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## Racial Disparities in Prostate Cancer Among Black Men: Epidemiology and Outcomes

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## Abstract

Prostate cancer has the widest racial disparities of any cancer, and these disparities appear at every stage of the cancer continuum. This review focuses on the disparities in prostate cancer between Black and White men, spanning from prevention and screening to clinical outcomes. We conduct an expansive review of the literature on racial disparities in prostate cancer, interpret the findings, and discuss areas of unmet need in research. We provide an overview of epidemiologic concepts necessary to understanding the current state of prostate cancer disparities, discuss the complexities of studying race, and review potential drivers of disparities in incidence and mortality. We argue that the cause of this disparity is multifactorial and due to a combination of social and environmental factors. The path forward needs to focus on enrolling and retaining Black men in prostate cancer clinical trials and observational studies and identifying potential interventions to improve prevention and clinical outcomes in Black men.

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## Introduction

In the United States (U.S.), Black men have two times the prostate cancer mortality and 60% greater incidence than White men.(1) Mortality rates differ by state, with some of the highest prostate cancer mortality rates in the Southeastern U.S.(2) At a global level, excess prostate cancer mortality rates are evident in regions of low income with a large population of men of African ancestry, including Brazil, the Caribbean, and sub-Saharan Africa.(3)

These disparities are more complex when we look at cancer survival. Overall prostate cancer-specific survival rates are lower among Black men compared to White men, although a large proportion of the disparity may be explained by a higher proportion of cancers diagnosed at an advanced stage.(4,5) Among men treated in equal access systems, such as the Veterans Affairs, or in clinical trials with both access and standardized treatment, Black men actually have similar or potentially improved prostate cancer specific mortality compared to White men after accounting for differences in clinical factors.(6) This finding was supported by another group, which found a racial disparity in prostate cancer-specific mortality in a nationally represented registry, but not in an equal access healthcare system. (5) At the same time, Black men with prostate cancer continue to have increased overall mortality due to death from other causes.(6)

We hypothesize, and there is data to support, that the racial disparities in the U.S. are due to a combination of social (e.g. racism), economic, access to care, environmental, lifestyle, and genetic ancestry differences across Black and White men. The contribution of each factor appears to impact every stage of the cancer continuum spanning from incidence, screening, diagnosis, treatment, to outcomes. In this commentary, we discuss the potential contributors to racial disparities in prostate cancer across the continuum from screening to disease incidence to survival. We summarize some of the major findings on the topic, present the unanswered questions in the field, and make recommendations on how to address unmet needs.

## Epidemiologic concepts: Incidence, mortality, fatality, and survival

To guide a clear discussion on prostate cancer disparities, it is essential that the reader understand the concepts of cancer incidence, mortality, fatality, and survival. The formulas for these measures are described in Table 1. *Incidence* and *mortality* are estimates of disease burden at the population level generally presented per 100 000 individuals. Incidence rates in prostate cancer are driven both by the burden of disease due to risk factors as well as the intensity of screening, primarily by prostate-specific antigen (PSA). Mortality rates are mainly determined by both incidence and prognosis. As such, mortality rates may be higher in one group vs. another when incidence rates differ, even if prognosis is similar. *Fatality* is estimated in cancer cases only, not the total population. *Survival* is the inverse of fatality, and is determined by the natural history of disease, stage at diagnosis, and therapeutic efficacy. Its estimation can be affected by length and lead time biases, which are consequences of cancer screening. *Length bias* arises because screening is more likely to detect slow-growing tumors. *Lead time* is the amount of time between when a cancer is diagnosed via screening and when the cancer would have been diagnosed clinically due to symptom onset. This lead time can make it appear as if survival has improved when in truth the survival is equal, and only appears longer because of the lead time. With PSA screening, the estimated lead time is about 7-10 years. The concepts of length and lead time bias are important in comparing survival since differences may appear due to differences in screening prevalence rather than intrinsic biologic differences.

It is critical to understand what is meant by similar survival or mortality in the prostate cancer literature. On a population level, it is indisputable that Black men in the U.S. have higher prostate cancer mortality rates than White men. However, the demonstrated higher incidence rates will drive a higher population mortality in Black compared to White men, even if survival is similar. For example, data from the Surveillance Epidemiology End Results (SEER) show a 1.6-fold increased age-adjusted incidence of prostate cancer in Black vs White men, and a 2.1-fold increased mortality. Part of the excess mortality rate at a population level can be explained by the excess incidence rates. Data in equal access systems and controlling for differences in the distribution of clinical factors suggest Black men with prostate cancer have similar or potentially improved survival compared to White men(6), although survival differences remain in some settings.(7,8) If case fatality was identical between Black and White men, one would expect a population mortality rate of closer to 1.6, matching the incidence. Still, in the real-world setting, Black men are diagnosed later with more advanced prostate cancer, receive less guideline concordant treatment, have less access to care, lower insurance rates, lower socioeconomic status, and have more comorbid conditions. As will be discussed later, the increased incidence may also be driven by disparities that impact survival estimates.

