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The Precise Role of Ethnicity and Family History on Aggressive Prostate Cancer: A Review Analysis

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Introduction

Prostate cancer is the most common cancer affecting men in the Western world (1–4). In the United States, it is the second leading cause of cancer related deaths after lung and bronchus carcinoma (1,2) No definitive causes of prostate cancer (PCa) have been identified to date but, increasing age, a positive family history and sub-Saharan African ancestry are strongly linked to its development (3,5). African-American men (AAM) have the highest reported incidence rates in the United States (1,2,6) and their mortality from the disease is markedly higher than that of European-American men (EAM) (7). Conversely, Asian-American men and Pacific Islanders (API), American Indian and Alaskan Native (AI/AN) men, and Hispanic men all have lower incidence and mortality rate as compared to EAM (1). The reasons for these differences are unclear. It is known that the socioeconomic factors, non financial barriers, cultural behaviors and genetic susceptibility vary among the groups (2,4,8,9–12). Its management (via measures ranging from primary prevention through screening to therapeutic intervention) imposes a substantial economic burden on individuals and society as a whole (13). The purpose of this review is to examine how ethnicity and family history impact on aggressiveness of local disease and disease recurrence.

Prostate Cancer Incidence and Mortality Rates

Incidence Rates

Data from the National Cancer Institute SEER Program following prostate cancer in both AAM and EAM from 1975–2002; and Hispanic, API, AI/AN men from 1992–2002 showed that in the United States, the PCa incidence rates were highest for AAM (243/100,000) and lowest for AI/AN men (70.7/100,000) (1). A closer review of the data demonstrated a steady and parallel rise in PCa incidence for both AAM and EAM from the 1970s to late 1980s. After the introduction of serum prostate specific antigen (PSA) screening in the early 1990s, PCa incidence rates soared to their highest level in 1992 for EAM (237.6/100,000) and a year later for AAM (342.8/100,000). The incidence then declined sharply for both AAM and EAM until 1995. But, over the next 7 years until 2002, AAM had a marginal decline in their rates, whilst EAM experienced an increase. Compared to EAM (156/100,000), Hispanics (141/100,000), and API men (104.2/100,000) had lower incidence rates in the United States (1).

The reasons for the steeply rising incidence during the late 1980s and early 1990s for both AAM and EAM are unclear but probably reflect the improved detection of PCa by measuring serum PSA (7,14). Since the introduction of PSA, the age at diagnosis and distribution of disease stage and grade has changed significantly (7,14). In the 1980s, the median age at diagnosis for AAM and EAM was 70 and 72 years respectively. However, during 1998–2002, men were diagnosed at a younger age, 65 years for AAM and 68 years for EAM (1). In addition to the younger age at diagnosis seen during the PSA era, so too was there a shift in the type of disease being diagnosed. During the periods 1975 – 1978 and

1985–1989, 73% of PCa diagnoses were localized in comparison to the period 1995 –2001 where 91% of the diagnoses were localized (1). During these same periods, the proportion of diagnoses with distant disease declined from 20% to 16% to 5% (1).

After the harvesting effect or clearing of the prevalence of PCa, there was a return to a new incidence level, which is higher than the prePSA levels but more consistent with the natural history of the disease and the slow increase of an aging population per 100,000. Both PSA testing and improvements in transrectal ultrasonography, has resulted in more cases being detected from a pool of men with previously unsuspected disease than was the case about 20 years ago, thus having a dramatic influence on local and national trends in prostate cancer incidence in the United States (4).

Worldwide, the incidence of PCa in AAM is possibly exceeded only by rates in men of sub Saharan African descent in other countries, notably Jamaica and Trinidad and Tobago (3,15). For instance, in a 1998 analysis, Jamaican men of sub-Saharan descent were found to have a PCa incidence of 304/100,000 men. Conversely, rates in African countries like Nigeria appear to be substantially lower, but recent evidence suggests that this may be secondary to underreporting and poor data collection (16). Nevertheless, these differing incidence rates within populations of African descent may represent environmental as well as genetic differences (2,17). A similar variation in PCa incidence rates was observed in men of Japanese descent based on their country of origin and migratory patterns (18).

