METABOLIC SYNDROME, VITAMIN D STATUS

AND INCIDENCE OF PROSTATE CANCER

BY

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ABSTRACT

Background: Epidemiologic data on the role of metabolic syndrome on prostate cancer risk is inconsistent, and only one case-control trial has examined the combined relationship of metabolic syndrome and vitamin D deficiency.

Objective: To determine the association of metabolic syndrome and vitamin D insufficiency on prostate cancer.

Design: De-identified data for blood pressure, BMI, triglyceride, HDL, serum glucose, 25-hydroxyvitamin D, and prostate cancer diagnosis were collected retrospectively from the HERON database on 104 men who received care at the University of Kansas Medical Center from 2003 to 2012. Logistic regression was used to determine the association between metabolic syndrome, vitamin D concentration and prostate cancer.

Results: Vitamin D insufficiency was not significantly associated with prostate cancer and did not have a significant interaction with metabolic syndrome. High HDL (>60 mg/dL) was protective against prostate cancer (p=0.04, OR .173) compared to normal HDL (40-60 mg/dL). High systolic blood pressure (>135 mmHg) increased the risk of prostate cancer among general age-matched controls (p=0.03 OR=2.58) compared to normal blood pressure (<135 mmHg). No other elements of metabolic syndrome or the clustering of elements together were significant.

Conclusion: Metabolic syndrome with vitamin D insufficiency did not prove to be significantly associated with prostate cancer diagnosis. Only elevated systolic blood pressure (>135 mmHg) was significantly associated with an increased risk of prostate cancer, whereas high HDL was associated with a protective effect.

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Chapter I: Introduction

With an estimated 241,740 new diagnoses in 2012, prostate cancer remains the most common non-cutaneous cancer and leading cause of cancer death in men in the United States. In 2012 prostate cancer caused an estimated 28,170 deaths (1). The inter-relationships among disease states and prostate cancer development are not well understood. Internationally, variations in the prevalence of chronic diseases, including prostate cancer, suggest lifestyle factors may contribute to development. Metabolic syndrome is a clustering of several risk factors resulting from obesity and insulin resistance. It is much more prevalent in Western societies than in Eastern societies, a trend that is also true in prostate cancer prevalence. The potential role of metabolic syndrome in the development of prostate cancer is unclear due to inconsistent results among studies. Variation in vitamin D status among participants may explain some of the variation seen between studies. Vitamin D and metabolic syndrome both share common signaling pathways that together may influence the development of prostate cancer. However, only one study has examined the combined role of metabolic syndrome and vitamin D status on prostate cancer risk. An increase in prostate cancer risk in patients with both metabolic syndrome and vitamin D deficiency, as compared to men without metabolic syndrome and adequate vitamin D levels was reported in this study (2).

The current trends of rising obesity and low vitamin D levels within the U.S. may put men at greater risk for prostate cancer and identify a possible mechanism for prostate cancer prevention. The Center for Disease Control estimated that 35.1% of American men met the criteria for Metabolic Syndrome in 2006 (3). An estimated one fourth of the U.S. population were at risk for vitamin D inadequacy in 2001-2006, and eight percent

were at risk for deficiency (4). Vitamin D status, according to serum 25(OH) Vitamin D concentrations is outlined in **Table 1**. Older adults (over 51 years of age) are also at increased risk of vitamin D deficiency (4).

Table 1. Vitamin D status, according to IOM standards for serum 25(OH) vitamin D concentration.

Category	Serum Concentration Range (nmol/L)
Risk deficiency with leading to osteomalacia	<30
Risk inadequacy for bone and overall health	30-50
Adequate for bone and overall health	50-125
Potential adverse effects	≥125

Statement of Purpose

The aim of this study was to determine the association between metabolic syndrome with vitamin D insufficiency and prostate cancer by testing the following aims.

1. Investigate the association between metabolic syndrome and vitamin D inadequacy (<50 nmol/mL) on prostate cancer. I hypothesize that men with metabolic syndrome and vitamin D insufficiency will have a higher incidence of prostate cancer than men without metabolic syndrome who have adequate vitamin D.
2. Evaluate interaction between individual risk factors for metabolic syndrome and vitamin D (see Table 2) on incidence of prostate cancer, and the association between each risk factor.

Table 2. Risk factors for Metabolic Syndrome in Males (according to ATP III guidelines) (5)

Risk Factor	Defining Level
Abdominal Adiposity	Waist Circumference >102 cm (>40in)
Triglycerides	≥150 mg/dL
HDL	<40 mg/dL*
Blood Pressure	≥130/≥85 mmHg
Fasting Glucose	≥110 mg/dL

*40-60 mg/dL, and >60 mg/dL were added as HDL categories during the analysis.

My hypothesis is that the presence of risk factors associated with metabolic syndrome along with vitamin D insufficiency will correlate to an increased risk of developing prostate cancer. This study will provide the estimated risk of developing prostate cancer based on the presence of metabolic syndrome and vitamin D insufficiency. The knowledge of prostate cancer development gained through coordination and implementation of this project will help me counsel cancer patients as a future clinical oncology dietitian and guide the generation of future hypotheses.

Chapter II: Literature Review

Introduction

Metabolic syndrome is a cluster of risk factors centered on obesity, a growing epidemic in the United States (3). These risk factors are described with inclusion of clinical characteristics in **Table 2**. Clinical identification of metabolic syndrome uses criteria set by the National Cholesterol Education Program, Adult Treatment Panel III (ATP III). Three of the five characteristics must be present to diagnose metabolic syndrome. Those that have metabolic syndrome have increased risk of cardiovascular disease, as well as other chronic diseases (5).

Prostate cancer risk based on the presence of metabolic syndrome remains uncertain due to the heterogeneity between studies conducted, including: the populations studied, the criteria used to assess metabolic syndrome (diagnoses, anthropometric measurements, laboratory measures, etc.), and the end points measured (PSA dynamics, histologically confirmed prostate cancer, prostate cancer related death). One possible explanation for the mixed data separate from the heterogeneity may be the interaction of vitamin D with metabolic syndrome.

Vitamin D insufficiency and metabolic syndrome both share common signaling pathways that when combined, may produce a synergistic effect. Vitamin D and Lipoproteins have been demonstrated to form common compounds with the same receptor resulting in differing translational effects (6). The combination of metabolic syndrome with vitamin D insufficiency may result in an additive effect. This may be one reason for the inconsistencies among studies, as only one study to date has examined the

risk of developing prostate cancer (2) with the combination of metabolic syndrome and vitamin D insufficiency.

Metabolic Syndrome and Prostate Cancer Risk

Mechanism: Metabolic syndrome may interact to promote prostate cancer through several pathways. As previously described each individual risk factor involved may contribute to an increased risk of prostate cancer, and together may provide a synergistic effect. One hypothesis centers around the role of insulin resistance and the increase in insulin growth factor-I (IGF-1), leading to increased cell proliferation and growth (7). Insulin resistance is often seen with obesity, which as described leads to hormonal changes (decreasing testosterone and sex-hormone binding globulin (SHBG), and increasing estradiol concentration) which could promote different prostate cancer types (8). The influence of lipid raft signaling from altered lipid homeostasis and increase in androgen signaling from sympathetic nervous system signaling with the effects of obesity and insulin resistance is not fully understood. Further research is needed to determine if individual risk factors have an additive effect on risk of developing prostate cancer.

Evidence: Current evidence on the role of metabolic syndrome and the incidence of prostate cancer is inconsistent, however several studies have shown a significantly increased risk of prostate cancer due to the additive effect of multiple risk factors. Two case controls studies show significant increases in prostate cancer risk with the combination of at least three elements (9-11). Although, one study found statistical significance only in African-Americans but not Caucasians (11). Two cohort studies also showed significant increases in risk with three or more risk factors, but failed to show

significance with individual risk factors (2, 12). However, not all studies coincide with these findings.

Several studies have shown a lack of association or a protective effect between metabolic syndrome and prostate cancer. Two large cohorts failed to show an increased risk from a combination of three risk factors (13, 14). One cohort study even found a decreased risk of prostate cancer (RR 0.77, CI 0.6-0.98) with metabolic syndrome (14). The authors hypothesize that the reduced production of insulin after damage to the pancreas from long term Type II diabetes coincides with the reduction in risk. The discrepancy in findings among research studies may be explained by their heterogeneity as described earlier.

The heterogeneity in study design may have resulted in the diverging overall findings. Study designs differed in populations studied, some restricting race, others using European populations who don't routinely screen with prostate specific antigen (PSA) which may have increased the rate of advanced cancers. Other factors include the variance in measurement of risk factors (diagnosis vs. standardized measurements), variance in risk factors collected (collecting only three selected risk factors vs. information on all five), standards used for diagnosing metabolic syndrome (ATP III guidelines, vs. alternate standards), and study design (cross-sectional vs. cohort). These factors limit the generalizability of the studies. Another possible explanation for the variability among metabolic syndrome studies on the incidence of prostate cancer may involve the vitamin D status of the participants.

Vitamin D, Metabolic Syndrome, and Prostate Cancer Risk

Mechanism: An interaction between metabolic syndrome and vitamin D insufficiency may come from shared signaling pathways between the two factors. Obesity results in increases in lipoprotein remnants. These remnants act as ligands for peroxisome-proliferator-activated receptors (PPAR) especially PPAR-γ (15). PPARs are known to influence adipogenesis, lipid metabolism, insulin sensitivity, and inflammation in relation to metabolic syndrome (2). PPAR-γ and vitamin D receptor both bind to a common receptor, Retinoid X receptor forming heterodimers which are highly expressed in prostate tissue (6). These heterodimers are known to influence each other's target gene, regulating prostate cell growth and apoptosis (6, 15). Active vitamin D has also been shown to regulate IGF leading to decreased IGF-II expression, and increased production of insulin-like growth factor binding protein III (16). This complex relationship of signaling pathways is not fully understood but suggests vitamin D status may play a role in metabolic syndrome and prostate cancer development.

Evidence: To my knowledge only one study has examined the combined effect of metabolic syndrome with vitamin D status demonstrating a positive relationship with risk of prostate cancer. A recent cohort study found that elevated blood pressure, increased body mass index (BMI), and low HDL increased the risk of prostate cancer (OR 3.36, p 0.02) (2). Men who were also vitamin D deficient (<40 nmol/L), had an eight fold increase in risk (OR 8.03 p=0.05) compared to men without vitamin D insufficiency and free of metabolic syndrome (2).

