and 95% CI of probability of having a positive biopsy among 519 men with biopsies during follow-up

	Negative Biopsy during follow-up (N=373)	Positive Biopsy during follow-up (N=146)	Age-adjusted OR (95% CI)
Metabolic Conditions			
No metabolic components	210	80	1
Diabetes alone	7	1	0.34(0.04, 2.85
Hypertensive alone	79	33	1.01(0.62, 1.65)
Obesity alone	41	22	1.49(0.83, 2.68)
Diabetes and Hypertensive	5	4	1.69(0.44, 6.59)
Hypertensive and Obese	24	5	0.50(0.18, 1.37)
All three components	3	1	0.72(0.07, 7.09)

Chapter 6

Conclusions

Summary of Findings

In summary, the findings from this dissertation suggest that metabolic disturbances influence both the risk and detection of prostate cancer. The findings from Chapter 2 highlight that type 2 diabetes, obesity and hypertension alone and in combination were differentially associated with prostate cancer risk. When combined together applying a modified definition of the metabolic syndrome, the presence of these three conditions at baseline slightly decreased the risk of prostate cancer over 15 years of follow-up. Men who were hypertensive and obese at baseline had a lower incidence rate of prostate cancer than did men without either condition, while men with hypertension alone were at increased risk of disease. The presence of diabetes alone at baseline was associated with decreased incidence of prostate cancer when compared to men with none of these metabolic conditions.

The metabolic conditions evaluated in this dissertation also influenced the detection of prostate cancer, through their influence on the changes in serum PSA levels over time as illustrated in Chapters 3 and 4 and their influence on the likelihood and results of prostate biopsies. The presence of type 2 diabetes at baseline was associated with an attenuated increased in PSA over the 15 years of follow-up after adjustment for age. Specifically, men with type 2 diabetes experienced less of a change in PSA when compared to men without type 2 diabetes at baseline. Hypertension did not influence the

change in PSA levels over time in this cohort. Obesity, specifically baseline BMI, was inversely associated with baseline PSA levels as well as the change in PSA over time in this cohort. Additionally, baseline BMI was positively associated with the annual percent change in prostate volume. The relation between BMI and PSA is in part due to the hemodilution of PSA, as baseline BMI was associated with both the baseline levels and rate of change in plasma volume and not associated with either baseline levels or annual percent change in PSA mass. The presence of multiple metabolic conditions together decreased the likelihood of biopsy when compared to men with no conditions and also decreased the probability of a positive biopsy result among the men who received biopsies in this study.

Discussion of Findings

Metabolic Syndrome and Prostate Cancer Risk

In this dissertation, a slight inverse association was observed between the presence of all three components of metabolic syndrome and prostate cancer. While there was an association between the presence of one component (hypertension) and an increase in the rate of prostate cancer adjusting for age, an increasing number of components was not found to be positively and consistently associated with prostate cancer. The discrepancy in results may in part be due to the varying definitions of metabolic syndrome used in the current and previous investigations (i.e., three vs. more than three components of the metabolic syndrome) or to the small number of prostate cancer cases detected among men with all three components. Additionally, while definitions of metabolic syndrome recommended by the WHO and Adult Treatment Panel III and modified versions were used in previous investigations, this dissertation focused on the combination of the components rather than the syndrome alone. Finally, it is possible that the differing results are due to the unaccounted influence of dyslipidemia on prostate cancer risk in the OCS.

A plausible etiologic hypothesis is that the metabolic syndrome reduces the risk of prostate cancer through the action of sex hormones. The cross-talk between androgens, sex hormone-binding globulin and insulin is thought to influence prostate cancer (26), and men with metabolic syndrome exhibit decreased testosterone levels (64), thus potentially decreasing their risk of prostate cancer. It is also possible that these results are

explained in part by a detection bias that results in a lower rate of prostate cancer among obese men.

Diabetes and Prostate Cancer Risk

A weak inverse association between diabetes and prostate cancer was observed in this dissertation, but it may have been a chance finding as only 9 cases of prostate cancer among diabetics were observed. Alternatively, these findings may obscure the changing association between insulin level and prostate cancer risk over the course of diabetes progression. Insulin levels are initially high in type 2 diabetes but fall over time due to the damage to the pancreatic ß cells. Therefore, the relation between diabetes and prostate cancer may change from positive to inverse as diabetes progresses. Unfortunately, information on insulin levels or the duration of diabetes was not available in the OCS.

Obesity and Prostate Cancer Risk

Obesity (BMI ≥30 kg/m^2) was minimally and inversely associated with prostate cancer in this cohort when compared to a BMI of less than 30 kg/m^2, which is similar to findings from previous studies (35, 47, 57). In addition, obesity has been differentially associated with aggressive versus non-aggressive prostate cancers; a reduced risk of low-grade disease and an increased risk of high-grade disease have been observed for obese men (40, 62, 63). The results from this dissertation, however, did not change when stratified by grade and stage of prostate cancer (data shown in Appendix 1). Alternatively, several studies, in addition to this dissertation, suggest that a detection bias associated with obesity may partly explain the inverse association between obesity and

prostate cancer incidence (7). While it is plausible that obesity can influence the growth of prostate cancer through the action of adipocytes, it is unclear if the associations seen in this study and in previous work are biased due to detection issues that occur among obese men.

Hypertension and Prostate Cancer Risk

It has been postulated that hypertension could increase the risk of prostate cancer through sympathetic nervous system activity that can result in androgen-mediated stimulation of prostate cancer growth (53). Men with both hypertension and obesity had a lower rate of prostate cancer in this dissertation compared to men with neither condition, and men with hypertension who were not obese were at increased risk. This apparent heterogeneity of effects may be influenced by the likelihood of these men receiving biopsies. Specifically, it is possible that men with both comorbidities are less likely to be biopsied, as a result of physician perception that these comorbidities are more life threatening than prostate cancer.

Diabetes and Prostate Cancer Detection

The results from this dissertation suggest that men with diabetes have slower increases in serum PSA levels over time, and this might account for the lower serum PSA levels observed among diabetics in cross-sectional studies (50, 51). The association between diabetes and serum PSA levels is hypothesized to vary with the duration of diabetes. Thus, it is plausible that as the duration of diabetes increases, the action of insulin decreases and testosterone increases, resulting in subsequent drops in serum PSA

levels. This is supported by findings that later-stage diabetes is characterized by lower levels of circulating insulin, which have been associated with lower prostate-cancer risk and serum PSA levels (49, 73). A lower risk in later-stage diabetes may be attributable to the androgen regulation of PSA levels. PSA cleaves insulin growth factor binding protein 3 (IGFBP-3), a major binding protein for insulin growth factor 1 (IGF-1), which is involved in insulin signaling and associated with an increase in prostate-cancer risk (74, 75).

