DIABETES AND PROSTATE CANCER AGGRESSIVENESS AT DIAGNOSIS AND PROGRESSION IN WHITE AMERICANS AND BLACK AMERICANS FROM THE NORTH CAROLINA-LOUISIANA PROSTATE CANCER PROJECT (PCaP)

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A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology in the Gillings School of Global Public Health.

Chapel Hill
2016

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ABSTRACT

Saira Khan: Diabetes and Prostate Cancer Aggressiveness at Diagnosis and Progression in White Americans and Black Americans from the North Carolina-Louisiana Prostate Cancer Project (PCaP)
(Under the direction of Andrew F. Olshan)

Epidemiological studies have established that diabetes is protective against incident prostate cancer (CaP). However, the existing literature on the association of diabetes with CaP aggressiveness at diagnosis and progression is inconsistent, and research in racially diverse cohorts is limited. The goal of this dissertation was to examine the relationship between diabetes and CaP in cohort of men with incident CaP from the North Carolina-Louisiana Prostate Cancer Project (PCaP), a population-based cohort of White Americans (Whites) and Black Americans (Blacks). Follow-up data for North Carolina participants was available from the Health Care Access and Prostate Cancer Treatment in North Carolina (HCaP-NC) cohort for on average 5 years after CaP diagnosis.

Specific aim 1 sought to assess the association between diabetes and CaP aggressiveness at diagnosis in Black and White participants in PCaP. High aggressive CaP was defined as Gleason sum ≥8, or prostate specific antigen >20 ng/ml, or Gleason sum =7 and clinical stage cT3-cT4. We found that diabetes was not associated with high aggressive CaP in the overall cohort (OR: 1.04; 95% CI: 0.79, 1.37), Whites (OR: 1.00; 95% CI: 0.65, 1.57), or Blacks (OR: 1.07; 95% CI: 0.75, 1.53).

Specific aim 2 sought to implement a CaP progression algorithm and to assess the association between diabetes and CaP progression in Black and White participants in HCaP-NC. 20.9% of HCaP-NC participants experienced CaP progression. Progression was more prevalent in Blacks (25.0%) than Whites (17.6%). Diabetes was not associated with

CaP progression in the cohort as a whole (HR: 0.86, 95%CI: 0.54, 1.35), Whites (HR: 1.03, 95%CI: 0.50, 2.13), or Blacks (HR: 0.77, 95% CI: 0.43, 1.39).

Although obesity was not part of our primary aims, given the close relationship between obesity and diabetes we also examined the association of obesity, independent of diabetes, with CaP aggressiveness and CaP progression. Obesity, independent of diabetes, was positively associated with high aggressive CaP in Whites only (OR: 1.98; 95% CI: 1.14, 3.43). No association was observed in Blacks or the cohort as whole. Similarly, obesity, independent of diabetes, was associated with CaP progression (HR: 1.79, 95% CI: 1.08, 2.97) in Whites only.

ACKNOWLEDGMENTS

I would like to thank my committee members, Andy Olshan, Jeannette Bensen, Jianwen Cai, Matthew Nielsen, and Melissa Troester for their continual guidance, support, feedback, and encouragement throughout the dissertation process. I would not have a completed dissertation without you. In addition, I would also like to thank both Laura Farnan and Laura Hendrix for their insight, guidance, and assistance throughout my dissertation.

Andy- Thank you being a great advisor and mentor. Your guidance was invaluable not only for my dissertation, but helping me navigate the entire PhD program. I always felt a little less stressed about what I was supposed to be doing after meeting with you. Thank you for you continual support and guidance from everything to finding a dissertation to a post-doc.

Jeannette- I will look back on my dissertation fondly, and that is because of you made it such a positive expertise for me. Thanks you for being there through every step of the process, answering all my questions, being encouraging, and providing me with all the support I needed.

Jianwen—Thank you for helping me better understand survival analysis! You were always patient with all my questions and took time to explain everything clearly.

Matt- Thank you for helping me understand the clinical aspects of prostate cancer, especially progression. I could not have made the ~ 800 progression graphs without your guidance. Thank you for all your support throughout the dissertation.

Melissa- I have a better understanding of cancer epidemiology because of you. You were my first introduction to cancer epidemiology at UNC with EPID 770. Your insights and suggestions made this a better dissertation.

Laura F.- You were the PCaP data guru! Thank you for all your help understanding the PCaP data, providing data sets, and answering all my questions. Also thank you for providing great insight and advise throughout my dissertation.

Laura H. – Thank you for the very cool PCaP maps! Also thank you for your advice and suggestions throughout my dissertation.

Finally, I would like to thank the research subjects participating in both PCaP and HCaP-NC for their invaluable contributions.

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LIST OF ABBREVIATIONS

AA:	African American
ADT:	Androgen Depravation Therapy
ADJ:	Adjusted
AIPC:	Androgen-Independent Prostate Cancer
AJCC:	American Joint Committee on Cancer
AIRC:	Atherosclerosis Risk in Communities study
AUA:	American Urological Association
BCR:	Biochemical Recurrence
BLACKS:	Black Americans
BMI:	Body Mass Index
BPH:	Benign Prostatic Hyperplasia
BRFSS:	Behavioral Risk Factor Surveillance System
CaP:	Prostate Cancer
CaPSURE:	Cancer or the Prostate Strategic Urologic Research study
CDC:	Centers for Disease Control and Prevention
CI:	Confidence Interval
DAG:	Directed Acyclic Graph
DM:	Diabetes Mellitus
DRE:	Digital Rectal Exam
FDA:	Food and Drug Administration
HCaP-NC:	Health Care Access and Prostate Cancer Treatment in North Carolina
HR:	Hazard Ratio
LHRH:	Luteinizing Hormone Releasing Hormone
NCI:	National Cancer Institute
OR:	Odds Ratio

PCaP:	North Carolina-Louisiana Prostate Cancer Project
PD:	Prevalence Difference
PSA:	Prostate Specific Antigen
PSADT:	Prostate Specific Antigen Doubling Time
RP:	Radical Prostatectomy
SEARCH:	Shared Equal Access Regional Cancer Hospital Database
SEER:	Surveillance Epidemiology and End Results
SES:	Socioeconomic Status
TNM:	Tumor, Node, Metastases
WHITES:	White Americans
WHO:	World Health Organization

CHAPTER 1: INTRODUCTION AND SPECIFIC AIMS

Prostate cancer is the most common incident cancer among men in the United States. According to Surveillance Epidemiology and End Results (SEER), 14% of men will be diagnosed with prostate cancer during their lifetime.[1] Black men are much more likely to be diagnosed with and die from prostate cancer than white men. The incidence rate, from 2008-2012, in black men is 214.5 cases per 100,000 person years compared to only 130.4 cases per 100,000 person years in white men.[1] Between 2008-2012 the age-adjusted death rate in black men was more than double that in white men. Numerous studies have shown that diabetes is associated with a reduced risk of incident prostate cancer.[2-20] However, the impact of diabetes on prostate cancer aggressiveness at diagnosis and progression is less clearly understood.

Diabetes has been linked with tumor aggressiveness in a few studies, using the Gleason score of incident tumors as a marker of aggressiveness[21-24]. A study among patients from Boston and Chicago found that both white and black men with diabetes had a higher grade (Gleason score 8-10)[25] at diagnosis as compared to men without diabetes, but that black men were more likely to be diagnosed with a higher Gleason score as compared to white men independent of diabetes.[21] By contrast another study among Veterans found diabetes was significantly associated with a higher biopsy Gleason score in white men but not black men.[23]

Beyond the impact of diabetes on prostate cancer incidence and aggressiveness at diagnosis, understanding the impact of diabetes on prostate cancer progression is also important. Current measures of prostate cancer progression often do not distinguish between recurrent (prostate cancer is detected after a period of non-detection) and

persistent (prostate cancer remains continually detectable even after definitive treatment) and were largely established in white men. Moreover, other available population-based data sources such as SEER and SEER-Medicare cannot establish measures of progression, as necessary post-treatment PSA measures are not available in these datasets.

The North Carolina-Louisiana Prostate Cancer Project (PCaP) is an ideal population-based cohort for assessing the impact of diabetes on prostate cancer aggressiveness at diagnosis and progression in both White Americans (Whites) and Black men (Black). The PCaP cohort is comprised of incident prostate cancer cases from North Carolina and Louisiana, half Black and half White at each site, all diagnosed with adenocarcinoma of the prostate through state tumor registries between July 2004 and August 2009. Black men (n= 1,130) were enrolled at the same rate as white men (n= 1,128) using a randomized recruitment method.[26] In addition, a subsequent study, Health Care Access and Prostate Cancer Treatment in North Carolina (HCaP-NC), followed North Carolina PCaP subjects for an average of 5 years after diagnosis.[27]

A composite measure of prostate cancer *aggressiveness at diagnosis* has previously been developed for PCaP. Key components of the PCaP aggressiveness algorithm include Gleason grade, clinical stage, and prostate specific antigen (PSA) at diagnosis. In this project, an algorithm for prostate cancer *progression* will be implemented in HCaP-NC. Because HCaP-NC is a well-characterized diverse population-based cohort with detailed clinical data, this sample provides an ideal context within which to establish a measure of prostate cancer progression up to an average of 5 years after diagnosis for both Blacks and Whites.

Specific Aim 1: To assess the association between self-reported diabetes and prostate cancer aggressiveness at diagnosis in Black and White participants in PCaP.

Rationale: Although research suggests that there is an association between diabetes and prostate cancer aggressiveness at diagnosis[21-24], the impact of race on this association is not clearly understood despite that fact that Blacks are more likely to be diagnosed with both diabetes and prostate cancer than their white counterparts. To date only two studies have examined race differences.[21,23]

Specific Aim 2a: To implement a prostate cancer progression algorithm in the HCaP-NC follow-up cohort.

Rationale: This aim seeks to implement a prostate cancer progression algorithm in the HCaP-NC cohort. This algorithm will refine the characterization of prostate cancer progression including distinguishing participants that have persistent vs. recurrent prostate cancer progression across treatment modalities including radical prostatectomy and radiation. Key inputs of the algorithm will be PSA values, PSA trend over time, and treatment failure. This progression algorithm will allow us to comprehensively classify the progression profile of both Black and White American prostate cancer participants in HCaP-NC.

Specific Aim 2b: To assess the association between self-reported diabetes and prostate cancer progression in Black and White participants in the HCaP-NC follow-up cohort.

Rationale: Although several studies have shown a protective association between diabetes and incident prostate cancer, the association between diabetes and progression is less clear. Some studies have suggested that there is no association between diabetes and prostate cancer recurrence[23,28,29] while other studies have suggested that diabetes may be

associated with an elevated risk of progression as measured by metastases and biochemical recurrence.[21,30-33] Moreover, similar to aggressiveness at diagnosis the potential differences in the effect of diabetes on prostate cancer outcomes by race is not well studied.

CHAPTER 2: BACKGROUND

2.1 Descriptive Epidemiology of Prostate Cancer

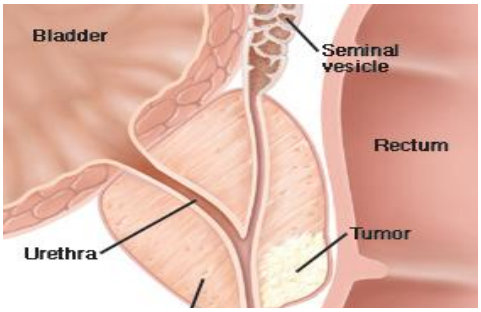
Prostate cancer is the most common incident cancer among men in the United States.[1] According to the Surveillance, Epidemiology, and End Results (SEER), 14% of men will be diagnosed with prostate cancer during their lifetime.[1] In 2016, there will be an estimated 180,890 new cases of prostate cancer.[1,34] This represents 21% of all incident cancer cases in men.[34]

Although the 5-year survival rate for prostate cancer is 98.9%, there will be estimated 26,120 deaths attributable to prostate cancer in 2016.[34] Survival in prostate cancer is stage dependent with the 5-year relative survival among men with localized prostate cancer at 100% compared to only 28.2% among those with distant (metastasized cancer).[1]

Black men are more likely to be diagnosed with and die from prostate cancer than their white counterparts. The incidence rate from 2008-2012 in black men is 214.5 cases per 100,000 person years compared to only 130.4 cases per 100,000 person-years in white men.[1] During this time period, the age-adjusted death rate in black men (46.3 per 100,000 person-years) was more than double that in white men (19.8 per 100,000 person-years).[1]

2.2. Prostate Anatomy and Prostate Cancer Biology

The prostate is located in front of the rectum, below the bladder, and wraps around the urethra. (Figure 1).[35-37] The main function of the prostate is to produce an alkaline fluid that assists in both the



(Taken from: http://cancer.uc.edu /cancerinfo/TypesOfCancer/ProstateCancer.aspx.)

Figure 1. Anatomy of Prostate

motility and nourishment of sperm[38] The prostate is generally the size of a walnut, but can be much larger in older men.[36]

The prostate is divided into four anatomic zones: the peripheral zone, the central zone, the transition zone, and the anterior fibromuscular stroma.[38,39] The peripheral zone lies against the rectum, and makes up the majority of healthy prostate gland.[39] The central zone surrounds the ejaculatory ducts. The transition zone is located in the center of the prostate and surrounds the urethra. The fibromuscular stroma consists primarily of muscle tissue, and is adjacent to the bladder.[39] Prostate cancer is generally a slow-growing cancer, and the vast majority of are adenocarcinomas—cancers that arises from gland cells.[36] Approximately 75% of prostate cancers originate in the peripheral zone, while about 15% arise from the transition zone.[38,39] Few prostate cancers arise from the central zone.[39]

2.3 Risk Factors and Symptoms of Prostate Cancer

Age is the single largest risk factor for prostate cancer. Prostate cancer is very rare in men under 40 years of age.[38,40] Approximately 60% of prostate cancer occurs in men 65 and older, and the median age at diagnosis is 66.[40,41] Other major risk factors include family history and race. Men with a father or brother who had prostate cancer have double the risk of prostate cancer. This risk is further increased if a first-degree relative was diagnosed with prostate cancer prior to 60 or if more than one relative was diagnosed.[38,40] As previously discussed, prostate cancer is more likely to occur and cause death in Blacks than other races.[38,40]

Men with prostate cancer are most commonly asymptomatic.[42] However, symptoms of prostate cancer, more common in men with advanced disease, can include difficulty initiating urination, interrupted urination, frequent urination, difficultly completely emptying bladder, pain during urination, blood in urine, persistent pain in back, hip, or pelvis, and painful ejaculation.[42]

2.4 Measures and Markers of Prostate Cancer Aggressiveness

This section discusses commonly used measures of prostate cancer aggressiveness at diagnosis including Prostate Specific Antigen (PSA), Gleason Score, the American Joint Committee (AJCC) Staging System, and defines frequently used composite measures of aggressiveness.

2.4.1 Prostate Specific Antigen (PSA)

The prostate specific antigen (PSA) is a glycoprotein produced by the prostate, and is responsible for liquefying seminal fluid.[43] The earliest descriptions of PSA described it as a marker for semen that could be used in forensic studies. In the early 1980s, studies from Roswell Park found that PSA could be detected in human serum and was elevated in patients with prostate cancer.[43] Subsequent research showed that PSA could be effectively used to monitor prostate cancer progression in *men with prostate cancer*. In 1986, the Food and Drug Administration (FDA) approved the use of PSA to monitor prostate cancer progression in these men.[44] It was not until 1994 that the FDA approved use of the PSA as a screening test in asymptomatic men.[44]

Thus, PSA tests have been used both as (1) a prostate screening test in men *not* diagnosed with prostate cancer and (2) as a marker to see if the prostate cancer was responding to treatment or recurred after treatment completion in men *with prostate cancer*. Traditionally, a PSA value of above 4.0 ng/mL was considered suspicious for prostate cancer and would warrant a prostate biopsy, but some studies have even suggested that the PSA threshold for biopsy be lowered to ≥ 2.5 ng/mL[43] However in May 2012, the U.S. Preventative Task Force recommended against using the PSA as a screening test for prostate cancer based on current evidence.[45] The Prostate Cancer Prevention Trial found that with the 4ng/mL cutoff, the PSA a test only had a sensitivity of 20.5%; the specificity was much higher at 93.6%.[46] Similarly, a pooled analysis by the American Cancer Society found that the sensitivity of the PSA test at the same threshold was 21% and the specificity

was 91%.[47] However, the sensitivity of the PSA for high grade prostate cancer (Gleason Score ≥ 8) was somewhat better at 51%.[47] The positive predictive value for the PSA is only 30%,[47] indicating that only a third of men with an elevated PSA actually have prostate cancer.

Specificity of PSA is problematic for screening because PSA can be elevated for a number of reasons other than prostate cancer. Non-cancerous reasons for a rise in PSA include prostatitis (inflammation of prostate), urinary tract infection, and benign prostatic hyperplasia (enlargement of the prostate).[44,48,49] Studies have further suggested that ejaculation can raise PSA levels for 24-48 hours following ejaculation.[50,51] In addition, "normal" PSA values can vary by race. PSA thresholds were largely established by studies in white men. More recent research has indicated that the PSA cutoff point may need to be lower in both Asian and Black men.[44,52] PSA values can also vary across assays. Different commercial assays of the same sample often produce discordant results.[53] Despite recent attempts by the World Health Organization (WHO) organization to standardize PSA assays, differences between assays still remain.[53] These differences can complicate comparisons of PSA across patients and over time. Furthermore, PSA-based screening can lead to over-diagnosis of indolent prostate cancer. Prostate cancer detected by PSA can be slow-growing, and ultimately have no real clinical impact on diagnosed individuals.[44] A study of unscreened men, who died from causes other than prostate cancer, found that over 40% of men aged 60 and older had prostate cancer on autopsy.[54] This percentage rose to almost 60% in men 80 and older.[54] Unnecessary treatment of such indolent cancers by radiation or surgery can result in complications including urinary incontinence, erectile dysfunction, increased bowel frequency, or rectal bleeding.[44,47]

2.4.2 Gleason Score

Gleason score is a commonly used marker of prostate cancer aggressiveness. The Gleason grading system is based on histologic patterns of carcinoma cells in prostate tissue.[55] Prostate cells are obtained via a biopsy, and are examined by a pathologist who will assign the Gleason grade. Gleason grades range from 1 to 5. Grade 1 cells closely resemble normal prostate cells—they are well-defined, have smooth edges, and are closely packed. [40,55] By contrast, grade 5 cells are poorly differentiated with cell borders that are "raggedly infiltrative"; these cells are clearly abnormal.[40,55] Grades 2 through 4 fall in between these two extremes.[40] In general, the tissue sample is assigned two separate grades. The primary grade is assigned to the predominant grade present in the tissue sample while the secondary grade is assigned to the second most prevalent grade in the tissue sample. These are summed to obtain the Gleason score, which ranges from 2-10. [55] There are a few exceptions to this rule. First, if 95% of the tumor consists of a single grade than that grade is multiplied by two to obtain the Gleason score.[40,55] Second, if there are three grades present in the tissue, the highest grade is always included in the Gleason score even if the larger area consists of the two lower grades.[40]

In general, higher Gleason scores are indicative of aggressiveness and suggest that cancer is likely to spread.[40] A Gleason score of 6 or less is referred to as "well-differentiated" or "low-grade", a score of 7 is referred to "moderately differentiated" or "intermediate-grade", and a score of 8 or greater is referred to "poorly differentiated" or "high grade".[40] However, one additional factor to consider is that identical Gleason scores can obtained in different ways. For example, if the primary grade is 4 and the secondary grade is 3, the Gleason Score is 7 (4+3). However, a Gleason Score of 7 can also be obtained with a primary grade of 3 and a secondary grade of 4 (3+4). This is important because the former (4+3) can potentially be prognostically worse given the predominant cancerous tissue is less

differentiated.[56] Research has suggested that a 4+3 Gleason score (vs. 3+4 score) is associated with increased prostate cancer mortality.[56]

2.4.3 American Joint Committee on Cancer (AJCC) Tumor, Node, Metastases (TNM) Staging System

The American Joint Committee on Cancer TNM Staging System can be used to determine a clinical stage which is based on a physical exam including a digital rectal exam (DRE), lab tests, biopsy, and imaging exams.[40] However, for men that undergo a radical prostatectomy a pathologic stage can also be determined. This is based on the surgical specimen and examination of any tissue that was removed during surgery, and is generally more accurate than the clinical stage.[40] Both staging methods use the same categories (discussed below) however, the T1 category is not used in pathologic staging.[40]

The TNM staging system consists of three categories: (1) The T categories that describe the clinical stage of the prostate cancer, (2) the N categories that describe whether the prostate cancer has spread regionally to the lymph nodes, and (3) the M categories that describe the whether the prostate cancer has metastasized.[40] The T, N, M stages are described in Table 1.[27]

Table 1. Description of TNM Clinical Stages

TNM Clinical Stages	
Tumor (T)	
T1	Tumor nonpalpable on DRE; tumor not seen on transrectal ultrasound (TRUS)
T1a	Incidental finding in transurethral resection of prostate (TURP) specimen, tumor ≤ 5% of specimen
T1b	Incidental finding in TURP specimen, tumor >5% of specimen
T1c	Non-palpable, not visable by TRUS, identified via biopsy after elevated PSA screen
T2	Tumor palpable on DRE or tumor visible on TRUS
T2a	Palpable or visible by TRUS, one lobe
T2b	Palpable or visible by TRUS, both lobes
T3	Tumor extends beyond prostate, possibly to seminal vesicles
T3a	Extracapsular extension; has not spread to seminal vesicles
T3b	Seminal vesicle involvement
T4	Cancer has spread to bladder neck, external sphincter, rectal, levator muscles, or pelvic side wall
Node (N)	
NX	Lymph nodes not assessed
N0	No regional lymph node involvement
N1	Metastases, regional lymph node(s)
Metastasis (M)	
MX	Distant metastases not assessed
M0	No distant metastases
M1a	Non-regional lymph node involvement
M1b	Bone involvement
M1c	Other sites involved

Taken from the PCaP Medical Abstraction Protocol[27]

2.4.4 Composite Measures of Aggressiveness: Stage Grouping

After the TNM stage is assigned, a further categorization is possible. The *stage group* takes into account the TNM stage along with Gleason score and PSA.[40] The stage group ranges from I to IV, where stage group I is the least advanced and stage group IV is the most advanced.[40] If Gleason score and PSA values are not available, the stage group classification can be based on the TNM stage alone.[40] The stage group along with the patient's age and health status is used clinically to help plan treatment and predict prognosis.[40] The stage groups are described in Table 2.

Table 2. Description of Prostate Cancer Stage Group

Stage Group	
Stage I	T1, N0, M0, Gleason score ≤ 6, and PSA less than 10 **OR** T2a, N0, M0, Gleason score ≤ 6, and PSA less than 10
Stage II A	T1, N0, M0, Gleason score = 7, and PSA less than 20 **OR** T1, N0, M0, Gleason score ≤ 6, and PSA ≥ 10 and <20 **OR** T2a or T2b, N0, MO, Gleason score ≤ 7, PSA <20
Stage IIB	T2c, N0, M0, any Gleason score, and any PSA **OR** T1 or T2, N0, M0, and Gleason score, PSA ≥ 20 **OR** T1 or T2, N0, M0, Gleason score ≥ 8, and any PSA
Stage III	T3, N0, M0, any Gleason score, and any PSA
Stage IV	T4, N0, M0, any PSA **OR** Any T, N1, M0, any Gleason score, and any PSA **OR** Any T, any N, M1, any Gleason score, and any PSA

Stage group definitions taken from American Cancer Society, Prostate Cancer Detailed Guide[40]

The advent of regular PSA screening (mid 1990s – early 2010s) has also had an impact on the stage at diagnosis in prostate cancer patients. PSA screening allows prostate cancers to be detected at an earlier stage, and allows detection of disease that would not have been detected by DRE alone.[57] This in turn has led to more prostate cancers being diagnosed at lower stages, and concurrently less prostate cancers being diagnosed at the higher stages (i.e. stage migration).[57] According to SEER from 1975-1987 to 1988-1997, the percent of white prostate cancer patients with late stage disease fell from 18.1% to 7.5%.[57] During the same time period, Black patients experienced a similar decrease in late stage disease from 27.2% to 12.4%.[57]

Interestingly, screening and earlier detection have not led to a corresponding decrease in Gleason scores over time. The majority of newly diagnosed tumors after PSA testing adoption were Gleason Grade 5 to 7.[58] One possible explanation for this is “grade inflation” over time. In a study by Albertson et al., pathologists assigned Gleason scores to tumors samples that were originally assigned a grade between 1990-1992. Blinded to the

original scores, the Gleason scores assigned by pathologists during re-examination from 2002-2004 were significantly higher, and the mean score increased from 5.95 to 6.8.[58] An editorial in the *Journal of the National Cancer Institute*, offers a few possible explanations. First, recently more Gleason scores are assigned using 3 Gleason grades. This method requires that the highest grade present be included even if it is a smaller portion of the tumor, and this in turn pushes the Gleason score upward.[59] Second, since current clinical guidelines suggest that low-grade tumors do not necessarily warrant treatment, there could be an inclination to assign higher grades so that tumors do not go untreated.[59]

2.4.5 Other Composite Measure of Aggressiveness: D'Amico and PCaP Classifications

In addition, to the stage grouping described above different measures of classification are often employed in prostate cancer research. The most frequently used research classification is the D'Amico classification. D'Amico and colleagues developed this classification system in 1998. This classification system was designed to group patients into low, intermediate, and high risk of biochemical recurrence following treatment with radical prostatectomy or radiation.[60] Risk groups are defined using Gleason score, pre-treatment PSA, and clinical TNM stage.[60] Under the D'Amico classification low risk is defined as clinical stage T1c or T2, PSA ≤ 10ng/ml, *and* Gleason score ≤ 6.[61] Intermediate risk is defined as clinical stage T2b, Gleason score of 7, *or* PSA >10 to ≤ 20 ng/ml.[61] High risk is defined as clinical stage T2c, PSA level >20 ng/mL, *or* Gleason score ≥ 8.[61]

In PCaP, an alternate measure of aggressiveness at diagnosis has previously been developed. Similar to the D'Amico classification key inputs for the PCaP measure of aggressiveness at diagnosis includes clinical stage, PSA, and Gleason score. This measure will be discussed in detail later.

