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Prostate Cancer Genetics: Variation by Race, Ethnicity, and Geography

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Abstract

Prostate cancer rates vary substantially by race, ethnicity, and geography. These disparities can be explained by variation in access to screening and treatment, variation in exposure to prostate cancer risk factors, and variation in the underlying biology of prostate carcinogenesis (including genomic propensity of some groups to develop biologically aggressive disease). It is clear that access to screening and treatment are critical influencers of prostate cancer rates, yet even among geographically diverse populations with similar access to care (e.g., low and medium income countries), African descent men have higher prostate cancer rates and poorer prognosis. To date, the proportion of prostate cancer that can be explained by environmental exposures is small, and the impact of these factors across different racial, ethnic, or geographical populations is poorly understood. In contrast, prostate cancer has one of the highest heritabilities of all major cancers. Numerous genetic susceptibility markers have been identified from family-based studies, candidate gene association studies, and genome-wide association studies. Some prostate cancer loci, including the risk loci found at chromosome 8q24, have consistent effects in all groups studied to date. However, replication of many susceptibility loci across race, ethnicity, and geography remains limited, and additional studies in certain populations (particularly in men of African descent) are needed to better understand the underlying genetic basis of prostate cancer.

Variation in Prostate Cancer Rates by Race, Ethnicity, and Geography

Prostate cancer is the leading non-cutaneous cancer in men in many parts of the world, although incidence and mortality rates vary substantially by population (**Figure 1**). Prostate cancer incidence rates tend to be highest in more developed parts of the world (e.g., North America, Western and Northern Europe, and Australia), in part reflecting access to medical care, including screening and early detection. In contrast, prostate cancer mortality is highest in men of African descent. Afro-Caribbean (AC) and Sub-sSaharan African (SSA) men suffer from the highest prostate cancer mortality in the world with rates ranging from 18.7-29.3 deaths per 100,000 populations based on 2012 GLOBOCAN data [1]. African American (AA) men have a similarly high mortality rate of 43 per 100,000 in the period

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2008-2011[2, 3]. These rates are substantially higher than other US men, including Whites (19.8 per 100,000), Hispanics (17.8 per 100,000) and Asian/Pacific Islanders (9.4 per 100,000). In contrast, East, Southeast, and South Central Asian men have the lowest rates of prostate cancer death (2.9, 31, and 6.7 per 100,000, respectively; **Figure 1**). Of note, North African men have rates near those of Asians and lower than the global average (7 per 100,000).

Additional epidemiological data support the high rates and poor outcomes of prostate cancer among African descent men. A population survey of unselected Ghanaian men demonstrated prostate cancer prevalence higher than that reported in AA men [4], suggesting that prostate cancer in SSA men is more common than reported from tumor registries. Autopsy studies confirm that the highest rates of latent prostate cancer is found in African descent men, with the lowest rates in Asian men [5]. A survey of biopsy-detected prostate cancer in SSA men revealed a high proportion of Gleason 8+ tumors [6]. Despite these consistent observations, variation in access to medical care and extent of cancer registration also vary by geography and confound the ability to make strong inferences about the relationship between race, ethnicity, and geography and prostate cancer aggressiveness based on epidemiological evidence alone.

Based on both epidemiological and biological data, there is growing evidence that prostate cancer risk, aggressiveness, and prognosis vary substantially by race, ethnicity, and geography. The evidence for a role of germline genomics in explaining this variation is explored in the subsequent sections.

Hereditary Prostate Cancer

Prostate cancer exhibits the highest reported heritability of any major cancer [7-10], yet unlike other cancers, the ability to define hereditary prostate cancer syndromes and identify hereditary cancer genes has been limited. Family-based linkage studies of hereditary prostate cancer focused largely on European descent populations to identify a series of genes responsible for hereditary prostate cancer. These include *HPC1* (1q24-25) [11-13], *PCAP* (1q42-43) [13-15], *HPCX* (Xq27-28) [16], *CAPB* (1q36) [13, 15], *HPC20* (20q13) [17], *HOXB13* [18, 19] and others. Among these, a series of loci were identified specifically or confirmed in Non-European descent families by family studies, including 12q24 [20], 1q24-25, 2p16, and 2p21 [20, 21], and 1p36 in Japanese [22] and AA[21]. Additional linkage signals have been detected in AA pedigrees at 2p21, 11q22, 17p11, 22q12, and Xq21 [23] among others. Many of these loci were validated across ethnic and geographic populations, suggesting common origins for some hereditary prostate cancer susceptibility.