Based on the growing literature on the disproportionate burden of prostate cancer among other Black men of West African ancestry, it is clear that this clearly follows the path of the African Slave Trade. The primary West African source populations for the African Slave Trade were the African countries – Benin, Nigeria, Ghana, Gambia and Senegal. Our critical review of the literature on these West African countries found that the true prostate cancer rates reported for West Africans by the WHO (World Health Organization) may be underestimated. The consistent higher incidence of prostate cancer relative to other groups, observed in populations of West African descent may be attributed to the fact that these populations share ancestral genetic factors that increase susceptibility to prostate cancer. However, the likely variability in risk across these populations of African men around the world may also suggest a potential and important influence of environmental/lifestyle factors acting on prostate cancer risk in these susceptible populations. To date the disparate incidence of prostate cancer in African American men in the US compared to their Caucasian counterparts is poorly understood. Although modifiable exposures related to lifestyle or environment is believed to play a major role in the etiology of prostate cancer, the specific causal factors remain elusive. To identify these causal factors and to better understand and address the global prostate cancer disparities seen in Black men, it is important to distinguish genetic and environmental determinants of prostate cancer in men of West African ancestry, especially the original African Slave Trade source population for African American men. (19)

Mortality Rates

Deaths from PCa in the United States are more than 2-fold higher in AAM than in EAM (7,20). The SEER data demonstrated that age adjusted mortality rates from 1998 to 2002 were 68.9/100,000 in AAM and 27.8/100,000 in EAM (20). Although this increase did not mirror the sharp increase seen with the incidence rates for both groups, mortality rates still increased from 1975 to 2001 in both groups, and peaked in 1993 for AAM (81.9/100,000) and in 1991 for EAM (36.5/100,000) before decreasing to 66.4/100,000 and 26.6/100,000, respectively, in 2001 (20). Reporting of mortality rate data for Hispanic, API and AI/AN men began in 1992 and their age adjusted mortality rates for 1998–2002 were 23, 18.3, and 12.1 per 100,000 men respectively. Collectively, among the Hispanic men, API, and AI/AN

men, decreasing trends in mortality rates have also been noted. The most significant factors likely contributing to this decline include earlier diagnosis of PCa at a stage that is amenable to curative therapy, the relative decline in deaths from distant disease and the earlier and more widespread use of androgen deprivation therapy (21,22).

A review of PCa mortality around the world, showed that Western Europe, Australia and North America had the highest rates, whilst Far East and India experienced the lowest rates. Worldwide, the highest mortality rates were observed in men of sub-Saharan African descent, particularly in Trinidad and Tobago, Jamaica and Brazil (2). In England, subgroup analysis showed the highest PCa mortality amongst men of Caribbean descent (23). Conversely, lower mortality rates of less than 5.5/100,000 were reported in China and Japan (2,4). Within Europe, there is a dichotomy of PCa mortality rates between Northern Europe (Sweden, Norway and Denmark) of 23–27/100,000 men and Southern Europe (Greece) with a mortality rate of 10.7/100,000 men. These international differences may be attributed to the prevalence of both environmental and genetic risk factors. Data from migration studies in men of Asian ancestry living in the United States showed that they had lower risks of prostate cancer as compared to EAM, but had a higher risk of PCa when compared to men of similar ancestry living in Asia (18,24).

Clinically Localized Prostate Cancer

A Multivariable analysis was conducted to examine disease-free survival difference between AAM and EAM after radical prostatectomy for local disease. The study cohort was composed of 791 men whose only prostate cancer treatment was radical prostatectomy performed between July 1990 and December 1999. The variables analyzed were age, preoperative prostate-specific antigen level, pathologic grade and stage, and race/ethnicity. Pathologic examination of all specimens was performed in a uniform manner according to an established protocol. Multivariable analysis based on Cox's proportional hazards regression model was performed to assess whether a significant difference in progression-free survival time between AAM and WM persisted after controlling for the main effects of other prognostic factors. The study cohort consisted of 229 AAM and 562 WM. Our results indicated that all variables, except age, had highly significant effects on progression-free survival, even in the presence of other predictors (25).