2.5. Possible Markers of Prostate Cancer Progression (Persistent or Recurrent)

This section discusses commonly used measures of prostate cancer progression including biochemical recurrence, positive surgical margins, seminal vesicle invasion, and the initiation of secondary treatment. Although PSA was previously discussed as a screening tool it will now be discussed as a marker of progression (i.e. biochemical recurrence).

2.5.1 Biochemical Recurrence

According to the NCI, biochemical recurrence (BCR) is an increase in PSA after definitive treatment with surgery of radiation.[62] A 2007 paper, identified 166 different definitions of biochemical recurrence in the literature.[63] Definitions are diverse and include variations such as two measures of 0.4 ng/mL and rising, PSA >0.2 ng/ml, PSA >0.4 ng/mL, 3 consecutive rises in PSA after nadir (the lowest PSA value observed) has been reached, two consecutive PSA values >0.2 ng/mL.[63,64] This variation in definition is further complicated by treatment type. After radical prostatectomy *any* PSA can be indicative of biochemical recurrence as the source of PSA production has been removed.[65] Thus nadir is a PSA equal to 0. However, after treatment with radiation, PSA production is still possible. This makes it difficult to definitively define an absolute nadir PSA.[65] According to the 2013 American Urological Association best practice statement, among patients that had a radical prostatectomy, biochemical recurrence is defined as "an initial PSA value =0.2 ng/mL followed by a subsequent confirmatory PSA value =0.2 ng/mL".[66] Among radiation patients, the current consensus definition is the "phoenix definition". Per this definition, biochemical recurrence is defined as a PSA of 2 ng/mL above nadir.[67]

Practically these variations in definition can have many clinical implications. For example, among patients treated with radiation, BCR defined as a PSA >0.2 ng/mL has a sensitivity of 91%, but a specificity of only 9%.[65] The 5-year BCR free survival using this definition is 15%.[65] By contrast using an alternate definition of BCR among radiation

patients, an increase of 2 ng/mL above nadir, the sensitivity is 74% and the specificity is much high at 82%.[65] The 5-year BCR free survival is also much higher at 68%.[65] In patients treated by radical prostatectomy a BCR defined as a PSA of 0.4 ng/mL and rising best predicted distant metastases.[63] These variations can complicate comparing recurrence rates across studies and populations.

2.5.2 PSA Doubling Time

PSA doubling time (PSADT) is most often calculated by taking the slope obtained from the linear regression of the log-transformed PSA by time and dividing by ln(2).[68] This calculation assumes first-order kinetics and that PSA is rising in an exponential manner.[68] A PSA working group that met at the National Cancer Institute (NCI) in 2006 recommends the following when calculating PSADT: (1) All PSA values should be ≥ 0.20 ng/ml, (2) all PSA values within the past 12 months should be included in the calculation, (3) only values from the past 12 months should be used, (4) a minimum of 3 PSA values is needed, and (5) PSA values should be obtained over a minimum of 3 months, with at least 4 weeks between PSA measures.[68] There is however variation in how PSADT is calculated across studies. Some studies calculate PSA using only two PSA measures and use values over a two-year period following biochemical recurrence.[23,30] Moreover PSADT can be impacted by a number factors including treatment type, type of PSA assay used, number of PSA measures used, and the length of time over which the PSA measures were taken.[68]

A shorter PSADT has been consistently associated with worse clinical outcomes. Men with a PSADT of less than 3 months have a high risk of death while men with a PSADT of greater than 15 months have a very low risk of death.[68] In general, a longer PSADT is associated with both a lower risk as well as a longer time to metastases, prostate-cancer specific mortality, and all-cause mortality.[68] Research shows this is analogous to a dose-response relationship, with decreases in PSADT associated with increasing times to metastases and death.[68]

2.5.3 Positive Surgical Margins (a Predictor of Progression)

The presence of positive surgical margins can be assessed in men that have undergone radical prostatectomy. A positive surgical margin is defined as, “tumor extending to the inked surface of the prostatectomy specimen”.[69] Positive surgical margins are found in 11-38% of radical prostatectomy patients.[69] Research has suggested they may be associated with many adverse clinical outcomes including BCR, local disease recurrence, and the use of secondary prostate cancer treatment.[69]

2.5.4 Seminal Vesicle Invasion (a Predictor of Progression)

Seminal vesicle invasion is defined as “prostate cancer penetrating the muscular wall of the seminal vesicle.”[70] The seminal vesicles are a pair of glands, located behind the prostate, that are responsible for producing the fluid component of semen. Seminal vesicle invasion is associated with biochemical recurrence.[70] Prior research suggests the 5-year BCR-free survival in men with seminal vesicle invasion range anywhere from 5-60%.[70]

2.5.5 Secondary Treatment

The presence of secondary treatment (treatment after initial curative therapy) can also be indicative of prostate cancer progression or recurrence. This generally refers to additional treatment after radical prostatectomy or completion of radiation therapy. Secondary treatments can include hormone therapy (androgen deprivation therapy), anti-androgens, or chemotherapy.[40]

Androgen deprivation therapy (ADT), as the name implies, is designed to lower androgen levels. The primary androgens, testosterone and dihydrotestosterone can stimulate prostate cancer growth.[40] There are several different treatment methods to lower androgen in men. The most extreme is orchiectomy or removal the testicles. The testicles are the primary source of androgen production, and removal can slow or eliminate prostate cancer growth.[40] Less extreme androgen deprivation therapies include luteinizing hormone releasing (LHRH) hormone analogs and antagonists. Both reduce androgen levels, but

analogs cause a temporary flare in testosterone levels after initiation. This can be problematic in men with bone metastases.[40] LHRH antagonists work similarly and do not cause this temporary flare.[40] A third possibility are anti-androgens. Anti-androgens work by binding to the androgen receptor, and blocking androgens from binding. This treatment method is generally not used alone, but in conjunction with LHRH analogs and antagonists.[40] A limitation of all androgen therapy is that in most men prostate cancer cells eventually develop androgen independent pathways. According to Schroeder et al. virtually all prostate cancers will become androgen independent over time.[71] It is estimated that every year 25,000 men will develop androgen-independent prostate cancer (AIPC).[72]

Chemotherapy is not generally used for localized prostate cancer treatment. However, chemotherapy can be used if the prostate cancer has metastasized.[40] The chemotherapy drug most commonly used in prostate cancer patients is docetaxel.[40] In the most advanced prostate cancer cases, where there are metastases to the bones, drugs such as bisphosphonates or Denosumab are used. These drugs work by blocking osteoclasts. Osteoclasts are found in healthy bone cells, but can become overactive when there is bone metastases.[40] These drugs reduce pain, help prevent bone fractures, and may slow progression of metastases. To the extent that the primary treatment for prostate cancer is commonly surgery or radiation, the initiation of these secondary treatments can be used as a marker of prostate cancer progression.

2.5.6 Limitations of Current Measures of Prostate Cancer Progression

There are several limitations to the current methods of measuring progression. First, there is no standard definition of “progression”. There are hundreds of definitions of biochemical recurrence, with different PSA cut points. Some require only one PSA measure while others require a rising trend in PSA.[63] Other possible measures of progression such as PSADT are not always calculated consistently. Second, these measure of progression do not distinguish between recurrent prostate cancer [prostate cancer that was successfully

treated (no PSA increase after nadir and no secondary treatment) *and* recurred] and prostate cancer that is persistent (prostate cancer that has never been successfully treated, i.e. treatment failure). Third, these measures of progression do not generally take into account long-term data.

2.6 Diabetes and Prostate Cancer

2.6.1 Diabetes and Incident Prostate Cancer

Several studies and meta-analyses have reported that diabetes reduces the risk of incident prostate cancer.[2-20,73-79] This is in contrast to most other cancers where diabetes is associated with an increased risk. A few possible mechanisms for this inverse association have been hypothesized. First, insulin is a growth factor for prostate cancer cells.[11] Thus men with diabetes, who have lower circulating insulin levels, may experience a slow or reduced growth of potential prostate cancer cells.[11] Second, diabetes has been shown to be associated with benign prostatic hyperplasia (BPH). While BPH is not a risk factor for prostate cancer directly, it is possible that the chance of a biopsy detecting prostate cancer in an enlarged prostate is reduced.[11] Finally, diabetics are likely to be taking other medications to manage their diabetes and other associated comorbidities. Medications such as statins (to lower cholesterol) and possibly metformin (to treat diabetes), commonly taken by diabetics, have also been associated with reduced prostate cancer risk.[11,80-82]

2.6.2 Literature Review on the Impact of Diabetes in Men with Prostate Caner

Table 3 summarizes previous literature on diabetes and prostate cancer. This table includes studies that were conducted among men *diagnosed* with prostate cancer. However, five of the studies in the table were conducted in a cohort of men undergoing prostate biopsy, and therefore not definitively diagnosed with prostate cancer.[83-87] This is clearly noted on the table, and these studies are excluded from the discussion that follows. Only studies with diabetes as the primary exposure were included, and studies looking at the impact of diabetes on incident prostate cancer were excluded. Studies were included

regardless of the prostate cancer outcome studied. The most common outcomes studied were mortality, Gleason score, and biochemical recurrence. PSA doubling time and metastases were less frequently studied. Since, a primary interest of this project is to examine race differences, any studies that directly examined *race differences* were denoted in the table.

Summary of Findings

Non-prostate cancer mortality was significantly higher in diabetic prostate cancer patients as compared to non-diabetic prostate cancer patients.[24,88-91] In addition, prostate cancer-specific mortality among diabetics vs. non-diabetics was also significantly higher in most studies.[24,92,93] Hazard ratios, for prostate cancer-specific mortality, in these studies were consistent ranging from 1.23 to 1.32.[24,92,93] By contrast, one study did report a non-significant hazard ratio for prostate cancer-specific mortality in diabetics vs. non-diabetics (HR: 0.80, 95% CI 0.51, 1.25).[90] This could be attributed to the fact that the study population in this study was recruited from a randomized clinical trial on treatment type.[90] Randomized clinical trials are not always representative of the general population. In general, however, the literature showed that mortality (both non-prostate cancer and prostate cancer specific) was higher in diabetic prostate cancer patients vs. those without diabetes.

Four studies observed a significant positive association between diabetes and high grade disease at biopsy or baseline.[21-24] In these studies high grade disease was either defined as a Gleason score ≥ 7 or a Gleason score of 8-10.[21-24] In the three studies that reported hazard ratios there was consistency among the results with hazard ratios ranging from 1.59 (white men only) to 1.85 (overall).[21,23,24] A study that looked at HbA1c levels, a marker of diabetes, noted a much stronger association (OR for diabetes among patients with HbA1c ≥ 7.8 vs. HbA1c <6.3: 6.60, 95% CI: 2.28, 19.08).[29] However, a study in the same population using a clinical diagnosis of diabetes as the primary exposure was consistent with other results.[23] One Chinese study noted no significant difference in mean

Gleason scores among diabetic and non-diabetic prostate cancer patients.[94] However, this study had a relatively smaller sample size as compared to other studies, and only looked at unadjusted group level differences in mean Gleason score.[94]

Several studies examined the impact of diabetes on biochemical recurrence. Most studies report a non-significant association between diabetes and biochemical recurrence or BCR-free survival.[23,28,29,32,95-97] However, some studies did report a significant, positive association in certain sub-groups. The Cancer or the Prostate Strategic Urologic Research (CaPSURE) study found that among men treated by radiation, history of diabetes was only associated with BCR in the low risk prognostic group (HR: 1.28, 95%CI: 1.28, 11.19).[28] The low risk prognostic group was defined using the D'Amico classification.[28] In addition, in men ≤ 69 years of age treated with radiation, diabetes was associated with time to treatment failure (HR: 2.17, 95%CI: 1.02, 4.62).[28] In Jayachandran et al., a study utilizing a Veterans Affairs medical database, there was a significant association observed between diabetes and BCR in white, obese men.[28] One matched case-control study did note an overall significant positive association between diabetes and BCR (HR:1.55, 95%CI: 1.03, 2.33).[31] This could be attributed to the fact that this study was a matched case-control study where the authors matched diabetic cases with non-diabetic controls on their 5-year risk of BCR using the preoperative Kattan nomogram. In addition, this study had a fairly liberal definition of BCR as compared to other studies, requiring only one PSA value of 0.2 ng/mL.[31]

These results suggest that diabetes may be associated with BCR, but that this association may be limited to sub-groups such as those undergoing radiation, or those who are white and obese, or ≤ 69 of age. A clear association between diabetes and BCR has not been established in the literature.

Only two studies examined diabetes and PSA doubling time. In Jayachandran et al. overall there was no significant difference between mean PSADT in men with and without diabetes (p=0.12).[23] In Oh et al., a study based in a Korean medical center, diabetes was

associated with a PSADT of less than 9 months in men treated with radical prostatectomy, although the confidence interval was wide (OR: 2.687, 95% CI: 1.008, 7.164).[30]

In summary, the literature suggests that in men with prostate cancer diabetes is positively associated with non-prostate cancer mortality, prostate-specific mortality, and higher Gleason score. Most studies show that diabetes is not significantly associated with BCR, although certain sub-groups may be at increased risk. Few studies explore PSADT, and results are inconsistent.

2.6.3 Studies Examining Diabetes and Race Differences

Three studies examined differences between Blacks and White men *diagnosed with* prostate cancer. In Mitin et al. a cohort of men with prostate cancer who were treated with radiation were studied.[21] Study subjects (n=16,286) were men diagnosed with prostate cancer at the Chicago Prostate Cancer Center, community based medical centers in the 21st Century Oncology Practice, 3 academic institutions in Boston, or 2 community hospitals in Massachusetts.[21] Diabetes status was self-reported and then verified by medical chart review by the treating radiation oncologist. Race was also based on self-report and categorized as black or non-black. Key outcomes included Gleason score 7 present (vs. Gleason score 7 absent) and Gleason score 8-10 present (vs. Gleason score 8-10 not present). Gleason score was measured at time of biopsy. Here the discussion will focus on Gleason score 8-10 present (vs. not present). Model covariates included black race, diabetes diagnosis, increasing age, PSA and DRE findings. Results showed that diabetes was associated with a Gleason Score 8-10 in both black patients (OR:1.84, 95%CI: 1.08, 3.13) and non-black patients (OR: 1.59, 95% CI: 1.33, 1.89).[21] Moreover, among non-diabetics, black race was associated with Gleason score 8-10 (OR: 1.36, (95% CI: 1.01, 1.83).[21] Among diabetic men, black race was associated with an elevated, but not statistically significant odds of Gleason score 8-10 (OR: 1.58, 95% CI: 0.98, 2.53).[21] This study suggests that among men treated with radiation, diabetes is associated with a higher

Gleason score independent of race. In addition, black patients tend to have higher Gleason scores independent of diabetes, although the results were not statistically significant in diabetics.[21]

Unlike Mitin et al., which was limited to men treated with radiation, the study population in Jayachandran et al. consisted of men with prostate cancer who were treated by radical prostatectomy at Veteran Affairs Medical Centers (n=1262).[23] Data from medical centers in West L.A and Palo Alto, California, Augusta, Georgia, and Durham, North Carolina were compiled into the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Diabetes status was determined from clinical notes, and based on physician diagnosis. Self-determined race was defined as black or white, and several outcomes including BCR and PSADT were examined. The adjustment set included age, year of surgery, race, BMI, clinical stage, biopsy Gleason score (except in analysis of high grade disease), center, and preoperative PSA.[23] All models included interaction terms for both race and obesity. Diabetes was associated with high grade disease in white (OR: 2.28, 95%CI: 1.33, 3.91), but not black men (OR: 1.45, 95%CI: 0.90, 2.23). By contrast diabetes was associated with seminal vesicle invasion in black men (OR: 2.01, 95% CI: 1.02, 3.99), but not white men (OR: 1.44, 95% CI:0.64, 3.25).[23] Diabetes was not associated with extra capsular extension or positive surgical margins in either black or white men.[23]

As previously mentioned, diabetes was significantly associated with time to BCR only in *white, obese* men (HR: 2.52, 95%CI: 1.40, 4.54).[23] In all other sub-groups including non-obese white and black (obese and non-obese) patients diabetes was not significantly associated with BCR.[23] Similarly, in white, obese men, the mean PSADT was shorter in men with diabetes than those without diabetes, although this difference was not statistically significant (p=0.24). [23] Surprisingly, the PSA doubling time was significantly *longer* in black men with diabetes then black men without diabetes (p=0.02).[23]

The third study to examine race differences was Wu et al.[33] This was a follow-up

study to Jayachandran et al., and also consisted men who had undergone radical prostatectomy in the SEARCH database (n=2058).[33] The key outcome in this study was metastases. Metastases were most frequently diagnosed via bone scans requested by physicians. Additional imaging or a biopsy subsequently confirmed metastases. Models were either adjusted for pre-operative or post-operative features. Pre-operative features included age, PSA, BMI, biopsy tumor grade, clinical stage, radical prostatectomy year, and center. Post-operative features included age, PSA, BMI, race, radical prostatectomy tumor grade, margin status, extracapsular extension, seminal vesicle invasion, lymph node status, radical prostatectomy year, and center.[33] Diabetes was not associated with metastases in black (HR:1.48, 95% CI: 0.43, 5.10) or white men (HR: 1.20, 95% CI: 0.51, 2.85) when adjusted for pre-operative features.[33] Similarly, when adjusted for post-operative features, diabetes was not associated with metastases in black (HR: 1.31, 95%CI: 0.34, 5.09) or white men (HR: 1.47, 95%CI: 0.55, 3.93).[33] However, obese men were at significantly increased risk for metastases independent of race.[33]

These studies do not show a consistent relationship between race, diabetes, and prostate cancer outcomes. In Mitin et al. diabetes was associated with a higher Gleason score in both black and non-black men, while in Jayachandran et al. diabetes was associated with a high Gleason score only in white men. These observed differences could possibly be attributed to differences in study populations. In Mitin et al. men were treated with radiation, while in Jayachandran et al. men were treated with radical prostatectomy.[21] In addition, in Mitin et al. the non-black category included white, Asian, and Native American men.[21] Jayachandran et al. showed that diabetes was associated with BCR only in white, obese men while Wu et al found that diabetes was associated with metastases only in obese men regardless of race. [23,33]

The differences in treatment type and outcomes across these studies make it difficult to assess the impact of race, and the study proposed here will add valuable insight on the role of race and its impact on the relationship between diabetes and prostate cancer.

Table 3 begins on the next page.

Table 3. Summary of Literature Review

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
Bensimon, 2014[92]	Cohort— Men from the UK newly diagnosed with non-metastatic prostate cancer between 1 April 1998 and 31 December 2009, followed until 1 October 2012	Linked 4 databases from the UK: the National Cancer Data Repository, the Clinical Practice Research Datalink, the Hospital Episodes Statistics database, and the Office for National Statistics database.	11,920	No	Diagnosis of Type 2 diabetes or prescriptions of anti-diabetic drugs (metformin, sulfornylureasof anti-diabetic drugs (metformin, sulfonylureas, thiazolidinediones, insulins, and others) at any time prior to the prostate cancer diagnosis.	Prostate cancer mortality and all-cause mortality	Age, year of cohort entry, ethnicity, excessive alcohol use, body mass index, smoking status, CVD comorbidities, Antihypertensives, NSAIDs, statins, 5-alpha reductase inhibitors, and the following prostate cancer-related variables: PSA levels, Gleason score, radical prostatectomy, radiation therapy, chemotherapy, and androgen-deprivation thpy.	HR for mortality in those with Type 2 diabetes vs. those w/o diabetes Prostate Cancer Mortality: HR: 1.23 (1.04, 1.46) All-cause Mortality: HR: 1.25 (1.11–1.40)
Chan, 2005[28]	Cohort- a community based cancer registry	CaPSURE study (Cancer of the Prostate Strategic Urologic Research Endeavor)	6722	Yes	Diabetes self-reported	Men undergoing RP: Recurrence was defined as two or more consecutive post-treatment PSA values of 0.2ng/ml or greater, or initiation of second treatment at least six months after	Varied depending on model, but included: Body size at diagnosis, diagnostic age, number of comorbidities, race, and relationship status, education, PSA, T-stage, Gleason group, BMI,	*OR of diabetes for men with prostate cancer (Black vs. white): OR: 2.47 (1.74, 3.50) *Prior history of diabetes was not associated w/ clinical features of PCa at diagnosis *Among men undergoing RP:

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
						surgery Men undergoing radiation Recurrence was defined as 3 or more consecutive follow-up PSA tests above the post-treatment nadir, or initiation of a 2nd treatment at or after 6 months of the first treatment; Clinical features of prostate cancer: Clinical stage, PSA at diagnosis, Gleason Score		There was no association between history of diabetes and recurrence *Among men that had radiation: Overall No association between diabetes and recurrence. *In low prognostic group: HR for recurrence (diabetic vs. not): HR: 3.79 (1.28, 11.19). * In men <=69, time to treatment failure HR: 2.17 (1.02. 4.62)
Chamie, 2012[88]	Retrospective cohort-veterans with non-metastatic prostate cancer diagnosed in 1997-2004 at the Greater Los Angles and Long Beach Veterans Affairs Medical Centers and	California Cancer Registry; Medial Records	1031	No	Medical chart review	5-Year and 10-Year Survival Rate; Non-prostate cancer mortality	Comorbidities, Mobility Device, History of alcoholism, Current Smoker, Race/Ethnicity/ D'Amico tumor risk, BMI, VA site	Diabetes without end-organ damage: *5-year survival rate: 0.79 (0.71, 0.86); *10-year survival rate 0.57 (0.41, 0.70) Diabetes with end-organ

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
	followed until 2010.							damage: *5-year survival, 0.57 (0.32, 0.75); *10 year survival rate 0.36 (0.12, 0.61). Non-prostate cancer mortality among men with diabetes without end-organ damage (vs. no-comorbidities): HR: 2.32 (1.32, 4.08) Non-prostate cancer mortality among men with diabetes WITH end-organ damage (vs. no-comorbidities): HR: 2.43 (1.15, 5.17)
Chiou, 2012[98]	Retrospective cohort-Patients were >=20 years of age and were included if the indication for hospital admission was a diagnosis of type 2 DM or malignancy	Admission data from Chang Gung Memorial Hospital in Linkou, Taiwan	2905 with PCa	No	Fasting glucose level >126 mg/dL or a postprandial glucose level >200mg/dL	Mortality determined from death certificates	Age and gender	*Mortality among prostate cancer patients without DM (vs. DM patients without cancer): HR: 0.47 (0.38, 0.59). *Morality among prostate cancer patients with DM (vs. DM patients

