THE ROLE OF OBESITY IN ASYMPTOMATIC PROSTATE INFLAMMATION: A CROSS-SECTIONAL STUDY OF VETERANS AFFAIRS PATIENTS IN OREGON

by

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A THESIS

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CERTIFICATE OF APPROVAL

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ABSTRACT

Background: Each year, prostate cancer affects one in six men and kills one in thirty five. It is the second leading cause of cancer death in men, topped only by lung cancer[3,4]. Recent studies have shown that chronic inflammation of the prostate may be involved in cancer development, possibly through the disruption of oxidative balance and elevated chemokine levels[17-24]. In addition, obesity has been associated with both prostate cancer[25-39] and systemic body inflammation[40-44].

Objectives: In this cross-sectional study of 661 Caucasian VA patients in Oregon, we determine if there is an association between obesity and prostate inflammation, specifically Type IV asymptomatic prostate inflammation, based on NIH consensus classification[8,9].

Methods: Using univariate analyses and multivariate logistic regression, we built models to understand the relationship between BMI and prostate inflammation (IV) and adjusted for variables including: age, prostate-specific antigen levels, family history of cancer, digital rectal examination findings, statin-use, and prostate volume.

Results: Univariate analysis showed that mean BMI was statistically significantly different between cases (patients with inflammation) and controls (no inflammation) and that when modeled alone, BMI was a significant predictor of inflammation (p-value = 0.03 for both). Backwards stepwise model-building showed that BMI is not an independent predictor of inflammation. On the other hand, prostate volume and family history of cancer were significant predictors of inflammation. Our models showed that the odds of inflammation increased by approximately 70% as prostate volume doubled

and were 42% greater for a man with a family history of cancer compared to one with no family history of cancer.

Conclusions: In this study, obesity does not appear to be an independent predictor of asymptomatic prostate inflammation. Future studies should attempt to circumvent the shortfalls of our study, namely the temporal limitation inherent in its cross-sectional design and address the question in a broader sense to include other races and ethnicities and other types of prostate inflammation.

BACKGROUND

Introduction

Most men will report having prostate problems at some point in their lives, the main ailments being prostate enlargement, inflammation, and cancer [1]. These diagnoses become more prevalent as men age, with half the men over 50 and 80 percent of men over 70 suffering from prostate enlargement, also known as benign prostatic hyperplasia (BPH) [2]. It is estimated that prostate cancer, the most serious of the above diagnoses, will occur in one in six men, and one in 35 will die from the disease. Indeed, prostate cancer is the second-leading cause of cancer death in the US, accounting for about 10% of deaths from cancer in men[3]. It is estimated that in 2008, there will be 186,320 new cases of prostate cancer and 28,660 deaths[4]. On the other hand, prostate inflammation accounts for about 25% of doctor visits by young and middle-aged men reporting problems in the urinary and genital systems according to the National Institute of Health[5]. Many studies have found a link between various cancers (i.e. stomach, liver, large intestine) and inflammation [6], though it has been difficult to determine the involvement of inflammation in prostate cancer. Haverkamp et al provide a good review of relevant literature and emphasize the role of chronic inflammation in prostate cancer, though they note that a direct relationship between inflammation and prostate cancer is yet to be determined[7].

Prostate inflammation is less severe than cancer, and its treatment is likewise less intrusive—usually involving prescription of anti-inflammatory drugs and antibiotics. Cancer, on the other hand, may require painful and expensive surgical procedures, radiation, or hormone therapy. Thus, if the link between inflammation and prostate cancer is established in the near future, it will be worth exerting more effort toward

preventing prostate cancer by means of treating and preventing inflammation. The focus of this study is to identify clinical factors associated with the presence of prostate inflammation among men at a high risk of prostate cancer. It is hoped that this knowledge will lead to a better understanding of prostate inflammation and the many processes in which it is involved.

In the pages that follow, we will describe prostate inflammation as well as its risk factors and the many physical processes with which it is associated, like BPH and prostate cancer. In addition, I will discuss the importance of obesity in prostate cancer etiology and systemic inflammation. These complicated relationships helped formulate the rationale for this study, which aims to identify the relationship between obesity and prostate inflammation with the hope of finding a future target for the prevention of prostate inflammation and perhaps prostate cancer.

What is prostate inflammation?

Prostate inflammation, also known as prostatitis, encompasses four disorders of the male prostate gland. Shown below is a chart representing the NIH consensus classification of prostatitis syndromes[8,9].

Type	Symptoms	Cause & Diagnosis	Treatment
I. Acute bacterial prostatitis (least common; treatment is relatively simple)	Painful/frequent urination, pain in the genital area and lower back, fevers, and chills	Bacterial infection (usually *Escherichia coli*); bacteria and white blood cells in the urine	Anti-microbial and anti-inflammatory medications to clear infection and relieve pain
II. Chronic bacterial prostatitis (not very common; more difficult to treat and may take longer than Type I)	Pain in the lower back, testicles, and perineum. Frequent/urgent/painful urination if infection spreads to the bladder.	Recurrent bacterial infection (*E. coli,* other gram-negative organisms, or enterococcus); bacteria and white blood cells in the urine	Antibiotics and anti-inflammatory medications to clear infection and relieve pain
III. Chronic prostatitis/chronic pelvic pain syndrome (most common but least understood) A. Inflammatory	Urological pain	No infectious agent; Leukocytes and pro-inflammatory factors present in expressed prostatic secretions, semen, and postprostate massage urine	Antibiotics and anti-inflammatory drugs to relax glandular muscles and relieve pain; often ineffective
B. Non-inflammatory		No infectious agent and no evidence of inflammation	
IV. Asymptomatic inflammatory prostatitis (most common)	None	Excess concentrations of leukocytes in seminal fluids	None

Type IV prostatitis is not very well understood and inflammation is often found incidentally based on histology and in the absence of symptoms. Yet some estimates of its prevalence are over 30% (Carver et al)[10]. Thus, because little is known about its etiology and because it is so common, we have chosen to focus on type IV inflammation and obesity as a causative factor.