Cholesterol and Prostate Cancer Risk

Mechanism: Cholesterol may influence several possible pathways leading to the initiation and progression of prostate cancer. The prostate is a cholesterol rich tissue; therefore elevated serum cholesterol may result in the accumulation of cholesterol in the cell membrane forming large lipid rafts. These lipid rafts have been shown to have pro-carcinogenic cell signaling effects (17). The Akt and Sonic hedgehog pathways are cholesterol sensitive and are related to prostate carcinogenesis (17). In vitro reduction of cholesterol has been shown to induce apoptosis in prostate cancer cell lines through inhibition of phosphatidylinositol 3-kinase/Akt pathway (18, 19). The interaction between these pathways is not fully understood and is still being investigated.

Evidence: Due to the aforementioned mechanisms, elevated serum cholesterol levels may also be a factor in prostate cancer development, although it is not a criterion of metabolic syndrome. Several studies have shown a positive association between cholesterol and prostate cancer risk. A large cohort study showed that total cholesterol greater than 240 mg/dL compared to less than 160 mg/dL was positively associated with prostate cancer (HR 1.24, 95% CI 1.07-1.44), but lacked evaluation based on cancer stage/grades (20). A different cohort study that incorporated grade analysis also found a positive association between elevated cholesterol (>240 mg/dL vs. <200 mg/dL) and overall prostate cancer, as well as advanced prostate cancer (stage 3) (21). In a third study, Platz et al (22) found a decreased risk of prostate cancer with low total cholesterol level, especially in organ confined prostate cancer.

Not all studies that have been done on cholesterol and prostate cancer have found similar results. Smith et al (23) found no association between serum cholesterol and prostate cancer in a smoking population. In addition, the Campaign Against Cancer and Stroke cohort shows a decreased risk (HR 0.68, CI 0.4-1.18) of prostate cancer with elevated cholesterol (>240 mg/dL) compared to non-elevated cholesterol (<240 mg/dL) (24). These discrepancies in results may be due to the variability in serum cholesterol levels compared. In addition, variations also existed between participant populations; smoker vs. non-smokers, racial diversity, and inclusion and exclusion criteria.

Elevated Triglycerides and Prostate Cancer Risk

Mechanism: Elevated triglycerides may increase prostate cancer risk through lipoprotein signaling pathways. Hypertriglyceridemia results in the accrual of very low-density lipoproteins, chylomicrons, which are hydrolyzed, producing remnant lipoproteins. Lipoprotein remnants result in activation of Akt signal transduction, and mitogen-activated protein kinases, which increase prostate cancer cell proliferation (25). However, it is not well understood at what concentration similar results would occur in human subjects.

Evidence: The impact of elevated triglyceride levels on prostate cancer risk varies among the population studied and may only be significant with the presence of another chronic disease risk factor. A large cohort study found no significant association with high triglycerides and prostate cancer alone, but high triglycerides combined with high fasting glucose showed a significantly increased risk (HR 1.23, CI 1.01-1.48,

Triglycerides >1.71 mmol/L, Glucose >100 mg/dL) (26). The significance of these two risk factors with metabolic syndrome provides evidence for the additive effects seen.

Other studies have shown significant results with triglycerides alone. One study found significant associations with elevated triglycerides and prostate cancer in men 60-69 years (OR 2.10, CI 1.31-3.37) and 70 or greater (OR 1.91, CI 1.03-3.53), but not among men younger than 60 years (27). Excluding subjects that used statins in either study did not significantly alter the results. However, the significance may be explained by the increased risk of prostate cancer from age alone. An Austrian study found an increased risk for every log unit increase in triglycerides (28), providing evidence that the extent of triglyceride level, may increase your risk of prostate cancer. Triglycerides are not the only serum lipid marker involved with metabolic syndrome; HDL is also a risk factor.

Low HDL and Prostate Cancer Risk

Mechanism: High Density Lipoprotein (HDL) has been hypothesized to provide protection from prostate cancer due to its role in removing cholesterol from tissues, and ultimately from the body. HDL has also been shown to be anti-inflammatory, as it reduces circulating levels of inflammatory cytokines (29). In addition, preliminary research has also shown HDL to decrease tumor necrosis factor alpha (TNF-α) in animal models, decreasing tissue damage, which may help prevent prostate cancer initiation (30). The complete role of HDL in oncogenesis is unclear and further research is needed to determine possible interactions that may provide protection.

Evidence: The association with low HDL and prostate cancer risk is still not clear. One large Swedish cohort and one American case-control study found an inverse relationship between serum HDL concentration and prostate cancer risk (26, 31). An American study controlled for statin use, but found it had no effect on the association (31). Two case-control trials from America and Finland and one Norwegian cohort study found no significant association between HDL and prostate cancer (2, 13, 21). Several limitations may account for the variation in results. None of the studies controlled or accounted for dietary habits among participants and eating patterns greatly differ between Northern Europeans and Americans, which may have correlated to lipid profile changes. Few studies controlled for smoking habits among participants or included only smoking participants. Smoking has been identified to increase the risk of prostate cancer, and may have confounded the results. Further research with greater control of confounding variables is needed to determine if an association exists.

Blood Pressure and Prostate Cancer Risk

Mechanism: Blood pressure is another risk factor of metabolic syndrome, which may contribute to an increased risk of prostate cancer. Prostatic growth has been shown to be the result of a balance of sympathetic and parasympathetic activity (32). Elevated blood pressure may contribute to onocogenesis through the increase in sympathetic nervous system activity, which may in turn result in increased prostatic growth (33). The exact mechanism by which growth is stimulated is currently unknown.

Evidence: One large cohort study of Norwegian men found a significant association between blood pressure and prostate cancer risk (34). They found a 4% increase in risk

for every 18.3 mmHg increase in systolic blood pressure, which remained even when excluding those on antihypertensive medication from analysis (34). Two cohort studies and one case-control study found no significant association with increased blood pressure and prostate cancer risk (35-37). Fitzpatrick et al (35), found positive associations between blood pressure and heart rate with prostate cancer. However they observed inverse associations with antihypertensive medication use. Several limitations prevent comparison between these studies. Not all the studies controlled for use of anti-hypertensive medications, which could confound the results of associations observed. Dietary patterns were unknown, duration of hypertension or treatments of hypertension were also not controlled, and family history of hypertension was not collected in all of the studies. The combined limitation of these studies warrants further research on the subject.

Elevated Fasting Glucose and Prostate Cancer Risk

Mechanism: Elevated fasting glucose is a sign of insulin resistance, which plays a large role in metabolic syndrome, and may also have oncogenic properties. As described with metabolic syndrome, insulin resistance leads to an increase in IGF-1 (7). Elevated IGF-1 has been found to be predictive of prostate cancer (7). It has also been demonstrated to increase cell proliferation and decrease apoptosis (38). Increases in circulating insulin have also been shown to decrease insulin-like growth factor binding protein (IGFBP), resulting in a larger concentration of circulating IGF. Together, the combination has been demonstrated to increase the risk of developing prostate cancer (7).

Evidence: Studies examining the association of insulin resistance and prostate cancer vary according to the variable chosen to represent insulin resistance. In a cohort study of

men with benign prostatic hyperplasia, fasting glucose concentration was positively associated with prostate size (39). Nimptsch et al. (40) examined the role of glycemic index and glycemic load on prostate cancer risk based on food frequency questionnaires, but found no significant association with prostate cancer risk. However, the study relied on glycemic load which is highly dependent on the combination of foods eaten, and may not accurately reflect true blood glucose levels.

Several case-control and cohort studies have also used fasting glucose or presence of diabetes to classify insulin resistance. However, one cohort study found a positive association with fasting glucose level and prostate cancer risk (14). Type 2 diabetes is also another way to define insulin resistance. Three large cohort studies found no statistically significant association with blood glucose and prostate cancer risk, although, the studies varied in fasting and non-fasting blood glucose measurements (12, 13, 41). Three studies using self reported presence of diabetes found no statistically significant association with prostate cancer risk(9-11).

The generalizability of these studies remains difficult due to the heterogeneity between studies. The multiple criteria used to establish insulin resistance limits comparison between studies. Even studies using serum glucose are limited due to the difference in fasting or random glucose measures used. Type 2 diabetes reflects a more complex disease than insulin resistance alone and may not accurately reflect the role of insulin resistance in the development of prostate cancer. Further research with standardized measurements is needed to further explore this potential association.

Central Adiposity and Prostate Cancer Risk

Mechanism: There are several hypotheses regarding the role of obesity in prostate cancer initiation and progression. Obesity represents a complex change in metabolic factors and also increases the risk of several of the other metabolic syndrome risk factors (insulin resistance, blood pressure, and altered lipid homeostasis) (42). Abdominal adiposity is often the focus of studies due to its known role in increasing hormone production (43). Obese men have been shown to have altered circulating hormone levels including decreased serum testosterone, decreased SHBG, and increased estrogen concentrations (44). Testosterone is converted to dihydrotestosterone (DHT) in the prostate which binds to androgen receptors promoting DNA synthesis and cell proliferation (45). One study found a decrease in testosterone to be protective only against non-aggressive prostate cancer, but resulted in an increased risk of aggressive cancer (8). Increased estradiol concentrations were also shown to be protective against non-aggressive prostate cancer (8). Further studies are needed to determine the complex relationship involved with hormonal changes involved with obesity and prostate cancer development.

Evidence: A large amount of studies have used BMI as a marker of obesity, even though it is a nonspecific maker and does not differentiate between adipose tissue and fat free mass. Therefore, waist circumference and waist to hip ratio have been used to provide a more accurate tool for measuring obesity as well as abdominal adiposity. Several cohort studies including the Harvard Alumni Health Study, have found significant association between prostate cancer risk and measures of height, weight, BMI, waist to hip ratio, and waist circumference (46-48).

Hsing et al. (49) found a positive association with waist to hip ratio (>0.92 vs <0.86) and prostate cancer risk (OR 2.71, CI 1.66-4.41), but no significant association with BMI in a Chinese population of healthy weight men (average BMI 23.1). Two European cohorts found significant associations with waist circumference and waist to hip ratio and prostate cancer risk (50, 51). DeNunzio et al. (50) further divided men into categories based on obesity (BMI >30) and presence of central adiposity (Waist circumference >40 in). They found a large increase in prostate cancer risk in obese men without central adiposity, as well as those with or without obesity who have central adiposity. Inconsistencies may be due to differing study design, such as the varying markers of adiposity used (BMI, Waist Circumference, and Waist to Hip Ratio) and methods of collection (self-reported, standardized collection, self-reported weight trends through decades).