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
								without cancer): HR: 0.82 (0.59, 1.13)
Currie, 2012[89]	Retrospective cohort-Individuals w or w/o diabetes who developed a first tumor after Jan 1990 were identified and followed until Dec 2009	Data were obtained from >350 UK primary care practices.	1385 DM men with prostate cancer 1385 DM men with prostate cancer	No	Read code indicative of diabetes	Mortality	Age at baseline, smoking history, Charlson comorbidity index, year at diagnosis	HR death diabetes vs. non-diabetes: 1.19 (1.08, 1.31); in men diagnosed with prostate cancer
D'Amico, 2010[24]	Prospective cohort-Between Oct 1997 and July 2007, Men with prostate cancer treated with radiotherapy at the Chicago Prostate Cancer Center	Medical records/ Medical history obtained at consultation	5279	Not w/ regards to diabetes	Prevalent Diabetes (pDM) status determined at baseline consultation visit Favorable-risk PCa was defined as Gleason score < =7, with a PSA <=20 ng/mL and clinical Stage T2c or less. Stage T2c was removed from the standard high-risk classification for the purposes of our analysis.	1) Likelihood of Gleason score 8-10 vs. <+7 2) Prostate cancer specific mortality	1) PSA level, ethnicity, presence of a prostate nodule at the the DRE vs. no nodule 2) history of MI, treatment received, age, year of brachytherapy, and	*Specific outcome noted in "outcome measure" column* Exposure: pDM unless noted otherwise <u>Outcome Gleason Grade</u> 1) Adj OR: 1.85 (1.25, 2.74) <u>Outcome Mortality Measures</u> 2) Adj HR 1.28 (0.54, 3.03)

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
						3) Non-prostate cancer specific mortality	PCa risk group 3) history of MI, treatment received, age, year of bracytherapy,, and PCa risk group	3) Adj HR : 1.53 (1.13, 2.07)
						4) Non-prostate cancer specific mortality	4) history of MI, treatment received, age, and year of barchytherapy	4) Adj HR (pDM and high risk PCa vs. pDM and favorable risk PCa): 2.18 (1.06, 4.51)
						5) Diabetes related mortality	5)History of MI, treatment received, age, and year of brachytherapy	5) Adj HR (pDM and high risk PCa vs. favorable risk PCa): 5.23 (1.95, 14.0)
						6) All cause mortality	6)History of MI, treatment, age, year of brachy-therapy, and PCa risk group	6) Adj HR (pDM and high risk PCa vs. favorable risk PCa): 2.41 (1.24, 4.69) Other results non-sig.
Di Francesco, 2014[87]	Case–control - patients **undergoing prostate biopsy** at University G. D'Annunzio Chieti-Pescara, Italy	Likely medical records, but not clearly stated	266	No	Likely diabetes diagnosis in medical records, but not clearly stated how diabetes status was determined	Aggressive PCa (Gleason score >=7)	Matching by age	DM was associated with aggressive PCa, only in obese cases (OR 4.17; p<0.05). *In non-obese

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
								men, no association was noted between DM and PCa, regardless of grade.
Fukushima, 2012[83]	Retrospective cohort- Japanese men with serum PSA <10 ng/mL ***who underwent initial extended prostate biopsy*** from May 2001 to Nov 2010 at Tokyo Medical and Dental University and Cancer Institute Hospital	Medical chart review and self-report	2214	No	History of DM was determined by self-report and medication use	Prostate Cancer Grade as demined by biopsy and interpreted by pathologist. Low grade: Gleason score <=6, Intermediate grade: Gleson score =7, high grade: Gleason score: 8-10	Age, BMI, PSA, free/total PSA ration, prostate volume, DRE, family history of PCa, number of biopsy cores	RRs/ORs for history of DM and prostate cancer grade: All grade PCa (vs. no; cancer) Adj OR 1.33 (0.94, 1.87) Low grade PCa (vs. no cancer): Adj RR 1.08 (0.68, 1.68) Intermediate grade PCa (vs. no cancer) Adj RR: 1.43 (0.91, 2.22) High Grade PCa (vs. no cancer) Adj RR: 1.71 (0.87, 3.24) In obese men, high grade PCa (vs. no cancer): Adj RR 4.03 (1.15, 13.66)

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
Hong, 2012[84]	Retrospective cohort—***men who underwent multi core (>=12) core biopsy*** at Seoul National University Bundang Hospital, Korea	Medical records	3925	No	Patients asked whether they had diabetes before undergoing biopsy	Biopsy Gleason Score >=7	Age, BMI, DM, PSA, DRE finding, TRUS volume, Hypoechoic lesion on TRUS	OR for Gleason Score >=7 DM (vs. no DM:) Adj OR: 1.54 (1.03, 2.29)
Karlin, 2012[99]	Retro. cohort-cancer cases from 1999 to 2008 from center in Phoenix	Institutional Cancer Registry linked to electronic files	Prostate Cancer: 277 with DM; 4070 without DM	No	Diabetes determined using electronic record	Overall survival	Sex and age	HR for overall survival DM patients had lower survival: Adj HR: 1.36 (1.05, 1.76)
Jayachan-dran, 2010[23]	Retrospective cohort-patients undergoing radical prostatectomy between 1988 and 2008	Combined data from the Veterans affairs medical centers in West LA, Palo Alto, Augusta, and Durham into the Shared Equal Access Regional Cancer Hospital Database	1262	Yes; all results are stratified by Black, White and Obese and Non-obese	Diabetes determined by clinical notes and were based on clinical diagnosis from a physician	1) BCR defined as single PSA of >0.2 ng/mL, two concentrations at 0.2 ng/mL, or secondary treatment for an elevated postoperative PSA. 2) PSADT: calculated assuming first-order kinetics by dividing the natural log of 2 (0.693) by the slope of the linear	Age, Year of surgery, race, BMI, clinical stage, biopsy Gleason score (except in analysis of high grade disease), center, and preoperative PSA	<u>ORs for exposure to diabetes (vs. no DM) and PCa outcomes</u> *High grade disease <u>Overall:</u> OR: 1.73 (1.22, 2.45) <u>White:</u> OR 2.28 (1.33, 3.91) <u>Black:</u> OR: 1.45 (0.90, 2.33). *Extra capsular extension <u>Overall</u> OR: 1.25 (0.85, 1.83)

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
						regression line of the natural log of PSA over time. To be eligible, patients must have had a minimum of 2 PSA values, separated by at least 3 mo, and within 2 y after BCR. All PSA values within the first 2 y after BCR were used to calculate PSADT 3) High grade disease (Gleason score >=7), 4) ECE-extracapsular extension, 5) PSM--positive surgical margins, 6) SVI-seminal vesicle invasion		<u>White:</u> OR: 0.93 (0.53, 1.63); <u>Black:</u> OR: 1.64 (0.94, 2.85) *Positive surgical margins <u>Overall:</u> OR: 1.11 (0.81, 1.52) <u>White:</u> OR: 1.31 (0.82, 2.10); <u>Black:</u> OR: 1.01 (0.65, 1.55). *Seminal Vesicle Invasion <u>Overall</u> OR: 1.73 (1.04, 2.09) <u>White</u> OR: 1.44 (0.64, 3.25); <u>Black:</u> OR: 2.01 (1.02, 3.99) * Time to BCR after RP: <u>Overall:</u> HR: 0.94 (0.72, 1.23) <u>White</u>: HR: 1.24 (0.84, 1.85); <u>Black:</u> HR: 0.79 (0.55,

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
								1.14) White, obese: HR: 2.52 (1.40, 4.54) *Diabetes was associated with a *shorter* (non-sig) PSADT only in white, obese men
Kim, 2010[29]	Retrospective cohort-Men who underwent radical prostatectomy from 1988 to 2009, **who had DM, and a recorded HbA1c level**	Combined data from the Veterans affairs medical centers in West LA, Palo Alto, Augusta, and Durham into the Shared Equal Access Regional Cancer Hospital Database	247	No	Medical records. Patients were derived into tertiles of HbA1c level: <6.3 (tertile 1), 6.3-7.7 (tertile 2), >=7.8 (tertile 3)	Extracapsular extension, surgical margin status, seminal vesicle invasion, and lymph node status were determined at time of surgery. Gleason score from surgical specimen. BCR was defined as a single PSA value >0.2ng/mL, two values of 0.2 ng/mL, or secondary treatment for an elevated post-operative PSA	Age, Year, Center, race, BMI, PSA, and metformin usage	Reference (Tertile 1 HbA1c) *Gleason Score >= 4+3: Tertile 2 (vs 1): OR: 4.68 (1.68, 13.04). Tertile 3 (vs 1): OR: 6.60 (2.28, 19.08) *Extracapsular extension, positive surgical margin, seminal vesicle invasion, and lymph node metastasis were all non-significant. *Risk of recurrence was unrelated to HbA1c, but Gleason score was.

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
Liu, 2012[93]	Retrospective cohort-Cancer patients were followed from diagnosis until death or Dec 31, 2008.	Swedish Hospital Discharge Register and Swedish Cancer Registry	2217	No	Diabetes status determined from national register records	Prostate-cancer specific mortality	Age at diagnosis, sex, period, obesity, alcohol, smoking, SES, and diagnosis region	Prostate-specific mortality in those with DM (vs those w/o DM): HR:1.32 (1.23, 1.41)
Moses, 2012[86]	Retrospective cohort--Men who underwent ***prostate biopsy*** between Jan 2000 an dJuly 2009 at the Atlanta Veterans Affairs Medical Center	Medical records	3162	Yes, <u>stratified</u> by black vs. non-black	Diabetes was diagnosed by the patient's primary care provider or endocrinologist, determined using electronic medical record	Positive biopsy and high Gleason score (>=7)	Age, race, BMI, prostate volume, family history of prostate cancer, PSA and DRE, and interaction between PSA and DRE	Association between DM and PCa *among patients referred for biopsy* (referent non DM): <u>All participants:</u> biopsy-confirmed prostate cancer cases versus biopsy-confirmed disease-free controls OR: 1.26 (1.01, 1.55), <u>AA, cases vs. controls</u> OR: 1.22 (0.90, 1.65), 3) <u>White, cases vs. controls</u> OR: 1.26 (0.93, 1.70), 4) <u>Prostate cancer cases with Gleason score >=7</u> vs. biopsy

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
								confirmed disease free controls : OR: 1.27 (0.99, 1.64)
Mitin, 2011[21]	Retrospective cohort- Men diagnosed with PCa AND treated with radiation therapy between 1991 and 2010 at the Chicago Prostate cancer center, 1 of 20 community based medical centers in the 21st century oncology practice, at 1 of 3 academic institutions in Boston, or 2 community based medical centers in Massachusetts	Medical records	16,286	Yes—stratified by black vs. non-black	DM diagnosis was reported by the patient and then established through a medical chart review by the treating radiation oncologist at the initial evaluation	Gleason score 7 or 8-10 vs. 6 or less (at diagnosis)	black race, DM diagnosis, increasing age, PSA, DRE findings	Black patients: Outcome: GS 8-10 OR: 1.84 (1.08, 3.13), for exposure to DM vs. not Outcome: GS 7: OR: 1.27 (0.91, 1.78), for exposure to DM vs. not Non-black patients: Outcome: GS 8-10 OR: 1.59 (1.33, 1.89), for exposure to DM vs. not Outcome: GS 7 OR: 1.09 (0.97, 1.23), for exposure to DM vs. not Non-diabetics: Outcome GS 8-10: OR: 1.36 (1.01. 1.83), for black (vs. non-black)

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
								Outcome GS7: OR: 1.38 (1.17, 1.63), for black (vs. non-black) <u>Diabetics</u> Outcome GS 8-10: OR: 1.58 (0.98, 2.53), for black (vs. non-black) Outcome GS7: OR 1.61 (1.17, 2.21), for black (vs. non-black) *_DM was associated with GS 8-10 regardless of race; black race tend to have higher Gleason score independent of diabete_s
Moreira, 2011[85]	Retrospective cohort - Men from the Durham VA ***undergoing prostate biopsy between 2001 and 2009***	Medical records	998 undergoing biopsy	Yes, <u>stratified</u> by black vs. non-black	DM determined by chart review	High grade prostate cancer (Gleason score 8-1-0)	pre-biopsy PSA, BMI, race, age at biopsy, year of biopsy, and DRE	ORs for history of DM and prostate cancer grade among men *undergoing prostate biopsy.* *All grade OR: 1.11 (0.82, 1.51)

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
								*Low grade OR: 1.12 (0.79, 1.60) * Intermediate grade OR: 0.96 (0.63, 1.45) * High grade OR: 2.13 (1.10, 4.12) ORs for history of DM and high grade PCa, stratified by race and obesity among men *undergoing prostate biopsy* <u>Overall</u> OR: 2.13 (1.10, 4.12) <u>White</u> OR: 2.64 (1.06, 6.59), <u>White Non-obese</u> OR: 1.35 (0.37, 4.89) <u>White Obese</u> OR: 5.81 (1.24, 27.12) <u>Black</u>

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
								OR: 1.27 (0.46, 3.49) <u>AA non-obese:</u> OR: 0.86 (0.22, 3.43) <u>AA obese:</u> OR 2.46 (0.45-15.17) Highest risk in obese, white men
Oh, 2013[30]	Retrospective cohort - patients who underwent RP for clinically localized PCa between Jan 2004 and June 2008 at CHA Bundang Medical Center, Korea	Medical Records	661	No	Diabetes status determined using medical records	**"PSADT** was calculated assuming first order kinetics by dividing the natural log of 2 (0.693) by the slope of the linear regression line of the natural log of PSA over time. In order to calculate PSADT, patients must have had a minimum of 2 PSA values, separated by at least 3 months, and within 2 years after biochemical	Age, BMI, DM, PSA, Pathologic Gleason Score, Extraprostatic extension of tumor, Seminal Vesicle invasion, Margin positivity	*PSADT of less than 9 months in men undergoing radical prostatectomy: OR 2.687 (1.008, 7.164), for exposure to DM (vs. no DM) *DM group had a lower rate of biochemical recurrence-free <u>survival</u> with difference approaching significance (log-rank, p = 0.077)

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
						recurrence" **"Biochemical recurrence** was defined as a single PSA value of >0.2 ng/ml, 2 measurements of 0.2 ng/ml, or secondary treatment for an elevated postoperative PSA."		
Ozbek, 2014[22]	100 consecutive patients that underwent RP at Okmeydani Training and Research Hospital in Istanbul, Turkey. 50 with DM and 50 w/o DM	Medical records	100	No	Diabetes status determined from medical records HbA1c levels	PSA level RP Tumor Grade (Gleason score >=7) Prostate volume	Not adjusted	* HbA1 C levels were higher in patients with high grade PCa ($p<0.05$) *Men with DM had lower PSA levels ($p=0.01$) *Men with DM were more likely to have Gleason score >=7 ($p=0.004$) *No association with DM and prostate volume ($p=0.316$)

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
Patel, 2010[31]	Matched case-control – DM men with RP between 1990 and 09 were matched to non-DM controls using their 5-year risk of BCR as calculated by the preop Kattan nomogram	Columbia University Urologic Oncology Database	616	No	Diabetes was determined from a baseline health questionnaire.	BCR, defined as 1 PSA value of 0.2 ng/m	Metformin use, Diabetes, Preoperative PSA, Pathologic Gleason sum, Surgical margin, Pathologic Stage. N stage, Race/ethnicity	Outcome: BCR Exposure: DM (vs no DM) HR: 1.55 (1.03, 2.33)
Rieken, 2013[95]	Retrospective cohort- men who underwent RP for clinically localized PC between 2000 and 2011	Eight US and European centers provided data into a centralized databank	6,863	No	Diabetes and Metformin use, unclear how diabetes status and metformin use was established	BCR was defined as PSA value[0.2 ng/ml on two consecutive visits Results <u>stratified</u> by lymph node metastasis, surgical margins, stage and gleason sum available.	PSA value, RP Gleason score, lymph node metastasis, positive surgical margins, extracapsular extension, seminal vesicle invasion	Outcome BCR Referent NO DM <u>All patients</u> DM, no metformin 0.99 (0.75, 1.30) DM metformin 0.84 (0.58, 1.22) * Results stratified by lymph node metastasis, negative surgical margins, positive surgical margins, Stage pT3a, RP Gleason sum <= 6, RP Gleason sum =7, and RP Gleason sum >=8 were not

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
								significant
Shetti, 2012[97]	Prospective cohort – consecutive patients with clinically localized prostate cancer stages T1b-T3c who underwent permanent interstitial brachytherapy by a single brachytherapist between April 1995 and May 2006	Patient visits/ medical records at Wheeling Hospital in Wheeling WV	1624	No	Not clear – diabetes likely determined by patient visits/medical records	Biochemical progression-free survival (bPFS). BPFS was defined as a PSA <= 0.40 ng/mL after nadir. Overall survival Cancer-specific survival	Diabetes, Age, PDA, Gleason score, Percent Positive Bx, BMI, Prostate volume, D90, D90, Clinical stage, XRT, ADT, ADT duration, Perineal Invasion, Hypertension, Hypercholestermia, Coronary Artery Disease, Tobacco User	*Overall survival (DM vs. no DM: HR: 1.542 (p= 0.011) *Biochemical progression-free survival (DM vs, no DM): Non-significant (p=0.960) *Cancer Specific survival among (DM vs, no DM): Non-significant (p=0.373)
Shiota, 2014[96]	Prospective cohort - men who had surgical treatment for PCa at at Kyushu University Hospital (Fukuoka, Japan) from 2008 to 2012.	Medical records	283	No	DM defined as the use of diabetes drugs at the time of surgery, or casual blood glucose level >= 200 mg/dl at the time of pre-surgical examination	BCR was defined as two consecutive postoperative PSA values _0.2 ng/ml.	Univariate (Some multivariate results, adjustment set not clear.	Association between diabetes and BCR-free survival: HR: 1.18 (0.41, 2.71) * Diabetes was associated with higher Gleason score (p=0.044)
Smith, 2008[90]	RCT but analyzed as a cohort here-- men treated with radiation therapy and short-term	Radiation Therapy Oncology Group Protocol 92-02	1554	No	Prevalent diabetes was determined by medical records and patient-reported past medical history and current	All-cause mortality Non-prostate cancer mortality Prostate	Age <70 v >=70, Race black v other, Tumor stage, Gleason score, PSA, weight, and treatment arm	Exposure: Diabetes All-cause mortality: HR: 1.77 (1.45, 2.16)

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
	versus long-term adjuvant goserelin for locally advanced prostate cancer				medications	Cancer Mortality		Prostate cancer mortality: HR: 0.80 (0.51, 1.25) Non-prostate cancer mortality: HR: 2.12 (1.69, 2.66)
Will, 1999[100]	Prospective cohort – PCa patients from 25 states aged 30 and older recruited in 1959 and 1960.	Questionnaire, death from death certificates	2523 with PCa	No	Diabetes was determined using baseline questionnaire	Death from prostate cancer	Not clear	Prostate cancer mortality Exposure: diabetes IDR: 1.12 (0.77, 1.64)
Wright, 2013[32]	Prospective cohort -men treated with radical prostatectomy (or radiation therapy for localized PCa between 2001–2010.	The Northwest Veterans Integrated Services Network (VISN 20) electronic medical record	1734	No	Serum glucose closest to the date of diagnosis was recorded. DM was based on provider recorded ICD9 diagnosis codes in the 12-month period prior to diagnosis	Recurrence following RP was defined as any PSA >= 0.2 ng/ml 6 months or more after surgery. For RT patients, PSA recurrence was defined by nadir PSA +2.0 ng /ml . Initiation of salvage therapy was also considered as evidence of progression. Salvage RT was defined	Age, race, body mass index, diagnosis of diabetes, treatment year, treatment, clinical stage, diagnostic PSA, Gleason Sum.	Risk of recurrence by American Diabetes Association serum glucose categories: >125 mg/dl = diabetes <100 mg/dl =referent 100-125 mg/dl: HR:1.50 (1.10, 2.04) >125 mg/dl: HR: 1.36 (0.95, 1.95)

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
						as radiation received >1 year after primary treatment date		
Wu, 2013[33]	Retrospective cohort - US veterans with prostate cancer (PCa) and treated with RP between 1988 and 2010.	Shared Equal-Access Regional Cancer Hospital (SEARCH) database	2058	Yes- stratified by black, white and obesity status	Diabetes status determined by medical chart review	Metastases. "Metastatic disease was identified most commonly by bone scan in response to rising PSA levels at the physician's discretion, with equivocal findings confirmed by additional imaging or biopsy"	*Preoperative features: for age, PSA, BMI, biopsy tumour grade, clinical stage, RP year, and centre; * Post-operative features: for age, PSA, BMI, race, RP tumour grade, margin status, extracapsular extension, seminal vesicle invasion, lymph node status, RP year, and centre	*2.4% of patients had metastases. Multivariable HRs for metastases risk associated with diabetes: * Adjusted for preoperative features: White: HR 1.20 (0.51, 2.85), Black HR 1.48 (0.43, 5.10) Adjusted for post-operative features: White HR: 1.47 (0.55, 3.93) Black HR: 1.31 (0.34, 5.09) *Diabetes was not associated with PCa metastases in black or white men

Author, Year	Study Type & Study Population	Data Source	Sample Size	Race [a]	Exposure Measure	Outcome Measure	Adjustment Set	Key Results
Yeh, 2012[91]	Prospective cohort- diabetic and Non-diabetic adults from the CLUE II cohort in Washington County, Maryland	CLUE II (Give Us a Clue to Cancer and Heart Disease) cohort. Cancer incidence was ascertained using county and state cancer registries. Mortality data were obtained from death certificates	2481 adults diagnosed with cancer; specific number for prostate cancer not given	No	Diabetes was defined by self-reported use of diabetes medications at baseline.	Cancer Case Fatality Rate All-cause Mortality	Age, square of age, BMI, smoking, education level, hypertension treatment, high cholesterol treatment	Death rates for prostate cancer patients with diabetes vs. those with no diabetes: Cancer case fatality rate: HR: 1.43 (0.31, 6.69) All-cause mortality: HR: HR: 2.32 (1.29, 4.19)
Zhang, 2013[94]	Retrospective cohort- a random selection of men with PCa treated at Department of Urology, Peking University First Hospital, China between 2000-2010	Medical charts	480	No	Diabetes status determined from chart review	Mean geometric means of PSA Free PSA Free PSA/ total PSA PSAD = total PSA/ prostate volume Gleason score T stage	None	No significant differences observed between diabetes group and non-diabetes group: Mean geometric PSA (p=0.806) Free PSA (p=0.363) fPSA/tPSA (p=0.324) Gleason scores (p=0.568) T stage (p=0.32)

[a] This column does not denote studies that addressed race by including race in the adjustment set. The studies had to present race-specific results for this column to be marked "yes".

CHAPTER 3: METHODOLOGY

3.1 Data Source: North Carolina-Louisiana Prostate Cancer Project (PCaP)

3.1.1 Overview

The North Carolina-Louisiana Prostate Cancer Project (PCaP) is a population-based cohort of patients with prostate cancer. All subjects were diagnosed with adenocarcinoma of the prostate between July 2004 and October 2007.[27,101] Patients in both states were identified through state tumor registries. In North Carolina, the Rapid Case Ascertainment Core Facility, a collaboration between the University of North Carolina-Lineberger Comprehensive Cancer Center and North Carolina Central Cancer Registry identified patients.[101] In Louisiana, the Louisiana Tumor Registry at the Louisiana State University Health Sciences Center identified patients.[101] Eligibility criteria for PCaP subjects included: resident of North Carolina or Louisiana- study areas, first diagnosis of histologically confirmed adenocarcinoma of the prostate, 40-79 years old at diagnosis, can complete the study interview in English, does not live in an institution (i.e. nursing home), is not cognitively impaired or in a severely debilitated physical state, and is not under the influence of alcohol, severely medicated, or apparently psychotic at the time of the interview.[101] Moreover, eligible men had to self-identify as at least part Black/Black or White American/White in response to the open-ended question, “What is you race?”.[101]

PCaP enrolled Blacks and Whites at an equal rate using a randomized recruitment method.[26] Each case that was ascertained was assigned a randomized number.[101] Cases were subsequently recruited into the study if their recruitment number was less than or equal for the race-specific sampling probability. The race-specific sampling probability for

Blacks was 100%, and 44% for Whites.[101] There are 1,130 Blacks and 1,1128 Whites in the study.[27]

3.1.2 Data Collection

Eligible patients were sent a letter explaining the PCaP study, and an enrollment specialist made a follow-up call one week later.[101] Individuals that agreed to participate were visited in-home by a Registered Nurse.[101] During the visit the nurse administered a questionnaire, took biologic samples, and made anthropometric measures.[27] In addition, the nurse obtained informed consent for the release of tumor tissue and medical records during the in-home visit. The study questionnaire included questions on a wide variety of topics including background characteristics, occupation, family history, health status, prostate cancer diagnosis and screening history, medication use, Non-steroidal anti-inflammatory drugs (NSAIDs), and vitamins and supplements.[101] Following the in-home visit, medical records were requested from the physicians (up to 3) of all consenting participants for standardized medical record abstraction.[101] A relational database was used to abstract information from medical records regarding “comorbid conditions, family history of prostate cancer, urologic symptoms, indications for diagnostic examinations, physical examinations and laboratory assays at or near diagnosis, imaging used in staging, clinical stage and grade, and initial treatment information”.[101]

3.1.3 HCaP-NC

HCaP-NC is the follow-up study of North Carolina PCaP participants.[27] PCaP participants were followed, on average, 5 years after diagnosis. Data was collected annually from telephone interviews and medical record abstraction.[27] The telephone interviews used standardized questionnaires. Follow-up medical records were available for 822 participants (456 White and 366 Black).