Despite the success of these discovery efforts, genetic testing for hereditary prostate cancer and recommendations for reduction of that risk based on genetic information have not evolved into clinical practice as has been the case for many other cancer sites. Recently, potentially clinically meaningful associations have been identified, including associations of inherited mutations in *BRCA2* and aggressive prostate cancer, with implications for treatment [24, 25].

Some loci identified by family studies have also been implicated in GWAS studies, and have been validated in multiple ethnic and racial groups. Among these are 12q24, 1q24-25 and 8q24 [26-28]. While the loci that would be detected by family studies vs. association (GWAS) studies are not expected to be the same, the fact that some loci are found commonly across populations and by using multiple methods provides interesting evidence for the role of these genes across the spectrum of prostate cancer etiology.

Candidate Gene Studies

Candidate gene association studies in prostate cancer and other diseases were quite common before the advent of the genome-wide association study. These studies began with the identification of pathways and genes that played a biologically plausible role in the etiology of a disease. From this information, associations of individual SNPs or haplotypes were studied. Many such studies have been published, but this approach came under scrutiny because they often used inappropriate sampling designs and were underpowered to detect relevant effects. Many associations could not be replicated, although many were replicated and may still represent valid candidate susceptibility genes. Similarly, few candidate associations have also been detected in GWAS studies, which tend to use a more stringent methodology. Variation (and lack of replication) in results of associations across race, ethnicity, and geography were generally not accounted for in making determinations about the validity of associations. Highly variable allele and haplotype frequencies, different patterns of linkage disequilibrium, and population stratification across groups were generally not taken into consideration, and could easily have led to lack of replication across studies and populations. Similar issues continue to affect GWAS studies (See below).

Genes involved in DNA damage and repair, carcinogen metabolism, inflammation, steroid hormone metabolism, and many others have been reported in candidate gene association studies and have involved populations worldwide (reviewed by Naylor [29]). Of the many candidates that have been considered few have also been reported in linkage or GWAS studies. Examples of candidate genes that have been identified using large gene panels or GWAS include the androgen receptor (*AR*; [26]), kallekrein genes (e.g., *KLK3*, that encodes prostate specific antigen; [30-32]), telomere-related genes (*TERT, TET*; [26, 33]), and loci containing carcinogen metabolism (*UGT1A8, CYP21A2*; [34]), microRNAs ([34]) or matrix metalloprotein genes ([34]). Many smaller studies have been undertaken in diverse populations around the world. However, the majority of these reports have not been validated in independent samples, and most of these candidate loci have not been reported in GWAS studies.

Genome-Wide Association Studies

Numerous prostate cancer susceptibility loci with a p-value of 10^{-8} have been reported to date using genome-wide association study (GWAS) approaches according to the NHGRI-EBI Catalog of Published Genome-Wide Association Studies (July 8, 2016; https://www.ebi.ac.uk/gwas/). CaP susceptibility loci are found on all chromosomes except 15, 16, 21, and 23. A summary of currently reported GWAS loci is found in **Table 1**.

As of July 2016, nearly 200 independent GWAS loci have been associated with CaP (NHGRI-EBI Catalog of Published Genome-Wide Association Studies, July 8, 2016; https://www.ebi.ac.uk/gwas/; **Table 1**). This includes numerous loci with multiple independent associations in the same region. In addition, associations have been reported with early onset CaP, aggressive CaP, or gene × gene interactions. Prostate cancer susceptibility loci are found on all chromosomes (**Table 1**). The majority of prostate cancer GWAS loci have been discovered in European descent populations. Of the 191 independent and replicated associations that reach genome-wide significance (i.e., $p<10^{-8}$), 123 (64%) were reported in European and European descent populations, 21 (11%) in Asian or Asian descent populations, and 45 (24%) in sample sets using multiple populations (e.g., European, Asian, AA, Hispanic, etc.). Only one locus (17q21) has reached genome-wide level significance in African descent populations to date [35]. This locus has since been validated as a prostate cancer risk locus in European descent populations [34]. A novel locus at Chromosome 10p14 was reported in a GWAS undertaken in a Ghanaian population [36], although this association did not reach genome-wide significance.