The above point also raises an important issue, namely what is the causal question that one is aiming to address in studies of racial disparities in prostate cancer.(9) In particular, the adjustment of clinical factors such as stage or grade of disease in part adjusts for disparities in screening, access to care, and other social factors that lead to these clinical differences. However, stage and grade also represent biological aspects of prostate cancer. A

clearly stated causal question in any study of prostate cancer racial disparities is critical to interpreting the results.

## Race versus genetic ancestry

In any discussion about racial disparities, it is necessary to discuss the meaning and history of race in the U.S. Race is a social classification of humans based on phenotype, perceived ancestry, and cultural factors.(10) It is not, and should not be used as, a biological variable. Kaplan and Bennet(11) outlined the three main challenges faced when using race/ethnicity in research as summarized in Table 2. Race is widely used in biomedical research, usually as a proxy for many risk factors, but it is not often clear what is meant by race in each study context. Race is not, in itself, a cause of pathological disease. It is essential for researchers to be critical of their use of the term “race” in research. If using race as a proxy for an unmeasured variable, it is necessary to describe and discuss the potential limitations. Genetic ancestry, racism, discrimination, and socioeconomic status are all common factors for which race is a proxy.

In prostate cancer research, genetic ancestry is commonly the factor of interest because of prostate cancer’s high heritability and the observation that men of African ancestry living in the United States, the Caribbean, and Sub-Saharan Africa have higher prostate cancer incidence.(3) Although humans broadly share ~99% of the genome, there are ancestry informative markers that can distinguish ancestry of origin of distinct populations. However, this genetic information is often unavailable in prostate cancer studies, and researchers are limited to the use of self-reported race by the participant or assigned by the investigator. Thus, it is imperative that researchers describe the limitations of using self-reported race as a proxy for genetic ancestry in this context and clearly describe that race is a social construct without a biological basis. The choice between using self-reported race or genetic ancestry, if both are available, depends on the researcher’s question of interest and proposed mechanism. Our goal is not to discourage anyone from studying racial disparities using self-reported race. It is essential that we describe these disparities and identify drivers of disparities in order to eliminate them. Our recommendation is that future researchers are more critical of their use of the term “race” in studies of prostate cancer disparities and to carefully consider the causal question being addressed.

## Disparities in prostate cancer incidence

There are few established risk factors for prostate cancer incidence overall. Prostate cancer is biologically and clinically heterogeneous, and this heterogeneity has impacts for understanding etiology.(12) For total prostate cancer, the established risk factors include older age, Black race/African ancestry, family history of prostate cancer, germline genetic risk loci, and taller height.(13) For the incidence of advanced or lethal prostate cancer, several additional promising factors have been identified including obesity, smoking, physical activity, vitamin D levels, common medications such as aspirin and statins, and certain dietary factors including lycopene and dairy/calcium.(13) Several of these factors (e.g. smoking, obesity, physical activity) also influence mortality outcomes after cancer diagnosis, both prostate cancer itself and death due to chronic diseases. Identifying the

drivers of racial disparities may have the potential to highlight additional prostate cancer etiological factors.

Prostate cancer has one of the highest heritability of any cancer.(14) To date, 269 single nucleotide polymorphisms (SNPs) have been replicated in multiethnic populations.(15) A polygenic risk score of these SNPs can distinguish a more than 10-fold difference in prostate cancer risk in men in the upper and lower decile of the polygenic risk score. Black men display a higher prevalence of several of the established risk loci associated with prostate cancer incidence compared to men of other races.(16,17) In addition, using the distribution of the 269-SNP polygenic risk score, Black men have a higher polygenic risk score. The top polygenic score decile was associated with an odds ratio of 5.06 (95% CI 4.84-5.29) in White men and 3.74 (95% CI 3.36, 4.17) in Black men when compared to those with average genetic risk in the 40-60% GRS category. Intriguingly, this polygenic risk score equally predicts lethal and nonlethal forms of prostate cancer. As such, differences in inherited genetic susceptibility may explain part of the racial disparity in prostate cancer incidence and mortality.