Another study examined the effect of race/ethnicity on PCa local treatment outcome and found that outcome is conditional. We examined the conditions of age, stage and year of diagnosis, and the role of race/ethnicity on disease-free survival in men who underwent consecutive radical prostatectomy as monotherapy from 1990 to 1999. Data were collected from 229 AAMs and 562 white American men prospectively in the Karmanos Cancer Institute Prostate cancer data bases. When the majority of the cohort had pathologically organ confined disease, race/ethnicity was not an independent predictor of disease-free survival. When the majority of the cohort had a mean age of 70 years or greater, race/ethnicity was not an independent predictor. In studies done in the late 1990s, when the stage of radical prostatectomy cases had shifted toward pathologically organ confined disease as the dominant stage, race/ethnicity was not an independent predictor. However, if the cohort was diagnosed at younger age and/or with more advanced prostate cancer, race/ethnicity became an independent predictor. In the early 1990s there was pathologically advanced disease in the majority of our cohort.(26).

Explanation of the racial differences

Lack of access to care has been suggested as being responsible for disproportionate advanced disease and mortality among AAM in comparison to EAM. Data from the Behavioral Risk Factor Surveillance Study (BRFSS) indicate that in recent years AAM are

as likely to be tested for prostate cancer by PSA as are EAM, 59.6% versus 55.5% respectively. Yet AAM continue to present with more advanced disease and higher mortality rates. Financial barriers or the lack of insurance have also been suggested as potential causes for the disparity. According to BRFSS, the insurance rates for AAM and EAM over the age of 50 years is 81% and 89 % respectively. That difference is statistically significant but in our opinion does not account for the entire disparity and perhaps it may only contribute to a small difference in access to care as demonstrated by the similar rate of PSA testing. (27)

Socio-economic status (SES) has also been reported as a contributing factor for prostate cancer racial disparity, but this issue is controversial. Studies that examined SES in a multi-variable analysis have demonstrated that SES does contribute to racial outcome disparity. However, no difference in PCa recurrence after radical prostatectomy was identified among AAM when lower income versus middle income was compared. Non-financial barriers such as poor health seeking behavior have been reported to delay diagnosis of PCa among AAM. Fear of the diagnosis of prostate cancer and distrust of the health care system appear to be the most dominant factors. Evidence has been reported that PCa treatment differences do contribute to survival disparity. African American men are less likely to be treated for PCa than EAM for similar stages of disease.[27]

We propose that a faster prostate cancer growth rate and/or an earlier transformation from latent to aggressive PCa among AAM compared to EAM contributes significantly to the racial disparity of advanced disease at diagnosis and a 2 to 3 times greater mortality rate among AAM versus EAM. We examined our autopsy series, RP results from the Wayne State University/Karmanos Cancer Institute and Detroit SEER data to study this issue.(27)

The autopsy study finds that the volume of PCa is similar among young (ages 20 to 60) AAM and EAM. The grade is also similar. However, among men who underwent RP, AAM demonstrated a greater PCa volume and higher grade tumors than EAM under age 70 years. The evidence suggests that prostate cancer is growing faster and an earlier transformation from latent to aggressive PCa among AAM than EAM is occurring. Sanchez-Ortiz et al. report that AAM with non-palpable PCa had higher prostatectomy Gleason scores, greater cancer volume, and greater tumor volume per ng/ml of serum PSA. If PCa starts at the same time as demonstrated in our autopsy study but reaches distant metastasis at a disproportionate rate of approximately 4 to1, AAM compared to EAM respectively, then one may also conclude that the cancer is growing faster in AAM than EAM. Alternate explanations for the conclusion is that the growth rate of PCa is identical in AAM and EAM, but PCa begins to grow earlier in AAM. One may assume therefore that clinically significant PCa begins at a later age in EAM and hence the growth rates are the same. One also may assume that the number of aggressive or rapidly growing tumors in AAM are greater than in EAM. A recent report concluded that extensive high grade PIN has been associated with increased risk of clinically significant PCa. The data suggest that at ages 40 to 49 years, a conversion to clinically significant PCa at disproportionate rates among AAM compared to EAM may be the beginning of PCa racial disparity. Support for these observations and conclusion are based on volume and Gleason grade analysis from the RP database that illustrates a higher Gleason grade PCa among AAM compared to EAM at early ages (40 to 49). This disparity continues in later decades. However, it is important to note that this significant development in disparity in volume, stage and grade occurred in just 2 decades or less in reference to the autopsy study. Also, the fact that this disparity is prevalent among men ages 40 to 49 minimizes if not eliminates any screening impact since screening recommendations for EAM began at 50 years [prior to recent National Comprehensive Cancer Network (NCCN) recommended changes in 2009] and 40 and 45 years (recommended by AUA and American Cancer Society respectively) for AAM. Because volume and grade are reflections of the biology of PCa, the analysis implies that PCa among