Hypertension and Prostate Cancer Detection

Hypertension was not associated with change in serum PSA levels over time in this cohort. The lack of an association between hypertension and change in serum PSA levels over time in our study may be in part due to the non-specificity of prescriptions for hypertensive medications or to hypertensive status being defined only at baseline. It is possible that some non-hypertensive men were prescribed medication because of cardiovascular disease. It is also plausible that men with hypertension in this cohort were being treated during follow-up; therefore, the effect of hypertension on serum PSA level is attenuated, resulting in little or no association.

Obesity and Prostate Cancer Detection

The hypothesis that a detection bias for prostate cancer exists among obese men is based on the following findings from previous studies: 1) Obese men have decreased cross-sectional PSA levels, due to either lower testosterone levels (7) or hemodilution of PSA among obese men (10); and 2) BMI is associated with larger prostate volumes,

impacting detection via digital rectal exams and biopsies (45, 46, 84). This dissertation expands on these previous findings by further elucidating these detection issues. The results of this dissertation suggest baseline obesity has more influence than BMI change on PSA level. This finding may be due to the mean rate of change in this cohort being very small, rather than the absence of an association of the rate of change in BMI with PSA over time. Baseline BMI was also inversely associated with the rate of change in PSA adjusting for age, baseline PSA and prostate volume and the rate of change in prostate volume and BMI. These results suggest that in addition to its influence on concomitant PSA levels, BMI also influences the annual percent change in PSA over the 15-years of follow-up. This finding is important, as the rate of change in PSA–PSA velocity—is currently the preferred measure used to diagnose prostate cancer. (13, 72) It is therefore possible that the resulting detection issues related to the influence of BMI on PSA may also limit the use of PSA velocity to screen obese men for prostate cancer.

Findings from this dissertation also suggest that the association between BMI and PSA is at least in part due to the hemodilution of PSA, as baseline obesity was associated with increased plasma volume but was not associated with PSA mass at baseline. Similar associations were seen longitudinally as well, as baseline obesity was associated with the rate of change in plasma volume but not associated with the annual percent change in PSA mass over time. This has important implications for prostate cancer screening and detection as current prostate cancer screening practices that use cross-sectional or repeated measures of PSA without taking into account this metabolic condition may result in missed or delayed diagnoses due to obese men being less likely to be referred for biopsy.

The findings from this dissertation further support the notion that these detection issues among obese men are also in part due to the influence of BMI on prostate volume. Baseline BMI was positively associated with the annual percent change in prostate volume. Most prostate cancers detected upon biopsy are very small, suggesting that detection is more difficult for men with larger prostates. It is therefore likely that fewer cancers are detected in obese men due to their larger prostate size or that diagnoses are delayed resulting in later stage disease at diagnosis. Previous studies have shown obese men are more likely to be diagnosed with later-stage disease and less likely to be diagnosed with early-stage disease (37, 38, 40), suggesting that the consequences of prostate volume's role in this detection issue among obese men has important implications in terms of prostate cancer aggressiveness.

Metabolic Conditions and Biopsy Detection

Overall, the findings that the presence of multiple conditions together results in a decreased risk of prostate biopsy may be indicative of a detection bias as described in previous chapters of this dissertation. Furthers supporting this hypothesis are the findings that the presence of 2 or 3 components is associated with a decreased likelihood of biopsy, while the presence of one component is associated with an increased risk. It may be that because men with multiple conditions have lower PSA levels, they are as a result less likely to be recommended for biopsy, resulting in a lower rate of biopsies among these groups when compared to men with none of these conditions.

Among those who received biopsies during follow-up, men with diabetes alone, hypertension and obesity or all three of the metabolic conditions were also less likely to

have a positive biopsy, suggesting that the detection of prostate cancer from biopsy tissue may be more difficult in the presence of these conditions. These results should be interpreted with caution as only 519 men in this cohort received biopsies during follow-up, thus limiting inferences we can make regarding the influence of these metabolic conditions on biopsy outcomes. Taken together with the findings regarding the likelihood of biopsy, these findings suggest that the influence of these conditions on prostate cancer may be in part be due to their influence on biopsy detection specifically.

Limitations of this Dissertation

This dissertation is limited by its reliance on self-report of diabetes and hypertension and may be underestimating the prevalence of these conditions in the OCS. However, diabetes diagnosis was validated among self-reported cases in a larger cohort study of diabetes in Olmsted County from 1950 to 2000 (65), and most studies show a concordance between self reports and medical records for chronic conditions such as diabetes and hypertension (80, 81). Additionally, diabetes and hypertension were measured only at baseline, and these analyses do not account for changes in these conditions during follow-up, which might have influenced subsequent prostate cancer risk and serum PSA levels. However, it is likely that not accounting for additional diagnoses of diabetes over time is attenuating the difference in prostate cancer risk and change in serum PSA levels in this cohort. Furthermore, age at diagnosis of diabetes and hypertension were not queried of men, thereby limiting the ability to make inferences about the progression of these conditions and the resulting influence on prostate cancer risk and serum PSA levels. The other aspect of the metabolic syndrome, dyslipidaemia was not assessed in this study because cholesterol levels were not available in the OCS. Therefore, this dissertation cannot infer the influence of cholesterol on prostate cancer risk or detection. Because of the lack of information on cholesterol levels over time, a modified version of the WHO definition of metabolic syndrome was used. In addition, longitudinal information on insulin and sex-steroid hormones were not available in this cohort, thereby limiting what inferences I could make regarding the role these hormones play in influencing the associations observed in this study.

Although the long follow-up period lends itself to problems associated with attrition, previous work in this cohort found that participant dropout was not associated with diabetes, hypertension, or serum PSA levels adjusting for age, thus suggesting the potential impact of this source of bias on these results may be limited (66). Our findings regarding the influence of obesity and diabetes on prostate cancer risk may be influenced by the role these conditions play in influencing prostate cancer detection. It is possible that the reduced risk of prostate cancer associated with diabetes and obesity in this study, is due to their influence on the detection of prostate cancer, rather than the incidence of disease.

