ASSOCIATION BETWEEN SNPS IN THE VITAMIN D BINDING PROTEIN, VITAMIN D STATUS, AND AGGRESSIVE PROSTATE CANCER BY RACE

by

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ABSTRACT

Prostate cancer incidence and mortality have been decreasing in recent years, but it remains the most commonly diagnosed cancer among men. Racial disparities exist in prostate cancer with African Americans (AAs) having notably higher rates of incidence and mortality, lower survival rates, and are more likely to be diagnosed with a higher-grade cancer compared to European Americans (EAs). Genome-wide association studies have revealed several single nucleotide polymorphisms (SNPs) within the vitamin D-related *GC* gene that may be associated with prostate cancer aggressiveness. In addition to SNPs, previous research has suggested that low levels of 25-hydroxyvitamin D (25(OH)D) may be related to prostate cancer risk and aggressiveness, though studies are inconsistent. Low levels of 25(OH)D are more common among AAs than other racial/ethnic groups, thus vitamin D and related genes may play a role in prostate cancer racial disparities. The current study utilized data from the North Carolina-Louisiana Prostate Cancer Project (PCaP) to assess the relationship between 28 *GC* SNPs, the combined genotypes for *rs7041* and *rs4588*, and a polygenic risk score with low levels of 25(OH)D and aggressive prostate cancer in AAs (n=524) and EAs (n=657). None of the combined genotype categories were significantly associated with aggressive prostate cancer among AAs, and only one significantly decreased risk among EAs (Gc1s-1s, OR: 0.38, 95% CI: 0.17, 0.85). Significant associations with aggressive prostate cancer were observed in the additive and dominant genetic models, but not the recessive model. Two SNPs in AAs (*rs222054* and *rs16847028*) and one SNP in EAs (*rs6817912*) significantly decreased the risk of high aggressive prostate cancer. Four SNPs among AAs (*rs4588,*

rs2282679, rs3755967 and *rs17467825*) and eight SNPs among EAs (*rs4588, rs7041, rs222040, rs705119, rs705120, rs2282679, rs3755967* and *rs17467825*) significantly increased the risk of having low levels of 25(OH)D. A polygenic risk score of two SNPs (*rs4588-CC* and *rs222054-CC*) reflecting higher levels of 25(OH)D significantly decreased the risk of high aggressive prostate cancer among AAs. There was no evidence of interaction between the polygenic risk score and 25(OH)D on the association with aggressive prostate cancer. This study identified two SNPs *GCrs4588* and *GCrs222054* that appear to affect levels of vitamin D and prostate cancer aggressiveness among AAs. Future studies should further examine the relationship of these SNPs with prostate cancer and 25(OH)D in AAs.

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LIST OF ABBREVIATIONS

AA ..... African American

DRE ..... Digital Rectal Exam

EA ..... European American

GWAS ..... Genome-Wide Association Study

LD ..... Linkage Disequilibrium

PCa ..... Prostate Cancer

PCaP ..... North Carolina-Louisiana Prostate Cancer Project

PSA ..... Prostate Specific Antigen

SEER ..... Surveillance, Epidemiology, and End Results

SES ..... Socioeconomic Status

SNP ..... Single Nucleotide Polymorphism

VDBP ..... Vitamin D Binding Protein

25(OH)D ..... 25-hydroxyvitamin D

CHAPTER 1
INTRODUCTION

Prostate Cancer Background

Prostate cancer ranked third among the most common types of cancers among all Americans accounting for 9.5% of all new cancer cases and 4.8% of all cancer deaths in 2018.[1] In 2019, this continues to be true with prostate cancer among men responsible for 20% of all new cases (174,650 new cases) and 10% of all cancer deaths (31,620 deaths).[2] A 7% reduction in incidence occurred annually among men during 2011 through 2015; this is believed to be a result of the recommendation given by the United States (US) Preventive Services Task Force against prostate-specific antigen (PSA) blood testing for all men in 2008.[2] This recommendation was revised in 2017, encouraging testing for men between the ages of 50 and 69.[2] According to the Surveillance, Epidemiology, and End Results (SEER) data from 2013-2015, the lifetime probability of developing invasive prostate cancer was 11.2% (1 in 9) with a 98% 5-year survival, and prostate cancer accounts for an estimated 10% of cancer deaths.[1,2] Although incidence and mortality has decreased over the years, prostate cancer remains as the most commonly diagnosed cancer among males accounting for 1 in every 5 new diagnoses and the second leading cause of cancer deaths in both 2018 and 2019.[2,3]

Racial Disparities

Incidence, Mortality, and Survival

Although incidence and mortality rates for prostate cancer have been steadily decreasing, the rates among African Americans (AA) are notably higher than those

among European Americans (EA). Based on cases from 2011-2015, incidence rates are higher for AAs (178.3 per 100,000 men) versus EAs (105.7 per 100,000 men) per year, making the risk of developing prostate cancer among AAs 1.68 times higher than the risk among EAs, after adjusting for age.[1] The conclusion is similar for mortality, the risk of dying from prostate cancer among AAs (39.9 per 100,000 men) is 2.19 times the risk among EAs (18.2 per 100,000), after adjusting for age.[1] Survival rates are far worse among AA compared to EA, which is believed to be related to tumor stage at diagnosis. In a follow-up analysis done by Jones et al., survival rates were significantly lower among AA compared to EAs (hazard ratio, 1.53; 95% CI, 1.13-2.08) after adjusting for age at diagnosis. High stage and tumor grade explained some of these disparities such that when adjusted for, survival slightly improved for AA compared to EAs (hazards ratio, 1.26; 95% CI, 0.92-1.73).[4]

Stage and Grade at Diagnosis and Progression

The Gleason grading system is an important tool in determining the prognosis and treatment in prostate cancer. In 2004, the use of the Gleason grading system in the categorization of prostate cancer was endorsed by the World Health Organization (WHO).[5] The grading scale ranges from 1-5, with numbers being assigned to the two regions that make up most of the tumor. The summation of these two numbers creates the number known as the Gleason sum; the first number represents the grade that makes up the larger portion of the tumor. The grade number is dependent on how the appearance of cells in cancerous tissue compares to cells in normal prostate cancer tissue. A score of 1 is considered to describe cells that are roughly uniform and similar in appearance to normal cells, while a score of 5 represents complete abnormal growth of cells within the tissue.[5,6] According to the 2005 International Society of Urological Pathology (ISUP)

consensus, a Gleason sum = 2 (1+1) is considered to describe adenosis of the prostate gland and therefore should no longer be diagnosed, and sums of 3 and 4 should be rare.[5] The lowest Gleason sum is commonly 6 and categorized as a low-grade tumor, while a Gleason sum between 8-10 is categorized as a high-grade tumor.[6]

Based on the data from SEER 18 2008-2014, 90% of cases were diagnosed at early stages, localized (78%) and regional (12%), while 5% and 4% were diagnosed at a late stage (distant) and unknown (un-staged), respectively.[1] The 5-year survival rates were 100%, 30% and 80% for early (localized and regional), late (distant) and unknown stages, respectively.[1,2] Thus, although incidence is higher for low grade/early stage compared to high grade/late stage, the survival rate is much lower for those with high grade/early stage prostate cancer.

Disparities exist between AA and EA in tumor stage, grade, and progression. According to SEER data for 2008-2014, higher proportions of localized and distant stages in prostate cancer were more likely to be found among AAs versus EAs.[2] In a study by Freeman et al., AA tended to present with more advanced/distant stages (30%) and histological grade (33%) compared to EA (12% and 19%).[7] In another study, the odds of a non-localized diagnosis were significantly greater among AAs compared to EAs (unadjusted OR = 2.02; 95% CI, 1.21-3.38) with 60% and 43% of non-localized prostate cancer diagnosis among AA and EAs in the study population, respectively.[4] Progression and transformation from latent to aggressive prostate cancer occurred more rapidly among AAs compared to EAs, with advanced or metastatic stages occurring at a ratio of 4:1 according to the Detroit SEER.[8]

Risk Factors

Age, race, and family history are the three definitive risk factors for prostate cancer. Several other potential risk factors may explain the racial disparities found in the diagnosis, treatment, and survival of prostate cancer between AAs and EAs.

As discussed previously, AA are more likely to be diagnosed with more aggressive forms of prostate cancer. Healthcare access, insurance, socioeconomic status (SES), and screening procedures such as digital rectal exams (DRE) and prostate specific antigen (PSA) testing are variables of interest in explaining the disparities found in aggressiveness of disease at diagnosis between AA and EA. In a study assessing race-stage associations between AA and EAs, understanding one's insurance coverage, SES factors, and medical care factors reduced the odds of a higher stage at diagnosis for AA compared to EA (race-stage OR) by 22%, 20%, and 11% respectively. Screening history and clinical factors reduced the odds by 11.2% and 12.8%, respectively. The race-stage odds ratio (OR=1.83; 95% CI:1.06-3.15) reduced by 74% in the final multivariable model (OR=1.21; 95 % CI:0.64-2.30) that included DRE, histological grade, education, and understanding one's insurance coverage.[4]

Racial disparities exist in treatments received which in turn have an effect on survival and mortality in prostate cancer. In a study by Mahal et al., a significant association was found between race and insurance status in receiving definitive treatment among men with high-risk prostate cancer. AA were not only more likely to be uninsured but also had the highest rate (27%) of not receiving definitive treatment among men with high-risk prostate cancer. The odds of receiving definitive treatment for insured men compared to uninsured men was greater among AA (AOR = 2.23; 95% CI: 1.72–2.88) versus EA (AOR = 1.47; 95% CI: 1.15–1.89), after adjusting for sociodemographic and

cancer-specific factors.[9] Healthcare access-related factors seemingly play an essential role in not only treatment but also in survival. In a study by Krimphove at el., survival among AA men was significantly worse compared to EA men (HR = 1.27; 95% CI: 1.20–1.34). After access to care was taken into consideration, there was no longer a significant difference in survival between the races (HR = 1.04; 95% CI: 0.97–1.12). When access to care and tumor characteristic were the same for both races, AA men were slightly more likely to survive compared to EA men (HR = 0.93; 95% CI: 0.86–1.01). It is estimated that access to care and tumor-related factors accounted for 84% and 4%, respectively, of the excess risk of death due to prostate cancer among AA men.[10]

Genetics

Genome-wide association studies (GWAS) have revealed several genetic variants which are believed to be associated with prostate cancer, but GWAS is limited in its ability to be generalizable to populations that are not of European or Asian descent. The US is only responsible for 19% of GWAS publications, with AA making up a small percentage of the study populations (3%) compared to EAs (79%).[11] Differences found in prostate cancer pathogenesis and progression influenced both diagnosis and treatment distinctly among AAs compared to EAs.[12] These differences have been examined in replications studies on an AA study population using known genetic risk variants from GWAS. These variants not only contributed to risk but also better captured the pattern of risk of prostate cancer in AAs.[13,14] The underrepresentation of AAs in genetic studies and some differences in the distribution of genetic polymorphisms between populations of different ancestry may explain some of the disparities seen among AAs with prostate cancer.

Vitamin D

Research has suggested that vitamin D status may be related to prostate cancer risk and aggressiveness. Determination of vitamin D status occurs through the measurement of circulating plasma levels of 25-hydroxyvitamin D (25(OH)D). Levels of 25(OH)D have been shown to differ by race, with higher frequency of vitamin D insufficiency or deficiency among AAs compared to other racial/ethnic groups. Deficiency can be a result of many factors such as low dietary intake and decreased endogenous synthesis with ultraviolet exposure. Individuals with darker skin pigmentation tend to have lower levels of vitamin D due to blocking of vitamin D synthesis by melanin. In a study by Egal et al., mean levels of 25(OH)D were lower in AAs than EAs with 28% of the total study population defined as hypovitaminosis D. A larger proportion of AAs (45%) than EAs (11%) had hypovitaminosis D.[15] It has been hypothesized that the racial disparity in vitamin D status may be contributing to the disparity of prostate cancer observed in AA. In a study by Shui et al., a significant inverse association was present between plasma 25(OH)D levels and lethal prostate cancer (OR = 0.43; 95% CI: 0.24-0.76).[16] Among men with cancer, the odds of having a higher clinical stage increased with lower levels of 25(OH)D (OR: 4.22; 95% CI: 1.52 – 11.74).[17] When comparing clinical stages, the odds of a prostate cancer diagnosis on biopsy increased with low levels of 25(OH)D in AA (OR = 2.43; 95% CI: 1.20 - 4.94).[17] In contrast, AA men with high aggressive prostate cancer actually had higher concentrations of 25(OH)D compared to AA men with low aggressive disease in the North Carolina-Louisiana Prostate Cancer Project (PCaP).[18] Thus, the relationship between 25(OH)D and prostate cancer disparities is complex and may be mediated by genetic susceptibility factors.

Proposal and Specific Aims

The purpose of this study was to examine the association between single nucleotide polymorphisms (SNPs) in a vitamin D-related gene and aggressive prostate cancer among AAs and EAs in a large population-based case-only study. Data on SNPs and prostate cancer aggressiveness were obtained from PCaP. High aggressive prostate cancer was classified based on clinical stage, PSA and Gleason score. My specific aims are as follows:

1) To describe the mean and standard deviation of 25(OH)D by combined genotypes of the vitamin D binding protein gene (*GC*) for the commonly studied *rs7041* and *rs4588* SNPs in AA and EA men diagnosed with prostate cancer;

2) To assess the relationship between the combined genotypes, 28 *GC* SNPs with both 25(OH)D and aggressive prostate cancer by race, and

3) To create a polygenic risk score in order to examine its association with both 25(OH)D and aggressive prostate cancer and its interaction with 25(OH)D by race.

Significance of Research

Prostate cancer continues to be the most commonly diagnosed cancer and second leading cause of cancer death among men in the US with AAs having the highest rate of incidence.[2,3] Although survival rates are highest for prostate cancer (98%) compared to other types of cancer, survival rates have been shown to be worse among AAs.[2,10] AAs are experiencing the highest mortality rates compared to all races combined (39.8 vs 19.2 per 100,000, respectively) and rates are more than doubled when comparing AAs to EAs (39.8 vs 18.1 per 100,000).[2] According to the Detroit SEER, advanced and metastatic stages occurred at a ratio of 4:1 and tumor progression and transformation occurred more

rapidly when comparing AAs to EAs.[8] Several studies have inferred that prostate cancer risk can be influenced by both vitamin D levels and *GC* SNPs rs7041 and rs4588.[19,20] This becomes problematic for the male AA population, who were more likely to possess alleles associated with decreasing levels of vitamin D and to be categorized as hypovitaminosis D compared to the male EA population.[15,21]

The lack of AAs in GWAS study populations (3%) speaks to the need for more research studies to be conducted within this population.[11] This study is focusing on the genetic determinants of aggressive prostate cancer among AA males. Results from this study can contribute to the current literature on the association between aggressive prostate cancer and the interaction of *GC* SNPs rs7041 and rs4588, and 25(OH)D levels for future use towards prevention interventions and personalized treatments.

CHAPTER 2
BACKGROUND & LITERATURE REVIEW

Vitamin D Pathway

Studies have suggested that vitamin D can potentially play an important role in reducing the risk of cancer and improving prognosis. However, a recent randomized controlled trial found no evidence for cancer prevention among older individuals randomized to receive 2000 IU vitamin D per day during a median follow-up of 5.3 years.[22] Effects of vitamin D supplementation are likely to be dependent on baseline vitamin D status, as well as genetic variation in genes involved in vitamin D metabolism, which is a major focus of the proposed study.

Synthesis of vitamin D occurs in multiple steps, beginning in the skin through ultraviolet exposure from the sun or absorption from diet and supplements. This process converts vitamin D into vitamin D_3, which binds to the vitamin D-binding protein (DBP) and travels to the liver.[23,24] In the liver, D_3 is converted into 25-hydroxyvitamin D, $25(OH)D_3$ (referred to as 25(OH)D) via 25-hydroxylase enzymes. The two protein-coding genes responsible for 25-hydroxylation are *CYP2R1* and *CYP27A1*. 25(OH)D is the main circulating form and most commonly used vitamin D metabolite to measure vitamin D status.[23,25] 25(OH)D binds to DBP and transports to the kidney where it hydrolyzes into 1,25-dihydroxyvitamin D, $1,25(OH)_2D_3$ (referred to as $1,25(OH)_2D$ or calcitriol), by 1α-hydroxylases; *CYP27B1* is the gene responsible for 1α-hydroxylation.[25] As described in Chapter 1, AAs have lower circulating concentrations of 25(OH)D compared to EAs,

however, most studies have found $1,25(OH)_2D$ concentrations to be similar between AAs and EAs, likely due to homeostatic regulation.

DBP binds to both forms of vitamin D metabolites and circulates them to target tissues. Usually bound, 25(OH)D is transported back to the liver or circulated through the blood, while bound $1,25(OH)_2D$ is transported to target sites such the kidney, intestine and bone.[25] $1,25(OH)_2D$ is the hormonal metabolite of vitamin D and binds to the nuclear vitamin D receptor (VDR) in target cells where it regulates the expression of about 200-300 genes.[24,25] $1,25(OH)_2D$ is self-regulated and degraded by the 24-hydroxylase enzyme and corresponding *CYP24A1* gene.[24] Thus, there are at least six possible genes involved in the overall vitamin D pathway which have been examined in epidemiologic studies: 25-hydroxylase (*CYP2R1* and *CYP27A1* genes), 1α-hydroxylase (*CYP27B1* gene), 24-hydroxylase (*CYP24A1* gene), VDR (*VDR* gene), and DBP (*GC* gene). Studies show that SNPs within some of these genes may affect circulating vitamin D levels and contribute to the risk of prostate cancer.