AAM is biologically and genetically more aggressive compared to EAM. Cancer is a genetic disease and the explanation and answer for differences in incidence and disease progression should begin there.(27)

Multiple genetic and biological pathways contribute to a more aggressive PCa and increased cell proliferation and metastasis among AAM than EAM. Factors such as diet, obesity and hypertension have been reported to impact PCa by association, and some mechanistic processes have been demonstrated. African American men have been reported to have a higher fat content diet,[28] are more obese (higher BMI),[29] and have a higher rate of hypertension than EAM.[30] The latter two are components of the metabolic syndrome. The mechanism associated with obesity and hypertension includes release of inflammatory cytokines, release of reactive oxides and thus oxidative stress, DNA damage and activation of NFkB. NFkB has been reported to cause PCa cell proliferation.[31] High fat content diet is associated with up-regulation of glucose-like growth factor 1 (IGF-1). This also impacts NFkB by way of the AKt-1 pathway.[32] The protein NFkB activates or up-regulates the androgen receptor (AR) protein expression and Gaston KE et al report that AR expression is 81% higher in PCa of AAM compared to EAM. Therefore, PCa may occur at a younger age and progress more rapidly in AAM than EAM due to racial differences in androgen receptor stimulation of the prostate. (33) Wallace et al. examined known metastasis-promoting genes, including autocrine motility factor receptor, CXCR4 and matrix metalloproteinase 9 (MMP9) using microarray technology and found that these genes were more highly expressed in tumors from AAM than EAM.[34] These genes may be impacted by environmental factors, including diet, obesity and inflammation.

Cytochrome P450 3A4 (CYP3A4) is a protein belonging to the cytochrome P-450 supergene family which is involved in the oxidative deactivation of testosterone to biologically less active metabolites. Inhibition of this transformation results in increased bioavailability of testosterone and increased conversion to dehydrotestosterone and androgen receptor stimulation. A germ-line genetic variant in the 5' regulatory region of the CYP3A4 gene (A to G transition) on chromosome 7 has been reported and named CYP3A4*1B and CYP3A4-V. Rebbeck et al in a study of EAM only, found the genetic variant of CYP3A4 to be associated with a higher clinical grade and stage prostate cancer.[35] However, the allele frequency of the variant G allele is differentially distributed across racial and ethnic groups. Powell et al. reported a strong association between race and genotype ($p=0.00002$) in that 8% of EAM and 83% of AAM had 1 or more copies of the G allele. When both races were included genotype was associated with progression free survival ($p=0.005$).[36] Downstream on Chromosome 7 domain CYP3A43 cytosine-to-guanine polymorphism, Bonilla et. al. found a highly significant association between CYP3A43 and high grade PCa detected in subjects younger than 60 years old. This study remained significant after controlling for ancestry.[37]

Recent studies have identified multiple single nucleotide polymorphisms (SNPs) at 8q24 associated with prostate cancer. Most studies were case-control studies that reported racial/ethnic specific SNPs associated with prostate cancer.[38] Also 4 regions have been identified that report different racial/ethnic distributions and odds ratios of SNPs associated with prostate cancer.[39] Combination of multiple SNPs carried considerably larger association with PCa. Haiman et al.measured population attributable risk (PAR) calculations of seven SNPs or variants and found that AAM had significantly higher association with PCa than EAM 68% versus 32% respectively.[38] Helfand et al. reported that the presence of multiple risk alleles was significantly associated with high grade disease in the biopsy and prostatectomy specimens of their cohort study population.[40]

Importance of Family History in Prostate Cancer

Recent genetic studies suggest that hereditary factors may be responsible for 5%–10% of prostate cancers. The risk increases in relatives of affected men. Men with a first degree relative with prostate cancer have a two to three fold increase in risk relative to the general population. This means that a brother, father, or son of a prostate cancer case has a risk of prostate cancer that is approximately double the population risk. Male relatives with two first-degree relatives have a five-fold increased risk, whereas, a family history of three first-degree relatives with prostate cancer gives rise to an increased risk of 11-fold in male relatives. Therefore, relatives with a stronger family history would be more likely to have prostate cancer over relatives of a single case, which means the more cases in a family the higher the risk to other male relatives. Therefore, the familial aggregation of prostate cancer is useful in studying the inherited risk to the disease. In addition, relatives of early onset cases would have a higher risk of having prostate cancer over that of later onset cases. It was also found that brothers of cases diagnosed under the age of 65 had a six-fold increased risk of developing prostate cancer under the age of 65 themselves. So, the three important modifiers of risk related to familial history of prostate cancer are: (1) the age of the man at risk, (2) the age of the affected relative, and (3) the number of relatives with prostate cancer (41).

It is clear that men with a family history of prostate cancer are greater risk of being diagnosed with prostate cancer and may be diagnosed at an earlier age than men with sporadic disease. However, is the cancer more aggressive and is their a greater risk of disease recurrence among men with a family history of prostate cancer compared men with sporadic disease? The following study reported in 1998 was conducted to address this issue. The study was performed in 2 parts. In both parts prostate specific antigen (PSA) progression was defined as a postoperative elevation in serum PSA greater than 0.2 ng./ml. Part 1 included 656 patients who underwent radical prostatectomy by the same surgeon. Men with a family history of prostate cancer in a father or brother (94) were compared to those with no history of prostate cancer in a father or brother (562). Part 2 comprised 52 men with a family history of prostate cancer consistent with hereditary prostate cancer (HPC). HPC is defined as a family with 3 generations affected, 3 first-degree relatives affected or 2 relatives affected before age 55 years. Each member of this HPC group was matched by postoperative Gleason score and postoperative pathological stage with a patient who also underwent radical prostatectomy in the same time frame by the same surgeon but who reported no family history of prostate cancer by telephone interview and questionnaire. RESULTS: In part 1, 94 probands (14%) reported a history of prostate cancer in the father or in at least 1 brother. The remaining 562 probands (85%) reported no known history of prostate cancer in the father or brother(s). There was no statistically significant difference in the probability of maintaining an undetectable PSA between these 2 groups. In part 2, 45 of 52 pairs (87%) were matched identically for all matching criteria. Mean follow time for the sporadic and hereditary groups was 5.4 and 5.1 years, respectively. There was no statistically significant difference in the probability of maintaining an undetectable PSA between the 2 groups. CONCLUSIONS: Men with an affected father or brother, or those with a family history consistent with HPC have the same outcome following radical prostatectomy as men with no family history of the disease. Combined with our previous studies, these findings suggest that there is no biologically important difference between hereditary and sporadic prostate cancers (42).

However, more recent studies have reported specific prostate cancer susceptibility genes or loci in families with prostate cancer that are associated with more aggressive disease and greater risk of recurrence than among men with sporadic disease. Medical record data on 505 affected men in 149 multiply-affected prostate cancer families were reviewed, and correlations of clinical traits within each family were calculated. Logarithm of odds (LOD)

score and nonparametric (NPL) linkage analyses were performed; white families were stratified by age of diagnosis, grade and stage of disease, and evidence of linkage to the other loci to increase genetic homogeneity. The current results suggest that *HPC1* linkage may be most common among families with more severe prostate cancer. Stratification by clinical characteristics may be a useful tool in prostate cancer linkage analyses and may increase our understanding of hereditary prostate cancer (43).

Evidence for the existence of major prostate cancer PCa susceptibility genes has been provided by multiple segregation analyses. Although genome-wide screens have been performed in over a dozen independent studies, few chromosomal regions have been consistently identified as regions of interest. In this study, a large number of PCa families in an International Consortium for Prostate Cancer Genetics (ICPCG). One approach was to combined linkage data from a total of 1,233 families to increase the statistical power of detecting linkage. Using parametric (dominant and recessive) and non-parametric analyses, they identified five regions with ‘suggestive’ linkage (LOD >1.86), including 5q12, 8p21, 15q11, 17q21, and 22q12.

While it is difficult to determine the true statistical significance of these findings, a conservative interpretation of these results would be that if major PCa susceptibility genes do exist, they are most likely located in the regions generating positive linkage signals in this large study. More than 90% of the study population was European American or European (44). An African American HPC (AAHPC) linkage analysis revealed four different chromosomal regions for 77 families at 11q22, 17p11, 2p21 and Xq21. The AAHPC also reported two regions for 16 families with '>6 affected' occurred at 2p21 and 22q12. Thus both the AAHPC and the ICPCG reported a susceptibility locus in the 22q12 region. In both studies the 22q12 region was associated with large families and aggressive prostate cancer and greater risk of recurrence (45).

There are several reports of genetic susceptibility to aggressive PCa which include loci 5q31, 4q, 7q31, 6q, 19q13, Xq27, 20q as well as the loci mentioned above (46). In aggregate, the above studies make three important points. First, no single approach will work for finding genes associated with prostate cancer. The disease is both genetically and phenotypically complex. Linkage, candidate gene association, and perhaps more importantly, functional studies are needed once a specific mutation or variant is suspected.

Second, a data set is only as strong as the phenotypes which define it. Those making progress in solving the problem of susceptibility to aggressive prostate cancer have done so because they have diligently obtained medical records, pathology reports, and tumor specimens. Partnerships with clinical colleagues are a vital part of solving problems in complex trait analyses.

Finally, data sets for both linkage and candidate gene evaluations are almost always limited by sample size. Meta-analyses or combined studies achieve greater power for evaluating more hypotheses, without the loss of statistical power that results when looking at subgroups. Investigators worldwide who are involved in research on genetic susceptibility to prostate cancer have formed a true community that has worked hard to build the infrastructure and obtain resources for carrying out large combined studies. Such an approach would certainly benefit those studying a host of complex diseases (46).

As demonstrated multiple genes and loci have been reported to be associated with aggressive hereditary PCa and disease recurrence. These genes and loci appear to be geographically and population based but clearly further research is necessary before we can

determine the genetic role of hereditary prostate cancer in aggressive disease and PCa progression in an individual patient.

References

1. American Cancer Society. Cancer facts and figures 2007. 2007 Available at http://www.cancer.org/docroot/STT/stt_0.asp.
2. American Cancer Society. Cancer facts and figures 2003. 2003 Available at http://www.cancer.org/docroot/STT/stt_0.asp.
3. Grönberg H. Prostate cancer epidemiology. Lancet. 2003; 361:859–864. [PubMed: 12642065]
4. Crawford ED. Epidemiology of prostate cancer. Urology. 2003; 62 suppl 1(6):3–12. [PubMed: 14706503]
5. Schaid DJ. The complex genetic epidemiology of prostate cancer. Hum Mol Genet, suppl. 2004; 13:R103–R121.
6. Brawley OW. Prostate cancer and black men. Semin Urol Oncol. 1998; 16:184–186. [PubMed: 9858323]
7. American Cancer Society. Cancer facts and figures for AAMs 2007–2008. Available at http://www.cancer.org/docroot/STT/stt_0.asp.
8. Liu L, Cozen W, Bernstein L, Ross RK, Deapen D. Changing relationship between socioeconomic status and prostate cancer incidence. J Natl Cancer Inst. 2001; 93:705–709. [PubMed: 11333293]
9. Powell IJ, Gelfand DE, Parzuchowski J, Heilbrun L, Franklin A. A successful recruitment process of African American men for early detection of prostate cancer. Cancer. 1995; 75:1880–1884.
10. Robbins AS, Whittemore AS, Thom DH. Differences in socioeconomic status and survival among white and black men with prostate cancer. Am J Epidemiol. 2000; 151:409–416. [PubMed: 10695600]
11. Powell IJ, Zhou J, Sun Y, Sakr WA, Patel NP, Heilbrun LK, et al. CYP3A4 genetic variant and disease-free survival among white and black men after radical prostatectomy. J Urol. 2004; 172:1848–1852. [PubMed: 15540736]
12. Gaston KE, Kim D, Singh S, Ford OH 3rd, Mohler JL. Racial differences in androgen receptor protein expression in men with clinically localized prostate cancer. J Urol. 2003; 170:990–993. [PubMed: 12913756]
13. Mettlin C. Recent developments in the epidemiology of prostate cancer. Eur J Cancer. 1997; 33:340–347. [PubMed: 9155514]
14. Jani AB, Vaida F, Hanks G, Asbell S, Sartor O, Moul JW, et al. Changing face and different countenances of prostate cancer: racial and geographic differences in prostate-specific antigen (PSA), stage, and grade trends in the PSA era. Int J Cancer. 2001; 96:363–371. [PubMed: 11745507]
15. Glover FE Jr, Coffey DS, Douglas LL, Cadogan M, Russell H, Tulloch T, et al. The epidemiology of prostate cancer in Jamaica. J Urol. 1998; 159:1984–1986. [PubMed: 9598503]
16. Delongschamp NB, Singh A, Haas GP. Epidemiology of prostate cancer in Africa: Another step in the understanding of the disease? Curr Prob Cancer. 2007; 31:226–236.
17. Ahluwalia B, Jackson MA, Jones GW, Williams AO, Rao MS, Rajguru S. Blood hormone profiles in prostate cancer patients in high-risk and low-risk populations. Cancer. 1981; 48:2267–2273. [PubMed: 7296478]
18. Haenszel W, Kurihara M. Study of Japanese migrants. I. Mortality form cancer and other diseases among Japanese in the United States. J. Natl Cancer Inst. 1968; 40:43–68. [PubMed: 5635018]
19. Odedina F, Akinremi T, Chinegwundoh F, Roberts R, et al. Prostate cancer disparities in Black men of African descent: a comparative literature review of prostate cancer burden among Black men in the United States, Caribbean, United Kingdom, and West Africa. Infectious Agents and Cancer. 2009; 4(Suppl 1):S2. [PubMed: 19208207]
20. Ries, LAG.; Eisner, MP.; Kosary, CL.; Hankey, BF.; Miller, BA.; Clegg, L., et al. SEER Cancer Statistics Review, 1975–2002. Bethesda, MD: National Cancer Institute; 2002. Available at http://seer.cancer.gov/csr/1975_2002/.