Finally, because this is a Caucasian sample of men, generalizing these findings to other racial groups may not be appropriate. The incidence rate of prostate cancer as well as the prevalence of the components of metabolic syndrome are thought to differ by race (9, 67); therefore, our effect estimates in Caucasians may not be applicable to other racial groups with different incidences of these conditions. However, the methods used in this study to estimate the effects of metabolic conditions on the incidence of prostate cancer can be applied to other populations from diverse settings.

Public Health Impact and Future Directions

The main finding of this dissertation that metabolic conditions influence both the risk and detection of prostate cancer have significant implications for the aging male population in the US. The prevalence of these conditions is only expected to increase in the coming years. Elucidating how these conditions influence risk is important because they are modifiable and provide potential prevention targets to decrease the incidence of prostate cancer. Currently, the methods we use to assess whether these conditions are related to prostate cancer risk are flawed. Combining these conditions into one syndrome and determining the corresponding risk does nothing to help further the understanding of how these conditions work together or separately to influence the risk of prostate cancer. In addition, while a quarter of the US population qualifies as having metabolic syndrome, according to [what definition], the remaining 75% may have some but not all of these conditions clustering together. Understanding how these different conditions influence risk helps us understand how these conditions are involved in the etiology of prostate cancer. Rather than combining them into one variable (purportedly a syndrome), we should also treat them as separate variables and estimate their component and joint effects on cancer risk. It is also possible that some of these conditions are more important than others in terms of their influence on prostate cancer risk, which cannot be determined with current methods of combining the conditions into a single metabolic syndrome. Therefore, moving forward, future research needs to move past just determining if the metabolic syndrome is associated with prostate cancer risk, and focus on elucidating how these conditions individually and in combination influence cancer risk. Larger samples, however, will be needed to achieve sufficient precision and power.

In addition to understanding how obesity, diabetes and hypertension influence risk of prostate cancer, it is crucial to gain a better understanding how these conditions also influence the detection of prostate cancer. With prostate cancer being a largely survivable cancer, it is imperative to diagnose the cancer in its early stages so all treatment options are available. Findings that obesity and diabetes affect the change in PSA over time are important, as this would have significant implications for prostate cancer screening. With the change in PSA currently used as the screening tool for prostate cancer, it is even more important to understand how the presence of comorbid metabolic conditions influence this test. The findings from this dissertation are alarming in that if diabetes and obesity really do affect PSA change, this may lead to less cancers being detected in men with these conditions or to delayed diagnoses in these groups. Delayed or missed diagnoses would impact treatment options and potentially prostate cancer specific survival. Furthermore, it remains to be demonstrated whether or not decreases in serum PSA levels drive the lower risk of prostate cancer observed among diabetic men and obese men. Finally, if future studies confirm the findings that a prostate cancer detection bias exists among obese and/or diabetic men, steps need to be taken to revise the current screening and diagnostic guidelines for prostate cancer so they take into account the presence of these conditions. It may be prudent to lower the cut-off for PSA when screening obese and or diabetic men for prostate cancer. In addition, specifically in obese men, it may be also worth biopsying a greater number of cores of the prostate to reduce the chance that the cancer may be missed due to increased prostate size. Therefore, future research should focus on elucidating what role obesity and diabetes play in influencing prostate cancer detection and whether these detection issues are

responsible for the inverse associations observed between these conditions and prostate cancer risk. Larger, more diverse samples are needed so that future prevention strategies can be modified if appropriate.

Conclusions

In summary, the findings from this dissertation suggest that the different combinations of metabolic conditions confer different risks of prostate cancer. Obesity and diabetes influence the detection of prostate cancer, through their influence on PSA levels. As these conditions become increasingly prevalent and continue to be modifiable, it is crucial to gain a better understanding of how they influence other prevalent diseases of aging, such as prostate cancer, so that new prevention strategies can be developed and existing ones can be modified. As current screening guidelines are revised for prostate cancer, it may be prudent to take into consideration the presence of these metabolic conditions.

Appendix 1

Equations and Extra Analyses from Chapter 2

Equations for Analyses from Chapter 2

Participants' person-time contribution began on the date they completed their baseline questionnaires and ended at the diagnosis of prostate cancer or the last date of passive surveillance chart review, whichever came first. Age-adjusted hazard (incidence rate) ratios and 95% confidence intervals measuring the associations between the metabolic characteristics and prostate cancer incidence were estimated using Cox proportional hazards regression (SAS procedure proc phreg) as shown in the following equations.

$$\lambda(time) = \lambda_o(time)e^{[(\beta_1 * DM)+(\beta_2 * Age50)+(\beta_3 * Age60)+(\beta_4 * Age70)]}$$

$$\lambda(time) = \lambda_o(time)e^{[(\beta_1 * HTN)+(\beta_2 * Age50)+(\beta_3 * Age60)+(\beta_4 * Age70)]}$$

$$\lambda(time) = \lambda_o(time)e^{[(\beta_1 * OBESE)+(\beta_2 * Age50)+(\beta_3 * Age60)+(\beta_4 * Age70)]}$$

where: time = person time at risk which began on the date they completed their baseline questionnaires and ended at the diagnosis of prostate cancer or the last date of passive surveillance chart review, whichever came first

DM = Diabetes and is defined as self-reported physician-diagnosed diabetes at baseline.

Obese = Obesity and was calculated using the measured height and weight from the clinic examination, with those ≥30 kg/m^2 classified as obese.

HTN = Hypertension was defined as those with high blood pressure at baseline or who reported using anti-hypertensive medication prior to baseline.

This same method was used for the individual components alone (no interaction term), obesity and DM, DM and hypertension and obesity and hypertension interactions, and all three components together as displayed in the Venn Diagram in Chapter 2.