3.2 Methodology for Specific Aim 1

Specific Aim 1: To assess the association between self-reported diabetes and prostate cancer aggressiveness at diagnosis in Black and White participants in PCaP.

3.2.1 Study Population

The study population for Specific Aim 1 will be the entire PCaP cohort.

3.2.2 Outcome

This aim utilized a previously developed measure of prostate cancer aggressiveness at diagnosis (Table 4).[101] In PCaP 49% of the cohort (n=1102) has non-aggressive tumors at diagnosis, 30% (n=675) had intermediate aggressive tumors, and 18% (n=396) had highly aggressive tumors.[27]

Table 4. Prostate Cancer Aggressiveness at Diagnosis

Outcome	Definition
Highly aggressive	• Gleason sum >=8 OR • PSA >20 ng/ml OR • Gleason sum=7 and stage cT3–cT4
Non-aggressive	• Gleason sum<7 and stage cT1–cT2 and PSA<10 ng/ml)
Intermediate aggressive	All other cases

In our study, Gleason score alone (Gleason score ≥7) was used as a secondary outcome.

3.2.3 Exposure

A self-reported measure of diabetes was used. The PCaP questionnaire asked the question, “Has a doctor or other health professional ever told you that you had diabetes of sugar diabetes?”. An inherent limitation of this measure is that it is self-reported. According to the Atherosclerosis Risk in Communities study (ARIC), the sensitivity of prevalent self-reported diabetes ranges from 58.5% to 70.8% and the specificity ranges from 95.6% to 96.8% depending on the reference definition employed.[102] Another potential limitation of this exposure measure is that we do not know when patients were diagnosed with diabetes, e.g.,

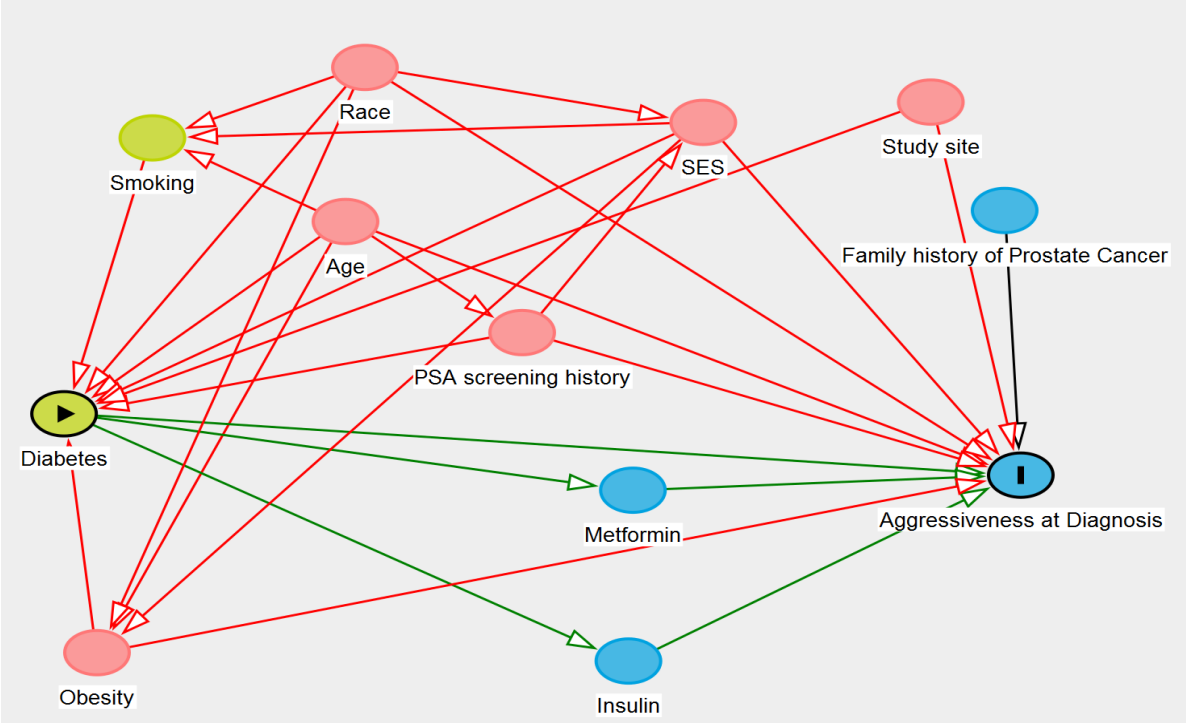
the duration of diabetes exposure or the severity of disease among diabetics. [27] It is important to note that we were interested in patients that already had diabetes prior to their prostate cancer diagnosis

Approximately 22% (n=475) of the PCaP cohort reported a diagnosis of diabetes. In PCaP, Africans Americans were more likely to have diabetes than their White counterparts. 27% of Blacks (n=291) in PCaP had diabetes compared to 17% of Whites (n=184).

3.2.4 Covariates

3.2.4.1 Covariate Selection-Directed Acyclic Graph

Potential confounding covariates were assessed using a directed acyclic graph (DAG). Based on previous research and data available in PCaP, the following variables were included in our DAG: age, screening history, diabetes medication including insulin and metformin, socioeconomic status (SES), and smoking. The DAG can be seen in Figure 2.



DAG was created using DAGitty (http://www.dagitty.net/).[103]

Figure 2. DAG for Specific Aim 1

The minimally sufficient adjustment set identified by the DAG included: age, obesity, screening history, race, SES, and study site. The brief descriptions below highlight the associations illustrated in the DAG.

Age: The risk of diabetes increases with increasing age. Some research suggests older patients may be more likely to have slow-growing, less aggressive cancer. As previously discussed, one study found that up 60% of men 80 and older have undiagnosed prostate cancer on autopsy.[54] Age is included in he adjustment set of all previous studies of diabetes and prostate cancer at diagnosis.

Obesity: Obesity is major risk factor for diabetes, and epidemiological evidence also suggests that obesity may be related to aggressive prostate cancer.[104] A previous PCaP study found that obesity was significantly associated with aggressiveness at diagnosis.[105]

Screening history: PSA screening history is a strongly associated with prostate cancer aggressiveness at diagnosis. Men who undergo frequent PSA screening are more likely to be diagnosed with early-stage prostate cancer, as PSA screening detects prostate cancer that may not be detectable using other clinical methods such as DRE.

Race: Blacks are at increased risk for diabetes. Compared to Non-Hispanic white adults, Non-Hispanic black adults have a 77% higher risk of being diagnosed with diabetes.[106] Moreover, black men are more likely to be diagnosed with and die from prostate cancer.[41]

SES: A lower socioeconomic status is associated with an increased risk of diabetes.[107] Moreover, a lower SES may also be associated with higher aggressiveness at diagnosis. Men from a lower SES may be less likely to have a regular source of healthcare. This in turn can delay the diagnosis of prostate cancer, and result in a higher aggressiveness at diagnosis.

Study site: Patient characteristics, access to healthcare, and quality of health services may vary across North Carolina and Louisiana. As such study site is included as a potential confounder in the DAG.

Variables not identified as potential confounders: It is hypothesized that insulin may increase the risk of prostate cancer risk while metformin may reduce prostate cancer risk, but the evidence is not conclusive.[108,109] Although metformin and insulin were included on the DAG as potential risk factors for aggressiveness at diagnosis, this has not be clearly established in the literature. However, assuming they were risk factors for aggressiveness at diagnosis, they would not be potential confounders. As can be seen on the DAG, these variables would be on the causal pathway from diabetes to aggressiveness at diagnosis, and as such would not be adjusted for. Finally, although family history of prostrate cancer is associated with our outcome, it is not a potential risk factor for diabetes. As such it is not a potential confounder.

3.2.4.2 Covariate Coding

Table 5 indicates how the covariates of interest were coded. Initial coding choices were based on prior PCaP research that assessed aggressiveness at diagnosis.[110] However, we reassessed the most appropriate coding choices by examining bivariate relationships between each covariate of interest and aggressiveness at diagnosis. Consistent with prior PCaP research, education was used a proxy for SES.

Table 5. Variable Coding for DAG-identified Minimally Sufficient Adjustment Set

Variable	Coding
Age	*continuous,* 40-79 years of age
BMI	*normal weight*: 18.5 to <25.0 kg/m^2
	overweight: 25.0 to <30.0 kg/m^2
	obese: ≥ 30.0 kg/m^2
PSA screening history	*yes:* participant had at least one PSA before prostate cancer diagnosis.
	no: participant did not have at least one PSA in the 12 months before prostate cancer diagnosis
Race	*White; Black*
Study Site	*North Carolina, Louisiana*
SES (Education)	*Less than high school* *High school graduate or some college* *College graduate or more*

3.2.5 Data Exploration

We began by a descriptive analysis of all the covariates. One-way frequencies were run for all categorical variables. For continuous variables, the distribution of each variable including the mean, median, range, and standard deviation were assessed. The amount of missing data was quantified, and the plausibility of any outliers was examined. Following univariate analyses, we conducted bivariate analyses with each covariate and aggressiveness at diagnosis. Aggressiveness at diagnosis was analyzed a 2-level variable (high-aggressive tumors vs. intermediate and non-aggressive tumors).

3.2.6 Analytic Strategy

3.2.6.1 Logistic Regression

Logistic regression was used to determine the relationship between diabetes and the dichotomous aggressiveness at diagnosis variable. Our primary models examined aggressiveness at diagnosis as a two-level outcome. It was analyzed as high-aggressive vs. intermediate and non-aggressive. This maximized power, and reflects the fact that patients

with high-aggressive tumors are clinically distinct. To begin we used an unadjusted, univariate logistic model with diabetes as the exposure and the dichotomous aggressiveness variable as the outcome. Multivariate analytic models were adjusted for the confounders identified by the DAG (Figure 2). Models were stratified by race to examine the role of race in the diabetes-aggressiveness association. Models were additionally stratified by treatment type. Most published studies are limited to single treatment types, and we stratified by treatment to determine if observed associations were restricted in some manner due the characteristics of participants within specific treatment groups

In a secondary analysis, we repeated all analyses with Gleason score alone as the outcome. Gleason score will be defined as a dichotomous outcome defined as Gleason score ≥7 vs. Gleason score <7. The proposed unadjusted and adjusted analytic models are described next.

The unadjusted logistic model will be expressed as[111]:

$$Logit\ P\ (aggressiveness) = \alpha + \beta_1\ (Diabetes)$$

Where:

α = *logit P(aggressiveness) for non-diabetics*

β_1 = *log odds ratio for aggressiveness in diabetics vs. non-diabetics.*

The fully adjusted logistic model will be expressed as:

$$Logit\ P\ (aggressiveness) = \alpha + \beta_1\ (Diabetes) + \beta_2\ (Race) + \beta_3\ (Age) + \beta_4\ (Overweight) + \beta_5\ (Obesity)^* + \beta_6\ (Screening\ History) + \beta_7\ (Less\ than\ high\ school\ education) + \beta_8\ (College\ graduate\ or\ higher) + \beta_7\ (Study\ Site)$$

The models were run for the cohort as whole, among Blacks, and Whites. We additionally stratified models by treatment type.

Sensitivity Analysis:* Given the complicated relationship between obesity and diabetes, we ran models both adjusting and non-adjusting for obesity. If obesity is a true confounder (as shown in Figure 2) than it should be in the adjustment set. However, it is

possible that there is an alternative pathway whereby diabetes also increases the risk for obesity. This would put obesity on the causal pathway between diabetes and aggressiveness at diagnosis. In this pathway, obesity is a mediator and should not be adjusted for. Prior research on diabetes and aggressiveness at diagnosis is not consistent, with some studies adjust for obesity[23,29] and other not adjusting for obesity.[21,24]

3.2.6.2 Linear Regression

Prevalence differences were calculated to allow for *direct* comparisons across races. Linear regression with a binomial distribution was used to calculate the prevalence differences of high aggressive CaP in diabetic men vs. non-diabetic men. Models were adjusted for confounders identified from our DAG and include race, age, screening history, education, and study site. Models were also be stratified by race to examine race differences.

The proposed unadjusted and adjusted analytic models are described next.

The unadjusted logistic model will be expressed as:

$$Prevalence\ (aggressiveness) = \alpha + \beta_1\ (Diabetes)$$

Where:

α = *Prevalence (aggressiveness) for non-diabetics*

β_1 = *prevalence difference of aggressiveness in diabetics vs. non-diabetics.*

The fully adjusted logistic model will be expressed as:

$$Prevalence\ (aggressiveness) = \alpha + \beta_1\ (Diabetes) + \beta_2\ (Race) + \beta_3\ (Age) + \beta_4\ (Overweight) + \beta_5\ (Obesity) + \beta_6\ (Screening\ History) + \beta_7\ (Less\ than\ high\ school\ education) + \beta_8\ (College\ graduate\ or\ higher) + \beta_7\ (Study\ Site)$$

Table 6 summarizes the proposed models for Aim 1.

Table 6. Proposed Models for Specific Aim 1

Model Number	Population	Outcome Grouping	Exposure	Confounders (Identified by DAG)	Stratification	Model
1 (primary model)	PCaP	High-aggressive vs. not (2-level, composite outcome)	Self-reported Diabetes	Age, BMI, PSA screening history, race, study site, education	None	Logistic Regression
2	PCaP	High-aggressive vs. not (2-level, composite outcome)	Self-reported Diabetes	Age, BMI, PSA screening history, race, study site, education	Race	Logistic Regression
3	PCaP	High-aggressive vs. not (2-level, composite outcome)	Self-reported Diabetes	Age, BMI, PSA screening history, race, study site, education	Treatment Type	Logistic Regression
4	PCaP	Gleason score ≥7 vs. not	Self-reported Diabetes	Age, BMI, PSA screening history, race, study site, education	None	Logistic Regression
5	PCaP	Gleason score ≥ 7 vs. not	Self-reported Diabetes	Age, BMI, PSA screening history, race, study site, education	Race	Logistic Regression
6	PCaP	High-aggressive vs. not (2-level, composite outcome)	Self-reported Diabetes	Age, BMI, PSA screening history, race, study site, education	None	Linear regression with binomial distribution
7	PCaP	High-aggressive vs. not (2-level, composite outcome)	Self-reported Diabetes	Age, BMI, PSA screening history, race, study site, education	Race	Linear regression with binomial distribution

3.2.7 Power for Aim 1 (Primary Model)

Figure 3 shows the estimated power for our primary model, logistic regression using the composite measure of aggressiveness as our outcome. Since approximately 18% of our cohort had high aggressive tumors at diagnosis (n=396), to calculate power we used a case:control ratio of 4.6. Since approximately 22% of the cohort had diabetes we assumed an exposure prevalence of 0.22. Power calculations were based assuming a maximum case number of 396.

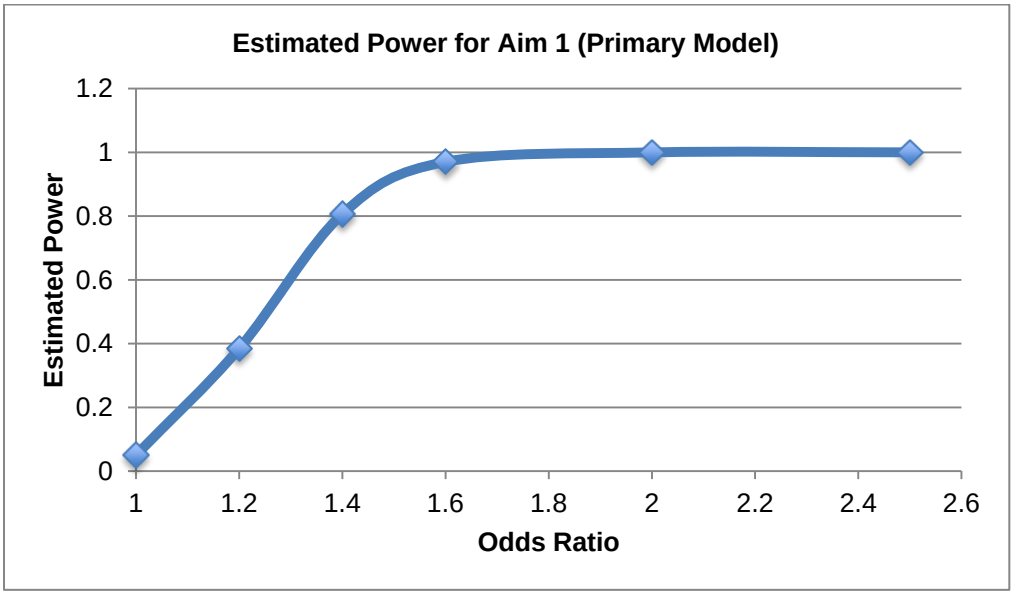


Figure 3. Estimated Power for Aim 1

We had greater than 80% power to detect odds ratios of 1.4 or higher.

3.3 Methodology for Specific Aim 2a

Specific Aim 2a: *To implement a prostate cancer progression algorithm in the HCaP-NC follow-up cohort.*

3.3.1 Study Population

The study population for Specific Aim2a was all HCaP-NC patients with follow-up data.

3.3.2 Outcome

This aim was designed to create a prostate cancer progression outcome. Outcome definitions are outlined in Table 7 on the next page. The primary outcome was a binary outcome of progression (yes/no). However, the definition of “progression” was dependent on treatment type. Within each treatment type, we further categorized patients into progression sub-types. Patients that undergo radical prostatectomy were categorized as having biochemical recurrence (BCR), persistent disease, other treatment failure, or successful treatment. Because patients that receive radical prostatectomy should have a post-treatment nadir PSA that is undetectable, a true measure of persistence could only be measured in this treatment group.

Patients that undergo radiation were categorized as having biochemical recurrence, treatment failure, or successful treatment. Because patients that undergo radiation do not typically achieve a post-treatment nadir PSA of 0, persistence could not be defined in this group. Patients that chose watchful waiting, did not receive treatment of any type, or received ADT as their primary treatment were excluded from all analyses.

Table 7. Prostate Cancer Progression Outcome

Treatment Type	Progression Sub-type	Proposed Definition
Radical Prostatectomy [a]	Biochemical recurrence	• PSA ≥ 0.2 ng/ mL confirmed with a 2nd PSA of ≥ 0.2 ng/ mL after achieving nadir. [American Urological Association (AUA) definition][66]. Nadir is defined as an undetectable PSA (PSA <0.1).
	Persistent disease	• Patient does not achieve nadir after surgery. Nadir is defined as an undetectable PSA (PSA <0.1).
	Other treatment failure	• Received post radical prostatectomy treatment for prostate cancer (secondary treatment). This includes radiation, androgen deprivation therapy, or chemotherapy. Adjuvant radiation or adjuvant ADT will not be considered secondary treatment. (Radiation or ADT that is ≤ 6 months after radical prostatectomy is considered adjuvant).
	Successfully treated	• None of the above
Radiation [b]	Progressing	• Nadir + 2 ng/ mL (Phoenix definition)[67]. Nadir will be defined as the lowest PSA achieved after initiation of radiation
	Other treatment failure	• Post radiation treatment for prostate cancer (secondary treatment). This includes radiation, androgen deprivation therapy or chemotherapy. Adjuvant ADT will not be considered secondary treatment. (ADT that is ≤ 1 year after start of radiation is considered adjuvant.
	Successfully treated	• None of the above
Watchful Waiting, no treatment recorded, or ADT as primary treatment [c]	Excluded from analysis	

[a] Patients will be required to have at least one PSA measure within 6 months of radical prostatectomy (RP). Patients with no PSA value within 6 months of RP will be excluded from analysis.
[b] If a patient receives both External Beam Radiation and Brachytherapy, it will be considered as one radiation treatment.
[c] If ADT occurs prior to radical prostatectomy, radical prostatectomy will be considered the primary treatment type. If ADT occurs less than one year before radiation, radiation will be considered the primary treatment type.

The first step in the creation of the progression outcome was manual assessment of progression in each HCaP-NC patient. For each patient, PSA measures and treatments received were graphed over calendar time. Using the definitions above each patient was manually assigned a progression outcome. The clinical team and other committee members reviewed the progression graphs of patients where the progression outcome was not clear based on the definitions in Table 7. The team came to consensus on the progression outcome of these patients, and this agreed upon progression outcome was used for all further analyses.

3.4 Methodology for Specific Aim 2b

Specific Aim 2b*: To assess the association between self-reported diabetes and prostate cancer progression in Black and White participants in the HCaP-NC follow-up cohort.*

3.4.1 Study Population

The study population for Specific Aim 2b was all HCaP-NC patients for which progression could be determined.

3.4.2 Outcome

This utilized the progression outcome developed in Aim 2a. Our primary outcome was be *time to progression* across all treatment modalities (e.g. biochemical recurrence, persistence, or treatment failure). Note that the definition of progression will vary by treatment type as outlined in Table 7 above. Time to progression was determined as described below.

Radical prostatectomy: Follow-up began on date of surgery. Patients with biochemical recurrence were recorded as having a progression event at first PSA ≥ 0.2 ng/mL after nadir given that there is a second confirmatory PSA ≥ 0.2 ng/mL (AUA definition). Persistent patients (those that never achieve nadir) were recorded as having a progression event 90 days after surgery. Patients that received secondary treatment were

recorded as having a progression event at date secondary treatment was initiated. For all other patients that were successfully treated, patients were censored at end of follow-up (i.e. date of last PSA measurement available).

Radiation: Follow-up began at date of radiation start. Patients were recorded as having a progression event at first PSA that is 2 ng/mL above nadir. Patients that received secondary treatment were recorded as having a progression event at date secondary treatment was initiated. For all other patients that were successfully treated, patients were censored at end of follow-up (i.e. date of last PSA measurement available).

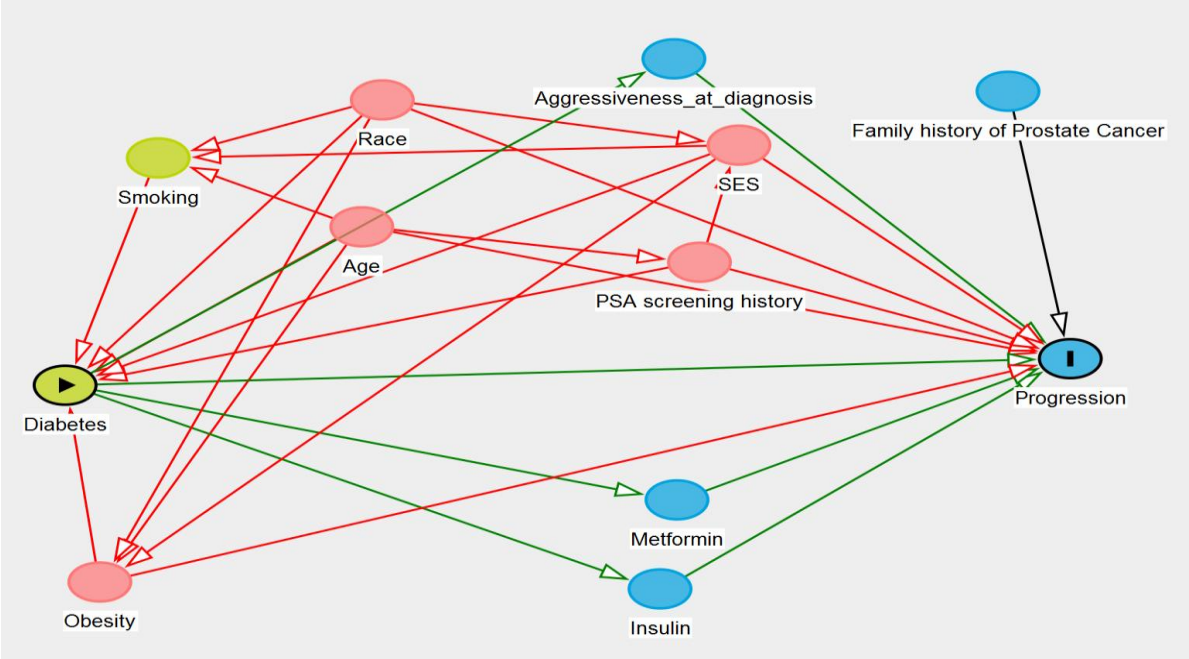
3.4.3 Exposure

The previously discussed self-reported measure of diabetes will be used.

3.4.4 Covariates

3.4.4.1 Covariate Selection-Directed Acyclic Graph

Potential confounding covariates were assessed using a directed acyclic graph (DAG). Because potential confounders conceptually have a similar relationship with progression as aggressiveness at diagnosis, the DAG was very similar to the one for Specific Aim 1. The main difference is, now, aggressiveness at diagnosis is included on the DAG as a potential confounder (Figure 4). However, as can be seen in the DAG, aggressiveness at diagnosis is on the causal pathway between diabetes and progression. As such we did adjust for it in our primary analysis. In addition, because all follow-up participants are form North Carolina, study site is not included in the DAG.