Differences in the prevalence of lifestyle factors associated with prostate cancer incidence and mortality between White and Black men could also explain some of this disparity. For example, Black men have significantly lower levels of vitamin D and higher prevalence of obesity and smoking.(18-20) The places where people live and work may also be a contributing factor by facilitating exposure to harmful physical and chemical exposures. (21-26) There is limited work on the effect of environmental exposures on prostate cancer, but a study found that men who lived in counties with low environmental quality were more likely to have advanced prostate cancer at diagnosis(26).

Three major areas of future investigation are needed in this area. First, many of the prostate cancer epidemiology studies have been in cohorts of primarily White men. There is thus an urgent need to examine risk factor associations in diverse populations and pool together cancer epidemiology cohorts for further investigation. Second, studies are needed to quantify how much of the disparity in prostate cancer incidence and mortality is due to lifestyle and environmental factors, and thus could be eliminated. Finally, a deeper understanding of the role of social determinants and the neighborhood environment in differences in exposure to risk factors as well as direct effects on the burden of prostate cancer. Importantly, there is a dearth of literature on how upstream factors such as racism affect downstream factors to lead to racial disparities in prostate cancer incidence.

## Disparities in prostate cancer screening

PSA screening prevalence is lower among Black men(27) even though incidence and mortality are higher in this population. In the Southern Community Cohort Study, a baseline PSA value among Black men in midlife accurately predicted future prostate cancer, including aggressive disease.(28) Still, the United States Preventive Services Task Force (USPSTF) recommendations lack specificity on this high-risk population.

In 2012, the USPSTF recommended against PSA screening for prostate cancer for all men (Grade D), explaining concerns about overdiagnosis and the potential harms of unnecessary treatment.(29) PSA screening rates subsequently declined(30,31) and there was a concomitant increase in *de novo* metastatic disease.(32) An analysis conducted within the Behavioral Risk Factor Surveillance System (BRFSS; 2012–2018) and the National Health Interview Survey (NHIS; 2005–2018) found that the absolute screening frequency declined by 11.6% in Black men and 9.3% in White men.(31) This larger decline in screening among Black men is concerning since they may benefit most from intense screening given their heightened risk of lethal prostate cancer.

Considering evidence from studies indicating that PSA screening effectively prevents metastatic disease and deaths from prostate cancer, in 2018, the USPSTF updated its recommendation for men aged 55 to 69 years to Grade C, and recommends that screening be selectively performed based on shared decision-making between the patient and the healthcare provider.(33) Neither the 2012(29) nor 2018(33) USPSTF statements provided specific recommendations for Black men, citing a lack of data on the risks and benefits of screening among this population. Indeed, only 4% of men in the PLCO trial were Black. Risk-stratified screening practices have the potential to reduce prostate cancer mortality among Black men. A microsimulation study found that annual screening in Black men aged 45-69 years reduced mortality and overdiagnosis.(34) However, additional evidence on the harms and benefits of PSA screening in this population is needed.

## Disparities in prostate cancer survival

There is intriguing data that after accounting for differences in stage or grade of disease at diagnosis, and in the setting of equal access (such as in a randomized trial), survival outcomes after prostate cancer diagnosis may be similar for Black and White men. For example, in a systematic review of clinical trial data of docetaxel among men with metastatic castration-resistant prostate cancer (mCRPC), White and Black men had similar overall survival (21.0 and 21.2 months, respectively).(35) Other studies comparing prostate cancer outcomes of Black and White men in RCTs found no significant differences in overall survival, progression-free survival, and biochemical progression-free survival.(36-38) An important question is the extent to which the experience in a controlled trial translates to that of the real-world patient experience. Some preliminary findings suggest that clinical trial findings may hold in registry data(39,40), an analysis of the PROCEED registry supported the findings from sipuleucel-T clinical trials and found that Black mCRPC patients treated with sipuleucel-T had longer overall survival than their White counterparts. (39)

For abiraterone acetate, there is even a suggestion that Black men may have improved outcomes.(41) Similarly, another study examining the responses of Black and White men with mCRPC to abiraterone acetate and prednisone found that median PSA progression-free survival was higher for Black patients (16.6 months, 95% CI 11.5, -) than for White patients (11.5 months, 95% CI 8.5-19.3).(42) Both of these studies indicate that Black men may have a greater response to abiraterone acetate compared to White men, based solely on PSA. However, given the similarity in other outcomes such as overall survival, as well as the

small sample sizes used in these trials, more research must be conducted to better understand potential racial disparities in responses to abiraterone acetate treatment.

These survival findings in clinical trials are not discordant from the population-level data showing that Black men have higher mortality than White men. As we described in a section above, survival is estimated among men with prostate cancer, while mortality and incidence are calculated among the entire population. Further, populations in clinical trials are not often representative of the general population. In this context, Black and White men have the same access to clinical care, while in the general population, Black men have lower access to high quality health care and early detection.

## Genomic differences in prostate cancer across self-reported race

Understanding prostate tumor biomarkers in Black men is essential for understanding, and eliminating, disparities in prostate cancer diagnosis and prognosis. Multiple studies have identified differences in tumor genomic profiles across racial groups. Among men with metastatic prostate cancer, genes with actionable mutations, including in DNA repair genes and *AR*, were more common in Black men than in White men.(43) These results support findings from clinical trials and equal access systems studies (e.g. the VA) that show Black men have the same, if not better, survival as White men when they have access to the same level of health care. And they show the importance of increasing the representation of Black men in all aspects of prostate cancer research.

### ***PTEN* loss and *TMPRSS2*:**

*ERG* fusion are more common in White men.(44-47) In particular, *PTEN* loss is associated with aggressive prostate cancer, and yet, despite being more common in White men, Black men have excess mortality.(48) The difference in the prevalence of *TMPRSS2:ERG* across racial groups is also intriguing given that this appears to be a unique molecular subtype. Interestingly, *TMPRSS2:ERG* fusions are largely mutually exclusive with mutations in tumor suppressor *SPOP*(49) and *SPOP* mutations are significantly more common in prostate tumors of Black men.(46,47) More research is needed to identify the reasons for these molecular differences across racial groups. Further, understanding these subtypes can better inform etiological epidemiology studies for prostate cancer, as risk factors may differ by genomic subtype.(50)

Current gene expression tests used for prostate cancer prognosis were developed in predominantly White men and it is important to assess whether these tests perform well in Black men. A study by Creed et al found that 48% of the 60 prostate cancer-related genes examined by three commercially available gene expression tests (Oncotype DX, Prolaris, and Decipher) are differentially expressed in Black vs. White patients, albeit the differences in expression were small.(51) The authors found that Decipher and Prolaris did not show different prognosis between Black and White men, but Oncotype DX estimated better prognosis for Black men than for White men.(51) It is important to note, however, that the study by Creed et al quantified gene expression by Nanostring and not the commercial panels, which affects the interpretation of their results.(51) After this study was published others explored whether these tests performed equally in Black and White men and found

that they predict clinical outcomes independently of race.(52-54) However, these studies had small numbers of Black participants, thus additional studies are necessary to confirm these findings.

## Diversity in clinical trials and observational studies

In order to address the many unanswered questions surrounding racial disparities in prostate cancer as well as in prostate cancer research broadly, it is essential that clinical trials and observational studies increase recruitment and retention of a racially diverse patient population. The importance of studying racially diverse populations is exemplified in the findings from a study in a predominantly Black population exploring the effect of a genomic test on prostate cancer patients' adoption of active surveillance.(55) In contrast to other studies, Black patients with lower health literacy who were randomized to receive the genomic test were less likely to choose active surveillance.(55) In a systematic review of Phase III prostate cancer clinical trials, 96% of total pooled participants were White; and Africa and the Caribbean comprised only 3% of countries represented.(56) Similarly, in clinical trials testing new therapies for mCRPC, only 3.3% of participants were Black men. (57)

Several studies have attempted to elucidate the factors underlying the underrepresentation of racial minorities in clinical trials. A review of multiple studies found that Black patients were less willing to participate in cancer clinical trials compared to non-Hispanic White patients.(58) However, this finding has been disputed in other studies which have observed no association between race and enrollment, refusal rates, or a decreased desire to participate in research.(59) Several structural barriers to Black participation in clinical trials have also been identified, including poverty, transportation, childcare, healthcare access, health insurance, and comorbidities, as well as lack of knowledge about clinical trials.(58) In order to increase Black participation, this study proposes a number of solutions, such as encouragement from doctors, friends, and family, and advertising on the importance of clinical trials, as well as providing parking, transportation, and availability during non-traditional hours.(58) Finally, it is important to hire Black staff members to clinical trials and to foster cultural sensitivity among researchers and healthcare providers.(58)

Increasing minority enrollment may also be achieved through formal, institution-wide changes. In a study at an NCI-designated Comprehensive Cancer Center, several changes involving leadership support, center-wide policy change, follow-up with clinical investigators, infrastructural process control, data analysis and reporting were implemented to increase minority participation. Following these interventions, minority accrual to therapeutic trials increased from 12.0% in 2005 to 14.0% in 2010.(60) Additionally, patient navigation programs, which strive to increase access to and knowledge of clinical trials via community health workers and other navigators, could be an effective solution to reduce refusal rates to cancer clinical trials (4-6%).(61) These strategies may help improve the racial diversity in clinical trials to reflect the heterogeneity of the general population.



## Conclusion and future directions

There is a clear disparity in prostate cancer incidence and mortality rates for Black men. There are multiple potential explanations for the excess population-level mortality observed among Black men: 1) higher overall incidence in Black men leads to higher mortality even with equal survival; 2) Black men are more likely to be exposed to harmful exposures that cause aggressive prostate cancer; 3) Lower access to care, lower prevalence of PSA screening, and less quality care leads Black men to be diagnosed at later stage and to receive inadequate treatment regimens; 4) Black men have higher genetic risk for prostate cancer.

Based on the totality of currently available data, we suspect that most of the current disparity in mortality in Black versus White men is likely due to both higher prostate cancer incidence and higher fatality among Black men. This higher incidence and fatality are at least in part caused by social factors linked to systemic racism and discrimination, although there remains discord in the prostate cancer research field on the extent to which this explains disparities. Black men lack access to high quality care, live in environments that expose to them to higher levels of harmful exposures, experience bias in health care settings, which harbors distrust in the medical system. There are established disparities in time to diagnosis, prevalence of screening by prostate-specific antigen (PSA), receipt of guideline-concordant treatments, and competing comorbidities associated with worse prostate cancer incidence and mortality. These disparities are consequences of how racism has shaped access to care, care-seeking behaviors, and unequal economic opportunity for Black men.

An important future endeavor should be to elucidate the mechanisms and risk factors leading to higher incidence of prostate cancer in Black men. This will not only improve our understanding of racial disparities in prostate cancer but will also help identify modifiable risk factors for prostate cancer. Further, it is important to disentangle the age-old question of “nature” versus “nurture” by assessing how much of these disparities is due to differences in germline genetics versus consequences of institutional racism. Specifically, to move this field forward, we need to determine what proportion of aggressive prostate cancer is due to germline genetics as opposed to systemic racism, lack of access to high quality medical care, and higher prevalence of harmful exposures. The answer to this question will also aid researchers in determining the causal question being addressed, and as a corollary whether tumor features like stage and Gleason score should be adjusted for in statistical models. Furthermore, as described earlier in this paper, it is essential that future etiologic epidemiology studies account for the heterogeneity of prostate cancer when designing the study and interpreting results.

For these questions to be answered, new and diverse data sources need to be created. It is imperative that more Black men are recruited and retained in prostate cancer clinical trials as well as in observational studies. In studies where germline genetics are the true risk factor of interest, researchers should access, or create datasets, with genetic data so that genetic ancestry can be studied in-depth. Further, researchers need to become more critical of the use of the term “race” in prostate cancer disparities research. Race can be used as a risk marker or as a proxy for another risk factor. The use of race as a risk marker is integral to understanding and describing racial disparities, it can help identify communities at high risk

who would benefit from an intervention. Using race as a risk factor is far more complex, race is a poor proxy for the true risk factor we can intervene on. Unfortunately, the true risk factor of interest is often unmeasured, and researchers are limited to using self-reported race as a proxy. In this context, researchers need to be clear and explicit about the true risk factor of interest and the hypothesized mechanisms by which it leads to racial disparities.

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**Table 1.**

Formulas for epidemiology measures for prostate cancer

Measure	Formula
Incidence	$\frac{\text{Number of new prostate cancer cases within a specified time period}}{\text{Total population at risk at the start of the time period}}$
Mortality	$\frac{\text{Number of deaths due to prostate cancer within a specified time period}}{\text{Total population at risk at the start of the time period}}$
Fatality	$\frac{\text{Number of deaths due to prostate cancer within a specified time period}}{\text{Number of prostate cancer cases at the start of the time period}}$

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**Table 2.**

## Challenges in using race in medical research

Concept	Key Issue
<b>Racial/ethnic identity is multi-layered and complex</b>	Potential for measurement error in using self-reported race as a proxy for genetic ancestry
<b>Distinguishing between race/ethnicity as a risk factor or a risk marker</b>	Race itself is not a cause of disease. Need to be specific in the causal question
<b>Avoiding contributing to racial/ethnic division of society</b>	Highlighting race can reinforce stereotypes and exacerbate racism

Adapted from Kaplan and Bennet 2003

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