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Disparities at Presentation, Diagnosis, Treatment and Survival in African American Men, Affected by Prostate Cancer

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Abstract

Background—Prostate cancer (PCa) remains the most common malignancy and the second leading cause of cancer death among men in the United States. PCa exhibits the most striking racial disparity, as African American men are at 1.4 times higher risk of being diagnosed, and two to three times higher risk of dying of PCa, compared to Caucasian men. The etiology of the disparity has not been clearly elucidated. The objective of this paper is to critically review the literature and summarize the most prominent PCa racial disparities accompanied by proposed explanations.

Methods—The present literature on disparities at presentation, diagnosis, treatment and survival of African American men affected by PCa was systematically reviewed. Original research as well as relevant review articles were included.

Results—African American men recurrently present with more advanced disease than Caucasian men, are administered different treatment regimens than Caucasian men, and have shorter progression-free survival following treatment. In addition, African American men report more treatment related side-effects that translates to the diminished quality of life.

Conclusions—PCa racial disparity exists at stages of presentation, diagnosis, treatment regimens and subsequent survival, and the quality of life. The disparities are complex in involving biological, socio-economic and socio-cultural determinants. These mounting results highlight an urgent need for future clinical, scientific and socio-cultural research involving transdisciplinary teams to elucidate the causes for PCa racial disparities.

Keywords

Prostate cancer; African American population; health disparities

Introduction

Prostate cancer (PCa) remains the most common malignancy and the second leading cause of cancer death among men in the United States. PCa exhibits the most striking racial disparity, as African American men are at 1.4 times higher risk of being diagnosed, and two to three times higher risk to die of PCa, compared to Caucasian men [1–2]. In addition, PCa

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is diagnosed in earlier age [3] and at a more advanced stage [4–5] among African American than among Caucasian men; the latter of which may help explain the significant mortality disparity. Differences in treatment of PCa may also be implicated in the mortality and survival rate disparities; for instance, African Americans, compared to Caucasians, have lower odds of being administered a radical prostatectomy [6], but greater odds of receiving radiation therapy or watchful waiting [7]. African American men with metastatic disease are less likely to receive hormonal therapies before death of PCa, compared to Caucasian men [8]. Additionally, cultural, social and psychological variables contribute into poorer outcomes of PCa in African American men. For example, physicians are less likely to discuss the treatment options and side effects with African American, compared to Caucasian males, potentially impeding on their ability to make an informed decision [9]. In addition, African American males, due to fears of threat to their masculinity, appear more reluctant to discuss their condition, thus depriving themselves of emotional support which is crucial for cancer survivors [10].

DeLancey et al [11] have examined racial and ethnic disparity trend in mortalities from major cancers, including PCa, for the period of 1975–2003. The authors concluded that overall disparities in mortality from those cancers for which regular screening procedures have been developed (colorectal, breast and prostate) have escalated. Thus, the goal of eliminating racial disparities in cancer cannot be achieved without coordinated and sustained efforts to provide high quality prevention, screening, and treatment to all segments of the population, including minorities. In addition, as emphasized by Jones et al [12], additional bio-behavioral studies are required to help identify interventions that will narrow the PCa gap between African Americans and Caucasians.

In light of these findings, the objective of this paper is to critically review the literature and summarize the most prominent PCa racial disparities to be accompanied by proposed explanations; these disparities exist and will be viewed at various levels, including stages of presentation, diagnosis, treatment regimens and subsequent survival, and the quality of life. The manuscript will focus on a comprehensive summary of the nature and purported causes for racial disparities in PCa related mortality and morbidity, thus facilitating their understanding in an effort to eradicate them.