Risk factors for Prostate Inflammation

Though it is generally considered idiopathic, there are a variety of conditions and procedures that are thought to increase the risk of prostatitis[11,12,13]. They include:

-history of bladder infection
-bladder outlet obstruction (i.e. an enlarged prostate (BPH), a tumor, or a stone)
-diabetes mellitus
-suppressed immune system
-urethral catheterization
-sexually transmitted diseases
-unprotected sexual intercourse
-performing vigorous activity with a full bladder
-jogging, cycling, or horseback riding

Prostate inflammation has also been linked with BPH and prostate cancer, as described below.

Inflammation and BPH

Gleason et al and Nickel et al have both suggested that inflammation is important in BPH development[14,15]. In Gleason's *in vitro* study, prostate cells taken from patients with BPH were cultured and examined for the role of PDGF (platelet-derived growth factor), a compound normally released as a consequence of the inflammatory response. The addition of PDGF to the culture media resulted in a dose-dependent increase in prostate cell proliferation, indicating that inflammation may be linked to BPH. In 1999, Nickel et al suggested that inflammation might be a component of BPH, after they found that all prostate specimens from patients diagnosed with BPH had histological inflammation, mainly periglandular. Though they also noted that the mean tissue surface area involved was only 1.1% and that volume was not associated with the type or degree of inflammation. Recently, Nickel et al conducted a literature review, in which they concluded that prostate inflammation and BPH may be linked by means of cytokines,

chemokines, and inflammatory mediators[16]. Also, in a 2006 review, Kramer et al found that chronic inflammation correlated closely with BPH disease progression by means of elevated expression of pro-inflammatory cytokine interleukin 17 (IL-17), causing an increase in IL-6 and IL-8 production. Both IL-6 and IL-8 are involved in BPH stromal growth[17].

Inflammation and Prostate Cancer

Approximately 20% of all human cancers are caused by certain chronic inflammatory states[6,18,19], leading scientists to ponder the possibility of prostate cancer being associated with chronic inflammation of the prostate. Studies have found positive correlations between inflammation and prostate cancer, though the American Cancer Society (ACS) states that these effects are yet to be proven[19] and the Prostate Cancer Foundation declares that such a correlation does not exist[20]. Brosman et al found that the ability of prostate cancer patients to mount an inflammatory response was significantly impaired compared to non-cancer controls, as observed after skin exposure to the irritant croton oil[21]. MacLennan et al found a significant association between the degree of prostate inflammation from needle biopsies and serum prostate specific antigen (PSA) levels and concluded that chronic inflammation may be an important risk factor for prostate cancer[22]. In a thorough review of literature, Platz et al concluded that there is strong evidence to indicate that inflammation is linked to cancer of the prostate, but whether the relationship is causative or merely indicative of an environment favorable to the development of cancer is unknown[23]. In a detailed examination of the surrounding biochemistry, Stock et al suggested that sustained inflammation could potentially lead to

cancer in the prostate by means of disruption of oxidative balance, genetic changes in immune cells, and elevated chemokine expression[24]. Lastly, De Marzo et al review pertinent studies and conclude that prostatitis might be linked with a subset of prostate cancers (ones that are manifest in younger men) but that more studies are needed to explicitly analyze the relationship between the various types and degrees of inflammation and prostate cancer[25].

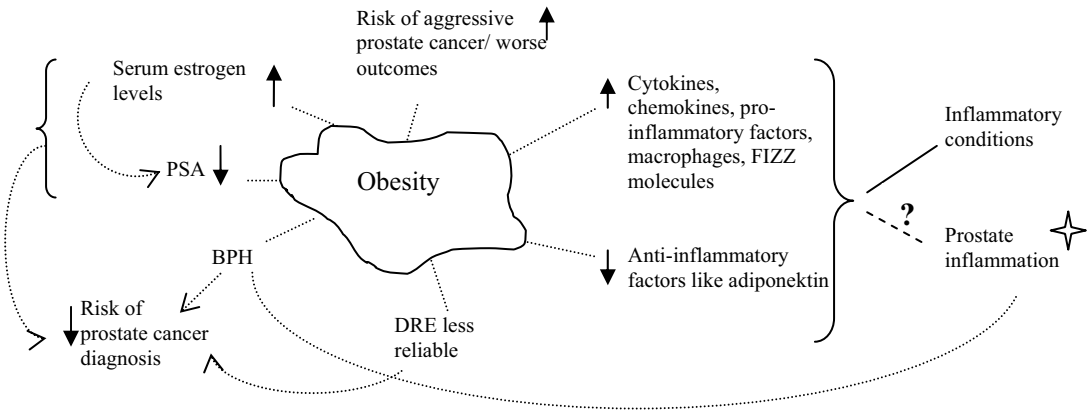
Obesity and Prostate Cancer

The direct and indirect health consequences of obesity create a burden on the US economy, accounting for 9.1% of national healthcare expenditure[26] or approximately $117 billion in total costs. In addition to its relationship to prostate inflammation, obesity is associated with increased risks of various health conditions, such as hypertension, osteoarthritis, dyslipidemia, type II diabetes, coronary heart disease, stroke, gall bladder disease, sleep apnea and other respiratory conditions, and cancers of the colon, breast, and endometrium, according to the Center for Disease Control (CDC)[27].