Many loci have been consistently shown to be associated with prostate cancer risk across populations, and suggest that these are strongly associated with risk in most settings. Han et al. demonstrated limited heterogeneity in the directionality of associated prostate cancer variants across populations [37-43]. However, many loci detected in European or Asian descent populations have not been replicated in African descent populations, or the magnitude of effect was less (or directionally opposite) by race [38-40]. A number of studies have attempted to validate reported associations in AA. Xu et al. [38] studied 868 cases and 878 controls and validated the loci at 8q24 ($p=0.034$ to $p=2\times10^{-5}$) and 3p12 ($p=0.029$). Waters et al. [39] studied 860 cases and 575 controls, and validated *KLK2/3* (19q13.33) and *NUDT10/11* (Xp11.22). Finally, Hooker et al. [41] validated 8q24 ($p=1\times10^{-4}$), 11q13.2 ($p=0.009$), *HNF1B/TCF2* (17q12; $p=0.008$), *KLK2/3* (19q13.33; $p=0.04$), and *NUDT11* (Xp11.22; $p=0.05$) in 454 cases and 301 controls. The validated loci were not consistent across these studies, perhaps due to relatively small sample sizes in each study. Chang et al.[42] studied a sample of nearly 8,000 men of African descent in the US and UK. This report only involved those loci that had been previously reported in non-African descent populations. They reported that the majority of the loci identified as prostate cancer susceptibility loci in White or Asian populations were not replicated in AA men. Only *JAZF1, MSMB, NUDT10/11* and a locus on 11q13 were validated as having effects similar to those in non-African descent populations. The remainder of the associations in AA men exhibited smaller effects than those reported in non-AA populations. Some of the AA associations were even in the opposite direction of the non-AA reports, and in many cases the 95% confidence intervals for AA men did not overlap the non-AA estimates. Using a GWAS approach, Haiman et al. also did not replicate most of the previously reported loci identified in European or Asian descent populations [35, 44]. Using over 9,500 AA prostate cancer cases and controls, Han et al. [37] reported that of established 82 GWAS hits, only 68 (83%) were directionally consistent with the original report, and 37% were significant at $p<0.05$. Similarly, the effect size of many loci is also smaller for the same locus in African descent populations compared to the original report of these loci in European or Asian descent populations (**Figure 2**).

In addition to a lack of replication for many loci, it has also been observed that AA exhibited smaller effects than those reported in non-AA populations. Some of the AA associations were even in the opposite direction to those of the non-AA reports, and in many cases the 95% confidence intervals for AA men did not overlap the non-AA estimates. Chang et al. [42] also reported that the magnitude of the odds ratio effect was smaller in AA men compared with the original reports in European or Asian descent populations (**Figure 2**).

A number of hypotheses have been proposed to explain the difficulty in replication and systematic differences in magnitudes of genetic effects by race and ethnicity. First, the underlying genomic susceptibility, and thus biology, for prostate cancer may differ fundamentally across racial or ethnic groups. This explanation is unlikely to be the case, as it implies that the biological basis for prostate cancer differs by race or ethnicity. However, this hypothesis cannot be ruled out based on available data.

A more likely explanation is that the risk alleles in European/Asian descent individuals are not the same as in African descent individuals. It is likely that the risk alleles and the underlying population structure of prostate cancer susceptibility loci differ by ethnicity, race, or geography, and that these differences are likely to influence the ability to detect genetic associations [45]. This hypothesis is supported by well-described differences in the genomic architecture of the genome by race and ethnicity. Linkage disequilibrium and haplotype diversity differ substantially by race and ethnicity [45, 46], as do allele frequencies at many loci across the genome. The capture of genomic variability is incomplete, and it is likely that many African-specific alleles have yet to be detected that may provide a better capture of the African genome. Thus, it is not hard to imagine that prostate cancer risk alleles and the frequencies of these alleles vary substantially across populations to affect the ability to detect associations in a GWAS setting. To address this hypothesis, additional studies using non-Caucasian populations will be required that employ genotyping panels that adequately capture African genomic variability. While generally unreported in the GWAS literature, similar arguments can be made regarding genomics of other populations that are genomically divergent from Caucasians, including Native Americans, middle eastern groups, and aboriginal populations in the Arctic, Oceania, and elsewhere.