1. Disparities between African American and Caucasian men at presentation

It is well-documented that African Americans PCa patients more frequently present with higher grade tumors. However, whether this disparity is due to lower access to screening or other socio-economic and education variables that prevent early diagnosis, or if tumors within the African American population tend to be more biologically aggressive is unclear. Observational data, generated over time, provides evidence that PCa may exhibit a biologically distinct, more aggressive behavior in African American men, reflected in the advanced stage at presentation. According to the Center of Disease Control and Prevention statistics [13], African American men are diagnosed with PCa on average 3 years younger than their Caucasian counterparts. Karami et al [14] compared the age at diagnosis in African Americans and Caucasians for the 12 most frequent cancers (including PCa) from 1996 to 2002 in the Surveillance, Epidemiology, and End Results (SEER) Program. In general, African Americans had an earlier age at diagnosis for invasive cancers (including PCa); however the reasons for this racial disparity are yet to be determined. Sanchez-Ortiz et al [15] examined the tumor volumes in a cohort of 37 African American men and a matched group of 35 Caucasian men with early PCa who underwent radical prostatectomy. It was concluded that African American men had greater overall tumor volumes despite similar preoperative variables, and 2.8 times more tumor in the prostate per ng/mL of serum PSA

compared with Caucasian men. Furthermore, the incidence of Gleason score upgrading after prostatectomy in African American patients was almost double that of Caucasian patients (49% vs. 26%). Moul et al [16–17], who analyzed PSA in 155 Caucasian and 46 African American men, also concluded that African American men had higher tumor volumes overall and for each clinical stage, and higher PSA values at initial diagnosis in African American than in Caucasian men. Morgan et al [18] reported similar findings, concluding that over 40% of cases of PCa in African American men would not be detected by tests using traditional age-specific reference ranges. In addition, Powell et al [19] provided evidence that PCa starts at the same frequency in African American and Caucasian men, but reaches distant disease at a disproportionate rate of 3:1, which is manifested in African American men being diagnosed with higher-grade lesions, earlier in life. The authors conclude that PCa may grow at faster rates in African American men and this warrants further investigation. Jones et al [20] evaluated race differences in stage at diagnosis of PCa. African Americans were significantly more likely than Caucasians to be diagnosed with PCa that had progressed beyond a localized stage (unadjusted odds ratio = 2.02). Adjusting only for age, the race-stage odds ratio was 1.83. Further adjustments for ever receiving the digital rectal examination or the PSA test, the histologic grade, education and the level of being informed about the disease and treatment and insurance coverage, the odds ratio was maximally reduced to 1.21, resulting in a 74.7% reduction in the magnitude of the odds ratio for the race-stage association. Similar findings were reported by Cooperberg et al [21] who analyzed a cohort of 5,343 men with the low-grade disease in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) – a registry of men with biopsy proven PCa. Although the study focused on patients with the low-grade cancer, the authors noted that the likelihood of a low-risk diagnosis is less likely among African Americans than among Caucasians. Pettaway et al [22] reported that African American patients in their study exhibited a significantly higher incidence of seminal vesicle involvement and aggressive cancers (Gleason score of 8 or more), and a trend toward decreased pathologically organ confined, margin negative disease (40% African American vs 53% Caucasian men). The authors also noted increased PSA levels in African American, compared to Caucasian men.

The mentioned above factors, which contribute to PCa racial disparity, may be rooted in inherited genetic and biological differences, prevalent in one race and ethnicity, and rare or absent in the other. Single Nucleotide Polymorphisms (SNPs) in numerous metabolic genes were reported to be associated with PCa in African Americans, but not in Caucasians [23]. The list of the most studied and promising target genes includes Cytochrome P450 17 α -hydroxylases-C-17,20-lyase (CYP17) [24], Cytochrome P₄₅₀ 3A4 (CYP3A4) [25], CD14 [26], calcium sensing receptor [27], androgen receptor (both its overall expression and the number of CAG repeats) [28–30], and variations around the region 24 on the long arm of chromosome 8 (8q24) [31]. Products of these genes are predominantly involved into an androgen metabolism, thus altering it to enable uncontrollable prostate growth that serves as a driving force for PCa initiation and progression. It is noteworthy that while the list of genes that may exhibit a small effect on the disparity keeps growing, gene(s) that may have a major role in the predisposition of African American men (or men of any other race and ethnicity) to PCa, have not yet been found, despite extensive efforts from multiple research groups. While the existence of such key gene(s) is still in exploration, researchers investigate biochemical and socio-cultural factors that might impact the disparity. Several biochemical mechanisms and/or factors may be linked to increased incidence and worse PCa prognosis in African American men. The latter includes, but is not limited to decreased serum vitamin D levels in darker-skinned individuals [32–33], Insulin-like growth factor 1 (IGF-1) and Insulin-like growth factor binding protein 3 (IGFBP3) ratio and serum concentrations [34–37], increased serum low density lipoprotein (LDL) levels [38], and decreased serum lycopene levels [39]. While validity of nearly all factors and their