Some studies have suggested that obesity is protective against prostate cancer because increased BMI is associated with a decrease in PSA levels[28,29,30]. It is still unclear, however, whether this is a true protective effect or simply the result of more "diluted" PSA caused by the greater volume of blood and fluids present in obese individuals. Adiposity also increases serum estrogen levels which may decrease PSA expression[31]. Some investigators also hypothesize that obesity increases prostate cancer risk because physicians are less likely to detect cancer when PSA levels are lowered and when digital rectal examinations (DREs) are less reliable due to large body size. BPH is

also associated with obesity [32-35] and it is more difficult to find cancerous cells in biopsies when the prostate is enlarged. Further, analyses show that obesity may be associated with an increased risk of aggressive prostate cancer (i.e. metastasis, worse tumor prognosis, and failed treatment) but a decreased risk of prostate cancer diagnosis [36-39]. Freedland et al provide a very thorough review of literature in order to make sense of what seems to be conflicting data. They conclude that "obesity may reduce the risk of nonaggressive disease while it may promote aggressive disease[40]". Figure 1 depicts the complex relationship between obesity and prostate cancer in a simplified manner.

Figure 1. Obesity is associated with a variety of outcomes in the body, including an altered risk of prostate cancer and an increased risk of systemic inflammation.



Obesity and Inflammation

Recent evidence suggests that obesity might play a role in chronic body (systemic) inflammation. Visceral adiposity has been linked with a variety of inflammatory conditions (such as vascular inflammatory disease or vasculitis[41]) through the release of adipokines, cytokines, chemokines, and other pro-inflammatory factors[42,43]. Fantuzzi has written that obese individuals have increased levels of inflammatory

markers such as C-reactive protein, interleukin-6, and tumor necrosis factor-α, as well as macrophages, leptin, and FIZZ ("found in inflammatory zone") molecules. In contrast, anti-inflammatory factors like adiponektin are decreased in obese individuals compared to lean individuals[43]. A 9-year prospective study by Fogarty et al found that weight increases in 1,222 subjects was linearly associated with an increase in systemic inflammation, as measured by C-reactive protein (CRP) levels[44]. Similarly, Esposito et al found that fat loss by liposuction was associated with a decrease in inflammatory status among obese women[45]. While to our knowledge there is little data directly assessing the association between obesity and prostate inflammation, there is ample (also depicted in Figure 1) evidence relating obesity to various other types of inflammation. This existing evidence together with the potential association between prostate inflammation and prostate cancer has prompted us to investigate further whether obesity is related to prostate inflammation.

Obesity and Prostate Inflammation: Aims

The relationship between obesity and prostate inflammation is of most interest to us in this study and is an area where there has been no research.

In this cross-sectional study of prostate biopsies from 661 men, we examine the relationship between BMI and Type IV prostatitis. We believe that the likelihood of asymptomatic inflammatory prostatitis increases as BMI increases and that obese individuals have a higher risk of prostate inflammation relative to normal individuals. Specifically, we hypothesize that:

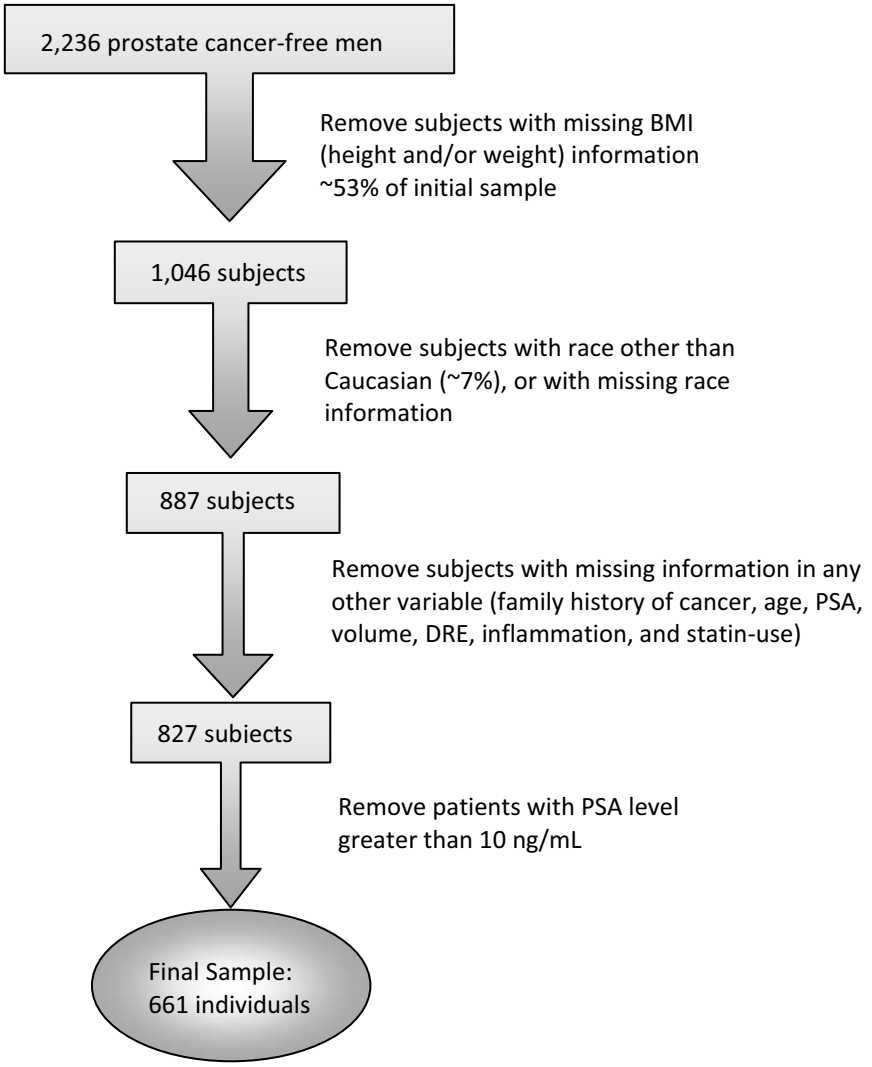
1) On average, subjects with prostate inflammation will have a higher BMI than subjects with no signs of inflammation (indicated through univariate analysis).
2) The odds of prostate inflammation in obese individuals are higher than the odds of inflammation in non-obese (normal and overweight) individuals, after adjusting for potential confounders and effect modifiers. This will be examined by modeling the relationship between BMI and prostatitis through logistic regression.

