ProCEED Pilot Study (Prostate Cancer Study of Ethnicity Exercise and Diet)

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THESIS

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LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
CI	Confidence Interval
FFQ	Food Frequency Questionnaire
GI	Glycemic Index
GL	Glycemic Load
HIPAA	Health Insurance Portability and Accountability Act
IGF	Insulin-Like Growth Factor
IGF-1	Insulin-Like Growth Factor (Protein 1)
IGF-2	Insulin-Like Growth Factor (Protein 2)
IGFBP	Insulin-Like Growth Factor Binding Protein
IGFBP-3	Insulin-Like Growth Factor Binding Protein 3
IPAQ	International Physical Activity Questionnaire
JBVAMC	Jesse Brown Veteran's Affairs Medical Center
MET	Metabolic Equivalent of Task
OR	Odds Ratio
ProCEED	Prostate Cancer Study of Ethnicity Exercise and Diet
PSA	Prostate Specific Antigen
RIA	Radioimmunoassay
RR	Relative Risk (or Rate Ratio)
SEER	Surveillance Epidemiology End Results
TNM	Tumor Lymph Node Metastasis

LIST OF ABBREVIATIONS (continued)

UIC	University of Illinois at Chicago
VA	Veteran's Administration

SUMMARY

The Prostate Cancer Study of Ethnicity, Exercise and Diet (ProCEED) pilot study was a case-control study that was undertaken to directly assess differences between the insulin-like growth factor (IGF) hormones, and dietary and lifestyle risk factors between men with and without prostate cancer. Interactions between serum insulin-like growth factor 1 (IGF-1) concentrations and dietary and lifestyle risk factors were also examined. A separate descriptive epidemiology assessment of prostate cancer in Illinois versus the United States was also performed.

The specific aims of the ProCEED Pilot Study were

1. to examine the epidemiology of prostate cancer in Illinois as compared to the United States, to see if prostate cancer in Illinois is representative of the US population;
2. to determine whether there are significantly different levels of IGF-1 and insulin-like growth factor binding protein 3 (IGFBP-3) in blood samples from prostate cancer cases compared to controls;
3. to assess differences between dietary and exercise intake in prostate cancer cases compared to controls, and to assess interactions between these variables and the IGF-1 hormone.

The clinical portions of this study were undertaken in the General Urology Clinic at the Jesse Brown Veteran's Administration Medical Center (JBVAMC), Chicago, Illinois. The urologist and/or clinical pharmacist on duty identified potential study subjects by reviewing charts of patients coming into the general urology clinic and asked the patients during their clinic appointment if they wished to participate in the study. One study visit and two phone interviews were required from each patient, for which they were paid \$20.00. The study visit consisted of: informed consent, a demographic interview, waist/hip circumference and height/weight measurements, a serum sample, a

SUMMARY (continued)

work and social history questionnaire, and the International Physical Activity Questionnaire (IPAQ). A dietitian followed-up with two phone calls within seven days of the study visit. The first phone call ascertained the Block Food Frequency Questionnaire (FFQ) and a 24-hour dietary recall. The second telephone interview collected a second 24-hour dietary recall.

A total of 84 subjects were enrolled in the study: 59 prostate cancer cases and 25 controls. The cases were significantly older 70.6 (sd=14.4) than controls 63.2 (sd=6.5), $p=.0020$. Racial makeup of cases and controls was proportional, with more African Americans in both groups (83% cases were African American versus 84% of controls). More cases than controls were not working at the time of the study (84.8% versus 62.5%, respectively), $p=.0053$. Although it appeared that cases were less likely to have graduated from high school than controls (37.3% cases with less than a high school education versus 13.0% of controls), the difference was not statistically significant $p=.232$. Cases were more likely than controls to have the following co-morbidities: overactive bladder disorder, erectile dysfunction, degenerative joint disease, and polyps (any location) (all $p<.05$).

Prostate cancer cases had been seen in the JBVMAC General Urology clinic for the following treatments: hormone therapy (37%), watchful waiting (27%), radical prostatectomy (37%), radiation (22%), brachytherapy (2%). Patients often receive more than one of the aforementioned treatments so the totals are greater than 100%. The total Gleason scores for the prostate cancer cases were as follow: 5 (1.7%), 6 (42.4%), 7 (37.3%), 8 (8.5%), 9 (10.2%).

In univariate lab analyses, plasma IGF-1, IGFBP-3 and the IGF-1/IGFBP-3 molar ratio were not statistically significantly different between groups. Mean free testosterone and mean free PSA were statistically significant between groups. In dietary univariate analyses, carbohydrate intake was

SUMMARY (continued)

statistically significantly higher in the prostate cancer group per data collected with both FFQ and 24-hour recall methods. In 24-hour recall dietary data, fiber intake was statistically significantly higher in the case group but cholesterol was significantly higher among controls. There were no differences between groups with respect to physical activity, or hours spent sedentary.

After controlling for independent covariates (fasting status, age, current alcohol use, education, and family cancer history), there was a statistically significant and slightly negative association for IGF-1 and prostate cancer (OR=0.96, CI=0.93–0.99). The association between IGFBP-3 and prostate cancer status was in the same direction, but was not statistically significant (OR=0.55, CI=0.21–1.45). The association between the IGF molar ratio and prostate cancer was similar in magnitude and direction to IGF-1 (OR=0.90, CI=0.82–0.98). In dietary multivariable analyses, adjusted carbohydrate intake, daily calorie intake, and age remained statistically significant predictors of prostate cancer (all $p < .05$) and total adjusted dietary fiber intake was a significant protective factor ($p = .0262$), after controlling for covariates. Effect modification between IGF-1 and the total daily intakes of fiber and carbohydrates showed borderline significance, but brought the associations toward the null.

In conclusion, in this predominately African American, inner-city population at high risk for prostate cancer, there were slightly decreased odds of developing the disease with elevated levels of IGF hormones. This clinical case-control study also found that carbohydrates, fiber, total daily calories, and age are significant predictors of prostate cancer, and that diets lower on the glycemic index (GI; lower simple carbohydrate and higher fiber intake) may be protective for prostate cancer. Additional larger studies of the interactive effects of carbohydrates, dietary fiber, and IGF-1 on the development of prostate disease are warranted.

I. INTRODUCTION

A. **Problem Statement and Rationale**

Prostate cancer has the highest incidence rate among men in the developed world (Coleman et al., 2008; Jemal et al., 2010; Nelen, 2007) but despite its marked prevalence, the natural history of prostate cancer is very poorly understood (Leitzmann and Rohrmann, 2012; Patel and Klein, 2009). There are incidence trends and patterns, however, which suggest possible environmental or gene-environment interaction etiologies. An example of such a trend exists among African American men, who consistently have the highest incidence rates in the United States (SEER Database, 2013) but incidence rates of prostate cancer are lower among black men in African countries (Chu et al., 2011), suggesting nongenetic etiologies. Another example is the incidence and mortality rates among Asian Americans, especially of Chinese and Japanese ancestry, which are higher in the United States than the extremely low rates of prostate cancer seen in their countries of origin (Cook et al., 1999; Haenszel and Correa, 1975; Haenszel and Kurihara, 1968; Shimizu et al., 1991; Tominaga, 1985).

As Haenszel and Correa (1975) described in their seminal work on stomach cancer and Japanese migration to the United States, diet is a major factor in most migratory patterns of disease. Using the example of Asian Americans versus Asians from China or Japan, the diet in Asia is low in fat and cholesterol, mostly soy and plant-based carbohydrate foods. When Asians migrate to the United States, diet changes to a more Western style that is usually higher in saturated fats, calories, oils, and the incidence of certain diseases including cardiovascular disease and cancer, increases.

It has been hypothesized that there is something about the Western lifestyle and diet that is a risk factor for prostate cancer, holding age constant. High fat and caloric diets result in high levels of a hormone called IGF, more specifically, IGF-1, in the bloodstream. This hormone has been studied as a potential risk factor for prostate cancer in several studies (Allen et al., 2007; J. M. Chan,

Stampfer, et al., 1998; J. M. Chan et al., 2002; W. Chen et al., 2004; Chokkalingam et al., 2001; Finne et al., 2000; Harman et al., 2000; Janssen et al., 2004; Lacey et al., 2001; Meyer et al., 2005; Oliver et al., 2004; Platz et al., 2005; Stattin et al., 2004; Wolk et al., 1998). The proposed mechanism by which IGF-1 could lead to carcinogenesis is as follows: levels of circulating IGF-1 may be positively related to tissue bioactivity while insulin-like growth factor IGFBP-3 may be inversely related to tissue bioactivity and tissue bioactivity may be a determinant of cell turnover rate in epithelial cell populations (Cohen, 1990; Preston-Martin, 1990). In other words, the alteration in cell turnover rate influences the risk of epithelial cell carcinomas such as breast, prostate, colon, and lung. Thus, it is hypothesized that a person with high IGF-1/IGFBP-3 ratios will have a higher cancer risk because of the billions of extra cell divisions in epithelial tissue in these individuals (Cohen, 1990; Preston-Martin, 1990; Renehan et al., 2004). Cancer risk has thus been hypothesized to be higher in those with a high IGF-1 level and, conversely, lower among those with a high IGFBP-3 level (Renehan et al., 2004). The overall goal of the ProCEED program was to advance the understanding of the IGF axis and its interplay with dietary/lifestyle risk factors for prostate cancer.

B. Study Overview

The ProCEED pilot study was a case-control study that was undertaken to directly assess differences between the IGF hormones, and dietary and lifestyle risk factors between men with and without prostate cancer. Interactions between serum IGF-1 concentrations and dietary and lifestyle risk factors were also examined. A separate descriptive epidemiology assessment of prostate cancer in Illinois versus the United States was also performed.

Informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization were obtained from subjects prior to any study procedures (see Appendices A and B).

The principal investigator obtained demographic information from the subjects (see Appendix C). All subjects were asked questions regarding exercise and work and social history (see Appendices D and E). Body composition (height/weight and waist/hip measurements) was assessed and blood samples were drawn from all subjects for ascertainment of the IGF-1 and IGFBP-3 immunoassays, testosterone, and prostate specific antigen (PSA) analyses (see Appendix F). Medical records for the cases were reviewed to complete the medical history and prostate cancer history forms (see Appendix G). Two follow-up phone calls were made (by a University of Illinois at Chicago [UIC] dietitian) within seven days of the study visit. The first phone call was a 30-minute review of the Block FFQ and a ten-minute 24-hour dietary recall (see Appendix H). The second telephone interview collected a second 24-hour dietary recall. The phone calls were made by study personnel who were blinded to case-control status.

C. **Purpose of the Pilot Study**

The specific aims of the ProCEED Pilot Study were

1. to examine the epidemiology of prostate cancer in Illinois as compared to the United States, to see if prostate cancer in Illinois is representative of the US population;
2. to determine whether there are significantly different levels of IGF-1 and IGFBP-3 in blood samples from prostate cancer cases compared to controls; and
3. to assess differences between dietary and exercise intake in prostate cancer cases compared to controls and to assess interactions between these variables and the IGF-1 hormone.

D. **Significance**

Epidemiology studies have suggested an association between the IGFs and prostate cancer that is mediated through the diet. As the etiology of prostate cancer is very poorly understood and has a huge and growing burden of disease, it is important to continue to examine novel causal pathways.

This study attempted to join bodies of literature together. There exist studies showing that IGF-1 and IGFBP-3 levels are influenced by diet. There are studies showing that the IGF-1 and IGFBP-3 levels are different in prostate cancer patients than in controls. This study also assessed interactions between the dietary/lifestyle variables and the IGF axis.

II. LITERATURE REVIEW

A. **Overview and Etiology of Prostate Cancer**

Prostate cancer has the highest incidence rate among men in the developed world (Coleman et al., 2008; Jemal et al., 2010; Nelen, 2007). Though the incidence of prostate cancer is high worldwide, survival rates are very high for this cancer (Quinn and Babb, 2002). This scenario creates a large prevalence pool of men living with the disease. Prostate cancer is generally a disease of the aged (Parkin et al., 2001; Quinn and Babb, 2002) and tends to be more prevalent in developed countries where the age distribution includes more men over the age of 65. As age demographics in many developing areas continue to shift, there will be greater numbers of older men in the population and thus the prevalence of prostate cancer may continue to increase over time (CDC, 2003; Lunenfeld, 2008)

Unfortunately, the natural history of prostate cancer is very poorly understood. The only established risk factors for prostate cancer are: age and race (most notably African American) and a positive family history (Leitzmann and Rohrmann, 2012; Patel and Klein, 2009)

These and additional proposed risk factors are categorized below as either nonmodifiable or modifiable.

1. **Non-modifiable characteristics**

Age is implicated in prostate cancer because of the suspected multistep process of cancer development (Carter et al., 1990; Scher and Heller, 2000). The reason why African American men have such a high incidence of prostate cancer is unknown. Studies have repeatedly demonstrated a higher risk among this group, which suggests that genetics are a strong predisposing factor (Gronberg et al., 1997; Haas and Sakr, 1997; Makridakis et al., 2005). Family history is also a risk factor that has been shown to increase risk, but only in younger men with prostate cancer (Bratt,

2002; Carter et al., 1992; Steinberg et al., 1990). In fact, men who have a family history of prostate cancer have an earlier average diagnosis of about seven years. Additionally, high levels of testosterone (which may or may not be nonmodifiable) in the bloodstream have also been shown to have an association with prostate cancer (Hsing, 2001). Having a vasectomy was also shown to be weakly associated with prostate cancer (Chacko et al., 2002).

2. **Modifiable characteristics**

Dietary fat primarily from animal sources has been shown to have a positive association with prostate cancer (Giovannucci et al., 1993; Shirai et al., 2002; Veierod et al., 1997). Additionally, the same studies show an increase in prostate cancer among those who eat more red meat and fewer fruits and vegetables. Dairy products and calcium were also found to be associated with increased risk (J. M. Chan, Giovannucci et al., 1998; J. M. Chan et al., 2001). Lycopene from tomato products has been thought to decrease risk of prostate cancer, given that lycopene is a powerful source of antioxidants (Giovannucci et al., 2002; Wei and Giovannucci, 2012). Also, selenium has been suspected as protective, but study results have been conflicting in this area, and further studies are needed (Algotar et al., 2013; Clark et al., 1998; Stratton et al., 2010).

Overweight and obesity have not been directly related to prostate cancer (Giles et al., 2003; MacInnis et al., 2003; Rodriguez et al., 2007). Alcohol drinking has not been found to increase or decrease risk (Albertsen and Gronbaek, 2002). Smoking has been shown to shorten survival time in patients with prostate cancer, but does not appear to be independently associated with prostate cancer incidence (Oefelein and Resnick, 2004).

B. Incidence of Prostate Cancer

Using data from the Surveillance Epidemiology End Results (SEER) database (National Cancer Institute) in the United States it is possible to track trends over time in prostate cancer incidence between the years of 1975–2010.

The United States had an enormously high overall adjusted incidence rate for the year 2010, at approximately 151 per 100,000 people (SEER Database, 2013). The incidence rate trends for prostate cancer were altered with the introduction of the PSA test in 1988. Figure 1 shows that screening of PSA caused the recorded incidence of prostate cancer in the United States to double from 111.6 to 235.9 per 100,000 between 1984 and 1992 (United States Preventive Services Tasks Force, 2002). The incidence rates began to drop again in 1992 as the number of unscreened individuals was exhausted (Parkin et al., 2001). After the incidence surge subsided, rates in the United States declined and then leveled off between 1992 and 1999.

Figure 1. Age-adjusted incidence rates for prostate cancer, 1975–2010. Data drawn from SEER (2013).

Incidence rates are systematically highest at 75% of cases in men over the age of 65 (Parkin et al., 2001; Quinn and Babb, 2002). As mentioned before, the overall incidence rate (according to the SEER Database, 2013) is 151 per 100,000 in the United States. However, there is a stunning difference in incidence when rates are examined by age.

As seen in Figure 1, prostate cancer incidence rates are highest among African Americans, at 234 per 100,000 in the United States in 2010. White men were the second most commonly diagnosed at a rate of 144 per 100,000. The rates of Asian/Pacific Islanders and Hispanics are lower than those of whites and African Americans in the United States (not shown).

C. **Insulin-Like Growth Factor and Binding Protein Overview**

Somatotropin (commonly known as human growth hormone) is secreted by the pituitary gland under the influence of growth hormone releasing hormone. The main function of IGF-1 is to mediate growth hormone activity (Bayes-Genis et al., 2000; Grimberg, 2003; Sara et al., 1982; Zapf et al., 1981) and is the major member of a protein family created by the liver in response to growth hormone stimulus. Thus, IGF-1 is very important in prenatal development, growth to adulthood, and metabolism. The IGF-1 hormone is produced mainly by hepatocytes that are used in the liver for metabolism, but it is also produced by many other cells in the body, where it may act in either a paracrine or autocrine manner (Carlsson-Skwirut et al., 1989).

The interactions of IGF, IGFBP, IGFBP proteases, and IGF receptors is called the “IGF axis.” The IGF axis affects many primary physiological and pathological processes including development, growth, metabolic regulation, tumorigenesis, and angiogenesis. Insulin-like growth factor 1 is an important mitogen and regulator of the cell cycle and apoptosis (Bayes-Genis et al., 2000; Grimberg, 2003; Sara et al., 1982; Zapf et al., 1981).

Insulin-like growth factor binding protein-3, the major IGF binding protein in the plasma, plays a pivotal role in the regulation of IGF activity and availability in the circulation and extracellular environment. It has a high binding affinity to IGF-1 and IGF-2 and can inhibit IGF actions, enhance IGF actions, or function independently as cell regulatory factors. Insulin-like growth factor binding proteins act as transporters of IGF, prolonging the life of IGF in the body (Baxter, 2000; K. Chan and Spencer, 1997; Kostecka and Blahovec, 1999; Wetterau et al., 1999).

Most important to the proposed study, IGFBP-3 has IGF-independent effects on cell growth. Although IGFBP-3 is a potent inhibitor of IGF activity, it also has IGF-independent anti-proliferative effects by facilitating apoptosis.

D. **Dietary/Lifestyle Correlates**

Studies have been performed correlating diet to IGF-1 and IGFBP-3 level. Holmes et al. (2002) examined the cross-sectional association between IGF-1/IGFBP-3 levels and the dietary factors energy, macronutrients, micronutrients, and specific foods in 1,037 women aged 43–69 years old who were participating in the Nurse's Health Study Cohort. An FFQ was utilized to measure the diet. Results of this study showed that higher energy intake (kcal/day) was positively associated with higher IGF-1 across the quintile categories (p for trend=.0006) as well as higher IGFBP-3 (p for trend=.02). Higher fat intake was also associated with lower IGFBP-3 level (p for trend=.0006). This association was strongest with saturated fat (p for trend=.0005). Dietary carbohydrate, fiber and other forms of fat (besides saturated fat) were not associated with IGF-1 or IGFBP-3. Higher intake of protein was associated with higher levels of IGF-1 (p for trend=.0002). This association was limited to animal protein (p for trend=.0002) and did not apply to vegetable protein. Vitamin D was positively associated with IGF-1 level (p for trend=.0009) as well as calcium from food sources (p

for trend=.0009). Vitamin A was positively related to increased IGF-1 (p for trend=.02). Lycopene was positively associated with increased levels of IGFBP-3 (p for trend=.0003). Vitamin C was positively associated with increased IGFBP-3 (p for trend=.03). Overall, this study found that a diet high in calories and saturated fat (a “Western diet”) was more likely to have increased IGF-1 levels.

Kaklamani et al. (1999) also evaluated the association between consumption of specific food groups/macronutrients and concentrations of IGF-1 and IGFBP-3 in a cross-sectional study of 115 healthy men and women between 30 and 84 years old. In this study, morning blood samples were taken and a questionnaire was administered to collect information on smoking, age, weight, coffee intake, as well as the intake of various foods (average consumption of several food items was assessed). The study found that there was a positive zero-order partial correlation between red meat, as well as oils and fats and the amount of IGF-1 ($p < .05$ for both). There was a negative correlation between IGF-1 level and bread consumption ($p < .05$). Serum IGFBP-3 levels were not significantly correlated with any of the specific food groups in this study. Upon regression analysis, overall fat intake was positively associated with IGF-1 level, whereas carbohydrates were negatively associated (p-values varied as models controlled for different covariates). Saturated fat was found to be negatively associated with IGFBP-3 level also (p-values varied as models controlled for different covariates).

Gunnell et al. (2003) examined the relationship of diet and IGF in a nested case-control study of 344 disease-free men aged 50–70 participating in the Prostate Testing for Cancer and Treatment Cohort Study in the United Kingdom. Stored blood samples were analyzed to determine the IGF-1 and IGFBP-3 levels. Subjects filled out a 114-item FFQ and provided information on occupation, smoking, and physical activity. Height and weight were also measured. Least-squares linear regression models were constructed to assess the relationship between mean change in growth factor

values for a one-standard-deviation increase in a dietary factor. After controlling for confounders, increased IGF-1 levels were seen in men consuming higher levels of calcium (p for trend=.035). There was a weaker association with dairy products. The IGFBP-3 levels were inversely associated with saturated fat (p for trend=.10). Insulin-like growth factor 1 tended to be lower and IGFBP-3 tended to be higher in those who ate tomatoes or lycopene-containing products. Men consuming more milk had higher levels of IGF-1 (p for trend=.04). The association between milk and IGF-1 was not attenuated by adding calcium to the model. This study found that increased intake of milk, dairy products, and calcium in the diet was associated with higher IGF-1 levels. Also, a greater intake of vegetables and tomato products was associated with a lower level of IGF-1.

Since the major studies in the literature show an association between eating animal proteins and saturated fat and IGF-1 and IGFBP-3, vegetarians (those who eat no meat, but eat varying amounts of dairy products) and vegans (those who eat neither meat nor dairy nor animal products) give epidemiologists an opportunity for a natural experiment studying these growth factors.