Furthermore, it is likely that the underlying etiology of prostate cancer is not only influenced by genes but also by exposures and gene by environment interactions. The different magnitudes of effect observed across race, ethnicity and geography (e.g., **Figure 2**) could be explained by the influence of contextual factors that influence prostate cancer susceptibility through gene-environment interactions that may vary by population. The number of confirmed environmental factors or exposures that influence prostate cancer risk and outcome are limited [47], but it is still possible that underlying genetic susceptibility may influence the effect of exposures that are not detectable on their own. To the degree that the frequencies of both the exposures and the susceptibility genotypes vary by race or ethnicity (which they are likely to do), it is possible that differences in etiology or severity of prostate cancer could be explained by complex interactions of these factors. There have been published examples of gene-environment interactions in prostate cancer, including novel and biological plausible interactions (e.g., [48, 49]). However, most of these have not been validated in independent sets or across populations, and the large post-GWAS evaluations of GWAS

loci have not shown convincing interaction results [50]. No major or replicated interaction studies have been undertaken across racially or ethnically diverse groups to be able to test the hypothesis that differences in gene-environment interactions could explain differences in prostate cancer etiology or severity.

Unlike many prostate cancer susceptibility loci for which variation and lack of replication has been observed, genetic variation on chromosome 8q24 has been widely and consistently associated with prostate and numerous other cancers across many populations [51]. Multiple independent regions conferring prostate cancer susceptibility have been identified at this locus [27, 28, 52], although no gene has been designated to be responsible for this cancer risk. Instead, regulation of the downstream gene *MYC* or regulation by lncRNAs has been reported [53-55]. Disease-associated variation at 8q24 has been confirmed in multiple populations. Indeed, the 8q24 locus was associated with prostate cancer in early admixture mapping studies [56] that identify susceptibility loci by exploiting different disease risks and genotype distributions by race. Ethnic specific mutations and haplotypes have been reported in African and European descent populations [57, 58]. The associations at 8q24 have been confirmed not only in African American, but also in two African populations [58]. Thus, the genetic contribution to prostate cancer risk at this locus can be considered a master regulator of cancer at multiple sites as well as across populations.

Tumor Biomarkers

In addition to the strong evidence for inherited genomic factors in CaP etiology, somatic alterations in prostate tumors may also play a role in CaP etiology. The biomarkers identified to date may improve screening for CaP (e.g., as an alternative or supplement to PSA testing) and might inform treatment choices and prognosis. A number of prostate tumor biomarkers have been identified that may define heterogeneity of CaP etiology [59, 60], have clinical implications for surveillance and treatment (reviewed in [61]), or correlate with aggressive phenotypes[62-69]. Among these are the TMPRSS2:ERG gene fusion/translocation[70], Ki-67 expression[64], biomarkers involved in androgen metabolism[65, 71] and genomic classifiers that use a whole-transcriptome microarray assays to analyze gene activity in prostate cancer specimens[72]. In general, the majority of the studies of these biomarkers has been in European- or Asian-descent populations, are there are limited data that evaluate whether these markers have similar distributions or confer similar effects on outcomes in African descent populations. A few papers have begun to report differences in biomarkers between AA and Caucasian men, including AMCAR, ERG, SPINK1, NXK3.1, GOLM1, AR, Ki67, and SRD5A2 [73, 74].

TMPRSS2:ERG translocations have been reported as having a different frequency by race. Magi-Galluzzi et al. [75] reported that the frequency of TMPRSS2:ERG translocations was highest in Japanese (71%) and Caucasians (62%) and much lower in AA (20%). Yamoah et al. [73] also reported significant differences in ERG expression between Caucasian and AA CaP cases. While the prognostic value of TMPRSS2:ERG translocations and ERG expression is not clear, it does not seem to correlate with clinical outcome in most studies[76]. However, the underlying marker distribution may identify tumor heterogeneity that informs CaP etiology and disparities. For example, it is becoming clear that the relationship of

potential CaP risk factors differs by TMPRSS2:ERG translocation status [59, 60, 77]. While not formally evaluating a racially diverse group, Pettersson et al. [78] reported that the relationship of obesity and lethal CaP varied by TMPRSS2:ERG translocation status. Since obesity has been associated with poorer CaP outcomes in some studies, and AA and Hispanic men tend to have greater rates of obesity than other racial/ethnic groups, this biomarker may prove valuable in understanding poor outcomes in some men.