METHODS

Sample Selection:

In order to understand the relationship between obesity and prostate inflammation, a sample of 1,046 prostate cancer-free men from the VA in Portland, Oregon was studied. These patients were referred for a transrectal ultrasound (TRUS) and a minimum of 6 biopsy cores due to elevated PSA levels and/or an abnormal DRE. The methods are described in further detail elsewhere [46]. Prostate biopsies were obtained between April 1992 and June 2006 by Dr. Mark Garzotto. As shown in Figure 2, the sample was restricted to 887 Caucasian men since a non-white proportion of 8% was considered too low for any meaningful and generalizable comparisons to be made. After systematically removing subjects with missing values for any of the variables of interest as well as all patients with PSA levels greater than 10 (explained in the Variables section), the sample was limited to 661 individuals.

Figure 2. How we arrived at the final sample of 881 individuals.



Variables:

Nine variables were considered to be most relevant to our research topic. They are listed and described in detail below, and some summary statistics and correlation coefficients are displayed in Table 1 and Table 2.

1. Patient ID

The identity of each subject was kept confidential except under circumstances where a data point was thought to be erroneous and was hence checked to see if it matched records. Each patient was assigned a unique identification number that was used throughout the data analysis process.

2. Age

Age, measured in years, was used as a continuous variable. Patients ranged from 44 to 81 years in age, with a mean of about 64 years and a standard deviation of 6.7 years.

3. Family History of Cancer

Based on recent evidence showing a possible link between inflammation and prostate cancer (see *Introduction*), and seeing as how prostate cancer has a genetic component[47], family history of cancer was considered an important variable to evaluate. This variable was treated as a dichotomous/binomial variable (0,1) with zero representing no family history of cancer. Approximately 20% of the patients in this study had a family history of prostate cancer among first-degree relatives.

4. PSA

A measure of total prostate-specific antigen (PSA in ng/mL), obtained at the same visit when the biopsy was taken, was used in the data analysis. All

patients included in our study had PSA levels less than or equal to 10 ng/mL. This was done as a precautionary measure to eliminate the possibility of having patients with undetected prostate cancer—the risk of cancer in men with PSA greater than 10 ng/mL is double the risk for those with PSA between 4 and 10 ng/mL and is more than three times the risk for those with PSA level less than 4 ng/mL[48]. PSA is a very sensitive but non-specific test used for the detection of cancer. The mean PSA in our sample was 5.2ng/mL and ranged from 0.05 to 10.0 ng/mL, with a standard deviation of 2.4 ng/mL. PSA was treated as both, a continuous variable and a dichotomous variable with zero coding for levels less than 4.0 ng/mL and one coding for levels equal to or greater than 4.0 ng/mL. The separation was done because normal PSA levels are between 0.0 and 4.0 ng/mL, and generally, patients with levels above 4.0 ng/mL obtain more tests and oftentimes prostate biopsies as they are more likely to have cancer. It is important to note that patients were referred for a biopsy due to abnormal PSA levels and/or DRE results, which means that the PSA distribution is not representative of the general population.

5. Prostate volume

Due to its association with prostate inflammation (previously described), prostate volume was considered an important variable, particularly in the final regression model. The average prostate volume was 46.6 cc and the range was from 3.0 cc to 205.9 cc. One subject was eliminated from data analysis because his prostate volume was exceedingly high and determined unfeasible (450.5 cc).

Volume was treated as a continuous variable and as a dichotomous variable, with prostate volume less than 40.0 cc regarded as normal and greater than or equal to 40.0 cc indicating BPH. It was difficult to come up with an appropriate value for stratification as there is no set volume that is clinically used to indicate BPH—it can be as low as 30 cc in some cases and as high as 45 cc in others. 40 cc was chosen somewhat arbitrarily, but it was also approximately equal to the median (40.5 cc).

6. DRE

Digital rectal examination is used to detect any abnormalities in the prostate tissue such as tumors or other tissue irregularities. DRE was treated as a dichotomous variable, with zero representing normal findings and one representing abnormal findings. About 44% of patients in this study had findings that were abnormal (either asymmetric, suspicious, or indicative of cancer (later shown absent)).

7. Inflammation

NIH Class IV prostate inflammation was the main outcome of interest and was treated as a dichotomous variable (0,1), indicating the absence or presence of inflammation—i.e., controls and cases, respectively. Approximately 29% of patients had asymptomatic prostate inflammation in this study, as indicated by their histological findings on biopsy (high concentrations of leukocytes in seminal fluids with no signs of infection).

8. Use of Statins

Close to half (47%) of patients in this study had used one ore more types of statin drugs in the past 30 days, including Atorvastatin, Fluvastatin, Simvastatin, Pravastatin, and Lovastatin, as ascertained from pharmacy records. Statins are molecules that inhibit 3-hydroxy-3-methylglutaryl conenzyme-A (HMG-CoA) reductase, which is involved in the production of cholesterol. Thus, their main purpose is to reduce cholesterol levels, thereby decreasing patients' risk of cardiovascular and cerebrovascular events[49]. Recent studies have shown that statins might play a role in the prevention of human cancers, specifically colorectal, prostate, breast, and skin cancers. At the same time, statins seem to have distinct effects on the process of inflammation by interfering with lymphocyte function and causing a shift from a pro-inflammatory to an anti-inflammatory state *in vitro*. Thus, it seemed appropriate to consider the effects of statin-use on the relationship between BMI and prostate inflammation considered herein. Statin-use was treated as a dichotomous (0,1) variable, irrespective of the given type, dose, or duration of drug treatment. This was done because each drug type has a different potency and patients may have taken multiple types of drugs, each with a varying dose and a different duration, thereby making calculations very complex and possible stratifications likewise complicated. As far as other types of anti-inflammatory drugs, namely NSAIDS (non-steroidal anti-inflammatory drugs), patients were asked to refrain from their use two weeks prior to the collection of biopsy specimens. It is therefore assumed that NSAID-use would not have had an impact on the relationship studied here.

9. BMI

Last, body mass index was our main predictor variable. It was calculated in kg/m^2 and was treated as a continuous variable in some analyses, and as a categorical variable in others. As a categorical variable, a BMI less than 25 kg/m^2 was considered normal; between 25 and 30 kg/m^2 was overweight; between 30 and 35 kg/m^2 was obese; and equal to or over 35 kg/m^2 was morbidly obese. Patient BMIs ranged from 4.1 to 62.6 kg/m^2, and their mean was 29.4 kg/m^2. In some analyses, such as in the evaluation of potential confounders, BMI was treated as a dichotomous variable for the comparison of obese men to normal men (where 265 observations (for the overweight men) were omitted) or obese men to non-obese men (comparison of those with BMI≥30 to those with BMI<30).

Table 1. Summary statistics of variables used in statistical analysis.

Variable	Mean	Std. Dev.	Min	Max
Age	63.894	6.655	44	81
Family Hx CA*	0.204	0.404	0	1
PSA	5.211	2.347	0.05	10
Prostate volume	44.9	25.496	3.04	205.9
DRE (abnormal)*	0.443	0.497	0	1
Inflammation*	0.286	0.452	0	1
Statin-use*	0.471	0.5	0	1
BMI	29.377	6.229	4.114	62.633

Hx = history; CA = cancer; DRE = digital rectal examination; BMI = body mass index.
*These variables were dichotomous, so mean values indicate proportion that was coded "yes" or "1" for given variable. i.e. A mean of 0.286 for inflammation is the same as saying 28.6% had prostate inflammation or were cases.

Table 2. Correlation coefficients for each pair of variables. Strongest correlations are shown in bold font, though none are particularly noteworthy.

	Fam Hx CA	Age	PSA	Volume	DRE	Inflammation	Statin-use
Fam Hx CA	1.000						
Age	-0.013	1.000					
PSA	0.022	**0.198**	1.000				
Volume	0.050	**0.202**	**0.217**	1.000			
DRE	-0.044	0.008	**-0.200**	**-0.244**	1.000		
Inflammation	-0.080	-0.056	-0.006	0.141	-0.039	1.000	
Statin-use	-0.011	0.069	0.001	-0.072	-0.011	0.027	1.000
BMI	-0.020	**-0.184**	-0.025	0.142	-0.051	0.085	**0.171**

A histogram of volume showed that the data were right skewed; therefore, a $\log_2$-transformation of this variable was carried out, resulting in a more symmetric distribution and a narrower range (not shown). Volume was then centered at the median of 40cc. Similarly, age was centered at 65 years and PSA at 5.2 ng/mL for more logical interpretation.

Statistical Analysis

All tests were performed in *STATA v. 10.0*, including Student's t-test, Pearson's Chi^2 test, for which a liberal p-value of 0.25 was used for the inclusion of all potentially significant explanatory variables in the main effects model. Variable-adjusted odds ratios (ORs) and corresponding confidence intervals were obtained using the Mantel-Haenszel approach to identify possible confounders. For this, a variable whose adjusted OR differed by 10% or more from the crude odds ratio was considered a confounder. After the creation of a main effects model, interaction terms were assessed for individual statistical significance by comparing the model with and without the interaction term. An alpha significance level of 0.1 was used to include individually significant interaction terms. When

these interaction terms were put together in the model along with other significant variables, an alpha of 0.05 was used to exclude terms that lost statistical significance. In addition to these traditional steps of model-building, a backwards stepwise regression approach was used to create additional models. All the models were compared with respect to various characteristics, such as fit and discriminative ability, which were obtained using *STATA*.

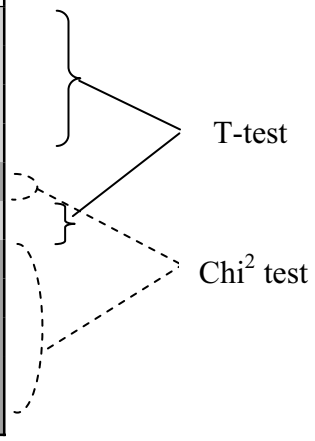
RESULTS

T-Tests and Chi^2 Tests:

Preliminary tests of differences were done to compare those with inflammation to those without inflammation, with respect to the variables listed above. Student's two-sided 2-sample t-tests were done for continuous variables and Pearson's Chi^2 tests were done for categorical variables, as shown in Table 3. Based on a significance level of 0.05, there was sufficient evidence to indicate that mean volume and mean BMI were higher in those with prostate inflammation versus those without inflammation (t-test p-value = 0.0003 and 0.03, respectively). Family history of cancer, on the other hand, seemed to be more prevalent in those with no inflammation (p-value = 0.04). In addition, when BMI categories were analyzed, it appeared that mean BMI was greater within the obese category for cases than controls, when obese and morbidly obese subjects were combined (p-value = 0.046). When these subcategories were analyzed separately, no significant differences were found and none of the other variables showed a statistically significant difference between cases and controls. Nevertheless, a liberal significance level of 0.25 was used to include all potentially important predictor variables in the preliminary (main effects) logistic regression model, so age was also included.

Table 3. Comparison of baseline characteristics between cases (with inflammation) and controls (no inflammation).

Characteristic	Inflammation	No Inflammation	p-value
Mean age (yrs)	63.31	64.13	0.151**
Mean volume (cc)	50.57	42.63	0.0003*
Log_2Volume (cc)			0.0004*
fPSA (ng/mL)	5.19	5.22	0.88
fPSA, categorical			0.862
Mean BMI (kg/m^2)	30.21	29.04	0.030*
BMI, categorical			0.172**
Statin use (%)	49.21	46.19	0.482
DRE Abnormal (%)	41.27	45.55	0.317
Family Hx Cancer (%)	15.34	22.46	0.040*



**p-value <0.05; **p-value<0.25*

Evaluation of Third Factors:

The crude odds ratio for the risk of inflammation between obese and normal weight patients (excluding overweight individuals) was calculated to be 1.37, though that did not reach statistical significance (95% confidence interval (CI) 0.86 to 2.18). Combining the normal and overweight categories as "non-obese" decreases the crude OR to 1.26 (95% CI 0.89 to 1.78).

To assess the presence of confounding and/or effect modification, odds ratios (OR) were examined within variable strata and adjusted odds ratios were calculated using the Mantel Haenszel (MH) approach, shown in Table 4.

Table 4. Stratified odds ratios for inflammation in obese (BMI≥30) vs. non-obese (BMI<30) individuals.

Stratification variable	Strata-specific OR	Adjusted OR	95% CI
By PSA	(0-<4) = 1.67 (4-10) = 1.14	OR_{MH} = 1.26	0.90 to 1.78
By Family history of cancer	(none) = 1.11 (present) = 2.43	OR_{MH} = 1.28	0.90 to 1.80
By DRE	(normal) = 1.53 (abnormal) = 0.96	OR_{MH} = 1.26	0.89 to 1.77
By Age	(<65) = 1.20 (≥65) = 1.30	OR_{MH} = 1.24	0.88 to 1.76
By Statin-use	(No) = 0.92 (Yes) = 1.64	OR_{MH} = 1.25	0.88 to 1.77
By Volume (BPH* indicator)	(<40) = 0.94 (≥40) = 1.64	OR_{MH} = 1.22	0.86 to 1.72

None of the adjusted odds ratios were different from the crude odds ratio by more than 10%. We therefore arrived at a preliminary/main effects model that included inflammation as the outcome of interest and BMI, volume, age, and family history of cancer as predictor variables (based on t-test and chi^2 test p-values <0.25).

Main effects model:

$$G(x) = \beta_0 + \beta_1(BMI) + \beta_2(Log_2Volume_c) + \beta_3(FamHxCA) + \beta_4(Age_c)$$

When put together in the model, all variables appeared to be significant in predicting inflammation (Wald's p-value<0.05) except for BMI. However, BMI was kept in the model despite Wald's p-value of 0.206 as it is our main explanatory variable of interest, and it was thought that after the addition of interaction terms, its significance in the model might change.

We assessed interactions by comparing the main effects model to models that included each interaction individually (reduced and full models, respectively). We first created all possible interaction terms between BMI, as a continuous variable, and each explanatory variable, as well as some interaction terms from among the explanatory variables based on biologic plausibility. We generated logistic regression models to obtain a Log-likelihood (LL) term. We then compared the full and reduced models using the equation $[(LL_{reduced} - LL_{full})*-2]$ to obtain a Chi^2 statistic and then a corresponding p-value for the significance of the interaction. Results were also verified by generating the full model including each interaction term and recording the corresponding Wald's test p-value. The results are shown below:

Table 5. P-values to aid in the evaluation of potential effect modifiers.

Interaction term	p-value
BMI x PSA_c	0.737
BMI x Family history of cancer	0.540
BMI x DRE	0.116
BMI x Age_c	0.855
BMI x Statin-use	0.098
BMI x $LogVolume_c$	0.177
PSA_c x $LogVolume_c$	0.780
PSA_c x Family history of cancer	0.455
PSA_c x Age_c	0.050
PSA_c x DRE	0.756
Statin-use x $LogVolume_c$	0.381
Age_c x $LogVolume_c$	0.172
$LogVolume_c$ x DRE	0.737

A "c" subscript indicates the variable was centered at the median.

Using a p=0.1 cut-off, we concluded that the highlighted interaction terms potentially modified the relationship between obesity and prostate inflammation. However, when they were incorporated into the model together, none of them

appeared to be significant except for PSA_c x Age_c .A backwards step-wise approach resulted in only age and family history of cancer being included in the model, as well as an interaction term between BMI and $LogVolume_c$, which lost significance once the corresponding variables were added to the model.

In addition, we modeled BMI as a categorical variable containing four groups and generated interaction terms using this variable instead of continuous BMI. A backwards step-wise method was used to generate this additional model. Lastly, since BMI did not appear significant in any of the models, we generated a final model excluding BMI.

Models:

Thus, there were four models that were worth exploring. Highlighted terms had a Wald's p-value<0.05, but some non-significant variables were kept when the corresponding interactions were statistically significant. Here, G(x) represents inflammation, and a "c" subscript indicates the variable was centered at the median.

1. $G(x) = \beta_0 + \beta_1(BMI_{cont}) + \beta_2(LogVolume_c) + \beta_3(FamHxCA) + \beta_4(Age_c) + \beta_5(PSA_c) + \beta_6(PSA_c * Age_c)$

2. $G(x) = \beta_0 + \beta_1(BMI_{cont}) + \beta_2(Age_c) + \beta_3(FamHxCA) + \beta_4(LogVolume_c)$

3. $G_(x) = \beta_0 + \beta_1(BMI_{cat\ 1}) + \beta_2(BMI_{cat\ 2}) + \beta_3(BMI_{cat\ 3}) + \beta_4(Age_c) + \beta_5(LogVolume_c) + \beta_6(FamHxCA)$

4. $G(x) = \beta_0 + \beta_1(Age_c) + \beta_2(LogVolume_c) + \beta_3(FamHxCA)$

The four models were compared with respect to their Goodness of Fit (GOF), Receiver Operating Curve (ROC) area estimates, as well as the Akaike and Bayesian Information Criteria (AIC and BIC). All had a good fit (p-value>0.40).

Table 6. Comparison of models 1, 2, 3, and 4.

	ROC	**AIC**	**BIC**
Model 1	0.63	775.45	806.91
Model 2	0.62	775.98	798.45
Model 3	0.62	779.24	810.70
Model 4	0.62	775.68	793.66
Results:	*Similar discriminative abilities*	*Model 5 has the lowest AIC*	*Model 1 has the lowest BIC*

Results did not clearly indicate that one model was much better than the others. Thus, all models were utilized for various interpretation purposes. Model 1 had a significant interaction term between PSA and age. Model 2 was used to understand the effect of BMI as a continuous variable, whereas 3 was used to assess the effect of categorical changes in BMI. In model 4 we excluded BMI since it was not significant in any of the models.

Table 7. Results of model 1 that includes BMI (continuous), age, logVolume, family history of cancer, and PSA as explanatory variables, as well as an interaction between PSA and age.

Variable	**Odds Ratio**	**Wald's p-value**	**95% Confidence Interval**	
			Lower	**Upper**
BMI (cont.)	1.017	0.228	0.989	1.046
Age_c	0.972	0.043	0.944	0.999
$LogVolume_c$	1.652	<0.001	1.276	2.138
Family Hx CA	0.574	0.018	0.362	0.909
PSA_c	0.967	0.400	0.894	1.046
PSA_c x Age_c	0.989	0.050	0.977	0.999

Table 8. Results of model 2 that includes BMI (continuous), logVolume, family history of cancer, and age as explanatory variables.

Variable	Odds Ratio	Wald's p-value	95% Confidence Interval	
			Lower	Upper
BMI (cont.)	1.019	0.191	0.991	1.047
$LogVolume_c$	1.626	<0.001	1.265	2.089
Family Hx CA	0.582	0.021	0.368	0.921
Age_c	0.972	0.042	0.946	0.999

Table 9. Results of model 3 that includes BMI (categorical), logVolume, family history of cancer, and age as explanatory variables.

Variable	Odds Ratio	Wald's p-value	95% Confidence Interval	
			Lower	Upper
BMI (overweight)	1.002	0.994	0.620	1.619
BMI (obese)	0.959	0.877	0.564	1.630
BMI (morbidly obese)	1.444	0.226	0.797	2.617
$logVolume_c$	1.643	<0.001	1.276	2.116
Family Hx CA	0.581	0.021	0.367	0.920
Age_c	0.971	0.038	0.9445	0.998

Table 10. Results of model 4 that includes logVolume, family history of cancer, and age as explanatory variables.

Variable	Odds Ratio	Wald's p-value	95% Confidence Interval	
			Lower	Upper
$logVolume_c$	1.670	<0.001	1.303	2.141
Family Hx CA	0.586	0.022	0.371	0.926
Age_c	0.968	0.018	0.943	0.995

DISCUSSION

Results:

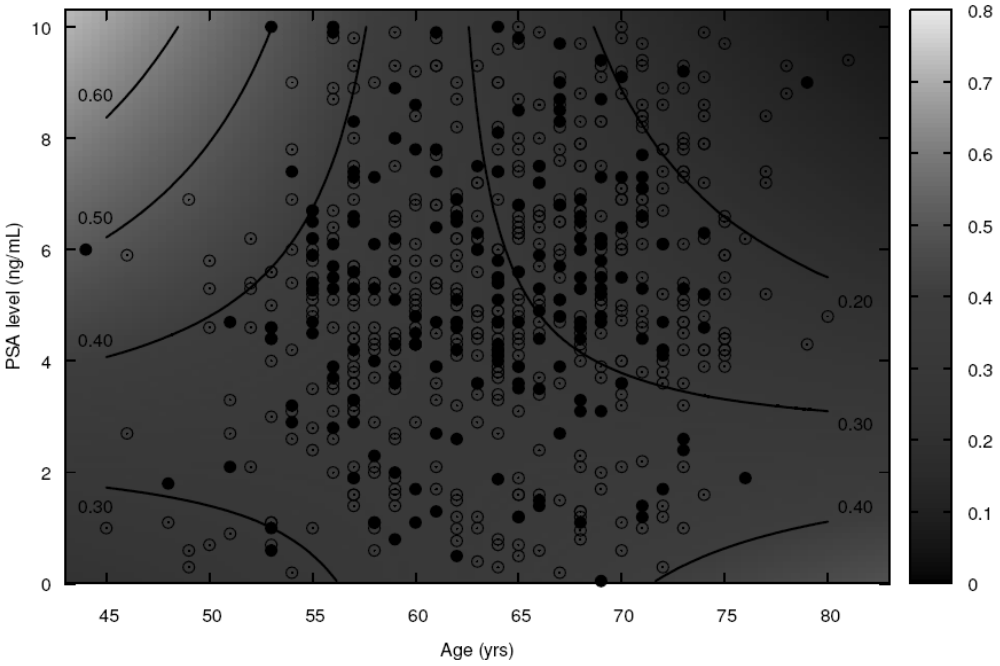
Logistic regression models 1 and 2 indicate that after adjusting for age, volume, family history of cancer, and significant interaction between age and PSA, a one unit increase in BMI does not significantly alter the odds of inflammation in our male subjects. In model 3, BMI again did not reach statistical significance within any of the categories (overweight, obese, and morbidly obese) and there was no statistically significant trend; however, the odds of inflammation in the morbidly obese is estimated to be 44% greater than the odds of inflammation in normal weight individuals. It should be emphasized that this value was not statistically significant (the 95% confidence interval ranged from a 21% decrease in the odds of inflammation to a 162% increase).