Allen et al. (2002) published a cross-sectional study where IGF-1 was examined in 292 total women. There were 99 meat-eaters, 101 vegetarians, and 92 vegans enrolled in the study. The objective of the study was to examine the role of diet in relation to circulating IGF-1 levels. Subjects in the study completed a questionnaire collecting information on age, anthropometric measures, smoking, and other lifestyle factors as well as a detailed FFQ. A nonfasting blood sample was also collected. Associations between diet and IGF-1 were analyzed by Analysis of Variance (ANOVA). After adjusting for age, the study found statistically significant heterogeneity in the mean IGF-1 blood levels: meat eaters had 30.9 nmol/L (95% Confidence Interval [CI] 29.3–32.7), vegetarians had 31.2 nmol/L (95% CI 29.5–32.9), and vegans had 27.0 nmol/L (95% CI 25.5–28.6) with a p for heterogeneity of 0.0006. Additionally, there was statistically significant heterogeneity with respect to

the mean IGF-1/IGFBP-3 ratio ($p=.0001$). The vegan diet, rich in plant foods and no dairy or meat was determined to have the lowest level of circulating IGF-1. The authors generalized this finding to Asian countries where a plant-based diet is eaten and rates of breast cancers are markedly lower than in Western countries.

Another study by Allen et al. (2007) was performed looking at the same parameters in men. There were 226 meat-eaters, 237 vegetarians, and 233 vegans enrolled in the cross-sectional study. Again, the objective of the study was to examine the role of diet in relation to circulating IGF-1 levels. Subjects in the study completed a questionnaire that collected information on age, anthropometric, smoking, and other lifestyle factors as well as a detailed FFQ. A nonfasting blood sample was also collected. Associations between diet and IGF-1 were analyzed by ANOVA. After adjusting for age, smoking status, exercise, time since last meal at venipuncture, and time between blood draw and processing, the study found statistically significant heterogeneity in the mean IGF-1 values: meat eaters had 20.1 nmol/L (95% CI 19.3–20.8), vegetarians had 20.1 nmol/L (95% CI 19.4–20.8), and vegans had 18.5 (95% CI 17.8–19.2) with a p for heterogeneity of 0.002. The authors related the finding that there were very low IGF-1 levels in vegan men to a possible reduction in their risk of prostate cancer. The author pointed out that there have been no studies to date on the rates of prostate cancer among vegans, but there are low rates in areas of the world where a primarily plant-based diet is eaten.

Lifestyle factors besides diet have also been studied in conjunction with IGF-1 and IGFBP-3. Allen et al. (2003) published another paper with additional data collected from the cross-sectional study of 292 women (99 meat-eaters, 101 vegetarians, and 92 vegans) where IGF-1 and IGFBP-3 levels and associations with lifestyle determinants such as waist circumference, weight, body mass index (BMI), as well as smoking and physical activity variables such as leisure time, vigorous

exercise, and job activity, were analyzed. All variables were derived from a subject-administered questionnaire. Associations between lifestyle factors and IGF-1 were analyzed by ANOVA. After adjustment for age, diet group, vigorous exercise, time of day at venipuncture, time since last eaten at venipuncture, and time between venipuncture and processing, there was no statistically significant heterogeneity of the mean IGF-1 concentrations for any of the following parameters: height, weight, waist circumference, leisure time, vigorous exercise, or job activity categories. There was, however, statistically significant heterogeneity among BMI categories with respect to IGF-1 levels ($p=.009$).

Another study that examined lifestyle factors and their effects on IGF was done by Voskuil et al. (2001). This study specifically looked at sedentary lifestyle, obesity, and central body fat distribution and their relationship to IGF-1 and IGFBP-3. This was a cross-sectional study that enrolled 225 premenopausal women ages 49–57 (women were already participating in the European Prospective Investigation into Cancer cohort study in the Netherlands). Plasma concentrations of IGF-1 and IGFBP-3 were determined by serology. On the day of venipuncture, height, weight, and waist and hip circumferences were measured. Habitual physical activity was assessed using a validated self-administered questionnaire. This study found that women in the highest tertile for physical activity had the lowest IGF-1 and IGFBP-3 levels. However, these differences were not statistically significant. The paper reported that activity in the lifestyle is not independently associated with the plasma IGF system.

E. **Insulin-Like Growth Factor Physiology and Prostate Cancer Risk**

The IGFs are mitogenic and anti-apoptotic molecules involved in the regulation of cell proliferation in the renewing epithelial cells of sites including breast, lungs, prostate, and colon. Insulin-like growth factors have the special dual properties of being endocrine hormones as well as

having characteristics of tissue growth factors (Pollack, 2007). The majority of circulating IGFs are bound with high affinity to IGFBPs, with 90% bound to IGFBP-3 and a separate protein known as acid-labile subunit. Published reviews have suggested that IGF physiology has important influences on cancer biology, cancer risk, and carcinogenesis (Schott et al., 2004).

As mentioned previously, the posited mechanism by which IGF-1 could lead to carcinogenesis is as follows: levels of circulating IGF-1 may be positively related to tissue bioactivity while IGFBP-3 may be inversely related to tissue bioactivity and tissue bioactivity may be a determinant of cell turnover rate in epithelial cell populations (Cohen, 1990; Preston-Martin, 1990). In other words, the alteration in cell turnover rate influences the risk of epithelial cell carcinomas such as breast, prostate, colon, and lung. Thus, it is hypothesized that a person with high IGF-1/IGFBP-3 ratios will have a higher cancer risk because of the billions of extra cell divisions in epithelial tissue in these individuals (Cohen, 1990; Preston-Martin, 1990; Renehan et al., 2004). Cancer risk is hypothesized to be higher in those with a high IGF-1 level and, conversely, cancer risk is lower among those with high IGFBP-3 levels (Renehan et al., 2004).

Additionally, along with the increased cell turnover rate, IGF-1 has an anti-apoptotic property as well. This further influences carcinogenesis because in the multistep process of an accumulation of “hits” leading to full transformation to cancer, survival of partially transformed clone cells with one or more hits is critical for carcinogenesis to proceed. Normal cells and partially transformed cells undergo apoptosis. Since IGFs are anti-apoptotic, the survival probability of the clone cells would be higher in a scenario with a higher IGF bioactivity. This increases the pool of “target cells” available for second or subsequent hits. It has been shown in studies of colon cancer that individuals with colonic neoplasm have a higher colonic epithelial cell turnover rate than noncancer patients (De Leon et al., 1988).

There have also been studies showing correlations between IGF-1, IGFBP-3 and prostate cancer. Ngo et al. (2003) evaluated the effects IGF-1 on the growth and apoptosis of prostate cancer cells in vitro. Serum was drawn from subjects after an 11-day diet and exercise intervention of aerobic exercise of 30–60 minutes per day and consumption of a restrictive low-fat, high fiber diet. When the IGF-1 was added to the post-DE serum in vitro, the reduction in prostate cancer cell growth and the induction of apoptosis in medium containing post-DE serum alone were reversed. This study showed that IGF-1 is an important factor in the serum for prostate cancer cell growth and survival.

In one of the first epidemiological studies of IGF-1 and prostate cancer, J. M. Chan et al. (1998) conducted a nested case-control study within the Physicians' Health Study on prospectively collected plasma from 152 cases and 152 controls to investigate possible associations between plasma IGF levels and prostate cancer risk. A strong positive association was observed between IGF-1 levels and prostate cancer risk. Men in the highest quartile of IGF-1 levels had a relative risk of 4.3 (95% CI 1.8–10.6) compared with men in the lowest quartile. Additionally, there was a statistically significant trend with respect to increasing quartiles of IGF-1 and the risk of prostate cancer: Quartile 1 Relative Risk (RR)=1, Quartile 2 RR=1.32 (95% CI 0.62–2.80), Quartile 3 RR=1.81 (95% CI 0.92–3.56), and Quartile 4 RR=2.41 (95% CI 1.23–4.74), p for trend=.006.

Wolk (1998) conducted a population-based, case-control study in Sweden of 210 patients with newly diagnosed, untreated prostate cancer and 224 matched controls. The mean serum IGF-1 level for case patients (158.4 ng/mL) was significantly higher than that for control subjects (147.4 ng/mL) ($P=.02$); corresponding mean serum IGFBP-3 levels were not significantly different between case patients (2668 ng/mL) and control subjects (2518 ng/mL) ($P=.09$). They found a moderately strong and statistically significant ($P=.04$) positive association between serum levels of IGF-1 levels

and risk of prostate cancer (OR=1.51; 95% CI=1.0–2.26 per 100 ng/mL increment); the association was particularly strong for men younger than 70 years of age (OR=2.93; 95% CI=1.43–5.97). No association was found between serum IGF-1 levels and disease stage. Serum IGFBP-3 levels were not significantly associated with increased risk of disease, and adjustment for IGFBP-3 had little effect on the association between IGF-1 levels and risk of prostate cancer

Stattin et al. (2000) performed a nested case-control study of participants within the Northern Sweden Health and Disease Cohort Study. Levels of plasma IGF-1 and IGFBP-3 from 149 men who had a diagnosis of prostate cancer between one month and ten years after venipuncture, and 298 control men were assessed. Case subjects had statistically significantly higher mean levels of IGF-1 (229 ng/ml 95% CI 218–240) than control men (214 ng/ml 95% CI 208–221). Conditional logistic regression analyses showed increases in prostate cancer risk with rising levels of IGF-1 (p for trend=.02) as well as IGFBP-3 (p for trend=.03). In subjects younger than 59 years at the time of blood collection, the risk associated with increased IGF-1 level was higher (p for trend=.01), while the risk associated with increased IGFBP-3 was lower than the corresponding risks in the full cohort and were not statistically significant. The conclusion of this study was that increased levels of plasma IGF-1 was associated with prostate cancer risk, especially among men in the younger age groups. This finding suggests that circulating IGF-1 concentrations may play a role in the early pathogenesis of prostate cancer. Stattin and his team published another report to update these findings in 2004 and the results still showed increasing risk of prostate cancer with increases in the IGF-1 hormone.

Harman et al. (2000) examined prostate volume by magnetic resonance imaging and PSA, IGF-1, IGF-2, and IGFBP-3 in a nested case-control study within the Baltimore Longitudinal Study on Aging. Serum samples were obtained approximately nine years before the diagnosis of prostate

cancer in cases. There were a total of 72 cases, 127 age-matched controls, and 76 additional men (normal subjects) with measured prostate volumes and no prostate cancer included in the study. Adjusted odds ratios (ORs) for the high versus low tertile were: for IGF-1, 3.1 (95% CI=1.1–8.7); for IGFBP-3, 0.71 (95% CI=0.3–1.7); and for PSA, 12.5 (95% CI=3.8–40.9). Prostate specific antigen was directly and significantly related ($r=.461$, $p<.0001$) to prostate volume, whereas IGF-1 and IGFBP-3 were not. High levels of IGF-1 were independently associated with increased risk of prostate cancer, but PSA level is a much stronger predictor of prostate cancer than IGF-1.

Chokkalingam et al. (2001) performed a case-control study in China to see if IGF-1 and IGFBP-3 are associated with prostate cancer. This was important because China is considered a “low-risk” population for prostate cancer. Plasma levels of the growth factors were measured for 128 newly diagnosed prostate cancer patients and 306 randomly selected population controls. Relative to the lowest quartile of IGF-1 level, mean in the highest quartile had 2.6 times the risk of prostate cancer. The trend was also significant: IGF-1 Quartile 1 OR=1.0, Quartile 2 OR=1.0, Quartile 3 OR=1.39 (95% CI 0.66–2.93), and Quartile 4 OR=2.63 (95% CI 1.19–5.79), with a p for trend of 0.01. In contrast, men with the highest levels of IGFBP-3 had a 46% decreased risk of prostate cancer relative to the lowest quartile. The trend approached statistical significance: IGFBP-3 Quartile 1 OR=1.0, Quartile 2 OR=0.84 (95% CI 0.45–1.58), Quartile 3 OR=0.55 (95% CI 0.27–1.13), and Quartile 4 OR=0.54 (95% CI 0.26–1.15), with a p for trend of 0.08. The authors concluded that their results were indicative of the fact that IGF-1 and IGFBP-1 are indeed determinants of prostate cancer. Janssen et al. (2004) studied 201 matched pairs (ages 55–70) to assess prostate cancer characteristics in a population-based screening study for prostate cancer. Regression analysis showed that only PSA levels at baseline and PSA at round two after four years are good predictors of prostate cancer, whereas total IGF-I, free IGF-I, and IGFBP-3 did not predict

the development of prostate cancer. Within the subjects with prostate cancer, there were no differences of IGF-I parameters with different tumor node metastasis categories and/or Gleason scores. This study suggested that the measurement of serum IGF-I and/or IGFBP-3 concentrations in addition to PSA does not improve the identification of men at high risk to develop early stages of prostate cancer. Janssen et al. (2004) studied 201 matched pairs (ages 55–70) to assess prostate cancer characteristics in a population-based screening study for prostate cancer. Regression analysis showed that only PSA levels at baseline and PSA at round two after four years are good predictors of prostate cancer, whereas total IGF-I, free IGF-I, and IGFBP-3 did not predict the development of prostate cancer. Within the subjects with prostate cancer, there were no differences of IGF-I parameters with different tumor node metastasis categories and/or Gleason scores. This study suggested that the measurement of serum IGF-I and/or IGFBP-3 concentrations in addition to PSA does not improve the identification of men at high risk to develop early stages of prostate cancer.

Lacey et al. (2001) reported results from 30 cases of histologically confirmed incident prostate cancer diagnosed between 1976 and 1989 (mean age at diagnosis, 70.6 years; SD, 7.8 years; range, 58–86) and 60 matched male controls (2:1 ratio). Cases (mean, 119.8 ng/ml; SD, 46.0) and controls (mean, 118.4 ng/ml; SD, 42.8) had nearly identical levels of IGF-1. The IGFBP-3 levels were also similar in cases (mean, 1042.5 ng/ml) and controls (mean, 1022.6 ng/ml). The t tests for case-control differences were not statistically significant. Regardless of variable format (e.g., continuous or categorical), neither IGF-1 nor IGFBP-3 was associated with prostate cancer.

J. M. Chan et al. (2002) conducted another study to determine whether plasma levels of IGF-1 and IGFBP-3 predicted more aggressive forms of prostate cancer among 530 case patients and 534 control subjects in a nested case–control study within the Physicians' Health Study. The IGF-1 and IGFBP-3 levels were measured in plasma samples. Conditional logistic regression models were used

to estimate the RRs for prostate cancer associated with IGF-1 and IGFBP-3, stratified on grade (Gleason score of ≥ 7 versus < 7) and stage (early, stage A or B prostate cancer versus advanced, stage C or D prostate cancer). The study found that plasma levels of IGF-1 and IGFBP-3 were predictors of advanced-stage prostate cancer RR=5.1 (95% CI 2.0–13.2) for highest versus lowest quartiles of IGF-1; RR=0.2 (95% CI 0.1–0.6) for highest versus lowest quartiles of IGFBP-3. Levels of IGF-1 and IGFBP-3 were not predictors of early stage prostate cancer. Neither was differentially associated with Gleason score. Men with high IGF-1 levels and low IGFBP-3 levels had an RR for advanced-stage prostate cancer of 9.5 (95% CI 1.9–48.4) compared with men with low levels of both. The authors concluded that circulating levels of IGF-1 and IGFBP-3 may predict the risk of developing advanced-stage prostate cancer, but their utility for screening patients with incident prostate cancer may be limited.

Janssen et al. (2004) studied 201 matched pairs (ages 55–70) to assess prostate cancer characteristics in a population-based screening study for prostate cancer. Regression analysis showed that only PSA levels at baseline and PSA at round two after 4 years are good predictors of prostate cancer, whereas total IGF-I, free IGF-I, and IGFBP-3 did not predict the development of prostate cancer. Within the subjects with prostate cancer, there were no differences of IGF-I parameters with different tumor node metastasis categories and/or Gleason scores. This study suggested that the measurement of serum IGF-I and/or IGFBP-3 concentrations in addition to PSA does not improve the identification of men at high risk to develop early stages of prostate cancer.

Oliver et al. (2004) performed a population-based case-finding exercise using the PSA test to examine whether associations between the IGF axis and cancer risk were apparent in the population. A matched case-control study was conducted among 7,383 men (50–70 years) receiving a PSA test as part of a case-finding exercise. Assays of IGF-I, IGF-II, IGFBP-2, and IGFBP-3 were performed

on cases and two controls. In multivariable analyses, the risk of prostate cancer increased across quartiles of IGF-I (highest versus lowest quartile, (OR=3.00; 95% CI=1.50–6.01; p(trend) 0.005). Associations between the IGFs and cancer risk were stronger for advanced cases. Their findings suggest that both IGF-I is associated with an increased risk of screen-detected prostate cancer.

Meyer et al. (2005) assessed the association of prediagnostic plasma levels of IGF-1, IGF-2, IGFBP-2, and IGFBP-3 and subsequent occurrence of prostate cancer in a case-control study nested in the SUPplémentation en Vitamines et Minéraux Anti-oXydants trial. The study was a primary prevention trial testing a daily supplementation with low-dose antioxidant vitamins and minerals in male and female middle-aged volunteers in France. One hundred prostate cancer cases were diagnosed among 4,855 participants over a nine-year follow-up period. For each case, four age-matched controls were selected randomly. Frozen baseline plasma samples were used to measure IGF-I, IGF-II, IGFBP-2, and IGFBP-3. Conditional logistic regression was used to assess the association between these four biochemical markers and prostate cancer risk. After controlling for the intervention group in the trial and the other IGF axis variables, the ORs and 95% CI comparing the upper quartile to the baseline quartile were 1.83 (95% CI, 0.85–3.95), 1.05 (95% CI, 0.35–3.18), 0.79 (95% CI, 0.39–1.58), and 0.42 (95% CI, 0.12–1.52) for IGF-I, IGF-II, IGFBP-2, and IGFBP-3, respectively. More suggestive associations for IGF-I and IGFBP-3 were observed with advanced and aggressive cancers. These results suggest that IGF axis variables are not long-term predictors of the occurrence of prostate cancer.

Platz et al. (2005) identified 462 prostate cancer cases and controls in the Health Professionals Follow-up Study. They measured plasma concentrations of IGF-1 and IGFBP-3, and found that men with higher concentrations of IGF-1 (comparing extreme quartiles OR=1.37, 95% CI 0.92–2.03, p-trend=.05) and IGFBP-3 (OR=1.62, 95% CI 1.07–2.46, p-trend=.08) had a higher risk

of prostate cancer. After statistical adjustment, these associations were attenuated for both IGF-1 (OR=1.17, 95% CI 0.69–1.99, p-trend=.29) and IGFBP-3 (OR=1.40, 95% CI 0.80–2.44, p-trend=.56). No significant association was found for IGF-1 with regionally invasive or metastatic prostate cancer, although the number of these cases was small (n=42).

Allen et al. (2007) analyzed the association between prediagnostic serum concentrations of IGF-I and IGFBP-3 and prostate cancer risk in a case-control study nested in the European Prospective Investigation into Cancer and Nutrition. This study included 630 prostate cancer cases and 630 matched controls. There was no significant difference in the association of peptide hormones and prostate cancer by stage of disease, although the association of serum IGF-I concentration with risk was slightly stronger for advanced-stage disease, and no association for IGFBP-3 was observed.

F. **African Americans and Insulin-Like Growth Factor**

The rates of prostate cancer among African American males are the highest in the world (SEER Database, 2013). Since the rates of prostate cancer among African men in Africa are so much lower than those among African Americans (Chu et al., 2011), there are likely environmental risk factors or gene-environment interactions determining this incidence in the United States among African American men.

It is also documented that African Americans in inner cities eat significantly more fat and sodium and less fiber than their Caucasian counterparts (Airhihenbuwa et al., 1996; Robinson, 2008) due to a number of factors including the lack of availability of fresh produce in certain urban areas. Since high fat and calorie diets are related to IGF-1 and IGFBP-3 levels, and since IGF-1 and IGFBP-3 have been shown to be associated with prostate cancer in various aforementioned studies,

it is important to assess whether levels of these growth factors differ by race within the United States. This can help answer the question of whether the IGFs are part of the causal chain that leads to prostate cancer.

Platz et al. (1999) investigated whether plasma IGF-1 and IGFBP-3 levels varied by race in healthy US men who were 47–78 years old between 1993 and 1995 in a nested case-control study within the Health Professionals follow-up study. In all, there were a total of 63 African Americans, and a random sample of 75 Asians and 75 Caucasians in this study. The study found that Caucasians had the highest median levels of IGF-1 (224 ng/ml), followed by Asians (208 ng/ml) and then African Americans (205 ng/ml). Median IGFBP-3 concentration was similar between Caucasians and Asians, but was 13% lower in African Americans.

Winter et al. (2001) conducted a study to determine race and overall plasma levels of IGF-1 and IGFBP-3 in a group of men at higher risk for prostate cancer development. The cross-sectional study consisted of 105 men (63 African American and 42 Caucasian) aged 35–69 years with no personal history of prostate cancer but having a first-degree relative with the disease, unless they were African American and thus already at high risk. Nonparametric Wilcoxon Tests were used to assess the relationships between the plasma levels and the categorical covariates (e.g., race) and between the continuous variables using Spearman correlation coefficients. The mean plasma IGF-1 levels were not significantly different between African Americans (162.3 ng/ml), and Caucasians (172.1 ng/ml). However, the mean plasma level of IGFBP-3 was lower in African Americans (2789 ng/ml) than in Caucasians (3216 ng/ml) men, and this difference was statistically significant ($p=.0045$). The results of this study demonstrated a lower IGFBP-3 among African Americans than in Caucasian men. The conclusion was that this discrepancy could explain in part the increased risk of prostate cancer among African American men.

Another study by Winter's Group (Tricoli et al., 1999) evaluated the relationship between plasma levels of IGF-1, IGFBP-3 and race within a group of men aged 35–69 years old at increased risk of prostate cancer. The cross-sectional study consisted of 169 men total (85 African American, 84 Caucasian). This study also enrolled men with no history of prostate cancer but having a first-degree relative with the disease unless they were African American and thus already at high risk. Nonparametric Wilcoxon Tests were used to assess the relationships between the plasma levels and the categorical covariates (e.g., race) and between the continuous variables using Spearman correlation coefficients. The study showed that the mean plasma concentrations of IGFBP-3 were significantly lower among African Americans (2657 ng/ml) than in Caucasians (2965 ng/ml), ($p=0.0062$). The IGF-1 plasma levels correlated positively with the IGFBP-3 levels. The results of this study demonstrated that the concentrations of IGFBP-3 were associated with race among men at risk for prostate cancer.