mechanism(s) of action in PCa continue to be debated, additional research, involving African American participants, is needed to shed light on the biochemical, genetic and epigenetic mechanisms, underlying the unfortunate racial disparity.

In addition to biological differences at presentation, the cited studies emphasized that their cohorts of African American, compared to Caucasian men, had lower levels of educational attainment [20, 40–41], were more likely to belong to lower Socio-Economic Status (SES) group [20, 23, 40–42] and to be unmarried [20, 40–41]. As discussed further in this review, these variables were shown to significantly correlate with PCa treatment choices and survival. Adequate health insurance coverage may be another major determinant that enables detection of tumor in a curable stage, thus improving treatment outcomes and reducing disparity. Ross et al [43] have used the The Behavioral Risk Factor Surveillance System (BRFSS) data to examine the patterns of PCa screening depending on demographical and socio-economic characteristics including race, income, health insurance status, education, marital status and general health condition. BRFSS uses confidential telephone interviews to collect the data from participants through relevant questionnaires. Although African American men were overall more likely to report a recent PSA test, or combined PSA and DRE exam, compared to Caucasian men (odds ratio 1.67 and 1.61, respectively), the absence of health insurance coverage was associated with substantially diminished use of PCa screening in men of all races (56% insured men vs 25% uninsured men). Similar findings were reported by Scales et al [44] who examined the pattern of PCa screening in younger (40–49 year old) men by race and socio-economic characteristics. The authors have found that younger African American men were more likely to report a PSA test (50%) compared to Caucasian men (36%), however, the absence of health insurance substantially limited access to screening (1.78 for an insured man using non-insured as a reference). The absence of an adequate health insurance may thus be one of the factors contributing to PCa disparity, as recent data from the U.S. Center for Disease Control and Prevention showed that about ~15–20% of African Americans are uninsured whereas only ~10–15% of whites lack health insurance; however, Hispanics are by far the least insured racial group as nearly one-third of this group lacks insurance, but this population does not appear to suffer as great of a prostate cancer burden) [45].

All these data support the need for additional research that may further elucidate the reasons for described biological and socio-cultural differences, and establishing the mechanisms of their relation to PCa racial disparity. It should also be recognized that biological and sociocultural variables may exert a tandem effect in causing this disparity; researchers should therefore include both types of data in future studies and consider a multifactorial basis for the finding that African Americans present with higher grade PCa. The data also suggests the need for early PCa detection, especially among younger African American men, and the concept of lowering the serum PSA threshold for biopsy from 4 ng/mL to 2.5 ng/mL. Additionally, it highlights the importance of developing alternative markers for the early detection of PCa in that particular affected population.

2. Disparities in PCa diagnosis and disease management

Selecting a treatment regimen for PCa, especially a low-grade, early stage disease, can be difficult and complex [46]. Patients newly diagnosed with PCa have to face plethora of factors, including their personal feelings and attitudes towards PCa diagnosis and desired quality of life following treatment; opinions of family members and friends; physician's recommendations; a limited evidence of benefits versus possible side effects; and finally, financial burden of the treatment itself and, in some cases, the subsequent supportive care.