A meta-analysis on measures of obesity and prostate cancer risk found overall weak positive associations (rate ratios 0.96-1.12) with obesity and prostate cancer (52). The study included 31 cohort studies and 25 case-control studies, which contained information on measures of adiposity and prostate cancer development or mortality. Results were stratified for BMI showing an increased overall risk (rate ratio 1.05 per 5 kg/m^2 increment, CI 1.01-1.08), increased risk of advanced prostate cancer (rate ratio 1.12 per 5 kg/m^2, CI 1.01-1.23), but no significant association was found with localized prostate cancer (52). There was also an increased risk based on waist circumference (rate ratio 1.03 per 10 cm increment, CI 0.99-1.07), and waist to hip ratio (RR 1.11 per 0.1 increment, CI 0.95-1.30) but they were not significant (52). Continued work confirms positive associations with obesity and risk of advanced or metastatic cancer (53). Recent

evidence shows direct correlation between body shape and changes in IGFs and IGFBPs (53). The difference in the strength of association seen in these studies may be due to the heterogeneity of the population and methods used. BMI also fails to detect sarcopenic obesity, the loss of muscle mass and gain of fat mass, which affects this aging population and may prevent studies using BMI as a tool to see more significant results.

Chapter III: Materials and Methods

Study Overview

A retrospective data set was compiled by searching electronic medical records, and the cancer registry database for patients at University of Kansas Hospital (KUH) using a medical informatics database. The primary aim was to determine if there is an association between metabolic syndrome with vitamin D insufficiency and prostate cancer. The secondary aim was to determine if there is an association of prostate cancer with each individual metabolic syndrome risk factor on incidence of prostate cancer and with interaction with vitamin D.

Data Extraction

Participants were male patients of the University of Kansas Hospitals and Clinics from 2003-2012. Three cohorts of patients were extracted based on characteristics outlined in **Table 3**. All patients had at least one laboratory value for each measure to ensure metabolic syndrome and vitamin D status could be evaluated.

HERON, the medical informatics database used, is an integration of data collected from the KUH electronic medical record (EMR), billing system, and national cancer registry, which includes clinical and biomedical data (54). The database was queried through use of the Informatics for Integrating Biology & the Bedside (i2b2) tool (version 1.6). Search terms are outlined in **Appendix A**. This work was supported by a CTSA grant from NCRR and NCATS awarded to the University of Kansas Medical Center for Frontiers: The Heartland Institute for Clinical and Translational Research # UL1TR000001 (formerly #UL1RR033179). The contents are solely the responsibility of

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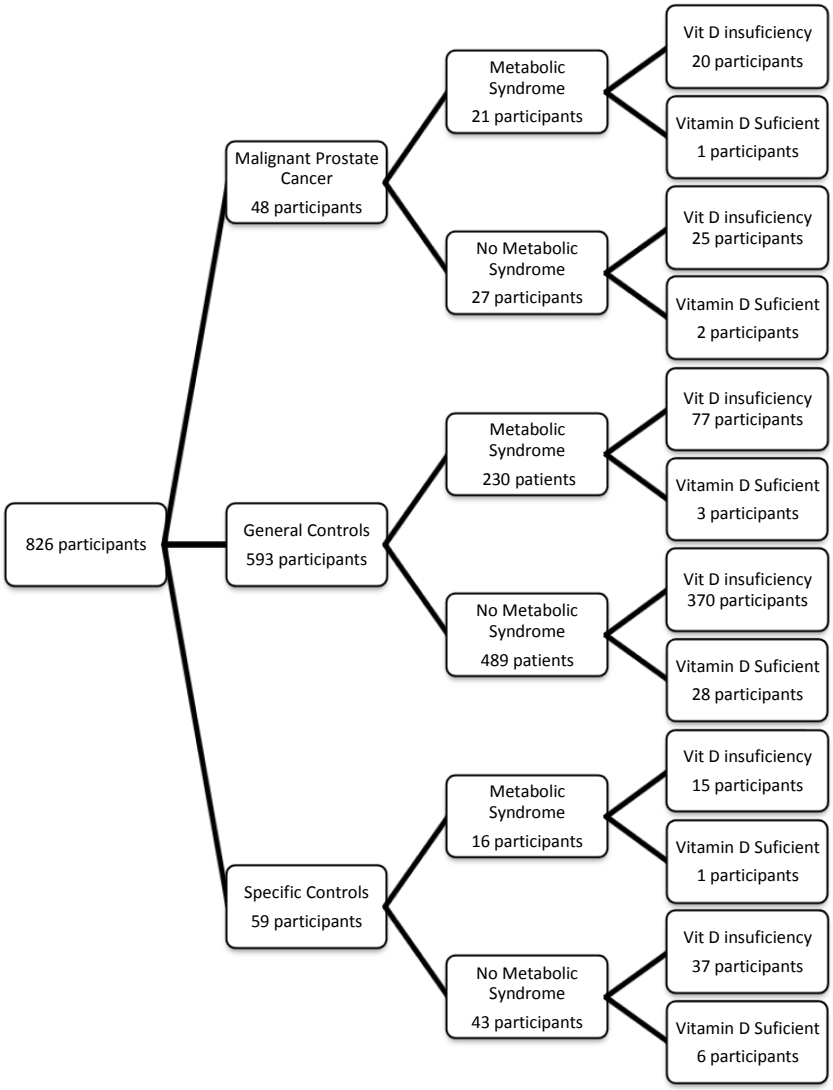
University of Kansas Medical Center Human subjects training was completed prior to accessing the HERON database. Patient information was de-identified including a random date shift; therefore there was no direct contact with patients or their medical records. Use of de-identified data is exempt for approval by the Human Subjects Committee/Institutional Review Board. However, approval from the Data Request Oversight Committee was required, before the data set could be extracted. De-identified patient data sets were stored on secured servers within KUMC. No hard copies of the data set were produced. Participant division is illustrated in **Figure 1**.

Table 3. Inclusion and Exclusion Criteria for the HERON Database Search

Cohort 1 (Cases)	**Cohort 2** (Specific Controls)	**Cohort 3** (General Controls)
Inclusion	**Inclusion**	**Inclusion**
Histologically confirmed prostate cancer BMI Serum Triglycerides Serum HDL Blood Pressure Fasting glucose Serum 25(OH) Vitamin D	Age 40-50 PSA >2.5 50-60 PSA >3.5 >60 PSA >6 PSA:free PSA, or family history BMI Serum Triglycerides Serum HDL Blood Pressure Fasting glucose Serum 25(OH) Vitamin D	Age 40-50 PSA <2.5 50-60 PSA <3.5 >60 PSA >4 <6 PSA:free PSA, or family history BMI Serum Triglycerides Serum HDL Blood Pressure Fasting glucose Serum 25(OH) Vitamin D
Exclusion*	**Exclusion***	**Exclusion***
• Cancer other than prostate or skin cancer • Kidney disease • Liver disease	• Cancer other than skin cancer (basal or squamous cell carcinoma) • Kidney disease • Liver disease	• Cancer other than skin cancer (basal or squamous cell carcinoma) • Kidney disease • Liver disease

* Determined by presence of appropriate International Classification of Diseases, 9th edition codes within electronic medical records at KUMC.

Figure 1. Database participant counts



Lab values were based on physician orders and were analyzed by KUH laboratory. BMI was calculated based on recorded height and weight. Blood pressure was taken by nursing staff. Glucose measures were taken as part of a chemistry panel.

Several criteria were used to develop cases and controls. National cancer registry data were used to verify histologically confirmed prostate cancer. Cases were classified

as men with clinically relevant prostate cancer. Histological type was taken from the cancer database. Surveillance Epidemiology and End Results (SEER) coding was used to classify cancer staging information. Control cohorts were divided by age-related PSA values as outlined in **Table 3**.

Statistical Analysis

The software program SPSS for Windows, version 20 (56) was used for all statistical analyses. Prior to initiating the outcome measures, the data was examined for distribution with particular attention to variable ranges, central tendency (mean and median), dispersion (standard deviation) and missing values. The numbers of values recorded across the variables were highly inconsistent. e.g blood pressure measures were taken several times a day and also several days in a row while other measures (give example here) were measured only once in a while. This resulted in large number of missing values for some variables. To deal with this inconsistency, data were aggregated into one median measure for each variable per patient. Median was chosen to best capture the central value during the study period because median is not sensitive to extreme observations and outliers. Since our main aim was to study the association of these measures with the prostate cancer status (dichotomous: yes, no) of the subjects, we modeled these risk factors using their median values with the prostate cancer as outcome. Since the outcome variable is dichotomous we performed logistic regression analysis. A Pearson correlation matrix was compiled to determine correlation between variables. Such correlation allowed us to determine if a high linear correlation existed between the predictor variables. We noticed that there was high degree of correlation between glucose 2010 and glucose 2011 and therefore we dropped glucose 2010 from the multiple logistic

regression model. Boxplots and histograms were constructed for both non-aggregated and aggregated data to examine the distribution of the data. The plots were consistent before and after aggregating the data. The plots are illustrated in **Appendixes B-D**. Boxplots and histograms were used to visualize cases and controls and determine distribution patterns of the variables.

Prostate Cancer Risk Analysis

To determine the primary research question, the median values were used for metabolic syndrome characteristics and vitamin D as described above. T-test was run for each variable to assess significant differences between cancer and non-cancer cases.

Metabolic syndrome elements were also categorized based on ATP III metabolic syndrome criteria outline in **Table 2**, vitamin D was dichotomized as sufficient or insufficient base on IOM guidelines (55). Logistic regression models were built using prostate cancer as the dependent variable and metabolic syndrome criteria and vitamin D as categorical variables. Interactions between each metabolic syndrome variable and vitamin D were also tested using logistic regression models (i.e. diastolic and vitamin D). Chi-square test of deviance was used to assess the interaction of metabolic syndrome with vitamin D status. Test of interaction was performed for metabolic syndrome and vitamin D status as both continuous and categorical variables (categorized based on ATP III criteria). The analyses were also carried out for both the specific control group with age adjustment and for the general age matched control group.

Chapter IV: Results

Baseline demographic information is shown in **Table 4**. Age and HDL were the only two variables with significant difference between cases and controls. Our study found a large amount of participants with vitamin D insufficiency (89-94%). Metabolic syndrome occurred more among prostate cancer cases than in controls (42% vs. 27-32%) however the difference was not statistically significant.