Challenges and Needs

The observation of highly variable prostate cancer rates by race, ethnicity and geography has interesting biological, clinical, and public health implications. However, there are relatively little data that explain these disparities. There have been few consistent associations of exposures or environmental factors with prostate cancer etiology across populations. Prostate cancer has the highest heritability of any major cancer[7, 79], and many genetic susceptibility loci have been identified, primarily in men of European and Asian descent. However, most GWAS-identified loci have not been replicated in African descent populations[35, 42, 44, 80]. There is a pressing need to identify African-specific alleles and thereby elucidate the etiology of prostate cancer in AA and Afro-Caribbean men, who have the highest prostate cancer mortality rates in the world.

A number of benefits will derive from an improved elucidation of prostate cancer genetics across populations. Improved understanding of population genetics by multi-ethnic studies of prostate cancer and other diseases can inform our understanding of genetics in general. Population genomic features strongly influence the ability to detect and interpret genetic associations, and may provide benefits and challenges to disease gene detection[81]. Diversity in population genomic structure and differences in allele frequency and linkage disequilibrium mean that a single approach to all association studies may not be successful [45, 81]. The lack of replication across race, ethnicity, and geography is not only a feature of prostate cancer[43], but of many GWAS studies of disease and non-disease traits[82], and can be explained by a variety of factors including limited capture of ethnic-specific alleles, limited consideration of population-specific linkage disequilibrium, and inadequate knowledge of population substructure. These explanations are consistent with the observation that most GWAS studies to date have been undertaken using SNP panels based on the European or Asian genome, with limited representation of the African or other minority population genomes[83]. A more complete representation of the human genome may improve our ability to identify susceptibility loci, particularly in Africa where haplotype diversity in SSA is large and levels of linkage disequilibrium are relatively low. Localization and fine mapping of susceptibility alleles and improved evaluation of population structure in African descent populations to avoid biases due to population stratification will be facilitated by studies of representative populations from around the world [45].

Second, by understanding evolutionary and population genetics relationships across races, ethnicities, and geographies, we may be better able to understand why risk allele frequencies (and thus population risk differences) vary across populations. Basic knowledge about population genetics in ancestral populations may also improve the understanding of admixed populations, including African Americans and Hispanics/Latinos.