Vitamin D Related Genes

Prostate Cancer

The most studied vitamin D gene is *VDR* which has multiple common SNPs that have been investigated in relation to cancer risk. For three *VDR* SNPs, prostate cancer risk increased (*FokI- rs2228570*) and even doubled (*rs2107301* and *rs2238135*) among men who possessed the rare allele compared to those who possessed the common allele, with the highest risk among men who were homozygous for the rare allele.[26,27] Among men with prostate cancer, *VDR* SNPs were associated with increased risk for tumor progression (*rs6823* and *rs2071358*) and risk of death (*rs3782905, rs7299460,* and *rs1168314*).[28] Haplotypes of *VDR* associated with prostate cancer showed risk increasing

as the number of risk alleles increased.[29] Other haplotypes demonstrated a significant association with both aggressive (p=0.02) and lethal prostate cancer (p= 0.01).[16,30] Some studies have shown that haplotype frequencies may be significantly different among AAs with prostate cancer compared to AAs without cancer (p = 0.059).[26] In addition to the risk of prostate cancer, *VDR* SNPs were also associated with high PSA levels ($p<0.05$) and Gleason scores ($p<0.05$).[29]

Other vitamin D pathway genes and haplotypes possibly associated with prostate cancer include *CYP2R1, CYP27A1, CYP27B1, CYP24A1,* and *GC.* SNPs in *CYP24A1, CYP27B1*, and *VDR* showed a significant increase in the risk of tumor progression (*VDR*: *rs6823* and *rs2071358*, *CYP24A1*: *rs927650* and *rs2762939*) and death (*VDR*: *rs3782905*, *rs7299460*, and *rs11168314*, *CYP27B1*: *rs3782130* and *CYP24A1*: *rs3787557, rs4809960, rs2296241, rs2585428,* and *rs6022999*) among men diagnosed with prostate cancer.[28] Pathway analysis showed a significant association between lethal prostate cancer and a set of SNPs (p = .008) that included the following genes: *CYP27A1, CYP2R1, CYP27B1, GC, CYP24A1, RXRA*, and *VDR*, but when genes were examined individually, only individual sets of *CYP27A1* were associated with lethal prostate cancer (p = .02).[16]

Although some studies exist showing strong evidence of associations between vitamin D-related gene SNPs and prostate cancer, not all studies are supportive.[31,32] Small sample sizes along with low frequency of SNPs may have reduced power to observe any moderate effects of SNPs on disease risk in some of these studies.

GC Gene

SNPs (rs7041and rs4588)

The *GC* gene may be particularly important in determining vitamin D metabolite concentrations given that it encodes the DBP which is responsible for vitamin D transport. A few studies have examined the relationship and interactions between *GC* SNPs (rs7041 and 4588), prostate cancer, 25(OH)D levels and DBP levels (Table 2.1). Significant associations were observed between *GC* SNPs (*rs7041-T* and *rs4588-A*) related to low levels of 25(OH)D and increased prostate cancer risk *(rs4588*: OR 1.20, 95% CI 1.01-1.41 ; *rs7041*: OR 1.19, 95 % CI 1.02-1.38).[19,20] When examining the genotypes within *rs7041* and *rs4588*, lower levels of 25(OH)D were associated with the 'AA' genotype in *rs7041*, 'TT' genotype in *rs4588* and 'AT/AT + AG/AT' haplotypes.[33] Genotypic variations of these two SNPs have been linked to differences in 25(OH)D levels between AAs and EAs. Both SNPs were found to have significant associations with 25(OH)D among AAs ($p < 0.01$).[34] In a study by Powe et al., AAs are more likely to have the "T" allele at *rs7041* ($p<0.001$), which is also the allele associated with decreasing levels of 25(OH)D in AAs. In the same study, SNPs (*rs7041* and *rs4588*) and race explained 9.9% and 7.3%, respectively, of the variation present in 25(OH)D levels.[21] Other studies have combined these two SNPs to create combined genotypes and found that certain genotypes were significantly associated with colorectal cancer in males or lung cancer.[35]

Vitamin D Binding Protein Levels

Different *GC* genotypes are associated with levels of DBP. 25(OH)D binds to DBP to be transported to target cells to freely circulate or for conversion into the hormonal form of vitamin D. According to the 'free hormone hypothesis,' biological

activity is dependent on the unbound form of vitamin D metabolites, also known as 'free' or 'bioavailable' 25(OH)D, versus its protein-bound form.[36] For this reason, studies have examined possible associations and interactions occurring between DBP levels, levels of circulating 25(OH)D, *GC* SNPs and prostate cancer risk. In a study by Powe et al., differences in DBP levels were observed between AAs and EAs, with lower mean levels in AAs.[21] The 'T' allele in *rs7041* and the 'A' allele in *rs4588* were associated with decreasing levels of DBP in both races. AAs were more likely to have the 'T' allele in *rs7041* ($p< 0.001$) and least likely to have the 'A' allele in *rs4588* ($p<0.001$).[21]

Research has suggested that risk of cancer decreases in the presence of high levels of DBP, but some studies have proposed the association was a result of the interaction occurring between DBP and 25(OH)D.[37–39] Among men with high levels of DBP, low levels of 25(OH)D were associated with decreased risk for overall prostate cancer but increased risk of advanced prostate cancer.[40,41]

Vitamin D Levels and Genetic Interactions

Some vitamin D-related genes and SNPs are associated with different corresponding levels of 25(OH)D, while other gene SNPs appear to be interacting with 25(OH)D levels to affect prostate cancer risk. Risk alleles for *GC* and *CYP27B1* tag SNPs, in particular, have been associated with levels of 25(OH)D. Three tag SNPs in the *GC* gene (*rs12512631, rs2282679* and *rs1155563*) were found to be significantly associated with 25(OH)D levels ($p=0.0004$), but there were two SNPs in *GC* (*rs2298849* and *rs2282679*) and one in *CY27PB1* (*rs10877012*) that resulted in an association only among AA individuals.[19,42]

Several studies have found evidence of interactions occurring between vitamin-D related SNPs and levels of 25(OH)D in association with prostate cancer risk. Significant

associations were observed between one *VDR* SNP (*rs11574143*) and risk of prostate cancer only among men with low levels of 25(OH)D (p=0.0007).[19] Risk of total and aggressive prostate cancer increased among men with low levels of 25(OH)D who possessed the less functional allele for *VDR* SNP *FokI*.[43] In contrast, among those who carried the less functional allele for *VDR FokI* but were categorized with high levels of 25(OH)D, risk decreased by 60-70% for total and aggressive prostate cancer.[43] Other observed vitamin-D related gene associations revealed SNPs may have a different effect on aggressive and non-aggressive disease. For example, *CYP24A1 rs6013897* was associated with low levels of 25(OH)D and a decreased risk of aggressive prostate cancer but an increased risk for non-aggressive disease (p=0.0002).[44] Different levels of 25(OH)D can also create different associations for a SNP and disease. Associations between five SNPs in *GC* (*rs1155563*) and *CYP2R1* (*rs2060793, rs12794714, rs1562902,* and *rs11023374*) and fatal prostate cancer risk were dependent upon the amount of circulating 25(OH)D present.[31]

Another method used to observe associations between SNPs, 25(OH)D and prostate cancer is the use of genetic risk scores. Studies have created genetic risk scores in order to find new associations or strengthen existing ones by considering more than one SNP or gene in the model. In a study by Signorello et al., a risk score was created using the sum of risk alleles in three SNPs (*GC*:*rs2298849, rs2282679* and *CYP27B1*:*rs10877012*) which ranged between 1 and 5 among AA. Among individuals with a score of 5, the risk for vitamin D insufficiency was six times greater compared to those with a score of 1 (p=0.01).[42] Another study coded SNPs in four genes (*GC, CYP241, CYP2R1*, and *DHCR7*) according to the number of alleles associated with low 25(OH)D which were then combined in order to create a polygenic risk score ranging

from 0 to 8. Among men with a score of 6-8 reflecting low concentrations of 25(OH)D, the risk of aggressive prostate cancer decreased compared to those with 0-1 (OR for 6–8 vs. 0–1 alleles, 0.66; 95% CI, 0.44–0.98).[44]

These studies underscore the importance of considering interactions between vitamin D-related SNPs and levels of 25(OH)D in relation to the risk of prostate cancer aggressiveness. Levels of vitamin D and respective SNPs may infer main effects individually with prostate cancer risk, but as the studies above demonstrated, interaction between the two may alter the associations observed.

Table 2.1 Summary table of studies that examined the GC gene in relation to either/or prostate cancer, 25(OH)D and interactions								
Author ,Yr	**Country**	**case/ control**	**Vit-D**	**Gene/SNPs**	**Results: SNPs and PCa**	**Results: SNPs and other cancers**	**Results: Vit-D and SNPs**	**Results: Interactions**
Ahn, 2009	USA	749 / 781	25(OH)D, $1,25(OH)_2D$	GC	None of the SNPS examined were associated with cancer risk overall.		Associated with serum 25(OH)D levels: GC rs12512631, rs2282679, rs7041, rs1155563.	
Gilbert, 2014	UK	1275 / 2062	25(OH)D $1,25(OH)_2D$	VDBP	VDBP SNPs rs4588-A and rs7041-T, representing low levels of 25(OH)D, were associated with PCa risk.		rs2282679-G, rs4588-A, rs7041-T, rs1155563-C were associated with both 25(OH)D and $1,25(OH)_2D$ concentrations	
Shui, 2015	USA	518 / 2986	25(OH)D	GC	No statistically significant relationship was observed.			GC: rs1155563, association with fatal PCa differed with circulating 25(OH)D level.

Mondul, 2013	USA	10018 / 11052	25(OH)D	GC/ rs2282679				Polygenic score of 4 SNPs revealed statistically significantly lower risk of aggressive PCa among men with a greater number of low Vit-D alleles.
Shui, 2012	USA	1260 / 1331	25(OH)D	GC	Pathway analyses found that the set of SNPs that included all 7 genes were associated with risk of lethal PCa.			Adjusting for 25(OH)D levels did not change the results of the pathway analyses.
Yuan, 2018	USA	HPFS - 18,225	25(OH)D	GCrs4588 and GCrs7041	SNPs rs7041 and rs4588 were not associated with risk of advanced PCa			
Maneechay, 2015	Thailand	CRC: 282/282 Breast: 101/101	25(OH)D	GCrs7041 and GCrs4588		Significant associations between SNP rs7041 (TG/GG)	The proportions of subjects with low serum vitamin D (< 20	

		Lung: 113/113				and lung cancer. GCrs7041 (TG/GG) were significantly associated with CRC and rs4588 (CA/AA) were significantly associated with CRC. When SNP combinations (rs7041-rs4588) were examined, the TT-CA combination had a significant protective association with lung cancer.	ng/ml) in those harboring CA or AA genotypes of rs4588 (41.7%) was significantly higher than the CC genotype (15.5%, p-value < 0.01).	
Abbas, 2008	Germany	3,464 / 3,008	25(OH)D	*GC* gene (rs4588 and rs7041) - Gc1s, Gc1f (combined: Gc1), and Gc2		Gc2-2 genotype significantly decreased risk of postmenopausal breast cancer compared to Gc1s allele carriers.	25(OH)D differed significantly in control group by *GC* genotype, being lowest in Gc2 allele carriers.	No interaction between 25(OH)D status and *GC* genotype was observed

CHAPTER 3
RESEARCH METHODS

1. Background

The study utilizes data from the North Carolina-Louisiana Prostate Cancer Project (PCaP), a population-based case-only study examining determinants of racial differences in prostate cancer aggressiveness. This study used data from an ancillary project titled "Vitamin D and Related Genes, Race, and Prostate Cancer Aggressiveness" to estimate associations between vitamin-D related SNPs and prostate cancer aggressiveness.

2. Sample Size

A subset of the PCaP population consisting of 1200 research subjects with data on vitamin D status and related genes were utilized. All research subjects diagnosed with high aggressive prostate cancer in PCaP (n = 302) and 112 research subjects diagnosed with Gleason score = 4+3 (all other intermediate aggressive cancer research subjects were excluded) were included and comprised the high aggressive cases. A random subset (n = 786) of research subjects diagnosed with low aggressive cancer were included as the comparison group. A random subset was selected because there were many more low-aggressive cancer cases than needed for analyses. The selection of research subjects for this ancillary study was completed prior to any 25(OH)D3 lab measurements or data analyses.[18]

3. PCaP Methods

3.1 Study Population

Eligible participants of PCaP were "residents of the North Carolina (NC) and of

histologically confirmed adenocarcinoma of the prostate between July 2004 and July2009."[18] As explained in the paper by Schroeder et al., participants were recruited from 42 counties in North Carolina and 13 parishes surrounding New Orleans in Louisiana. Enrollment was broken down into two phases for Louisiana, one each for pre- and post- Hurricane Katrina. The first phase lasted from July 2004 through August 2009, the remainder of the time was considered the second phase which included 8 additional parishes. Participants needed to "complete the study interview in English, not live in an institution (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. Eligible men also must self-identify as at least part African American/Black or Caucasian American/ White in response to the open-ended interview question ''What is your race?'' Participants who indicate more than one group are asked if one best describes them; if not, multiple groups are recorded."[45]

3.2 Rapid Case Ascertainment Eligible

"Eligible North Carolina patients [were] identified by the Rapid Case Ascertainment Core Facility, a collaborative effort of the UNC-Lineberger Comprehensive Cancer Center and the North Carolina Central Cancer Registry (NCCCR). North Carolina state law mandates regular reporting of all newly diagnosed cancers (excluding non-melanoma skin cancers), and the NCCCR is authorized to release contact and eligibility information to PCaP by the North Carolina Advisory Committee on Cancer Coordination and Control. In Louisiana, eligible patients [were] identified by the Louisiana Tumor Registry (LTR) in the School of Public Health at LSUHSC. LTR operations are mandated by Louisiana law, which directs all hospitals, pathology laboratories, health care facilities, and medical care providers to report cancer cases or

provide LTR staff with access to this information. Case ascertainment field representatives abstract[ed] pathology reports, review[ed] information used to screen eligibility and ensure[d] that ascertainment in hospitals and local urology clinics [was] as complete and rapid as possible. These data [were] entered into a relational database that [was] regularly downloaded into the PCaP Subject Tracking Database."[45]

3.3 Randomized Recruitment

"Caucasian Americans account[ed] for a greater proportion of North Carolina patients than African Americans; therefore, a randomized recruitment procedure [was] used to generate comparable ascertainment and enrollment rates by race and state over the entire enrollment period. This sampling method improve[d] efficiency without compromising estimation of main effects and risk difference modification (additive scale interactions) by race, and appropriate analysis require[d] only that sampling probabilities are included as stratum-specific offset terms in some analytic models. To apply randomized recruitment, each ascertained case [was] assigned a random number and recruited only if that number [was] less than or equal to its race-specific sampling probability, which [was] 100% for African Americans and 44% for Caucasian Americans."[45]

3.4 Physician Notification

"Recruitment beg[an] with a mailed request to the diagnosing physician for permission to contact their patient, as mandated by the North Carolina and Louisiana cancer registries. Written physician permission [were] not required; instead, physicians [were] given 3 weeks to notify PCaP if a patient should not be contacted for any reason, including ineligibility due to mental illness or impairment, nursing home residence, or severe physical debilitation. Passive physician permission, and access to patient

information under a limited waiver of consent to identify and contact potential PCaP participants, was approved by the UNC and LSUHSC IRBs and DoD HSRRB."[45]

3.5 Enrollment

"Patients with active or passive physician consent [were] sent an introductory letter and brochure describing PCaP. One week later an experienced enrollment specialist call[ed] to confirm eligibility, explain the study, answer questions, solicit participation, and schedule an in-home visit. Demographic and pathology report data (without personally identifiable information) [were] retained for cases who [could] not be contacted or who decline[d] participation, so that characteristics of non- participants [could] be compared with those of participants to assess potential selection bias. Reasons for declining participation [were] recorded when known. Enrollment specialists [were] required to make multiple attempts to contact each potential participant. If a valid phone number [could] not be identified, the patient's urologist [was] asked to provide the patient with the PCaP introductory letter at his next appointment. Patients who [could] not be contacted within 90 days [were] sent a letter asking them to contact the study directly. If no contact [was] made within the next 30 days, the patient [was] classified as ''unable to contact.''[45]

3.6 Data Collection

"Prior to their participation in PCaP, all men signed an informed consent and provided signed release for medical records and tumor specimens. Research subjects were visited in their home by a trained registered nurse who conducted a structured interview, performed anthropometric measurements, and collected biospecimens. The majority of visits were completed on the average within four months of diagnosis. Structured questionnaires were used to collect information about lifestyle factors, family

history of prostate cancer, cancer screening history, and prescribed and over-the-counter medications used in the prior two weeks, which included non-steroidal anti-inflammatory drugs (NSAIDs), vitamins and supplements. Men were asked to report usual dietary intake in the year prior to diagnosis using the National Cancer Institute Diet History Questionnaire (DHQ) modified to capture foods common to the geographic areas (e.g., Cajun and creole foods). The modified DHQ inquired about frequency of intake and usual portion size for 124 food items, and food preparation methods. Questionnaire responses were linked to the DHQ Nutrient Database through the Diet*Calc software, and intakes of macronutrients, micronutrients, and minerals, including calcium, were computed. After the in-home visit, medical records and tumor tissue samples were collected for each research subject who provided authorization for release."[18]

3.7 Biologic Sample Collection, Processing and Storage

"To identify men for whom specimen collection may be contraindicated, participants [were] asked if they [had] a bleeding disorder, [were] taking blood thinners, had any prior problems giving blood, or [were] allergic to local anesthetics. Nurses [were] trained to respond to adverse events, and participants [were] observed for at least 90 min after sample donation.

Patient-specific barcode-labeled kits for biologic sample collection [were] prepared in advance. Biologic sample tracking by the PCaP Specimen Tracking Database [began] when sample labels [were] printed, and receipt of each sample [was] registered when it [was] scanned into the database after the study visit. After collection, samples [were] transported under appropriate conditions to UNC or LSUHSC tissue procurement facilities (TPF) or the UNC tissue culture facility (TCF). With the exception of yellow top blood samples (see below), Louisiana samples under[went] initial processing and

short-term storage at the LSUHSCTPF prior to monthly batch-shipping to the UNC TPF for long-term storage."[45]

3.8 Anthropometric Measurements

"Weight (to the nearest 0.1 kg), height, and waist and hip circumferences (in cm) [were] measured after biologic sample collection using standardized instruments. Participants [were] asked their usual weight and height at age 25 and their weight 1 year prior to the visit."[45]

3.9 Study Questionnaires

"Study nurses administer[ed] a series of structured questionnaires that solicit[ed] information regarding:

Background characteristics: self-described race and ancestry, marital status, religion, education, income, tobacco use, physical activity.

Occupation: current employment, occupation and industry; longest and second longest occupation and industry; military service; occupations associated with pesticide use.

Family history: prostate cancer in first- and second- degree relatives.

Health status: general health and comorbid conditions.

Health care: usual sources of care, health insurance, traditional health beliefs, perceived access, and quality of care.

Prostate cancer diagnosis and screening history: PSA tests, digital rectal exams, urinary and sexual symptoms, previous prostate biopsies.

Medication survey: all prescription and over-the- counter medications and supplements used in the prior 2 weeks (transcribed by study nurses).

Non-steroidal anti-inflammatory drugs (NSAIDs): frequency and duration of use for prescription and over-the-counter NSAIDs taken during the past 5 years at least once a month for 1 week or longer, with product name show cards to aid recall.