Table 4. Mean values of PSA, DBP, SBP, BMI, Glucose, HDL, Triglyceride, and Vitamin D level among cases and controls and results of t-test

Characteristic	Prostate Cancer Cases n = 48	High Risk Controls n = 59	General Controls n=593
Age, years, ±SD	70.9±8.3	65.9 ±23.8	66.6±8.5
Years since diagnosis, ±SD	6.9±5.8	-	
Race			
White or Caucasian, No.	37	48	509
Black or African American, No.	9	5	53
American Indian Alaskan Native, No.	0	0	1
Asian, No.	0	1	6
Native Hawaiian or Pacific Islander, No.	1	4	1
Other, No.	5	1	24
Prostate Specific Antigen, ng/mL (SD)	1.7 (2.4)	5.55 (3.43)	1.18(0.9)
Diastolic Blood Pressure, mmHg (SD)	74.21 (7.62)	74.26 (7.76)	74.36(8.0)
Systolic Blood pressure, mmHg (SD)	129.55 (11.43)	129.60 (13.18)	125.4(12.1)
Body Mass Index, kg/m^2 (SD)	28.65 (5.22)	28.31 (4.94)	29.77(8.1)
Glucose, mg/dL (SD)	108.62 (16.76)[a]	108.52 (19.26)	111.99(25.4)[a]
HDL, mg/dL (SD)	43.27 (9.90)	49.62 (12.75)[a]	44.80(11.5)
Triglyceride, mg/dL (SD)	129.30 (99.78)	107.69 (62.34)	121.06(71.44)
Vitamin D, ng/mL (SD)	32.10 (11.60)	34.68 (11.86)	33.22(11.1)
Sufficient, No. (%)	3 (6.3)	7 (11.9)	36 (6.1)
Insufficient, No. (%)	45 (93.7)	52 (88.1)	557 (93.9)
Metabolic Syndrome, No. (%)	21(43.7)	16(27.1)	193(32.5)

[a] denotes significance between cohorts $p<0.05$.

The categorical logistic regression models using ATP III guidelines for diagnosis of metabolic syndrome showed no significant results for individual variables, interaction of individual variables with vitamin D, or number of diagnostic metabolic syndrome criteria. Test of interactions showed no significant associations.

The analysis with specific high-risk control showed that the participants with high HDL concentration (>60 mg/dL) had a significantly reduced the incidence of prostate cancer ($p=0.04$, OR 0.173) compared to men with normal HDL concentration (40-60 mg/dL). The odds of having prostate cancer for the people having high HDL concentration are one sixth of the odds of having the prostate cancer with normal HDL. No other significant results were found using specific controls in any of the other variables or tests for interaction with vitamin D.

The logistic regression model with age-matched general controls found that the odds of having prostate cancer for the participants with a high systolic blood pressure (>130 mmHg) to be 2.6 times of odds of developing prostate cancer for participants with normal systolic blood pressure (<130 mmHg) ($p=0.03$). No other metabolic syndrome factors or vitamin D were found to be significant with age-matched general controls.

Chapter V: Discussion

Implications

Our study found that high systolic blood pressure and high HDL concentration to significantly impact the incidence of prostate cancer. Only one other study to date has examined the dual relationship, which found HDL to be mildly protective and a clustering of metabolic syndrome factors with vitamin D deficiency to greatly increase the risk of prostate cancer. Our study represents only a small population of men residing in the Kansas City metropolitan area. Further prospective studies are needed to determine if an association exists.

Vitamin D insufficiency was found in almost all of the participants (94%) in the study. This is a stark contrast to the Institute of Medicine reports that suggest 25% of the population is at risk of insufficiency (55). The low numbers of participants with sufficient vitamin D may have limited our ability to find significant associations with prostate cancer. Sampling bias may also have occurred as a result of physicians only testing those who are at risk of deficiency, as Vitamin D testing is not often reimbursed by insurance.

Optimal levels of HDL (>60 mg/dL) were found to significantly decrease the incidence of prostate cancer compared to men with normal HDL concentration (40-60 mg/dL). Evidence of the protective effect of HDL on prostate cancer is not clear. To date, two studies have found HDL concentration to be protective against prostate cancer (26, 31). Higher HDL may provide the protection seen by significantly reducing circulating cholesterol and inflammatory cytokines, resulting in decreased incidence. These finding provide further evidence that HDL may be protective against prostate cancer.

This study found that systolic blood pressure was the only element within metabolic syndrome to have a statistically significant association with prostate cancer, but this relationship was not observed with specific controls. Previous studies on blood pressure have yielded inconsistent results depending on controls for anti-hypertensive use (35-37). A major limitation is the inability to control for home medication use. Another limitation is that most blood pressure records are the result of inpatient stays, which may not accurately reflect true resting blood pressure. Further interpretation cannot be made without the ability to control for these cofactors.

Strengths and Limitations

This study has many strengths. It used only cases with histologically confirmed prostate cancer verified with the national cancer registry data. De-identified data helped protect the security of patient information while still allowing for investigational research. The study was one of the first to use datasets from HERON for a retrospective study, and helped aid in the development of the data set request process and i2b2 development.

The use of retrospective data in a case-control study inherently introduces many limitations. The reliance of previously existing laboratory measures made it impossible to ascertain all five metabolic syndrome criteria and vitamin D concentration at one point in time. Therefore true ascertainment of metabolic syndrome was not established, however it was assumed that these variables over time could still have a significant impact on the development of prostate cancer. Although ATP III criteria uses waist circumference for diagnosis of obesity, waist circumference was only recorded in the EMR in about 10% of

participants. BMI was used as a surrogate measure of obesity, but does not reflect body composition directly. Sarcopenic obesity, a common problem among prostate cancer survivors, is not detected by BMI. Fasting glucose was also not widely recorded in the EMR, therefore a glucose measurement from a chemistry panel had to be chosen which may not represent a true fasting state from all participants. Using matched case controls based on seasonal vitamin D analysis was not possible due to the de-identification time shift.

The sample size of this study was limited by the availability of retrospective data from the KUH hospital system, and lacks sufficient power to determine risk of developing prostate cancer. However, we obtained patterns and estimates of risk on developing prostate cancer. Although HERON contains a wealth of information, most of it is a mixture of laboratory data from 2003 to the present. This condensed the length of the trial to roughly four years, which limits the ability to accurately reflect the possible association that chronic conditions such as metabolic syndrome could have on the development of prostate cancer.

Conclusion

Clumping of metabolic syndrome elements and interaction with Vitamin D was not found to be associated with prostate cancer. Optimal HDL (>60 mg/dL) was found to be protective against prostate cancer. Systolic blood pressure was found to be a significant risk factor for prostate cancer in age-matched controls, however the inability to control for medication use limits this data. Further prospective research is needed to confirm if further associations exist. Medical informatics tools, like HERON, represent a

wealth of information that is constantly growing and evolving to meet the needs of research.

Chapter VI: References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA: a cancer journal for clinicians 2012;62(1):10-29. doi: 10.3322/caac.20138.
2. Tuohimaa P, Tenkanen L, Syvala H, et al. Interaction of factors related to the metabolic syndrome and vitamin D on risk of prostate cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2007;16(2):302-7. doi: 10.1158/1055-9965.epi-06-0777.
3. Ervin RB. Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003-2006. In: Statistics NCfH, ed. National Health Statistics Report, 2009.
4. Looker A C. Johnson C L. Lacher D A. CMSR, Sempos C. Vitamin D Status: United States, 2001-2006. In: Statistics NCfH, ed., 2011.
5. Grundy SM, Becker D, Clark L. T. Cooper R S., Denke M., Howard Wm. J., Hunninghake D B., Illingworth D R. Luepker R V., McBride P., McKenney J M., Pasternak R., Stone N. Van Horn L. . Third report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). In: Program NCE, ed., 2004.
6. Peehl DM, Feldman D. The role of vitamin D and retinoids in controlling prostate cancer progression. Endocrine-related cancer 2003;10(2):131-40.
7. Barnard RJ, Aronson WJ, Tymchuk CN, Ngo TH. Prostate cancer: another aspect of the insulin-resistance syndrome? Obesity reviews : an official journal of the International Association for the Study of Obesity 2002;3(4):303-8.
8. Platz EA, Leitzmann MF, Rifai N, et al. Sex steroid hormones and the androgen receptor gene CAG repeat and subsequent risk of prostate cancer in the prostate-specific antigen era. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2005;14(5):1262-9. doi: 10.1158/1055-9965.epi-04-0371.
9. Pelucchi C, Serraino D, Negri E, et al. The metabolic syndrome and risk of prostate cancer in Italy. Annals of epidemiology 2011;21(11):835-41. doi: 10.1016/j.annepidem.2011.07.007.
10. Beebe-Dimmer JL, Dunn RL, Sarma AV, Montie JE, Cooney KA. Features of the metabolic syndrome and prostate cancer in African-American men. Cancer 2007;109(5):875-81. doi: 10.1002/cncr.22461.
11. Beebe-Dimmer JL, Nock NL, Neslund-Dudas C, et al. Racial differences in risk of prostate cancer associated with metabolic syndrome. Urology 2009;74(1):185-90. doi: 10.1016/j.urology.2009.03.013.
12. Lund Haheim L, Wisloff TF, Holme I, Nafstad P. Metabolic syndrome predicts prostate cancer in a cohort of middle-aged Norwegian men followed for 27 years. American journal of epidemiology 2006;164(8):769-74. doi: 10.1093/aje/kwj284.
13. Martin RM, Vatten L, Gunnell D, Romundstad P, Nilsen TI. Components of the metabolic syndrome and risk of prostate cancer: the HUNT 2 cohort, Norway. Cancer causes & control : CCC 2009;20(7):1181-92. doi: 10.1007/s10552-009-9319-x.
14. Jaggers JR, Sui X, Hooker SP, et al. Metabolic syndrome and risk of cancer mortality in men. European journal of cancer (Oxford, England : 1990) 2009;45(10):1831-8. doi: 10.1016/j.ejca.2009.01.031.