III. RESEARCH DESIGN AND METHODS

A. Study Design

The ProCEED pilot study was a case-control study that was undertaken to directly assess differences between the IGF hormones, and dietary and lifestyle risk factors between men with and without prostate cancer. Interactions between serum IGF-1 concentrations and dietary and lifestyle risk factors were examined. A separate descriptive epidemiology assessment of prostate cancer in Illinois versus the United States was also performed.

Informed consent and HIPAA authorization were obtained from subjects prior to any study procedures (see Appendices A and B). The principal investigator obtained demographic information from the subjects (see Appendix C). All subjects were asked questions regarding exercise and work and social history (see Appendices D and E). Body composition (height/weight and waist/hip measurements) was assessed and blood samples were drawn from all subjects for ascertainment of the IGF-1 and IGFBP-3 immunoassays, testosterone, and PSA analyses (see Appendix F). Medical records for the cases were reviewed to complete the medical history and prostate cancer history forms (see Appendix G). Two follow-up phone calls were made (by a UIC dietitian) within seven days of the study visit. The first phone call was a 30-minute review of the Block FFQ and a ten-minute 24-hour dietary recall (see Appendix H). The second telephone interview collected a second 24-hour dietary recall. The phone calls were made by study personnel who were blinded to case-control status.

B. Study Population

Identification of study subjects was done as follows. At JBVAMC, identification of study subjects was done by reviewing the charts of patients coming into the general urology clinic each

day. Identified patients were approached by the attending physician or clinical pharmacist on duty, and, if the patient was interested in participating, the study visit was conducted that day.

1. **Cases**

All cases were selected from among prostate cancer patients at the JBVAMC.

Selection criteria for the cases are listed below:

- Resident of Illinois for at least five years
- Diagnosis of biopsy-proven prostate adenocarcinoma
- No medical history of stroke, dementia, or Alzheimer's disease
- African American or Caucasian race
- Aged 50 or older

2. **Controls**

Controls were also selected from the General Urology clinic at JBVAMC. Specific control selection criteria are listed below:

- Resident of Illinois for at least five years
- Male sex
- No history of prostate adenocarcinoma
- Two normal PSA tests (at least one within the past year)
- No benign prostate hyperplasia or other prostate-related abnormality
- Normal digital rectal exam at the clinic during the enrollment visit
- No medical history of stroke, dementia, or Alzheimer's disease
- African American or Caucasian race (non-Hispanic)
- Aged 50 or older

C. **Procedures**

1. **Study visit**

Subjects were paid \$20.00 for their participation. The study visit was approximately 40 minutes, and consisted of the following (see Appendices A–H):

- Informed consent
- Waist/Hip Circumference and height/weight measurements
- Serum samples
- Demographic interview
- Work and Social History Questionnaire
- IPAQ

A UIC dietitian made two follow-up telephone calls to the subjects within seven days of the study visit. The first phone call was a 30-minute review of the Block Brief FFQ and a ten-minute 24-hour dietary recall (see Appendix H). The second telephone interview collected a second 24-hour dietary recall. The telephone calls were made by dietitians who were blinded to case-control status.

2. **Medical records review**

Medical records were reviewed to complete the medical history forms. Additionally, for prostate cancer cases, the study personnel recorded the following clinical information: PSA levels, prostate biopsy/results clinical tumor lymph node metastasis (TNM) staging of prostate cancer (where available), surgery and treatment for prostate cancer.

3. **Handling, storage, and analysis of blood samples**

All blood samples were centrifuged and the plasma portion was immediately frozen after the draw. The samples were drawn and immediately stored at JBVAMC in a -70°C freezer until the end of the study. Blood samples were stored in the freezer with study ID numbers as the

only identifiers. Quest Diagnostics batch-processed the samples for the protocol-specified assays at the end of the study. Hard-copy lab reports were shipped from Quest Diagnostics to the principal investigator for data entry.

4. **Adverse events**

Any adverse event (AE) resulting from the blood sampling procedure was to be reported within 24 hours and recorded in the patient study data forms and will be presented as part of the annual report to the Internal Review Board (IRB). Information that will be collected is as follows: AE name, AE date, AE time, the relatedness of AE to blood draw, any medical attention sought for AE, any necessary follow-up for the AE, and the resolution of AE. No AEs were reported during the study.

D. **Study Endpoints and Hypotheses**

The specific aims and hypotheses of this study are shown in Table I.

E. **Data Management**

Each subject enrolled in the study had a folder of pre-prepared case report forms on which data were recorded. All data were manually entered into an excel database by the principal investigator. Source data for the ProCEED Pilot Study came from the following sources: patient interviews, study personnel reports (from the study visit), follow-up phone calls, laboratory assay reports, and patient medical charts.

The demographics information was collected via an interview with the subject, and by reviewing medical records. Data fields include: primary medical doctor, date of study visit, date of

informed consent, date of HIPAA form, date of birth, ethnicity, primary language, English spoken, primary insurance type, and whether subject had been in a clinical trial within the past year.

TABLE I
SPECIFIC AIMS AND HYPOTHESES

Specific aim	Hypothesis
1. To examine the epidemiology of prostate cancer in Illinois as compared with that of the United States.	1. Illinois will be similar to the United States with respect to prostate-cancer incidence due to a similar population make-up.
2. To determine whether there are significantly different levels of IGF-1 and/or IGFBP-3 in prostate cancer cases compared to controls.	2. Prostate cancer cases would have significantly higher levels of IGF-1 than controls. Cases would have significantly lower levels of IGFBP-3 than controls.
3. To assess differences between dietary and exercise intake in prostate cancer cases compared to controls, and to assess interactions between these variables and the IGF-1 hormone	3. Differences in prostate cancer risk are attributed, in part, to interactions between lifestyle factors and the IGF axis. Certain foods (e.g., dairy and saturated fat) will track with levels of IGF-1 and IGFBP-3.

The majority of the information for the medical history form was obtained from medical records review, but family cancer history was obtained by asking the subject directly. Data fields included check boxes for major disease classifications in each body system with onset date; resolution and comments; medications in the past 30 days; surgery/hospitalization in the patient's lifetime; vasectomy status; PSA within the previous two years; prostate biopsy/results clinical TNM staging of prostate cancer (where available); and surgery and treatment for prostate cancer

Data for the Study Visit and Adverse Event form was recorded when the subject was in the clinic. Data fields included hip/waist circumference; height/weight; date and time of blood draw; time subject woke up that morning; phlebotomist's name and signature; comments about blood

draw; AE name, AE date, AE time, relatedness of AE to blood draw, medical attention sought for AE, follow-up if necessary for AE, and resolution of AE.

The Block Brief FFQ and the 24-hour dietary recall information were both collected via a telephone interview conducted by a licensed dietitian who was blinded to the case/control status of the subjects.

Work and Social History form was self-administered by the subjects. Data fields included work status, hours per week worked, job title, business/industry type, current relationship type, smoking history, and education completed.

The IPAQ form collected information on the subjects' physical activity levels, and was administered during the study visit.

Assay reports from the central laboratory were sent to the principal investigator by Quest Diagnostics and were filed in each subject's study binder.

F. **Statistical Analysis**

Univariate analyses for demographic/social characteristics, clinical characteristics, lab values, dietary data, and exercise data were performed by cases versus controls. Values are presented as means and standard deviations for the continuous variables and as frequencies and percentages for the categorical variables. Probability values for the differences in all case/control comparisons were derived using t tests for continuous variables and chi-square tests for proportions, as applicable. Clinical prostate cancer characteristics for the cases were described without a comparison, as means and standard deviations or as frequencies and percentages, where appropriate.

The specific aims of this study as delineated in Table I will be analyzed as described in the following sections.

1. **Specific aim 1**

The first objective of this project was to perform a descriptive epidemiology study to examine Illinois and US prostate cancer incidence trends for the years 1986–2000, by race, to ascertain whether the trends over time by race are similar between the Illinois and US populations.

Illinois prostate cancer incidence rates over time for African Americans and Caucasians for the years 1986–2000 were derived from the Illinois State Cancer Registry (Illinois Department of Public Health [IDPH], 2005; Qaio, 2005). The US 1986–2000 incidence rates over time were derived from the SEER registry (SEER Database, 2013). Incidence rates were calculated by year, race, and region, adjusted by age.

To ascertain differences in prostate cancer incidence rates by race between Illinois and the United States, rate ratios (RRs for Illinois/the United States) were estimated. This measure enables the direct comparison of rates between the two regions. Risk Ratios were calculated by dividing rates for Illinois by rates from the United States for each time period of interest, by race. The RRs were estimated for three time periods that reflect the prevalence of PSA test use for the screening of prostate cancer: 1986–1990 (“pre-PSA phase,” before PSA screening was routinely used), 1991–1995 (the “PSA uptake phase”) and 1996–2000 (after “PSA widespread use”).

2. **Specific aim 2**

The second aim of this study was to determine whether there are significantly different levels of IGF-1 and/or IGFBP-3 in prostate cancer cases compared to controls. To test this, logistic regression was performed with the outcome variable being dichotomous prostate cancer status (0=control, 1=prostate cancer), and the main independent variable was continuous serum levels of IGF-1 (and IGFBP-3, in the second modeling process). Values for the IGF-1 and IGFBP3

variables were log transformed in initial analyses, but doing so did not meaningfully change the results/distribution, as the original values were approximately normally distributed.

The regression modeling of prostate cancer status and IGF-1 and IGFBP-3 were performed utilizing SAS PROC logistic, controlling for independent covariates that were statistically significant in the univariate analyses. Variable inclusion was informed by assessing potential confounders in the univariate analyses (demographic/social characteristics, clinical characteristics, labs, diet, and exercise variables), and goodness-of-fit was assessed at each step using the maximum log likelihood method.

3. **Specific aim 3**

The final objective of this study was to assess differences between prostate cancer cases and controls with respect to dietary intake and exercise, and to assess potential interactions between these variables and the IGF-1 hormone. Dietary intake was measured using a 24-hour recall and also the Block Brief 2000 FFQ. Exercise level was measured using the IPAQ. Values for Block Brief 2000 FFQ, 24-hour recalls, IGF-1, and IPAQ variables were log transformed in initial analyses, but doing so did not meaningfully change the results/distribution, as the original values were approximately normally distributed. Thus, the original, nontransformed lab values were utilized in the final statistical analyses. Also, due to the small sample size, all were analyzed as continuous variables.

Dietary data were adjusted using the residual energy method (Brown et al., 1994; Willett et al., 1997), which enables a measure of nutrient intake that is independent of the effect of total calorie intake. This is helpful in removing bias, especially if total calorie intake is associated with disease. The first step consists of creating residuals from a regression model with total caloric intake as the independent variable and absolute nutrient intake as the dependent variable:

Step one model: Absolute nutrient intake= b_1 total calorie intake

The model in step one produces the nutrient residuals, which represent the difference between the actual observed value of the nutrient and the value predicted by the regression equation. The residual variance measures the amount by which the actual values of the nutrient differ from the predicted values.

In step two, the residuals of the nutrient are used in the multivariate disease risk model in place of the absolute nutrient values that were collected. This gives an estimate of the nutrient value controlling for total calorie intake:

Step two model: Disease= b_1 nutrient residual

The residuals are by definition a measure of nutrient intake uncorrelated with total energy intake, so it is necessary to also control for total calories separately in the full multivariate model.

Univariate comparisons between groups for the dietary data collected with the FFQ and the 24-hour recall method, were performed using the residual energy adjustment method, and ORs and p-values for the univariate comparisons were generated using logistic regression, controlling only for daily calorie intake.

Pearson correlation coefficients and p-values were run to assess similarity in measurement between the two dietary collection methods: FFQ and 24-hour recall for the main nutrients. Since there was statistically significant positive correlation between the methods ranging between 29%–46% (depending on the dietary parameter), multivariable analysis was conducted for the FFQ data only. Prior to model building, Pearson correlation coefficients were also run between carbohydrate intake and fiber for the FFQ data. These two were not statistically significantly correlated, so both were used as independent variables in the statistical model.

A multivariate logistic regression model was constructed to assess simultaneously the effects of diet, physical activity, and the IGF-1 hormone on the odds of prostate cancer. Interaction terms were tested to assess potential effect modification between IGF-1 and the dietary variables in predicting prostate cancer. Goodness-of-fit was determined by -2 log likelihood methods.

G. **Sample Size and Power Calculation**

At the outset of the study, calculations were performed to determine how much power this pilot study will have to detect a difference in IGF-1 levels between cases and controls. Based on the available literature, it was considered to be the goal of the study to obtain the “gold standard” enrollment numbers (218 cases and 110 controls), as shown in Table II. However, after nearly three years of study enrollment there were not enough suitable participants found. Since the study was underpowered, it was thus a committee decision to make this into a pilot study.

TABLE II

POWER TABLE / SAMPLE SIZE

Odds ratio	Cases	Controls
1.75	218	110
2.00	140	71
3.00 ^a	69	35

Note. Power=70%^a; alpha=10% (this is because it is a pilot study); exposure in controls=25%; ratio of cases: controls 2:1

^a Alpha of 0.05 for 3.00 OR would require 88 cases and 45 controls

IV. RESULTS—SPECIFIC AIM #1:
RACIAL TRENDS IN PROSTATE CANCER INCIDENCE RATES FOR ILLINOIS AND
THE UNITED STATES: 1986–2000

A. **Introduction**

Adenocarcinoma of the prostate is the most common cancer among men in the United States, and the third most common cancer among men globally (Jemal et al., 2010; Parkin et al., 2001; Quinn and Babb, 2002). Incidence rates in the United States and globally are systematically highest (75% of cases) in men over the age of 65 (Parkin et al., 2001; Quinn and Babb, 2002) and thus prostate cancer is more prevalent in areas where the age distribution includes greater numbers of men over the age of 65, such as the United States and other developed countries. During the years of 1992–1999 the United States had an extremely high overall incidence rate at 165.5 cases per 100,000 persons (SEER Database, 2013) and prostate cancer has been reported to account for 33% of all cancer diagnoses among men in the United States (Jemal et al., 2010). Additionally, enormous racial disparities exist with respect to this disease. Incidence rates in the year 2000 were highest among African Americans, at 257.3 per 100,000, and Caucasian men were the second most commonly diagnosed at a rate of 158.7 per 100,000 (SEER Database, 2013).

The incidence rate trends for prostate cancer in the United States were altered with the introduction of the PSA test in 1986 (United States Preventive Services Tasks Force, 2002). The recorded incidence of prostate cancer in the United States doubled between the years of 1984 (111.6 per 100,000) and 1992 (235.9 per 100,000). The incidence rates are thought to have declined again in 1992 as the number of unscreened individuals was exhausted (Parkin et al., 2001). After the surge in incidence subsided (between 1992 and 1999), rates in the United States declined and then leveled off.

Compared to other state and central cancer registries across the United States, Illinois has been previously reported to have lower prostate cancer incidence rates (Dolecek, Shen, and Snodgrass, 2001; Howe, 1995; McWhorter, 1993). Whether this is due to screening, case ascertainment, or differential risk factor profiles is currently not known. In the 2001 report on the status of cancer in Illinois, prostate cancer was noted as having the highest age-adjusted incidence rates among Illinois males for the years 1994–1998. Rates were 129.4/100,000 overall, 119.1/100,000 for whites and 60% higher for African Americans, at a rate of 198.7/100,000 (Dolecek, Shen, and Snodgrass, 2001).

The objective of this descriptive study was to further examine Illinois and US prostate cancer incidence trends for the years 1986–2000 by race to ascertain whether the trends over time by race are similar between the Illinois and US populations.

B. **Methods**

Illinois prostate cancer incidence rates over time for African Americans and Caucasians for the years 1986–2000 were derived from the Illinois State Cancer Registry (IDPH, 2005; Qaio, 2005). The Illinois State Cancer Registry has been collecting cancer data from various sites across the state each year since 1986 and has received gold certification for each year of data collected since 1996 from the North American Association of Central Cancer Registries (2005) and the IDPH (2005), reflecting both completeness of the registry and death certificate clearance. This is the highest rating granted by the association, which began certifying registries for data collected in the year 1995. The US 1986–2000 incidence rates over time were derived from the SEER registry (SEER Database, 2013). Incidence rates are presented in Figure 2 by year, race, and region, adjusted by age.

To ascertain differences in prostate cancer incidence rates by race between Illinois and the United States, rate ratios (RRs for Illinois/the United States) were estimated. This measure enables the direct comparison of rates between the two regions. Risk Ratios were calculated by dividing rates for Illinois by rates from the United States for each time period of interest, by race. The RRs were estimated for three time periods that reflect the prevalence of PSA test use for the screening of prostate cancer: 1986–1990 (“pre-PSA phase,” before PSA screening was routinely used), 1991–1995 (the “PSA uptake phase”) and 1996–2000 (after “PSA widespread use”). The 95% CIs for the RRs were calculated using PEPI version 4.0 (Abrahmson, 2002).

C. **Results**

Figure 2 illustrates the prostate cancer incidence pattern expected in the United States based on previous reports. In the pre-PSA period (1986–1990), trends by race in prostate cancer incidence rates were similar for both the United States and Illinois, although lower rates were apparent in Illinois. Table III shows that RRs for prostate cancer in Illinois compared with the US population were significantly lower at 0.78 (95% CI 0.60–0.99) for Caucasians and 0.76 (95% CI 0.62–0.95) for African-Americans.

Figure 2 shows that during the PSA-uptake period (1991–1995), prostate cancer incidence rates increased for all groups. Caucasians in the United States and Illinois both experienced incidence peaks in 1992. African Americans experienced later incidence peaks in both the United States (1993) and in Illinois (1994). Incidence rates among Illinois and US Caucasians decreased similarly between the years 1992 and 1995. African Americans from the United States followed the pattern of the Caucasian groups, but the decrease had a later onset, from 1993 to 1995. Illinois

African Americans demonstrated a unique trend to the other three groups, with an increase that leveled off late in this period.

Table III shows that RRs for the PSA-uptake period demonstrate lower incidence in Illinois than the United States, by race: 0.82 for Caucasians (95% CI 0.67–1.01) and 0.75 for African Americans (95% CI 0.63–0.89). The RR for prostate cancer among African Americans in Illinois relative to the United States remained statistically significantly lower during this period.

Figure 2. Prostate cancer incidence rates by race for United States and the State of Illinois, 1986–2000.

By 1997, prostate cancer rates in the PSA-widespread use phase (1996–2000) were relatively stable among all groups with the exception of the Illinois African Americans, whose rates have continued to decline through 1999, per Figure 2. Comparing the rates between the United States and

Illinois, the rate ratios for African Americans and for Caucasians were 0.81 (95% CI 0.68–0.97) and 0.86 (95% CI 0.69–1.07), respectively, during this period. The RRs for both Caucasians and African Americans increased, indicating less of a difference between Illinois and US incidence rates. However, the RR for African Americans still demonstrate significantly lower incidence in Illinois as compared to the United States during this period.

D. **Discussion**

The objective of this descriptive study was to examine Illinois and US prostate cancer incidence trends for the years 1986–2000, to ascertain whether the trends were similar in these two populations, by race. Prostate cancer incidence trends in the United States between 1986 and 2000 can be classified into three distinct phases in the United States: Pre-PSA from 1986–1990, PSA-“uptake” from 1991–1995 and PSA-widespread use from 1996–2000. Illinois prostate cancer rates also mirrored these three distinct incidence phases. The RRs for all three phases reflect lower rates of prostate cancer in Illinois in both race groups, agreeing with published data on Illinois prostate cancer incidence (Dolecek, Shen, and Snodgrass, 2001; Howe, 1995; McWhorter, 1993).

The trends in incidence rates over time were similar among US and Illinois Caucasians. Additionally, the rate difference between the two Caucasian groups is shrinking, as evidenced by RRs becoming closer to 1.0 and narrowing trends in incidence rates. African Americans in the United States, while demonstrating much higher incidence rates than Caucasians, followed the similar, expected incidence patterns over time. Illinois African Americans however, demonstrated a unique incidence pattern from the other three groups with rates continuing to decline in the most recent time period. This decline represents a decrease in disparities, as evidenced by lower rates among African Americans in Illinois compared to other parts of the country.

In this study, we found decreases in health disparities in the state of Illinois that were not seen in the United States. The recent prostate cancer incidence pattern in Illinois was unique with the rates in African Americans declining into the most recent period and the racial disparities narrowing.

TABLE III

PROSTATE CANCER INCIDENCE MEASURES FOR ILLINOIS AND THE UNITED STATES: PRE-PSA (1986–1990), PSA-UPTAKE (1991–1995) AND PSA-WIDESPREAD USE (1996–2000) PERIODS

	Caucasian	African American	IL Caucasian	IL African American	US Caucasian	US African American
	Incidence Rates per					
Years	RR (CI) ^a	RR (CI) ^a	100,000 (CI) ^b	100,000 (CI) ^b	100,000 (CI) ^c	100,000 (CI) ^c
1986–1990	0.78 (0.60–.99)	0.76 (0.62–0.95)	110 (108–112)	148 (142–153)	142 (141–144)	193 (187–198)
1991–1995	0.82 (0.67–1.01)	0.75 (0.63–0.89)	163 (161–165)	231 (225–238)	198 (197–199)	308 (302–315)
1996–2000	0.86 (0.69–1.07)	0.81 (0.68–0.97)	145 (144–147)	227 (221–233)	169 (168–170)	280 (275–285)

^a Sources: IDPH, Illinois State Cancer Registry, SEER, National Cancer Institute

^b Source: IDPH, Illinois State Cancer Registry, Incidence rates are adjusted for age

^c Source: SEER, National Cancer Institute, Incidence rates are adjusted for age

This suggests that more effective prostate cancer screening is taking place in Illinois African American populations than US African American populations. Unfortunately, data on PSA screening was not collected by the Behavioral Risk Factor Surveillance System during the years under study. Whether the differences between African Americans and Caucasians in Illinois were because of screening, case ascertainment or other risk factors requires further elucidation.

V. RESULTS—SPECIFIC AIM #2:

INSULIN-LIKE GROWTH FACTOR HORMONES AND PROSTATE CANCER IN AN INNER-CITY VETERANS ADMINISTRATION POPULATION: RESULTS FROM THE PROSTATE CANCER STUDY OF ETHNICITY, EXERCISE AND DIET PILOT STUDY

A. Introduction and Objective

Prostate cancer has the highest incidence of all noncutaneous cancers among men in the United States, and worldwide (Coleman et al., 2008; Nelen, 2007). In 2012, it is estimated to account for approximately 241,740 incident cancer diagnoses and nearly 30,000 deaths in the United States (SEER Stat Fact Sheets, 2012). Yet despite its marked prevalence, the only risk factors that have been firmly established are age, race, and a positive family history of prostate cancer (Leitzmann and Rohrmann, 2012; Patel and Klein, 2009). Insulin-like growth factors have been known to have an effect on cell proliferation, differentiation, and apoptosis (Jones and Clemmons, 1995; Monti et al., 2007; Pollack, 2007). Because of these properties, several studies have been undertaken to assess IGFs (particularly IGF-1 and its main binding protein: IGFBP-3) as potential risk factors of prostate cancer. Most of the existing studies examining this potential association have been nested case-control studies within a larger epidemiology cohort study or an existing clinical trial (Allen et al., 2007; J. M. Chan, Stampfer, et al., 1998; J. M. Chan et al., 2002; C. Chen et al., 2005; Harman et al., 2000; Janssen et al., 2004; Lacey et al., 2001; Meyer et al., 2005; Oliver et al., 2004; Platz et al., 2005; Stattin et al., 2000; Stattin et al., 2004; Wolk et al., 1998). There has been much variability between studies of the IGFs and prostate cancer with respect to the subject population and methodology, and thus the direction, consistency, and magnitude of the results.

The ProCEED study was a case-control pilot project that was designed specifically to examine whether serum concentrations of IGF-1 and IGFBP-3 and lifestyle risk factors were different in prostate cancer patients versus control patients in a predominately African American Veteran's Administration (VA) urology clinic. This report will describe the analyses for the laboratory assays (comparisons of IGF hormone levels between groups).

B. **Materials and Methods**

Data on demographics, social history, medical history, prostate cancer clinical characteristics (for cases), dietary and exercise intake, and a blood sample for ascertainment of serum IGF-1 and IGFBP-3 levels were collected during the study for each participant.

1. **Subjects**

Between 2006 and 2009, men were recruited from a general urology clinic at the JBVAMC. To be eligible for the study, all subjects were required to be a resident of Illinois; have no medical history of stroke, dementia, or Alzheimer's; be aged 50 or older; and be either African American or Caucasian. Prostate cancer cases were required to have a diagnosis of biopsy-proven prostate adenocarcinoma (any stage). Noncancer controls were required to have no history of prostate cancer or benign prostate hypertrophy (BPH), have two normal PSA tests (at least one within one year of study enrollment), and have a normal digital rectal exam at the study visit. The recruitment process was such that the urologist or clinical pharmacist on duty invited any of their eligible patients to participate in the study. Study procedures were explained to all eligible participants, who were asked to provide written informed consent. The human subjects review board at JBVAMC and the Office of the Protection of Research Subjects (OPRS) at the UIC approved the study. Subjects who consented to participate were reimbursed \$20 for their participation in the study.

Prostate cancer cases enrolled in the ProCEED study had been seen in the JBVMAC General Urology clinic for the following treatments: hormone therapy (37%), watchful waiting (27%), radical prostatectomy (37%), radiation (22%), and brachytherapy (2%). Patients often receive more than one of the aforementioned prostate cancer treatments, hence the total is greater than 100%. The total Gleason scores for the prostate cancer cases were distributed as follows: 5 (1.7%), 6 (42.4%), 7 (37.3%), 8 (8.5%), 9 (10.2%).

2. **Data collection**

Data for the ProCEED Pilot Study came from the following sources: patient interviews, clinical progress notes, laboratory assay reports, and patient medical charts. The demographics, work history, social history, exercise, and family cancer history information were collected via personal interview in the clinic between the principal investigator and the subject. The medical history and medication use data were collected by review of medical records and progress notes. Two follow-up phone calls, performed by a registered dietitian, collected information on acute and chronic dietary intake.

3. **Venipuncture/laboratory values**

Blood was drawn from each subject during the study visit for determination of serum IGF-1, IGFBP-3, free PSA, and free testosterone. The blood draws were all done in the morning. In the original protocol, participants were required to be fasting. However, enrollment was very difficult since very few participants came to the clinic in a fasted state. Thus the protocol was amended to simply collect information from the patients about their morning food and beverage intake, and control for this variable in the analysis. Information on food and beverage intake was then coded as follows: 0=fasted, 1=nonfasted-coffee only, 2=nonfasted-breakfast eaten.

Blood samples were centrifuged immediately after the study visits and stored as serum in a freezer at -70°C . Serum samples were transferred on dry ice at the end of the study to the laboratory for processing. Plasma levels of IGF-1 and IGFBP-3 were quantified by direct radioimmunoassay (RIA) at Quest Diagnostics at the Nichols Institute (San Juan Capistrano, California). All samples (cases and controls) were analyzed in a single batch, meaning that kits with identical lot numbers were used. The assays were all performed by the same individual, who was blinded to the case/control status of the participants. The intra-assay coefficients of variation for the RIA assay have been reported to range from 9.5 to 13.8%, where greater than 15% is considered to be acceptable (Carmina et al., 1999; W. Chen et al., 2004; Kurek et al., 2000). Free testosterone and free PSA were both processed at the Quest Diagnostics clinical laboratory in Wood Dale, Illinois. Assay reports from Quest Diagnostics laboratory were then sent to the principal investigator for entry into the study database.

4. **Statistical analysis**

The main objective of the ProCEED study was to compare IGF-1 levels between cases and controls, and to ascertain whether there was a statistically significant association between serum IGF-1 and prostate cancer disease status. The hypothesis was that there would be a positive association between IGF-1 and prostate cancer.

Data generated from the assays for IGF-1 and IGFBP3 were reported from Quest Diagnostics in ng/mL. Values for IGF-1, IGFBP-3, and the IGF molar ratio were all log transformed in the initial analyses, but doing so did not change the results/distribution, as the original values were approximately normally distributed. Thus, the original, nontransformed lab values were utilized in the final statistical analyses. Following Carmina et al. (1995), the IGF-1/IGFBP-3 molar ratio was calculated as

$$(0.13 \times \text{IGF-1}) \div (0.025 \times \text{IGFBP-3}).$$

This ratio has been proposed to reflect tissue bioavailability of IGF-1. Due to the small sample size, the IGF-1 and IGFBP3 hormones were examined as continuous variables.

Univariate analyses of sociodemographic characteristics, medical history, cancer family history, laboratory values, dietary intake, and exercise data were conducted by cases versus controls using t tests (sd) for continuous variables and χ^2 tests for categorical variables.

Multivariable logistic regression modeling was informed by the univariate analyses whereby statistically significant confounders ($p < .05$) were carried forward as covariates one-by-one into the regression models. However, some of the variables that were found to be significant in univariate analyses, but introduced collinearity into the regression models, were dropped from the final models. The variables that were dropped for this reason were work status, the other lab hormone levels (PSA and testosterone), medical conditions that arose likely as secondary to prostate cancer treatment (erectile dysfunction and overactive bladder), and family overall cancer history. When the fasting status variable was tested against the IGF-1 and IGFBP-3 variables it was not statistically significantly correlated with IGF hormones, but it was still controlled for in multivariable analyses. All models were based on logistic regression methods using prostate cancer status as the dependent variable. The best-fitting model was ascertained by using the likelihood ratio chi-square test. All data were analyzed with SAS version 9.2.

C. **Results**

As displayed in Table IV, a total of 84 subjects were enrolled in the study: 59 prostate cancer cases and 25 noncancer controls. Racial makeup was proportional between groups, with African Americans predominant in both groups (83% cases versus 84% of controls), but cases were

statistically significantly older than controls (70.6 versus 63.2 years old, $p=.002$). The BMI and waist circumference were comparable between groups. Significantly more cases than controls reported that they were “not working” at the time of the study (84.8% versus 62.5% $p=.0053$), but this was likely due to the fact that the cases were also older. Controls were more likely to smoke than cases, and cases were statistically significantly more likely to currently drink alcohol at the time of the interview visit than controls (64.4% versus 8.3%, $p<.0001$). Cases were less likely to have graduated from high school than controls (37.3% cases with less than a high school education versus 13.0% of controls, $p=.0232$).

Table V shows that the univariate laboratory data comparisons for plasma IGF-1, IGFBP-3, and the IGF-1/IGFBP-3 molar ratio were not statistically significant between groups. The mean level of IGF-1 was lower than that of the noncancer controls (153.2 ng/mL versus 166.4 ng/mL). The IGFBP-3 univariate analyses showed nearly identical means between groups (2.9 ng/mL versus 3.0 ng/mL). Mean free testosterone and mean free PSA were statistically significantly different between groups, but these results were attributed to the prostate cancer disease status.

Tables VI through VIII display the multivariable analyses for the associations of prostate cancer and IGF-1, IGFBP-3, and the IGF molar ratio, respectively. After controlling for fasting status and the variables that were found to be possible confounders in the univariate analyses (age, current alcohol use, education, and family cancer history), there were negative associations for IGF-1 and prostate cancer (OR 0.96, C.I. 0.93–0.99), and for the IGF molar ratio and prostate cancer (OR 0.90, C.I. 0.82–0.98), which were both statistically significant. The association between IGFBP-3 and prostate cancer status was also negative, but was not found to be statistically significant (OR 0.55, C.I. 0.21–1.45).

TABLE IV
PATIENT SOCIODEMOGRAPHIC CHARACTERISTICS
BY PROSTATE CANCER STATUS

Variable	Cases (n=59)	Controls (n=25)	p value
Age (mean, sd)	70.6 (14.4)	63.2 (6.5)	0.0020 ^a
Race (<i>n</i> , %)			0.9155 ^b
African American	49 (83.1)	21 (84.0)	
White	10 (16.9)	4 (16.0)	
BMI (mean, sd)	30.9 (7.7)	29.8 (6.1)	0.2422 ^a
Waist circumference (mean, sd)	109.3 (10.8)	107.3 (11.0)	0.5316 ^a
Work status			
Not working	50 (84.8)	15 (62.5)	0.0053 ^b
Part time	6 (10.2)	2 (8.3)	
Full time	3 (5.1)	7 (29.2)	
Smoking status			
Smokes currently	17 (28.8)	9 (37.5)	0.2081 ^b
Never smoked	9 (15.3)	6 (25.0)	
Used to smoke / Quit	33 (55.9)	9 (37.5)	
Alcohol status			
Drinks alcohol currently	38 (64.4)	2 (8.3)	<.0001 ^b
Never drank alcohol	3 (5.1)	10 (41.7)	
Used to drink alcohol / quit	18 (30.5)	12 (50.0)	
Education level			0.0232 ^b
Did not graduate HS	22 (37.3)	3 (13.0)	
High school graduate	15 (25.4)	6 (26.1)	
Any college	22 (37.3)	14 (60.9)	
Family HX of cancer	31 (52.5)	7 (29.2)	0.0541 ^b
Family HX of prostate cancer	15 (25.4)	2 (8.3)	0.0821 ^b

^a t test

^b Cochran Mantel-Haenzel test

TABLE V
LABORATORY DATA

Variable	Cases (n=59) (mean, sd)	Controls (n=25) (mean, sd)	t test p value
IGF-1 (ng/mL)	153.2 (50.7)	166.4 (48.3)	.2793
IGFBP-3 (ng/mL)	2900 (915.8)	3000 (725.1)	.745
IGF-1 / IGFBP-3 molar ratio	0.28 (0.09)	0.31 (0.10)	.8292
Free testosterone (ng/mL)	35.5 (48.3)	52.8 (24.6)	.0001
Free PSA (ng/mL)	1.12 (1.86)	0.5 (1.15)	.0319

Note. The N varied for the laboratory testing: IGF-1 test had 58 cases / 24 controls, IGFBP-3 had 59 cases / 25 controls, Free testosterone had 57 cases/ 24 controls, and Free PSA had 33 cases / 24 controls.

TABLE VI
ASSOCIATION OF IGF-1 AND PROSTATE CANCER

Variable	Point estimate	p value	OR (C.I.) for the association of IGF-1 and prostate cancer ^a
IGF-1	-0.042	0.013	0.96 (0.93–0.99)
Age	0.059	0.158	
Alcohol use	-1.68	0.258	
Education	0.228	0.639	
Family cancer history	2.373	0.025	
Fasting status	-0.118	0.687	

^a Controlling for covariates

TABLE VII
ASSOCIATION OF IGFBP3 AND PROSTATE CANCER

Variable	Point estimate	p value	OR (C.I.) for the association of IGFBP-3 and prostate cancer ^a
IGFBP-3	−0.599	0.226	0.55 (0.21–1.45)
Age	0.016	0.575	
Alcohol use	−0.875	0.261	
Education	−0.398	0.246	
Family cancer history	1.426	0.081	
Fasting status	−0.059	0.827	

^a Controlling for covariates

TABLE VIII
ASSOCIATION OF IGF MOLAR RATIO AND PROSTATE CANCER

Variable	Point estimate	p value	OR (C.I.) for the association of IGF ratio and prostate cancer ^a
IGF molar ratio	−0.103	0.025	0.90 (0.82–0.99)
Age	1.05	0.132	
Alcohol use	0.267	0.13	
Education	1.019	0.962	
Family cancer history	7.511	0.047	
Fasting status	0.952	0.854	

^a Controlling for covariates

D. **Discussion**

Despite the large and growing burden of prostate cancer globally, its causes are still poorly understood, and thus it remains important to continue to elucidate risk factors for the disease. There are conflicting scientific reports on the effects of the IGF hormones on the development and progression of prostate cancer. Insuline-like growth factor-1 is a hormone that is hypothesized to influence the growth and progression of prostate cancer via its mitogenic and anti-apoptotic properties (Monti et al., 2007; Pollack, 2007). Insulin-like growth factor binding protein-3 is the most active binding protein for IGF-1, and it is believed to affect prostate cancer by regulating the bioavailability of IGF-1 or perhaps through independent anti-apoptotic effects (Monti et al., 2007; Pollack, 2007).

As the existing studies had largely been conducted within other large cohorts assembled for various research purposes, the ProCEED Pilot Study was designed to specifically assess the effects of IGFs and lifestyle risk factors on prostate cancer status. The pilot study was undertaken in an older, predominantly African American, inner-city hospital clinic population, as this setting is where the risk of prostate cancer is perceived to be highest.

In multivariable analyses, this pilot study found a statistically significant negative association for the IGF-1 hormone and the risk of developing prostate cancer, but no significant association for IGFBP-3 levels and prostate cancer status. Thus, given the data on Table VI, for each one ng/mL change in IGF-1 value, the prostate cancer risk decreases by 4%. As a one ng/ml change is not that meaningful, it is helpful to multiply the beta coefficient from the logistic regression output by 10 and exponentiate it for a more meaningful result. After this calculation, the OR changed to 0.660 and thus for every 10 ng/mL increase in the value of IGF-1, the log odds of developing prostate cancer decreases by 34%.

It is probable that the association found between prostate cancer status and IGF-1 would have been stronger if the study had been larger, and if power had not been an issue. Additionally, J. M. Chan et. al. (2002) posited that IGF-1 is a greater predictor of prostate cancer progression than of incident disease. This study accepted all prostate cancer cases regardless of stage, and 44% of the patients had a Gleason score of six or less, representing localized disease. Unfortunately the sample was also not large enough to stratify the analysis on advanced versus localized disease. Based on the Chan hypothesis, it would be possible that with a predominately advanced-disease sample we would have seen stronger, or even perhaps positive, associations.

The main strength of this study is that it was specifically designed to assess IGF-1/IGFBP-3 and prostate cancer status. The biological samples were drawn in the clinic, immediately frozen, were not thawed for any other purpose until the IGF assays, and were not stored in a freezer for longer than 2.5 years (storage range was 4–30 months). Once consented, participants in the study were very compliant and there was a 100% collection rate for blood samples in the pilot study. Electronic medical records at the VA are very complete and accessible, and this facilitated the screening of potential subjects for inclusion/exclusion criteria as well as additional data collection post-enrollment.

There are several limitations to this study that should be noted. This was designed to be a pilot study, and thus it was underpowered to determine causality. With the sample size it was not possible to perform stratified risk analyses of IGF hormone quartile levels. It was also not possible to stratify on advanced versus localized prostate cancer. Though this was intentional, participants were predominantly low-income African Americans that were enrolled at one VA hospital in a major urban area. Thus, the generalizability of our findings to men with prostate cancer seen in other treatment settings may be limited. The sociodemographic homogeneity of participants also may limit

the generalizability of our findings to the prostate cancer population at large. Additionally, the number of noncancer controls enrolled was less than planned due to the difficulty of finding appropriate subjects meeting the criteria. It was not possible to calculate the recruitment rate (number of consented patients / number of approached patients) due to the fact that the urologist and/or pharmacist, not the principal investigator, who conducted the subsequent study visits, approached all eligible patients in the exam rooms. The blood samples collected for the assays of IGF-1 and IGFBP3 were only taken at one time-point, and thus may not be representative of circulating hormone levels over time. Additionally, the blood samples were drawn after the disease was diagnosed so it is unknown whether subjects changed health behaviors or their diet, which may lead to IGF status being higher or lower than it would have been before their cancer diagnosis. This could explain the level of IGF-1 being lower in the case group, but it is not possible to know for sure. As with any case-control study, the subjects' ability to recall information from past behavior, exposures, and experiences may be limited, and can affect the accuracy of the data, however it is not expected that this problem was different between cases and controls. Recall bias also did not affect the ascertainment of the serum IGFs, which were the primary endpoints of the study.

E. **Conclusion**

In this predominately African American, inner-city population at high risk for prostate cancer, there were slightly decreased odds of developing the disease with elevated IGF hormone levels.

VI. RESULTS—SPECIFIC AIM #3:

COMBINED EFFECTS OF INSULIN-LIKE GROWTH FACTOR-1 AND LIFESTYLE RISK FACTORS ON PROSTATE CANCER STATUS: RESULTS FROM THE PROSTATE CANCER STUDY OF ETHNICITY, EXERCISE AND DIET PILOT STUDY

A. Introduction and Objective

Prostate cancer has the highest incidence rate of all cancers among men in the developed world, with 903,500 new cases estimated to have occurred in 2008 (Jemal et al., 2010). Yet despite its marked incidence, the only risk factors that have been firmly established are age, race, and a positive family history of prostate cancer (Leitzmann and Rohrmann, 2012; Patel and Klein, 2009). There are, however, interesting prostate cancer incidence patterns that lead researchers to examine possible environmental or gene-environment interaction theories. An example of such a pattern exists among African American men, who consistently have the highest incidence rates of prostate cancer in the United States (SEER Database, 2013) but the incidence rates of prostate cancer are much lower among black men in African countries (Chu et al., 2011) suggesting potential nongenetic etiologies. Another example is the incidence rates among Asian American men of Chinese and Japanese descent, which are higher than the extremely low rates of prostate cancer seen among men in their countries of origin (Cook et al., 1999; Haenszel and Correa, 1975; Haenszel and Kurihara, 1968; Shimizu et al., 1991).

Haenszel and Kurihara (1968) described in their seminal work on stomach cancer and Japanese migration to the United States that diet is likely a major factor in migratory patterns of disease. Diet is theorized to influence the risk of cancer through its effects on hormone levels, growth factors, and antioxidation (Heald et al., 2003). It has been hypothesized that there is something about the Western lifestyle and diet that is a risk factor for prostate cancer. High fat and

caloric diets have been reported to result in high levels of IGF-1, in the bloodstream (Preston-Martin, 1990; Renehan et al., 2004). Insulin-like growth factors are hypothesized to have a role in cancer development through their influence on cell proliferation, differentiation, and apoptosis. Because of these properties, several studies have been undertaken to assess IGFs (particularly IGF-1) as independent risk factors for prostate cancer, with much variability between studies with respect to the results (Allen et al., 2007; J. M. Chan et al., 1998; J. M. Chan et al., 2002; C. Chen et al., 2005; Harman et al., 2000; Janssen et al., 2004; Lacey et al., 2001; Meyer et al., 2005; Oliver et al., 2004; Platz et al., 2005; Stattin et al., 2000; Stattin et al., 2004; Wolk et al., 1998).

The ProCEED study was a case-control pilot study that was undertaken to assess relationships between potentially modifiable lifestyle risk factors and the IGF-1 hormone in predicting prostate cancer in a predominately African American VA urology clinic. It was hypothesized that intake of saturated fat would be positively related to prostate cancer status.

B. **Materials and Methods**

Data on demographics, social history, medical history, prostate cancer clinical characteristics (for cases), dietary and exercise intake, and a blood sample for ascertainment of serum IGF-1 and IGFBP-3 levels were collected during the study for each participant.

1. **Subjects**

Between 2006 and 2009, men were recruited from a general urology clinic at the JBVAMC. To be eligible for the study, all subjects were required to be a resident of Illinois; have no medical history of stroke, dementia, or Alzheimer's; be aged 50 or older; and be either African American or Caucasian. Prostate cancer cases were required to have a diagnosis of biopsy-proven prostate adenocarcinoma (any stage). Noncancer controls were required to have no history of

prostate cancer or benign prostate hypertrophy (BPH), have two normal PSA tests (at least one within one year of study enrollment), and have a normal digital rectal exam at the study visit. The recruitment process was such that the urologist or clinical pharmacist on duty invited any of their eligible patients to participate in the study. Study procedures were explained to all eligible participants, who were asked to provide written informed consent. The human subjects review board at JBVAMC and the Office of the Protection of Research Subjects (OPRS) at the UIC approved the study. Subjects who consented to participate were reimbursed \$20 for their participation in the study.