Vitamins and supplements (including herbal products)."[45]

3.10 Medical Records Retrieval and Abstraction

"Medical records [were] requested from the diagnosing physician of consenting participants. Trained staff use[d] a relational database designed specifically for PCaP to abstract information concerning comorbid conditions, family history of prostate cancer, urologic symptoms, indications for diagnostic examinations and biopsies, prostate cancer screening examinations, physical examinations, and laboratory assays at or near diagnosis, imaging examinations used in staging, clinical stage and grade (as recorded), and initial treatment information. In addition, abstractors independently derive[d] clinical stage according to a standardized protocol. Pathologic stage, grade and other prostatectomy data [were] recorded[ed] separately, when available. Approximately 10% of medical records [were] selected at random and abstracted to assess consistency between abstractors."[45]

4. Variables

4.1 Outcome: Aggressive Prostate Cancer

Participants were classified into three categories of aggressiveness at diagnosis based upon Gleason grade, clinical stage and PSA. The three categories are as follows: "High aggressive cases: Gleason sum ≥ 8, or PSA >20 ng/ml at diagnosis, or Gleason sum = 7 AND stage T3-T4; low aggressive cases: Gleason sum <7 AND diagnosed at stage T1-T2 AND PSA <10 ng/ml at diagnosis; intermediate aggressive cases: all other cases".[18] As described in Section 2 above, all high aggressive cases and intermediate

aggressive cases who had Gleason sum =7 (4+3) were combined and referred to as the 'high aggressive' case group. The comparison group, or control group, was created from a random sample of low aggressive cases with Gleason sum <7, stage T1-T2, and PSA<9 ng/ml.[18]

4.2 Exposure:

Main Exposure: GC Gene and Tag SNPs

Tag SNPs (n=28) in the *GC* gene were identified using HapMap and were classified as National Institute of Environmental Health Sciences SNPs by identifying those with minor allele frequency (MAF) >5% and nonsynonymous polymorphisms possibly functionally relevant in AA and EA populations. Genotyping was performed using DNA extracted from whole blood samples and plated at either LSU or UNC before being sent to the Environmental Genomics Core at UNC where Illumina GoldenGate or Sequenom assays were utilized. Hardy-Weinberg equilibrium was calculated for each SNP to determine whether the genotype frequencies observed in the sample population differed from the expected frequencies. For this study, the focus is on the *GC* gene and its tag SNPs as the manuscript reporting results for other genes is currently under development. Table 3.1 reports the SNPs and genotype frequencies by race and case-control status in PCaP.

Vitamin D Assessment

"During in-home visits, study nurses collected 6.5 ml of fasting venous blood into lavender top (EDTA) tubes which were wrapped in foil and transported on ice at 4°C to the Blood and Tissue Procurement Core Laboratory at LSU or the BioSpecimen Processing Facility at UNC. The majority of PCaP blood samples were processed to serum, plasma and DNA on the same or the following day and aliquoted and stored at -

80°C. Plasma concentrations of 25(OH)D were determined using LC-MS/MS at Heartland Assays, Inc. PCaP plasma samples were stored at -80°C for up to eight years prior to measurement; concentrations of 25(OH)D3 in stored samples has been reported to be quite stable even at -20°C for up to ten years."[18]

4.3 Potential Confounders and/or Effect Modifiers

Age: Included as a continuous variable in years for men between 40-79 years old.

Race: Included as a categorical variable dichotomized into AA and EA through self-identification from the study questionnaires.

Study Site: Sites included were from North Carolina (University of North Carolina) or Louisiana (Louisiana State University) post-hurricane Katrina.

Family History: Included as a categorical variable dichotomized as follows: 'No affected 1st degree relative' and 'At least 1 affected 1st degree relative'.[18] Obtained by self-report from study questionnaire.

Education: Included as a categorical variable as follows: less than 8th grade or some high school, high school graduate or vocational/ technical school, some college or college graduate and, some graduate training or graduate/professional degree.[18] Obtained by self-report from study questionnaire.

PSA screening history: Included as a categorical variable as 0, 1–7 and, >7 screenings.[18] Obtained by self-report from study questionnaire.

BMI: During the study visit, measurements for weight, height and waist circumference were obtained by trained Registered Nurses. This variable was included as a continuous variable (kg/m^2).

Smoking Status: Included as a categorical variable as follows: non-smoker, former smoker, and current smoker. Obtained by self-report from study questionnaire.

Alcohol Intake: Included as a continuous variable (g/day) and obtained by self-report from study questionnaire.

NSAID Use: Included as a categorical variable dichotomized into 'yes' and 'no' responses. Obtained by self-report from study questionnaire.

Physical Activity: Included as a continuous variable (MET-hours/week) through self-reported physical activity from the study questionnaire.

Season of blood draw: Included as a categorical variable as follows: winter (Dec 21-Mar 22), spring (Mar 21- Jun 20), summer (Jun 21-Sep 20), and fall (Sep 21-Dec 20).[18]

Total Energy Intake: Included as a continuous variable (kcal/day) through self-report from the study questionnaire.

5. Analysis

5.1 Missing Data

Based on previous analyses from this dataset, we anticipated very few missing data points for outcome, exposure and covariates. Any participants with missing data in the variables of interest were excluded from analyses.

5.2 Statistical Methods

All analysis was completed using SAS version 9.4 statistical software. All tests were two-sided with significance level alpha=0.05.

1. Descriptive statistics were performed to describe the study population in terms of demographic and other characteristics by race and case status. Means and standard deviations, were reported for continuous variables and frequencies and proportions were reported for categorical variables.
2. 25(OH)D was categorized as a 2-level variable, using a different cut-point for each race given the different distribution of 25(OH)D for AAs and EAs.

Based on the distributions the following cut-points were chosen: <15ng/ml for AA and <20ng/ml for EA.

3. Univariate analysis of age and ancestry were modeled separately against each outcome, prostate cancer aggressiveness and 25(OH)D (2-level) to assess potential confounding.
4. AIM 1:
    a. For Aim 1 specifically, *rs7041* was relabeled to remain consistent with other studies.[46] The 'C' and 'A' alleles were replaced with 'G' and 'T' alleles respectively.
    b. Combined genotypes of the *GC* gene were created based on the commonly studied *rs7041* and *rs4588* SNPs as previously described in other studies for Gc1s (*rs7041-G* and *rs4588-C*), GC1f (*rs7041-T* and *rs4588-C*) and Gc2 (*rs7041-T* and *rs4588-A*).[46] The following combined genotypes were examined for this study: Gc1f-1f, Gc1s-1s, Gc1s-1f, Gc2-2, Gc2-1f, Gc2-1s or Gc1f-x, and Gc2-x. Genotype frequencies and concentration of 25(OH)D were considered when selecting the reference group among each race. For both races the second most frequent genotype and second highest 25(OH)D concentration were selected as the reference group for the analysis of this aim.
    c. Means and standard deviations were calculated for 25(OH)D by the combined genotypes of the *GC* gene by race and prostate cancer aggressiveness.
5. AIM 2:

a. Multivariable logistic regression was used to examine the association between combined genotypes and aggressive prostate cancer by race after adjusting for age and ancestry (African ancestry among AAs and European ancestry among EAs).

b. Associations between each individual SNP (30 SNPs in AAs and 28 SNPs in EAs) and each 2-level outcome (aggressive prostate cancer or 25(OH)D level) were examined using logistic regression with adjustment for age and ancestry. Analyses were performed for three genetic models: additive, dominant and recessive models.

   For the additive model, the most frequent homozygous genotype (homozygous wildtype) was selected as the reference group. Mean and standard deviations of 25(OH)D were reported for each genotype in all models.

c. The dominant model assumes that possessing one copy of the 'dominant' allele has the same effect as having two copies. The minor allele for each SNP was selected as the 'dominant' allele. Heterozygotes were combined with homozygous variant carriers in comparison to the homozygous wildtype carriers, which were used as the reference group. An adjusted multivariable logistic regression was performed between each of the *GC* SNPs and both outcomes, aggressive prostate cancer and 25(OH)D concentrations. Mean and standard deviations of 25(OH)D were reported for each genotype category.

d. The recessive model assumes that two copies of the 'recessive' allele are needed to observe an effect. The minor allele for each SNP was selected as

the ‘recessive’ allele. Heterozygotes were combined with homozygous wildtype carriers and used as the reference group in comparison to the homozygous variant carriers. An adjusted multivariable logistic regression was performed between each of the *GC* SNPs and both outcomes, aggressive prostate cancer and 25(OH)D concentrations. Mean and standard deviations of 25(OH)D were reported for each genotype category.

6. AIM 3:
    a. For each race separately, a polygenic score was created using the SNPs that were statistically significantly associated with 25(OH)D concentrations in the recessive model. All SNPs were checked for linkage disequilibrium (LD) by race using LDlink.[47] For any SNPs that were in LD with each other, all but one were removed. Moving forward with the remaining SNPs by race, the genotype with the highest 25(OH)D concentration was given a score of 1 and the other genotype category was given a score of 0. Scores were added together to create a polygenic risk score for all participants, with higher scores representing higher 25(OH)D concentrations.
    b. Using an adjusted multivariable logistic regression, the association between the following variables was assessed: 1) polygenic risk score and prostate cancer aggressiveness; 2) 25(OH)D and prostate cancer aggressiveness stratified by polygenic risk score; and 3) polygenic risk score and prostate cancer aggressiveness stratified by 25(OH)D.
    c. A multivariable logistic regression analysis was also used to examine

whether the interaction term between the polygenic risk score and 25(OH)D was statistically significant at $p<0.10$ in relation to the outcome of aggressive prostate cancer.

CHAPTER 4
RESULTS

Descriptive Characteristics of the Participants (Table 4.1)

After excluding research subjects with missing data, the final study population was 1181 male participants, of which 524 (44%) identified as AA and 657 (56%) as EA. As shown in Table 4.1, the average age of diagnosis was similar between both races (AA: 61.5 ± 7.9yrs, EA: 64.1 ± 7.7yrs). The level of vitamin D (25(OH)D ng/ml) was higher on average among EA research subjects (24.7 ± 9.7ng/ml) than AA research subjects (17 ± 7.4ng/ml). In this study, AA participants with less than 15ng/ml and EA with less than 20ng/ml of 25(OH)D were categorized as having low vitamin D status. High aggressive prostate cancer was more prevalent among AAs (41% vs 29% in EAs). Most participants of both races in the study did not have prior family history of prostate cancer in a first degree relative (71% for AAs and 75% for EAs).

Confounding (Table 4.2)

Variables for age and ancestry (African and European) were assessed as possible confounders between prostate cancer aggressiveness, *GC* gene SNPs and vitamin D levels. Associations were examined between each variable (age and ancestry) and dichotomous 25(OH)D and prostate cancer aggressiveness. Age was significantly associated with both 25(OH)D and cancer aggressiveness in at least one or both races, therefore it was adjusted for in the final regression models for both races. African ancestry was significantly associated with 25(OH)D, but not cancer aggressiveness.

European ancestry was not significantly associated with aggressive prostate cancer or 25(OH)D levels. Despite these findings, previous literature and studies on prostate cancer have adjusted for ancestry, therefore both age and ancestry were included in their respective final models (African ancestry in AA models and European ancestry in EA models).

Combined Genotypes of GCrs7041 and GCrs4588 (Table 4.3)

Mean levels of 25(OH)D and the most common combined genotypes present within the study population varied by race. The most frequent combined genotypes were Gc1f-1f among AAs and GC1s-1s among EAs (Table 4.3). Mean levels of 25(OH)D were noticeably lower among AAs compared to EAs, with 18.7ng/ml and 27.4ng/ml being the highest mean values by combined genotype for AAs and EAs, respectively. None of the combined genotype categories were significantly associated with aggressive prostate cancer among AAs, and only one was significantly associated among EAs. EA individuals with the Gc2-1f combined genotype had a decreased risk of having high aggressive prostate cancer compared to those with the most frequent combined genotype, Gc1s-1s (OR: 0.38, 95%CI: 0.17, 0.85).

GC Gene SNPs, 25(OH)D and Prostate Cancer Aggressiveness (Tables 4.4-4.16)

Additive Model (Tables 4.4-4.7)

In the additive model, three SNPs among AAs (Table 4.4) and one SNP among EAs (Table 4.5) were significantly associated with high aggressive prostate cancer. The odds of high aggressive prostate cancer decreased by 45% for *GCrs6817912* (OR: 0.55, 95%CI: 0.31,0.98) among EAs, and 36% and 31% for *GCrs16847028* and *GCrs16847015* (*rs16847028* OR: 0.64, 95%CI: 0.43, 0.96 and *rs16847015* OR:0.69, 95%CI: 0.49, 0.98), respectively among AAs for each copy of the 'A' allele. For

GCrs222054 and *GCrs16847015*, the odds of high aggressive prostate cancer decreased by 37% for each copy of the 'G' allele (*rs222054* OR: 0.63, 95%CI: 0.45, 0.87) among AAs. When examining the relationship between *GC* SNPs and risk of low vitamin D status, four SNPs among AAs (Table 4.6) and eight SNPs among EAs (Table 4.7) were statistically significant. For both races, the odds of low vitamin D increased for each copy of the 'C' allele in *GCrs2282679* (AA: OR: 1.65, 95%CI:1.08, 2.51; EA: OR: 1.81, 95%CI: 1.39, 2.36), the 'G' allele in *GCrs17467825* (AA: OR: 1.85, 95%CI: 1.21, 2.83; EA: OR: 1.83, 95%CI: 1.41, 2.40), and the 'A' allele in *GCrs3755967* (AA: OR: 1.67, 95%CI: 1.11, 2.53; EA: OR: 1.86, 95%CI: 1.42, 2.43). Among AAs, the odds of low vitamin D decreased by 35% for each copy of the 'G' allele in *GCrs222054* (OR: 0.65, 95%CI: 0.47, 0.90). Four SNPs increased the odds of low vitamin D for each copy of the 'A' allele (*GCrs4588* OR: 1.89, 95%CI: 1.45, 2.48; *GCrs7041* OR: 1.63, 95%CI: 1.27, 2.09; *GCrs705119* OR: 1.57, 95%CI: 1.22, 2.02; and *GCrs705120* OR: 1.55, 95%CI: 1.20, 1.98) and one SNP for each copy of the 'G' allele (*GCrs222040* OR: 1.58, 95%CI: 1.23, 2.03) among EAs.

Recessive Model (Tables 4.8-4.11)

When examining the association between the SNPs and prostate cancer aggressiveness using the recessive genetic model (Table 4.8-4.9), no associations were statistically significant in either race. However, results for the *GCrs7041* SNP among EAs showed a suggestion of a protective association (OR: 0.63, 95%CI: 0.39, 1.02, p-value:0.0579) with high aggressive prostate cancer (Table 4.9).

In the recessive model, nine SNPs were found to be associated with low levels of 25(OH)D. Among AAs with both copies of the recessive allele in the *GCrs222054* SNP, the odds of having low vitamin D levels (below 15ng/mL) decreased compared to

heterozygote or homozygote wildtype carriers (OR: 0.33, 95%CI: 0.11, 0.998, p-value: 0.0496) (Table 4.10). Eight SNPs were found to increase the odds of having low vitamin D status (below 20ng/mL) among EAs with both copies of the recessive allele compared to heterozygote or homozygote wildtype carriers (*rs4588* OR: 2.80, 95%CI: 1.58, 4.97; *rs7041* OR: 2.02, 95%CI: 1.35, 3.04; *rs22040* OR: 2.04, 95%CI: 1.35, 3.08; *rs705119* OR: 2.15, 95%CI: 1.41, 3.27; *rs705120* OR: 2.08, 95%CI: 1.36, 3.18; *rs2282679* OR: 2.64, 95%CI: 1.49, 4.66; *rs3755967* OR: 2.65, 95%CI: 1.50, 4.67 and *rs17467825* OR: 2.64, 95%CI: 4.66, 3.08) (Table 4.11).

Dominant Model (Tables 4.12-4.15)

In the dominant model, when examining the association between *GC* SNPs and prostate cancer aggressiveness, only three SNPs had a statistically significant association. Among AAs (Table 4.12), individuals who were heterozygotes or homozygous variant in either the *GCrs222054* or *GCrs16847028* SNP had a decreased risk of developing high aggressive prostate cancer compared to those who were homozygous wildtype carriers (*rs222054* OR: 0.55, 95%CI: 0.38, 0.80 and *rs16847028* OR: 0.61, 95%CI: 0.39, 0.94). Only one SNP was statistically significantly associated with high aggressive prostate cancer among EAs (Table 4.13) using the dominant model (*rs6817912* OR: 0.51, 95%CI: 0.28,0.93), while there was a suggestion of an association with two other SNPs (*Grs705125* OR: 0.68 95%CI: 0.47, 1.00 and *GCrs3733359* OR: 0.56 95%CI: 0.31, 1.01). In relation to levels of 25(OH)D, thirteen SNPs total were significantly associated with low levels of vitamin D among both races, five among AAs (Table 4.14) and eight among EAs (Table 4.15). Four of these SNPs (*GCrs4588, GCrs2282679, GCrs3755967* and *GCrs17467825*) were statistically significantly associated with low levels of vitamin D in both races (<15 ng/mL in AAs and <20ng/mL in EAs). For both AA and EA

individuals, being heterozygotes or homozygous variant carriers for *rs4588*, *rs2282679*, *rs3755967*, and *rs17467825* had an increased risk of having low levels of vitamin D compared to individuals who were homozygous wildtype carriers (AA: *rs4588* OR:1.66, 95%CI: 1.06, 2.61; *rs2282679* OR: 1.86, 95%CI:1.13, 3.06; *rs3755967* OR: 1.88, 95%CI: 1.16, 3.05; *rs17467825* OR: 2.05, 95%CI: 1.26, 3.36; EA: *rs4588* OR: 2.05, 95%CI: 1.45, 2.91; *rs2282679* OR: 1.96, 95%CI:1.39, 2.77; *rs3755967* OR: 2.03, 95%CI: 1.43, 2.87; *rs17467825* OR: 1.99, 95%CI: 1.40, 2.82). The SNPs *GCrs7041* (OR:1.78, 95%CI: 1.19, 2.64), *GCrs222040* (OR:1.65, 95%CI: 1.12, 2.44), *GCrs705119* (OR:1.57, 95%CI: 1.07, 2.30) and *GCrs705120* (OR:1.55, 95%CI: 1.06, 2.26) had the same positive associations but only among EAs. Using the dominant model, only one SNP was statistically significantly associated with a decreased risk of low levels of vitamin D and it only occurred among AA individuals (*rs222054* OR: 0.66, 95%CI: 0.45, 0.96).

Polygenic Risk Score (Table 4.16)

Thirteen SNPs were statistically significantly associated with vitamin D status in the recessive model and were considered for creation of the polygenic risk score. All SNPs within each race were checked for LD and removed accordingly, with only two SNPs remaining for each race . The SNPs used to create the polygenic risk scores were *GCrs4588* and *GCrs222054* for AAs and *GCrs4588* and *GCrs7041* for EAs. Values of the polygenic risk score were 0, 1 or 2 depending on number of homozygous variant genotypes that were present for each of the two SNPs per race. Across both races, the average level of 25(OH)D increased as the score increased, with AAs still having a lower average 25(OH)D than EAs within each strata of polygenic risk score (Table 4.16). Among AAs, the odds of high aggressive prostate cancer decreased among those with a

score=2 compared those with a score=0 (OR: 0.54, 95%CI: 0.31, 0.94), while there was no association among EAs.

In stratified analyses (Table 4.16), there was a suggestion of an increased risk for low levels of vitamin D among AAs and a decreased risk among EAs for all levels of the polygenic risk scores, but none of these reached statistical significance. When assessing the relationship between the polygenic risk score and prostate cancer aggressiveness stratified by 25(OH)D, the risk of having high aggressive prostate cancer appeared to decrease among AA and increase among EA with a score above 0 across both levels of 25(OH)D, but none reached statistical significance. Based on the interaction term p-value, there was no significant interaction between the polygenic risk score and levels of vitamin D in relation to high aggressive prostate cancer (p= 0.83 for AAs and 0.96 for EAs).

Summary of statistically significant results (Tables 4.17 and 4.18)

A summary of the results for the SNPs which had at least one statistically significant association across the three different genetic models can be found in Tables 4.17 (AAs) and 4.18 (EAs). The written summary of these results can be found in the Discussion section (Chapter 5).

Table 4.1 Study participant demographics by race		
Characteristics	**African Americans (n=524)**	**European Americans (n=657)**
Age, mean (SD)	61.5 (7.9)	64.1 (7.7)
African Ancestry, mean (SD)[a]	0.90 (0.15)	-
European Ancestry, mean (SD)[a]	-	0.97 (0.07)
25(OH)D, mean (SD)[b]	17.6 (7.4)	24.7 (9.7)
25(OH)D, n (%)[c]		
High	311 (59)	469 (71)
Low	213 (41)	188 (29)
PCa Aggressiveness, n (%)[d]		
High	217 (41)	187 (28)
Low	307 (59)	470 (72)
Family history in first degree relative, n (%)		
Yes	141 (29)	154 (25)
No	349 (71)	467 (75)

[a] continuous variable, African ancestry was only included in AA analysis and European ancestry was only included in EA analysis
[b] continuous variable
[c] categorical variable, <15ng/ml for AA and 20ng/ml for EA is considered low
[d] defined as the severity of the cancer at diagnosis based on combinations of the Gleason score, morphologic stage, and PSA as follows: high aggressive, Gleason sum ≥ 8 OR PSA > 20 ng/mL OR Gleason sum = 7 (4 +3) OR Gleason sum = 7 and stage T3- T4; low aggressive, Gleason sum < 7 and stage T1-T2 and PSA < 9 ng/mL

Table 4.2 Assessment of confounding for age and ancestry		
Assessment of confounding, p-values	**African Americans (n=524)**	**European Americans (n= 657)**
Age[a]		
PCa aggressiveness[b]	**0.0119**	**<.0001**
25(OH)D[b]	**0.0398**	0.8924
African Ancestry[a]		
PCa aggressiveness[b]	0.7993	-
25(OH)D[b]	**0.0357**	-
European Ancestry[a]		
PCa aggressiveness[b]	-	0.5720
25(OH)D[b]	-	0.7955

[a] continuous variable
[b] 2-level categorical variables; comparison group are cases for aggressiveness and low for 25(OH)D status

Table 4.3 Combined rs7041 and rs4588 genotypes by race						
African Americans			**Aggressiveness (n)**			
Genotype	**rs7041**	**rs4588**	**High**	**Low**	**Mean 25(OH)D (SD)**	**OR (95%CI)***
Gc1f-1f	TT	CC	109	162	17.5 (7.46)	1.0 (ref)
Gc1s-1s	GG	CC	7	14	17.3 (7.18)	0.74 (0.29, 1.90)
Gc1s-1f	TG	CC	56	73	18.7 (7.74)	1.14 (0.75, 1.74)
Gc2-2	TT	AA	6	5	15.2 (8.33)	1.78 (0.53, 5.99)
Gc2-1f	TT	CA	28	36	16.4 (6.96)	1.16 (0.67, 2.00)
Gc2-1s or Gc1f-x	TG	CA	10	11	17.0 (5.32)	1.35 (0.56, 3.29)
Gc2-x	TG	AA	0	1	17.0 (-)	<0.001 (<0.001, >999.9)
European Americans			**Aggressiveness (n)**			
Genotype	**rs7041**	**rs4588**	**High**	**Low**	**Mean 25(OH)D (SD)**	**OR (95%CI)***
Gc1s-1s	GG	CC	58	138	27.4 (13.5)	1.0 (ref)
Gc1f-1f	TT	CC	1	10	28.5 (7.21)	0.24 (0.03, 1.90)
Gc1s-1f	TG	CC	41	74	25.5 (7.17)	1.32 (0.80, 2.15)
Gc2-2	TT	AA	17	35	21.2 (7.06)	1.16 (0.60, 2.23)
Gc2-1f	**TT**	**CA**	**8**	**50**	**22.2 (7.28)**	**0.38 (0.17, 0.85)**
Gc2-1s or GC1f-x	TG	CA	60	160	23.2 (6.84)	0.89 (0.58, 1.37)
Gx2-x	TG	AA	-	-	-	-
*Both models were adjusted for age and ancestry						

Table 4.4. Additive model - Genotype frequencies and association between SNPs and aggressive prostate cancer among African Americans				
Gene + SNP rs#	**Genotype**	**African American (N = 524) case/control**	**OR, 95% CI***	**P-value***
GCrs4588	CC	172/249	Ref	Ref
	AC	38/47	1.15 (0.72, 1.85)	0.92
	AA	6/6	1.43 (0.45, 4.57)	0.63
Additive (per allele)			1.21 (0.68, 2.16)	0.52
GCrs7041	AA	143/208	Ref	Ref
	AC	67/85	1.14 (0.77, 1.68)	0.31
	CC	7/14	0.71 (0.27, 1.87)	0.41
Additive (per allele)			1.01 (0.73, 1.40)	0.95
GCrs188812	AA	158/220	Ref	Ref
	AT	56/76	1.03 (0.69, 1.55)	0.14
	TT	3/11	0.35 (0.10, 1.28)	0.11
Additive (per allele)			0.87 (0.62, 1.23)	0.44
GCrs222016	GG	50/92	Ref	Ref
	AG	111/144	1.41 (0.92, 2.16)	0.40
	AA	56/71	1.46 (0.88, 2.42)	0.33
Additive (per allele)			1.21 (0.94, 1.56)	0.13
GCrs222023	GG	69/99	Ref	Ref
	AG	104/134	1.09 (0.72, 1.64)	0.38
	AA	39/65	0.86 (0.51, 1.44)	0.40
Additive (per allele)			0.94 (0.73, 1.22)	0.65
GCrs222040	GG	78/101	Ref	Ref

	AG	106/153	0.90 (0.61, 1.33)	0.97
	AA	33/52	0.82 (0.48, 1.40)	0.55
Additive (per allele)			0.90 (0.70, 1.17)	0.44
GCrs222049	CC	158/236	Ref	Ref
	CG	52/66	1.16 (0.76, 1.77)	0.51
	GG	7/5	2.16 (0.67, 6.99)	0.25
Additive (per allele)			1.25 (0.88, 1.78)	0.21
GCrs222054	CC	156/179	Ref	Ref
	CG	54/115	0.54 (0.36, 0.79)	0.14
	GG	7/13	0.69 (0.27, 1.78)	0.89
Additive (per allele)			**0.63 (0.45, 0.87)**	**0.01**
GCrs705117	GG	105/165	Ref	Ref
	AG	89/113	1.23 (0.84, 1.79)	0.66
	AA	23/29	1.26 (0.67, 2.35)	0.68
Additive (per allele)			1.16 (0.88, 1.53)	0.29
GCrs705119	AA	145/214	Ref	Ref
	AC	67/81	1.22 (0.82, 1.82)	0.17
	CC	5/12	0.62 (0.20, 1.89)	0.30
Additive (per allele)			1.06 (0.75, 1.48)	0.75
GCrs705120	CC	53/84	Ref	Ref
	AC	106/143	1.16 (0.76, 1.78)	0.65
	AA	54/76	1.14 (0.70, 1.88)	0.77
Additive (per allele)	AA	54/76	1.07 (0.84, 1.37)	0.59
GCrs705124	GG	127/171	Ref	Ref
	AG	79/110	0.98 (0.68, 1.43)	0.30
	AA	11/26	0.59 (0.28, 1.24)	0.16

Additive (per allele)			0.87 (0.65, 1.15)	0.32
GCrs705125	CC	67/110	Ref	Ref
	AC	105/136	1.28 (0.85, 1.91)	0.47
	AA	45/60	1.25 (0.75, 2.07)	0.66
Additive (per allele)			1.13 (0.88, 1.45)	0.33
GCrs1352845	AA	133/181	Ref	Ref
	AG	57/81	0.94 (0.62, 1.41)	0.85
	GG	27/45	0.81 (0.47, 1.38)	0.49
Additive (per allele)			0.91 (0.71, 1.16)	0.44
GCrs1491710	AA	86/111	Ref	Ref
	AC	96/148	0.80 (0.54, 1.19)	0.45
	CC	32/47	0.86 (0.50, 1.48)	0.87
Additive (per allele)			0.90 (0.69, 1.16)	0.42
GCrs1873590	AA	174/242	Ref	Ref
	AG	42/60	0.98 (0.63, 1.54)	0.28
	GG	1/5	0.27 (0.03, 2.34)	0.24
Additive (per allele)			0.88 (0.59, 1.32)	0.53
GCrs2282679	AA	180/268	Ref	Ref
	AC	33/33	1.45 (0.86, 2.45)	0.29
	CC	4/6	0.89 (0.24, 3.22)	0.64
Additive (per allele)			1.22 (0.81, 1.85)	0.35
GCrs3733359	GG	123/176	Ref	Ref
	AG	73/112	0.93 (0.64, 1.35)	0.14
	AA	21/18	1.68 (0.85, 3.31)	0.10
Additive (per allele)			1.12 (0.85, 1.48)	0.42
GCrs3755967	GG	178/263	Ref	Ref

	AG	35/38	1.36 (0.82, 2.24)	0.36
	AA	4/6	0.88 (0.24, 3.20)	0.67
Additive (per allele)			1.18 (0.79, 1.77)	0.43
GCrs3775152	CC	109/160	Ref	Ref
	AC	92/111	1.23 (0.84, 1.78)	0.05
	AA	16/36	0.64 (0.34, 1.22)	0.08
Additive (per allele)			0.94 (0.72, 1.23)	0.65
GCrs4364228	AA	86/113	Ref	Ref
	AG	93/146	0.82 (0.56, 1.21)	0.27
	GG	37/48	1.02 (0.61, 1.71)	0.63
Additive (per allele)			0.97 (0.75, 1.25)	0.81
GCrs6817912	GG	177/244	Ref	Ref
	AG	39/58	0.94 (0.60, 1.48)	0.34
	AA	1/5	0.29 (0.03, 2.52)	0.28
Additive (per allele)			0.85 (0.57, 1.29)	0.45
GCrs10488854	GG	164/242	Ref	Ref
	AG	49/61	1.18 (0.77, 1.81)	0.97
	AA	4/4	1.43 (0.35, 5.86)	0.70
Additive (per allele)			1.18 (0.81 1.73)	0.39
GCrs16846912	AA	138/177	Ref	Ref
	AG	70/113	0.79 (0.55, 1.16)	0.90
	GG	9/17	0.68 (0.29, 1.57)	0.51
Additive (per allele)			0.81 (0.60, 1.09)	0.16
GCrs16847015	CC	162/207	Ref	Ref
	AC	53/88	0.78 (0.53, 1.17)	0.23
	AA	2/12	0.22 (0.05, 1.01)	0.07

Additive (per allele)			**0.69 (0.49, 0.98)**	**0.04**
GCrs16847019	GG	166/237	Ref	Ref
	AG	49/67	1.04 (0.68, 1.60)	0.83
	AA	2/3	0.88 (0.15, 5.37)	0.87
Additive (per allele)			1.03 (0.69, 1.52)	0.90
GCrs16847024	GG	182/269	Ref	Ref
	AG	31/35	1.27 (0.75, 2.14)	0.90
	AA	4/3	1.81 (0.40, 8.28)	0.54
Additive (per allele)			1.29 (0.83, 2.01)	0.26
GCrs373749	GG	149/216	Ref	Ref
	AG	62/81	1.10 (0.74, 1.63)	0.69
	AA	6/9	0.94 (0.32, 2.71)	0.83
Additive (per allele)			1.05 (0.75, 1.47)	0.76
GCrs16847028	GG	179/227	Ref	Ref
	AG	36/75	0.61 (0.39, 0.95)	0.63
	AA	2/5	0.58 (0.11, 3.06)	0.73
Additive (per allele)			**0.64 (0.43, 0.96)**	**0.03**
GCrs17467825	AA	176/258	Ref	Ref
	AG	35/36	1.43 (0.86, 2.39)	0.17
	GG	3/6	0.63 (0.15, 2.59)	0.38
Additive (per allele)			1.16 (0.77, 1.77)	0.47
* adjusted for age and African ancestry				

Table 4.5. Additive model - Genotype frequencies and association between SNPs and aggressive prostate cancer among European Americans				
Gene + SNP rs#	**Genotype**	**European American (N = 657) cases/control**	**OR, 95% CI***	**P-value***
GCrs4588	CC	100/222	Ref	Ref
	AC	69/210	0.76 (0.53, 1.10)	0.16
	AA	17/35	1.05 (0.55, 1.99)	0.55
Additive (per allele)			0.90 (0.69, 1.19)	0.46
GCrs7041	CC	58/138	Ref	Ref
	AC	102/234	1.04 (0.70, 1.54)	0.16
	AA	26/98	0.65 (0.38, 1.11)	0.06
Additive (per allele)			0.84 (0.65, 1.08)	0.18
GCrs188812	AA	156/377	Ref	Ref
	AT	26/87	0.75 (0.46, 1.21)	0.15
	TT	5/6	1.71 (0.50, 5.88)	0.28
Additive (per allele)			0.91 (0.61, 1.35)	0.63
GCrs222016	AA	140/328	Ref	Ref
	AG	42/134	0.73 (0.49, 1.10)	0.21
	GG	5/8	1.29 (0.40, 4.15)	0.49
Additive (per allele)			0.83 (0.59, 1.18)	0.31
GCrs222023	GG	168/402	Ref	Ref
	AG	16/53	0.68 (0.37, 1.25)	0.98
	AA	0/2	<0.001 (<0.001, >999.9)	0.97
Additive (per allele)			0.65 (0.36, 1.17)	0.15
GCrs222040	AA	60/141	Ref	Ref

	AG	101/233	1.02 (0.69, 1.51)	0.23
	GG	26/95	0.67 (0.39, 1.15)	0.09
Additive (per allele)			0.85 (0.66, 1.10)	0.21
GCrs222049	CC	164/412	Ref	Ref
	CG	22/58	0.96 (0.56, 1.63)	0.97
	GG	1/0	>999.9 (<0.001, >999.9)	0.97
Additive (per allele)			1.06 (0.64, 1.77)	0.82
GCrs222054	CC	100/235	Ref	Ref
	CG	72/198	0.91 (0.63, 1.31)	0.68
	GG	15/37	0.99 (0.51, 1.92)	0.90
Additive (per allele)			0.96 (0.73, 1.26)	0.76
GCrs705117	AA	138/335	Ref	Ref
	AG	48/125	0.95 (0.64, 1.40)	0.26
	GG	1/10	0.25 (0.03, 2.02)	0.20
Additive (per allele)			0.85 (0.59, 1.22)	0.38
GCrs705119	CC	61/147	Ref	Ref
	AC	101/235	1.05 (0.72, 1.55)	0.23
	AA	25/88	0.72 (0.42, 1.24)	0.15
Additive (per allele)			0.89 (0.69, 1.14)	0.35
GCrs705120	CC	63/151	Ref	Ref
	AC	99/231	1.05 (0.72, 1.55)	0.25
	AA	25/87	0.73 (0.42, 1.25)	0.17
Additive (per allele)			0.89 (0.69, 1.15)	0.37
GCrs705124	GG	155/377	Ref	Ref
	AG	25/83	0.77 (0.50, 1.26)	0.08
	AA	7/7	2.11 (0.71, 6.28)	0.12

Additive (per allele)			1.01 (0.69, 1.47)	0.97
GCrs705125	AA	136/302	Ref	Ref
	AC	45/151	0.67 (0.45, 0.99)	0.33
	CC	6/15	0.82 (0.31, 2.20)	1.00
Additive (per allele)			0.75 (0.54, 1.04)	0.08
GCrs1352845	AA	163/392	Ref	Ref
	AG	19/64	0.70 (0.40, 1.23)	0.87
	GG	4/14	0.56 (0.18, 1.76)	0.50
Additive (per allele)			0.73 (0.48, 1.10)	0.13
GCrs1491710	AA	185/462	Ref	Ref
	AC	2/8	0.51 (0.09, 2.72)	0.43
	CC	0/0	-	-
Additive (per allele)			0.51 (0.10, 2.72)	0.43
GCrs1873590	AA	186/467	Ref	Ref
	AG	0/3	<0.001 (<0.001, >999.9)	0.99
	GG	0/0	-	-
Additive (per allele)			<0.001 (<0.001, >999)	0.99
GCrs2282679	AA	101/231	Ref	Ref
	AC	68/203	0.80 (0.55, 1.15)	0.16
	CC	18/35	1.16 (0.62, 2.17)	0.41
Additive (per allele)			0.95 (0.72, 1.25)	0.71
GCrs3733359	GG	171/405	Ref	Ref
	AG	15/63	0.54 (0.29, 0.98)	0.23
	AA	1/2	1.46 (0.13, 16.48)	0.58
Additive (per allele)			0.60 (0.34, 1.06)	0.08
GCrs3755967	GG	100/222	Ref	Ref

	AG	69/213	0.75 (0.52, 1.08)	0.11
	AA	18/35	1.12 (0.60, 2.11)	0.40
Additive (per allele)			0.92 (0.70, 1.21)	0.53
GCrs3775152	AA			
	AC			
	CC			
Additive (per allele)				
GCrs4364228	AA	162/405	Ref	Ref
	AG	24/63	0.95 (0.56, 1.58)	0.84
	GG	1/2	1.17 (0.10, 13.29)	0.88
Additive (per allele)			0.96 (0.60, 1.56)	0.88
GCrs6817912	GG	172/402	Ref	Ref
	AG	14/66	0.49 (0.26, 0.90)	0.19
	AA	1/2	1.44 (0.13, 16.27)	0.56
Additive (per allele)			**0.55 (0.31 0.98)**	**0.04**
GCrs10488854	GG	185/465	Ref	Ref
	AG	2/5	0.70 (0.12, 4.21)	0.70
	AA	0/0	-	-
Additive (per allele)			0.70 (0.12, 4.21)	0.70
GCrs16846912	AA	187/467	Ref	Ref
	AG	0/3	<0.001 (<0.001, >999.9)	0.99
	GG	0/0	-	-
Additive (per allele)			<0.001 (<0.001, >999)	0.99
GCrs16847015	CC	172/423	Ref	Ref
	AC	15/45	0.80 (0.43, 1.48)	0.98
	AA	0/2	<0.001 (<0.001, >999.9)	0.97