15. Shulman AI, Mangelsdorf DJ. Retinoid x receptor heterodimers in the metabolic syndrome. The New England journal of medicine 2005;353(6):604-15. doi: 10.1056/NEJMra043590.
16. Stewart LV, Weigel NL. Vitamin D and prostate cancer. Experimental biology and medicine (Maywood, NJ) 2004;229(4):277-84.
17. Solomon KR, Freeman MR. Do the cholesterol-lowering properties of statins affect cancer risk? Trends in endocrinology and metabolism: TEM 2008;19(4):113-21. doi: 10.1016/j.tem.2007.12.004.
18. Li YC, Park MJ, Ye SK, Kim CW, Kim YN. Elevated levels of cholesterol-rich lipid rafts in cancer cells are correlated with apoptosis sensitivity induced by cholesterol-depleting agents. The American journal of pathology 2006;168(4):1107-18; quiz 404-5. doi: 10.2353/ajpath.2006.050959.
19. Oh HY, Lee EJ, Yoon S, Chung BH, Cho KS, Hong SJ. Cholesterol level of lipid raft microdomains regulates apoptotic cell death in prostate cancer cells through EGFR-mediated Akt and ERK signal transduction. The Prostate 2007;67(10):1061-9. doi: 10.1002/pros.20593.
20. Kitahara CM, Berrington de Gonzalez A, Freedman ND, et al. Total cholesterol and cancer risk in a large prospective study in Korea. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2011;29(12):1592-8. doi: 10.1200/jco.2010.31.5200.
21. Mondul AM, Weinstein SJ, Virtamo J, Albanes D. Serum total and HDL cholesterol and risk of prostate cancer. Cancer causes & control : CCC 2011;22(11):1545-52. doi: 10.1007/s10552-011-9831-7.
22. Platz EA, Clinton SK, Giovannucci E. Association between plasma cholesterol and prostate cancer in the PSA era. International journal of cancer Journal international du cancer 2008;123(7):1693-8. doi: 10.1002/ijc.23715.
23. Smith GD, Shipley MJ, Marmot MG, Rose G. Plasma cholesterol concentration and mortality. The Whitehall Study. JAMA : the journal of the American Medical Association 1992;267(1):70-6.
24. Mondul AM, Clipp SL, Helzlsouer KJ, Platz EA. Association between plasma total cholesterol concentration and incident prostate cancer in the CLUE II cohort. Cancer causes & control : CCC 2010;21(1):61-8. doi: 10.1007/s10552-009-9434-8.
25. Sekine Y, Koike H, Nakano T, Nakajima K, Takahashi S, Suzuki K. Remnant lipoproteins induced proliferation of human prostate cancer cell, PC-3 but not LNCaP, via low density lipoprotein receptor. Cancer epidemiology 2009;33(1):16-23. doi: 10.1016/j.canep.2009.04.004.
26. Van Hemelrijck M, Garmo H, Holmberg L, et al. Prostate cancer risk in the Swedish AMORIS study: the interplay among triglycerides, total cholesterol, and glucose. Cancer 2011;117(10):2086-95. doi: 10.1002/cncr.25758.
27. Hayashi N, Matsushima M, Yamamoto T, Sasaki H, Takahashi H, Egawa S. The impact of hypertriglyceridemia on prostate cancer development in patients aged >/=60 years. BJU international 2011. doi: 10.1111/j.1464-410X.2011.10358.x.
28. Ulmer H, Borena W, Rapp K, et al. Serum triglyceride concentrations and cancer risk in a large cohort study in Austria. British journal of cancer 2009;101(7):1202-6. doi: 10.1038/sj.bjc.6605264.
29. Jacobs EJ, Gapstur SM. Cholesterol and cancer: answers and new questions. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for

Cancer Research, cosponsored by the American Society of Preventive Oncology 2009;18(11):2805-6. doi: 10.1158/1055-9965.epi-09-1027.

30. Calabresi L, Rossoni G, Gomaraschi M, Sisto F, Berti F, Franceschini G. High-density lipoproteins protect isolated rat hearts from ischemia-reperfusion injury by reducing cardiac tumor necrosis factor-alpha content and enhancing prostaglandin release. Circulation research 2003;92(3):330-7.
31. Magura L, Blanchard R, Hope B, Beal JR, Schwartz GG, Sahmoun AE. Hypercholesterolemia and prostate cancer: a hospital-based case-control study. Cancer causes & control : CCC 2008;19(10):1259-66. doi: 10.1007/s10552-008-9197-7.
32. Wang JM, McKenna KE, McVary KT, Lee C. Requirement of innervation for maintenance of structural and functional integrity in the rat prostate. Biology of reproduction 1991;44(6):1171-6.
33. Gann PH, Daviglus ML, Dyer AR, Stamler J. Heart rate and prostate cancer mortality: results of a prospective analysis. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 1995;4(6):611-6.
34. Martin RM, Vatten L, Gunnell D, Romundstad P. Blood pressure and risk of prostate cancer: Cohort Norway (CONOR). Cancer causes & control : CCC 2010;21(3):463-72. doi: 10.1007/s10552-009-9477-x.
35. Fitzpatrick AL, Daling JR, Furberg CD, Kronmal RA, Weissfeld JL. Hypertension, heart rate, use of antihypertensives, and incident prostate cancer. Annals of epidemiology 2001;11(8):534-42.
36. Friedman GD. Blood pressure and heart rate: no evidence for a positive association with prostate cancer. Annals of epidemiology 1997;7(7):486-9.
37. Wallner LP, Morgenstern H, McGree ME, et al. The effects of type 2 diabetes and hypertension on changes in serum prostate specific antigen levels: results from the Olmsted County study. Urology 2011;77(1):137-41. doi: 10.1016/j.urology.2010.07.516.
38. Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. Journal of the National Cancer Institute 2000;92(18):1472-89.
39. Kim WT, Yun SJ, Choi YD, et al. Prostate size correlates with fasting blood glucose in non-diabetic benign prostatic hyperplasia patients with normal testosterone levels. Journal of Korean medical science 2011;26(9):1214-8. doi: 10.3346/jkms.2011.26.9.1214.
40. Nimptsch K, Brand-Miller JC, Franz M, Sampson L, Willett WC, Giovannucci E. Dietary insulin index and insulin load in relation to biomarkers of glycemic control, plasma lipids, and inflammation markers. The American journal of clinical nutrition 2011;94(1):182-90. doi: 10.3945/ajcn.110.009555.
41. Tande AJ, Platz EA, Folsom AR. The metabolic syndrome is associated with reduced risk of prostate cancer. American journal of epidemiology 2006;164(11):1094-102. doi: 10.1093/aje/kwj320.
42. Ashley FW, Jr., Kannel WB. Relation of weight change to changes in atherogenic traits: the Framingham Study. Journal of chronic diseases 1974;27(3):103-14.
43. Solomon CG, Manson JE. Obesity and mortality: a review of the epidemiologic data. The American journal of clinical nutrition 1997;66(4 Suppl):1044S-50S.
44. Gapstur SM, Kopp P, Gann PH, Chiu BC, Colangelo LA, Liu K. Changes in BMI modulate age-associated changes in sex hormone binding globulin and total testosterone, but not bioavailable testosterone in young adult men: the CARDIA Male Hormone Study. International journal of obesity (2005) 2007;31(4):685-91. doi: 10.1038/sj.ijo.0803465.

45. Hsing AW, Reichardt JK, Stanczyk FZ. Hormones and prostate cancer: current perspectives and future directions. The Prostate 2002;52(3):213-35. doi: 10.1002/pros.10108.
46. Lee IM, Sesso HD, Paffenbarger RS, Jr. A prospective cohort study of physical activity and body size in relation to prostate cancer risk (United States). Cancer causes & control : CCC 2001;12(2):187-93.
47. Dal Maso L, Zucchetto A, La Vecchia C, et al. Prostate cancer and body size at different ages: an Italian multicentre case-control study. British journal of cancer 2004;90(11):2176-80. doi: 10.1038/sj.bjc.6601859.
48. Friedenreich CM, McGregor SE, Courneya KS, Angyalfi SJ, Elliott FG. Case-control study of anthropometric measures and prostate cancer risk. International journal of cancer Journal international du cancer 2004;110(2):278-83. doi: 10.1002/ijc.20110.
49. Hsing AW, Deng J, Sesterhenn IA, et al. Body size and prostate cancer: a population-based case-control study in China. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2000;9(12):1335-41.
50. De Nunzio C, Albisinni S, Freedland SJ, et al. Abdominal obesity as risk factor for prostate cancer diagnosis and high grade disease: A prospective multicenter Italian cohort study. Urologic oncology 2011. doi: 10.1016/j.urolonc.2011.08.007.
51. Pischon T, Boeing H, Weikert S, et al. Body size and risk of prostate cancer in the European prospective investigation into cancer and nutrition. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2008;17(11):3252-61. doi: 10.1158/1055-9965.epi-08-0609.
52. MacInnis RJ, English DR. Body size and composition and prostate cancer risk: systematic review and meta-regression analysis. Cancer causes & control : CCC 2006;17(8):989-1003. doi: 10.1007/s10552-006-0049-z.
53. Rowlands MA, Holly JM, Gunnell D, et al. The relation between adiposity throughout the life course and variation in IGFs and IGFBPs: evidence from the ProtecT (Prostate testing for cancer and Treatment) study. Cancer causes & control : CCC 2010;21(11):1829-42. doi: 10.1007/s10552-010-9610-x.
54. Waitman LR, Warren JJ, Manos EL, Connolly DW. Expressing observations from electronic medical record flowsheets in an i2b2 based clinical data repository to support research and quality improvement. AMIA Annual Symposium proceedings / AMIA Symposium AMIA Symposium 2011;2011:1454-63.
55. A. Catharine Ross CLTALY, Heather B. Del Valle E, Committee to Review Dietary Reference Intakes for Vitamin D, Calcium, Institute of M. Dietary Reference Intakes for Calcium and Vitamin D. Washington, D.C.: The National Academies Press %@ 0309163943, 2011.
56. SPSS Inc. (2011). **SPSS Base 20.0 for Windows User's Guide**. SPSS Inc., Chicago IL.