Prostate cancer cases enrolled in the ProCEED study had been seen in the JBVAMC General Urology clinic for the following treatments: hormone therapy (37%), watchful waiting (27%), radical prostatectomy (37%), radiation (22%), brachytherapy (2%). Patients often receive more than one of the aforementioned prostate cancer treatments, hence the total is greater than 100%. The total Gleason scores for the prostate cancer cases were distributed as follows: 5 (1.7%), 6 (42.4%), 7 (37.3%), 8 (8.5%), 9 (10.2%).

2. **Data collection**

Data for the ProCEED Pilot Study came from the following sources: patient interviews, clinical progress notes, laboratory assay reports, and patient medical charts. The demographics, work history, social history, diet, exercise, and family cancer history information were collected via personal interview with the subject. The medical history and medication use data were collected by review of medical records and progress notes.

3. **Dietary assessment**

Telephone interviews by registered dietitians were conducted to collect information on subjects' diet using (1) the Block Brief 2000 FFQ to measure chronic food intake, and (2) 24-hour food recalls on two different days within seven days of the study visit, to measure acute food

intake. The response rate for the follow-up phone calls was proportional in both groups: 47/59 (80%) for the cases and 20/25 (80%) for the controls. No proxy interviews took place for the dietary data collection.

Reliability and validity of the Block Brief FFQ instrument has been previously reported (Block et al., 1990). This FFQ contains a food list of about 70 items, and took approximately 20 minutes to administer per subject in this older population. The questionnaire was designed to provide estimates of usual and customary dietary intake. The food item list for this questionnaire was developed from the National Health and Nutrition and Examination Survey III dietary recall data, and the nutrient database was developed from the US Department of Agriculture's Nutrient Database for Standard Reference. Individual portion size was asked during the interview, and standard pictures of portion sizes were sent home with the subject at the end of the study visit to be used during the telephone call. If a subject had lost their portion picture sheet, another copy was sent to their home, and the phone call was conducted at a later time. Block Brief 2000 FFQ data were collected on optical scan forms during the interviews, which were sent to Nutrition Quest Inc. for scanning and data processing. An SAS dataset of FFQ data was sent back to the principal investigator for inclusion in the study database, and the dietary data were used in the analysis as provided.

Two detailed interviews to collect 24-hour dietary recall data were collected on separate days within seven days of the study visit. This 24-hour recall data was analyzed using the Nutrition Data System for Research, software based on the US Department of Agriculture comprehensive food and nutrient database, containing more than 160,000 ingredient combinations and more than 18,000 foods (Dennis et al., 1980). Data were collected by a registered dietitian and were entered into the Nutrition Data System for Research by a registered dietitian for analysis. Reports for all nutrients

were produced separately for each of the two days day the subject was interviewed. At analysis the nutrient intake for the two days were averaged together for each parameter (for example: day 1 total cholesterol + day 2 total cholesterol / 2), and the average was used to describe their intake. Subjects that had only one 24-hour recall interview had values for the single interview used to describe their intake.

4. **Exercise data**

Physical activity during the previous week was assessed in the clinic using the IPAQ short form, consisting of nine items. This short form questionnaire was designed specifically for adults, and assesses three specific types of activity: walking, moderate-intensity activities, and vigorous-intensity activities (IPAQ scoring manual ref). Reliability and validity of the short form instrument have been reported, with repeatability of measures stated to be 0.76 (Spearman's r) across twelve countries (Craig et al., 2003).

The items on the IPAQ form produced separate scores for the following activities: walking, moderate-intensity, and vigorous-intensity activity. Exercise scores were all reported as continuous metabolic equivalent of task (MET) minutes per week. Metabolic equivalent of task score values are coefficients that properly weight each activity in terms of energy expenditure (walking=3.3 METs, moderate physical activity=4.0 METs and vigorous physical activity=8.0 METs). The MET-minutes per week were computed by multiplying the MET score by minutes performed and then by the amount of times a person performed the activity during the previous week (IPAQ scoring manual ref). The IPAQ sitting variable was not included as part of any of the summary scores of physical activity, and was analyzed as a continuous variable, and reported in hours per week to reflect actual time spent in sitting/sedentary.

5. **Venipuncture/laboratory values**

Blood was drawn from each subject during the study visit for determination of serum IGF-1. The blood draws were all done in the morning, and participants were not required to have fasted. Information on food and beverage intake before the blood draw was taken at the time of the draw, with fasting status recorded as follows: 0=fasted, 1=nonfasted-coffee only, 2=nonfasted-breakfast eaten. Blood samples were centrifuged immediately after the study visits, and stored as serum in a -70°C freezer. Serum samples were transferred on dry ice at the end of the study to the laboratory for processing. Plasma levels of IGF-1 and IGFBP-3 were quantified by direct RIA at Quest Diagnostics at the Nichols Institute (San Juan Capistrano, California). All samples (cases and controls) were analyzed in a single batch, meaning that kits with identical lot numbers were used. The assays were all performed by the same individual who was blinded to the subjects' case/control status. Laboratory reports from Quest Diagnostics were sent to the principal investigator for entry into the study database.

6. **Statistical analysis**

The objective of this study was to assess relationships between potentially modifiable lifestyle risk factors and the IGF-1 hormone in predicting prostate cancer.

Values for Block Brief 2000 FFQ, 24-hour recalls, IGF-1, IGFBP-3, and IPAQ variables were log transformed in initial analyses, but doing so did not meaningfully change the results/distribution, as the original values were approximately normally distributed. Thus, the original, nontransformed lab values were utilized in the final statistical analyses. Also, due to the small sample size, all were analyzed as continuous variables. Dietary data was adjusted using the residual energy method (Brown et al., 1994; Willett et al., 1997). As this was a small pilot study, no imputation methods were used to model missing values in the database.

Univariate case-control comparisons for patient characteristics and physical activity data were performed using t tests (sd) for continuous variables and X^2 tests for categorical variables. Univariate comparisons for the dietary data collected with the FFQ and the 24-hour-recall method were adjusted using the residual energy method, and thus ORs and p-values for the univariate comparisons were generated using logistic regression, controlling only for daily calorie intake.

Pearson correlation coefficients and p-values were run to assess similarity in measurement between the two dietary collection methods FFQ and 24-hour recall for the main nutrients. Since there was statistically significant positive correlation between the methods ranging between 29%–46% (depending on the dietary parameter), multivariable analysis was conducted for the FFQ data only. Prior to model building, Pearson correlation coefficients were also run between carbohydrate intake and fiber for the FFQ data. These two were not statistically significantly correlated, so both were used as independent variables in the statistical model.

A multivariate logistic regression model was constructed to assess simultaneously the effects of diet, physical activity, and the IGF-1 hormone on the odds of prostate cancer. Interaction terms were tested to assess potential effect modification between IGF-1 and the dietary variables in predicting prostate cancer. Goodness-of-fit was determined by -2 log likelihood methods. All data were analyzed with SAS version 9.2 (28).

C. **Results**

As displayed in Table IX, a total of 84 subjects were enrolled in the study: 59 prostate cancer cases and 25 noncancer controls. Racial makeup was proportional between groups, with African Americans predominant in both groups (83% cases versus 84% of controls), but cases were statistically significantly older than controls (70.6 versus 63.2 years old, $p=.002$). The BMI and waist

circumference were comparable between groups. Controls were more likely to smoke than cases. Controls had a higher mean IGF-1 than cases, which was unexpected, but this difference was not statistically significant.

TABLE IX
PATIENT CHARACTERISTICS BY PROSTATE CANCER STATUS

Variable	Cases (n=59)	Controls (n=25)	<i>p</i>
Age (mean, sd)	70.6 (14.4)	63.2 (6.5)	.0020 ^a
Race (n, %)			
African American	49 (83.1)	21 (84.0)	.9155 ^b
White	10 (16.9)	4 (16.0)	
BMI (mean, sd)	30.9 (7.7)	29.8 (6.1)	.2422 ^a
Waist circumference (mean, sd)	109.3 (10.8)	107.3 (11.0)	.5316 ^a
Smoking status			
Smokes currently	17 (28.8)	9 (37.5)	.2081 ^b
Never smoked	9 (15.3)	6 (25.0)	
Used to smoke / quit	33 (55.9)	9 (37.5)	
Hormone IGF-1 ng/mL (mean, sd)	153.2 (50.7)	166.4 (48.3)	.2793 ^c

^a *t* test

^b CMH=Cochran Mantel-Haenzel test

^c The *N* varied for the laboratory testing: IGF-1 test had 58 cases / 24 controls, IGFBP-3 had 59 cases / 25 controls.

Univariate comparisons for the Block Brief FFQ dietary variables and the 24-hour recalls (Tables X and XI) indicate that cases had a statistically significantly higher daily total carbohydrate intake than controls (224 g/day versus 192, $p=.0286$). Dietary fiber intake was higher in cases than controls (13 g/day versus 10, $p=.0251$) in 24-hour recall data, while total cholesterol intake was lower in cases than controls (254 mg/day versus 338, $p=.0449$). The two dietary collection methods yielded similar results (with respect to direction) for most of the parameters, including: total protein, total carbohydrates, total cholesterol, and total dietary fiber intake.

TABLE X
RELATIONSHIPS BETWEEN FFQ DIETARY VALUES AND PROSTATE CANCER*

Variable	Case mean ^a (sd)	Control mean ^a (sd)	OR (CI) ^b	p^b
Mean total calories (kcal/day)	1,884 (699)	1803 (637)	1.0 (0.999–1.001)	0.6535
Mean total protein (g/day)	67.0 (30)	70.0 (23)	0.96 (0.922–1.005)	0.0869
Mean total fat (g/day)	80.9 (31)	79.5 (34)	0.99 (0.953–1.027)	0.5887
Mean total carbohydrates (g/day)	223.6 (91)	192.4 (76)	1.02 (1.002–1.037)	0.0286
Mean total cholesterol (mg/day)	248.1 (135)	276.4 (134)	1.00 (0.991–1.002)	0.1687
Mean total fiber (g/day)	18.3 (9)	16.2 (6)	1.04 (0.950–1.138)	0.3984

^a Unadjusted means

^b Adjusted with residual energy method, controlling for daily calorie intake based on logistic regression, prostate cancer status as dependent variable.

TABLE XI
RELATIONSHIPS BETWEEN 24-HOUR RECALL DIETARY
VALUES AND PROSTATE CANCER*

Variable	Case mean ^a (sd)	Control mean ^a (sd)	OR (CI) ^b	<i>p</i> ^b
Mean total calories (kcal/day)	1556 (530)	1614 (650)	1.00 (0.999–1.001)	0.7127
Mean total protein (g/day)	62 (24)	69 (33)	0.99 (0.960–1.024)	0.6153
Mean total fat (g/day)	61 (28)	71 (33)	0.95 (0.910–1.001)	0.0543
Mean total carbohydrates (g/day)	185 (68)	156 (83)	1.02 (1.004–1.045)	0.0191
Mean total cholesterol (mg/day)	254 (158)	338 (197)	1.0 (0.992–1.000)	0.0449
Mean total fiber (g/day)	13 (6)	10 (7)	1.20 (1.023–1.399)	0.0251

^a Unadjusted means

^b Adjusted with residual energy method, controlling for daily calorie intake based on logistic regression, prostate cancer status as dependent variable.

In Table XII, the IPAQ exercise data showed that the two groups were largely sedentary, with average hours of sitting per day ranging from 12 hours for controls to 14 for cases. This did not include hours where the person was asleep. There were no statistically significant differences found between groups in comparisons of physical activity levels.

In multivariable analysis (Table XIII), carbohydrate intake (OR 1.19, *p*=.0364), daily calorie intake (OR=1.02, *p*=.0391) and age (OR 1.12, *p*=.0311) remained statistically significant predictors of prostate cancer, and total fiber intake was a significant protective factor (OR 0.60, *p*=.0262) after controlling for covariates. Assessment of effect modification between IGF-1 and the total daily intakes of fiber and carbohydrates showed borderline significance.

TABLE XII**PHYSICAL ACTIVITY BY PROSTATE CANCER STATUS, MEAN (SD)**

Variable	Cases (n=59)	Controls (n=25)	<i>p</i> ^a
Walking (MET-MINS / WK ^b)	322.2 (460)	464.6 (1115)	0.5422
Moderate exercise (MET-MINS / WK ^b)	156.7 (372)	76.5 (218)	0.2227
Vigorous exercise (MET-MINS / WK ^b)	292.9 (1557)	69.1 (164)	0.2800
Sitting (hours / day)	14.1 (4)	12.1 (6)	0.9538

^a *p* values based on *t* tests

^b Met-minutes per week is calculated by: (MET constant × minutes spent doing the activity) × times week. The MET constants are 3.3 for walking, 4.0 for moderate activity, and 8.0 for vigorous activity.

TABLE XIII**MULTIVARIABLE RELATIONSHIPS BETWEEN ADJUSTED DIETARY NUTRIENT VALUES, IGF-1, AND PROSTATE CANCER, ADJUSTED FOR COVARIATES^a**

Covariate	OR (CI) ^b	<i>p</i> ^b
Mean total carbohydrates (g/day)	1.19 (1.01–1.40)	0.0364
Mean total fiber (g/day)	0.60 (0.39–0.94)	0.0262
Mean total cholesterol (mg/day)	1.01 (0.97–1.05)	0.5858
Mean total fat (g/day)	1.06 (0.79–1.44)	0.6713
Mean total protein (g/day)	1.13 (0.81–1.56)	0.4763
Total calories (kcal/day)	1.00 (1.00–1.01)	0.0391
IGF-1 (ng/mL)	1.26 (0.84–1.88)	0.2578
IGF-1 × Carbohydrates	0.99 (0.99–1.00)	0.0662
IGF-1 × Fiber	1.00 (1.00–1.00)	0.0521
IGF-1 × Cholesterol	1.00 (0.99–1.00)	0.4388
IGF-1 × Fat	1.00 (0.99–1.00)	0.8146
IGF-1 × Protein	0.99 (0.99–1.00)	0.4887
Hours spent sitting	0.82 (0.62–1.08)	0.9162
Age	1.07 (1.00–1.15)	0.0311
BMI	1.03 (0.92–1.15)	0.2843

^a Adjusted with residual energy method, controlling for daily calorie intake.

^b Based on logistic regression, prostate cancer status as dependent variable.

D. **Discussion**

Despite the large and growing burden of prostate cancer globally, its causes are still poorly understood, and thus it remains important to continue to discover risk factors for the disease. To our knowledge, this is the first study that has assessed specifically the interaction effects between the IGF-1 hormone and diet and their combined influence on prostate cancer status. This study found in multivariable models that carbohydrates, fiber, total calorie intake, and age were all significant contributors to the odds of having prostate cancer, controlling for covariates. The interaction that was tested in the model between carbohydrates and IGF-1 reached borderline significance (probably not significant due to the small numbers in this pilot study). As carbohydrates directly influence the insulin response, it was not surprising that there seemed to be some level of effect modification operating, which was related to prostate cancer status.

There have been few studies that directly assess the effects of carbohydrate intake and their relationship to prostate cancer. A recent report from the Malmö prospective cohort study of $n=10,578$ men in Sweden found that high daily intakes of simple carbohydrates such as low-fiber cereal, cake, biscuits, pasta, rice, and sweetened beverages were all significantly associated with a risk of prostate cancer (all $p<.05$) (Drake et al., 2012). Another case-control study of $n=1,294$ Italian men found that starchy food consumption is associated with 40% increased odds of developing prostate cancer (OR 1.4, 95% CI 1.1–1.8) (Bidoli et al., 2005). In vivo evidence has also suggested that carbohydrate intake has a direct influence on prostate cancer biology (Freedland et al., 2008; Mavropoulos et al., 2009; Venkateswaran et al., 2007).

Fiber intake and its influence on prostate cancer development has also not been widely documented. In the North Carolina-Louisiana Prostate Cancer Project, a population-based study of men ages 40–79, also found that dietary fiber intake was inversely associated with aggressive

prostate cancer (Tabung et al., 2012). Another case control study (n=478 cases and n=373 controls) also found fiber to be inversely related to risk of prostate cancer (OR=0.56; 95% CI=0.35–0.89) (Lewis et al., 2009).

Augustin et al. (2004) assessed the relationship of GI and glycemic load (GL) with prostate cancer risk in a multicenter case-control study of men 46–74 years of age in Italy. Cases were 1,204 men admitted for incident, histologically confirmed prostate cancer. Controls were 1,352 men admitted for acute, nonmalignant conditions unrelated to long-term modifications of diet. Compared to the lowest quintile of GI, the ORs were 1.23, 1.24, 1.47, and 1.57 for subsequent levels of GI. The corresponding values for GL were 0.91, 1.00, 1.20, and 1.41. Thus, this study found direct relations between dietary GI/GL and prostate cancer risk.

The diet consumed among participants in this study population was not very dissimilar from that of the average US dietary intake. Table XIV displays the Block Brief FFQ data from this study compared against national means available from the National Health and Nutrition and Examination Survey III (Rhodes, 2012) and the US dietary intake recommendations (Institute of Medicine, 2013). Protein, fat, and carbohydrate intake all exceeded the recommended daily allowances in both groups. The two groups in the study reported lower (kcal/day) intake (1,884 for cases versus 1,803 for controls) than the recommended daily allowance for this age group of 2,000 kcal/day or than the national mean of 2,202 kcal/day. For total protein intake (g/day), the cases were lower than controls (61.5 versus 71.1) but both groups were lower than the national average of 88.3 g/day. For percent of total fat intake (%), cases were again lower than controls (35.5% versus 39.6%), and these were both higher than the national average of 33.7%. With respect to total carbohydrates (g/day), cases were higher than controls (223.6 versus 192.4), which was lower than the national average of 258 g/day.

TABLE XIV

**ADJUSTED FFQ DIETARY AVERAGES BY PROSTATE CANCER STATUS
VERSUS NATIONAL MEANS AND NATIONAL RECOMMENDATIONS**

Variable	Cases (n=47)	Controls (n=20)	US adult males ^a (ages 60–69)	RDA ^b males (ages 50–70)
Mean total calories (kcal/day)	1,884	1,803	2,202*	2,000**
Mean total protein (g/day)	66	72	88.3*	56 **
Mean total fat (% kcal/day)	35.50%	39.60%	33.7%*	25–35%**
Mean total carbohydrates (g/day)	221	199	258*	130**

^a National Health and Nutrition and Examination Survey

^b Recommended daily allowance—dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids 2002/200.

The main strength of this study was that it was designed to assess interactions between potentially modifiable risk factors and IGF-1, and their effects on prostate cancer status. The follow-up rate for the dietary interview telephone calls was good, with 80% compliance in both groups. The biological samples were drawn in the clinic, immediately frozen, were not thawed for any other purpose until the IGF assays, and were not stored in a freezer for longer than 2.5 years (storage range was 4–30 months). Once consented, participants in the study were very compliant and there was a 100% collection rate for blood samples in the pilot study. Electronic medical records at the VA are very complete and accessible, and this facilitated the screening of potential subjects for inclusion/exclusion criteria as well as additional data collection post-enrollment.

There are several limitations to this study that should be noted. This was designed to be a pilot study, and thus it was underpowered to determine causality. With the sample size it was not possible to perform stratified risk analyses of the dietary data, physical activity levels, or IGF hormones. It was also not possible to stratify on advanced versus localized prostate cancer. Though this was intentional, participants were predominantly low-income African Americans that were enrolled at one VA hospital in a major urban area. Thus, the generalizability of our findings to men with prostate cancer seen in other treatment settings may be limited. The sociodemographic homogeneity of participants also may limit the generalizability of our findings to the prostate cancer population at large. Additionally, the number of noncancer controls enrolled was less than planned due to the difficulty of finding appropriate subjects meeting the criteria. It was not possible to calculate the recruitment rate (number of consented patients/number of approached patients) due to the fact that the urologist and/or pharmacist, and not the principal investigator who conducted the subsequent study visits, approached all eligible patients in the exam rooms. The blood samples collected for the assays of IGF-1 were only taken at one time-point, and thus may not be representative of circulating hormone levels over time. Additionally, the blood samples were drawn after the disease was diagnosed so it is unknown whether subjects changed health behaviors or their diet, which may lead to IGF status being higher or lower than it would have been before their cancer diagnosis. This could explain the level of IGF-1 being lower in the case group, but it is not possible to know for sure. As with any case-control study, the subjects' ability to recall information such as past behavior, dietary information, exposures and experiences may be limited, and can affect the accuracy of the data, however it is not expected that this problem was different between cases and controls.

E. **Conclusion**

This clinical case-control study in an inner-city, predominately African American, VA population found that daily intakes of: carbohydrates, fiber and total calories, and also age are significant predictors of prostate cancer. Thus, these results suggest that diets lower on the GI (lower simple carbohydrate and higher fiber intake) may be protective for prostate cancer. Additional larger studies of the interactive effects of carbohydrates, dietary fiber, and IGF-1 on the development of prostate disease are warranted.

VII. CONCLUSION

The ProCEED pilot study was a case-control study that was undertaken to examine the epidemiology patterns of prostate cancer in the state of Illinois versus the United States, and to directly assess differences between the IGF hormones, and dietary and lifestyle risk factors between men with and without prostate cancer. Interactions between serum IGF-1 concentrations and dietary and lifestyle risk factors were also examined.

The first objective of the study was to examine the epidemiology of prostate cancer in Illinois as compared to the United States from 1986 to 2000, to see if prostate cancer research done in Illinois is representative of the US population. The a priori hypothesis was that Illinois would be similar to the United States with respect to prostate cancer incidence, due to a similar population make-up. Three time periods were examined: Pre-PSA from 1986 to 1990, PSA-“uptake” from 1991 to 1995, and PSA-widespread use from 1996 to 2000. Incidence rates of prostate cancer were slightly lower for Illinois versus the United States for all time periods, in both race groups, which was not initially predicted.