Additive (per allele)			0.75 (0.41, 1.37)	0.34
GCrs16847019	GG	187/464	Ref	Ref
	AG	0/6	<0.001 (<0.001, >999.9)	0.98
	AA	0/0	-	-
Additive (per allele)			<0.001 (<0.001, >999)	0.98
GCrs16847024	GG	185/467	Ref	Ref
	AG	2/3	1.07 (0.16, 7.10)	0.95
	AA	0/0	-	-
Additive (per allele)			1.07 (0.16, 7.10)	0.95
GCrs373749	GG			
	AG			
	AA			
Additive (per allele)				
GCrs16847028	GG	155/372	Ref	Ref
	AG	27/92	0.72 (0.45, 1.16)	0.12
	AA	5/6	1.72 (0.50, 5.93)	0.26
Additive (per allele)			0.88 (0.60, 1.30)	0.52
GCrs17467825	AA	100/218	Ref	Ref
	AG	69/208	0.76 (0.52, 1.09)	0.13
	GG	18/35	1.10 (0.59, 2.07)	0.45
Additive (per allele)			0.92 (0.70, 1.20)	0.53
* adjusted for age and European ancestry				

Table 4.6 Additive Model - Genotype frequencies by 25(OH)D cut-point and association between SNPs and vitamin D status among African Americans

Gene + SNP rs#	Genotype	African American (N = 524) below/above*	25(OH)D Mean, SD	OR, 95% CI*	P-value*
GCrs4588	CC	163/258	17.8 (7.54)	Ref	Ref
	AC	41/44	16.6 (6.57)	1.57 (0.97, 2.52)	0.94
	AA	7/5	15.3 (7.96)	2.60 (0.79, 8.53)	0.23
Additive (per allele)				1.64 (0.90, 2.98)	0.11
GCrs7041	AA	150/201	17.2 (7.36)	Ref	Ref
	AC	54/98	18.4 (7.41)	0.79 (0.53, 1.18)	0.24
	CC	9/12	17.3 (7.18)	1.23 (0.49, 3.11)	0.49
Additive (per allele)				0.91 (0.65, 1.26)	0.56
GCrs188812	AA	152/226	17.8 (7.50)	Ref	Ref
	AT	56/76	16.9 (7.05)	1.07 (0.72, 1.61)	0.63
	TT	5/9	16.4 (7.02)	0.83 (0.27, 2.55)	0.70
Additive (per allele)				1.02 (0.72, 1.43)	0.93
GCrs222016	GG	54/88	17.6 (7.42)	Ref	Ref
	AG	113/142	17.4 (7.71)	1.39 (0.91, 2.13)	0.08
	AA	46/81	17.9 (6.64)	1.04 (0.63, 1.73)	0.56
Additive (per allele)				1.03 (0.80, 1.32)	0.81
GCrs222023	GG	62/106	17.6 (6.45)	Ref	Ref
	AG	103/135	17.4 (6.85)	1.25 (0.82, 1.88)	0.24
	AA	41/63	17.6 (7.48)	1.01 (0.60, 1.68)	0.65

Additive (per allele)				1.02 (0.80, 1.32)	0.85
GCrs222040	GG	74/105	17.4 (7.52)	Ref	Ref
	AG	106/153	17.2 (7.06)	1.02 (0.69, 1.51)	0.70
	AA	32/53	18.9 (7.92)	0.90 (0.53, 1.54)	0.65
Additive (per allele)				0.96 (0.74, 1.25)	0.78
GCrs222049	CC	165/229	17.4 (7.47)	Ref	Ref
	CG	46/72	17.6 (7.06)	0.87 (0.57, 1.33)	0.23
	GG	2/10	21.3 (6.58)	0.27 (0.06, 1.23)	0.11
Additive (per allele)				0.76 (0.52, 1.09)	0.14
GCrs222054	CC	148/187	17.1 (7.58)	Ref	Ref
	CG	61/108	18.1 (6.91)	0.71 (0.49, 1.05)	0.40
	GG	4/16	19.3 (7.44)	0.29 (0.09, 0.90)	0.06
Additive (per allele)				**0.65 (0.47, 0.90)**	**0.01**
GCrs705117	GG	110/160	17.4 (7.54)	Ref	Ref
	AG	79/123	17.8 (7.37)	1.02 (0.70, 1.49)	0.34
	AA	24/28	17.0 (6.54)	1.55 (0.82, 2.90)	0.16
Additive (per allele)				1.15 (0.88, 1.52)	0.31
GCrs705119	AA	153/206	17.3 (7.56)	Ref	Ref
	AC	53/95	18.0 (7.01)	0.80 (0.53, 1.20)	0.31
	CC	7/10	18.2 (6.58)	1.21 (0.42, 3.44)	0.57
Additive (per allele)				0.89 (0.63, 1.27)	0.51
GCrs705120	CC	57/80	17.6 (7.54)	Ref	Ref
	AC	100/149	17.5 (7.29)	0.95 (0.62, 1.45)	1.00
	AA	52/78	17.6 (7.21)	0.90 (0.55, 1.47)	0.69
Additive (per allele)				0.95 (0.74, 1.21)	0.66
GCrs705124	GG	128/170	17.5 (7.51)	Ref	Ref

	AG	73/116	17.6 (7.23)	0.81 (0.56,1.19)	0.83
	AA	12/25	18.1 (7.16)	0.60 (0.29, 1.24)	0.26
Additive (per allele)				0.79 (0.60, 1.06)	0.11
GCrs705125	CC	74/103	17.6 (7.98)	Ref	Ref
	AC	99/142	17.5 (7.40)	1.04 (0.70, 1.55)	0.66
	AA	39/66	17.7 (6.26)	0.92 (0.55, 1.53)	0.65
Additive (per allele)				0.97 (0.75, 1.24)	0.80
GCrs1352845	AA	129/185	17.3 (7.02)	Ref	Ref
	AG	47/91	18.6 (8.01)	0.72 (0.47, 1.10)	0.02
	GG	37/35	16.4 (7.74)	1.44 (0.86, 2.43)	0.04
Additive (per allele)				1.08 (0.84, 1.37)	0.56
GCrs1491710	AA	73/124	18.1 (7.36)	Ref	Ref
	AC	101/143	17.5 (7.14)	1.18 (0.79, 1.74)	0.74
	CC	39/40	15.9 (7.85)	1.57 (0.92, 2.67)	0.14
Additive (per allele)				1.24 (0.96, 1.60)	0.11
GCrs1873590	AA	164/252	17.8 (7.41)	Ref	Ref
	AG	44/58	16.7 (7.11)	1.09 (0.70, 1.70)	0.12
	GG	5/1	9.92 (4.33)	7.57 (0.87, 66.0)	0.07
Additive (per allele)				1.29 (0.87, 1.93)	0.20
GCrs2282679	AA	174/274	17.8 (7.50)	Ref	Ref
	AC	34/32	16.1 (6.21)	1.85 (1.09, 3.14)	0.47
	CC	5/5	16.0 (8.24)	1.90 (0.53, 6.80)	0.61
Additive (per allele)				**1.65 (1.08, 2.51)**	**0.02**
GCrs3733359	GG	125/174	17.3 (6.99)	Ref	Ref
	AG	70/115	18.2 (7.81)	0.83 (0.57, 1.21)	0.40
	AA	17/22	16.7 (7.99)	1.00 (0.51, 1.98)	0.77

Additive (per allele)				0.92 (0.70, 1.22)	0.56
GCrs3755967	GG	170/271	17.8 (7.46)	Ref	Ref
	AG	38/35	16.3 (6.63)	1.88 (1.13, 3.12)	0.45
	AA	5/5	16.0 (8.24)	1.91 (0.53, 6.86)	0.61
Additive (per allele)				**1.67 (1.11, 2.53)**	**0.01**
GCrs3775152	CC	99/170	18.2 (7.22)	Ref	Ref
	AC	91/112	16.9 (7.50)	1.32 (0.91, 1.93)	0.47
	AA	23/29	17.1 (7.56)	1.29 (0.70, 2.38)	0.70
Additive (per allele)				1.20 (0.92, 1.57)	0.18
GCrs4364228	AA	81/118	17.5 (7.41)	Ref	Ref
	AG	98/141	17.2 (7.09)	0.98 (0.66, 1.44)	0.89
	GG	34/51	18.4 (8.02)	0.91 (0.54, 1.54)	0.73
Additive (per allele)				0.96 (0.75, 1.23)	0.75
GCrs6817912	GG	173/248	17.4 (7.24)	Ref	Ref
	AG	36/61	18.2 (7.50)	0.82 (0.52, 1.30)	0.17
	AA	4/2	18.4 (14.12)	2.58 (0.47, 14.4)	0.23
Additive (per allele)				0.95 (0.64, 1.43)	0.82
GCrs10488854	GG	162/244	17.8 (7.47)	Ref	Ref
	AG	46/64	16.9 (7.12)	1.05 (0.68, 1.62)	0.36
	AA	5/3	15.01 (5.67)	2.38 (0.56, 10.2)	0.26
Additive (per allele)				1.15 (0.79, 1.69)	0.45
GCrs16846912	AA	124/191	17.6 (7.22)	Ref	Ref
	AG	77/106	17.4 (7.49)	1.09 (0.75, 1.59)	0.96
	GG	12/14	17.7 (8.69)	1.23 (0.55, 2.77)	0.69
Additive (per allele)				1.10 (0.82, 1.48)	0.53
GCrs16847015	CC	148/221	17.4 (7.04)	Ref	Ref

	AC	56/85	18.0 (7.99)	0.94 (0.63, 1.40)	0.14
	AA	9/5	15.7 (9.61)	2.38 (0.78, 7.31)	0.12
Additive (per allele)				1.11 (0.79, 1.55)	0.55
GCrs16847019	GG	168/235	17.6 (7.36)	Ref	Ref
	AG	43/73	17.3 (7.20)	0.77 (0.50, 1.19)	0.64
	AA	2/3	22.4 (11.9)	0.96 (0.16, 5.83)	0.93
Additive (per allele)				0.80 (0.54, 1.20)	0.28
GCrs16847024	GG	181/270	17.6 (7.32)	Ref	Ref
	AG	29/37	17.1 (7.62)	1.17 (0.69, 1.99)	0.82
	AA	3/4	15.4 (9.16)	1.12 (0.25, 5.12)	0.97
Additive (per allele)				1.14 (0.73, 1.77)	0.57
GCrs373749	GG	147/218	17.6 (7.36)	Ref	Ref
	AG	58/85	17.7 (7.49)	0.98 (0.66, 1.46)	0.69
	AA	7/8	16.4 (6.70)	1.24 (0.44, 3.51)	0.67
Additive (per allele)				1.03 (0.73, 1.43)	0.89
GCrs16847028	GG	160/246	17.6 (7.27)	Ref	Ref
	AG	49/62	17.4 (7.84)	1.23 (0.80, 1,88)	0.89
	AA	4/3	14.6 (5.94)	1.70 (0.37, 7.76)	0.58
Additive (per allele)				1.24 (0.85, 1.82)	0.26
GCrs17467825	AA	166/268	17.8 (7.43)	Ref	Ref
	AG	38/33	16.11 (6.81)	2.00 (1.20, 3.36)	0.58
	GG	5/4	14.7 (7.47)	2.51 (0.65, 9.72)	0.41
Additive (per allele)				**1.85 (1.21, 2.83)**	**0.005**

* <15ng/ml = below
** adjusted for age and African ancestry

Table 4.7 Additive Model - Genotype frequencies by 25(OH)D cut-point and association between SNPs and vitamin D status among European Americans					
Gene + SNP rs#	**Genotype**	**European American (N = 657) below/above***	**25(OH)D Mean, SD**	**OR, 95% CI**	**P-value**
GCrs4588	CC	68/254	26.7 (11.5)	Ref	Ref
	AC	91/188	23.0 (6.93)	1.81 (1.26, 2.62)	0.74
	AA	26/26	21.2 (7.06)	3.77 (2.05, 6.92)	0.001
Additive (per allele)				**1.89 (1.45, 2.48)**	**<.0001**
GCrs7041	CC	41/155	27.3 (13.5)	Ref	Ref
	AC	96/240	24.0 (7.02)	1.51 (0.99, 2.29)	0.67
	AA	51/73	22.2 (7.35)	2.65 (1.61, 4.35)	0.0003
Additive (per allele)				**1.63 (1.27, 2.09)**	**0.0001**
GCrs188812	AA	148/385	24.8 (9.96)	Ref	Ref
	AT	37/76	23.9 (8.40)	1.27 (0.82, 1.97)	0.53
	TT	3/8	25.9 (6.40)	0.98 (0.26, 3.75)	0.84
Additive (per allele)				1.18 (0.81, 1.71)	0.39
GCrs222016	AA	134/334	24.6 (10.21)	Ref	Ref
	AG	50/126	24.7 (8.23)	0.99 (0.67, 1.45)	0.85
	GG	4/9	25.7 (6.57)	1.11 (0.34, 3.68)	0.85
Additive (per allele)				1.01 (0.72, 1.41)	0.98
GCrs222023	GG	168/402	24.45 (9.84)	Ref	Ref
	AG	17/52	25.5 (8.09)	0.77 (0.43, 1.38)	0.36
	AA	1/1	25.0 (10.3)	2.42 (0.15, 38.9)	0.48
Additive (per allele)				0.85 (0.49, 1.46)	0.55

GCrs222040	AA	44/157	27.2 (13.4)	Ref	Ref
	AG	94/240	24.0 (7.03)	1.39 (0.92, 2.10)	0.46
	GG	50/71	22.2 (7.41)	2.53 (1.54, 4.14)	0.0004
Additive (per allele)				**1.58 (1.23, 2.03)**	**0.0003**
GCrs222049	CC	167/409	24.7 (9.96)	Ref	Ref
	CG	21/59	24.4 (7.22)	0.87 (0.51, 1.48)	0.98
	GG	0/1	29.6 (-)	<0.001 (<0.001, >999.9)	0.98
Additive (per allele)				0.85 (0.50, 1.42)	0.53
GCrs222054	CC	101/234	24.2 (8.27)	Ref	Ref
	CG	77/193	24.8 (11.4)	0.93 (0.65, 1.32)	0.34
	GG	10/42	26.9 (7.73)	0.55 (0.27, 1.15)	0.13
Additive (per allele)				0.83 (0.63, 1.09)	0.18
GCrs705117	AA	139/334	24.7 (10.4)	Ref	Ref
	AG	47/126	24.31 (7.38)	0.89 (0.61, 1.32)	0.65
	GG	2/9	27.9 (7.62)	0.54 (0.11, 2.52)	0.47
Additive (per allele)				086 (0.60, 1.22)	0.39
GCrs705119	CC	47/161	27.0 (13.2)	Ref	Ref
	AC	93/243	24.1 (7.01)	1.31 (0.88, 1.96)	0.26
	AA	48/65	22.0 (7.51)	2.54 (1.55, 4.18)	0.0002
Additive (per allele)				**1.57 (1.22, 2.02)**	**0.0004**
GCrs705120	CC	49/165	26.8 (13.1)	Ref	Ref
	AC	92/238	24.1 (7.01)	1.31 (0.88, 1.95)	0.30
	AA	47/65	22.0 (7.53)	2.46 (1.50, 4.03)	0.0004
Additive (per allele)				**1.55 (1.20, 1.98)**	**0.0006**
GCrs705124	GG	150/382	24.8 (9.99)	Ref	Ref
	AG	32/76	24.4 (8.24)	1.08 (0.68, 1.70)	0.77

	AA	5/9	24.0 (7.17)	1.42 (0.47, 4.32)	0.58
Additive (per allele)				1.12 (0.78, 1.62)	0.54
GCrs705125	AA	124/314	24.8 (10.5)	Ref	Ref
	AC	56/140	24.2 (7.62)	1.01 (0.70, 1.47)	0.45
	CC	8/13	25.8 (9.67)	1.56 (0.63, 3.87)	0.34
Additive (per allele)				1.10 (0.81, 1.49)	0.56
GCrs1352845	AA	163/392	24.5 (9.93)	Ref	Ref
	AG	17/66	25.9 (7.80)	0.61 (0.35, 1.08)	0.02
	GG	8/10	24.3 (8.94)	1.95 (0.75, 5.04)	0.07
Additive (per allele)				0.96 (0.65, 1.40)	0.82
GCrs1491710	AA	183/464	24.7 (9.68)	Ref	Ref
	AC	5/5	19.8 (6.41)	2.59 (0.71, 9.51)	0.15
	CC	-	-	-	-
Additive (per allele)				2.59 (0.71, 9.51)	0.15
GCrs1873590	AA	185/468	24.7 (9.65)	Ref	Ref
	AG	3/0	12.9 (3.62)	<0.001 (<0.001, >999.9)	0.98
	GG	-	-	-	-
Additive (per allele)				>999 (>0.001, >999)	0.98
GCrs2282679	AA	73/259	26.4 (11.4)	Ref	Ref
	AC	89/182	23.1 (6.94)	1.74 (1.21, 2.50)	0.75
	CC	26/27	21.3 (7.07)	3.44 (1.89, 6.26)	0.001
Additive (per allele)				**1.81 (1.39, 2.36)**	**<.0001**
GCrs3733359	GG	168/408	24.6 (9.92)	Ref	Ref
	AG	18/60	25.1 (7.51)	0.72 (0.41, 1.26)	0.09
	AA	2/1	22.8 (8.24)	4.90 (0.44, 54.5)	0.16
Additive (per allele)				0.87 (0.53, 1.44)	0.60