Surprisingly, family history of cancer seems protective against inflammation; that is, the odds of inflammation in those with *no* family history of cancer is 1.7 to 1.74 (1/0.586 to 1/0.574 in models 4 and 1, respectively) times the odds in those *with* a family history of cancer. One would expect that, since a family history of cancer would increase the risk for prostate cancer in an individual, perhaps by reverse reasoning an inflammatory state in the prostate is more likely (as inflammation is a possible precursor to cancer). On the other hand, it can be likewise argued that a family history of cancer would make individuals more conscious of their prostate health, and therefore concerned enough to incorporate some preventive habits in their lives (such as dietary alterations) or get screened at a younger age[50]. There is no data that would allow us to explore this possibility, so we cannot ascertain why family history of cancer seems protective against prostate inflammation in our sample. Since a family history of prostate cancer is a risk

factor for prostate cancer, it is also possible that inflammation protects against prostate cancer.

The risk of prostate inflammation increased with increasing volume in all the models. That is, with every doubling of volume, the odds of inflammation increased by about 65% (63 to 67 percent in the models). So we can expect that a patient with prostate volume 80 cc would have a 65% increased risk of prostate inflammation compared to a man with 40 cc, after adjusting for PSA levels, family history of cancer, BMI, and age. In both model 1, the interaction term between PSA and age was marginally statistically significant (p-value 0.049 and 0.044). Figure 3 below depicts how the probability of inflammation changes as PSA levels and age change. It appears that in younger individuals, increasing PSA levels predict increases in the probability of inflammation, whereas in older individuals, an increase in PSA levels does not necessarily mean an increase in the probability of inflammation. It should be noted that the discriminative ability of the model was not very good (ROC area = 0.63) and in the extreme ends of the spectrum, there are very few data points, so this graph should be used mainly to see how age and PSA influence one another.

Figure 3. The estimated probability of prostate inflammation based on age and PSA.



Solid points represent those with inflammation and open points represent those without.

Thus, all in all, it is clear that in this study, obesity and overweight are not independent predictors of prostate inflammation, whereas age and prostate volume—i.e., BPH—are predictive of inflammation, and family history of cancer seems protective of prostate inflammation.

Study Limitations:

This study has temporal limitations due to its cross-sectional design. Nevertheless, recent studies provide strong evidence in support of obesity as a cause of inflammation. It is also of note that our initial sample size of 1,046 patients makes up less than half of the sample of 2,236 patient data that was originally available for use. The reason for our sample size reduction is that height and weight information (used for BMI calculation) was only available for those 1,046 patients. Our final sample of 661 subjects included 189 cases and 472 controls.

Misclassification of outcome is possible, especially in obese individuals or in those with BPH, where inflammation is more likely to be missed. This differential misclassification would underestimate the crude odds ratio and bias it towards the null. Selection bias is possible, but not likely, as the missing information seems to be dispersed randomly. A simple comparison of the patient data with BMI available to the data where BMI was not available shows the following:

-Patients with BMI data were 4.2% more likely to have a family history of cancer,
-Those with BMI data were on average 1.2 years younger than those without BMI data,
-Those with BMI data had, on average, PSA levels 0.79 ng/mL higher than those without BMI data,
-Patients with BMI data had a mean prostate volume about 5.62 cc greater than the mean volume of patients with no BMI data available, and
-Those with BMI data were 6.8% less likely to have abnormal DRE findings, compared to those without BMI information.

Even though the above mean comparisons were statistically significant at the 0.05 level, the differences are not considerably large to merit special attention. These comparisons were done after the removal of missing points for each variable in each group and the correction or removal of outliers and extreme points.

As previously mentioned, we were not able to explore the relationship between obesity and prostate inflammation within different ethnic or racial groups due to the small sample size. This sample is most likely not representative of the general population for another reason: the patients were referred for biopsy due to high PSA levels and/or abnormal PSA, so the sample misses individuals with no abnormal symptoms. Also, statin-use was treated as a categorical variable and it would have been more useful if

treated as a continuous variable to determine whether it had an effect on our model. Lastly, it is important to consider other variables such as socioeconomic status that were not considered in our analyses, and that may act as confounders.

CONCLUSIONS AND IMPLICATIONS

Though this study did not show a statistically significant association between obesity and asymptomatic prostate inflammation in the multivariate logistic regression model, there were some interesting trends in both the univariate and regression analyses. Namely, cases have an average body mass index 1.2 kg/m^2 greater than controls When inflammation was modeled alone with BMI (continuous), the odds ratio of inflammation for a one-unit increase in BMI was 1.030 ($p = 0.031$). Perhaps a one-unit difference in BMI is not biologically significant, but a 40% increase in risk for morbidly obese relative to normal weight individuals, albeit statistically non-significant, merits some attention and hopefully a more thorough exploration in the future of the effect of obesity on prostate inflammation.

We hope that this research project has set the stage for prospective studies that would better evaluate the potential relationship between obesity and all types of prostate inflammation—not only asymptomatic. Future studies can improve upon ours by having a more informative quantitative classification of statin-use and a larger sample size that would allow race-specific analyses.

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