Additional Analyses from Chapter 2

Prostate Cancer Stage and Grade Results

The models were then stratified and compared by disease stage (Pathological stage A/B vs. Pathological Stage C/D) and disease grade (Gleason Score < 7 vs. Gleason ≥ 7) at diagnosis

Age-adjusted Hazard Ratios and 95% Confidence Intervals of the Associations of the Metabolic Conditions with Prostate Cancer Risk, Stratified by Grade and Stage of Prostate Cancer

	Low Grade (Gleason <7) N=44	High Grade (Gleason ≥ 7) N=56	Localized Disease (path stage A/B) N=22	Advanced disease (path stage C/D) N=17
Obese	1.10(0.50, 2.43)	1.13(0.52, 2.46)	0.98(0.55, 1.73)	0.57(0.17, 1.95)
Hypertension	1.08(0.56, 2.07)	2.37(1.20, 4.67)	2.25(1.33, 3.81)	1.42(0.48, 4.19)
Diabetes	2.89(0.61, 13.72)	n/a	2.39(0.65, 8.79)	2.37(0.93, 6.10)
All 3*	0.46(0.11, 1.87)	n/a	0.96(0.93, 9.79)	n/a

-Each component was modeled separately independent of the presence of absence of the other components and compared to men without that component (i.e. Men with diabetes vs. men without diabetes)
*Men with all three components were compared to men without any of the components

Age-adjusted Hazard Ratios and 95% Confidence Intervals of the Associations of the Metabolic Conditions with Prostate Cancer Risk, Stratified by Grade and Stage of Prostate Cancer using the Venn Diagram Approach

	Low Grade (Gleason <7)	High Grade (Gleason ≥ 7)	Localized Disease (Path stage A/B)	Advanced disease (Path stage C/D)
Obese only	1.15(0.41, 3.04)	1.34(0.53, 3.35)	0.24(0.05, 1.21)	n/a
Hypertension only	1.02(0.49, 2.13)	2.53(1.22, 5.27)	1.18(0.35, 3.92)	n/a
Diabetes only	n/a	n/a	n/a	n/a
Obese and DM	n/a	n/a	n/a	n/a
***DM and HTN**	4.64(0.55, 39.11)	n/a	3.87(0.34, 44.37)	n/a
***HTN and Obese**	0.98(0.22, 4.45)	2.46(0.52,11.78)	0.29(0.05, 1.84)	n/a
All 3	2.08(0.24, 18.03)	n/a	0.88(0.08, 9.42)	n/a

Each component was modeled either alone or in combination with the other components as displayed in the Venn Diagram approach in Chapter 2

Appendix 2

Equations and Extra Analyses from Chapter 3

Equations

Linear mixed effects regression models were used to estimate the annual percent change in serum PSA levels by regressing each measure on time from initial blood draw and adjusting for 10-year baseline age groups. Interaction terms with time were included to allow for different slopes across these age groups. These models also included terms for diagnosis of diabetes or hypertension and interaction terms to compare intercepts and slopes among those with and without a diagnosis. Because of the skewed distribution, serum PSA levels were natural log-transformed, and therefore, annual changes represent percent changes per year assuming an exponential growth curve.

Diabetes Equation

$$\log PSA = (\beta_0 + \beta_{0j}) + (\beta_1 * diabetes) + (\beta_2 * age50) + (\beta_3 * age60) + (\beta_4 * age70)$$
$$+(\beta_5 + \beta_{5j} * time) + (\beta_6 * age50 * time) + (\beta_7 * age60 * time) + (\beta_8 * age70 * time)$$
$$+(\beta_8 * diabetes * time)$$

where: Diabetes is defined at baseline and time is defined as time since baseline PSA blood draw

β_0 = average intercept (offset by individual random effects β_{0j})

β_2- β_4 = offset for intercepts for older age decades (reference = 40 year olds)

β_5 := average rate of change over time (offset by individual random effects β_{4j})

$\beta_6 - \beta_8$= offsets to the slopes for the older age decades.

B_9 = coefficient to compare different slopes over time by diabetes status

Hypertension Equation

$$\log PSA = (\beta_0 + \beta_{0j}) + (\beta_1 * HTN) + (\beta_2 * age50) + (\beta_3 * age60) + (\beta_4 * age70)$$
$$+(\beta_5 + \beta_{5j} * time) + (\beta_6 * age50 * time) + (\beta_7 * age60 * time) + (\beta_8 * age70 * time)$$
$$+(\beta_8 * HTN * time)$$

where: Hypertension is defined at baseline and time is defined as time since baseline PSA blood draw

β_0 = average intercept (offset by individual random effects β_{0j})

β_2- β_4 = offset for intercepts for older age decades (reference = 40 year olds)

β_5 := average rate of change over time (offset by individual random effects β_{4j})

$\beta_6 - \beta_8$= offsets to the slopes for the older age decades.

B_9 = coefficient to compare different slopes over time by diabetes status

Additional Analyses from Chapter 3

Additional linear mixed models were run to estimate the association of baseline diabetes or hypertension with annual percent change in PSA, regressing each measure on time from initial blood draw and adjusting for 10-year baseline age groups. These models also investigated interactions between age and time, diabetes and time, age and diabetes and the three-way interaction of age, time and diabetes as shown in the following tables:

Table 4: Adjusted Beta Coefficients and Standard Errors of the Annual Percent Change in PSA Associated with Baseline Diabetes (DM)

Main effects	**Crude (Separately)**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
	Beta(SE), p-value	**Beta(SE), p-value**	**Beta(SE), p-value**	**Beta(SE), p-value**	**Beta(SE), p-value**	**Beta(SE), p-value**
DM[1]	0.005(0.155), 0.976	-0.193(0.139), 0.167	-0.079(0.134), 0.556	-0.067(0.134), 0.620	0.018(0.792), 0.982	0.05(0.793), 0.948
Age[2]	0.032(0.003), <0.0001	0.032(0.003), <0.0001	0.032(0.003), <0.0001	0.031(0.003), <0.0001	0.031(0.003), <0.0001	0.031(0.003), <0.0001
Time[3]	0.035(0.003), <0.0001	--	0.034(0.003), <0.0001	-0.017(0.014), 0.048	-0.017(0.014), 0.048	-0.013(0.015), 0.040
Interactions						
Age*DM	--	--	--	--	-0.0014(0.013), 0.914	-0.002(0.013), 0.875
Time*DM	--	--	--	-0.030(0.013), 0.024	-0.030(0.013), 0.024	-0.142(0.082), 0.082
Age*Time	--	--	--	0.001(0.0003), 0.0002	0.001(0.0003), 0.0002	0.001(0.0003), 0.007
Age*Time*DM	--	--	--	--	--	0.002(0.001), 0.166

[1]DM is defined at baseline: Self-reported diagnosis of condition or medication use prior to baseline
[2]Age is defined as age at baseline blood draw
[3]Time is defined as time from baseline blood draw to current round blood draw

Table 4: Adjsuted Beta Coefficients and Standard Errors of the Annual Percent Change in PSA Associated with Baseline Hypertension (HTN)

Main effects	Crude (Separately)	Model 1	Model 2	Model 3	Model 4	Model 5
	Beta(SE), p-value	Beta(SE), p-value	Beta(SE), p-value	Beta(SE), p-value	Beta(SE), p-value	Beta(SE), p-value
HTN[1]	0.265(0.071), 0.0002	0.052(0.067), 0.436	0.069(0.065), 0.291	0.077(0.065), 0.235	0.211(0.343), 0.540	0.218(0.343), 0.526
Age[2]	0.032(0.003), <0.0001	0.031(0.003), <0.0001	0.032(0.003), <0.0001	0.030(0.003), <0.0001	0.031(0.003), <0.0001	0.031(0.003), <0.0001
Time[3]	0.035(0.003), <0.0001	--	0.034(0.003), <0.0001	-0.016(0.015), 0.261	-0.016(0.015), 0.261	-0.005(0.017), 0.7554
Interactions			--			
Age*HTN	--	--	--	--	-0.002(0.006), 0.691	-0.002(0.006), 0.672
Time*HTN	--	--	--	-0.005(0.006), 0.402	-0.005(0.006), 0.407	-0.044 (0.034), 0.197
Age*Time	--	--	--	0.001(0.0003), 0.0004	0.001(0.0003), 0.0004	0.001(0.0003), 0.021
Age*Time*HTN	--	--	--	--	--	0.001(0.0006), 0.246

[1]HTN are defined at baseline: Self-reported diagnosis of condition or medication use prior to baseline
[2]Age is defined as age at baseline blood draw
[3]Time is defined as time from baseline blood draw to current round blood draw

Appendix 3

Equations for Chapter 4

Linear mixed-effects models were used to examine the association of baseline obesity with annual percent change in PSA and annual percent change in prostate volume. These models included age and a categorical measure for obesity (BMI<30, BMI ≥30) as well as an interaction (product) term between obesity and time to compare the slope of PSA among those who were obese and not obese. (Equation 1) Additional models were fit to assess the association of baseline BMI (treated as continuous), baseline BMI based on the WHO cut-offs, and repeated measures of BMI with the annual percent changes in PSA and prostate volume.

Equation (1)

$$\log PSA = (\beta_0 + \beta_{0j}) + (\beta_1 * obese) + (\beta_2 * age50) + (\beta_3 * age60) + (\beta_4 * age70)$$
$$+(\beta_5 + \beta_{5j} * time) + (\beta_6 * age50 * time) + (\beta_7 * age60 * time) + (\beta_8 * age70 * time)$$
$$+(\beta_8 * obese * time)$$

where: Obese is categorized into BMI < 30, BMI ≥ 30 and time is defined as time since baseline blood draw

β_0 = average intercept (offset by individual random effects β_{0j})

β_2- β_4 = offset for intercepts for older age decades (reference = 40 year olds)

β_5 := average rate of change over time (offset by individual random effects β_{4j})

$\beta_6 - \beta_8$= offsets to the slopes for the older age decades.

B_9 = coefficient to compare different slopes over time by obesity status

-Similar models were also run for baseline BMI, obesity @ baseline, and BMI categorized by WHO cut-offs at baseline.

A longitudinal 2-step analytic approach was used to examine the associations of the individual intercepts and slopes of BMI and prostate volume with the annual percent change in PSA. First, the annual percent change in PSA, BMI and prostate volume were estimated by individually regressing each measure on time from initial blood draw and age (10-year categories) using linear mixed-effects regression models. Interaction (product) terms were included to allow for different slopes across these age groups. Fixed and random effects were included to reflect both the mean effect and allow for individual variation in the baseline intercept and change over time. An overall annual change in each measure for each man was estimated by combining the average longitudinal change in time (fixed effects) with the individual changes (random effects). Similarly, both fixed and random effects allowed determination of an overall baseline intercept for each age decade and allowed for offsets for individual variation. (Equations 2-4) Because of their skewed distributions, PSA level and prostate volume were log-transformed, and therefore, annual changes represent percent changes per year. The change in BMI reflects annual absolute changes.

Equation (2)

$$\log PSA = (\beta_0 + \beta_{0j}) + (\beta_1 * age50) + (\beta_2 * age60) + (\beta_3 * age70) + (\beta_4 + \beta_{4j} * time)$$
$$+(\beta_5 * age50 * time) + (\beta_6 * age60 * time) + (\beta_7 * age70 * time)$$

Equation (3)

$$BMI = (\beta_0 + \beta_{0j}) + (\beta_1 * age50) + (\beta_2 * age60) + (\beta_3 * age70) + (\beta_4 + \beta_{4j} * time)$$
$$+(\beta_5 * age50 * time) + (\beta_6 * age60 * time) + (\beta_7 * age70 * time)$$

Equation (4)

$$\log Volume = (\beta_0 + \beta_{0j}) + (\beta_1 * age50) + (\beta_2 * age60) + (\beta_3 * age70) + (\beta_4 + \beta_{4j} * time)$$
$$+(\beta_5 * age50 * time) + (\beta_6 * age60 * time) + (\beta_7 * age70 * time)$$

where: time is defined as time since baseline measurement of either PSA, volume or BMI.

β_0 = average intercept (offset by individual random effects β_{0j})

β_1- β_3 = offset for intercepts for older age decades (reference = 40 year olds)

β_4 := average rate of change over time (offset by individual random effects β_{4j})

β_5 – β_7= offsets to the slopes for the older age decades.

The second step of this approach was to estimate the effects of predicted intercepts of PSA, BMI and prostate volume and the predicted slopes of BMI and prostate volume on the predicted annual percent change in PSA (all derived from the mixed model in step 1), using linear regression models adjusting for age. (Equation 5)

Equation (5)

$$slopePSA = \beta_0 + (\beta_1 * age) + (\beta_2 * \hat{psa}\text{int}) + (\beta_3 * \hat{bmi}\text{ int}) + (\beta_4 * \hat{vol}\text{ int}) + (\beta_5 * \hat{bmi}slope)$$
$$+(\beta_6 * \hat{vol}slope)$$

where:

psaslope= estimated psa slope calculated by combining the population average effects with the individual random effects from step 1

psaint = estimated psa intercept calculated by combining the population average effects with the individual random effects from step 1

bmiint= estimated bmi intercept calculated by combining the population average effects with the individual random effects from step1

volint= estimated prostate volume intercept calculated by combining the population average effects with the individual random effects from step 1

bmislope= estimated bmi slope calculated by combining the population average effects with the individual random effects from step 1

volslope= estimated prostate volume slope predicted from step 1.