The second objective of this study was to determine whether there are significantly different levels of IGF-1 and IGFBP-3 in blood samples from prostate cancer cases compared to controls. It was originally posited that prostate cancer cases would have significantly higher levels of IGF-1 than controls, and that cases would have significantly lower levels of IGFBP-3 than controls. In reality, the two groups were not statistically significantly different with respect to the IGF axis variables in univariate analyses. In multivariable analyses of the associations of prostate cancer and IGF-1, IGFBP-3, and the IGF molar ratio, (controlling for fasting status, age, current alcohol use, education, and family cancer history), there were actually statistically significant negative associations for IGF-1 and prostate cancer and for the IGF molar ratio and prostate cancer that were both statistically

significant. The association between IGFBP-3 and prostate cancer status was also negative, but was not found to be statistically significant. The results of this analysis were opposite of what was originally theorized perhaps due to small sample size. Further, the small sample size did not allow for stratification based on severity, as other studies have done of prostate cancer and IGF hormones in the literature.

The final objective of this study was to assess differences between dietary and exercise intake in prostate cancer cases compared to controls, and to assess interactions between these variables and the IGF-1 hormone. The hypotheses for this objective were: (1) dairy and saturated fat (animal food intake) would be positively correlated with levels of IGF-1 and IGFBP-3, and (2) prostate cancer cases would have less exercise exposure than controls. The data did not support the hypothesis that the exercise levels of cases and controls were different. The two groups were both largely sedentary, and there were no statistically significant differences found between groups in comparisons of physical activity levels in any analyses. With respect to the dietary variables, it was suspected initially that fat and protein (nutrients from animal foods) would be found to be predictors of prostate cancer, but the study data did not show this to be true. Multivariable analyses actually demonstrated that carbohydrate intake and daily total calorie intake were statistically significant predictors of prostate cancer, and total fiber intake was a significant protective factor, after controlling for covariates. Thus, interestingly, diets high on the GI were found to be more predictive of prostate cancer risk in this population than a diet heavy in animal proteins and fats. When the interactive effects of IGF-1 and the dietary variables were assessed, there was slight borderline statistically significant effect modification operating between IGF-1 and the total daily intakes of fiber and carbohydrates. However the ORs for these interaction terms were at the null value ($IGF1 \times$

carbohydrates=0.99 and $\text{IGF1} \times \text{fiber}=1.00$) so it is difficult to assess exactly what the meaning of these interaction terms are in this small, underpowered sample.

This study unfortunately did not reach the planned target enrollment of 218 cases and 110 controls. After nearly three years of recruitment clinic visits, the study enrolled 59 cases and 25 controls. The recruitment rates were thus 27% of target for the cases and 23% of target for the controls. It was particularly challenging to find control subjects that were suitable for the study, as the recruitment occurred in a urology clinic and most patients being seen there had some form of prostatic abnormality. In subsequent studies, it would be better to recruit the control arm from a general medicine or orthopedic clinic, but the logistics of bringing another clinic into this dissertation study were too complicated to execute. That being said, the subjects we did enroll as controls were suitable, and met all inclusion/exclusion criteria, but there were just very few in number.

Perhaps if the control arm was recruited from a different patient pool, and it had been possible to enroll more controls, the two groups may not have been so similar with regard to IGF axis lab values, sedentary lifestyle, and other variables that were posited to be different in the study hypotheses. It is difficult to pinpoint the true extent of the effect of the small study sample.

Despite the small sample, the effects of carbohydrates and fiber were not attenuated, no matter what other covariates were added to the multivariable model. Additionally, only a few studies in the literature reported on the independent effects of carbohydrates and fiber on the risk of prostate cancer, and none of them also looked at potential interactive effects of the IGF hormones. Given that the (GI) has been implicated in a number of disease states such as diabetes, obesity, and cardiovascular disease, the logical next step for this area of research would be to continue to assess

the IGF axis and the GI as covariates with potential to interact and modify the risk of prostate cancer in a larger sample.

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APPENDICES

APPENDIX A

VA RESEARCH CONSENT FORM

Department of Veterans Affairs

VA RESEARCH CONSENT FORM

Subject Name: _____ Date: _____

Title of Study: ProCEED (Prostate Cancer Study of Ethnicity, Exercise and Diet)Principal Investigator: Dr. Z.Wu and Dr. R. Sharifi VAMC: Jesse Brown**Why am I being asked?**

You are being asked to be a subject in a research study about exercise, lifestyle, diet, and hormone levels in African-American and Caucasian patients with and without prostate cancer. The study is being directed by Dr. Sharifi and Dr. Wu at the Jesse Brown VA Medical Center. This study is also being conducted as part of Katrine Wallace's doctoral studies at University of Illinois at Chicago (UIC). The study is sponsored by the U.S. Department of Defense, Congressionally Directed Medical Research Programs.

You have been asked to participate in the research because you either: 1) have a diagnosis of prostate cancer (you are being recruited for the case group), or 2) you do not have a diagnosis of prostate cancer (you are being recruited for the control group) and you may be eligible to participate. We ask that you read this form and ask any questions you may have before agreeing to be in the research. We ask that you read this form and ask any questions you may have before agreeing to be in the research.

Your participation in this research is voluntary. Your decision whether or not to participate will not affect your current or future relations with JBVAMC, or the University of Illinois. If you decide to participate, you are free to withdraw at any time without affecting that relationship.

Why is this research being done? What is the purpose of this research?

The goal of this research study is to learn whether diet, exercise and lifestyle factors affect levels of certain hormones that we all have in our body (called IGF-1 and IGFBP-3). We will assess how these lifestyle factors and hormones affect the risk prostate cancer.

SUBJECT'S IDENTIFICATION (I.D. plate of give name - last, first, middle)

In Lieu of **VA FORM 10-1086**

Subject's Initials _____

ProCEED Pilot Study (2005-0049), Version 6, [1/14/08], Page 1 of 8

APPENDIX A (continued)

VA RESEARCH CONSENT FORM
 (Continuation Page 2)

Subject Name: _____ **Date:** _____

Title of Study: ProCEED (Prostate Cancer Study of Ethnicity, Exercise and Diet)
Principal Investigator: Dr. Z.Wu and Dr. R. Sharifi **VAMC:** Jesse Brown
What are the procedures involved?

If you agree to be in this research, you will participate in one 40-minute study visit today, and two telephone interviews within the next 2 weeks, where the following activities will occur:

- 1) Anthropometric Measurements: Body measurements, including the distance around your waist and hips. These measurements will be taken while you are standing up. Your weight and height will also be taken with a scale. There is little pain or risk involved with these measurements. (10 minutes)
- 2) Blood Samples: You will be asked to provide a blood sample. About 1 ounce (6 teaspoons) of blood will be drawn. (10 minutes)
- 3) Lifestyle/Behavioral Information: You will be asked to complete 4 questionnaires about your eating, activity, and lifestyle. (20 minutes)
- 4) Telephone Interviews: Within 2 weeks of your study visit, you will be contacted by phone twice to complete two short phone interviews with a member of the study staff who is a dietitian from University of Illinois at Chicago (UIC). During these phone calls, you will be asked questions about your diet. (40 minutes for the first call and 10 minutes for the second call)

All procedures that will be done during the study (including the labs that we will perform - PSA, testosterone, IGF-1 and IGFBP-3) will be done for research purposes only and will NOT become part of your medical chart.

Your medical records will be reviewed by study personnel for items that are pertinent to the study such as: medical history, prostate cancer history, medication use, and surgery history.

Your blood sample will be stored for up to 5 years in a freezer at Jesse Brown VA. When the study is over, blood samples will be analyzed for PSA, testosterone, IGF-1 and IGFBP-3, as well as some exploratory analyses related to androgen and Vitamin D metabolism, immune system function, and antioxidant metabolism. Your blood samples will be destroyed after they are used.

In Lieu of **VA FORM 10-1086** Subject's Initials _____
 ProCEED Pilot Study (2005-0049), Version 6, [1/14/08], Page 2 of 8

APPENDIX A (continued)

Department of Veterans Affairs

VA RESEARCH CONSENT FORM

(Continuation Page 3)

Subject Name: _____ Date: _____

Title of Study: ProCEED (Prostate Cancer Study of Ethnicity, Exercise and Diet)Principal Investigator: Dr. Z. Wu and Dr. R. Sharifi VAMC: Jesse Brown**What are the potential risks and discomforts?**

The research has several risks:

There is a minor risk involved in drawing blood from your arm. A blood draw may cause bruising, pain, minor bleeding and very rarely, infection at the place on your arm where the blood was taken. All blood draws will be done using sterile techniques by a trained technician. In the event of a physical injury, which may result from the blood sampling procedure, the VA will provide first-aid medical treatment.

You may experience discomfort due to the types of questions being asked. You do not have to answer all the questions.

There is also a risk of loss of your confidentiality. To reduce this risk, the only people who will know that you are a research participant are members of the research team and members of the UIC and VA Institutional Review Boards (a safety board for research participants). No information about you, or given by you during the research, will be told to others without your written approval, except:

When the results of the research are published or discussed in conferences, no information will be included that would identify you personally.

All computer files and written information will be stored in a locked office to which only study staff will have the key. Computer records will be kept without names of participants—only identification numbers.

Data from this study will be transported to UIC for storage and analysis. Study data will be kept de-identified in the database and on the data collection forms, but there will be a master list of linking your name to the study ID number assigned to you. The list will be locked in a cabinet at the VA and will only be accessible to the principal investigator. Your identity will only need to be de-identified if there is an abnormality in your blood work. If an abnormality is found, it will be reported by Dr. Zhigang Wu within 24 hours to your primary care doctor for follow-up. Thus, this list will be kept for your protection.

In Lieu of **VA FORM 10-1086** Subject's Initials _____
ProCEED Pilot Study (2005-0049), Version 6, [1/14/08], Page 3 of 8

APPENDIX A (continued)

VA RESEARCH CONSENT FORM
 (Continuation Page 4)

Subject Name: _____ Date: _____

 Title of Study: ProCEED (Prostate Cancer Study of Ethnicity, Exercise and Diet)

 Principal Investigator: Dr. Z. Wu and Dr. R. Sharifi VAMC: Jesse Brown
BENEFITS:
Are there benefits to taking part in this research?

There is no direct benefit to you for participating in this research study. However, the knowledge gained from this study may in the future, benefit others at risk for prostate cancer.

What other options are there?

The only alternative is to choose not to participate.

Will I be told about new information that may affect my decision to participate?

During the course of the study, you will be informed of any significant new findings (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation, that might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study may be re-obtained.

What about privacy and confidentiality?

If you participate in the research, your authorization will be required to have access to your private medical records. You will be asked to sign a separate authorization form to allow us to have this access. If you do not provide this authorization, you may not participate in the research.

The only people who will know that you are a research subject are members of the research team, and, if appropriate, your physicians and nurses. No information about you, or provided by you during the research, will be disclosed to others without your written permission, except:

- if necessary to protect your rights or welfare (for example, if you are injured and need emergency care); or
- when the UIC Institutional Review Board monitors the research or consent process; or
- when the JBVAMC Research and Development Committee monitors the research or consent process, or
- when the Government Accounting Office (GAO), the Office for Human Research Protections (OHRP) or other governmental regulatory agencies monitor the research; or
- if required by law.

In Lieu of **VA FORM 10-1086** Subject's Initials _____
 ProCEED Pilot Study (2005-0049), Version 6, [1/14/08], Page 4 of 8

APPENDIX A (continued)

Department of Veterans Affairs

VA RESEARCH CONSENT FORM
 (Continuation Page 5)

Subject Name: _____ **Date:** _____

Title of Study: ProCEED (Prostate Cancer Study of Ethnicity, Exercise and Diet)
Principal Investigator: Dr. Z. Wu and Dr. R. Sharifi **VAMC:** Jesse Brown

When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity.

The results of this study may be published, but my records will not be revealed unless required by law.

It should be noted that representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as a part of their responsibility to protect human subjects in research.

Guidelines:

Your individual study information will never be made public. The only way we will present the information publicly is in aggregate (together with the other subjects in the study). No identifying information will ever leave the VA facility, or will ever be used publicly. De-identified paper study records will be kept in a locked office and a locked file cabinet at UIC, only accessible by the research assistant and Drs Wu and Sharifi. Electronic study data will be password protected and only accessible by the research assistant and Dr. Zhigang Wu. Hard copy data will be destroyed 5 years after the last patient is enrolled.

What if I am injured as a result of my participation?

If you are injured or harmed from taking part in this research study, medical care (emergency or immediate non-emergency) for the injury will be provided to you at no cost by the VA. The VA has not set aside funds for other payments if research subjects are injured or harmed. You have not given up any legal rights or released the VA or its agents from liability for negligence by signing this form.

In the event of a research-related injury or if you experience an adverse event, please immediately contact Dr. Zhigang Wu at (312) 996-2242 pager #4401 during the day or after business hours. If you need emergency hospitalization in a private hospital because you are unable to come to the VA, have a family member or friend contact Dr. Wu so that the VA can coordinate your care and any related costs with the private hospital. The VA will pay the costs of any emergency hospitalization related to the research.

What are the costs for participating in this research?

In Lieu of **VA FORM 10-1086** Subject's Initials _____
 ProCEED Pilot Study (2005-0049), Version 6, [1/14/08], Page 5 of 8

APPENDIX A (continued)

VA RESEARCH CONSENT FORM
 (Continuation Page 6)

Subject Name: _____ **Date:** _____

Title of Study: ProCEED (Prostate Cancer Study of Ethnicity, Exercise and Diet)
Principal Investigator: Dr. Z.Wu and Dr. R. Sharifi **VAMC:** Jesse Brown

Some veterans pay co-payments for medical care and services provided by the VA. These co-payment requirements will continue to apply to standard medical care and services provided by the VA that are not part of this study. You will be expected to pay these costs according to your usual method of payment. Except for required co-payments, there are no additional costs to you for being part of this study.

Will I be reimbursed for any of my expenses or paid for my participation in this research?
Guidelines:

You will be paid \$20 for being in this study. You will be paid in cash at the end of the study visit.

Will your cells, tissues, blood, or other biological materials be used to develop commercial products?

Your blood sample will be used only for research purposes and will be destroyed after the lab tests are processed.

Can I withdraw or be removed from the study?

Your participation in this research is VOLUNTARY. If you choose not to participate, that will not affect your relationship with JBVAMC or your health care provider, or your right to health care or other services to which you are otherwise entitled. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without affecting your future care at JBVAMC. You may withdraw from this study at any time without penalty or loss of VA or other benefits to which you are entitled.

The investigator may withdraw you from participating in this research without your consent, if necessary. If you experience serious side effects or if you become ill during the research, you may have to drop out, even if you would like to continue. The investigators, Dr. Wu or Dr. Sharifi, will make the decision and let you know if it is not possible for you to continue. The decision may be made either to protect your health and safety, because it is part of the research plan that people who develop certain conditions may not continue to participate, or because the sponsor of the research has decided to stop the research, or for any reason the investigator feels is appropriate.

In Lieu of **VA FORM 10-1086** Subject's Initials _____
 ProCEED Pilot Study (2005-0049), Version 6, [1/14/08], Page 6 of 8

APPENDIX A (continued)

Department of Veterans Affairs	VA RESEARCH CONSENT FORM (Continuation Page 7)
Subject Name: _____ Date: _____	
Title of Study: <u>ProCEED (Prostate Cancer Study of Ethnicity, Exercise and Diet)</u>	
Principal Investigator: <u>Dr. Z. Wu and Dr. R. Sharifi</u> VAMC: <u>Jesse Brown</u>	
<p><u>Who should I contact if I have questions regarding the research?</u></p> <p>The main researchers conducting this study are Katrine Wallace (312) 413-8825, and Dr. Zhigang Wu (312) 996-2242 pager #4401. You may ask any questions you have now. In case there are medical problems or questions, you have been told that you can call Dr. Wu at (312) 996-2242 pager #4401 during the day or after hours.</p> <p><u>Who should I contact if I wish to voice concerns or complaints about this research study?</u> <u>Who can I talk to about my rights as a research subject?</u></p> <p>You may contact the JBVAMC Research and Development Office at (312) 569-6616 or (312) 569-7426. You may also contact the UIC Office for the Protection of Research Subjects at (312) 996-1711 or 1-866-789-6215 (toll free) or e-mail OPRS at uicirb@uic.edu.</p> <p><u>Who can I talk to about my rights as a JBVAMC patient?</u></p> <p>If you want to talk to someone about your rights as a JBVAMC patient you should contact the Patient Advocate Office at the Jesse Brown VA Medical Center at (312) 569-6146.</p> <p>If you have concerns about specific study procedures or directions, you must contact the doctor or research staff as described above.</p> <p><u>Remember</u></p> <p><u>Your participation in this research is voluntary.</u> Your decision whether or not to participate will not affect your current or future relations with JBVAMC or the University of Illinois. If you decide to participate, you are free to withdraw at any time without affecting that relationship.</p> <p>You will be given a copy of this signed form for your information and to keep for your records.</p> <p>In Lieu of VA FORM 10-1086 Subject's Initials _____ ProCEED Pilot Study (2005-0049), Version 6, [1/14/08], Page 7 of 8</p> <div style="border: 1px solid black; width: 200px; height: 40px; margin-left: auto; margin-top: 10px;"></div>	

APPENDIX A (continued)

Department of Veterans Affairs

VA RESEARCH CONSENT FORM
 (Continuation Page 8)

Subject Name: _____ **Date:** _____

Title of Study: ProCEED (Prostate Cancer Study of Ethnicity, Exercise and Diet)
Principal Investigator: Dr. Z. Wu and Dr. R. Sharifi **VAMC:** Jesse Brown
Research Subjects' Rights:

I have read or have had read to me all of the above. Katrine Wallace (or designee) has explained the study to me and answered all of my questions. I understand what the study is about and how and why it is being done. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me. My rights as a research subject have been explained to me. I voluntarily consent to participate in this study. I will receive a signed copy of this consent form.

 Signature of Subject

 Date

 Signature of Witness

 Date (must be same as subject's)

 Printed Name of Witness

 Signature of Legally Authorized Representative

 Date (must be same as subject's)

 Printed Name of Legally Authorized Representative

 Relationship

 Signature of Investigator

 Date (must be same as subject's)

 In Lieu of **VA FORM 10-1086** Subject's Initials _____
 ProCEED Pilot Study (2005-0049), Version 6, [1/14/08], Page 8 of 8

APPENDIX B

VA AUTHORIZATION FOR RELEASE OF PROTECTED HEALTH INFORMATION FOR RESEARCH PURPOSES

VA Department of Veterans Affairs	VA Authorization for Release of Protected Health Information for Research Purposes
<p> Subject Name: _____ Date: _____ </p> <p> Title of Study: ProCEED Pilot Study (Prostate Cancer Study of Ethnicity, Exercise and Diet) </p> <p> Principal Investigator: <u>Wu/Sharifi</u> VAMC: <u>Jesse Brown VAMC</u> </p>	
<hr/> <p> You have been asked to be part of a research study under the direction of Drs. Wu and Sharifi and their research team. This study is being done as part of Katrine Wallace's doctoral studies at University of Illinois at Chicago. The purpose of this study is to learn whether diet, exercise and lifestyle factors affect levels of certain hormones that we all have in our body (called IGF-1 and IGFBP-3). The study will assess whether an interaction between lifestyle factors and these hormones lead to a higher risk prostate cancer among African-Americans </p> <p> By signing this document, you will authorize the Veterans Health Administration (VHA) to provide Drs. Wu and Sharifi and their research team to use and disclose the following information about you: </p> <p style="margin-left: 40px;"> Demographic Information (e.g. Name, Address, Phone Number), Medical Records : (e.g.: history and physical exam notes, progress notes, consultation reports, laboratory test results (PSA), operative reports), Blood samples (your blood will be tested for PSA level, testosterone level, IGF-1 hormone level, IGFBP-3 hormone level). </p> <p> The information that will be released includes information regarding the following conditions: </p> <p> ☐ Drug Abuse ☒ Alcoholism or Alcohol (you will fill out a dietary survey which asks about this information) ☐ Testing for or Infection with Human Immunodeficiency Virus (HIV) ☐ Sickle cell anemia </p> <p> The research team may also need to disclose the information to others as part of the study process. The others may include representatives of the study sponsor(s): Department of Defense (sponsor pending), authorized representatives of the Human Studies Subcommittee that will monitor this study, and/or other regulatory officials responsible for oversight of human subject protection. </p> <p> If you do not sign this authorization, you will not participate in the study. </p>	
SUBJECT'S IDENTIFICATION (I.D. plate of give name - last, first, middle) ProCEED Pilot Study Version 1 6/7/2005	<div style="border: 2px solid blue; padding: 10px; text-align: center;"> <div style="font-size: 2em; font-weight: bold; letter-spacing: 5px;">APPROVED</div> <div style="color: red; font-weight: bold; margin: 5px 0;">JUN 08 2005</div> <div style="font-size: 0.8em; font-weight: bold;">UNIVERSITY OF ILLINOIS AT CHICAGO INSTITUTIONAL REVIEW BOARD</div> </div>

VA FORM

APPENDIX B (continued)

Department of Veterans Affairs
VA Authorization for Release of Protected
Health Information for Research Purposes

Subject Name: _____ (Continuation Page)

Title of Study: ProCEED Pilot Study (Prostate Cancer Study of Ethnicity Exercise and Diet)

Principal Investigator: Wu/Sharifi VAMC: Jesse Brown VAMC

This authorization to use your information will expire at the end of the research study.

You can revoke this authorization, in writing, at any time. To revoke your authorization, you must write to the Release of Information Office at this facility or you can ask a member of the research team to give you a form to revoke the authorization. Your request will be valid when the Release of Information Office receives it. If you revoke this authorization, you will not be able to continue to participate in the study. This will not affect your right as a VHA patient to treatment or benefits outside the study.

If you revoke this authorization, Drs Wu and Sharifi and their research team can continue to use information about you that was collected before receipt of the revocation. The research team will not collect information about you after you revoke the authorization.