GCrs3755967	GG	69/253	26.7 (11.5)	Ref	Ref
	AG	93/189	23.0 (6.92)	1.81 (1.26, 2.61)	0.84
	AA	26/27	21.3 (7.07)	3.56 (1.95, 6.50)	0.001
Additive (per allele)				**1.86 (1.42, 2.43)**	**<.0001**
GCrs3775152	AA				
	AC				
	CC				
Additive (per allele)					
GCrs4364228	AA	162/405	24.7 (9.98)	Ref	Ref
	AG	25/62	24.45 (7.36)	1.01 (0.61, 1.66)	0.87
	GG	1/2	23.7 (5.19)	1.26 (0.11, 13.9)	0.86
Additive (per allele)				1.02 (0.64, 1.63)	0.92
GCrs6817912	GG	166/408	24.6 (9.93)	Ref	Ref
	AG	20/60	25.0 (7.50)	0.82 (0.48, 1.40)	0.13
	AA	2/1	22.8 (8.24)	4.96 (0.45, 55.1)	0.17
Additive (per allele)				0.96 (0.59, 1.57)	0.88
GCrs10488854	GG	185/465	24.7 (9.67)	Ref	Ref
	AG	3/4	19.67 (7.06)	1.88 (0.38, 9.35)	0.44
	AA	-	-	-	-
Additive (per allele)				1.88 (0.38, 9.35)	0.44
GCrs16846912	AA	186/468	24.67 (9.67)	Ref	Ref
	AG	2/1	20.2 (5.92)	5.16 (0.46, 57.5)	0.18
	GG	-	-	-	-
Additive (per allele)				5.16 (0.46, 57.5)	0.18
GCrs16847015	CC	173/422	24.5 (9.84)	Ref	Ref
	AC	14/46	25.7 (7.61)	0.74 (0.40, 1.38)	0.33

	AA	1/1	25.0 (10.3)	2.47 (0.15, 39.8)	0.46
Additive (per allele)				0.74 (0.40, 1.38)	0.33
GCrs16847019	GG	186/465	24.7 (9.64)	Ref	Ref
	AG	2/4	24.9 (12.1)	1.24 (0.23, 6.85)	0.80
	AA	-	-	-	-
Additive (per allele)				<0.001 (<0.001, >999)	0.80
GCrs16847024	GG	188/464	24.7 (9.69)	Ref	Ref
	AG	0/5	25.43 (2.73)	<0.001 (<0.001, >999.9)	0.98
	AA	-	-	-	-
Additive (per allele)				0.76 (0.53, 1.10)	0.98
GCrs373749	GG				
	AG				
	AA				
Additive (per allele)					
GCrs16847028	GG	146/381	24.9 (10.1)	Ref	Ref
	AG	39/80	23.4 (7.34)	1.28 (0.83, 1.96)	0.52
	AA	3/8	27.6 (9.39)	0.98 (0.26, 3.75)	0.83
Additive (per allele)				1.18 (0.82, 1.71)	0.37
GCrs17467825	AA	69/249	26.6 (11.5)	Ref	Ref
	AG	91/186	23.0 (6.87)	1.77 (1.23, 2.56)	0.78
	GG	26/27	21.3 (7.07)	3.50 (1.92, 6.39)	0.0009
Additive (per allele)				**1.83 (1.41, 2.40)**	**<.0001**

* <20ng/ml = below
** adjusted for age and European ancestry

Table 4.8 Recessive model - Genotype frequencies and association between SNPs and aggressive prostate cancer among African Americans				
Gene + SNP rs#	**Genotype**	**African American (N = 524) case/control**	**OR, 95% CI***	**P-value***
GCrs4588	AC+CC	210/296	Ref	Ref
	AA	6/6	1.39 (0.44, 4.44)	0.58
GCrs7041	AA+AC	210/293	Ref	Ref
	CC	7/14	0.68 (0.26, 1.76)	0.42
GCrs188812	AA+AT	214/296	Ref	Ref
	TT	3/11	0.35 (0.10, 1.27)	0.11
GCrs222016	AG+GG	161/236	Ref	Ref
	AA	56/71	1.17 (0.77, 1.76)	0.47
GCrs222023	AG+GG	173/233	Ref	Ref
	AA	39/65	0.82 (0.52, 1.28)	0.37
GCrs222040	AG+GG	184/254	Ref	Ref
	AA	33/52	0.87(0.54, 1.41)	0.58
GCrs222049	CC+CG	210/302	Ref	Ref
	GG	7/5	2.09 (0.65, 6.72)	0.22
GCrs222054	CC+CG	210/294	Ref	Ref
	GG	7/13	0.84 (0.33, 2.16)	0.72
GCrs705117	AG+GG	194/278	Ref	Ref
	AA	23/29	1.13 (0.62, 2.06)	0.68
GCrs705119	AA+AC	212/295	Ref	Ref
	CC	5/12	0.57 (0.19, 1.71)	0.32
GCrs705120	AC+CC	159/227	Ref	Ref

	AA	54/76	1.04 (0.69, 1.56)	0.86
GCrs705124	AG+GG	206/281	Ref	Ref
	AA	11/26	0.59 (0.29, 1.23)	0.16
GCrs705125	AC+CC	172/246	Ref	Ref
	AA	45/60	1.08 (0.69, 1.67)	0.75
GCrs1352845	AA+AG	190/262	Ref	Ref
	GG	27/45	0.82 (0.49, 1.38)	0.46
GCrs1491710	AA+AC	182/259	Ref	Ref
	CC	32/47	0.97 (0.60, 1.60)	0.92
GCrs1873590	AA+AG	214/302	Ref	Ref
	GG	1/5	0.27 (0.03, 2.35)	0.24
GCrs2282679	AA+AC	213/301	Ref	Ref
	CC	4/6	0.84 (0.23, 3.04)	0.79
GCrs3733359	AG+GG	196/288	Ref	Ref
	AA	21/18	1.73 (0.89, 3.36)	0.10
GCrs3755967	AG+GG	213/301	Ref	Ref
	AA	4/6	0.84 (0.23, 3.04)	0.79
GCrs3775152	AC+CC	201/271	Ref	Ref
	AA	16/36	0.58 (0.31, 1.09)	0.09
GCrs4364228	AA+AG	179/259	Ref	Ref
	GG	37/48	1.14 (0.71, 1.82)	0.60
GCrs6817912	AG+GG	216/302	Ref	Ref
	AA	1/5	0.29 (0.03, 2.55)	0.27
GCrs10488854	AG+GG	213/202	Ref	Ref
	AA	4/4	1.38 (0.34, 5.62)	0.66
GCrs16846912	AA+AG	208/290	Ref	Ref

	GG	9/17	0.74 (0.32, 1.70)	0.47
GCrs16847015	AC+CC	215/295	Ref	Ref
	AA	2/12	0.24 (0.05, 1.07)	0.06
GCrs16847019	AG+GG	215/304	Ref	Ref
	AA	2/3	0.88 (0.14, 5.30)	0.88
GCrs16847024	AG+GG	213/304	Ref	Ref
	AA	4/3	1.75 (0.38, 7.99)	0.47
GCrs373749	AG+GG	211/297	Ref	Ref
	AA	6/9	0.91 (0.32, 2.61)	0.86
GCrs16847028	AG+GG	215/302	Ref	Ref
	AA	2/5	0.64 (0.12, 3.37)	0.60
GCrs17467825	AA+AG	211/294	Ref	Ref
	GG	3/6	0.60 (0.15, 2.45)	0.47
* adjusted for age and African ancestry				

Table 4.9 Recessive model - Genotype frequencies and association between SNPs and aggressive prostate cancer among European Americans				
Gene + SNP rs#	**Genotype**	**European American (N = 657) cases/control**	**OR, 95% CI***	**P-value***
GCrs4588	AC+CC	169/432	Ref	Ref
	AA	17/35	1.19 (0.64, 2.21)	0.59
GCrs7041	AC+CC	160/372	Ref	Ref
	AA	26/98	0.63 (0.39, 1.02)	0.06
GCrs188812	AA+AT	182/464	Ref	Ref
	TT	5/6	1.79 (0.52, 6.16)	0.35
GCrs222016	AA+AG	182/462	Ref	Ref
	GG	5/8	1.40 (0.44, 4.46)	0.57
GCrs222023	AG+GG	184/455	Ref	Ref
	AA	0/2	<0.001 (<0.001, >999.999)	0.98
GCrs222040	AA+AG	161/374	Ref	Ref
	GG	26/95	0.66 (0.41, 1.07)	0.09
GCrs222049	CC+CG	186/470	Ref	Ref
	GG	1/0	<0.001 (<0.001, >999.999)	0.98
GCrs222054	CC+CG	172/433	Ref	Ref
	GG	15/37	1.03 (0.55, 1.96)	0.92
GCrs705117	AA+AG	186/460	Ref	Ref
	GG	1/10	0.26 (0.03, 2.04)	0.20
GCrs705119	AC+CC	162/382	Ref	Ref
	AA	25/88	0.69 (0.43, 1.13)	0.14
GCrs705120	AC+CC	162/382	Ref	Ref

	AA	25/87	0.70 (0.43, 1.15)	0.16
GCrs705124	AG+GG	180/460	Ref	Ref
	AA	7/7	2.20 (0.74, 6.54)	0.15
GCrs705125	AA+AC	181/453	Ref	Ref
	CC	6/15	0.92 (0.34, 2.44)	0.86
GCrs1352845	AA+AG	182/456	Ref	Ref
	GG	4/14	0.59 (0.19, 1.83)	0.36
GCrs1491710	AA+AC	187/470	Ref	Ref
	CC	0/0	-	-
GCrs1873590	AA+AG	186/470	Ref	Ref
	GG	0/0	-	-
GCrs2282679	AA+AC	169/434	Ref	Ref
	CC	18/35	1.27 (0.69, 2.34)	0.44
GCrs3733359	AG+GG	186/468	Ref	Ref
	AA	1/2	1.55 (0.14, 17.5)	0.72
GCrs3755967	AG+GG	169/435	Ref	Ref
	AA	18/35	1.28 (0.70, 2.35)	0.43
GCrs3775152	AA+AC			
	CC			
GCrs4364228	AA+AG	186/468	Ref	Ref
	GG	1/2	1.17 (0.10, 13.4)	0.90
GCrs6817912	AG+GG	186/468	Ref	Ref
	AA	1/2	1.55 (0.14, 17.5)	0.72
GCrs10488854	AG+GG	187/470	Ref	Ref
	AA	0/0	-	-
GCrs16846912	AA+AG	187/470	Ref	Ref

	GG	0/0	-	-
GCrs16847015	AC+CC	187/468	Ref	Ref
	AA	0/2	<0.001 (<0.001, >999.999)	0.98
GCrs16847019	AG+GG	187/470	Ref	Ref
	AA	0/0	-	-
GCrs16847024	AG+GG	187/470	Ref	Ref
	AA	0/0	-	-
GCrs373749	AG+GG			
	AA			
GCrs16847028	AG+GG	182/464	Ref	Ref
	AA	5/6	1.82 (0.53, 6.26)	0.34
GCrs17467825	AA+AG	169/426	Ref	Ref
	GG	18/35	1.25 (0.68, 2.30)	0.48
* adjusted for age and European ancestry				

Table 4.10 Recessive Model - Genotype frequencies by 25(OH)D cut-point and association between SNPs and vitamin D status among African Americans					
Gene + SNP rs#	**Genotype**	**African American (N = 524) below/above***	**25(OH)D Mean, SD**	**OR, 95% CI***	**P-value***
GCrs4588	AC+CC	204/302	17.6 (7.39)	Ref	Ref
	AA	7/5	15.3 (7.96)	2.38 (0.73, 7.80)	0.15
GCrs7041	AA+AC	204/299	17.6 (7.39)	Ref	Ref
	CC	9/12	17.3 (7.18)	1.34 (0.54, 3.35)	0.53
GCrs188812	AA+AT	208/302	17.6 (7.39)	Ref	Ref
	TT	5/9	16.4 (7.02)	0.82 (0.27, 2.49)	0.72
GCrs222016	AG+GG	167/230	17.4 (7.60)	Ref	Ref
	AA	46/81	17.9 (6.64)	0.84 (0.55, 1.27)	0.40
GCrs222023	AG+GG	165/241	17.5 (7.30)	Ref	Ref
	AA	41/63	17.6 (7.48)	0.88 (0.56, 1.37)	0.57
GCrs222040	AG+GG	180/158	17.3 (7.24)	Ref	Ref
	AA	32/53	18.9 (7.92)	0.89 (0.55, 1.45)	0.64
GCrs222049	CC+CG	211/301	17.5 (7.38)	Ref	Ref
	GG	2/10	21.3 (6.58)	0.27 (0.06, 1.27)	0.10
GCrs222054	CC+CG	209/295	17.5 (7.37)	Ref	Ref
	GG	4/16	19.3 (7.44)	**0.33 (0.11, 0.998)**	**0.05**
GCrs705117	AG+GG	189/283	17.6 (7.46)	Ref	Ref
	AA	24/28	17.0 (6.54)	1.53 (0.84, 2.80)	0.16
GCrs705119	AA+AC	206/301	17.5 (7.40)	Ref	Ref
	CC	7/10	18.2 (6.58)	1.31 (0.47, 3.71)	0.61
GCrs705120	AC+CC	157/229	17.5 (7.37)	Ref	Ref

	AA	52/78	17.6 (7.21)	0.93 (0.62, 1.40)	0.72
GCrs705124	AG+GG	201/286	17.5 (7.40)	Ref	Ref
	AA	12/25	18.1 (7.16)	0.65 (0.32, 1.33)	0.24
GCrs705125	AC+CC	173/245	17.5 (7.64)	Ref	Ref
	AA	39/66	17.7 (6.26)	0.90 (0.57, 1.41)	0.64
GCrs1352845	AA+AG	176/276	17.7 (7.35)	Ref	Ref
	GG	37/35	16.4 (7.74)	1.59 (0.96, 2.64)	0.07
GCrs1491710	AA+AC	174/267	17.8 (7.24)	Ref	Ref
	CC	39/40	15.9 (7.85)	1.43 (0.88, 2.32)	0.15
GCrs1873590	AA+AG	208/310	17.6 (7.36)	Ref	Ref
	GG	5/1	9.92 (4.33)	7.43 (0.85, 64.7)	0.07
GCrs2282679	AA+AC	208/306	17.6 (7.36)	Ref	Ref
	CC	5/5	16.0 (8.24)	1.73 (0.48, 6.15)	0.40
GCrs3733359	AG+GG	195/289	17.6 (7.31)	Ref	Ref
	AA	17/22	16.7 (7.99)	1.08 (0.56, 2.10)	0.82
GCrs3755967	AG+GG	208/306	17.6 (7.36)	Ref	Ref
	AA	5/5	16.0 (8.24)	1.73 (0.48, 6.15)	0.40
GCrs3775152	AC+CC	190/282	17.6 (7.36)	Ref	Ref
	AA	23/29	17.1 (7.56)	1.14 (0.63, 2.03)	0.67
GCrs4364228	AA+AG	179/259	17.4 (7.23)	Ref	Ref
	GG	34/51	18.4 (8.02)	0.92 (0.57, 1.49)	0.74
GCrs6817912	AG+GG	209/309	17.5 (7.29)	Ref	Ref
	AA	4/2	18.4 (14.12)	2.68 (0.48, 14.9)	0.26
GCrs10488854	AG+GG	208/308	17.6 (7.40)	Ref	Ref
	AA	5/3	15.01 (5.67)	2.35 (0.55, 10.0)	0.25
GCrs16846912	AA+AG	201/297	17.5 (7.31)	Ref	Ref

	GG	12/14	17.7 (8.69)	1.19 (0.53, 2.64)	0.67
GCrs16847015	AC+CC	204/306	17.6 (7.31)	Ref	Ref
	AA	9/5	15.7 (9.61)	2.43 (0.80, 7.40)	0.12
GCrs16847019	AG+GG	211/308	17.5 (7.32)	Ref	Ref
	AA	2/3	22.4 (11.9)	1.02 (0.17, 6.17)	0.99
GCrs16847024	AG+GG	210/307	17.6 (7.35)	Ref	Ref
	AA	3/4	15.4 (9.16)	1.09 (0.24, 4.99)	0.91
GCrs373749	AG+GG	205/303	17.6 (7.38)	Ref	Ref
	AA	7/8	16.4 (6.70)	1.25 (0.44, 3.51)	0.68
GCrs16847028	AG+GG	209/308	17.6 (7.39)	Ref	Ref
	AA	4/3	14.6 (5.94)	1.63 (0.36, 7.40)	0.53
GCrs17467825	AA+AG	204/301	17.6 (7.36)	Ref	Ref
	GG	5/4	14.7 (7.47)	2.24 (0.58, 8.63)	0.24

* <15ng/ml = below
** adjusted for age and African ancestry

Table 4.11Recessive Model - Genotype frequencies by 25(OH)D cut-point and association between SNPs and vitamin D status among European Americans					
Gene + SNP rs#	**Genotype**	**European American (N = 657) below/above***	**25(OH)D Mean, SD**	**OR, 95% CI**	**P-value**
GCrs4588	AC+CC	159/442	25.0 (9.81)	Ref	Ref
	AA	26/26	21.2 (7.06)	**2.80 (1.58, 4.97)**	**0.0004**
GCrs7041	AC+CC	137/395	25.2 (10.0)	Ref	Ref
	AA	51/73	22.2 (7.35)	**2.02 (1.35, 3.04)**	**0.0007**
GCrs188812	AA+AT	185/461	24.6 (9.70)	Ref	Ref
	TT	3/8	25.9 (6.40)	0.94 (0.25, 3.58)	0.92
GCrs222016	AA+AG	184/460	24.6 (9.71)	Ref	Ref
	GG	4/9	25.7 (6.57)	1.12 (0.934, 3.68)	0.86
GCrs222023	AG+GG	185/454	24.6 (9.66)	Ref	Ref
	AA	1/1	25.0 (10.3)	2.47 (0.15, 39.8)	0.52
GCrs222040	AA+AG	138/397	25.2 (10.0)	Ref	Ref
	GG	50/71	22.2 (7.41)	**2.04 (1.35, 3.08)**	**0.0007**
GCrs222049	CC+CG	188/468	24.7 (9.66)	Ref	Ref
	GG	0/1	29.6 (-)	<0.001 (<0.001, >999.999)	0.98
GCrs222054	CC+CG	178/427	24.5 (9.78)	Ref	Ref
	GG	10/42	26.9 (7.73)	0.57 (0.28, 1.17)	0.13
GCrs705117	AA+AG	186/460	24.6 (9.68)	Ref	Ref
	GG	2/9	27.9 (7.62)	0.55 (0.12, 2.58)	0.45
GCrs705119	AC+CC	140/404	25.2 (9.96)	Ref	Ref
	AA	48/65	22.0 (7.51)	**2.15 (1.41, 3.27)**	**0.0004**
GCrs705120	AC+CC	141/403	25.2 (9.94)	Ref	Ref