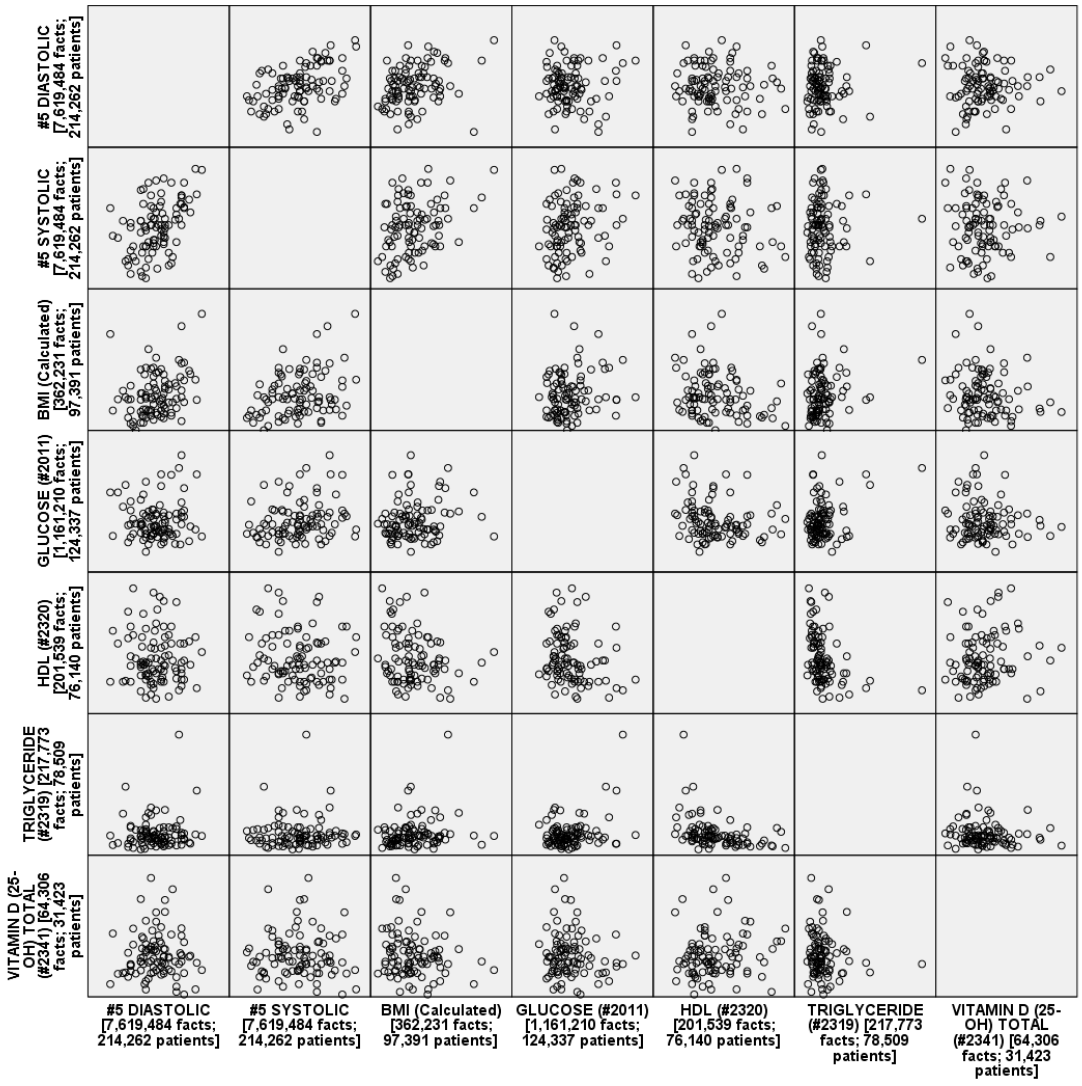
APPENDIX A. HERON Search Term Criteria

Table 3. HERON Search Criteria

Group	Terminology
1	• Male
2	• BMI
3	• Diastolic • Systolic
4	• Triglyceride
5	• HDL
6	• PSA • Histologically confirmed prostate cancer • Family history of malignant neoplasm of the prostate
7	• Glucose 2010 • Glucose 2011 • Glucose Fasting
8	• Vitamin D (25-OH) Total
9 (excluding)	• Malignant Neoplasms of bone, breast, skin, digestive organs, lip, oral cavity, pharynx, lymphatic, hematopoietic, respiratory, and unspecified sites • Cirrhosis of liver • Liver failure • Chronic renal failure Renal failure, uspecified

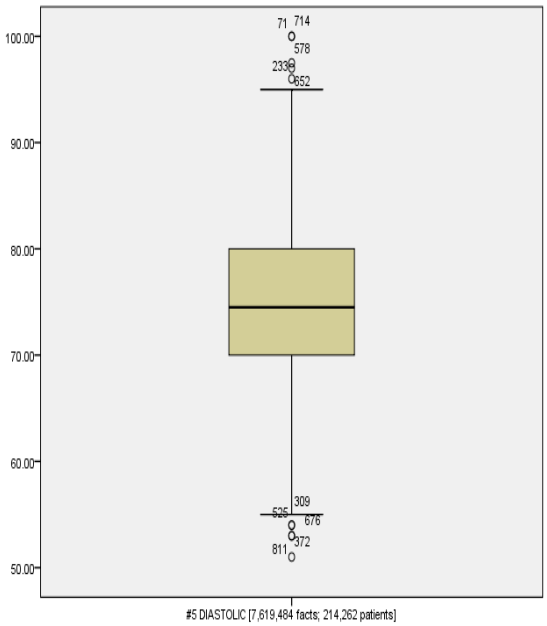
The term "and" was applied between group terms, within groups the term "or" was applied