The adjusted predicted values of the intercepts and slopes of plasma volume and PSA mass were also estimated using linear mixed-effects regression models that individually regressed each measure on time from initial blood draw and age (10-year categories) and included a categorical measure for obesity (BMI<30, BMI ≥30), as well as an interaction term to compare the intercept and slope among those who were obese and not obese where appropriate. (Equations 6-8) Because of the skewed distribution, PSA mass was log-transformed, and therefore, annual changes represent percent changes per year. The change in plasma volume reflects annual absolute changes. The means and standard deviations of the predicted slopes and intercepts of PSA mass and plasma volume from the mixed models were then compared across levels of age and baseline obesity.

Equation (6)

$$\log PSA = (\beta_0 + \beta_{0j}) + (\beta_1 * BMI) + (\beta_2 * age50) + (\beta_3 * age60) + (\beta_4 * age70)$$
$$+(\beta_5 + \beta_{5j} * time) + (\beta_6 * age50 * time) + (\beta_7 * age60 * time) + (\beta_8 * age70 * time)$$
$$+(\beta_8 * BMI * time)$$

Equation (7)

$$plvolume = (\beta_0 + \beta_{0j}) + (\beta_1 * BMI) + (\beta_2 * age50) + (\beta_3 * age60) + (\beta_4 * age70)$$
$$+(\beta_5 + \beta_{5j} * time) + (\beta_6 * age50 * time) + (\beta_7 * age60 * time) + (\beta_8 * age70 * time)$$
$$+(\beta_8 * BMI * time)$$

where plvolume = annual absolute change in plasma volume

-PSA and PSA mass (PSA (ng/mL) x Plasma Volume) were log transformed and represent annual percent changes.

Equation (8)

$$\log PSAmass = (\beta_0 + \beta_{0j}) + (\beta_1 * BMI) + (\beta_2 * age50) + (\beta_3 * age60) + (\beta_4 * age70)$$
$$+(\beta_5 + \beta_{5j} * time) + (\beta_6 * age50 * time) + (\beta_7 * age60 * time) + (\beta_8 * age70 * time)$$
$$+(\beta_8 * BMI * time)$$

Bibliography

1. Crawford ED. Epidemiology of prostate cancer. Urology. 2003;62:3-12.

2. National Cancer I. Estimated new cases and deaths of prostate cancer. 2009 7/06/18/ [cited; Available from: http://www.cancer.gov/cancertopics/types/prostate

3. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. JAMA.303:235-41.

4. Centers for Disease C, Prevention. Health, United States, 2007. 2007 2009/02/20/ [cited; Available from: http://www.cdc.gov/nchs/data/hus/hus07.pdf#070

5. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA. 2002;287:356-9.

6. Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the United States. JAMA. 2001;286:1195-200.

7. Freedland SJ, Platz EA. Obesity and Prostate Cancer: Making Sense out of Apparently Conflicting Data. Epidemiol Rev. 2007.

8. Werny DM, Thompson T, Saraiya M, Freedman D, Kottiri BJ, German RR, et al. Obesity is negatively associated with prostate-specific antigen in U.S. men, 2001-2004. Cancer Epidemiol Biomarkers Prev. 2007;16:70-6.

9. Fowke JH, Signorello LB, Chang SS, Matthews CE, Buchowski MS, Cookson MS, et al. Effects of obesity and height on prostate-specific antigen (PSA) and percentage of free PSA levels among African-American and Caucasian men. Cancer. 2006;107:2361-7.

10. Banez LL, Hamilton RJ, Partin AW, Vollmer RT, Sun L, Rodriguez C, et al. Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. JAMA. 2007;298:2275-80.

11. Freedland SJ, Platz EA, Presti JC, Jr., Aronson WJ, Amling CL, Kane CJ, et al. Obesity, serum prostate specific antigen and prostate size: implications for prostate cancer detection. J Urol. 2006;175:500-4.

12. Consedine NS, Morgenstern AH, Kudadjie-Gyamfi E, Magai C, Neugut AI. Prostate cancer screening behavior in men from seven ethnic groups: the fear factor. Cancer Epidemiology Biomarkers Prevention. 2006;15:228-37.

13. Greene KL, Albertsen PC, Babaian RJ, Carter HB, Gann PH, Han M, et al. Prostate specific antigen best practice statement: 2009 update. J Urol. 2009;182:2232-41.

14. Andriole GL, Crawford ED, Grubb RL, 3rd, Buys SS, Chia D, Church TR, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 2009;360:1310-9.

15. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009;360:1320-8.

16. Ford ES, Giles WH. A comparison of the prevalence of the metabolic syndrome using two proposed definitions. Diabetes Care. 2003;26:575-81.

17. Cowey S, Hardy RW. The Metabolic Syndrome: A High-Risk State for Cancer? American Journal of Pathology. 2006;169:1505-22.

18. Blaha M, Elasy TA. Clinical Use of the Metabolic Syndrome: Why the Confusion? Clinical Diabetes. 2006;24:125-31.

19. Laaksonen DE, Laukkanen JA, Niskanen L, Nyyssonen K, Rissanen TH, Voutilainen S, et al. Serum linoleic and total polyunsaturated fatty acids in relation to prostate and other cancers: a population-based cohort study. IntJ Cancer. 2004;111:444-50.

20. Ogden CL, Yanovski SZ, Carroll MD, Flegal KM. The epidemiology of obesity. Gastroenterology. 2007;132:2087-102.

21. Centers for Disease C, Prevention. Health, United States, 2008. 2008 2009/02/20/ [cited; Available from: http://www.cdc.gov/nchs/data/hus/hus07.pdf#070

22. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation. 2010;121:e46-e215.

23. Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, et al. Diabetes trends in the U.S.: 1990-1998. Diabetes Care. 2000;23:1278-83.

24. Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, et al. The continuing increase of diabetes in the US. Diabetes Care. 2001;24:412.

25. Bailes BK. Diabetes mellitus and its chronic complications. AORN J. 2002;76:266-76, 78-82; quiz 83-6.

26. Lund Haheim L, Wisloff T, Holme I, Nafstad P. Metabolic syndrome predicts prostate cancer in a cohort of middle-aged Norwegian men followed for 27 years. American Journal of Epidemiology. 2006;164:769.

27. Hammarsten J, Hogstedt B. Clinical, haemodynamic, anthropometric, metabolic and insulin profile of men with high-stage and high-grade clinical prostate cancer. Blood Press. 2004;13:47-55.