	AA	47/65	22.0 (7.53)	**2.08 (1.36, 3.18)**	**0.0007**
GCrs705124	AG+GG	182/458	24.7 (9.71)	Ref	Ref
	AA	5/9	24.0 (7.17)	1.40 (0.46, 4.26)	0.55
GCrs705125	AA+AC	180/454	24.6 (9.66)	Ref	Ref
	CC	8/13	25.8 (9.67)	1.56 (0.63, 3.83)	0.33
GCrs1352845	AA+AG	180/458	24.7 (9.68)	Ref	Ref
	GG	8/10	24.3 (8.94)	2.05 (0.79, 5.30)	0.14
GCrs1491710	AA+AC	188/469	24.7 (9.65)	Ref	Ref
	CC	-	-	-	-
GCrs1873590	AA+AG	188/468	24.7 (9.66)	Ref	Ref
	GG	-	-	-	-
GCrs2282679	AA+AC	162/441	25.0 (9.81)	Ref	Ref
	CC	26/27	21.3 (7.07)	**2.64 (1.49, 4.66)**	**0.0008**
GCrs3733359	AG+GG	186/468	24.7 (9.66)	Ref	Ref
	AA	2/1	22.8 (8.24)	5.08 (0.46, 56.4)	0.19
GCrs3755967	AG+GG	162/442	25.0 (9.80)	Ref	Ref
	AA	26/27	21.3 (7.07)	**2.65 (1.50, 4.67)**	**0.0008**
GCrs3775152	AA+AC				
	CC				
GCrs4364228	AA+AG	187/467	24.7 (9.67)	Ref	Ref
	GG	1/2	23.7 (5.19)	1.25 (0.11, 13.9)	0.85
GCrs6817912	AG+GG	186/468	24.7 (9.66)	Ref	Ref
	AA	2/1	22.8 (8.24)	5.08 (0.46, 56.4)	0.19
GCrs10488854	AG+GG	188/469	24.7 (9.65)	Ref	Ref
	AA	-	-	-	-
GCrs16846912	AA+AG	188/469	24.7 (9.65)	Ref	Ref

	GG	-	-	-	-
GCrs16847015	AC+CC	187/468	24.6 (9.84)	Ref	Ref
	AA	1/1	25.0 (10.3)	2.53 (0.16, 40.7)	0.51
GCrs16847019	AG+GG	188/469	24.7 (9.65)	Ref	Ref
	AA	-	-	-	-
GCrs16847024	AG+GG	188/469	24.7 (9.65)	Ref	Ref
	AA	-	-	-	-
GCrs373749	AG+GG				
	AA				
GCrs16847028	AG+GG	185/461	24.6 (9.66)	Ref	Ref
	AA	3/8	27.6 (9.39)	0.93 (0.24, 3.57)	0.92
GCrs17467825	AA+AG	160/435	24.9 (9.78)	Ref	Ref
	GG	26/27	21.3 (7.07)	**2.64 (1.49, 4.66)**	**0.0009**

* <20ng/ml = below
** adjusted for age and African ancestry

Table 4.12 Dominant Model - Genotype frequencies and association between SNPs and aggressive prostate cancer among African Americans

Gene + SNP rs#	Genotype	African American (N = 524) cases/control	OR, 95% CI*	P-value*
GCrs4588	CC	172/249	Ref	Ref
	AA+AC	44/53	1.18 (0.75, 1.85)	0.47
GCrs7041	AA	143/208	Ref	Ref
	AC+CC	74/99	1.08 (0.74, 1.59)	0.68
GCrs188812	AA	158/220	Ref	Ref
	AT+TT	59/87	1.06 (0.72, 1.57)	0.77
GCrs222016	GG	50/92	Ref	Ref
	AA+AG	167/215	1.42 (0.94, 2.14)	0.09
GCrs222023	GG	69/99	Ref	Ref
	AA+AG	143/199	1.02 (0.69, 1.50)	0.93
GCrs222040	GG	78/101	Ref	Ref
	AG+AA	139/205	0.88 (0.61, 1.28)	0.50
GCrs222049	CC	158/236	Ref	Ref
	CG+GG	59/71	1.23 (0.82, 1.84)	0.31
GCrs222054	CC	156/179	Ref	Ref
	CG+GG	61/128	**0.55 (0.38, 0.80)**	**0.0019**
GCrs705117	GG	105/165	Ref	Ref
	AA+AG	112/142	1.24 (0.86, 1.77)	0.25
GCrs705119	AA	145/214	Ref	Ref
	AC+CC	72/93	1.16 (0.79, 1.71)	0.46

GCrs705120	CC	53/84	Ref	Ref
	AA+AC	160/219	1.16 (0.77, 1.73)	0.48
GCrs705124	GG	127/171	Ref	Ref
	AA+AG	90/136	0.91 (0.64, 1.30)	0.60
GCrs705125	CC	67/110	Ref	Ref
	AA+AC	150/196	1.27 (0.87, 1.86)	0.22
GCrs1352845	AA	133/181	Ref	Ref
	AG+GG	84/126	0.89 (0.62, 1.28)	0.53
GCrs1491710	AA	86/111	Ref	Ref
	AC+CC	128/195	0.82 (0.56, 1.18)	0.28
GCrs1873590	AA	174/242	Ref	Ref
	AG+GG	43/65	0.93 (0.60, 1.44)	0.73
GCrs2282679	AA	180/268	Ref	Ref
	AC+CC	37/39	1.36 (0.83, 2.23)	0.22
GCrs3733359	GG	123/176	Ref	Ref
	AA+AG	94/130	1.03 (0.72, 1.47)	0.88
GCrs3755967	GG	178/263	Ref	Ref
	AA+AG	39/44	1.29 (0.80, 2.08)	0.30
GCrs3775152	CC	109/160	Ref	Ref
	AA+AC	108/147	1.08 (0.76, 1.54)	0.29
GCrs4364228	AA	86/113	Ref	Ref
	AG+GG	130/194	0.87 (0.61, 1.25)	0.45
GCrs6817912	GG	177/244	Ref	Ref

	AA+AG	40/63	0.89 (0.57, 1.39)	0.61
GCrs10488854	GG	164/242	Ref	Ref
	AA+AG	53/65	1.19 (0.79, 1.81)	0.41
GCrs16846912	AA	138/177	Ref	Ref
	AG+GG	79/130	0.78 (0.54, 1.12)	0.17
GCrs16847015	CC	162/207	Ref	Ref
	AA+AC	55/100	0.72 (0.49, 1.06)	0.23
GCrs16847019	GG	166/237	Ref	Ref
	AA+AG	51/70	1.04 (0.68, 1.57)	0.87
GCrs16847024	GG	182/269	Ref	Ref
	AA+AG	35/38	1.31 (0.79, 2.16)	0.29
GCrs373749	GG	149/216	Ref	Ref
	AA+AG	68/90	1.08 (0.74, 1.59)	0.68
GCrs16847028	GG	179/227	Ref	Ref
	AA+AG	38/80	**0.61 (0.39, 0.94)**	**0.03**
GCrs17467825	AA	176/258	Ref	Ref
	AG+GG	38/42	1.31 (0.81, 2.13)	0.27
* adjusted for age and African ancestry				

Table 4.13 Dominant Model - Genotype frequencies and association between SNPs and aggressive prostate cancer among European Americans

Gene + SNP rs#	Genotype	European American (N = 657) cases/control	OR, 95% CI*	P-value*
GCrs4588	CC	100/222	Ref	Ref
	AA+AC	86/236	0.80 (0.57, 1.14)	0.22
GCrs7041	CC	58/138	Ref	Ref
	AA+AC	128/332	0.93 (0.64, 1.35)	0.69
GCrs188812	AA	156/377	Ref	Ref
	AT+TT	31/93	0.82 (0.52, 1.29)	0.39
GCrs222016	AA	140/328	Ref	Ref
	AG+GG	47/142	0.77 (0.52, 1.14)	0.19
GCrs222023	GG	168/402	Ref	Ref
	AA+AG	16/55	0.66 (0.36, 1.21)	0.18
GCrs222040	AA	60/141	Ref	Ref
	AG+GG	127/328	0.92 (0.63, 1.34)	0.67
GCrs222049	CC	164/412	Ref	Ref
	CG+GG	23/58	1.01 (0.60, 1.70)	0.98
GCrs222054	CC	100/235	Ref	Ref
	CG+GG	87/235	0.92 (0.65, 1.31)	0.66
GCrs705117	AA	138/335	Ref	Ref
	AG+GG	49/135	0.89 (0.60, 1.32)	0.57
GCrs705119	CC	61/147	Ref	Ref
	AA+AC	126/323	0.96 (0.67, 1.40)	0.84

GCrs705120	CC	63/151	Ref	Ref
	AA+AC	124/318	0.97 (0.67, 1.40)	0.86
GCrs705124	GG	155/377	Ref	Ref
	AA+AG	32/90	0.89 (0.56, 1.40)	0.60
GCrs705125	AA	136/302	Ref	Ref
	AC+CC	51/166	0.68 (0.47, 1.00)	**0.05**
GCrs1352845	AA	163/392	Ref	Ref
	AG+GG	23/78	0.67 (0.40, 1.13)	0.13
GCrs1491710	AA	185/462	Ref	Ref
	AC+CC	8-Feb	0.51 (0.10, 2.72)	0.43
GCrs1873590	AA	186/467	Ref	Ref
	AG+GG	0/3	>999.999 (<0.001, >999.999)	0.99
GCrs2282679	AA	101/231	Ref	Ref
	AC+CC	86/238	0.85 (0.60, 1.21)	0.37
GCrs3733359	GG	171/405	Ref	Ref
	AA+AG	16/65	0.56 (0.31, 1.01)	**0.05**
GCrs3755967	GG	100/222	Ref	Ref
	AA+AG	87/248	0.81 (0.57, 1.14)	0.22
GCrs3775152	AA			
	AC+CC			
GCrs4364228	AA	162/405	Ref	Ref
	AG+GG	25/65	0.95 (0.57, 1.58)	0.85
GCrs6817912	GG	172/402	Ref	Ref

	AA+AG	15/68	**0.51 (0.28, 0.93)**	**0.03**
GCrs10488854	GG	185/465	Ref	Ref
	AA+AG	5-Feb	0.70 (0.12, 4.21)	0.70
GCrs16846912	AA	187/467	Ref	Ref
	AG+GG	0/3	>999.999 (<0.001, >999.999)	0.99
GCrs16847015	CC	172/423	Ref	Ref
	AA+AC	15/47	0.77 (0.41, 1.42)	0.40
GCrs16847019	GG	187/464	Ref	Ref
	AA+AG	0/6	>999.999 (<0.001, >999.999)	0.98
GCrs16847024	GG	185/467	Ref	Ref
	AA+AG	3-Feb	1.07 (0.16, 7.10)	0.95
GCrs373749	GG			
	AA+AG			
GCrs16847028	GG	155/372	Ref	Ref
	AA+AG	32/98	0.79 (0.50, 1.23)	0.30
GCrs17467825	AA	100/218	Ref	Ref
	AG+GG	87/243	0.81 (0.57, 1.14)	0.23
* adjusted for age and European ancestry				

Table 4.14 Dominant Model - Genotype frequencies by 25(OH)D cut-point and association between SNPs and vitamin D status among African Americans

Gene + SNP rs#	Genotype	African American (N = 524) below/above*	25(OH)D Mean, SD	OR, 95% CI**	P-value**
GCrs4588	CC	163/258	17.8 (7.54)	Ref	Ref
	AA+AC	48/49	16.4 (6.72)	**1.66 (1.06, 2.61)**	**0.03**
GCrs7041	AA	150/201	17.2 (7.36)	Ref	Ref
	AC+CC	63/100	18.3 (7.37)	0.83 (0.57, 1.22)	0.35
GCrs188812	AA	152/226	17.8 (7.50)	Ref	Ref
	AT+TT	61/85	16.9 (7.03)	1.048 (0.71, 1.55)	0.81
GCrs222016	GG	54/88	17.6 (7.42)	Ref	Ref
	AA+AG	159/223	17.5 (7.37)	1.27 (0.85, 1.91)	0.24
GCrs222023	GG	62/106	17.6 (6.45)	Ref	Ref
	AA+AG	144/198	17.5 (7.73)	1.17 (0.79, 1.73)	0.43
GCrs222040	GG	74/105	17.4 (7.52)	Ref	Ref
	AG+AA	138/206	17.6 (7.31)	0.99 (0.68, 1.44)	0.96
GCrs222049	CC	165/229	17.4 (7.47)	Ref	Ref
	CG+GG	48/82	18.0 (7.07)	0.79 (0.53, 1.20)	0.27
GCrs222054	CC	148/187	17.1 (7.58)	Ref	Ref
	CG+GG	65/124	18.3 (6.96)	**0.66 (0.45, 0.96)**	**0.03**
GCrs705117	GG	110/160	17.4 (7.54)	Ref	Ref
	AA+AG	103/151	17.7 (7.21)	1.10 (0.77, 1.58)	0.61
GCrs705119	AA	153/206	17.3 (7.56)	Ref	Ref

	AC+CC	60/105	18.0 (6.95)	0.83 (0.56, 1.23)	0.34
GCrs705120	CC	57/80	17.6 (7.54)	Ref	Ref
	AA+AC	152/227	17.5 (7.25)	0.93 (0.62, 1.39)	0.72
GCrs705124	GG	128/170	17.5 (7.51)	Ref	Ref
	AA+AG	85/141	17.7 (7.21)	0.78 (0.54, 1.11)	0.16
GCrs705125	CC	74/103	17.6 (7.98)	Ref	Ref
	AA+AC	138/208	17.5 (7.06)	1.00 (0.69, 1.47)	0.99
GCrs1352845	AA	129/185	17.3 (7.02)	Ref	Ref
	AG+GG	84/126	17.8 (7.88)	0.92 (0.64, 1.33)	0.67
GCrs1491710	AA	73/124	18.1 (7.36)	Ref	Ref
	AC+CC	140/183	17.1 (7.34)	1.26 (0.87, 1.83)	0.22
GCrs1873590	AA	164/252	17.8 (7.41)	Ref	Ref
	AG+GG	49/59	16.6 (7.15)	1.20 (0.78, 1.85)	0.41
GCrs2282679	AA	174/274	17.8 (7.50)	Ref	Ref
	AC+CC	39/37	16.1 (6.44)	**1.86 (1.13, 3.06)**	**0.02**
GCrs3733359	GG	125/174	17.3 (6.99)	Ref	Ref
	AA+AG	87/137	17.9 (7.84)	0.85 (0.60, 1.22)	0.39
GCrs3755967	GG	170/271	17.8 (7.46)	Ref	Ref
	AA+AG	43/40	16.2 (6.78)	**1.88 (1.16, 3.05)**	**0.01**
GCrs3775152	CC	99/170	18.2 (7.22)	Ref	Ref
	AA+AC	114/141	16.9 (7.50)	1.32 (0.92, 1.88)	0.13
GCrs4364228	AA	81/118	17.5 (7.41)	Ref	Ref

	AG+GG	132/192	17.5 (7.35)	0.96 (0.67, 1.39)	0.83
GCrs6817912	GG	173/248	17.4 (7.24)	Ref	Ref
	AA+AG	40/63	18.2 (7.92)	0.88 (0.56, 1.37)	0.57
GCrs10488854	GG	162/244	17.8 (7.47)	Ref	Ref
	AA+AG	51/67	16.8 (7.02)	1.11 (0.73, 1.69)	0.63
GCrs16846912	AA	124/191	17.6 (7.22)	Ref	Ref
	AG+GG	89/120	17.5 (7.62)	1.11 (0.78, 1.59)	0.57
GCrs16847015	CC	148/221	17.4 (7.04)	Ref	Ref
	AA+AC	65/90	17.8 (8.14)	1.02 (0.70, 1.50)	0.91
GCrs16847019	GG	168/235	17.6 (7.36)	Ref	Ref
	AA+AG	45/76	17.5 (7.44)	0.78 (0.51, 1.19)	0.25
GCrs16847024	GG	181/270	17.6 (7.32)	Ref	Ref
	AA+AG	32/41	16.9 (7.73)	1.17 (0.71, 1.94)	0.54
GCrs373749	GG	147/218	17.6 (7.36)	Ref	Ref
	AA+AG	65/93	17.5 (7.40)	1.00 (0.68, 1.47)	0.99
GCrs16847028	GG	160/246	17.6 (7.27)	Ref	Ref
	AA+AG	53/65	17.2 (7.75)	1.25 (0.82, 1.90)	0.29
GCrs17467825	AA	166/268	17.8 (7.43)	Ref	Ref
	AG+GG	43/37	16.0 (6.85)	**2.05 (1.26, 3.36)**	**0.0041**
* <15ng/ml = below ** adjusted for age and African ancestry					

Table 4.15 Dominant Model - Genotype frequencies by 25(OH)D cut-point and association between SNPs and vitamin D status among European Americans

Gene + SNP rs#	Genotype	European American (N = 657) below*/above	25(OH)D Mean, SD	OR, 95% CI**	P-value**
GCrs4588	CC	68/254	26.7 (11.5)	Ref	Ref
	AA+AC	117/214	22.7 (6.97)	**2.05 (1.45, 2.91)**	**<.0001**
GCrs7041	CC	41/155	27.3 (13.5)	Ref	Ref
	AA+AC	147/313	23.5 (7.15)	**1.78 (1.19, 2.64)**	**0.0046**
GCrs188812	AA	148/385	24.8 (9.96)	Ref	Ref
	AT+TT	40/84	24.1 (8.24)	1.25 (0.82, 1.90)	0.31
GCrs222016	AA	134/334	24.6 (10.21)	Ref	Ref
	AG+GG	54/135	24.8 (8.12)	0.995 (0.69, 1.45)	0.98
GCrs222023	GG	168/402	24.45 (9.84)	Ref	Ref
	AA+AG	18/53	25.5 (8.07)	0.81 (0.46, 1.42)	0.46
GCrs222040	AA	44/157	27.2 (13.4)	Ref	Ref
	AG+GG	144/311	23.5 (7.17)	**1.65 (1.12, 2.44)**	**0.01**
GCrs222049	CC	167/409	24.7 (9.96)	Ref	Ref
	CG+GG	21/60	24.5 (7.20)	0.86 (0.51, 1.46)	0.57
GCrs222054	CC	101/234	24.2 (8.27)	Ref	Ref
	CG+GG	87/235	25.2 (10.9)	0.86 (0.61, 1.21)	0.38
GCrs705117	AA	139/334	24.7 (10.4)	Ref	Ref
	AG+GG	49/135	24.5 (7.42)	0.87 (0.59, 1.28)	0.47
GCrs705119	CC	47/161	27.0 (13.2)	Ref	Ref