The VHA complies with the requirements of the Health Insurance Portability and Accountability Act of 1996 and its privacy regulations and all other applicable laws that protect your privacy. We will protect your information according to these laws. Despite these protection, there is a possibility that your information could be used or disclosed in a way that it will no longer be protected. Our Notice of Privacy Practices (a separate document) provides more information on how we protect your information. If you do not have a copy of the Notice, the research team will provide one to you.

I have read this authorization form and have been given the opportunity to ask questions. If I have questions later, I understand I can contact Katrine Wallace (312-413-8825). I will be given a signed copy of this authorization form for my records. I authorize the use of my identifiable information as described in this form.

Subject's Initials _____

APPENDIX B (continued)

Department of Veterans Affairs
VA Authorization for Release of Protected
Health Information for Research Purposes

Subject Name: _____ (Continuation Page)

Title of Study: ProCEED Pilot Study (Prostate Cancer Study of Ethnicity Exercise and Diet)

Principal Investigator: Wu/Sharifi _____ VAMC: Jesse Brown VAMC

Signature of Participant or Person Authorized
To Sign for Participant (Attach authority to sign,
e.g., Power of Attorney)

The Paperwork Reduction Act of 1995 requires us to notify you that this information collection is in accordance with the clearance requirements of section 3507 of the Act. We may not conduct or sponsor, and you are not required to respond to, a collection of information unless it displays a valid OMB number. We expect that the time expended by all individuals completing this form will average 2 minutes. This includes the time to read the instructions, gather the necessary facts and fill out the form. The purpose of this form is to specifically outline the circumstances under which we may disclose data.

The execution of this form does not authorize the release of information other than that specifically described. The information requested on this form is solicited under Title 38, U.S.C. The form authorizes release of information that you specify in accordance with the Health Insurance Portability and Accountability Act, 45 CFR Parts 160 and 164, 5 U.S.C. 552a, and 38 U.S.C. 5701 and 7332. Your disclosure of information requested on this form is voluntary. However if the information, including Social Security Number (SSN) (the SSN will be used to locate records for release) is not furnished completely and accurately, Department of Veterans Affairs will be unable to comply with the request.

VA Form 10-5345 March 2003

Subject's Initials _____

VA FORM
ProCEED Pilot Study
Version 1
6/7/2005

APPENDIX C

PROCEED PILOT STUDY DEMOGRAPHIC FORM

	PATIENT ID	SITE ID
	☐ ☐ ☐ ☐	☐ ☐
Patient Medical Record # _____		
Primary MD: _____		
Date of Study Visit: _____ / _____ / _____		
Date of Informed Consent: _____ / _____ / _____		
Date of HIPAA Form: _____ / _____ / _____		
Date of Birth: _____ / _____ / _____		
Ethnicity (check box):	☐ African American (non-Hispanic) ☐ Caucasian (non-Hispanic)	
Primary Language: _____		
Resident of Illinois	☐ yes _____ (years) ☐ no*	
Speaks fluent English:	☐ yes ☐ no*	
Primary Insurance Type: (check box)	<div style="display: flex; justify-content: space-between;"> <div> ☐ PPO ☐ HMO ☐ FFS / Private Pay ☐ VA ☐ No insurance / Self pay </div> <div> ☐ Medicaid ☐ Medicare ☐ Medical Supplemental ☐ Federal Employees ☐ No insurance / Charity </div> </div>	
Clinical Trial (past year)	☐ yes _____ <div style="margin-left: 150px;">Sponsor, drug/device, date(s)</div> ☐ no	

APPENDIX D

PROCEED PILOT STUDY EXERCISE QUESTIONNAIRE

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (August 2002)

SHORT LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15–69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health-related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation

Translation from English is supported to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ

International collaboration on IPAQ is on-going and an *International Physical Activity Prevalence Study* is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective*. Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

APPENDIX D (continued)

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

_____ **days per week**

☐

No vigorous physical activities

Skip to question 3

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐

Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

_____ **days per week**

☐

No moderate physical activities

Skip to question 5

APPENDIX D (continued)

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐

No walking

Skip to question 7

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐

Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐

Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

SHORT LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised August 2002.

APPENDIX E

PROCEED PILOT STUDY WORK AND SOCIAL QUESTIONNAIRE

PATIENT ID

□ □ □ □

SITE ID

□ □

WORK HISTORY FORM

What is your current work status? (check box):

- ☐ Working full time at job
- ☐ Working part time (because of your health)
- ☐ Working part time (not related to your health)
- ☐ On leave from work
- ☐ Temporarily laid off
- ☐ Unemployed or between jobs (looking for work)
- ☐ Disabled and unable to work (i.e., disabled before current health problem)
- ☐ Retired
- ☐ Other _____

Which description below best describes your work? (check box):

- ☐ Professional, technical and related tasks
- ☐ Administrative and managerial tasks
- ☐ Sales related tasks
- ☐ Service tasks (general maintenance and/or repair)
- ☐ Agriculture tasks (farming, animal husbandry, forestry, fishing and/or hunting)
- ☐ Production/Manufacturing and related tasks, transport equipment operators and laborers
- ☐ Armed forces

If you work at a job, what is your job title? _____

How many hours per week do you work at a job, or at home? _____ (hours)

APPENDIX E (continued)**PATIENT ID****SITE ID****SOCIAL HISTORY FORM**

Which of the following best describes your current relationship?

- ☐ Living with a spouse or partner
- ☐ In a significant relationship, but not living together
- ☐ Not in a significant relationship
- ☐ Widowed

Do you smoke cigarettes? ☐ yes
☐ no

If "yes", at what age did you start? _____ (years old)

How many packs do you smoke per day _____ (packs)

Do you drink alcohol? ☐ yes
☐ no

If "yes", how many total alcoholic drinks (1 drink = 1 bottle of beer, 1 glass of wine, 1 shot of liquor) have you had in the past 7 days? _____ (drinks)

How much education did you complete?
(check box)

- ☐ Grade school or less
- ☐ Some high school or technical school
 - ☐ High school or technical school graduate
 - ☐ Some college
 - ☐ College graduate
 - ☐ Graduate or professional school after college

APPENDIX F

PROCEED PILOT STUDY VISIT AND AE FORM

PATIENT ID

SITE ID

☐☐☐☐

☐☐

ADVERSE EVENTS:

Please note below any adverse events (AEs) that occurred during the course of the study visit (or reported up to 24 hours after). Please also indicate whether the AE was related to the study blood draw, what medical attention was sought for the patient, if any follow-up is necessary, and whether the AE has resolved.

Adverse Event	Event date	Event time	Related to blood draw? (yes/no)	Medical attention sought	Follow-up necessary	Resolved? (yes/no)

Use additional forms as necessary

APPENDIX F (continued)

PATIENT ID

□ □ □ □

SITE ID

□ □

BODY COMPOSITION

Patient Height: _____

Patient Weight: _____

Waist Circumference _____

Hip Circumference _____

BLOOD DRAW

Phlebotomist name: _____

Date of Blood draw: _____ / _____ / _____

Time of Blood draw ____ : ____ (please use 24-hour clock)

Comments: _____

Phlebotomist signature: _____

APPENDIX G

PROCEED PILOT STUDY MEDICAL HISTORY FORM

PATIENT ID

SITE ID

FAMILY MEMBER CANCER HISTORY

Has any member of the patient's family had cancer? ☐ Yes ☐ No (skip)

Check ☐	Cancer Site	Relationship to Patient	Comments
☐	Prostate		
☐	Breast		
☐	Lung/Bronchus		
☐	Colon/Rectum		
☐	Stomach		
☐	Bone/Joints		
☐	Cervix		
☐	Corpus Uteri		
☐	Esophagus		
☐	Eye		
☐	Gallbladder		
☐	Hodgkins Lymphoma		
☐	Non-Hodgkins Lymphoma		
☐	Kaposi Sarcoma		
☐	Kidney/Renal		
☐	Larynx		
☐	Leukemia (Lymphatic)		
☐	Leukemia (Myeloid & Monocytic)		
☐	Melanoma		
☐	Mesothelioma		
☐	Myeloma		
☐	Oral cavity/pharynx		
☐	Ovary		
☐	Pancreas		
☐	Soft Tissue		
☐	Stomach		
☐	Testis		
☐	Thyroid		
☐	Urinary Bladder		

APPENDIX G (continued)**PATIENT ID****SITE ID**

□□□□

□□

MEDICAL HISTORY

Check ☐	MD Diagnosis in the past	Approximate onset date	Resolved?	Comments
Cardiac				
☐	High Blood Pressure			
☐	Heart Attack			
☐	Chest Pain (angina)			
☐	Heart Arrhythmia/ palp			
☐	Stroke			
☐	Other cardiac			
EENT				
☐	Sinus Infections			
☐	Food Allergies			
☐	Drug Allergies			
☐	Seasonal Allergies			
☐	Nasal Polyps			
☐	Cataracts			
☐	Glaucoma			
☐	Hearing Loss			
☐	Vision Problems (other than glasses)			
☐	Other EENT			
GI				
☐	Gastric Reflux			
☐	Heartburn			
☐	Ulcers			
☐	Hemorrhoids			
☐	IBS			
☐	Blood in stool			
☐	Other GI			

APPENDIX G (continued)

PATIENT ID

SITE ID

□□□□

□□

Check ☐	MD Diagnosis in the past	Approximate onset date	Resolved?	Comments
Respiratory				
☐	Asthma			
☐	Emphysema			
☐	Bronchitis			
☐	Pneumonia			
☐	Tuberculosis			
☐	COPD			
☐	Other:			
Endocrine				
☐	Diabetes–Insulin Controlled			
☐	Diabetes–Non-Insulin			
☐	Hypothyroid			
☐	Hyperthyroid			
☐	Other endocrine:			
Musculo-skeletal				
☐	Rheumatoid arthritis			
☐	Osteoarthritis			
☐	Gout			
☐	Other MS:			
Neurologic				
☐	Seizures			
☐	Insomnia			
☐	Restless Leg Syndrome			
☐	Headaches			
☐	Migraines			
☐	Other Neuro:			

APPENDIX G (continued)

PATIENT ID

□□□□

SITE ID

□□

Check ☐	MD Diagnosis in the past	Approximate onset date	Resolved?	Comments
Liver				
☐	Hepatitis			
☐	High Cholesterol			
☐	Other:			
Kidney				
☐	Kidney Stones			
☐	Urinary Tract Infections			
☐	Other Kidney			
Skin				
☐	Psoriasis			
☐	Urticaria			
☐	Eczema			
☐	Acne			
☐	Other Skin:			
Immunological				
☐	HIV			
☐	Lupus			
☐	MS			
☐	Other Immuno:			
Psychological				
☐	Depression			
☐	Anxiety			
☐	Other Psych:			
Alcohol/Drug Abuse				
☐	Alcohol			
☐	Marijuana			
☐	Cocaine			
☐	Amphetamines			
☐	Barbituates			
☐	Other:			

APPENDIX G (continued)

PATIENT ID

SITE ID

MEDICATION USE IN PAST 30 DAYS

Has patient taken any medication in the past month? ☐ Yes ☐ No (skip)

Medication	Dose	Times per day	Start date	Stop date	Indication

SURGERY / HOSPITALIZATION HISTORY

Has patient ever been hospitalized or had surgery? ☐ Yes ☐ No (skip)

Reason	Dates	Comments

Has patient ever had a vasectomy? ☐ Yes ☐ No

PSA HISTORY

Record the patient's previous (within past 2 years) PSA measurements:

Date	PSA Level	Normal Range	Comments

APPENDIX G (continued)

**THE FOLLOWING FORMS ARE FOR
PROSTATE CANCER CASES ONLY!**

**IF THE PATIENT IS A CONTROL,
PLEASE DISCONTINUE FILLING OUT
THE MEDICAL HISTORY FORM AT
THIS POINT**

APPENDIX G (continued)**PATIENT ID**

□□□□

SITE ID

□□

PROSTATE BIOPSY AND CLINICAL TNM STAGING FORM**DRE****Digital Rectal Exam at the time of biopsy (check all that apply):**

Date	Findings	Right	Left
	Normal / enlarged	☐	☐
	Nodular	☐	☐
	Extracapsular extension	☐	☐
	Seminal Vesicle Invasion	☐	☐

BIOPSY**Procedure (check one):**

Date	Type
	☐ Core Needle Biopsy – transrectal
	☐ TURP
	☐ Other (specify) _____

BIOPSY RESULTS

	Regions		
	Right	Left	Unknown
Number performed			
Number positive			
Primary Gleason (code to highest)			
Secondary Gleason (code to highest)			
Total Gleason score (code to highest)			

Total # of Biopsies done _____

Total # of Biopsies positive _____

APPENDIX G (continued)**PATIENT ID**

□ □ □ □

SITE ID

□ □

BIOPSY RESULTS – TURP

Percent Involved	Primary Gleason*	Secondary Gleason*	Total Gleason*
%			

*code to highest

2002 – CLINICAL STAGING OF DISEASE (TNM)

Date	T	N	M

SURGERY AND TREATMENT

(check all that apply)

Procedure	Start Date / Date of Procedure	Stop date (if applicable)
☐ Watchful waiting		
☐ Radical Prostatectomy		
☐ Lymphadenectomy		
☐ Radiation		
☐ Brachytherapy		
☐ Other (specify) _____		

APPENDIX H

PROCEED PILOT STUDY FOOD FREQUENCY QUESTIONNAIRE

RESPONDENT ID NUMBER

0	1	2	3	4	5	6	7	8	9

TODAY'S DATE

☐ Jan ☐ Feb ☐ Mar ☐ Apr ☐ May ☐ Jun ☐ Jul ☐ Aug ☐ Sep ☐ Oct ☐ Nov ☐ Dec	DAY <input type="text"/> YEAR <input type="text"/>
--	---

BRIEF FOOD QUESTIONNAIRE

This form is about the foods you usually eat. It will take about 15 - 25 minutes to complete.

- Please answer each question as best you can. Estimate if you aren't sure.
- Use only a No. 2 pencil.
- Fill in the circles completely, and erase completely if you make any changes.

Please print your name in this box.

SEX

☐ Male
☐ Female

If female, are you pregnant or breast feeding?

☐ No
☐ Yes
☐ Not female

AGE

0	9
1	0
2	1
3	2
4	3
5	4
6	5
7	6
8	7
9	8

WEIGHT
pounds

0	9
1	0
2	1
3	2
4	3
5	4
6	5
7	6
8	7
9	8

HEIGHT
ft., in.

0	9
1	0
2	1
3	2
4	3
5	4
6	5
7	6
8	7
9	8

This form is about your usual eating habits in the past year or so. This includes all meals or snacks, at home or in a restaurant or carry-out. There are two kinds of questions for each food.

HOW OFTEN, on average, did you eat the food during the past year?

*Please DO NOT SKIP any foods. Mark "Never" if you didn't eat it.

HOW MUCH did you usually eat of the food?

*Sometimes we ask how many you eat, such as 1 egg, 2 eggs, etc., ON THE DAYS YOU EAT IT.
 *Sometimes we ask "how much" as A, B, C or D. LOOK AT THE ENCLOSED PICTURES. For each food, pick the picture (bowls or plates) that looks the most like the serving size you usually eat. (If you don't have pictures: A=1/4 cup, B=1/2 cup, C=1 cup, D= 2 cups.)

EXAMPLE: This person drank apple juice twice a week, and had one glass each time. Once a week he ate a "C"-sized serving of rice (about 1 cup).

TYPE OF FOOD	HOW OFTEN IN THE PAST YEAR							HOW MUCH EACH TIME SEE PORTION SIZE PICTURES FOR A-B-C-D						
	NEVER	A FEW TIMES per YEAR	ONCE per MONTH	2-3 TIMES per MONTH	ONCE per WEEK	TWICE per WEEK	3-4 TIMES per WEEK	5-6 TIMES per WEEK	EVERY DAY					
Apple juice	☐	☐	☐	☐	☒	☐	☐	☐	☐	How many glasses each time	☒ 1	☐ 2	☐ 3	☐ 4
Rice	☐	☐	☐	☐	☒	☐	☐	☐	☐	How much each time	☐ A	☐ B	☒ C	☐ D

PLEASE DO NOT WRITE IN THIS AREA

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APPENDIX H (continued)

TYPE OF FOOD	HOW OFTEN IN THE PAST YEAR									HOW MUCH EACH TIME SEE PORTION SIZE PICTURES FOR A-B-C-D				
	NEVER	A FEW TIMES per YEAR	ONCE per MONTH	2-3 TIMES per MONTH	ONCE per WEEK	TWICE per WEEK	3-4 TIMES per WEEK	5-6 TIMES per WEEK	EVERY DAY					
How often do you eat each of the following foods all year round?														
Eggs, including egg biscuits or Egg McMuffins (Not egg substitutes)	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many eggs each time	☐ 1	☐ 2	☐ 3	☐ 4
Bacon or breakfast sausage, including sausage biscuit	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many pieces	☐ 1	☐ 2	☐ 3	☐ 4
Cooked cereals like oatmeal, cream of wheat or grits	☐	☐	☐	☐	☐	☐	☐	☐	☐	Which bowl	☐ A	☐ B	☐ C	☐ D
Cold cereals like Corn Flakes, Cheerios, Special K, fiber cereals	☐	☐	☐	☐	☐	☐	☐	☐	☐	Which bowl	☐ A	☐ B	☐ C	☐ D
Which cereal do you eat most often? MARK ONLY ONE: ☐ Bran Buds, Raisin Bran, Fruit-n-Fiber, other fiber cereals ☐ Product 19, Just Right, Total ☐ Other cold cereal, like Corn Flakes, Cheerios, Special K														
Cheese, sliced cheese or cheese spread, including on sandwiches.	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many slices	☐ 1	☐ 2	☐ 3	☐ 4
Yogurt (not frozen yogurt)	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
How often do you eat each of the following fruits?														
Bananas	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many each time	☐ 1/2	☐ 1	☐ 2	☐ 3
Apples or pears	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many	☐ 1/2	☐ 1	☐ 2	☐ 3
Oranges, tangerines, not including juice	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many	☐ 1/2	☐ 1	☐ 2	☐ 3
Applesauce, fruit cocktail, or any canned fruit	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Any other fruit, like grapes, melon, strawberries, peaches	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D

APPENDIX H (continued)

TYPE OF FOOD	HOW OFTEN IN THE PAST YEAR									HOW MUCH EACH TIME SEE PORTION SIZE PICTURES FOR A-B-C-D				
	NEVER	A FEW TIMES per YEAR	ONCE per MONTH	2-3 TIMES per MONTH	ONCE per WEEK	TWICE per WEEK	3-4 TIMES per WEEK	5-6 TIMES per WEEK	EVERY DAY					
How often do you eat each of the following vegetables, including fresh, frozen, canned or in stir fry, at home or in a restaurant?														
French fries, fried potatoes or hash browns	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
White potatoes not fried, incl. boiled, baked, mashed & potato salad	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Sweet potatoes, yams, or sweet potato pie	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Rice, or dishes made with rice	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Baked beans, chili with beans, pintos, any other dried beans	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Refried beans	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Green beans or green peas	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Broccoli	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Carrots, or stews or mixed vegetables containing carrots	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Spinach, or greens like collards	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Cole slaw, cabbage	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Green salad	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Raw tomatoes, including in salad	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ 1/4	☐ 1/2	☐ 1	☐ 2
Catsup, salsa or chile peppers	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many TBSP.	☐ 1	☐ 2	☐ 3	☐ 4
Salad dressing or mayonnaise (Not lowfat)	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many TBSP.	☐ 1	☐ 2	☐ 3	☐ 4
Any other vegetable, like corn, squash, okra, cooked green peppers, cooked onions	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Vegetable soup, vegetable beef, chicken vegetable, or tomato soup	☐	☐	☐	☐	☐	☐	☐	☐	☐	Which bowl		☐ B	☐ C	☐ D

APPENDIX H (continued)

PLEASE DO NOT WRITE IN THIS AREA														
<div style="display: flex; justify-content: space-between;"> <div> <p>TYPE OF FOOD</p> </div> <div> <p>HOW OFTEN IN THE PAST YEAR</p> <p>NEVER A FEW TIMES per YEAR ONCE per MONTH 2-3 TIMES per MONTH ONCE per WEEK TWICE per WEEK 3-4 TIMES per WEEK 5-6 TIMES per WEEK EVERY DAY</p> </div> <div> <p>HOW MUCH EACH TIME</p> <p>SEE PORTION SIZE PICTURES FOR A-B-C-D</p> </div> </div>														
MEATS														
Do you ever eat chicken, meat or fish? ☐ Yes ☐ No IF NO, SKIP TO NEXT PAGE														
Hamburgers, cheeseburgers, meat loaf, at home or in a restaurant	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much meat	☐ 1/8 lb.	☐ 1/4 lb.	☐ 1/2 lb.	☐ 3/4 lb.
Tacos, burritos, enchiladas, tamales	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Beef steaks, roasts, pot roast, or in frozen dinners or sandwiches	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Pork, including chops, roasts, or dinner ham	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
When you eat beef or pork, do you ☐ Avoid eating the fat ☐ Sometimes eat the fat ☐ Often eat the fat ☐ I don't eat meat														
Mixed dishes with meat or chicken, like stew, corned beef hash, chicken & dumplings, or in frozen meals	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Fried chicken, at home or in a restaurant	☐	☐	☐	☐	☐	☐	☐	☐	☐	# medium pieces	☐ 1	☐ 2	☐ 3	☐ 4
Chicken or turkey not fried, such as baked, grilled, or on sandwiches	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
When you eat chicken, do you ☐ Avoid eating the skin ☐ Sometimes eat the skin ☐ Often eat the skin ☐ N/A														
Fried fish or fish sandwich, at home or in a restaurant	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Any other fish or shellfish <u>not</u> fried, including tuna	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Hot dogs, or sausage like Polish, Italian or Chorizo	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many	☐ 1	☐ 2	☐ 3	☐ 4
Bologna, sliced ham, turkey lunch meat, other lunch meat	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many slices	☐ 1	☐ 2	☐ 3	☐ 4
When you eat lunch meats, are they ☐ Usually low-fat ☐ Sometimes ☐ Rarely low-fat ☐ N/A														

APPENDIX H (continued)