28. Laukkanen JA, Laaksonen DE, Niskanen L, Pukkala E, Hakkarainen A, Salonen JT. Metabolic syndrome and the risk of prostate cancer in Finnish men: a population-based study. Cancer Epidemiol Biomarkers Prev. 2004;13:1646-50.

29. Fowke JH, Motley SS, Cookson MS, Concepcion R, Chang SS, Wills ML, et al. The association between body size, prostate volume and prostate-specific antigen. Prostate Cancer ProstaticDis. 2006.

30. Andersson SO, Wolk A, Bergstrom R, Adami HO, Engholm G, Englund A, et al. Body size and prostate cancer: a 20-year follow-up study among 135006 Swedish construction workers. J Natl Cancer Inst. 1997;89:385-9.

31. Engeland A, Tretli S, Bjorge T. Height, body mass index, and prostate cancer: a follow-up of 950000 Norwegian men. BrJ Cancer. 2003;89:1237-42.

32. Putnam SD, Cerhan JR, Parker AS, Bianchi GD, Wallace RB, Cantor KP, et al. Lifestyle and anthropometric risk factors for prostate cancer in a cohort of Iowa men. AnnEpidemiol. 2000;10:361-9.

33. Veierod MB, Laake P, Thelle DS. Dietary fat intake and risk of prostate cancer: a prospective study of 25,708 Norwegian men. IntJ Cancer. 1997;73:634-8.

34. Giovannucci E, Rimm EB, Liu Y, Leitzmann M, Wu K, Stampfer MJ, et al. Body mass index and risk of prostate cancer in U.S. health professionals. J Natl Cancer Inst. 2003;95:1240-4.

35. Hubbard JS, Rohrmann S, Landis PK, Metter EJ, Muller DC, Andres R, et al. Association of prostate cancer risk with insulin, glucose, and anthropometry in the Baltimore longitudinal study of aging. Urology. 2004;63:253-8.

36. Schuurman AG, Goldbohm RA, Dorant E, van den Brandt PA. Anthropometry in relation to prostate cancer risk in the Netherlands Cohort Study. Am J Epidemiol. 2000;151:541-9.

37. MacInnis RJ, English DR. Body size and composition and prostate cancer risk: systematic review and meta-regression analysis. Cancer Causes Control. 2006;17:989-1003.

38. Gong Z, Neuhouser ML, Goodman PJ, Albanes D, Chi C, Hsing AW, et al. Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. Cancer Epidemiol Biomarkers Prev. 2006;15:1977-83.

39. Rodriguez C, Patel AV, Calle EE, Jacobs EJ, Chao A, Thun MJ. Body mass index, height, and prostate cancer mortality in two large cohorts of adult men in the United States. Cancer Epidemiol Biomarkers Prev. 2001;10:345-53.

40. Wright ME, Chang SC, Schatzkin A, Albanes D, Kipnis V, Mouw T, et al. Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. Cancer. 2007;109:675-84.

41. Freedland SJ, Giovannucci E, Platz EA. Are findings from studies of obesity and prostate cancer really in conflict? Cancer Causes Control. 2006;17:5-9.

42. Freedland SJ, Partin AW. Obesity and prostate cancer detection and progression. RevUrol. 2004;6:214-6.

43. Baillargeon J, Pollock BH, Kristal AR, Bradshaw P, Hernandez J, Basler J, et al. The association of body mass index and prostate-specific antigen in a population-based study. Cancer. 2005;103:1092-5.

44. Kristal AR, Chi C, Tangen CM, Goodman PJ, Etzioni R, Thompson IM. Associations of demographic and lifestyle characteristics with prostate-specific antigen (PSA) concentration and rate of PSA increase. Cancer. 2006;106:320-8.

45. Dahle SE, Chokkalingam AP, Gao YT, Deng J, Stanczyk FZ, Hsing AW. Body size and serum levels of insulin and leptin in relation to the risk of benign prostatic hyperplasia. J Urol. 2002;168:599-604.

46. Hammarsten J, Hogstedt B. Hyperinsulinaemia as a risk factor for developing benign prostatic hyperplasia. EurUrol. 2001;39:151-8.

47. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. 2006;15:2056-62.

48. Tande AJ, Platz EA, Folsom AR. The metabolic syndrome is associated with reduced risk of prostate cancer. Am J Epidemiol. 2006;164:1094-102.

49. Rodriguez C, Patel AV, Mondul AM, Jacobs EJ, Thun MJ, Calle EE. Diabetes and risk of prostate cancer in a prospective cohort of US men. American Journal of Epidemiology. 2005;161:147-52.

50. Werny DM, Saraiya M, Gregg EW. Prostate-specific antigen values in diabetic and nondiabetic US men, 2001-2002. Am J Epidemiol. 2006;164:978-83.

51. Fukui M, Tanaka M, Kadono M, Imai S, Hasegawa G, Yoshikawa T, et al. Serum prostate-specific antigen levels in men with type 2 diabetes. Diabetes Care. 2008;31:930-1.

52. Beebe-Dimmer JL, Dunn RL, Sarma AV, Montie JE, Cooney KA. Features of the metabolic syndrome and prostate cancer in African-American men. Cancer. 2007;109:875-81.

53. Gann PH, Daviglus ML, Dyer AR, Stamler J. Heart rate and prostate cancer mortality: results of a prospective analysis. Cancer EpidemiolBiomarkers Prev. 1995;4:611-6.

54. Powell IJ. Epidemiology and pathophysiology of prostate cancer in African-American men. J Urol. 2007;177:444-9.

55. Division of N, Physical A. Overweight and Obesity. 2007 7/06/18/ [cited; Available from: http://www.cdc.gov/nccdphp/dnpa/obesity/

56. Kumar V CRSRSL. Basic Pathology. Philidelphia: W.B. Saunders Company; 1992.

57. Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. Gastroenterology. 2007;132:2208-25.

58. Jacobsen SJ, Girman CJ, Guess HA, Rhodes T, Oesterling JE, Lieber MM. Natural history of prostatism: longitudinal changes in voiding symptoms in community dwelling men. JUrol. 1996;155:595-600.

59. Jacobsen SJ, Guess HA, Panser L, Girman CJ, Chute CG, Oesterling JE, et al. A population-based study of health care-seeking behavior for treatment of urinary symptoms. The Olmsted County Study of Urinary Symptoms and Health Status Among Men. ArchFamMed. 1993;2:729-35.