21. Chu KC, Tarone RE, Freeman HP. Trends in prostate cancer mortality among black men and white men in the United States. Cancer. 2003; 97:1507–1516. [PubMed: 12627516]
22. Lu-Yao G, Albertsen PC, Stanford JL, Stukel TA, Walker-Corkery ES, Barry MJ. Natural experiment examining impact of aggressive screening and treatment on prostate cancer mortality in two fixed cohorts from Seattle area and Connecticut. BMJ. 2002; 325:740. [PubMed: 12364300]
23. Wild SH, Fischbacher CM, Brock A, Griffiths C, Bhopal R. Mortality from all cancers and lung, colorectal, breast and prostate cancer by country of birth in England and Wales, 2001–2003. Br J Cancer. 2006; 94:1079–1085. [PubMed: 16523198]
24. Yu H, Jarris RE, Gao YT, Gao R, Wynder EL. Comparative epidemiology of cancer of colon, rectum, prostate and breast in Shanghai, China versus the United States. Int J Epidemiol. 1991; 20:76–81. [PubMed: 2066247]
25. Powell IJ, Dey J, Dudley A, Pontes JE, Cher ML, Sakr W, et al. Disease-free survival difference between African Americans and whites after radical prostatectomy for local prostate cancer: a multivariable analysis. Urology. 2002; 59:907. [PubMed: 12031379]
26. Powell IP, Banerjee M, Bianco FJ, Wood DP Jr, Dey J, Lai Z, et al. The effect of race/ethnicity on prostate cancer treatment outcome is conditional: a review of Wayne State University data. J Urol. 2004; 171(4):1508–1512. [PubMed: 15017209]
27. Powell IJ, Bock C, Ruterbusch J, Sakr w. Evidence Supports a Faster Growth Rate and/or Earlier Transformation to Clinically Significant Prostate Cancer in Black Than in White American Men and Influences Racial Progression and Mortality Disparity. J OF UROLOGY. 2010 May.Vol. 183:1792–1797.
28. Whittemorre AS, Kolonel LN, Wu AH, et al. Prostate cancer in relation to diet, physical activity, and body size in blacks, whites, and Asians in the U. S. Canada. J Natl Cancer Inst. 1995; 87:652. [PubMed: 7752270]
29. Amling, Cl; Riffenburgh, RH.; Sun, L., et al. Pathologic variables and recurrence rates as related to obesity and race in men with prostate cancer undergoing radical prostatectomy. J Clin Oncol. 2004; 22:430.
30. Gokce N, Holbrook M, Duffy SJ, et al. Effect of race and hypertension on flow-mediated and nitroglycerin-mediated dilatation of the brachial artery. Hypertension. 2001; 38:1349. [PubMed: 11751716]
31. Sonnenberg GE, Krakower GR, Kissebah AH. A novel pathway to the manifestations of metabolic syndrome. Obes Res. 2004; 12:180. [PubMed: 14981209]
32. Hsing AH, Sakoda LC, Chua S Jr. Obesity, metabolic syndrome, and prostate cancer. Am JClin Nutr. 2007; 86:843.
33. Gaston KE, Kim D, Singh S, et al. Racial differences in androgen receptor protein expression in men with clinically localized prostate cancer. J Urol. 2003; 170:990. [PubMed: 12913756]
34. Wallace TA, Prueitt RL, Yi M, et al. Tumor immunobiological differences in prostate cancer between African American and European American men. Cancer Res. 2008; 68:927. [PubMed: 18245496]
35. Rebbeck TR, Jaffe JM, Walker AH, et al. Modification of clinical presentation of prostate tumors by a novel genetic variant in CYP3A4. J Natl Cancer Inst. 1998; 90:1225. [PubMed: 9719084]
36. Powell IP, Zhou J, Sun Y, et al. CYP3A4 genetic variant and disease-free survival among white and black men after radical prostatectomy. J Urol. 2004; 72:1848. [PubMed: 15540736]
37. Bonilla C, Hernandez W, Kittles R, et al. CYP3Agene cluster, population stratification, and prostate cancer risk. J Urol, suppl. 2009; 181:818. abstract 2258.
38. Haiman CA, Patterson N, Freedman ML, et al. Multiple regions within 8q24 independently affect risk for prostate cancer. Nat Genet. 2007; 39:638. [PubMed: 17401364]
39. Robbins C, Torres JB, Hooker S, et al. Confirmation study of prostate cancer risk variants at 8q24 in African Americans identifies a novel risk locus. Genome Res. 2007; 17:1717. [PubMed: 17978284]
40. Helfand BT, Loeb S, Cashy J, et al. Tumor characteristics of carriers of the decode 8q24 prostate cancer susceptibility alleles. J Urol. 2008; 179:2197. [PubMed: 18423739]

41. D. M. Mandal: Genetics of prostate cancer: Role of family history. www.medschool.Lsuhsc.edu/genetics_center/louisiana/article_prostatecancer2_p.htm.

42. Bova GS, Partin AW, Isaacs SD, Carter BS, Beaty TL, Isaacs WB, Walsh PC. Biological aggressiveness of hereditary prostate cancer: long-term evaluation following radical prostatectomy. J Urol. 1998 Sep; 160(3 Pt 1):660–663. [PubMed: 9720516]

43. Goode E, Stanford J, Peters M, Janer M, et al. Clinical Characteristics of Prostate Cancer in an Analysis of Linkage to Four Putative Susceptibility Loci. Clinical Cancer Research. 2001 Sep.Vol. 7:2739–2749. [PubMed: 11555587]

44. Xu J, Dimitrov L, Chang B, Adams T. A combined genome-wide linkage scan for prostate cancer susceptibility genes in 1,233 families conducted by the ICPCG. Am. J. Hum. Genet. 2005; 77:219–229. [PubMed: 15988677]

45. Baffoe-Bonnie A, Kittles RA, Gillanders E, Ou L, George A, Ahaghotu C. Genome-wide linkage of 77 families from the African American hereditary prostate cancer study (AAHPC). Prostate. 2006; 67:22–31. [PubMed: 17031815]

46. Ostrander E, Kwon E, Stanford J. Genetic Susceptibility to Aggressive Prostate Cancer. Cancer Epidemiol Biomarkers Prev. 2006 Oct.15(10) 2006.