Zeliadt et al [9] emphasize the fact that African American men are usually supplied with fewer treatment options by physicians, are more concerned about the spread of the tumor and less likely to read all the additional information provided about the cancer diagnosis and treatment options. These trends may possibly lead to higher levels of treatment regret [7]. In addition, African American men may be more concerned about the side effects of invasive treatments – incontinence, bowel dysfunctions and permanent sexual impairment – and therefore more prone to favor “watchful waiting” – an option to delay aggressive treatments until there are clinical signs of the disease progression [47]. An increased 1.4 times odds ratio of being administered a watchful waiting in the African American population was reported by Shavers et al [47–48]. While, due to a “silent” nature of some PCas, it might be beneficial for a patient to delay aggressive treatments, a wrongfully administered or inadequately monitored “watchful waiting” may result in the advanced disease, for which effective treatment options are limited [48].

Penson et al [49] aimed to evaluate whether shared decision making in treatment selection for PCa differs by race. A total of 193 family pairs completed surveys. Discussions between patients and family members about treatment options occurred “very” often among 26% of African American and 52% of Caucasian families, leading to a conclusion that African American families were less likely to discuss treatment options among themselves. In further support of the importance of shared decision making, marital status was found to be an important predictor of a PCa treatment choice in men of all races and ethnicities, including African Americans, as reported by Denberg et al [50]. In their study of over 27,000 men (10% African Americans), married men were significantly more likely to receive any form of curative therapy, compared to unmarried men (61% vs 44%, respectively). The authors present several possible explanations for this effect, including perception of responsibilities towards the spouse, increased emotional well-being and increased participation of the spouse and the patient in the informed decision making. Because the PCa treatment outcomes may be dependent on the emotional climate within the family, it is important to facilitate decision making discussion within minority families to improve survival.

Age may also affect patient-physician communication and quality of treatment available to African Americans. Mullins et al [41] have examined the historical SEER database of Medicare patients with PCa and reported that older, African American men with PCa are at increased risk of not being staged by the physician. This issue is of high importance because accurate staging is crucial for proper treatment. In addition, the odds of having a diagnosis of distant metastatic disease was higher for African American men and also for older men in any racial group, compared with the 65–69 years old men. However, there was a decrease in staging disparities after the 1995 publication of National Comprehensive Cancer Network, American Urological Association and American College of Radiology staging guidelines, as reported by Abraham et al [40]. The authors examined 96,986 study subjects (9,686 African American) and concluded that the racial disparities in the likelihood of getting PCa staging tests (bone scan and pelvic imaging) decreased substantially in 1995 – 1999 as compared to 1991 – 1994. The authors emphasize the positive effect that the new PCa staging guidelines had on reducing PCa staging disparity.

Moses et al [7, 51] investigated the role of ethnicity in primary treatment choice by utilizing data abstracted from Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) – a registry of men with biopsy proven PCa. 4,284 men were selected of which 7% were African Americans. The authors reported that African American men were less likely to have radical prostatectomy than radiation therapy or androgen deprivation therapy compared with Caucasian men. There was a noted greater likelihood of African American population receiving an overall nondefinitive therapy, possibly due to more aggressive

disease behavior in that racial group. The use of nondefinitive therapy, especially androgen deprivation therapy for a low-grade disease, has not been ruled out in clinical trials and may lead to increased mortality and morbidity [52]. It is worth mentioning that Caucasian men are significantly less likely to receive an androgen deprivation therapy for a low-grade disease, as compared to African American men. In addition, it was found [50] that lower socio-economic status (SES) predicted lower rates of prostatectomy compared with radiotherapy among African Americans. A similar conclusion was drawn by Coopenberg et al [21] who determined that patients of lower SES are less likely to be treated by radical prostatectomy. This conclusion is in accordance with the fact that African Americans are more likely to belong to lower SES group, and subsequently less likely to be treated with radical prostatectomy. In addition, there may be cultural or personal reasons, specific to African American population, which do not favor the choice of radical prostatectomy – for example, an increased fear of permanent side effects which always accompany this type of surgery. In support of this hypothesis, Peay et al [53] have reported that Caucasian men were three times more likely to choose surgery over external beam radiation, and African Americans were disproportionately likely to choose the external beam radiation alone (32% vs 19%). The reasons for this striking racial treatment preference are not known. