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Biological Determinants of Health Disparities in Prostate Cancer

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Abstract

Purpose of review—Prostate cancer mortality rates are highest among men of African ancestry in the United States and globally. Environmental exposures and ancestry-related factors may influence tumor biology and induce a more aggressive disease in this population. Here, we summarize the most recent advances in our understanding of race/ethnic differences in the tumor biology of prostate cancer with an emphasis on the excess disease burden among African-Americans.

Recent findings—Results from several DNA methylation studies showed an increased prevalence in DNA hypermethylation at disease-related loci in tumors from African-American patients compared with tumors from European-American patients. Analyses of genome-wide gene expression in prostate tumors revealed frequent alterations in the expression of genes related to immunobiology among the African-American patients, consistent with immune response differences between them and their European-American counterparts. Lastly, population differences in the frequency of oncogenic ETS-related gene rearrangements were evaluated in three studies which showed that these alterations manifest themselves most commonly in tumors from men of European ancestry, but are significantly less frequent in men of African ancestry, while least common in men of Asian ancestry.

Summary—Analysis of tumor markers indicates that tumor biological differences may exist between prostate cancer patients of African ancestry and those of European or Asian ancestry. These differences could affect disease aggressiveness and response to therapy.

Keywords

prostate cancer; health disparity; tumor marker; genetics; outcome

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(Introduction)

Disease characteristics of prostate cancer show significant geographical and ethnic variations [1]. Prostate cancer is more common in North America and Europe than in less affluent countries [2;3], but it remains unresolved whether the low reported occurrence rates for this disease in some geographic locations, such as Sub-Saharan Africa, are factually correct or an artifact of inadequate cancer surveillance. Yet, incidence and mortality rates of prostate cancer are significantly higher in men of African ancestry when compared with men from other population groups in the United States, the Caribbean, the United Kingdom, and in parts of South America [4;5•]. It is well recognized that prostate tumors tend to develop earlier as a clinical disease and are more aggressive at diagnosis in African-American men than in European-American men [6;7]. In addition, studies in West and Central Africa showed a notable prevalence of high grade and aggressive prostate tumors in men visiting hospitals in Nigeria, Senegal, Cameroon, and Kenya [5•].

The health disparity seen in prostate cancer within the United States has been attributed to several inter-related factors, including differences in socioeconomic status and lifestyle exposures, access to healthcare, racial and ethnic discrimination, language and cultural barriers, and a delayed disease diagnosis in socio economically deprived communities. Recently, research efforts have begun to concentrate on molecular mechanisms in tumor biology and ancestry-related aspects that may contribute to the existing prostate cancer health disparities. Previous epidemiological studies have shown that African-American men have significantly higher plasma PSA levels than European-American men [8;9], although the size of the prostate is similar in both groups of men [10]. The latter observation suggests that a generally enhanced androgenic and growth stimulatory effect is not present in the gland of men of African ancestry that would explain the elevated blood PSA levels [10]. Genome-wide genetic association studies described multiple genetic susceptibility loci for prostate cancer. The best characterized risk locus for the disease is located at 8q24, and several studies showed that this locus may confer a higher risk for prostate cancer in men of West African ancestry than in men of European ancestry because some risk-conferring single nucleotide polymorphisms occur at an increased frequency in ancestral West African men [11–14]. However, the aforementioned factors do not fully explain the observed differences in disease aggressiveness and mortality amongst the various race/ethnic groups in the United States. Therefore, it has been suggested that either still unrecognized ancestry-related factors or inter-ethnic differences in environmental exposures influence tumor biology and cause a more aggressive disease in some patient groups like men of African ancestry. One study addressed this question by analyzing prostate autopsy material from a total of 1056 African-American and European-American men who did not have a prior diagnosis of prostate cancer, and by comparing the autopsy findings with findings from the analysis of resected tumors. While the cancer prevalence and disease presentation was similar between the two race/ethnic groups at the subclinical stage, amongst patients with clinically detected prostate tumors, African-American men tended to have a more aggressive disease than European-American men by microscopic evaluation. The latter findings support the hypothesis that differences in tumor biology may exist between the two patient groups,

leading to a faster growth rate and a more rapid transformation of tumors in men of African ancestry [7].

Evidence of race/ethnic differences in the tumor biology of prostate cancer

Most investigations into race/ethnic differences in tumor biology have compared African-American with European-American prostate cancer patients residing in the United States. Few studies have included patients of Asian descent, while even less have included patients of Hispanic/Latino and Native American descent. Several notable observations were made comparing prostate cancer patients of European, African, and Asian ancestry. Consistent differences in tumor biology between these patient groups were observed using 1) the analysis of DNA methylation patterns [15–17], 2) analysis of acquired genomic alterations and expression analysis of ETS related gene 1 (*ERG*) alterations [18•;19;20••;21•], and 3) genome-wide gene expression analysis [22••;23] (Table 1).

Differences in DNA methylation

Epigenetic DNA alterations are commonly detected in human prostate tumors [24]. Alterations in DNA methylation are amongst the earliest somatic changes that can be detected in cancerous lesions of the prostate and occur at the stage of proliferative inflammatory atrophy, a precursor lesion in human prostate cancer development. Increased DNA methylation can lead to numerous downstream effects, including inactivation of *PTEN*, which may be the most significant tumor suppressor gene in prostate cancer, or a loss of *GSTP1* expression, which is observed in 90% of prostate cancers [24]. Recently, a member of the zinc finger superfamily, termed Kaiso, was found to be overexpressed in prostate tumors from African-American patients [25•]. Nuclear translocation of this protein is induced by epidermal growth factor receptor signaling. Interestingly, Kaiso recognizes clusters of methylated CpG nucleotides and also induces migration and invasion of prostate cancer cells, suggesting that aberrant Kaiso expression in tumors from African-American men may enhance disease aggressiveness by mechanisms that include aberrant DNA methylation of cancer-related genomic loci.

Given the importance of epigenetic DNA alterations in the development and progression of prostate cancer, the occurrence of aberrant DNA methylation at disease-related loci in tumors from African-American patients has been evaluated by several investigators over the years. In these studies, a pattern emerged consistent with an increased prevalence of DNA hypermethylation at disease-related loci in African-American tumors when compared with similar stage tumors from European-American men [15–17]. The first study published in 2003 found a difference in the methylation status of *CD44*, the receptor for hyaluronic acid which also interacts with other ligands, such as osteopontin, collagens, and matrix metalloproteinases [15]. The second investigation observed an increased methylation of the *GSTP1* locus in tumors of the African-American patients [16], while the most recent study reported methylation differences for multiple loci in cancerous and non-cancerous prostate tissue [17]. These findings will have to be followed up using state-of-the-art techniques with genome-wide coverage of CpG islands. Nevertheless, the consistency in the observations among the three reports suggests that gene silencing differences through epigenetic mechanisms may likely exist between patients of different race/ethnic descent. To date, we

do not know what mechanisms may lead to race/ethnic differences in DNA methylation patterns, and whether these patterns are induced by environmental exposures, intrinsic differences in tumor biology, including cancer metabolism and metabolism-induced epigenetic alterations, or a combination of these factors. Recently, racial differences in gene-specific DNA methylation were reported to exist at birth [26]. In this particular study, the authors examined DNA methylation levels at 26,485 autosomal CpGs in blood samples from 107 African-American and 94 European-American newborns. Most notable, they observed significant differences in DNA methylation levels affecting cancer-related loci and pathways associated with pancreatic, prostate, bladder cancers and melanoma. The authors hypothesized that exposure associated with maternal diets may have caused the observed differences in the newborns.

Differences in acquired chromosomal aberrations

The acquisition of either loss-of-function or gain-of-function mutations in cancer-related genes and frequent chromosomal aberrations leading to both gene deletions and amplification are a hallmark of cancer. Hence, several research groups have investigated the occurrence of chromosomal alterations in prostate cancer, comparing tumors from African-Americans with tumors from European-Americans. In three studies, DNA copy number alterations in prostate tumors from the two patient groups were analyzed and compared [18•; 27;28]. The first study analyzed 16 tumors from each patient group and did not observe significant differences in chromosomal aberrations between the patients [27]. The second study identified multiple regions that showed differences in allelic loss and gain between the two patient groups, but did not validate the findings in another patient cohort [28]. The third and most recent study evaluated genomic alterations in both a discovery and validation cohort and described chromosomal aberrations whose occurrence is most divergent between tumors from African-American and European-American men. The data from this study revealed common genomic alterations that appeared to be rather specific to African-American tumors and commonly affected loci encoding genes related to immune function [18•]. Other pathways that could be distinctively affected by chromosomal aberrations in tumors from African-American patients included catecholamine metabolic processes and neurotransmitter transport, suggesting possible differences in the beta adrenergic signaling pathway between African-American and European-American patients.

Recurrent genomic rearrangements at cancer-related loci like the *TMPRSS2:ERG* gene fusion, which lead to fusion transcripts and oncogenic over-expression of *ERG*, are signature mutations of human prostate tumors and have important biological and clinical implications [29–31]. Tumors carrying them fall into a distinct molecular subclass [32]. Previously, ETS family-associated gene fusion events, involving *ERG*, *ETV1* or *ETV5*, were reported to be less common in radical prostatectomy samples from Japanese prostate cancer patients when compared with the reported prevalence of these genetic alterations in tumors from European and European-American patients [33]. Three additional studies have examined the frequency of these recurrent *ERG* gene fusions in European, European-American, Chinese, Japanese, and African-American prostate cancer patients [19;20••;21•]. While common in European and European-American patients (~50% frequency), these alterations were found to be significantly less frequent in African-American patients (24% to 31% frequency), and rather

uncommon in patients from Asia (2% to 16% frequency) in these studies. This pattern may not be restricted to *TMPRSS2:ERG* rearrangements. The inactivation of the *PTEN* tumor suppressor may follow a similar trend, but currently only one study has examined the frequency of 10q deletions across population groups comparing European with Chinese patients [19]. A loss of *PTEN* occurs commonly in prostate tumors of European patients (40% to 50%). However, the study by Mao *et al.* found 10q deletions to be uncommon in the Chinese patients (14%). Two other studies evaluated the frequency of *PTEN* alterations in patients from China and Japan. Unfortunately, these studies did not include European patients in their analysis for a direct comparison. *PTEN* mutations were detected in 16% of mostly high grade prostate tumors from Chinese patients [34]. In contrast, a *PTEN* mutation was not detected in the Japanese patient cohort and a *PTEN* loss occurred in only 2 out of 18 tumors (11%) [35]. The different frequency of *ERG* rearrangements and possibly *PTEN* loss between prostate cancer patients of European and Asian descent indicate that prostate tumors in Asian populations may arise from pathogenic mechanisms that are different from Western populations, which may be due to differences in environmental risk factors. Thus, prostate tumor biology may display an unexpected global heterogeneity between men of European, African and Asian descent with respect to acquired mutational events that define the natural history of the disease, but may also define disease aggressiveness [31]. These differences between patient groups may have clinical implications because tests to detect *TMPRSS2:ERG* fusion events are being developed as a biomarker for early detection of prostate cancer [36•]. Current data indicate that such a test may not perform as well in Asian and African-American patients as it does in patients of European ancestry.

Differences in gene expression patterns

Genome-wide gene expression profiling studies of human tumors led to the discovery of both disease subtypes and expression patterns that are predictive of disease outcome. These studies can be hypothesis-generating instruments that allow researchers to examine the phenotypic diversity of tumors and assist in discovering more subtle differences in tumor biology that are not readily accessible by other techniques. Thus, using this discovery tool can be very advantageous in exploring tumor biological differences in cancer health disparity research where we do not expect large differences between patient populations. Using a technique termed “Differential Display Analysis”, a novel prostate-specific gene, *PCGEMI*, that encodes a long non-coding RNA with a cell growth promoting function was discovered [37;38]. Further analyses revealed that this gene was most highly expressed in prostate tumors of African-American patients [38]. However, *PCGEMI* has not been further examined in recent years, and we do not know whether this candidate gene may have an important oncogenic function in prostate cancer biology, particularly with respect to the African-American population.

We and others have used genome-wide gene expression profiling to investigate candidate differences in tumor biology between African-American and European-American prostate cancer patients [21•;22••;23;39]. From these studies, the consistent observation emerged that immunobiological differences may exist in tumors from the two patient groups. An analysis of 69 macro-dissected tumors from 33 African-American and 36 European-American patients that were matched on clinicopathological characteristics (patient’s age, Gleason