DAG was created using DAGitty (http://www.dagitty.net/).[103]

Figure 4. DAG for Specific Aim 2b

The minimally sufficient adjustment set identified by the DAG included: age, obesity, screening history, race, SES, study site, and aggressiveness at diagnosis. However, given that over 94% of the analytic cohort had a history of PSA screening, screening was not included in our final models.

3.4.4.2 Covariate Coding

Covariate coding was similar to that described in Specific Aim 1. However, due to limited sample size BMI (obese/non-obese) and education (college degree/no college degree) were coded as binary variables.

3.4.5 Data Exploration

Data exploration was similar to that described in specific Aim 1. We began by a descriptive analysis of all the covariates. Following univariate analyses, we conducted survival analysis for time to progression with each covariate.

3.4.6 Analytic Strategy

Survival analysis was used to determine the relationship between diabetes and time to progression (yes/no) using the entire HCaP-NC cohort. Definitions of progression vaired by treatment type as outlined in Table 7. To begin we compared time to progression in diabetic patients vs. non-diabetic patients using Kaplan Meir plots. Differences in survival between diabetics and non-diabetics were evaluated using the log-rank test.[112] The log rank test tests the null hypothesis that $S_{diabetics}(t) = S_{non\text{-}diabetics}(t)$ for all t, where t =time and S=survival.[112] We used an *a-priori* alpha = 0.05 to determine if survival probabilities are significantly different. The analysis was repeated, stratifying by race.

Next we calculated hazard ratios (HRs) for time to progression (yes/no) in diabetic patients vs. non-diabetic patients using Cox proportional hazards. For all analyses, we first assessed the proportional hazard assumption. The proportional hazard assumption for each categorical covariate was assessed by visually examining Kaplan-Meier and log-(log) plots. For continuous variables, the proportional hazard assumption was assessed using Schoenfeld Residuals. If the plots or Schoenfeld residuals indicated a potential violation of the proportional hazards assumption, we determined whether the interaction between time and that covariate was statistically significant (p-value ≥ 0.05) in an unadjusted model. Time was assessed using a liner, exponential, and cubic term. If the interaction was statistically significant, we retained an interaction term between that covariate and the appropriate measure of time (i.e. if the time trend is linear, we will use linear measure of time) in our final model.

Adjusted multivariable models will be adjusted for the confounders identified by the DAG (Figure 4). Models will be stratified by race to assess the role of race in the diabetes-progression association.

Sensitivity Analysis:* Although we did not adjust for aggressiveness at diagnosis in our primary analysis as discussed (it is on the causal pathway) we will adjust for both our

composite measure of prostate cancer aggressiveness and Gleason score in a sensitivity analysis. This will be done to maintain consistency with prior literature.

The unadjusted Cox proportional hazard model will be expressed as the following (given non-diabetics are the reference and assumption of proportional hazards is met)[112]:

$$h(t) = h_0(t)\ exp\ [\ \beta_1(Diabetes)\ ]$$

Where,

The null hypothesis is given by $h(t) = h_0(t)$

$h_0(t)$ = hazard for progression of a non-diabetic individual at time t

exp [β_1] = hazard ratio for time to progression in diabetics vs. non-diabetics

The multivariable Cox model will be expressed as the following (given non-diabetics are the reference and assumption of proportional hazards is met):

$$h(t) = h_0(t)\ exp\ [\ \beta_1(Diabetes) + \beta_2(Treatment\ type) + \beta_3(Race) + \beta_4(Age) +$$

$$\beta_5(Obesity) + \beta_6(Screening\ History) + \beta_7(College\ Education) +$$

The proposed analyses for specific aim 2b are summarized in table 8.

Table 8. Proposed Analyses for Specific Aim 2b

Model Number	Population	Outcome Grouping	Exposure	Confounders	Stratification	Analyses
1	HCaP-NC	Progression (yes/no)	Self-reported diabetes	Age, obesity, race, and college education [a]	None	Kaplan-Meir plots with log-rank test Cox Proportional Hazards
2	HCaP-NC	Progression (yes/no)	Self-reported diabetes	Age, obesity, PSA , race, and college education [a]	Race	Kaplan-Meir plots with log-rank test Cox Proportional Hazards

[a] PSA screening history was identified as confounder by our DAG. However, it was not included in our final models as over 94% of the analytic cohort for Specific Aim 2b had a history of PSA screening.

3.4.7 Power for Aim 2b

A two-sided log rank test was used to calculate power for Aim 2. Since 22% of the HCaP cohort had diabetes and, on average, we have 5-years of follow-up data, power was calculated assuming a 22% frequency of diabetes and 5-years of follow-up time. Previous research indicates that 20-30% of the prostate cancer patients will experience prostate cancer progression,[23] and as such the estimated power in the graph below is calculated assuming that 25% of non-diabetics will have prostate cancer progression. Figure 5 shows the estimated power for Aim 2.

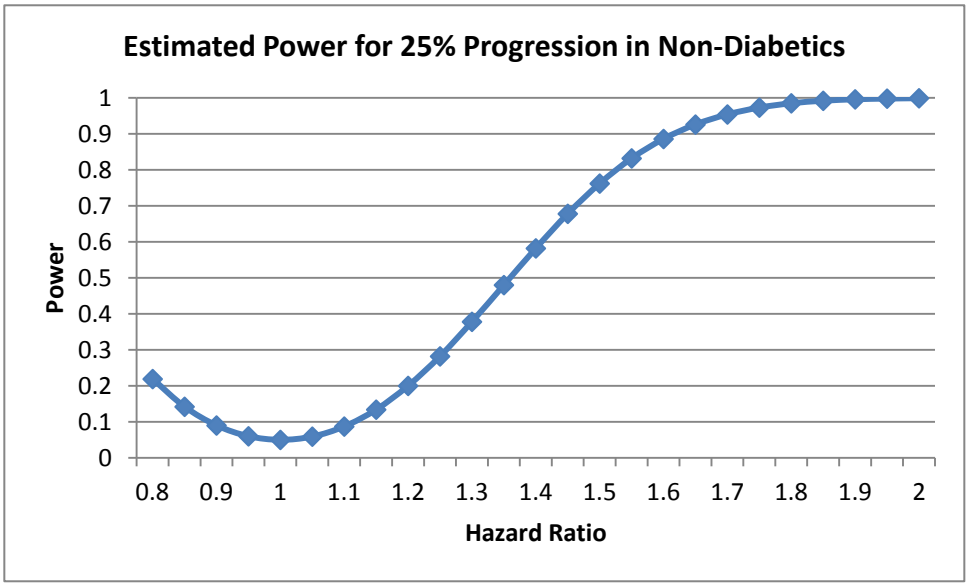


Figure 5. Estimated Power for Aim 2b

We have greater than 80% power to detect hazard ratios greater than 1.5.

CHAPTER 4: THE ASSOCIATION OF DIABETES AND OBESITY WITH PROSTATE CANCER AGGRESSIVENESS AMONG BLACK AMERICANS AND WHITE AMERICANS IN A POPULATION-BASED COHORT

4.1 Introduction

Prostate cancer (CaP) is the most common incident cancer among men in the United States. The Surveillance Epidemiology and End Results (SEER) reported that, 14% of men will be diagnosed with CaP during their lifetime.[1] An estimated 220,800 new cases of CaP and 27,540 CaP deaths occurred in the United States during 2015.[113] CaP is a disease of disparities. Black Americans (Blacks) are more likely to be diagnosed with and die from CaP than White Americans (Whites). The incidence of CaP from 2008-2012 is higher in Blacks at 214.5 cases per 100,000 compared to 130.4 cases per 100,000 in Whites.[1] The age-adjusted death rate in Blacks was more than double that in Whites between 2008-2012.[1]

Numerous studies have shown that diabetes is associated with a reduced risk of incident CaP.[73-79,114] Possible explanations for this inverse association include lower circulating levels of growth factors, such as insulin and testosterone, and decreased CaP detection among diabetic men.[23,75,115] Diabetics are more likely to be obese than their non-diabetic counterparts.[116] Digital rectal exam (DRE) detection and prostate biopsy are more difficult in obese men, and obese men may have lower levels of prostate specific antigen (PSA), either of which could contribute to lower CaP detection rates.[75,115,117,118]

Studies among men diagnosed with CaP show that diabetes and obesity are positively associated with CaP aggressiveness.[21,23,24,105,118-123] The positive association between diabetes and CaP aggressiveness is hypothesized to result from high aggressive prostate CaP surviving in a low-insulin, poor growth environment, an increased likelihood that CaP that does get detected is aggressive, and the changing glucose profile of diabetics

throughout the CaP course.[23,115] Newly diagnosed diabetics, in particular, likely have high insulin levels that create an environment that promotes CaP growth.[115] The positive association between diabetes and CaP aggressiveness observed in the literature is limited to studies with clinic or hospital-based populations or patients undergoing a single treatment type. Few studies have included sufficient numbers of Black men to examine the role of race on the diabetes-CaP aggressiveness association, and the two existing studies have yielded different results.[21,23]

We examined the association of diabetes and obesity, independent of diabetes, with high aggressive CaP at diagnosis, defined as a Gleason sum ≥8, or PSA >20 ng/ml, or Gleason sum =7 and clinical stage cT3-cT4. Our study population was a large, population-based cohort of men who had incident CaP, were over-sampled for Blacks, were diagnosed in the PSA screening era, and participated in the North Carolina-Louisiana Prostate Cancer Project (PCaP). This analysis builds on previous PCaP research that found obesity was associated with CaP aggressiveness at diagnosis, by accounting for the diabetic status of PCaP research subjects.[105]

4.2 Methods

4.2.1 Study Population and Data Collection

PCaP has been described in detail.[101] PCaP is a population-based cohort of research subjects with incident CaP. All research subjects were diagnosed with adenocarcinoma of the prostate between July 2004 and August 2009, and were identified using state tumor registries. Eligibility criteria for PCaP research subjects included: resident of North Carolina or Louisiana- study areas, first diagnosis of histologically confirmed adenocarcinoma of the prostate, 40-79 years old at diagnosis, could complete the study interview in English, did not live in an institution (i.e. nursing home), not cognitively impaired or in a severely debilitated physical state, and not under the influence of alcohol, severely medicated, or apparently psychotic at the time of the interview. Moreover, eligible men had

to self-identify as African American/Black or Caucasian/White in response to the open-ended question, “What is your race?”.

PCaP enrolled Blacks and Whites at an equal rate using a randomized recruitment method.[26] Participation rates were 62% in North Carolina, 73% in pre-hurricane Katrina Louisiana, and 63% in post-hurricane Katrina Louisiana. 1,130 Blacks and 1,128 Whites enrolled in PCaP.

We excluded 25 research subjects that were underweight [body mass index (BMI) < 18.5] and 84 research subjects with missing information on the outcome (CaP aggressiveness) from our analytic group. Furthermore, 17 research subjects were excluded due to missing information on diabetes (4 research subjects responded they did not know their diabetes status and 13 research subjects did not have their diabetes status recorded). Additional research subjects were excluded due to missing covariate information (screening history, body mass index (BMI), or education) (n=83). Our final analytical sample included a total of 2049 research subjects (94% of PCaP research subjects with CaP aggressiveness defined at diagnosis) of which 1058 were White and 991 were Black. Although Black research subjects were more likely to be excluded than White research subjects, the overall distribution of CaP aggressiveness, diabetes, and covariates was similar for Blacks in the full PCaP cohort and Blacks in the analytic sample. However, excluded Black men were more likely to be from Louisiana (74.1% excluded men vs. 52.7% included men), less likely to have a college education (5.9% vs. 15.8%), less likely to be obese (28.0% vs. 39.8%), and less likely to receive either RP nor radiation (43.2 % vs. 64.8%) than those included in the analytic cohort. Similar to Black men, excluded White men were more likely to be Louisiana (68.6% vs. 52.4%), less likely to have a college education (14.3% vs. 43.6%), and less likely to receive either RP nor radiation (51.5% vs. 72.3%) than those included in the analytic cohort. Excluded white men were also more likely to be diabetic (27.7% vs. 16.7%) than included white men.

The primary outcome was high aggressive CaP based on a composite of diagnostic PSA, clinical stage and Gleason sum. We also evaluated CaP aggressiveness solely based on Gleason sum. The sample consisted of 2207 research subjects (98% of the PCaP cohort) when the analysis was restricted to Gleason sum,

Research subjects who agreed to participate were visited by a Registered Nurse. The nurse administered a questionnaire, took biologic samples, and made anthropometric measures during an in-home visit. The nurse also obtained informed consent for the interview and specimen collection and release of tumor tissue and medical records. The study questionnaire included questions on comorbidities, such as diabetes, education level, and CaP screening history.

Medical records were requested from the physicians (up to 3) of all consenting research subjects for standardized medical record abstraction. Medical record abstraction included information regarding physical examinations and laboratory assays at or near diagnosis, clinical stage, Gleason sum, PSA measures, and initial CaP treatment.

4.2.2 Outcome, Exposure, and Covariate Measurement

Our primary outcome of interest was a composite measure of CaP aggressiveness *at diagnosis* [101]. High aggressive CaP was defined as Gleason sum ≥8, or PSA >20 ng/ml, or Gleason sum =7 and clinical stage cT3-cT4. Low aggressive CaP was defined as Gleason sum <7 and clinical stage cT1-cT2 and PSA <10 ng/ml. Other CaP was defined as intermediate aggressive. Low aggressive and intermediate aggressive CaP were collapsed into a single category in all our analytic models. We also analyzed CaP aggressiveness using Gleason sum alone to allow comparison with previous studies. Gleason sum was analyzed as a binary variable with high aggressiveness defined as Gleason sum ≥ 7.

Our primary exposures of interest are diabetes and obesity, independent of diabetes. PCaP research subjects self-reported diabetes status when asked the question, “Has a doctor or other health professional ever told you that you had diabetes or sugar diabetes?”.

Responses were recoded as “yes”, “no”, “refused”, or “don’t know”. Research subjects who did not know their diabetes status or refused to answer were excluded from our analysis (n=17, 0.8% of PCaP cohort). Obesity was determined using body mass index (BMI). BMI was calculated using standardized anthropometric measurements at the home visit, and research subjects were categorized as normal (BMI 18.5 to <25), overweight (BMI 25 to <30), or obese (BMI ≥ 30) using World Health Organization classifications. We removed BMI from our adjustment set in a sensitivity analysis, because obesity may be both a precursor and result of diabetes. In addition, in another sensitivity analysis we examined the association of diabetes with aggressiveness at diagnosis only among obese men.

Covariates were selected based on known confounders in the literature and to maintain consistency with prior PCaP studies and included race, age, screening history, education, and study site. Race was based on self-report, and all research subjects were categorized as either White or Black. Age was calculated based on age at diagnosis and coded as a continuous variable. Screening history was based on self-report and defined as having at least one PSA or Digital Rectal Exam (DRE) prior to CaP diagnosis. Education was based on self-report and categorized as less than high school, high school graduate or some college, or college graduate and above. Study site was categorized as North Carolina or Louisiana.

Research subjects were categorized as having undergone radical prostatectomy (RP) or radiation using medical records. Research subjects who had both RP and radiation were included in the RP group. The radiation group included research subjects who had either external beam radiation or brachytherapy. Research subjects who did not receive treatment, were on watchful waiting, or only received Androgen Deprivation Therapy (ADT) were included in analyses of the entire cohort, but were not included in treatment-stratified analyses due to limited sample size.

4.2.3 Statistical Analysis

Logistic regression was used to assess the association between diabetes and BMI with the composite binary outcome (aggressive CaP at diagnosis) in our primary analysis. Multivariable models were adjusted for race, age, screening history, education, and study site. Models were stratified by race to examine race differences. Models were stratified by treatment type to facilitate comparison with other single-treatment studies. We ran multivariable models without adjustment for BMI in a sensitivity analysis.

Logistic regression was used to assess the association between diabetes and BMI with Gleason sum alone using the same adjustment set as analyses with our composite outcome. Models were stratified by race.

Prevalence differences were calculated to allow for *direct* comparisons across races in a secondary analysis. Linear regression with a binomial distribution was used to calculate the prevalence differences of high aggressive CaP. Diabetes and BMI were our exposures of interest. Models were adjusted for race, age, screening history, education, and study site, and were also stratified by race to examine race differences.

All analyses were conducted using SAS 9.4 (Cary, NC).

4.3 Results

4.3.1 Characteristics of the PCaP Cohort (Table 9)

The mean age of research subjects at diagnosis was 63 years. The majority of research subjects had CaP screening using PSA or DRE prior to CaP diagnosis. Research subjects were enrolled in approximately equal numbers in North Carolina and Louisiana. Approximately half of the cohort was a high school graduate or had some college education. PCaP research subjects were more likely to be overweight or obese than normal weight. 21.6% of the cohort had diabetes, and 17.9% of the cohort had high aggressive CaP using our composite measure of aggressiveness.

Blacks (n=991) were slightly younger than Whites (n=1058). Whites were more likely than Blacks to have undergone CaP screening prior to diagnosis. There were approximately equal numbers of Whites and Blacks at each study site. Whites were more likely to be college graduates or above, while blacks were more likely to have less than a high school education. Blacks were more likely to have diabetes (26.8%) than Whites (16.7%), and were more likely to have high aggressive CaP at diagnosis (20.6% vs. 15.3%).

Sixty-eight percent of the PCaP cohort was treated with RP or radiation. Treated research subjects were more likely to have diabetes (24.9% vs. 20.1%), less likely to be from North Carolina (43.5% vs. 49.3%), more likely to have less than a high school education (24.8% vs. 17.1%), more likely to have high aggressive CaP (23.4% vs. 15.4%), and were older in age at diagnosis (66 years vs. 63 years). Whites were more likely to have received treatment than Blacks.

4.3.2 Diabetes and Obesity (Table 10)

The OR for diabetes and high aggressive CaP was close to the null after adjustment for age, race, CaP screening history, study site, education, and BMI (OR: 1.04; 95% CI: 0.79, 1.37). The association of diabetes and high aggressive CaP was similar in race-specific adjusted models for Whites (OR: 1.00; 95% CI: 0.65, 1.57) or Blacks (OR: 1.07; 95% CI: 0.75, 1.53). Obesity, adjusted for diabetes, was associated with an elevated odds of high aggressive CaP in the overall cohort (OR: 1.37; 95% CI: 0.99, 1.92) and Whites (OR: 1.98; 95% CI: 1.14, 3.43), but not Blacks (OR: 1.09; 95% CI: 0.71, 1.67) in adjusted models.

Models *not* adjusted for BMI in a sensitivity analysis did not show an association between diabetes and high aggressive CaP [Overall (OR: 1.10; 95% CI: 0.84, 1.45), Whites (OR: 1.14; 95% CI: 0.73, 1.76), or Blacks (OR: 1.09; 95% CI: 0.77. 1.55)]. In addition, models restricted to only obese men did not show an association between diabetes and high aggressive CaP [Overall (OR: 1.00; 95% CI: 0.68, 1.47), Whites (OR: 0.79; 95% CI: 0.43, 1.43), or Blacks (OR: 1.19; 95% CI: 0.71. 2.00)].

We examined treatment specific ORs to facilitate comparison with existing literature. Most published studies are limited to single treatment types, and we examined if observed associations were restricted in some manner due the characteristics of research subjects within specific treatment groups. Treatment specific ORs, similar to those observed in the cohort overall, did not show an association between diabetes and high aggressive CaP (Table A 1). No association was observed between obesity, independent of diabetes, and high aggressive CaP in treatment-stratified models. Race-specific models did not reveal differences between Whites or Blacks regardless of treatment type.

Research subjects who received both RP and radiation were included in the RP group, so we conducted a sensitivity analysis where research subjects that received both RP and radiation were excluded from the RP group. Results were similar (data not shown). The observed ORs for Gleason sum ≥ 7 (in diabetics vs. non-diabetics) were similar for the overall cohort (OR: 0.93; 95% CI: 0.75, 1.16), and race-specific groups [Whites (OR: 0.96, 95% CI: 0.68, 1.34); Blacks (OR 0.92, 95% CI: 0.69, 1.23)]. Obesity, independent of diabetes, was associated with Gleason sum ≥ 7 in both the overall cohort (OR: 1.36; 95% CI: 1.06, 1.76) and Whites (OR: 1.51; 95% CI: 1.03, 2.20), but not Blacks (OR: 1.23; 95% CI: 0.87. 1.75)

4.3.3 Prevalence Differences

Direct comparisons of effect estimates (ORs) between races were uninterruptable due to the differing baseline prevalence of high aggressiveness CaP among unexposed Whites and unexposed Blacks in our case-only cohort. To address this, we calculated prevalence differences (PD) in a supplementary analysis (Table A 2). Prevalence differences showed directions of association that were consistent with the results based on ORs. Namely, diabetes was not associated with a higher prevalence of aggressive CaP in the cohort as a whole, or in Whites or Blacks after adjusting for age, race, screening history, study site, education, and BMI. However, obesity, independent of diabetes, was associated

with a 7% (PD: 0.07; 95% CI: 0.01, 0.14) increase in the prevalence of high aggressive CaP in Whites and a 4% increased prevalence in the cohort as a whole (PD: 0.04; 95% CI: 0.00, 0.09). The prevalence difference in Blacks was close to the null (PD: 0.01; 95% CI: -0.06, 0.08), although the estimate is imprecise.

4.4 Discussion

Self-reported diabetes was not associated with a composite measure of CaP aggressiveness at diagnosis in this population-based cohort of Whites and Blacks with CaP. We did not observe any differences in this association between Whites and Blacks. However, we found that obesity, independent of diabetes, was associated with high aggressive CaP in Whites using our composite measure of CaP aggressiveness.

Several studies have reported a positive association between diabetes and CaP aggressiveness at diagnosis.[21,23,24,123] However, unlike our study, these studies were restricted to clinical patient sets receiving a common treatment, with an outcome of Gleason sum alone.[21,23,24,123] Moreover, only one of these studies adjusted for obesity in their analyses.[23] D'Amico et al. reported a positive association between diabetes and Gleason sum 8-10 (OR: 1.85, 95% CI: 1.25, 2.74) among radiation patients.[24] Kang et al reported that both type 1 diabetes (OR: 2.05, 95% CI: 1.28, 3.27) and type 2 diabetes (OR: 1.58, 95% CI: 1.26, 1.99) were associated with Gleason sum 8-10 in another study that used the same cohort [123]. Jayachandran et al. reported that diabetes was associated with Gleason sum ≥ 7 (OR: 1.73, 95% CI: 1.22, 2.45) among RP patients from the Shared Equal Access Regional Cancer Hospital Database (SEARCH).[23] By contrast, we did not find an association between diabetes and our composite outcome of CaP aggressiveness, Gleason sum ≥ 7, or Gleason sum ≥8 in our population-based cohort as a whole, or in treatment-stratified analyses.

Our results were consistent with the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) study. Chan et al. reported that a history of diabetes was

not associated with higher Gleason score in multivariate analysis.[28] Although Chan et al. is not population-based, it is similar to our study in its inclusion of men treated with either radiation or RP and use of a self-reported measure of diabetes. However, unlike our study, Chan et al. modeled diabetes at baseline as the outcome of interest with Gleason score as a covariate in a multivariable model, and this could potentially explain the lack of association observed.[28] The model was designed to predict diabetes status and not Gleason score, and it is possible that in the presence of other covariates that are strong risk factors for diabetes, including BMI, age, and race, Gleason score no longer remains a significant predictor.

Only two studies examined racial differences in the diabetes-CaP aggressiveness association among men *diagnosed with CaP.*[21,23] Mitin et al. reported that diabetes was associated with a Gleason sum 8-10 in Blacks (OR: 1.84, 95% CI: 1.08, 3.13) and nonblacks (OR: 1.59, 95% CI: 1.33, 1.89) treated with radiation.[21] By contrast, Jayachandran et al. reported that diabetes was associated with high-grade disease (Gleason sum ≥ 7) in Whites (OR: 2.28, 95% CI: 1.33, 3.91), but not Blacks (OR: 1.45, 95% CI: 0.90, 2.23) treated with RP. [23] Our results did not show a positive association between diabetes and our composite measure of high aggressive CaP in either Whites or Blacks. Sensitivity analyses with Gleason sum ≥7 as our outcome were consistent with our CaP aggressiveness composite outcome, and we did not observe an association between diabetes and Gleason sum ≥7 in the overall cohort or either race-group. Results stratified by treatment type were consistent with our CaP aggressiveness composite outcome, and no significant association was observed between diabetes and Gleason sum ≥ 7 (data not shown). Some studies only reported association between diabetes and a higher Gleason sum cut-point (i.e. Gleason sum ≥ 8). Therefore we examined the association using this higher cut-point [21,24]. The higher cut-point did not impact our results, and no significant associations were observed in either race-group or in results stratified by treatment type (data not shown).