	AA+AC	141/308	23.6 (7.19)	**1.57 (1.07, 2.30)**	**0.02**
GCrs705120	CC	49/165	26.8 (13.1)	Ref	Ref
	AA+AC	139/303	23.6 (7.20)	**1.55 (1.06, 2.26)**	**0.02**
GCrs705124	GG	150/382	24.8 (9.99)	Ref	Ref
	AA+AG	37/85	24.3 (8.10)	1.11 (0.72, 1.71)	0.62
GCrs705125	AA	124/314	24.8 (10.5)	Ref	Ref
	AC+CC	64/153	24.4 (7.83)	1.06 (0.74, 1.52)	0.76
GCrs1352845	AA	163/392	24.5 (9.93)	Ref	Ref
	AG+GG	25/76	25.6 (7.99)	0.79 (0.48, 1.28)	0.33
GCrs1491710	AA	183/464	24.7 (9.68)	Ref	Ref
	AC+CC	5-May	19.8 (6.41)	2.59 (0.71, 9.51)	0.15
GCrs1873590	AA	185/468	24.7 (9.65)	Ref	Ref
	AG+GG	Mar-00	12.9 (3.62)	>999.999 (<0.001, >999.999)	0.98
GCrs2282679	AA	73/259	26.4 (11.4)	Ref	Ref
	AC+CC	115/209	22.8 (6.98)	**1.96 (1.39, 2.77)**	**0.0001**
GCrs3733359	GG	168/408	24.6 (9.92)	Ref	Ref
	AA+AG	20/61	25.0 (7.49)	0.79 (0.46, 1.35)	0.39
GCrs3755967	GG	69/253	26.7 (11.5)	Ref	Ref
	AA+AG	119/216	22.7 (6.96)	**2.03 (1.43, 2.87)**	**<.0001**
GCrs3775152	AA				
	AC+CC				
GCrs4364228	AA	162/405	24.7 (9.98)	Ref	Ref

	AG+GG	26/64	24.5 (7.27)	1.02 (0.62, 1.66)	0.95
GCrs6817912	GG	166/408	24.6 (9.93)	Ref	Ref
	AA+AG	22/61	24.9 (7.48)	0.89 (0.53, 1.49)	0.65
GCrs10488854	GG	185/465	24.7 (9.67)	Ref	Ref
	AA+AG	4-Mar	19.7 (7.06)	1.88 (0.38, 9.35)	0.44
GCrs16846912	AA	186/468	24.67 (9.67)	Ref	Ref
	AG+GG	1-Feb	20.2 (5.92)	5.16 (0.46, 57.5)	0.18
GCrs16847015	CC	173/422	24.5 (9.84)	Ref	Ref
	AA+AC	15/47	25.7 (7.61)	0.77 (0.42, 1.42)	0.41
GCrs16847019	GG	186/465	24.7 (9.64)	Ref	Ref
	AA+AG	4-Feb	24.9 (12.1)	1.24 (0.23, 6.85)	0.80
GCrs16847024	GG	188/464	24.7 (9.69)	Ref	Ref
	AA+AG	0/5	25.4 (2.73)	>999.999 (<0.001, >999.999)	0.98
GCrs373749	GG				
	AA+AG				
GCrs16847028	GG	146/381	24.9 (10.1)	Ref	Ref
	AA+AG	42/88	23.7 (7.58)	1.25 (0.83, 1.89)	0.29
GCrs17467825	AA	69/249	26.6 (11.5)	Ref	Ref
	AG+GG	117/213	22.8 (6.92)	**1.99 (1.40, 2.82)**	**0.0001**

* <20ng/ml = below

** adjusted for age and European ancestry

Table 4.16 Polygenic risk score –Association between polygenic risk score and aggressive prostate cancer and vitamin D status

		Aggressiveness (n)					Low 25(OH)D	High 25(OH)D		Low 25(OH)D	High 25(OH)D	
Race	**Polygenic riskscore**	**High**	**Low**	**Mean 25(OH)D (SD)**	**OR for high aggressive PCa (95%CI)[c]**			**OR for high aggressive PCa (95%CI)[d]**		**OR for high aggressive PCa (95%CI)[e]**	**OR for high aggressive PCa (95%CI)[e]**	
AA[a]	0	38	40	15.8 (6.59)	1.0 (ref)		1.0 (ref)	1.85 (0.75, 4.56)		1.0 (ref)	1.0 (ref)	p for interaction : 0.83[f]
	1	125	157	17.6 (7.69)	0.89 (0.54, 1.49)		1.0 (ref)	1.52 (0.92, 2.49)		0.99 (0.46, 2.11)	0.74 (0.36, 1.53)	
	2	**54**	**110**	**18.3 (7.07)**	**0.54 (0.31, 0.94)**		1.0 (ref)	1.94 (0.93, 4.07)		0.48 (0.20, 1.17)	0.47 (0.22, 1.01)	
EA[b]	0	87	248	22.7 (6.95)	1.0 (ref)		1.0 (ref)	0.80 (0.47, 1.45)		1.0 (ref)	1.0 (ref)	p for interaction : 0.96[f]
	1	42	84	25.7 (7.19)	1.37 (0.87, 2.15)		1.0 (ref)	0.71 (0.28, 1.79)		1.36 (0.55, 3.38)	1.41 (0.82, 2.41)	
	2	58	138	27.3 (13.5)	1.17 (0.79, 1.75)		1.0 (ref)	0.96 (0.44, 2.07)		1.08 (0.48, 2.43)	1.25 (0.78, 2.01)	

[a]Black: rs4588 and rs222054
[b]White: rs4588 and rs7041
[c] association between polygenic risk score and prostate cancer aggressiveness; adjusted for age and ancestry
[d] association between 25(OH)D and prostate cancer aggressiveness stratified by polygenic risk score; adjusted for age and ancestry
[e] association between polygenic risk score and prostate cancer aggressiveness stratified by 25(OH)D; adjusted for age and ancestry
[f] p-value for interaction term for polygenic risk score and 25(OH)D; adjusted for age and ancestry

Table 4.17 Model summaries for SNPs by prostate cancer aggressiveness and 25(OH)D among African Americans						
GC SNPs	**Aggressive PCa[a]**			**25(OH)D[b]**		
	Additive	**Recessive**	**Dominant**	**Additive**	**Recessive**	**Dominant**
rs4588	1.21 (0.68, 2.16)	1.39 (0.44, 4.44)	1.18 (0.75, 1.85)	1.64 (0.90, 2.98)	2.38 (0.73, 7.80)	**1.66 (1.06, 2.61)**
rs222054	**0.63 (0.45, 0.87)**	0.84 (0.33, 2.16)	**0.55 (0.38, 0.80)**	**0.65 (0.47, 0.90)**	**0.33 (0.11, 0.998)**	**0.66 (0.45, 0.96)**
rs16847015	**0.69 (0.49, 0.98)**	0.24 (0.05, 1.07)	0.72 (0.49, 1.06)	1.11 (0.79, 1.55)	2.43 (0.80, 7.40)	1.02 (0.70, 1.50)
rs16847028	**0.64 (0.43, 0.96)**	0.64 (0.12, 3.37)	**0.61 (0.39, 0.94)**	1.24 (0.85, 1.82)	1.63 (0.36, 7.40)	1.25 (0.82, 1.90)
rs2282679	1.22 (0.81, 1.85)	0.84 (0.23, 3.04)	1.36 (0.83, 2.23)	**1.65 (1.08, 2.51)**	1.73 (0.48, 6.15)	**1.86 (1.13, 3.06)**
rs3755967	1.18 (0.79, 1.77)	0.84 (0.23, 3.04)	1.29 (0.80, 2.08)	**1.67 (1.11, 2.53)**	1.73 (0.48, 6.15)	**1.88 (1.16, 3.05)**
rs17467825	1.16 (0.77, 1.77)	0.60 (0.15, 2.45)	1.31 (0.81, 2.13)	**1.85 (1.21, 2.83)**	2.24 (0.58, 8.63)	**2.05 (1.26, 3.36)**

[a] OR for high aggressive PCa

[b] OR for low 25(OH)D, defined as <15ng/ml

Table 4.18 Model summaries for SNPs by prostate cancer aggressiveness and 25(OH)D among European Americans						
GC SNPs	**Aggressive PCa[a]**			**25(OH)D[b]**		
	Additive	**Recessive**	**Dominant**	**Additive**	**Recessive**	**Dominant**
rs4588	0.90 (0.69, 1.19)	1.19 (0.64, 2.21)	0.80 (0.57, 1.14)	**1.89 (1.45, 2.48)**	**2.80 (1.58, 4.97)**	**2.05 (1.45, 2.91)**
rs7041	0.84 (0.65, 1.08)	0.63 (0.39, 1.02)	0.93 (0.64, 1.35)	**1.63 (1.27, 2.09)**	**2.02 (1.35, 3.04)**	**1.78 (1.19, 2.64)**
rs705119	0.89 (0.69, 1.14)	0.69 (0.43, 1.13)	0.96 (0.67, 1.40)	**1.57 (1.22, 2.02)**	**2.15 (1.41, 3.27)**	**1.57 (1.07, 2.30)**
rs705120	0.89 (0.69, 1.15)	0.70 (0.43, 1.15)	0.97 (0.67, 1.40)	**1.55 (1.20, 1.98)**	**2.08 (1.36, 3.18)**	**1.55 (1.06, 2.26)**
rs222040	0.85 (0.66, 1.10)	0.66 (0.41, 1.07)	0.92 (0.63, 1.34)	**1.58 (1.23, 2.03)**	**2.04 (1.35, 3.08)**	**1.65 (1.12, 2.44)**
rs2282679	0.95 (0.72, 1.25)	1.27 (0.69, 2.34)	0.85 (0.60, 1.21)	**1.81 (1.39, 2.36)**	**2.64 (1.49, 4.66)**	**1.96 (1.39, 2.77)**
rs3755967	0.92 (0.70, 1.21)	1.28 (0.70, 2.35)	0.81 (0.57, 1.14)	**1.86 (1.42, 2.43)**	**2.65 (1.50, 4.67)**	**2.03 (1.43, 2.87)**
rs17467825	0.92 (0.70, 1.20)	1.25 (0.68, 2.30)	0.81 (0.57, 1.14)	**1.83 (1.41, 2.40)**	**2.64 (1.49, 4.66)**	**1.99 (1.40, 2.82)**
rs6817912	**0.55 (0.31 0.98)**	1.55 (0.14, 17.5)	**0.51 (0.28, 0.93)**	0.96 (0.59, 1.57)	5.08 (0.46, 56.4)	0.89 (0.53, 1.49)

[a] OR for high aggressive PCa

[b] OR for low 25(OH)D, defined as <20ng/ml

CHAPTER 5
DISCUSSION

Summary

In this study, the relationship between *GC* SNPs, prostate cancer aggressiveness and levels of vitamin D were examined. This was accomplished by using genetic models to assess the differing risks with varied genotypes and the creation of combined genotypes (*GCrs7041* and *GCrs4588*) and polygenic risk scores.

When assessing the relationship between combined genotypes of *GCrs7041* and *GCrs4588*, a similar model was used as described in the Abbas et al. study which examined these genotypes in relation to breast cancer.[46] In the current study individuals with the Gc2-2 genotype had the lowest concentration of 25(OH)D of all combined genotypes in both races, consistent with the results from other studies.[33,46] The Abbas et al. study used the most frequent combined genotype as the referent group (Gc1s-1s), which was consistent with the referent group used among EAs in the current study, but not among AAs where Gc1f-1f was the most frequent combined genotype. When examining the relationship with aggressive prostate cancer, only the Gc2-1f combined genotype was associated with a statistically significant decreased risk of high aggressive prostate cancer among EAs. No other associations were statistically significant in either race. Not many studies have studied the relationship of these combined genotypes in relation to prostate cancer but results from a study by Maneechay et al. showed that Gc2-1f significantly decreased risk for lung cancer. [35]

When examining the associations between the *GC* SNPs and aggressive prostate

cancer across all three models (Table 4.17 and 4.18), only four SNPs were statistically significant (*rs6817912, rs222054, rs16847028 and rs16847015)*. In both the additive and dominant models for AAs, the *GCrs222054* and *GCrs16847028* SNPs were significantly associated with decreased risk of aggressive prostate cancer. These results suggest that having at least one copy of the 'G' allele in *GCrs222054* and at least one copy of 'A' in *GCrs16847028*, reduces the risk of high aggressive prostate cancer in AAs. *GCrs6817912* had the same effect on aggressiveness but only among EAs, suggesting that EAs with at least one copy of the 'A' allele in this SNP have a decreased risk of high aggressive prostate cancer. There was no evidence of an association between SNPs and prostate cancer aggressiveness in the recessive model, likely due to reduced power in the recessive model analyses given the smaller number of subjects who were homozygous variant for the minor allele for each of the SNPs.

Our study found a slight suggestion of a decreased risk (Table 4.9 p-value = 0.058) of high aggressive prostate cancer in the recessive model for the *GCrs7041* SNP among EAs, implying the presence of a protective association occurring among individuals who were homozygous for the 'A' allele in *GCrs7041*. This contradicts the findings in the study by Gilbert et al., where *GCrs7041-T* (labeled as *GCrs7041-A* in our study) significantly increased the risk of prostate cancer.[20] Additionally, our study looked at the effect for each additional copy of the 'A' allele in *rs7041* (Table 4.5) among EAs and found no significant association. Other studies have examined *GCrs7041* in relation to overall or advanced prostate cancer and found no significant associations.[19,39] This current study stratified the *GC* SNPs by race and examined associations with high aggressive prostate cancer, which could partially explain why the results differed from the Gilbert et al. study where total prostate cancer was the outcome and healthy disease-

free controls were the comparison.[20]

Evidence of associations between *GC* SNPs and low levels of 25(OH)D were found in nine SNPs (*rs4588, rs7041, rs222040, rs705119, rs705120, rs2282679, rs3755967, rs17467825* and *rs222054*) across all three models (Tables 4.17 and 4.18), which are consistent with the findings of other studies.[19,21,35] Eight of these SNPs significantly increased the risk of having low levels of 25(OH)D among EAs only (*rs4588, rs7041, rs222040, rs705119, rs705120, rs2282679, rs3755967* and *rs17467825*), while among AAs, only three of the SNPs increased the risk for the dominant and additive models (*rs2282679*, *rs3755967*and *rs17467825*), and one SNP was associated with increased risk of having low 25(OH)D for the dominant model only (rs4588). Also, among AAs, the rs222054 SNP was associated with lower odds of having low 25(OH)D across all three genetic models (Table 4.17). Our findings are consistent with the results for others studies indicating that *GCrs2282679* and *GCrs7041* are associated with differences in 25(OH)D levels.[19,20] Specifically, our results were consistent with other studies which indicated that *rs7041-A* in EAs and *rs2282679*-C in both races increased the risk of low levels of 25(OH)D.[20] Additionally, our results were consistent with previous studies which indicated that the 'A' allele in *GCrs4588* is associated with low levels of 25(OH)D among EAs.[20,21,35] Results were similar for AAs, but only reached statistical significance for the dominant model of *GCrs4588,* and not the additive or recessive models. When comparing the mean levels of 25(OH)D of *GCrs4588* in the dominant model (Tables 4.14 and 4.15), the average level of 25(OH)D was greater in the 'CC' genotype compared to the 'AA+AC' genotype for both AAs and EAs, which was consistent with the findings from the Maneechay et al. study conducted in a Thai population.[35]

In the current study, the polygenic risk score awarded a point to individuals carrying the genotype associated with the higher level of vitamin D based off the dominant model. Among AAs with a polygenic risk score of two (*rs4588-CC* and *rs222054-CC*) indicating higher 25(OH)D concentrations, the risk of high aggressive prostate cancer was decreased. However, in previous analyses of PCaP, AA men with higher 25(OH)D concentrations were found to have higher odds of high aggressive prostate cancer.[18] Thus, it is not clear why a polygenic risk score indicating high 25(OH)D would be associated with lower odds of high aggressive prostate cancer in this same population. Among both races, there were no significant findings when the model was stratified by score or the 2-level 25(OH)D, nor was there evidence of interaction between the polygenic risk score and 25(OH)D in relation to aggressive prostate cancer.

Mean levels of plasma 25(OH)D were on average lower in AAs and a greater percentage were categorized as possessing what is considered to be low levels of vitamin D. These findings matched results from other studies which indicated that AAs have lower levels of vitamin D and/or insufficiency when compared to EAs. [7,15,17,21]

Strengths and Limitations

Some limitations in our study resulted from a relatively small sample size. While PCaP used a randomized recruitment procedure which allowed for a comparable enrollment rate for both races, the number of high aggressive cases and low aggressive "controls" enrolled were not equal. Due to the lack of genetic studies on AAs, the inclusion of approximately equal numbers of AAs and EAs in the study is an important strength. The generalizability of the study is limited to AA and EA men living in the Southern United States, though we would expect frequency of SNPs in vitamin D-related genes to be representative of similar populations in other parts of the country. Diagnosis

of prostate cancer was physician confirmed in addition to self-reported, and histological characteristics were also collected in order to distinguish between high aggressive and low aggressive cases. Although race was self-identified, ancestry was measured for all participants and was adjusted for in all models. All visits were completed within four months of diagnosis which provides information on characteristics of recently diagnosed individuals, but it restricts our ability to observe any changes occurring before diagnosis. For example, 25(OH)D was collected post-diagnosis, therefore we cannot determine whether circulating levels were consistent or changed before and after diagnosis.

Significance and Recommendations

Findings from our study suggest that more in-depth research needs to be conducted which further assesses the possible relationships between combined genotypes of *GCrs7041* and *GCrs4588* in relation to prostate cancer in both AAs and EAs. In the dominant model, levels of 25(OH)D were lower in both AAs and EAs in the *rs4588* 'AA+AC' genotype, suggesting that the 'A' allele may increase the risk of low 25(OH)D. Our study only found evidence of risk increasing with the 'A' allele among EAs and not AAs. For *rs7041,* significant associations were only found for EAs and not AAs. There is contradicting literature on whether these SNPs are related to prostate cancer, but these differences may be explained by different populations being studied and effects of other unmeasured genetic variants. Some studies that have examined the relationship between the two SNPs and either overall or lethal prostate cancer risk reported no significant associations.[19,39] In studies such as Gilbert et al. specific alleles in these SNPs were examined with prostate cancer risk and significant associations emerged.[20] Our findings suggest that different alleles in *GC SNPs* may have varying effects on risk among AAs and EAs in relation to both vitamin D status and aggressive prostate cancer. Results from

the additive, dominant and recessive models showed one SNP (*rs222054*) among AAs specifically to be associated with a decreased risk of high aggressive prostate cancer and increased risk of low levels of 25(OH)D which is a novel finding, not yet reported in previous studies among AAs. Findings from the polygenic risk score revealed evidence of risk of aggressive prostate cancer significantly decreasing among AAs possessing a score of two (*rs4588-CC and rs222054-CC*), indicating that these two specific SNP genotypes were related to higher levels of 25(OH)D and decreased risk of aggressive cancer. In conclusion, this study identified a novel polygenic risk score combining two SNPs *GCrs4588* and *GCrs222054* that appear to have an effect on levels vitamin D and prostate cancer aggressiveness among AAs. Future studies should specifically study these SNPs individually, combined and included in risk score analysis.

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