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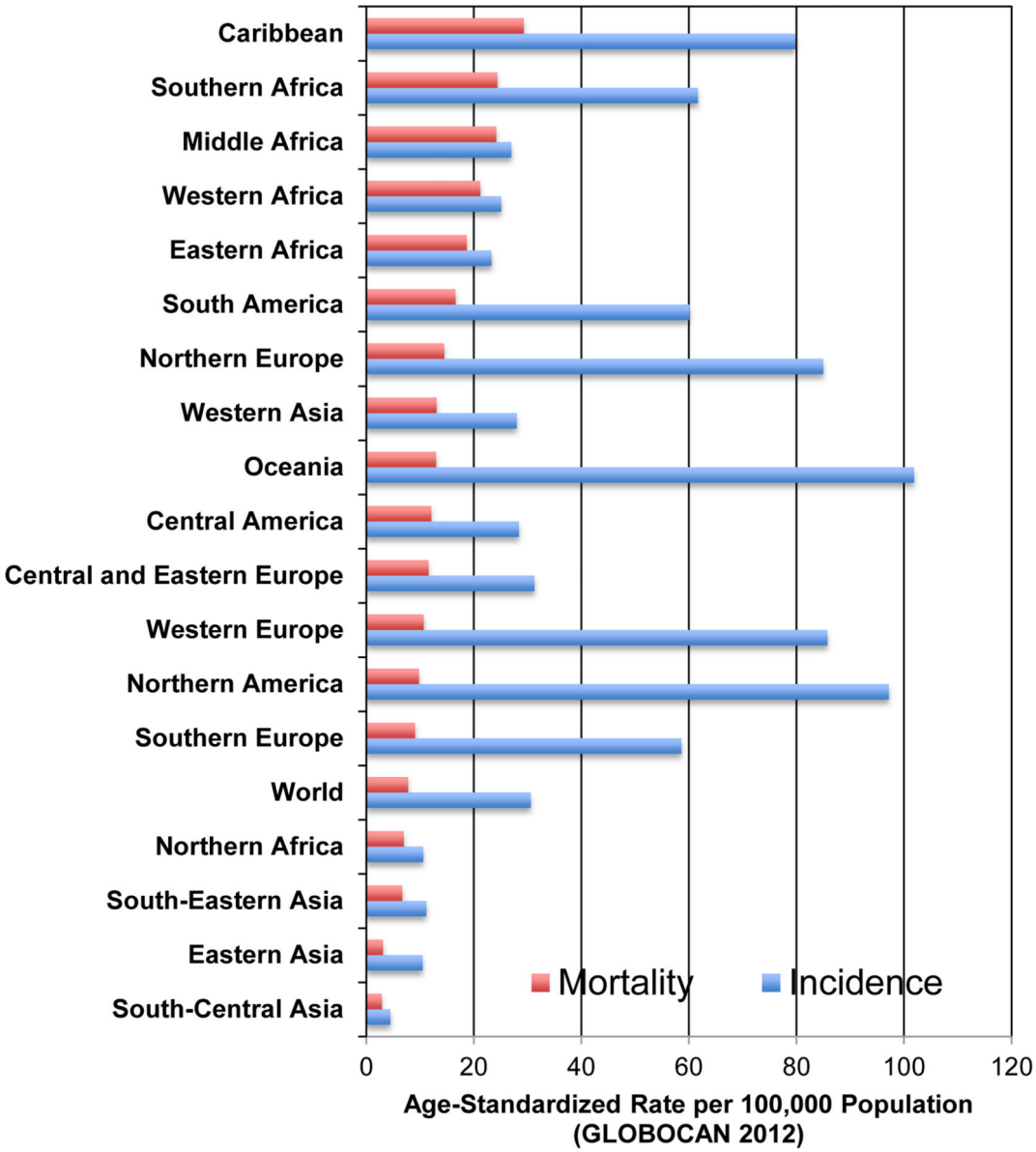