APPENDIX B. Pearson Correlation Matrix

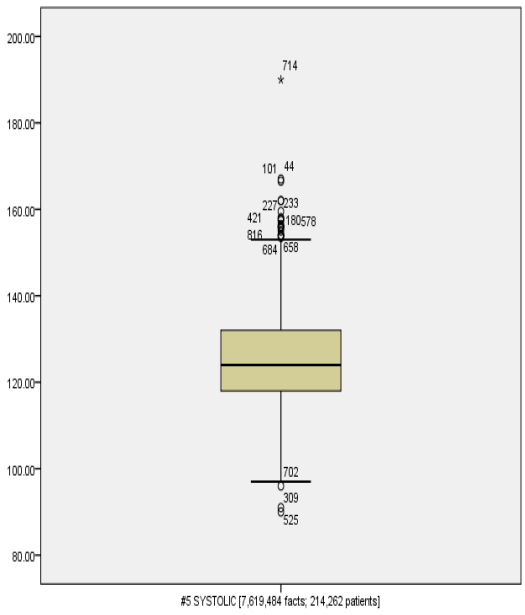


APPENDIX C. Independent Variable Boxplots

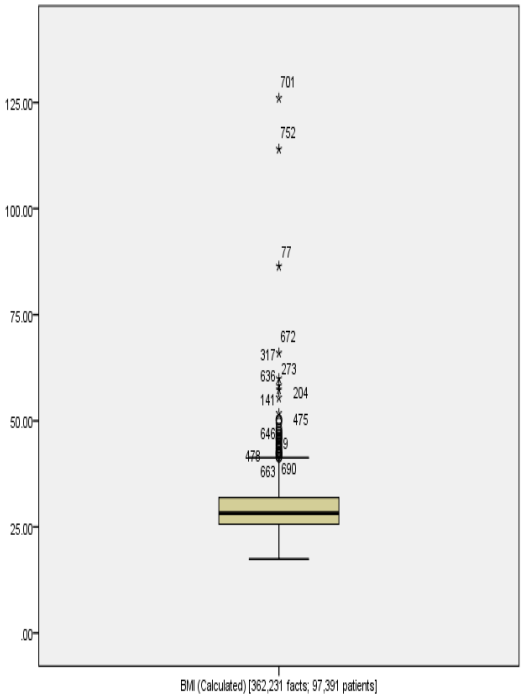
Diastolic boxplot



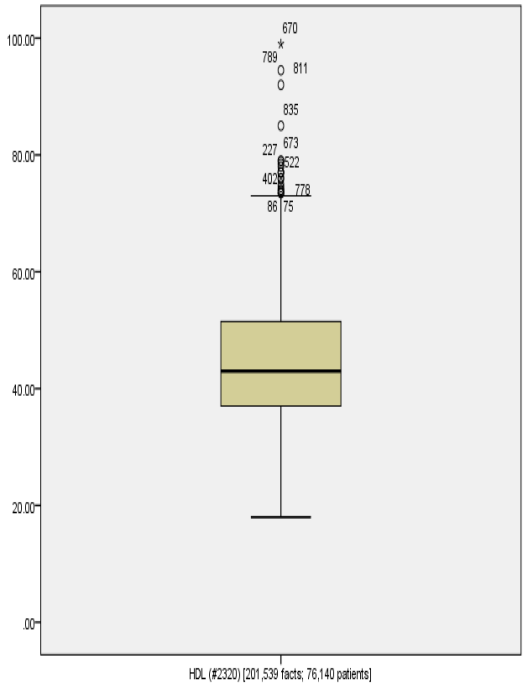
Systolic Boxplot



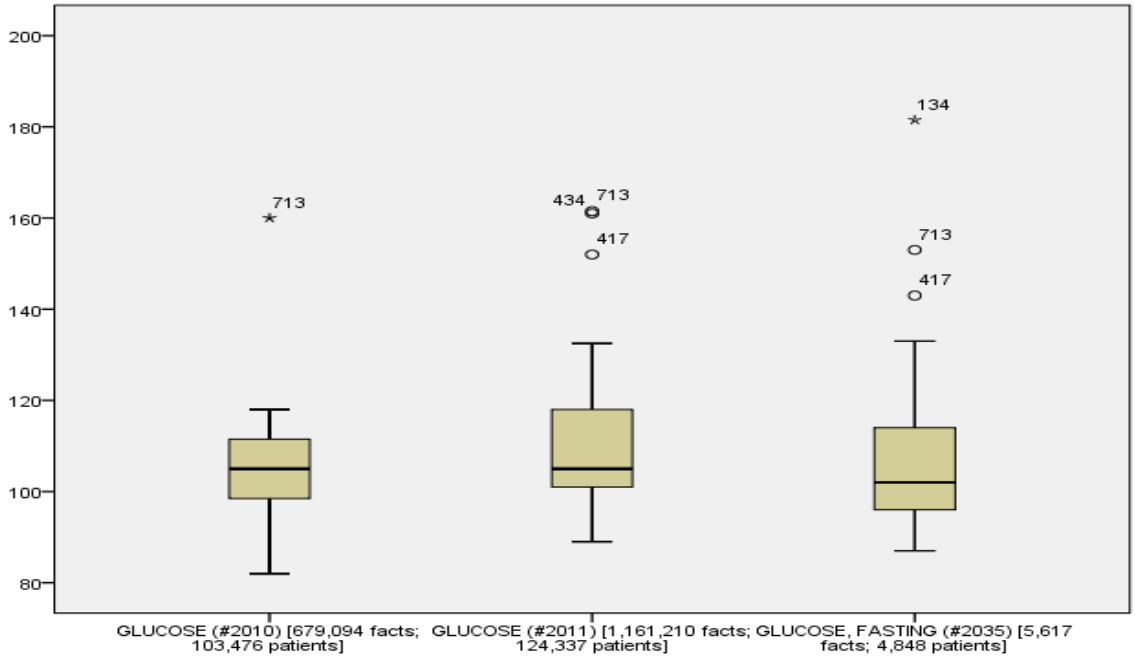
BMI Boxplot



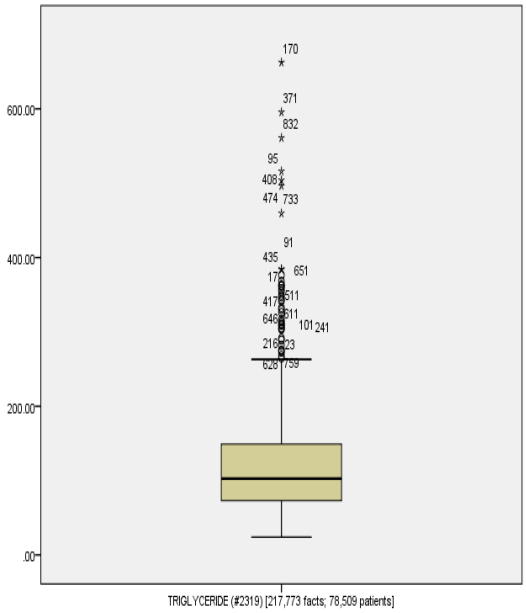
HDL Boxplot



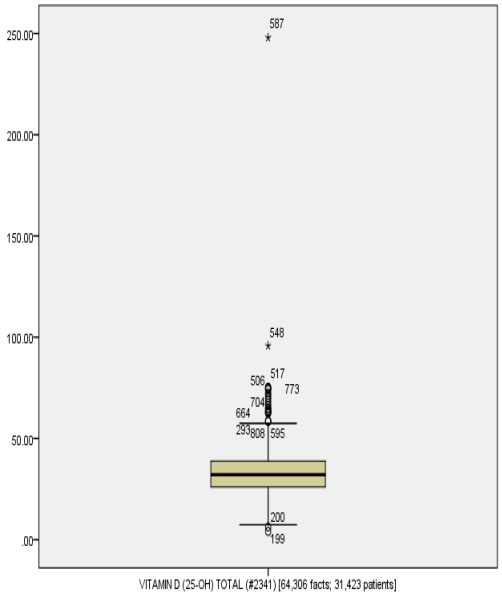
Glucose Boxplots



Triglyceride Boxplot

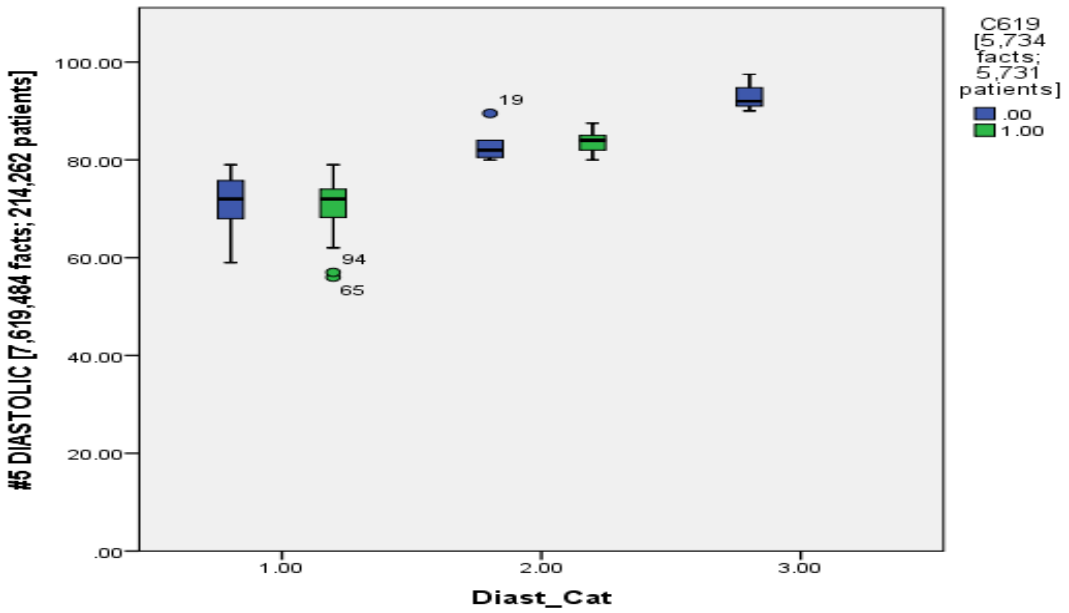


Vitamin D Boxplot

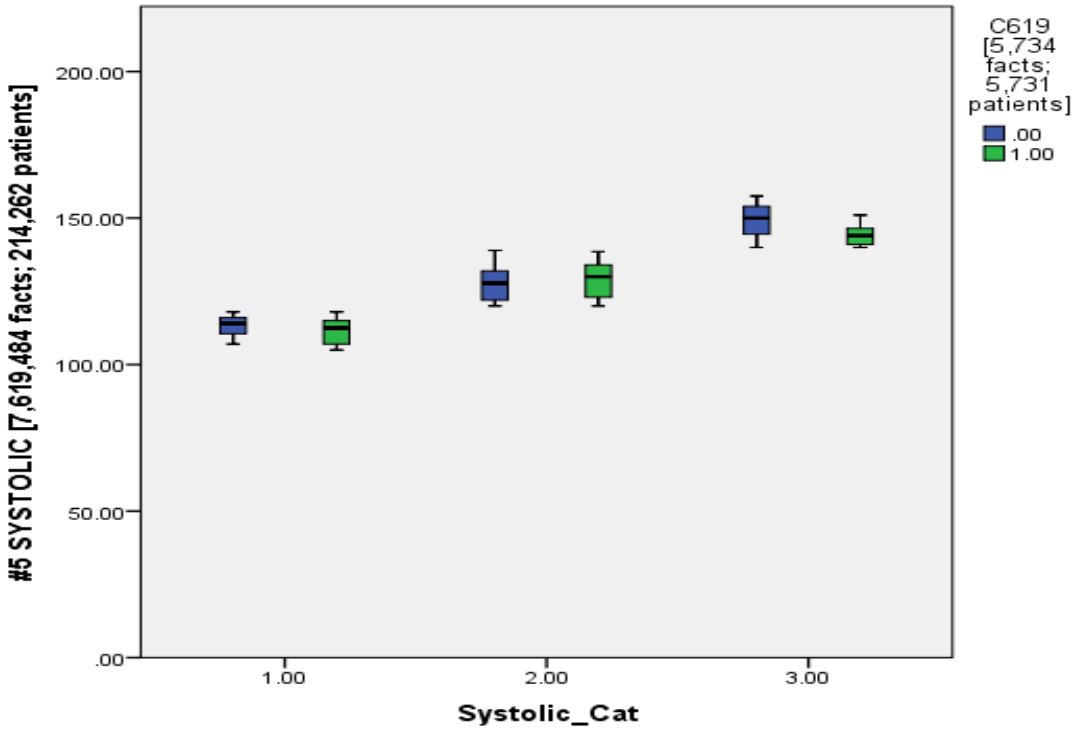


APPENDIX D. Categorical Case/Control boxplot comparison

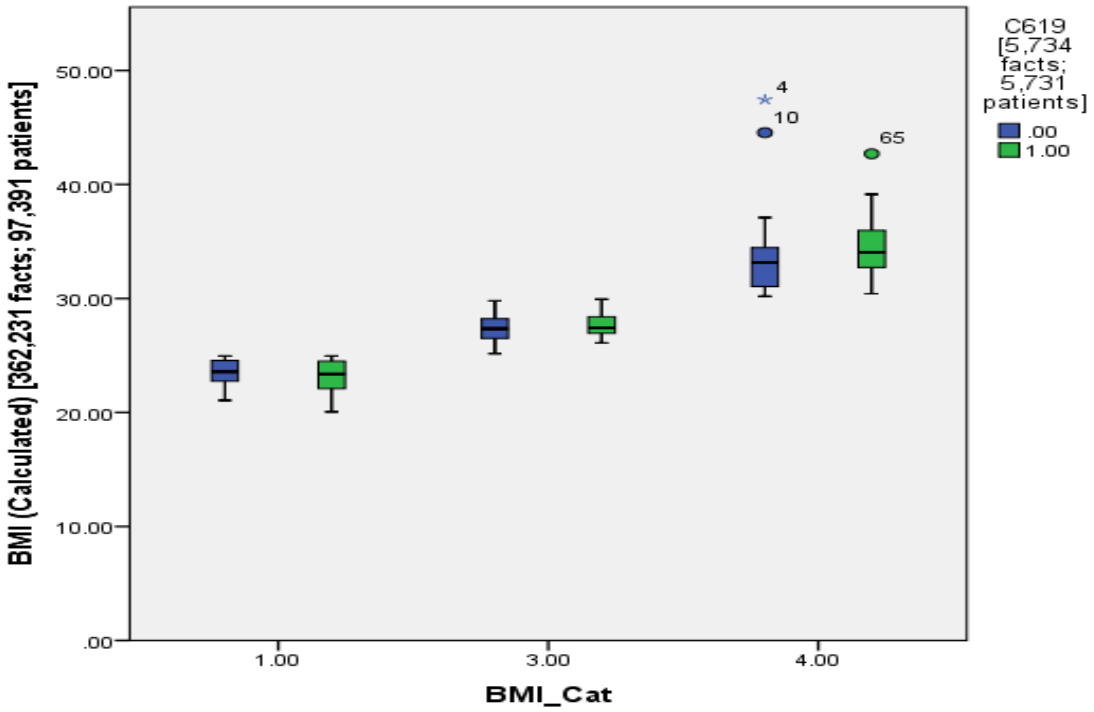
Diastolic case control categorical boxplots comparison



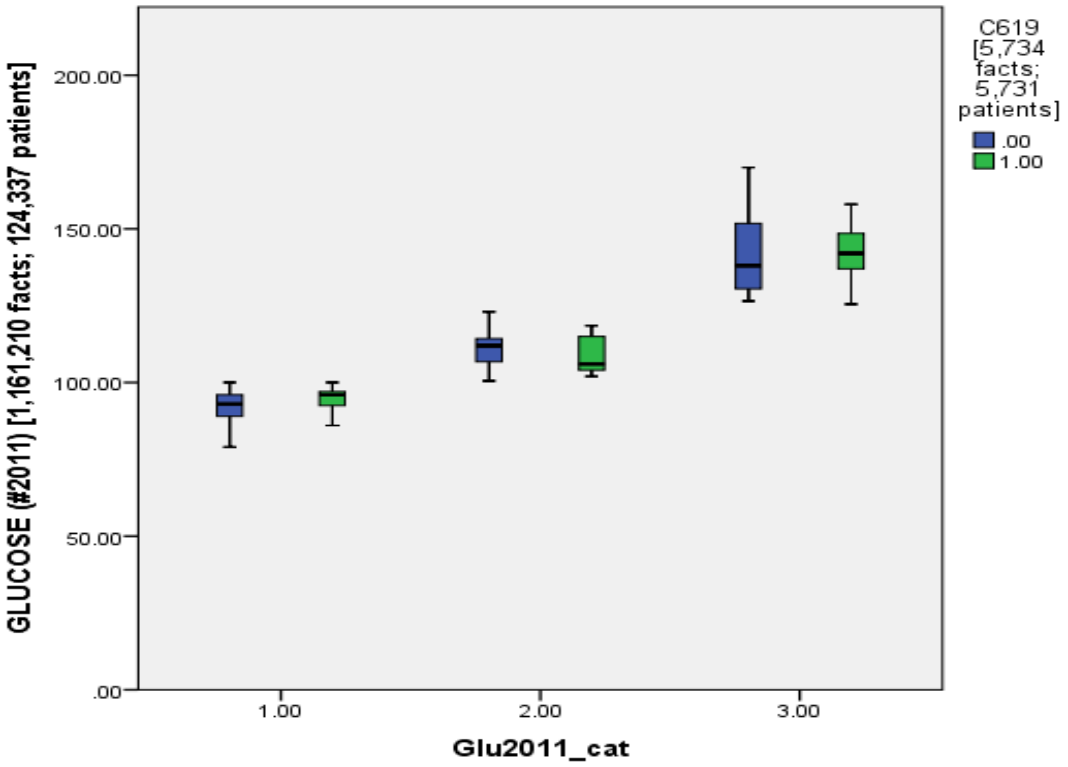
Systolic case control categorical boxplots comparison