score, disease stage, PSA at diagnosis, largest tumor nodule) identified numerous differences in the expression of genes related to immunobiology [22••]. These genes clustered in pathways related to immune response, host defense, cytokine signaling and chemotaxis, and inflammation. Most of the immune-related genes were expressed higher in tumors from African-American patients than in those from European-American patients. Previously, it was observed that low-grade chronic inflammation in the non-cancerous prostate gland is more prevalent in African-American men [8]. Thus, it is possible that the observed gene expression differences in the tumors are partly due to a low-grade chronic inflammation that is more prevalent in African-American tumors. Furthermore, several known metastasis-promoting genes, including *AMFR*, *CXCR4*, and *MMP9*, were more highly expressed in tumors from African-Americans than European-Americans [22••;39]. *AMFR* encodes the autocrine motility factor receptor, which increases cancer metastasis by targeting the tumor suppressor, KAI1, for degradation [40]. Intriguingly, a prominent interferon gene signature was also detected in African-American tumors that may relate to either an unknown etiologic agent in disease pathology (e.g., an infection), to acquired genetic alterations in the cancer cells, or to intrinsic differences in the immune response between patients of African ancestry and those of European ancestry. This particular signature appears to be identical to previously identified interferon-related gene signatures that were induced by both tumor-stroma interactions and acquired resistance to DNA damage [41–44]. Most notable, the interferon-related signature in these studies was found to be consistently associated with either metastasis or poor disease outcome. Because several genes that constitute the interferon signature are known to have an immunosuppressive activity in the tumor microenvironment, like indolamine-2,3-dioxygenase, it is our hypothesis that the immunologic profile in African-American tumors is immunosuppressive in nature, inhibiting the host response directed against cancer cells. The observed difference in the tumor immunobiology of prostate cancer between African-American and European-American patients may also have implications for cancer therapy. Clinical trials of immunotherapy for prostate cancer have been conducted and the Sipuleucel-T (PROVENGE®) autologous vaccine has been approved for treatment of patients with castrate-resistant metastatic prostate cancer [45]. The data presented in this review suggest that African-American and European-American patients might respond differently to these types of therapy.

Conclusions

The analysis of tumor markers showed that biological differences may exist in prostate cancer among patients of African, European or Asian ancestry. These alterations may arise because of ancestry-related factors, including differences in immune function, or may manifest themselves because of inter-ethnic differences in environmental exposures and in the tumor microenvironment that define pathogenetic (e.g., *ERG* rearrangement frequency and DNA methylation patterns) and tumor immunobiological mechanisms in prostate cancer development. These differences could also affect early disease detection and the response to therapy, and contribute to a distinct disease presentation of prostate cancer among men of African ancestry, including the excess mortality in this patient group in the United States and globally.

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Abbreviations:

ETS	erythroblast transformation-specific family of transcription factors
ERG	v-ets erythroblastosis virus E26 oncogene homolog (avian) or ETS related gene 1
PSA	prostate specific antigen

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Bullet Points

- Men of African ancestry experience a disproportionately high prostate cancer mortality in the United States and globally
- Analysis of tumor markers indicates that tumor biological differences exist between prostate cancer patients of African ancestry and those of European or Asian ancestry
- Race/ethnic differences in acquired mutations and immunobiology in prostate tumors may affect early disease detection and the response to therapy, and contribute to a distinct disease presentation of prostate cancer among men of African ancestry

Table 1:

Reports of race/ethnic differences in the biology of prostate cancer

Tumor marker	Observation	Reference
DNA methylation	Increased prevalence of <i>CD44</i> hypermethylation in African-American (AA) tumors	{Woodson, 2003 19827 /id}
	Increased prevalence of <i>GSTP1</i> hypermethylation in AA tumors	{Enokida, 2005 20978 /id}
	Increased prevalence of hypermethylation at several loci in AA prostate tissue	{Kwabi-Addo, 2010 21268 /id}
Acquired genomic alterations	Low frequency of ERG rearrangements and PTEN inactivation in Chinese tumors	{Mao, 2010 20690 /id}
	Significant difference in the frequency of TMPRSS2-ERG gene fusion events between European-American (EA), AA and Japanese patients. Highest frequency in EA, lowest in Japanese patients.	{Magi-Galluzzi, 2011, 22239 /id}
	ERG fusion oncogene expression is significantly higher in EA than in AA tumors (based on immunohistochemistry and <i>in situ</i> hybridization analysis).	{Rosen, 2012 22577 /id}
Genome-wide gene expression	Prominent tumor immunobiological differences between AA and EA tumors related to immune response and inflammation. Presence of a distinct interferon-related gene signature in AA tumors.	{Wallace, 2008 18028 /id}
	Gene ontology terms prevalent in AA tumors included interleukins, chromatin maintenance, and myeloid dendritic cell proliferation.	{Reams, 2009 20021 /id}
	Distinct DNA copy number alterations in AA tumor. The alterations commonly affect loci that encode genes related to immune response, which the authors confirmed by a genome-wide gene expression analysis.	{Rosen, 2012 22577 /id}