60. Melton LJ, III. History of the Rochester Epidemiology Project. Mayo Clin Proc. 1996;71:266-74.

61. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Diabetes mellitus and risk of prostate cancer (United States). Cancer Causes Control. 1998;9:3-9.

62. Gong Z, Agalliu I, Lin DW, Stanford JL, Kristal AR. Obesity is associated with increased risks of prostate cancer metastasis and death after initial cancer diagnosis in middle-aged men. Cancer. 2007;109:1192-202.

63. Rodriguez C, Freedland SJ, Deka A, Jacobs EJ, McCullough ML, Patel AV, et al. Body mass index, weight change, and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev. 2007;16:63-9.

64. Nakhla AM, Rosner W. Stimulation of prostate cancer growth by androgens and estrogens through the intermediacy of sex hormone-binding globulin. Endocrinology. 1996;137:4126-9.

65. Burke JP, O'Brien P, Ransom J, Palumbo PJ, Lydick E, Yawn BP, et al. Impact of Case Ascertainment on Recent Trends in Diabetes Incidence in Rochester, Minnesota. American Journal of Epidemiology. 2002;155:859-65.

66. Gades NM, Jacobson DJ, McGree ME, Lieber MM, Roberts RO, Girman CJ, et al. Dropout in a longitudinal, cohort study of urologic disease in community men. BMCMed Res Methodol. 2006;6:58.

67. Fowke JH, Signorello LB, Underwood W, III, Ukoli FA, Blot WJ. Obesity and prostate cancer screening among African-American and Caucasian men. Prostate. 2006;66:1371-80.

68. National Cancer I. Estimated new cases and deaths of prostate cancer. 2007 7/06/18/ [cited; Available from: http://www.cancer.gov/cancertopics/types/prostate

69. Bonovas S, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: a meta-analysis. Diabetologia. 2004;47:1071-8.

70. Muller H, Raum E, Rothenbacher D, Stegmaier C, Brenner H. Association of diabetes and body mass index with levels of prostate-specific antigen: implications for correction of prostate-specific antigen cutoff values? Cancer Epidemiol Biomarkers Prev. 2009;18:1350-6.

71. Loeb S, Roehl KA, Helfand BT, Kan D, Catalona WJ. Can prostate specific antigen velocity thresholds decrease insignificant prostate cancer detection? J Urol. 2010;183:112-6.

72. Vickers AJ, Wolters T, Savage CJ, Cronin AM, O'Brien MF, Pettersson K, et al. Prostate-Specific Antigen Velocity for Early Detection of Prostate Cancer: Result from a Large, Representative, Population-based Cohort. Eur Urol. 2009.

73. Parekh N, Lin Y, Marcella S, Kant AK, Lu-Yao G. Associations of lifestyle and physiologic factors with prostate-specific antigen concentrations: evidence from the National Health and Nutrition Examination Survey (2001-2004). Cancer Epidemiol Biomarkers Prev. 2008;17:2467-72.

74. Djavan B, Bursa B, Seitz C, Soeregi G, Remzi M, Basharkhah A, et al. Insulin-like growth factor 1 (IGF-1), IGF-1 density, and IGF-1/PSA ratio for prostate cancer detection. Urology. 1999;54:603-6.

75. Djavan B, Waldert M, Seitz C, Marberger M. Insulin-like growth factors and prostate cancer. World J Urol. 2001;19:225-33.

76. Waters KM, Henderson BE, Stram DO, Wan P, Kolonel LN, Haiman CA. Association of diabetes with prostate cancer risk in the multiethnic cohort. Am J Epidemiol. 2009;169:937-45.

77. Kasper JS, Liu Y, Giovannucci E. Diabetes mellitus and risk of prostate cancer in the health professionals follow-up study. Int J Cancer. 2009;124:1398-403.

78. Bonovas S, Filioussi K, Sitaras NM. Statin use and the risk of prostate cancer: A metaanalysis of 6 randomized clinical trials and 13 observational studies. Int J Cancer. 2008;123:899-904.

79. Han JH, Choi NY, Bang SH, Kwon OJ, Jin YW, Myung SC, et al. Relationship between serum prostate-specific antigen levels and components of metabolic syndrome in healthy men. Urology. 2008;72:749-54; discussion 54-5.

80. Skinner KM, Miller DR, Lincoln E, Lee A, Kazis LE. Concordance between respondent self-reports and medical records for chronic conditions: experience from the Veterans Health Study. J Ambul Care Manage. 2005;28:102-10.

81. El Fakiri F, Bruijnzeels MA, Hoes AW. No evidence for marked ethnic differences in accuracy of self-reported diabetes, hypertension, and hypercholesterolemia. J Clin Epidemiol. 2007;60:1271-9.

82. Dubois D, Dubois EF. Nutrition Metabolism Classic - a Formula to Estimate the Approximate Surface-Area If Height and Weight Be Known (Reprinted from Archives Internal Medicine, Vol 17, Pg 863, 1916). Nutrition. 1989;5:303-11.

83. Boer P. Estimated lean body mass as an index for normalization of body fluid volumes in humans. Am J Physiol. 1984;247:F632-6.

84. Fowke JH, Motley SS, Cookson MS, Concepcion R, Chang SS, Wills ML, et al. The association between body size, prostate volume and prostate-specific antigen. Prostate Cancer ProstaticDis. 2007;10:137-42.

85. Grubb RL, 3rd, Black A, Izmirlian G, Hickey TP, Pinsky PF, Mabie JE, et al. Serum prostate-specific antigen hemodilution among obese men undergoing screening in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Cancer Epidemiol Biomarkers Prev. 2009;18:748-51.

86. Fowke JH, Motley SS, Wills M, Cookson MS, Concepcion RS, Eckstein CW, et al. Prostate volume modifies the association between obesity and prostate cancer or high-grade prostatic intraepithelial neoplasia. Cancer Causes Control. 2007;18:375-84.

87. Freedland SJ, Aronson WJ, Kane CJ, Presti JC, Jr., Amling CL, Elashoff D, et al. Impact of obesity on biochemical control after radical prostatectomy for clinically localized prostate cancer: a report by the Shared Equal Access Regional Cancer Hospital database study group. J Clin Oncol. 2004;22:446-53.

88. Amling CL, Riffenburgh RH, Sun L, Moul JW, Lance RS, Kusuda L, et al. Pathologic variables and recurrence rates as related to obesity and race in men with prostate cancer undergoing radical prostatectomy. J Clin Oncol. 2004;22:439-45.