Among the two studies that looked at race differences, Mitin et al. included men treated with radiation between 1991 and 2010 and Jayachandran et al. included men treated with RP between 1988 and 2008. Our study, by contrast, included men diagnosed with CaP between 2004 and 2009. The FDA did not approve use of PSA as a screening test in asymptomatic men until 1994.[44] Thus Mitin et al. and Jayachandran et al. included men from the pre-PSA and PSA screening eras, while our cohort came from the PSA-screening era. Cohorts that include men from the pre-PSA screening era, who are likely to have more aggressive CaP at diagnosis, may be more likely to show a positive relationship between diabetes and CaP aggressiveness at diagnosis. As anticipated we observed a consistent, strong inverse association between a positive history of PSA or DRE screening prior to CaP diagnosis and high aggressiveness CaP at diagnosis in the overall cohort, Whites, and Blacks. Neither of the other two studies that examined race differences adjusted for screening history.[21,23]

Given the close relationship between diabetes and obesity, we investigated the role of obesity, independent of diabetes, on CaP aggressiveness. This analysis builds on a previous PCaP study that found obesity, *not* adjusted for diabetes, was associated with high aggressive CaP in Whites [Obese (OR: 2.00; 95% CI: 1.13, 3.54), Severely obese (OR: 2.09; 95% CI: 1.06, 4.14)] but not Blacks [Obese (OR: 1.38; 95% CI: 0.85, 2.23), Severely obese (OR: 1.71; 95% CI: 1.00, 2.90)].[105] Our results, which were consistent with previous PCaP reports, showed that obesity, independent of diabetes, was positively associated with our composite measure of high aggressive CaP in Whites, but not in Blacks. Obesity, independent of diabetes, was associated with Gleason sum ≥ 7 both in the whole cohort and Whites. The cohort-level association is likely driven by Whites, since no association was observed with obesity, independent of diabetes, and Gleason sum ≥ 7 in Blacks.

Two other studies have examined racial differences in the obesity-CaP aggressiveness association, and our results are consistent with those observed in an earlier

study utilizing the SEARCH database.[120] This study reported that moderate and severe obesity were significantly associated with pathologic Gleason sum ≥7 in Whites (OR: 2.35; 95% CI: 1.12, 4.91), but not Blacks (OR: 1.48; 95% CI: 0.71, 3.12).[120] Spangler et al., by contrast, reported that obesity was not associated with Gleason sum in Whites or Blacks.[124] This inconsistency may result from Spangler et al. having a patient cohort from a single, academic health system that may not be representative of the larger CaP population.[124]

Our results suggest the impact of obesity on CaP aggressiveness may vary across race, so we examined prevalence differences to further elucidate the role of race. ORs across races cannot be compared directly in our case-only cohort, because the prevalence of high aggressive CaP in the unexposed (i.e. those with a normal BMI) is not comparable. Blacks with a normal BMI were more likely to have high aggressive CaP (22%) than Whites with a normal BMI (12%) in our cohort. The prevalence of high aggressive CaP in obese Whites is 20%. This prevalence is lower than the prevalence of high aggressive CaP in Blacks with a *normal* BMI. Our findings suggest that obesity may increase the prevalence of high aggressive CaP only when the baseline prevalence of high aggressive CaP is relatively low, and this may explain why obesity did not increase the prevalence of high aggressive CaP in Blacks. Prevalence differences were consistent with the direction of association for ORs. We found that obesity, independent of diabetes, was associated with a 7% increase in the prevalence of high aggressive CaP in Whites and no significant difference was observed in Blacks.

A key strength of our study is that it is a *population-based* study of both Whites and Blacks diagnosed with CaP. PCaP is a large, well-characterized, cohort from the PSA screening era with detailed epidemiologic, interview, and clinical data, which allow for analytic adjustment for factors such as CaP screening history. To our knowledge, previous studies that examined racial differences in the association of diabetes and CaP aggressiveness at diagnosis were not population-based, encompassed both the pre-PSA

and PSA screening eras, did not adjust for CaP screening history, and were limited to patients receiving a single treatment modality. Thus our results may provide a more valid assessment of diabetes and CaP aggressiveness at diagnosis, and can be generalized to the broader population of both Blacks and Whites with CaP and diabetes, particularly in the southeastern U.S. In addition, our study included all treatments types received by the CaP population.

Our study used self-reported diabetes and therefore has some limitations. An Atherosclerosis Risk in Communities study (ARIC), reported that the sensitivity of prevalent self-reported diabetes ranges from 58.5% to 70.8% and the specificity ranges from 95.6% to 96.8% depending on the reference definition employed.[102] 21.6% of all research subjects reported having diabetes while 25.5% of research subjects 65 and older reported having diabetes in our cohort. This prevalence is similar to estimates by the Centers for Disease Control and Prevention (CDC), were 25.9% of individuals 65 and older in the US have diabetes.[125] However, it is likely that at least some men in our cohort have undiagnosed diabetes. The direction of the resulting bias is uncertain. It is possible that men with high aggressive CaP at diagnosis are more likely to have undiagnosed diabetes, as these men are the least likely to have a regular source of healthcare, resulting in a bias away from the null. Another potential limitation of our diabetes measure is that we do not know when research subjects were diagnosed and cannot evaluate the duration of diabetes exposure, or the severity of disease among diabetics, or how well diabetes was controlled. In addition, Black research subjects were more likely than White research subjects to be excluded from our analytic sample due to missing exposure, outcome, or covariate information. If excluded research subjects were more likely to have aggressive CaP, results in Blacks could be more biased than Whites.

The PCaP cohort allowed us the unique opportunity to make population-based estimates of the association between diabetes and CaP aggressiveness at diagnosis, and to specifically examine this association in a significant number of Black men.

4.5 Conclusion

Our results suggest that diabetes may not be associated with CaP aggressiveness at diagnosis in men with CaP. Our results further suggest that association of obesity with CaP aggressiveness in men diagnosed with CaP may by limited to Whites. Future studies with large numbers of both Whites and Blacks with detailed information on diabetes duration and management are needed to further elucidate any racial differences that may exist between in CaP aggressiveness.

Table 9. PCaP Research Subject Characteristics

	All research Subjects (n= 2049)	Whites (n=1058)	Blacks (n=991)
Age years (Mean, SD)	63.0 (7.9)	64.1 (7.9)	61.7 (7.8)
Screening History (n, %) [a]			
Yes	1838 (89.7)	996 (94.1)	842 (85.0)
No	211 (10.3)	62 (5.9)	149 (15.0)
Study Site			
North Carolina	973 (47.5)	504 (47.6)	469 (47.3)
Louisiana	1076 (52.5)	554 (52.4)	522 (52.7)
Education (n, %)			
Less than high school	399 (19.5)	100 (9.5)	299 (30.2)
High school graduate or some college	1032 (50.4)	497 (47.0)	535 (54.0)
College graduate or above	618 (30.2)	461 (43.6)	157 (15.8)
BMI (n, %) [b]			
Normal	374 (18.3)	172 (16.3)	202 (20.4)
Overweight	881 (43.0)	486 (45.9)	395 (39.9)
Obese	794 (38.8)	400 (37.8)	394 (39.8)
Treatment [c]			
RP	1012 (49.4)	551 (52.1)	461 (46.5)
Radiation	395 (19.3)	214 (20.2)	181 (18.3)
Neither	642 (31.3)	293 (27.7)	349 (35.2)
Diabetes (n, %) [d]			
Yes	443 (21.6)	177 (16.7)	266 (26.8)
No	1606 (78.4)	881 (83.3)	725 (73.2)
CaP Aggressiveness [e]			
Low	1045 (51.0)	586 (55.4)	459 (46.3)
Intermediate	638 (31.1)	310 (29.3)	328 (33.1)
High	366 (17.9)	162 (15.3)	204 (20.6)

[a] Screening history was based on self-report and defined as having at least one PSA or DRE prior to CaP diagnosis

[b] Research subjects were categorized as normal (BMI 18.5 to <25), overweight (BMI 25 to <30), or obese (BMI ≥ 30)

[c] Research subjects that had both RP and radiation were included in the RP group while the radiation group included research subjects who had either external beam radiation or brachytherapy

[d] Based on self-report

[e] High aggressive CaP was defined as Gleason sum ≥8, or PSA >20 ng/ml, or Gleason sum =7 and clinical stage cT3-cT4. Low aggressive CaP was defined as Gleason sum <7 and clinical stage cT1-cT2 and PSA <10 ng/ml. All other other cases were defined as intermediate aggressive CaP

Table 10. Prevalence Odds Ratios (OR) for High Aggressive CaP

	All Research Subjects (n=2049)			Whites (n=1058)			Blacks (n=991)		
	# of subjects	# with outcome	Adjusted OR [a]	# of subjects	# with outcome	Adjusted OR [b]	# of subjects	# with outcome	Adjusted OR [b]
Diabetes									
No	1606	276	Ref	881	130	Ref	725	146	Ref
Yes	443	90	1.04 (0.79,1.37)	177	32	1.00 (0.65, 1.57)	266	58	1.07 (0.75, 1.53)
BMI									
Normal	374	64	Ref	172	20	Ref	202	44	Ref
Over-weight-	881	140	1.03 (0.74, 1.44)	486	64	1.29 (0.75, 2.24)	395	76	0.93 (0.60, 1.42)
Obese	794	162	1.37 (0.99, 1.92)	400	78	1.98 (1.14, 3.43)	394	84	1.09 (0.71, 1.67)

[a] Model included diabetes, age in years, race, screening history, study site, education, and BMI
[b] Model included diabetes, age in years, screening history, study site, education, and BMI

CHAPTER 5: THE ASSOCIATION OF DIABETES AND OBESITY WITH PROSTATE CANCER PROGRESSION IN A WHITE AMERICAN AND BLACK AMERICAN COHORT: HCAP-NC

5.1 Introduction

Prostate cancer (CaP) is the most common cancer in men in the United States, and 14% of men will be diagnosed with CaP during their lifetime.[1] There will be an estimated 180,890 new cases of CaP and 26,120 CaP deaths in the U.S. during 2016.[34] CaP is a cancer that disproportionally affects Black Americans (Blacks) who are more likely to be diagnosed with and die from CaP.[1] In addition, 20-30% of men treated with radical prostatectomy and 30-50% of men treated with radiation will experience CaP recurrence within 10 years.[126]

Previous studies have suggested that both diabetes and obesity may be associated with CaP recurrence.[23,28,31,32,127] Insulin is a growth factor for CaP cells.[128,129] Diabetics, with potentially lower circulating levels of insulin, are hypothesized to have a low-growth environment, where there is “selection pressure” that allows only more aggressive CaP to survive.[23] Obesity, a strong risk factor for diabetes, is also potentially associated with both CaP aggressiveness at diagnosis and recurrence.[116,127] Specifically, obese men are more likely to have lower testosterone levels and hyperinsulinemia, both of which have been associated with CaP aggressiveness at diagnosis and recurrence [127,130-134]. Moreover, CaP may be harder to detect in obese men. Obese men can have lower Prostate Specific Antigen (PSA) levels, larger prostates, and less accurate Digital Rectal Exams (DRE).[127,135] Factors such as these can all contribute to the diagnosis of CaP at a later, more aggressive stage, which potentially increases the risk for subsequent CaP progression (recurrence or persistence).

We examined the association of diabetes and obesity with CaP progression in the Health Care Access and CaP Treatment in North Carolina (HCaP-NC) cohort, a follow-up study of North Carolina men participating in the North Carolina-Louisiana CaP Project (PCaP). Previous research on diabetes and obesity has been limited to clinically-based sample groups and only one study examined racial differences in the association between diabetes and CaP recurrence [23]. Moreover, the two studies that examine racial differences between obesity and CaP recurrence have reported inconsistent results [120,124]. HCaP-NC is a population-based cohort of men with incident CaP, followed for on average 5 years after diagnosis, over-sampled for Blacks, and included detailed clinical, epidemiologic and interview data, making it an ideal cohort to study the association of obesity and diabetes on CaP progression in both White Americans (Whites) and Blacks.

5.2 Methods

5.2.1 Study Population and Data Collection

PCaP has been described in detail previously [136]. Briefly, PCaP is a population-based cohort of men from North Carolina and Louisiana diagnosed with histologically confirmed first diagnosis of adenocarcinoma of the prostate between July 2004 and October 2007 by state tumor registries. Eligible men were 40-79 years old at CaP diagnosis, able to complete the study interview in English, did not live in an institution (i.e. nursing home), and were not cognitively impaired at the time of the interview. Moreover, eligible men had to self-identify as African American/Black or Caucasian/White in response to the open-ended question, “What is your race?”

Research participants were visited, in-home, by a Registered Nurse. The nurse administered a questionnaire, took biologic samples, and made anthropometric measures. The study questionnaire included questions on comorbidities such as diabetes, education level, and CaP screening history. Medical records abstraction included information regarding physical examinations and laboratory assays at or near diagnosis, clinical stage, Gleason

grade, PSA measures, and initial CaP treatment. Informed consent for the interview and specimen collection as well as release of tumor tissue and medical records was obtained during the in-home visit.

North Carolina PCaP participants were invited to participate in HCaP-NC, the follow-up study, in 2009. The follow-up cohort has been described previously [137]. Briefly, 822 research participants were enrolled in HCaP-NC, 366 Black and 456 White. Research participants completed questionnaires and provided permission for medical records release annually for 3 years. On average, research participants were 5 years post diagnosis at the completion of follow-up. Follow-up medical records (n=822) were received for 80% of baseline PCaP research subjects from North Carolina (n=1031). Follow-up medical record abstraction included post-treatment PSA values, and any secondary treatment received.

5.2.2 Analytic Sample

HCaP-NC included follow-up medical records for 822 research participants. Men were excluded if the CaP progression status could not be determined. The exclusions included: men who received no treatment or only watchful waiting (n=59), received ADT as the primary treatment (n=31), were men treated with radical prostatectomy with no PSA measure within 6 months of surgery (n=33), or had missing information essential to determine progression status including missing treatment date, missing PSA values, (n=24), or other clinical factors that hampered determination (n=3). ADT was considered the primary treatment type if the research participant received only ADT or ADT was given more than one year prior to radiation initiation (if ADT was received prior to radical prostatectomy, radical prostatectomy was considered the primary treatment type). Clinical factors for exclusion included CaP progression at time of diagnosis and included 2 men with PSAs >100 at diagnosis, and a man that received chemotherapy as initial CaP treatment. Ultimately, CaP progression was determined for 672 research participants. An additional 20 men were excluded for missing exposure or covariate information, and 5 for underweight

BMI. The final analytic cohort consisted of 647 research participants.

5.2.3 Outcome, Exposure, and Covariates

The primary outcome evaluated in this study is CaP progression, which we defined by PSA levels and treatment patterns in the follow-up period. Progression was defined as either prostate cancer persistence after unsuccessful first course of treatment or recurrence among men for whom initial treatment was successful. For each man, following up began on date of treatment start and follow-up ended at either date of progression for men with progression or date of last PSA measure available for men that were censored.

Research participants treated initially with radical prostatectomy were categorized as having a CaP progression event if the man had biochemical recurrence (BCR), persistent disease, or treatment failure. BCR was determined using the definition recommend by the American Urological Association (AUA) and was defined as a PSA ≥ 0.2 ng/ mL, confirmed with a 2nd PSA of ≥ 0.2 ng/ mL after achieving nadir.[66] Nadir was defined as an undetectable PSA (PSA <0.1). Men with BCR were recorded as having CaP progression at first PSA ≥ 0.2 ng/mL after nadir, given that there was a second confirmatory PSA.[66] Persistence was defined as not achieving nadir within 6 months after surgery. Men with persistence were recorded as having CaP progression at 90 days after surgery. We chose 90 days because men that are successfully treated with radical prostatectomy typically achieve nadir within 90 days. No man with BCR had a time-to-event of less than 90 days. Treatment failure was defined as post radical prostatectomy treatment for CaP (secondary treatment) after achieving nadir and included radiation, androgen deprivation therapy, or chemotherapy. Research participants were recorded as having a progression event at the date the secondary treatment was initiated. All other men were considered successfully treated and were censored at end of follow-up (i.e. date of last PSA measurement available). Adjuvant radiation and adjuvant ADT were not considered secondary treatment. Radiation or ADT

that was initiated ≤ 6 months after radical prostatectomy was considered adjuvant. All other men were considered successfully treated.

Research participants treated initially with radiation (either external beam radiation or brachytherapy) were categorized as having a CaP progression event if the man had BCR or treatment failure. Men treated with radiation do not typically achieve a post-treatment nadir PSA that is undetectable[138], and as such persistence cannot be defined in this group. BCR was determined using the Phoenix definition and was defined as Nadir + 2 ng/ mL.[67] Nadir was defined as the lowest PSA achieved after initiation of radiation. Men with BCR were recorded as having a CaP progression at the first PSA that was 2 ng/mL above nadir (Phoenix definition).[67] Treatment failure was defined as post-radiation treatment for CaP (secondary treatment) and included radiation, ADT, or chemotherapy. Research participants were recorded as having a CaP progression event on the date the secondary treatment was initiated. All other research subjects were considered successfully treated and were censored at the end of follow-up (i.e. date of last PSA measurement available). Adjuvant ADT, defined as ADT initiated ≤ 1 year after start of radiation, was not considered a secondary treatment.

Examples of men with the more common CaP progression outcomes and successful treatment can be seen in appendix figures B 1-B 9.

Our primary exposures of interest are diabetes and obesity. At baseline, men self-reported diabetes status during the in-home interview when asked the question, “Has a doctor or other health professional ever told you that you had diabetes or sugar diabetes?” Responses were recoded as “yes”, “no”, “refused”, or “don’t know”. Obesity was determined using body mass index (BMI) and calculated based on anthropometric measurements made by the study nurse at the time of the baseline PCaP in-home visit. Men were categorized as obese if BMI was ≥ 30 using the World Health Organization cut-point.[139] We analyzed obesity as dichotomous variable to maximize power.

Covariates were selected based on known confounders in the literature and to maintain consistency with prior PCaP studies and included self-reported race, age at diagnosis, and education. We also describe the prevalence of screening history and CaP aggressiveness in our cohort, but they were not included in our final model. Race was based on self-report, and all research participants were categorized as either White or Black. Age was calculated based on age at diagnosis and coded as a continuous variable. Education was also based on self-report at baseline and men were categorized as having a college degree or not. Screening history was based on self-report and defined having at least one PSA or DRE prior to CaP diagnosis. High CaP aggressiveness was defined both using Gleason sum alone (Gleason sum ≥ 8) and a composite measure of CaP aggressiveness that has been previously developed for PCaP.[101] High aggressive tumors were defined as Gleason sum ≥8, or PSA >20 ng/ml, or Gleason sum =8 and clinical stage cT3-cT4 in the composite measure.[101]

5.2.4 Statistical Analysis

Progression-free survival was compared in both diabetic and non-diabetic men and obese and non-obese men using Kaplan-Meier plots. Kaplan Meier plots were truncated at 6 years of follow-up (average follow-up was 5 years), because only 5 patients had more than six years of data. However, all men including those with greater than 6 years of follow-up (n=5) were retained in all analytical models.

The Cox Proportional Hazards model was used to assess the association of diabetes and obesity independent of diabetes with CaP progression in our primary analysis. Multivariable models were adjusted for race, age, and education. (We did not include CaP screening history in our model as greater than 94% of our cohort was screened). The proportional hazard assumption for each categorical covariate was assessed by examining the log(-log (Survival Probability)) plots. If the plots indicated a potential violation of the proportional hazards assumption, we examined whether the interaction between time and

the relevant covariate was statistically significant (p-value ≤ 0.05). For continuous variables, the proportional hazard assumption was assessed using Schoenfeld Residuals. To examine racial differences, models were stratified by race.

In a secondary model, we examined obesity without adjustment for diabetes using the approach described previously.

All analyses were conducted using SAS 9.4 (Cary, NC).

5.3 Results

5.3.1 Characteristics of HCaP-NC Cohort

The analytic cohort consisted of 647 research participants of whom 363 were Whites and 284 were Blacks. The prevalence of diabetes (17.9% analytic cohort vs. 20.2% HCaP-NC), obesity (38.2% vs. 37.8%), college education (41.3% vs. 37.8%), Gleason sum ≥8 (8.9% vs. 10.2%), and our composite measure of high aggressive CaP (12.8% vs. 15.0%) were similar in our analytic cohort as compared to the overall HCaP-NC cohort. However, excluded Black men were less likely to have a college education (8.6% included men vs. 23.6% excluded men) and more likely to have high aggressive CaP (34.2% vs. 14.4%) than Black men included in the analytic cohort. Excluded White men were more likely to diabetic (28.6% vs. 13.0%) and less likely to have a college education (38.7% vs. 55.1%) than White men included in the analytic cohort.

The CaP progression status of research participants can be seen in Table 11. In total, 20.9% of the cohort had a CaP progression. Across men treated initially with either radical prostatectomy or radiation, BCR occurred in 11.0% of men (n=71) and treatment failure occurred in 4.1% (n=26) of men. 5.9% (n=38) of men treated initially with radical prostatectomy had persistent progression. Blacks were more likely to have CaP progression (25.0%) as compared to Whites (17.6%).

Research participant characteristics by race and progression status can be seen in Table 12. Men who were successfully treated versus those who had CaP progression were

equally likely to have diabetes as those who had CaP progression (18.0% vs 17.8%, respectively). Blacks were more likely to be diabetic than Whites. Obesity was more frequent in research participants with CaP progression than those that were successfully treated. This difference was more pronounced in Whites (45.3% of Whites with CaP progression were obese compared to 30.1% of those with successful treatment) than Blacks (46.5% of Blacks with progression were obese compared to 44.6% of those with successful treatment). Whites were more likely to be college educated than Blacks regardless of whether they had CaP progression or treatment success. Greater than 94% of the cohort was screened regardless of whether the man had CaP progression. High aggressive CaP at diagnosis was more prevalent in men who experienced CaP progression (26.7%) than those with treatment success (9.2%). The prevalence of high aggressive CaP at diagnosis was similar in White men (28.1%) and Black men (25.4%) with CaP progression. The age at diagnosis was similar for those with CaP progression or treatment success.

5.3.2 Time to Progression

The mean progression-free survival time was 5.0 years calculated based on the Kaplan-Meier estimator of the progression-free survival probability. Kaplan-Meier plots for diabetes and obesity are presented in Figures 6 and 7, respectively. Kaplan-Meier survival estimates indicated no differences in progression-free survival for diabetics vs. non-diabetics (log rank test p-value =0.92). However, Kaplan-Meier estimates for obesity indicated that non-obese men had a better survival probability than obese men (log rank test p-value = 0.03). No violation of the proportional hazard assumption was found for our primary exposures or our model covariates.

Table 13 shows hazard ratios (HRs) and 95% confidence intervals for CaP progression in the analytic cohort. Race-stratified models are also presented. Diabetes was not associated with CaP progression in the overall cohort (HR: 0.86, 95%CI: 0.54, 1.35)

after adjustment for obesity, age at diagnosis, race, and college education. Race-stratified models similarly showed no association between diabetes and CaP progression in Whites (HR: 1.03, 95% CI: 0.50, 2.13) and a weakly decreased HR among Blacks (HR: 0.77, 95% CI: 0.43, 1.39). However, obesity independent of diabetes was positively associated with CaP progression in Whites (HR: 1.79, 95% CI: 1.08, 2.97), but not the cohort as a whole (HR: 1.40, 95%CI: 0.99, 1.99) or Blacks (HR: 1.15, 95% CI: 0.71, 1.86).

Because obesity independent of diabetes was significantly associated with CaP progression in Whites, in a secondary model we examined the impact of obesity without adjustment for diabetes. Results were consistent with our primary analysis. Obesity was associated with CaP progression in Whites (HR: 1.80, 95% CI: 1.09, 2.96), but not Blacks (HR: 1.10, 95% CI: 0.69, 1.76) or the overall cohort (HR: 1.37, 95% CI: 0.97, 1.93) in multivariable models.

5.4 Discussion

Self-reported diabetes was not associated with CaP progression among Whites or Blacks in this population-based cohort with incident CaP. Obesity was associated CaP progression in Whites only, unadjusted and adjusted for diabetic status.