Figure 1.
Global Prostate Cancer Incidence and Mortality by World Region

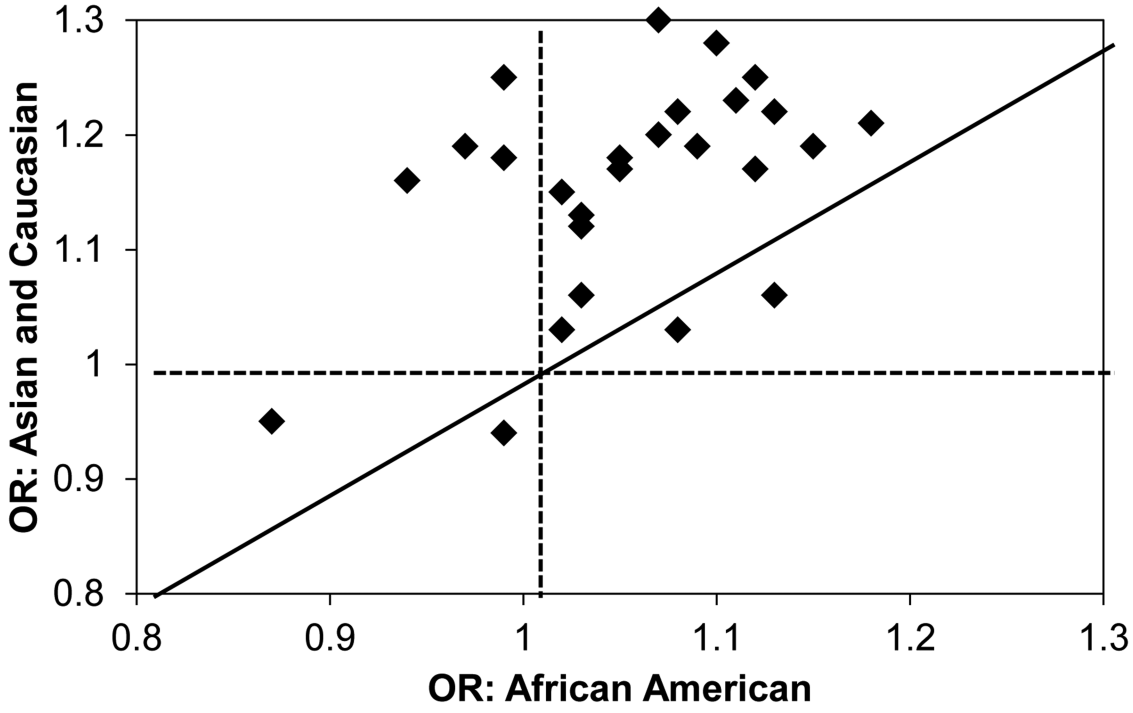

Figure 2.
Odds Ratio (OR) Effects Estimated in Caucasian, Asian, and AAGWAS Studies.

Table 1

Reported Prostate Cancer GWAS (July 8, 2016). Includes associations reported at $p<10^{-8}$ and validated in at least one independent sample.

Locus	Mapped Gene(s)	Most Significantly Associated SNP(s) - Risk Allele
1p36.22	*PEX14*	rs636291-A
1q21.3	*KCNN3*	rs1218582-G, rs17599629-G, rs17599629-G
1q32.1	*LOC105371702 - SLC41A1, MDM4*	rs1775148-C, rs4245739-A
2p11.2	*GGCX - VAMP8*	rs10187424-A
2p15	*EHBP1*	rs721048-A, rs2430386-T
2p21	*THADA*	rs1465618-?
2p24.1	*C2orf43*	rs13385191-G
2p25.1	*LOC105373426 - NOL10, GRHL1*	rs9287719-C, rs11902236-A, rs9287719-C
2q31.1	*ITGA6*	rs12621278-?
2q37.3	*MLPH*	rs2292884-G
2q37.3	*FARP2*	rs3771570-A
2q37.3	*LOC105373955 - LOC105373957*	rs7584330-C
3p11.2	*LINC00506*	rs17181170-?, rs9284813-?
3p12.1	*LOC285232 - LINC00506*	rs17023900-G, rs2660753-T, rs17023900-G
3q13.2	*SIDT1*	rs7611694-A
3q21.3	*EEFSEC*	rs10934853-A
3q23	*ZBTB38*	rs6763931-T
3q26.2	*PRKCI*	rs71277158-T
3q26.2	*LOC105374210*	rs10936632-A
4q13.3	*LOC105377273, AFM*	rs10009409-T, rs10009409-T, rs1894292-G
4q22.3	*PDLIM5*	rs12500426-?, rs17021918-?
4q24	*LOC643675 - TET2*	rs7679673-C, rs7679673-?
5p12	*FGF10*	rs2121875-G
5p15.33	*TERT*	rs7725218-G, rs12653946-T, rs2242652-G
5q35.2	*LOC105377732*	rs6869841-A
6p21.1	*FOXP4*	rs1983891-T
6p21.32	*NOTCH4 - LOC101929163*	rs3096702-A
6p21.32	*BTNL2 - HLA-DRA*	rs115306967-G
6p21.33	*CCHCR1*	rs130067-G
6p22.1	*TRIM31, TRIM31-AS1*	rs115457135-A
6p24.2	*NEDD9*	rs4713266-C, rs4713266-C
6q14.1	*MYO6*	rs9443189-G
6q21	*ARMC2*	rs2273669-G
6q22.1	*RFX6*	rs339331-T
6q25.2	*RGS17*	rs1933488-A
6q25.3	*SLC22A1 - SLC22A2*	rs651164-?, rs9364554-T, rs651164-G, rs7758229-T

Locus	Mapped Gene(s)	Most Significantly Associated SNP(s) - Risk Allele
7p12.3	*TNS3*	rs56232506-A, rs56232506-A
7p15.3	*LINC01162*	rs12155172-A
7q21.3	*LMTK2*	rs6465657-?, rs6465657-C
8p21.2	*SLC25A37 - NKX3-1*	rs10503733-T
8p21.2	*EBF2*	rs11135910-A, rs1512268-?, rs1512268-?
8q24.21	*PRNCR1 - LOC105375752, CCAT2, CASC8, CASC21, PCAT2*	rs12682344-G, rs6983267-G, rs10505477-A, rs16901979-A, rs445114-T, rs6983267-G, rs1016343-T, rs13254738-C, rs6983267-G, rs16901979-A, rs1456315-?, rs6983267-G, rs6983267-G, rs6983561-C, rs16901979-A, rs1447295-A, rs10505483-T, rs16902094-G, rs6983267-G, rs4242384-C, rs4242384-C, rs1447295-A, rs1447295-A, rs4242382-A, rs1447295-A, rs4242384-?, rs7837688-?, rs1456315-?, rs188140481-A, rs4242382-A
9p21.3	*CDKN2B-AS1*	rs17694493-G
9q31.2	*RAD23B - LINC01509*	rs817826-C
10q11.22	*MSMB - LOC105378288*	rs10993994-?, rs76934034-T, rs76934034-T, rs10993994-T, rs10993994-T, rs3123078-?, rs10993994-T, s10993994-T
10q24.32	*LOC105378460, TRIM8*	rs3850699-A
10q26.12	*LINC01153 - LOC105378523*	rs11199874-?
11p15.5	*MIR4686 - ASCL2*	rs7126629-C, rs7127900-?
11q13.3	*LOC105369366 - LOC105369367*	rs7130881-G, rs10896449-G, rs11228565-A, rs7931342-G, rs7130881-?, rs7929962-T
11q22.2	*MMP7 - MMP20*	rs11568818-A
11q23.2	*HTR3B*	rs11214775-G, rs11214775-G
12q13.11	*LOC105369750, TUBA1C - LOC101927267, KRT78 - RPL7P41*	rs80130819-A, rs80130819-A, rs10875943-C, rs902774-A
12q24.21	*LOC105369996 - TBX5*	rs10774740-G, rs1270884-A
13q22.1	*RNU6-66P - LINC00393*	rs9600079-T
14q22.1	*FERMT2, LOC105370500*	rs8008270-G
14q23.1	*SIX1 - SIX4*	rs7153648-C
14q24.1	*RAD51B, LOC100996664, LOC105370544*	rs7141529-G
14q24.2	*LOC101928075*	rs8014671-G
15q21.1	*LOC105370802 - LOC105370803*	rs4775302-?
16q22.2	*PHLPP2*	rs12051443-A
17p13.3	*VPS53 - FAM57A*	rs684232-G
17q12	*HNF1B*	rs4430796-A, rs4430796-A, rs7501939-C, rs7501939-?, rs7501939-?, rs8064454-C
17q21.32	*FLJ40194 - MIR6129*	rs11650494-A
17q21.33	*ZNF652*	rs7210100-?
17q24.3	*CASC17*	rs1859962-G, rs1859962-G, rs4793529-T, rs1859962-?, rs17765344-A
18q23	*SALL3 - ATP9B*	rs7241993-G
19q13.2	*PCAT19, DPF1 - PPP1R14A*	rs11672691-G, rs8102476-C, rs11672691 -G
19q13.33	*KLK3*	rs2735839-G, rs17632542-T
19q13.42	*MIR4752 - LILRA5*	rs103294-C

Locus	Mapped Gene(s)	Most Significantly Associated SNP(s) - Risk Allele
20q13.13	*ADNP*	rs12480328-T
20q13.33	*LOC105372710, ZGPAT*	rs2427345-G, rs6062509-A
21q22.3	*TMPRSS2 - LOC105372809*	rs1041449-G
22q11.21	*TBX1*	rs2238776-G
22q13.2	*RPS25P10 - BIK*	rs5759167-G, rs5759167-?
Xp11.22	*NUDT11 - LINC01496, XAGE3, CXorf67*	rs5945619-C, rs2807031-C, rs1327301-?, rs2807031-C, rs5945572-A
Xp22.2	*SHROOM2*	rs2405942-A
Xq12	*BMI1P1 - OPHN1*	rs5919432-A
Xq13.1	*NLGN3 - GJB1, TEX11 - SLC7A3*	rs4844289-G, rs4844289-G, rs6625711-A