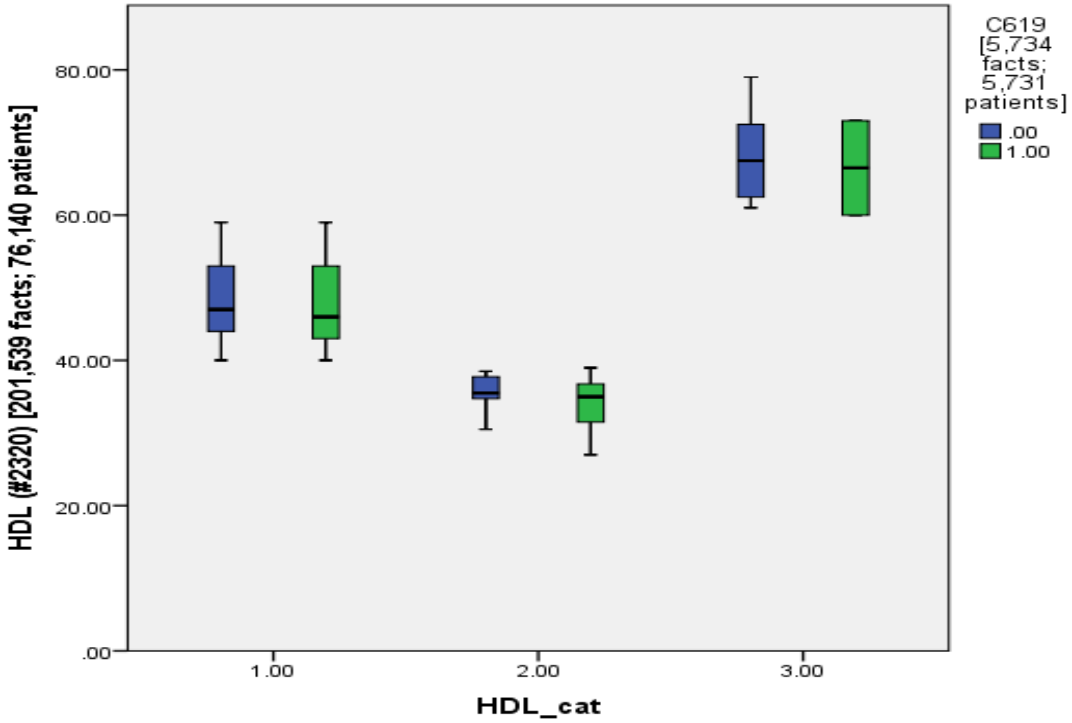
BMI case control categorical boxplots comparison



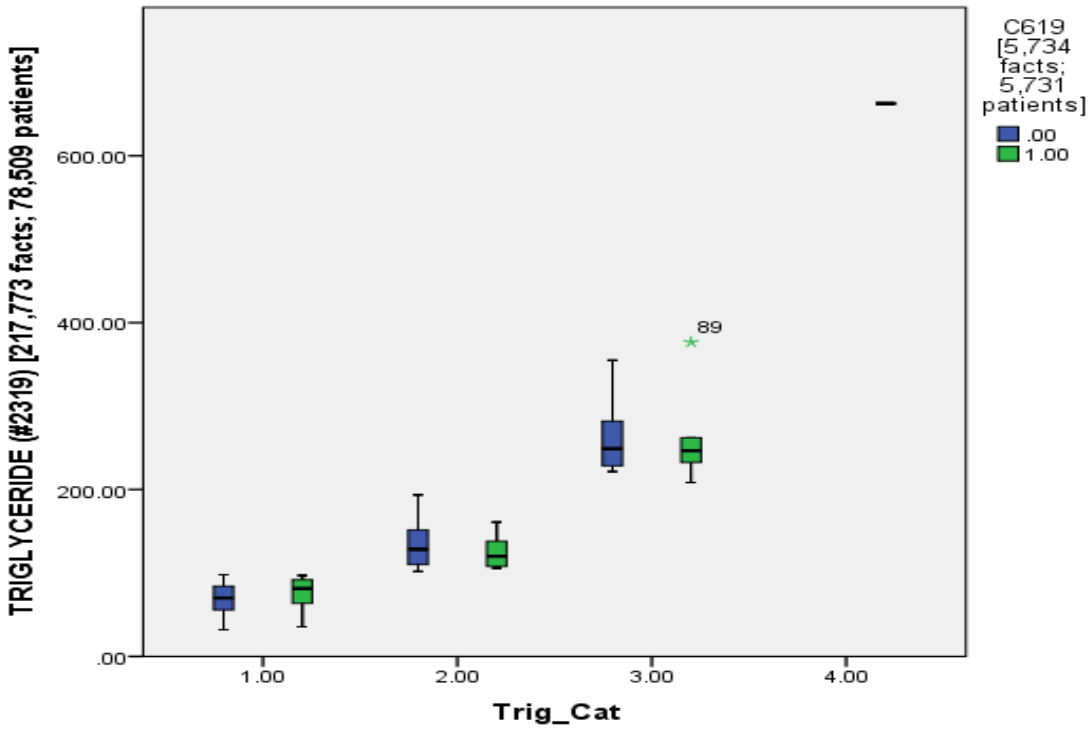
Glucose case control categorical boxplots comparison



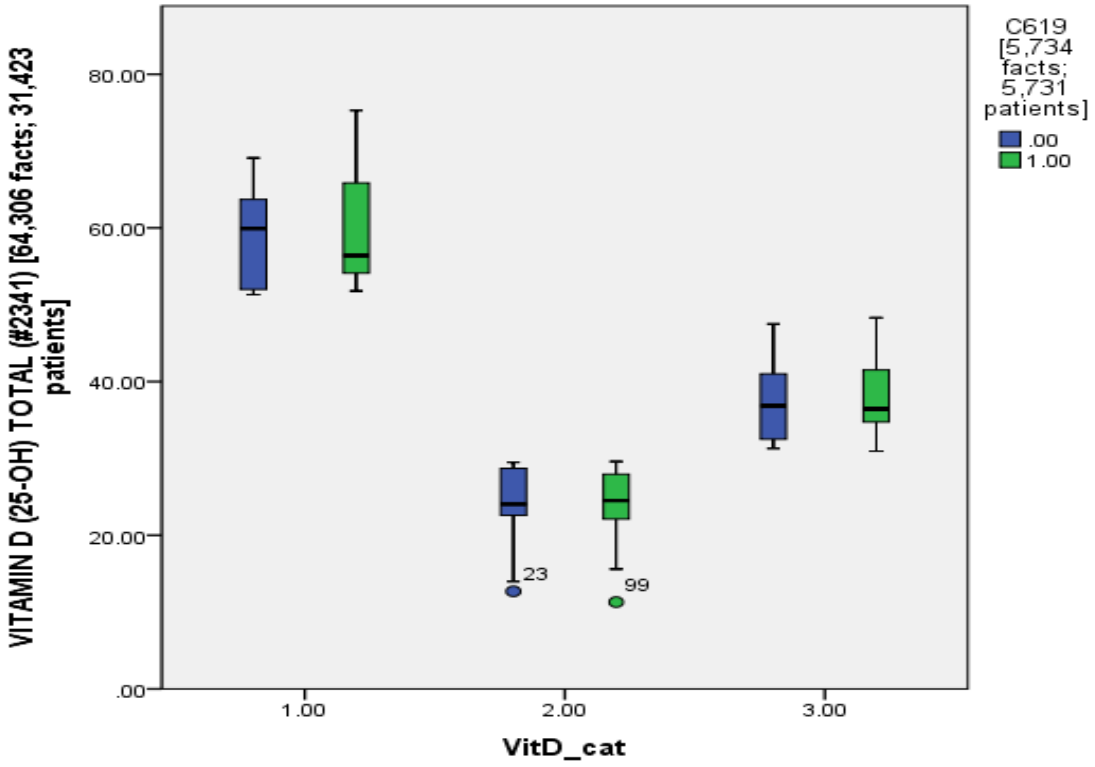
HDL case control categorical boxplots comparison



Triglyceride case control categorical boxplots comparison



Vitamin D case control categorical boxplots comparison



APPENDIX E. Descriptive statistics of baseline participants.

Summary of Independent Variables					
Variable	N	Minimum	Maximum	Mean	SD
BMI	107	20.06	47.45	28.460	5.05
Triglycerides	107	32.00	662.5	117.388	81.599
HDL	107	27.00	79.00	46.776	11.938
Blood Pressure					
Diastolic	107	56.00	97.50	74.238	7.658
Systolic	107	105.00	157.50	129.579	12.369
Glucose	95	79.00	170.00	108.568	17.947
Vitamin D	106	11.30	75.30	33.509	11.758

APPENDIX F. Overall Participant Independent Variable Characteristics

Associations of levels of DBP, SBP, BMI, Glucose, HDL, Triglycerides, and Vitamin D on risk of prostate cancer			
Variable	**B (SE)**	**P**	**Odds Ratio**
Diastolic (mmgHg) >85	-0.471(.852)	0.580	0.624
Systolic (mmHg) >135	-0.790 (.877)	0.368	0.454
BMI (kg/m^2) >28	-0.625 (.561)	0.265	0.535
Glucose (mg/dL) >110	0.601 (.869)	0.489	1.825
HDL (mg/dL) <40	-0.975 (.766)	0.203	0.377
Triglycerides (mg/dL) >150	.024 (1.001)	0.981	1.025
Vitamin D <50	-.0782 (.865)	0.366	0.457

Categories compared to a normal reference range as described in Table 4 above.