Consistent with our study, most previous clinic-based studies have observed no *overall* association between diabetes and BCR.[23,28,30,95-97] However, there are some exceptions. Chan et al. observed a positive association between diabetes and BCR in the Cancer of the Prostate Strategic Urologic Research Endeavor (CAPSURE) only among the sub-group of patients that were in a low-risk D'Amico prognostic group.[28] In addition, Patel et al. also observed a positive association between diabetes and BCR (HR: 1.55, 95%CI: 1.03, 2.33) among patients treated with radical prostatectomy in the Columbia University Oncology Database.[31] This study matched men with diabetes with non-diabetic controls using their 5-year risk of recurrence according to the preoperative Kattan nomogram.[31] Both the D'Amico risk-group classification and the Kattan nomogram are designed to predict risk

of CaP recurrence, and could be thought of as proxies for the outcome, CaP progression.[60,61,140] Matching or stratification by these measures could partially explain why results from Chan et al. and Patel et al. are inconsistent with other findings.[28,31] It is possible that matching on the clinical risk of recurrence using the Kattan nomogram, such as that done by Patel et al, resulted in otherwise weak predictors of BCR (i.e. diabetes) having a positive association with BCR. One potential reason that Chan et al. may have observed an association only in the low-prognostic D'Amico risk group could be that low-risk men have a greater susceptibility to the effects of diabetes while men in the high D'Amico risk groups have a uniformly greater risk or recurrence regardless of exposure status.[28]

Research examining racial differences in the association between diabetes-CaP progression is limited. Only one previous study of radical prostatectomy patients (n=1262), has examined racial differences in the association of diabetes with BCR.[23] Jayachandran et al., reported diabetes was significantly associated with BCR only in *white, obese* men from the Shared Equal-Access Regional Cancer Hospital (SEARCH) database, consisting of men from Veterans Affairs Hospitals. No association was observed in black men regardless of obesity status.[23] The authors suggest that race and obesity may modify the association between diabetes and BCR.[23] However, when we restricted our analysis to obese men, we observed no association between diabetes and progression in obese men overall (HR: 0.74, 95%CI: 0.40, 1.34), White obese men (HRl 0,83, 95%CI; 0.32, 2.19), or Black obese men (HR: 0.67, 95% CI: 0.31, 1.45).

In contrast to diabetes, most prior studies have reported a positive association between obesity and BCR.[120-122,124,141,142] A 2011 meta-analysis reported that a 5kg/m^2 increase in BMI was significantly associated with BCR (RR: 1.21, 95% CI: 1,11, 1.31).[127] In our overall cohort, that had a similar number of Black and White men, we observed an elevated HR for CaP progression in obese men. The positive association between obesity and progression was statistically significant only in White men, both with and without

adjustment for diabetes. Two previous studies have examined racial differences in the obesity-BCR association. Jayachandran et al. reported that obesity was associated with BCR in both Blacks and Whites using the SEARCH database.[120] By contrast, a study at the University of Pennsylvania oncology clinics, Spangler et al. reported that obesity was significantly associated with BCR in Blacks but not European Americans although the HR was elevated.[124] Our identification of a statistically significant positive association in Whites is consistent with that observed in the SEARCH database. Unlike our study, both Jayachandran et al. and Spangler et al. were limited to patients that were treated with radical prostatectomy and had clinically-derived study populations.[120,124] Our study adds to the current evidence as we had a population-based, racially-diverse cohort of men that received either radical prostatectomy or radiation.

Another important factor to consider is model adjustment. Both Jayachandran et al. and Spangler et al adjusted for prostate tumor characteristics in their analytic models.[120,124] We chose not to adjust for prostate tumor characteristics in our primary models because tumor characteristics are a mediator between our primary exposures, diabetes and obesity, and CaP progression (i.e. obesity contributes to tumor aggressiveness at diagnosis which in turn promotes CaP progression). It is usually advisable that mediators not be part of the adjustment set.[143] However, to be comparable with prior literature in sensitivity analyses we adjusted for both Gleason sum ≥8 alone and our composite measure of high aggressive CaP.[101] Additional adjustment for Gleason sum ≥8 in our multivariable model did not impact results, and obesity remained positively associated with CaP progression in Whites both when we controlled for diabetes (HR: 1.69, 95%CI: 1.01, 2.81) and when we did not (HR: 1.70, 95%CI: 1.04, 2.82). No significant association was observed in Blacks or the cohort as a whole. When we adjusted for the composite measure of high aggressive CaP among Whites, the HR for obesity was of a similar magnitude to our primary model both when we did (HR: 1.62, 95% CI: 0.98, 2.69) and did not control for diabetes (HR: 1.33, 95%CI: 0.95,

1.86). No significant association was observed in Blacks or the cohort as a whole. Consistent with prior analyses, diabetes was not associated with CaP progression in the cohort as whole or in either race-group when we additionally adjusted for Gleason sum ≥8 or the composite measure of high aggressive CaP.

We also explored alternate BMI cut-points for obesity. Recent research has suggested that Blacks may be at risk for diabetes at lower BMIs than their White counterparts.[144] Because we did not observe an association between obesity and progression in Blacks, we examined obesity using a lower cut-point. Based on Chiu et al., we defined obesity in Blacks as a BMI of ≥26[144]. Our results were consistent with our prior analyses and no association was observed between obesity and CaP progression both when we did (HR: 1.24, 95% CI: 0.69, 2.21) and did not adjust for diabetes (HR: 1.18, 95% CI: 0.67, 2.09).

Our study was limited by the use of self-reported diabetes. The sensitivity of prevalent self-reported diabetes can range from 58.5% to 70.8% and the specificity can range from 95.6% to 96.8% depending on the reference definition employed.[102] However, our estimates of diabetes prevalence are consistent with recent estimates from the Behavioral Risk Factor Surveillance System (BRFSS).[145] According to BRFSS among individuals aged 65-74 in North Carolina the diabetes prevalence is 20.1% and 29.6% in Whites and Blacks respectively.[145] This is consistent with the diabetes prevalence in our cohort among both White men (18.3%) and Black men (31.3%) aged 65-74. However, it is likely that at least some men in our cohort have undiagnosed diabetes. The direction of the resulting bias is uncertain. It is possible that men with high aggressive CaP at diagnosis are more likely to have undiagnosed diabetes, as these men are the least likely to have a regular source of healthcare, resulting in a bias away from the null. Moreover, we do not know the duration of diabetes exposure, the severity of diabetes, or how well diabetes was controlled. However, when Jayachandran et al. adjusted for diabetes duration (<5 years or ≥

5 years), the association with BCR did not significantly change.[23] In the two studies that examined the association between HbA1C levels, a measure of diabetes severity, and recurrence results were inconsistent. [29,32] It is possible variations in diabetes management could have impacted our results.

A major strength of our analysis is that it is based on a large, well-characterized, population-based study of both White and Black men with incident CaP, followed for on average 5 years after diagnosis. This is the first study to define CaP progression in the HCaP-NC cohort, and to describe specific progression subtypes including persistence, BCR, and treatment failure. As such this population-based study adds to the limited and inconsistent clinic-based studies of obesity, diabetes and CaP progression among Blacks, and may be generalized to a broader population.

5.5 Conclusion

Our study found that diabetes was not associated with CaP progression in the cohort as a whole, Whites, or Blacks. Obesity independent of diabetes was associated with CaP progression in Whites, but not Blacks. Similarly, when we did not control for diabetes, obesity continued to be associated CaP progression only in Whites.

Table 11. HCaP-NC Cohort Progression Status by Primary Treatment Type and Race

	All (n=647)	Whites (n=363)	Blacks (n=284)
	n (% of All Research Participants)	n (% of All Whites)	n (% of All Blacks)
Radical Prostatectomy (n=469)			
Progression			
Biochemical Recurrence [a]	48 (7.4)	25 (6.9)	23 (8.1)
Persistence [b]	38 (5.9)	19 (5.2)	19 (6.7)
Treatment Failure [c]	25 (3.9)	9 (2.5)	16 (5.6)
No Progression	358 (55.3)	229 (63.1)	129 (45.4)
Radiation (n=178)			
Progression			
Biochemical Recurrence [d]	23 (3.6)	10 (2.8)	13 (4.6)
Treatment Failure [e]	1 (0.2)	1 (0.3)	0 (0.0)
No Progression	154 (23.8)	70 (19.2)	84 (29.8)
TOTAL PROGRESSION	135 (20.9)	64 (17.6)	71 (25.0)
TOTAL NO PROGRESSION	512 (79.1)	299 (82.4)	213 (75.0)

[a] Biochemical recurrence was defined using the American Urological Association (AUA) definition: a PSA ≥ 0.2 ng/ mL confirmed with a 2nd PSA of ≥ 0.2 ng/ mL after achieving nadir. Nadir was defined as an undetectable PSA (PSA <0.1).
[b] Research subject does not achieve nadir after radical prostatectomy. Nadir is defined as an undetectable PSA (PSA <0.1).
[c] CaP progression is defined by primary treatment failure. Subject received post radical prostatectomy treatment for CaP (secondary treatment).
[d] BCR was characterized using the Phoenix definition: Nadir + 2 ng/ mL. Nadir was defined as the lowest PSA achieved after initiation of radiation
[e] CaP Progression is defined by primary treatment failure. Subject received post radiation treatment for CaP (secondary treatment).

Table 12. Characteristics of HCaP-NC Research Participants

Characteristic	All		Whites		Blacks	
	Treatment Success (n=512)	CaP Progression (n=135)	Treatment Success (n=299)	CaP Progression (n=64)	Treatment Success (n=213)	CaP Progression (n=71)
	n (column%)	n (column %)	n (column%)	n (column%)	n (column%)	n (column%)
Diabetic						
No	420 (82.0)	111 (82.2)	261 (87.3)	55 (85.9)	159 (74.7)	56 (78.9)
Yes	92 (18.0)	24 (17.8)	38 (12.7)	9 (14.1)	54 (25.4)	15 (21.1)
Obese						
No	327 (63.9)	73 (54.1)	209 (69.9)	35 (54.7)	118 (55.4)	38 (53.5)
Yes	185 (36.1)	62 (45.9)	90 (30.1)	29 (45.3)	95 (44.6)	33 (46.5)
College Educated						
No	290 (55.6)	90 (66.7)	129 (43.1)	34 (53.1)	161 (75.6)	56 (78.9)
Yes	220 (43.4)	45 (33.3)	170 (56.9)	30 (46.9)	52 (24.4)	15 (21.1)
Race						
White	299 (58.4)	64 (47.4)	----	----	----	----
Black	213 (41.6)	71 (52.6)	----	----	----	----
Screening History [a]						
No	29 (5.7)	7 (5.2)	10 (3.3)	3 (4.7)	19 (8.9)	4 (5.6)
Yes	483 (94.3)	128 (94.8)	289 (96.7)	61 (95.3)	194 (91.1)	67 (94.4)
High Aggressive CaP at Diagnosis						
No	465 (90.8)	99 (73.3)	275 (92.0)	46 (71.9)	190 (89.2)	53 (74.7)
Yes [a]	47 (9.2)	36 (26.7)	24 (8.0)	18 (28.1)	23 (10.8)	18 (25.4)
Gleason Sum ≥ 8						
No	479 (93.6)	112 (83.0)	279 (93.3)	53 (82.8)	200 (93.9)	59 (83.1)
Yes	33 (6.5)	23 (17.0)	20 (6.7)	11 (17.2)	13 (6.1)	12 (16.9)
Age at Diagnosis [Mean (SD)]	62 (8)	61 (7)	63 (8)	63 (8)	60 (7)	59 (7)

[a] Screening history was based on self-report and defined having at least one PSA or DRE prior to CaP diagnosis

[b] Highly aggressive CaP was defined as Gleason sum ≥8, or PSA >20 ng/ml, or Gleason sum =8 and clinical stage cT3-cT4

Table 13. Adjusted Hazard Ratios (HRs) for CaP Progression

	All (n=647)				Whites (n=363)				Blacks (n=284)			
	No. events	Person-time (days)	Adjusted HR [a] (95% CI)	Adjusted HR [b] (95% CI)	No. events	Person-time (days)	Adjusted HR [c] (95% CI)	Adjusted HR [d] (95% CI)	No. events	Person-time (days)	Adjusted HR [c] (95% CI)	Adjusted HR [d] (95% CI)
Diabetic												
No	111	1784.1	Ref	----	55	1135.3	Ref	----	56	648.8	Ref	----
Yes	24	382.7	0.86 (0.54, 1.35)	----	9	154.2	1.03 (0.50, 2.13)	----	15	228.5	0.77 (0.43, 1.39)	----
Obese												
No	73	1365.5	Ref	Ref	35	885.9	Ref	Ref	38	479.6	Ref	Ref
Yes	62	801.3	1.40 (0.99, 1.99)	1.37 (0.97, 1.93)	29	403.6	**1.79 (1.08, 2.97)**	**1.80 (1.09, 2.96)**	33	397.7	1.15 (0.71, 1.86)	1.10 (0.69, 1.76)

[a] Model included diabetes, obesity, age at diagnosis, race, and college education
[b] Model included diabetes, age at diagnosis, race, and college education
[c] Model included diabetes, obesity, age at diagnosis, and college education
[d] Model included obesity, age at diagnosis, and college education

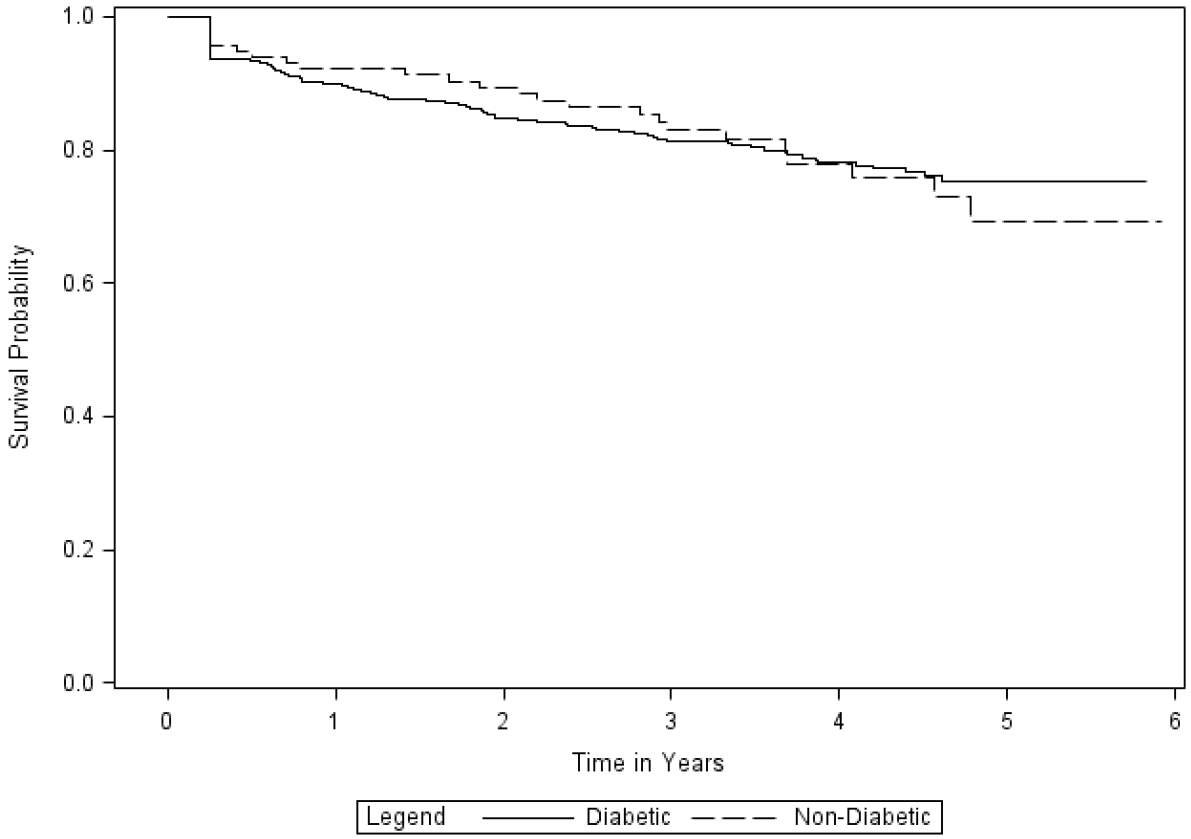


Figure 6. Kaplan-Meier Plot of Progression-Free Survival by Diabetes Status

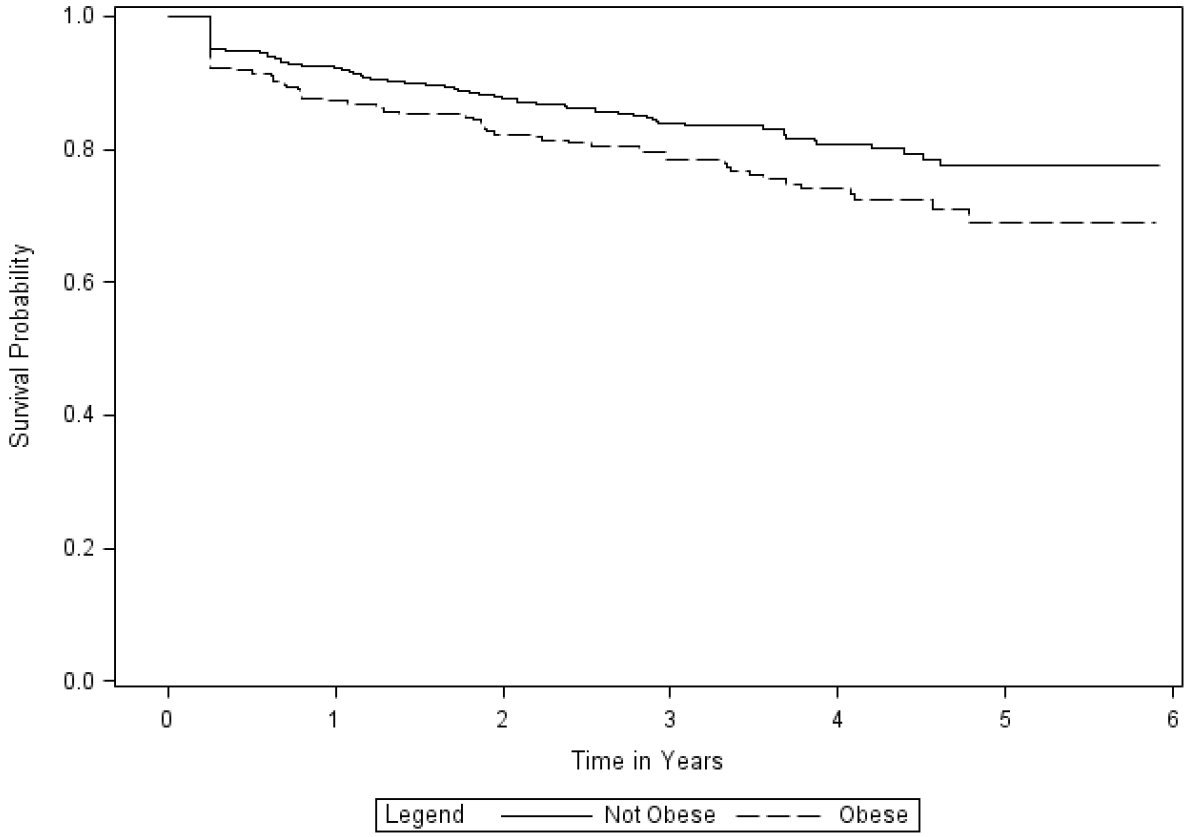


Figure 7. Kaplan-Meier Plot of Progression-Free Survival by Obesity Status

CHAPTER 6: CONCLUSIONS

6.1 Summary of Findings

The purpose of this dissertation was to utilize the North Carolina-Louisiana PCaP cohort, a large, well-characterized, population-based study of both White and Black research participants with incident CaP to investigate the association between diabetes and CaP aggressiveness. Additionally, we utilized the HCaP-NC cohort, the North Carolina PCaP sub-group followed for an average of 5 years after diagnosis, to explore the association between diabetes and CaP progression, defined as either persistence or recurrence of prostate cancer following definitive treatment. Moreover, because PCaP over-sampled black research participants we were able to investigate the role of race in both the diabetes-CaP aggressiveness and diabetes-CaP progression associations.

This study found that diabetes was not associated with high aggressive CaP at diagnosis in the cohort as a whole, Whites or Blacks. Similarly, in our follow-up cohort, we found that diabetes was not associated with CaP progression in the cohort as a whole, Whites, or Blacks. Although examining obesity was not part of our primary aims, there is a close relationship between obesity and diabetes, and obesity is one of the strongest known risk factors for diabetes.[116] As a result, our manuscripts (Chapter 4 and Chapter 5) also highlighted the association of obesity with CaP aggressiveness and progression. We found that obesity, independent of diabetes, was positively associated with high aggressive CaP in Whites, but not Blacks (Chapter 4). In Chapter 5, we similarly found that obesity, independent of diabetes, was positively associated with CaP progression in Whites, but not Blacks.

6.2 Strengths and Limitations

This was the first study to examine the association of diabetes with CaP aggressiveness and CaP progression using a racially diverse, *population-based* cohort of both Whites and Blacks. Previous studies that examined the diabetes-CaP aggressiveness and the diabetes-CaP progression associations were limited to clinic-based samples or single-treatment types. Our study included all treatment types typically seen in prostate cancer populations including radical prostatectomy and radiation. Aim 1 also included research subjects treated primarily with ADT or those that did not receive treatment. This is also the first study to classify the progression status of men from HCaP-NC, and specifically to classify men who progressed as recurrent or persistent.

The use of the PCaP population offered us several key advantages. Because PCaP enrolled Blacks and Whites at an equal rate using a randomized recruitment method, we had a large cohort of Black men, allowing us to examine race-specific associations. Moreover, detailed interview data allowed us to adjust for factors such as PSA and DRE screening history unlike other clinic-based studies. This is important given the strong inverse association between screening and CaP aggressiveness at diagnosis. Another unique feature of this study is that it is a population-based study with detailed *clinical* data, an average of 5-years of follow-up after diagnosis, including secondary treatment and post-treatment PSA monitoring values. This allowed us to determine progression in a *population-based* setting. As such our results our more generalizable and may improve validity over previous studies that did not include all treatments typically seen in prostate cancer patients, encompassed both the pre-PSA and PSA screening eras, and did not adjust for screening history.

Despite these strengths, our study did have some limitations. Our measure of diabetes is self-reported and thus likely failed to identify all men with diabetes. The direction of the resulting bias is uncertain. Men with undiagnosed diabetes are likely to be those with

limited access or interaction with the healthcare system. As such these men may be more likely to have a delayed CaP diagnosis, resulting in an increased risk for aggressive tumors at diagnosis and progression. This could bias our results away from the null. Even among men that reported having diabetes, we were not able to account for the severity or duration of diabetes. Throughout the disease-course, insulin-levels can fluctuate and treatment can change. Insulin promotes prostate cell growth[115], and men with higher insulin levels may be more likely to have more aggressive CaP and progression. We were unable to account for such changes over the disease-course.

Additional limitations include missing data for some PCaP participants. This includes the lack of detailed clinical follow-up data for Louisiana participants for whom progression status could not be determined, limiting our sample size and power. Moreover, in Aim 1 Black men were more likely to be excluded than White men due to missing exposure, outcome, or covariate data. Black men were also more likely to be excluded from HCaP-NC follow-up study than White men (Aim 2). These exclusions could have resulted in a selection bias. If excluded subjects were more likely to have high aggressive CaP or CaP progression then the results in Blacks could be more biased toward the null than the results in Whites.

6.3 Public Health Impact and Avenues for Further Research

Black men are more likely to be diagnosed with and die from prostate cancer.[1] However, in our study we found obesity, independent of diabetes, was associated with CaP aggressiveness and progression only in White men. Although our results would suggest that perhaps obesity, independent of diabetes, is a risk-factor for adverse outcomes only in White men, the potential for these risk-factors to impact Black men cannot be ruled out at this time.

Black men have a higher baseline prevalence of CaP aggressiveness and progression than their White counterparts even if they are non-diabetic or in the normal weight range. It is possible that we only observe an increase in the prevalence of CaP

aggressiveness and progression with exposure to factors such as diabetes and obesity when the baseline prevalence in relatively low. In Black men an effect may not be discernible given the high baseline prevalence. However, if this assumption is correct, it raises a broader question of why unexposed (i.e. non-diabetic or normal weight) Black men have higher baseline prevalence. There could be unknown, underlying genetic differences contributing to the increased prevalence of CaP aggressiveness and progression in Black men. Alternatively, external factors such as access to care may contribute to the increased baseline prevalence observed in Black men. It is probable that if there is an underlying biological process by which obesity or diabetes promotes CaP aggressiveness and progression in White men there is a similar biological process in Black men, although perhaps masked by stronger external factors. VanderWeele and Robinson recently suggested that the "effect of race" is rarely itself a causal effect, but usually an indication of other factors associated with race, namely socioeconomic disparities.[146] This could certainly be true in our study. Even though we accounted for SES by adjusting for education, there could be residual, unmeasured confounding by socioeconomic factors such as access to specialist care, distance to care, time from diagnosis to treatment, and access to follow-up care. If we could fully account for socioeconomic disparities throughout the life-course, it is possible that we would not observe racial differences in our outcomes.

Another factor to consider is that current PSA and BMI cut-points are not race-specific. A key factor for diagnostic biopsy referral is PSA levels, particularly during the time-period of our study when PSA screening was the standard of care. However, it has been recently suggested that Black men may have advanced CaP at lower PSA levels.[147] This could potentially lead to a delayed CaP diagnosis and an increased prevalence of high aggressive CaP at diagnosis. Moreover, Black men may also be at risk for diabetes at lower BMIs than White men.[144] If Black men are physiologically "obese", but not obese according to standard cut points, there could be exposure misclassification in our analysis. However, in

a sensitivity analysis we used race-specific BMI cut points for Black men, and our results were consistent with those obtained using standard cut-points. Nonetheless the racial differences we observed could partially be the artifact of less than ideal PSA and BMI cut points for racially diverse populations.

There are several areas for further research studies. Our study was the first study to evaluate diabetes and CaP aggressiveness and progression in a population-based cohort of Blacks and Whites. Future studies with large number of both Black men and White men can examine a more direct and comprehensive measure of diabetes. Both the duration of diabetes and time between diabetes diagnosis and CaP diagnosis could impact observed associations, and partially explain inconsistent results. A diagnosis of diabetes well before a CaP diagnosis may have a different effect from a diabetes diagnosis close to after a CaP diagnosis. In addition, diabetes management can vary greatly across patients and may differ significantly between clinic-based and population-based sample groups. Knowledge of a patient's diabetes medication could potentially impact observed associations given that metformin and insulin may have been differential effects on prostate cancer risk.[75,148]. An improved characterization of diabetes severity through measures of Hemoglobin A1c levels could also potentially improve validity. Two studies have examined hemoglobin A1c levels, either at the time of prostate cancer diagnosis or at time of radical prostatectomy, with risk of BCR.[29,32] However, this narrow time window may not fully capture the impact of diabetes on CaP aggressiveness and progression. Therefore, in addition to accounting for time between diabetes and prostate cancer diagnosis, diabetes duration and management, future studies could examine hemoglobin A1c levels as a time-varying covariate over an extended time range. This would better capture the changing glucose and insulin profile of diabetics over the disease-course.

In addition, because prostate cancer is often a slow progressing disease, analysis of cohorts with longer follow-up (e.g. 10 years) would provide valuable information about the

association of exposures such as diabetes and long-term prostate cancer outcomes. When we examined diabetes as a time-varying covariate in a sensitivity analysis (included an interaction term for time and diabetes), in PCaP with an average of 5 years of follow-up, there was an elevated hazard of progression at 3, 4, and 5 years with hazard ratios increasing at longer follow-up times in a dose-response fashion, although confidence intervals were wide.

Finally, this was the first study to determine the CaP progression status of research subjects from HCaP-NC. Although this document contains graphs of the 9 most common progression outcomes in Appendix B, graphs of PSA values over times including treatments received are available for all 822 HCaP-NC patients and can be utilized by researchers in the future to evaluate the association of a diverse array of factors with CaP progression. PCaP has information available on a large range of factors that could be examined in association with progression including, but not limited to food frequency, comorbidities, medications, and biomarkers.

In conclusion, this study found that diabetes was not associated with CaP aggressiveness at diagnosis or progression in Whites or Blacks. Obesity, independent of diabetes, was moderately associated with CaP aggressiveness and progression only in Whites. However, we cannot rule out an association in Blacks at this time. Obesity is associated with several adverse health outcomes, and our study suggests that CaP outcomes may also be adversely impacted by obesity. Men with prostate caner should be advised about the health benefits of maintaining an appropriate weight, and obese men should be monitored closely for CaP progression. Future studies with large numbers of both Whites and Blacks with detailed information on diabetes duration and management are needed to further elucidate any racial differences that may exist in the association of diabetes and obesity with CaP aggressiveness and progression.

APPENDIX A: AIM 1 SUPPLEMENTAL TABLES REFERENCED IN CHAPTER 4

Table A 1. Prevalence Odds Ratios (OR) for High Aggressive CaP by Treatment Type

RP [a]	All Research Subjects [c] (n=1012)	Whites [d] (n=551)	Blacks [d] (n=461)
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Diabetes			
No	Ref	Ref	Ref
Yes	0.96 (0.59, 1.59)	0.96 (0.42, 2.18)	1.00 (0.54, 1.88)
BMI			
Normal	Ref	Ref	Ref
Overweight	1.04 (0.60, 1.81)	0.85 (0.38, 1.91)	1.30 (0.61, 2.80)
Obese	1.50 (0.87, 2.61)	1.47 (0.66, 3.28)	1.56 (0.73, 3.39)

Radiation [b]	All Research Subjects [c] (n=395)	Whites [d] (n=181)	Blacks [d] (n=214)
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Diabetes			
No	Ref	Ref	Ref
Yes	1.24 (0.72, 2.12)	1.12 (0.46, 2.74)	1.29 (0.65, 2.55)
BMI			
Normal	Ref	Ref	Ref
Overweight	1.09 (0.51, 2.37)	1.21 (0.34, 4.29)	1.07 (0.40, 2.89)
Obese	1.58 (0.74, 3.39)	1.71 (0.48, 6.06)	1.57 (0.60, 4.09)

[a] Includes all research that received RP. Research subjects that received both RP and radiation were included in this group.
[b] Includes patients that received either external beam radiation or brachytherapy
[c] Model included diabetes, BMI, age, race, screening history, study site, education
[d] Model included diabetes, age, screening history, study site, education

Table A 2. Prevalence Differences (PD) for High Aggressive CaP

	All Research Subjects (n=2049)		Whites (n=1058)		Blacks (n=991)	
	Proportion with outcome (# with outcome/ # of subjects)	Adjusted PD [a]	Proportion with outcome (# with outcome/ # of subjects)	Adjusted PD [b]	Proportion with outcome (# with outcome/ # of subjects)	Adjusted PD [b]
Diabetes						
No	276/1606= 0.17	Ref	130/881= 0.15	Ref	146/725= 0.20	Ref
Yes	90/443= 0.20	0.00 (-0.04,0.04)	32/177= 0.18	0.00 (-0.07, 0.06)	58/266= 0.22	0.00 (-0.05, 0.06)
BMI						
Normal	64/374= 0.17	Ref	20/172= 0.12	Ref	44/202= 0.22	Ref
Over-weight	140/881= 0.16	-0.01 (-0.05, 0.03)	64/486= 0.13	0.01 (-0.05, 0.07)	76/395= 0.19	-0.02 (-0.00, 0.01)
Obese	162/794= 0.20	0.04 (0.00, 0.09)	78/400= 0.20	0.07 (0.01, 0.14)	84/394= 0.21	0.01 (-0.06, 0.08)

[a] Model Included diabetes, age in years, race, screening history, study site, education, and BMI
[b] Model included diabetes, age in years, screening history, study site, education, and BMI

APPENDIX B: AIM 2 SUPPLEMENTAL FIGURES REFERENCED IN CHAPTER 4

A research participant that was treated initially with radical prostatectomy and had treatment success. Follow-up begins on date of surgery; research subject is censored at date of last PSA measure available.

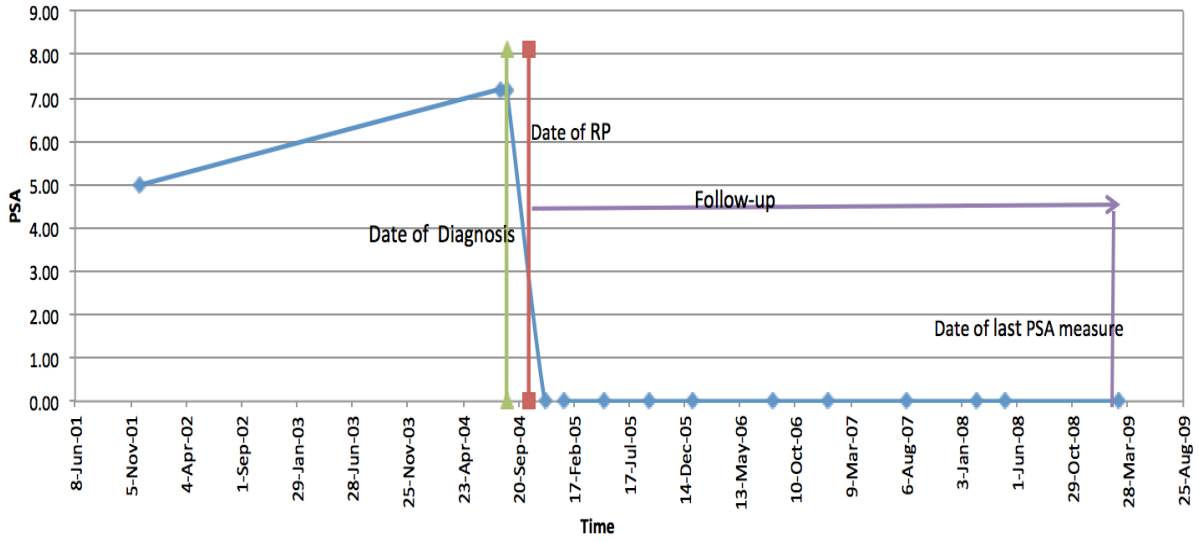


Figure B 1. Progression Outcome Example 1

A research participant that was treated initially with radical prostatectomy and had treatment success. Follow-up begins on date of surgery; research subject is censored at date of last PSA measure available

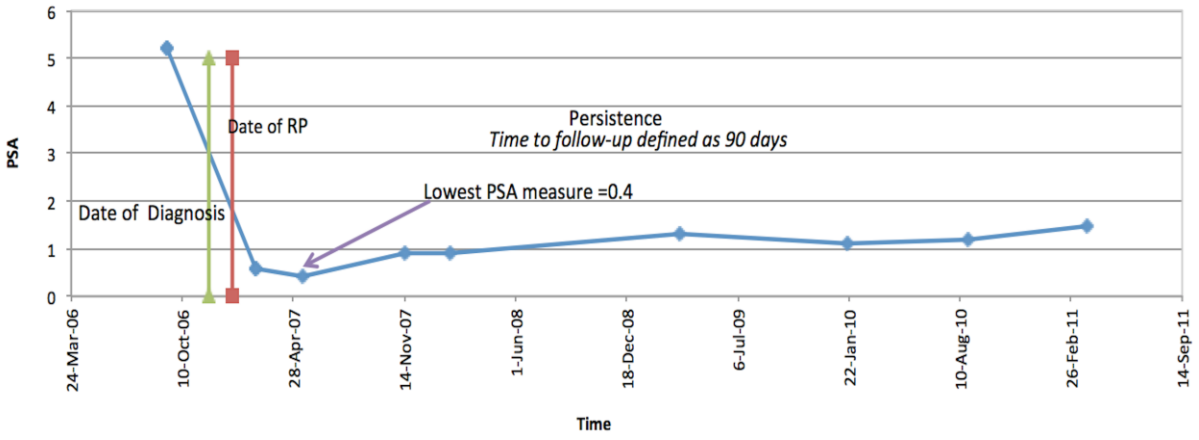


Figure B 2. Progression Outcome Example 2

A research subject treated initially with radical prostatectomy and had BCR using the American Urological Association (AUA) definition. Follow-up begins on date of surgery; CaP progression occurs on first PSA ≥ 0.2 after nadir, given there is a second confirmatory PSA ≥ 0.2.

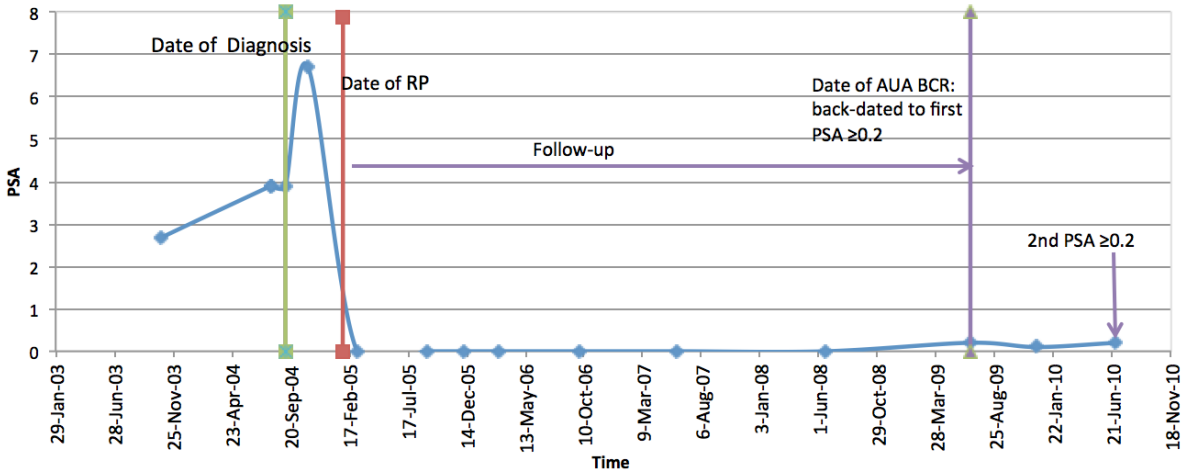


Figure B 3. Progression Outcome Example 3

A research participant that was treated initially with radical prostatectomy and had treatment failure. Radiation (secondary treatment) that was > 6 months after surgery was considered treatment failure. Follow-up begins on date of surgery; CaP progression occurs on date of radiation start (i.e. date of secondary treatment initiation).

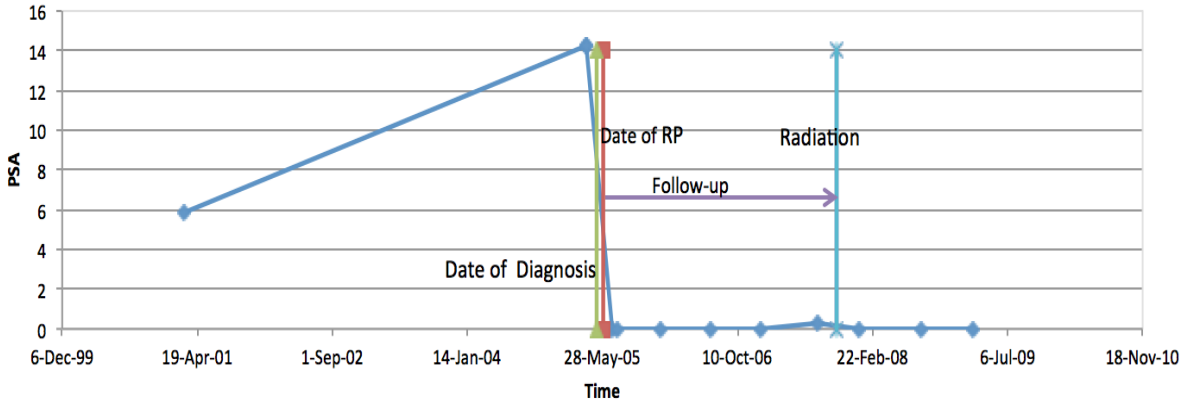


Figure B 4. Progression Outcome Example 4

A research participant that was treated initially with radical prostatectomy and had treatment success. Radiation (secondary treatment) that was ≤ 6 months after surgery was considered as adjuvant therapy and not treatment failure. Follow-up begins on date of surgery; research subject is censored at date of last PSA measure available

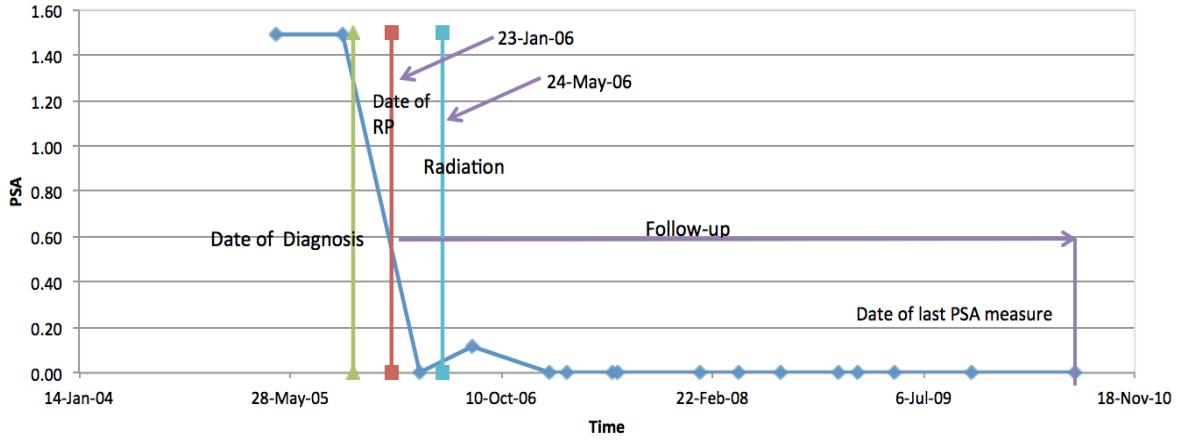


Figure B 5. Progression Outcome Example 5

A research participant that was treated initially with radiation and had treatment success. Follow-up begins on date of radiation start; research subject is censored at date of last PSA measure available.

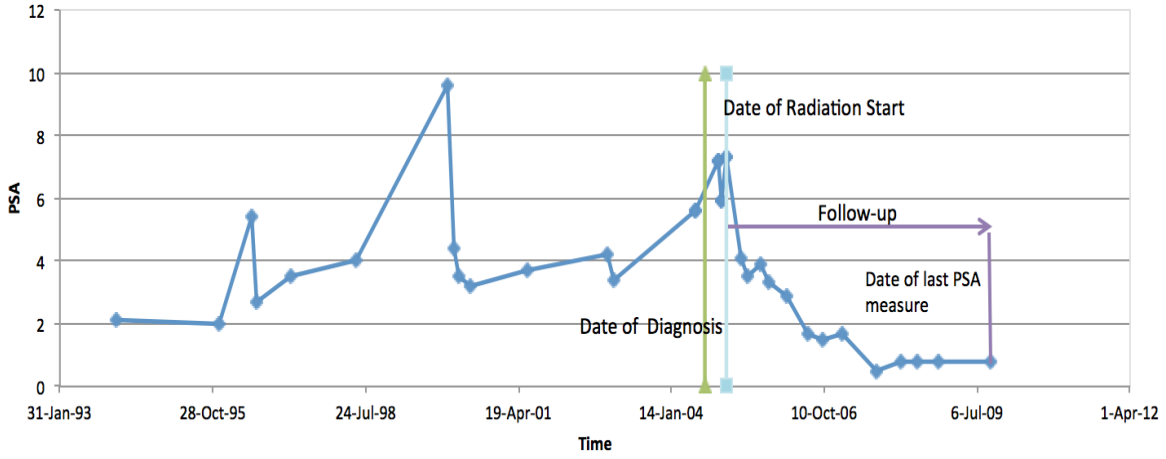


Figure B 6. Progression Outcome Example 6

A research participant that was treated initially with radiation and had BCR using the Phoenix definition. Nadir is defined as lowest PSA achieved after radiation initiation. Follow-up begins on date of radiation start; CaP progression occurs on date PSA level reaches nadir plus 2.

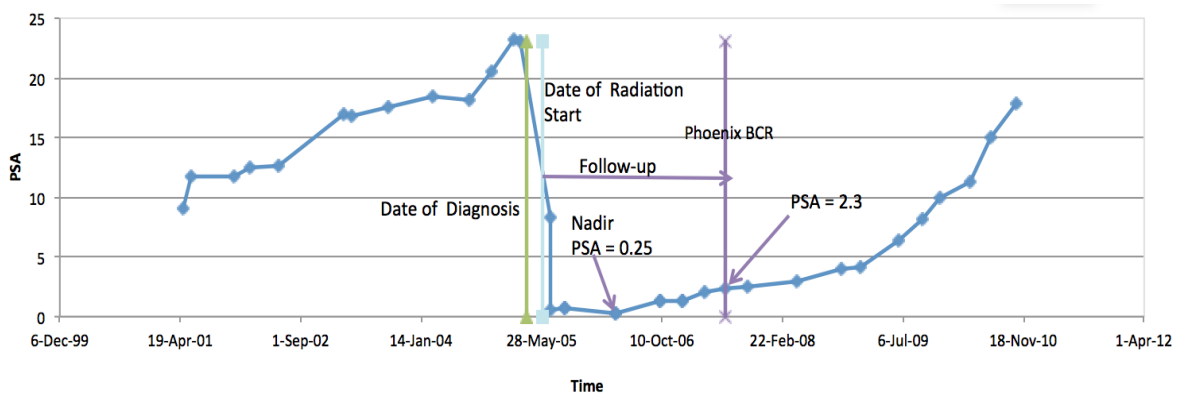


Figure B 7. Progression Outcome Example 7

A research participant that was treated initially with radiation and had treatment success. ADT (secondary treatment) that was ≤ 1 year after radiation was considered as adjuvant therapy and not treatment failure. Follow-up begins on date of surgery; research subject is censored at date of last PSA measure available.

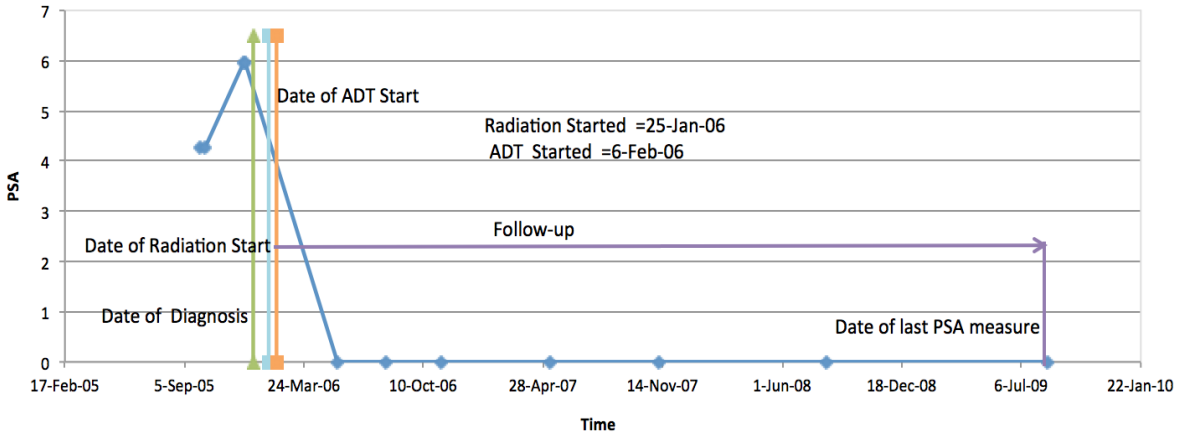


Figure B 8. Progression Outcome Example 8

A research participant that was treated initially with radiation and had treatment failure. ADT (secondary treatment) that was >1 year after radiation was considered treatment failure. Follow-up begins on date of surgery; CaP progression occurs on date of ADT start (i.e. date of secondary treatment initiation)

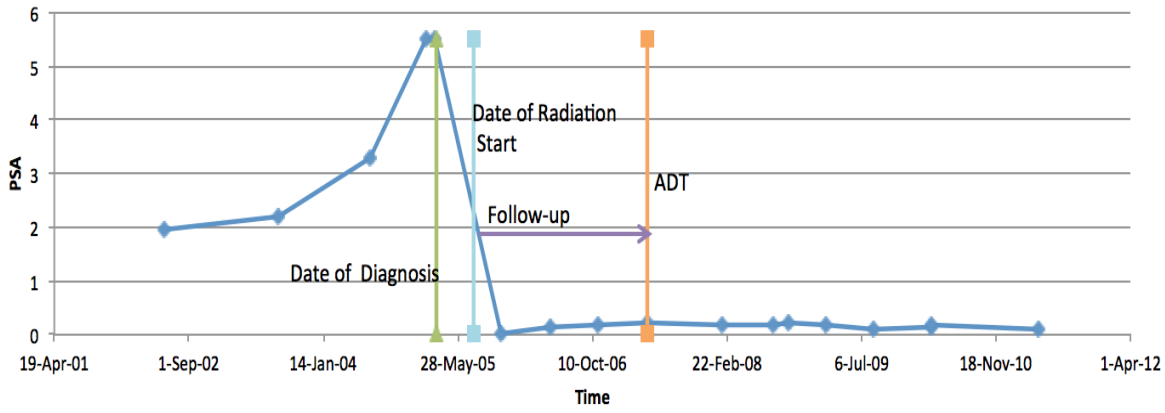


Figure B 9. Progression Outcome Example 9

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