PLEASE DO NOT WRITE IN THIS AREA														
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TYPE OF FOOD	HOW OFTEN IN THE PAST YEAR									HOW MUCH EACH TIME SEE PORTION SIZE PICTURES FOR A-B-C-D				
	NEVER	A FEW TIMES per YEAR	ONCE per MONTH	2-3 TIMES per MONTH	ONCE per WEEK	TWICE per WEEK	3-4 TIMES per WEEK	5-6 TIMES per WEEK	EVERY DAY					
Pasta, breads, spreads, snacks														
Spaghetti, lasagna, or other pasta <u>with</u> tomato sauce	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Cheese dishes <u>without</u> tomato sauce, like macaroni and cheese	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Pizza, including carry-out	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many slices	☐ 1	☐ 2	☐ 3	☐ 4
Biscuits, muffins	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many each time	☐ 1	☐ 2	☐ 3	☐ 4
Rolls, hamburger buns, English muffins, bagels	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many each time	☐ 1/2	☐ 1	☐ 2	☐ 3
White bread or toast, including French, Italian, or in sandwiches	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many slices	☐ 1	☐ 2	☐ 3	☐ 4
Dark bread like rye or whole wheat, including in sandwiches	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many slices	☐ 1	☐ 2	☐ 3	☐ 4
Tortillas	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many each time	☐ 1	☐ 2	☐ 3	☐ 4
Margarine on bread, potatoes or vegetables	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many pats (Tsp.)	☐ 1	☐ 2	☐ 3	☐ 4
Butter on bread, potatoes or vegetables	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many pats (Tsp.)	☐ 1	☐ 2	☐ 3	☐ 4
Peanuts or peanut butter	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many TBSP.	☐ 1	☐ 2	☐ 3	☐ 4
Snacks like potato chips, corn chips, popcorn (Not pretzels)	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
Doughnuts, cake, pastry, pie	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many pieces	☐ 1	☐ 2	☐ 3	☐ 4
Cookies (Not lowfat)	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many	☐ 1-2	☐ 3-5	☐ 6-7	☐ 8+
Ice cream, frozen yogurt, ice cream bars	☐	☐	☐	☐	☐	☐	☐	☐	☐	How much	☐ A	☐ B	☐ C	☐ D
When you eat ice cream or frozen yogurt, is it	☐ Usually low-fat ☐ Sometimes ☐ Rarely low-fat ☐ N/A													
Chocolate candy, candy bars	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many bars	☐ small	☐ medium	☐ large	☐ 2 large

APPENDIX H (continued)

TYPE OF BEVERAGE	HOW OFTEN IN THE PAST YEAR									HOW MUCH EACH TIME SEE PORTION SIZE PICTURES FOR A-B-C-D				
	NEVER	A FEW TIMES per YEAR	ONCE per MONTH	2-3 TIMES per MONTH	ONCE per WEEK	TWICE per WEEK	3-4 TIMES per WEEK	5-6 TIMES per WEEK	EVERY DAY					
How often do you drink the following beverages?														
Real orange or grapefruit juice, Welch's grape juice, Minute Maid juices, Juicy Juice	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many glasses each time	☐ 1	☐ 2	☐ 3	☐ 4
Hawaiian Punch, Sunny Delight, Hi-C, Tang, or Ocean Spray juices	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many glasses each time	☐ 1	☐ 2	☐ 3	☐ 4
Kool Aid, Capri Sun or Knudsen juices	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many glasses each time	☐ 1	☐ 2	☐ 3	☐ 4
Instant breakfast milkshakes like Carnation, diet shakes like Slimfast, or liquid supplements like Ensure	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many glasses or cans	☐ 1	☐ 2	☐ 3	☐ 4
Glasses of milk (any kind)	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many glasses	☐ 1	☐ 2	☐ 3	☐ 4
When you drink glasses of milk what kind do you <u>usually</u> drink? MARK ONLY ONE:	☐ Whole milk ☐ Reduced fat 2% milk ☐ Low-fat 1% milk				☐ Non-fat milk ☐ Rice milk ☐ Soy milk				☐ I don't drink milk or soy milk					
Cream, Half-and-Half or non-dairy creamer in coffee or tea	☐	☐	☐	☐	☐	☐	☐	☐	☐	Total TBSP. on those days	☐ 1	☐ 2	☐ 3-4	☐ 5+
Regular soft drinks, or bottled drinks like Snapple (<u>Not</u> diet drinks)	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many bottles or cans	☐ 1	☐ 2	☐ 3-4	☐ 5+
Beer	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many bottles or cans	☐ 1	☐ 2	☐ 3-4	☐ 5+
Wine or wine coolers	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many glasses	☐ 1	☐ 2	☐ 3-4	☐ 5+
Liquor or mixed drinks	☐	☐	☐	☐	☐	☐	☐	☐	☐	How many drinks	☐ 1	☐ 2	☐ 3-4	☐ 5+

APPENDIX H (continued)

During the past year, have you taken any vitamins or minerals regularly, at least once a month?

☐ No, not regularly ☐ Yes, fairly regularly →

(IF YES) WHAT DID YOU TAKE FAIRLY REGULARLY?

VITAMIN TYPE	HOW OFTEN					FOR HOW MANY YEARS?					
	DIDN'T TAKE	A FEW DAYS per MONTH	1-3 DAYS per WEEK	4-6 DAYS per WEEK	EVERY DAY	LESS THAN 1 YR.	1 YEAR	2 YEARS	3-4 YEARS	5-9 YEARS	10+ YEARS
Multiple Vitamins. Did you take...											
Regular Once-A-Day, Centrum, or Thera type	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Stress-tabs or B-Complex type	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Antioxidant combination type	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Single Vitamins (not part of multiple vitamins)											
Vitamin A (not beta-carotene)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Beta-carotene	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Vitamin C	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Vitamin E	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Folic acid, folate	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Calcium or Tums, alone or combined with vit. D or magnesium	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zinc	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Iron	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Selenium	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Vitamin D, alone or combined with calcium	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

If you took vitamin C or vitamin E:

How many milligrams of **vitamin C** did you usually take, on the days you took it?

☐ 100 ☐ 250 ☐ 500 ☐ 750 ☐ 1000 ☐ 1500 ☐ 2000 ☐ 3000+ ☐ don't know

How many IUs of **vitamin E** did you usually take, on the days you took it?

☐ 100 ☐ 200 ☐ 300 ☐ 400 ☐ 600 ☐ 800 ☐ 1000 ☐ 2000+ ☐ don't know

How often do you use fat or oil in cooking?

☐ Less than once per week ☐ A few times per week ☐ Once a day ☐ Twice a day ☐ 3+ per day

What kinds of fat or oil do you usually use in cooking? MARK ONLY ONE OR TWO

☐ Don't know, or Pam ☐ Butter/margarine blend ☐ Lard, fatback, bacon fat
☐ Stick margarine ☐ Low-fat margarine ☐ Crisco
☐ Soft tub margarine ☐ Corn oil, vegetable oil
☐ Butter ☐ Olive oil or canola oil

Did you ever drink more beer, wine or liquor than you do now? ☐ Yes ☐ No

Do you smoke cigarettes now? ☐ Yes ☐ No

IF YES, On the average about how many cigarettes a day do you smoke now?

☐ 1-5 ☐ 6-14 ☐ 15-24 ☐ 25-34 ☐ 35 or more

What is your ethnic group? (MARK ONE OR MORE)

☐ Hispanic or Latino ☐ Black or African American ☐ American Indian or Alaska Native
☐ White, not Hispanic ☐ Asian ☐ Native Hawaiian or Other Pacific Islander

Thank you very much for filling out this questionnaire. Please take a minute to go back and fill in anything you may have skipped.

PLEASE DO NOT WRITE IN THIS AREA

VITA

NAME: KATRINE WALLACE

EDUCATION:

2013 The University of Illinois-Chicago, Chicago, Illinois
PhD in Public Health-Epidemiology

1996 DePaul University, Chicago, Illinois
Master of Arts in Social Science

1993 DePaul University, Chicago, Illinois
Bachelor of Arts in Sociology

PROFESSIONAL EXPERIENCE:

Covidien Inc., Mansfield, Massachusetts, 2011–present
Director, Health Economics and Outcomes Research

The University of Illinois at Chicago, Chicago, Illinois, 2004–present
Research Fellow in the School of Public Health, Department of Epidemiology
& Biostatistics and the Institute for Health Research and Policy

Astellas Pharma US Inc., Deerfield, Illinois, 2008–2011
Assistant Director, Pharmacoepidemiology

Takeda Global Research and Development Ltd., Deerfield, Illinois, 2005–
2008
Pharmacoepidemiology and Outcomes Research Consultant

Abbott Laboratories, Abbott Park, Illinois, 2003–2005
Senior Manager, Health Economics and Outcomes Research

TAP Pharmaceutical Products, Inc., Lake Forest, Illinois, 2000–2003
Manager, Health Economics and Outcomes Research (2001–2003)
Senior Clinical Research Associate (2000–2001)

Baxter Healthcare Corporation, Round Lake, Illinois, 1996–1999
Clinical Research Associate/Monitor

Formations in Health Care, Chicago, Illinois, 1993–1996
Manager of Data and Report Processing

VITA (continued)

TEACHING/MENTORING ROLES:

University of Illinois at Chicago

EPID 400 Principles of Epidemiology—Teaching Assistant for graduate level course in the online format, gave interactive guidance on the internet, graded homework grading, and prepared and proctored tests for up to 50 students

EPID 501 Advanced Methods in Epidemiology—Teaching Assistant for 15 student PhD level course. Held weekly office hours to assist students with SAS programming and statistical methodology, lead four classroom sessions on the following statistical methods: logistic regression for case-control studies, poisson regression for cohort studies, conditional logistic regression for matched case-control studies, and multi-level analysis (RRM) for longitudinal data with missing values and repeated measures

RECENT PUBLICATIONS:

Furner S. E., K. L. Wallace, L. M. Arguelles, T. Miles, J. Goldberg. 2010. “Factors Associated with Self-Reported Health: A Twin Study of Older African American Women.” *Journal of Women and Aging* 22 (2): 83–93.

Wallace, K. L., S. E. Furner, V. F. Freeman, and F. M. Davis. 2006. “Racial Trends in Prostate Cancer Incidence Rates for Illinois and the United States; 1986–2000.” *Journal of Registry Management* 33 (4): 108–110.

Latini, D. M., D. F. Penson, K. L. Wallace, D. L. Lubeck, and T. F. Lue. 2006. “Longitudinal Differences in Psychological Outcomes for Men with Erectile Dysfunction: Results from ExCEED.” *Journal of Sexual Medicine* 3 (6): 1068–76.

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Furner, S. E., K. L. Wallace, L. M. Arguelles, T. Miles, J. and Goldberg. 2006. “A Twin Study of Depressive Symptoms among Older African American Women.” *Journal of Gerontology* 61 (6):P355–61.

Kane, C. J., W. W. Bassett, N. Sadetsky, S. Silva, K. L. Wallace, D. J. Pasta, M. R. Cooperberg, J. M. Chan, and P. R. Carroll. 2005. “Obesity and Prostate Cancer Clinical Risk Factors at Presentation: Data from CaPSURE, *Journal of Urology* 173 (3): 732–36

VITA (continued)

Arredondo, S. A., T. M. Downs, D. P. Lubeck, D. J. Pasta, S. J. Silva, K. L. Wallace, and P. R. Carroll. 2004. "Watchful Waiting and Health-Related Quality of Life for Patients with Localized Prostate Cancer: Data from CaPSURE." *Journal of Urology* 172 (5): 1830–34.

Cooperberg, M. R., J. M. Broering D. M. Latini, M. S. Litwin, K. L. Wallace, and P. R. Carroll. 2004. "Patterns of Practice in the United States: Insights from CaPSURE on Prostate Cancer Management." *Current Urology Reports*. 5 (3): 166–72.

Greene, K. L., M. V. Meng, E. P. Elkin, M. R. Cooperberg, D. J. Pasta, M. W. Kattan, K. L. Wallace, and P. R. Carroll. 2004. "Validation of the Kattan Preoperative Nomogram for Prostate Cancer Recurrence Using a Community Based Cohort: Results from Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE)." *The Journal of Urology*. 171 (6): 2255–59.

Wallace, K. L., A. Riedel, N. Joseph-Ridge, and R. Wortmann. 2004. "Increasing Prevalence of Gout and Hyperuricemia among Older Adults in a Managed Care Population." *Journal of Rheumatology* 31 (8): 1582–87.

Riedel, A., M. Nelson, N. Joseph-Ridge, K. L. Wallace, P. MacDonald, and M. Becker. 2004. "Compliance with Allopurinol among Managed Care Enrollees with Gout." *Journal of Rheumatology* 31 (8): 1575–81.

Riedel, A., M. Nelson, K. L. Wallace, N. Joseph-Ridge, M. Cleary, and A. Fam. 2004. "Prevalence of Comorbid Conditions and Prescription Medication Use among Older Patients with Gout and Hyperuricemia in a Managed Care Setting." *Journal of Clinical Rheumatology* 10 (6): 308–14.

Penson, D. F., D. M. Latini, K. L. Wallace, J. M. Henning, T. F. Lue, and D. L. Lubeck. 2003. "Is the Impact of Erectile Dysfunction on Quality of Life Different in Men with Prostate Cancer Than in Men with Erectile Dysfunction Due to Other Causes?: Results from the ExCEED Database." *The Journal of Urology* 169 (4): 1458–61.

Latini, D. M., D. F. Penson, D. L. Lubeck, K. L. Wallace, J. M. Henning, and T. F. Lue. 2003. "Longitudinal Differences in Disease-Specific Quality of Life for Men with Erectile Dysfunction." *The Journal of Urology*. 169 (4): 1437–42.

VITA (continued)

Penson, D.F., D. M. Latini, D. L. Lubeck, K. L. Wallace, J. M. Henning, and T. F. Lue. 2003. "Diabetic Men with Erectile Dysfunction Are Unique from the General Population of Impotent Men." *Diabetes Care* 26 (4): 1093–99.

Garoufalidis, M., and K. L. Wallace. 1996. "Medical Outcome Data Measurement Transcends Rehab Continuum." *Hospital Rehab* (5) 7: 91–94.

PRESENTED RESEARCH:

Wallace, K. L., S. Minor, and A. Krantz. 2007. "Prevalence of Heroin Use and Heroin-Related Asthma Symptoms in an Inner City Asthmatic Population." Podium presentation at the American Public Health Association Annual Meeting. Washington, DC, November 5.

Wallace, K. L., S. E. Furner, V. F. Freeman, and F. M. Davis. 2006. "Racial Trends in Prostate Cancer Incidence Rates for Illinois and the United States; 1986–2000." Poster presented at the American Public Health Association Annual Meeting. Boston, MA, November 8.

Furner, S. E., K. L. Wallace, L. M. Arguelles, T. Miles, and J. Goldberg. 2006. "A Twin Study of Factors Associated with Self-Reported Health among Older African American Women." Paper presented at the Gerontological Society of America Annual Meeting. Dallas, TX, November 18.

Pearce D., K. L. Wallace, A. Kulkarni, R. Balkrishnan, and S. Feldman. 2005. "Psoriasis and Work Productivity." Paper presented at American Academy of Dermatology 2005 Annual Meeting. New Orleans, LA, February.

Wallace, K. L., D. Chen, M. Heffernan, R. Langley, and A. Menter. 2005. "Quality of Life in Moderate to Severe Plaque Psoriasis Patients Receiving 24 Weeks of Adalimumab Therapy." Abstract. *Journal of the European Academy of Dermatology and Venereology* 18 (Supp. 2) 359.

Wallace, K. L., R. Hamlin, R. Langley, D. Chen. 2005. "Results of the DLQI Dermatology-Specific Quality of Life Measure in Moderate to Severe Plaque Psoriasis Patients Receiving 12 Weeks of Adalimumab Therapy." Paper presented at the summer meeting of the American Academy of Dermatology. New York, NY, July.

VITA (continued)

Wallace, K. L., B. Miller, M. Heffernan, and D. Chen. 2005. "Results of the SF-36 General Health Status Measure in Moderate to Severe Chronic Plaque Psoriasis Patients Treated with Adalimumab for 12 Weeks." Paper presented at the summer meeting of the American Academy of Dermatology. New York, NY, July.

Wallace, K. L., E. P. Elkin, D. M. Latini, and P. M. Carroll. 2004. "Timing of LHRH Treatment after PSA Failure in Prostate Cancer Patients: A Survival Analysis from the CaPSURE database." Paper presented at American Urological Association Annual Meeting.

Wallace, K. L., A. Riedel, N. Joseph-Ridge, and R. Wortmann. 2004. "Increasing Prevalence of Gout and Hyperuricemia among Older Adults in a Managed Care Population." Paper presented at the National Medical Association Annual meeting.

Riedel, A, M. Nelson, K. L. Wallace, N. Joseph-Ridge, M. Cleary, and A. Fam. 2004. "Prevalence of Comorbid Conditions and Prescription Medication Use among Older Patients with Gout in a Managed Care Setting." Paper presented at the National Medical Association Annual meeting.

Kane, C. J., W. W. Bassett, N. Sadetsky, S. Silva, K. L. Wallace, D. J. Pasta, M. R. Cooperberg, J. Chan, and P. R. Carroll. 2004. "Is obesity associated with more aggressive prostate cancer? (Data from CaPSURE)." Paper presented at American Urological Association Annual Meeting.

Arredondo, S. A., E. P. Elkin, P. L. Marr, D. M. Latini, K. L. Wallace, and P. R. Carroll. 2004. "Comorbidity and Health Related Quality of Life in Men with Prostate Cancer: Data from CaPSURE." Paper presented at American Urological Association Annual Meeting.

Chan, J. M., E. P. Elkin, S. Silva, K. L. Wallace, J. Broering, J., and P. R. Carroll. 2004. "Contemporary Complementary and Alternative Medicine Use among Men with Prostate Cancer-Data from CaPSURE." Paper presented at American Urological Association Annual Meeting.

Latini, D. M., E. P. Elkin, M. R. Cooperberg, N. Sadetsky, K. L. Wallace, and P. R. Carroll. 2004. "Differences in Clinical Characteristics and Disease-Free Survival for Latino, African-American, and Non-Latino White Men with Prostate Cancer: Data from CaPSURE?" Paper presented at American Urological Association Annual Meeting.

VITA (continued)

Meng, M. V., E. P. Elkin, D. M. Latini, K. L. Wallace, and P. R. Carroll. 2004. "Management of Patients with High-Risk Localized Prostate Cancer: Data from CaPSURE." Paper presented at American Urological Association Annual Meeting.

Purohit, R., S. Silva, D. P. Lubeck, K. L. Wallace, and P. R. Carroll. 2004. "Predictors of Adverse Health-related Quality of Life Outcomes in Men, Undergoing Androgen Deprivation Therapy." Paper presented at Urological Association Annual Meeting.

Wallace, K. L., A. Riedel, M. Nelson, N. Joseph-Ridge, P. MacDonald, and M. Becker. 2003. "Compliance with Allopurinol among Managed Care Enrollees with Gout." Paper presented at American College of Rheumatology.

Wallace, K. L., D. M. Latini, D. F. Penson, J. M. Henning, D. L. Lubeck, and T. F. Lue. 2003. "Longitudinal Differences in Psychological Adjustment for Men with Erectile Dysfunction: Results from ExCEED." Paper presented at International Society for Pharmacoeconomics and Outcomes Research.

Wallace, K. L., D. M. Latini, D. F. Penson, J. M. Henning, D. L. Lubeck, and T. F. Lue. 2003. "Predictors of Response to Erectile Dysfunction Treatment at 12 Months: Results from the ExCEED Database." Paper presented at International Society for Pharmacoeconomics and Outcomes Research.

Penson, D. F., D. M. Latini, K. L. Wallace, J. M. Henning, D. L. Lubeck, and T. F. Lue. 2003. "Predictors of Having More Than One Treatment for Erectile Dysfunction: Results from the ExCEED Database." Paper presented at American Urological Association.

Latini, D. M., D. F. Penson, K. L. Wallace, J. M. Henning, D. L. Lubeck, and T. F. Lue. 2002/2003. "Longitudinal Differences in Disease-Specific Quality of Life for Men with Erectile Dysfunction: Results from ExCEED." Abstract accepted for poster presentation at American Urological Association 2003, International Society for Sexual and Impotence Research 2002, and American Urological Association Western Section 2002.

Penson, D. F., D. M. Latini, K. L. Wallace, J. M. Henning, D. L. Lubeck, and T. F. Lue. 2002/2003. "Is the Impact of Erectile Dysfunction on Quality of Life Different in Men with Prostate Cancer Than in Men with Erectile Dysfunction Due to Other Causes? Results from the ExCEED Database." Paper presented at American Urological Association 2003, International Society for Sexual and Impotence Research 2002 and American Urological Association Western Section 2002.

VITA (continued)

Penson, D. F., D. M. Latini, D. L. Lubeck, K. L. Wallace, J. M. Henning, and T. F. Lue. 2002. "Diabetic Men with Erectile Dysfunction Are Unique from the General Population of Impotent Men: Results from the ExCEED Database." Paper presented at International Society for Sexual and Impotence Research 2002 and AUA Western Section 2002.

PROFESSIONAL MEMBERSHIPS:

American Public Health Association (APHA)
Society for Epidemiologic Research (SER)
International Society for Pharmacoepidemiology (ISPE)
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

SCIENTIFIC PEER REVIEW:

Peer Reviewer:

International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
American Public Health Association (APHA)
Society for Epidemiologic Research (SER)
The Journal of Rheumatology
Value in Health Journal

Grant Proposal Reviewer:

Chicago Department of Public Health (CDPH)—HIV/AIDS unit
University of Illinois—Seed grants for the EXPORT rural public health research program

FUNDED RESEARCH AWARDS:

National Institute on Aging Predoctoral Research Fellowship (\$22,000/yr), 2004–present

Midwest Roybal Society for Research on Health Promotion (\$5,000), 2005

US Department of Defense Prostate Cancer Research Traineeship (\$99,170), 2005–2008

Paul D. Doolen Award for the Study of Aging (\$4,000), 2006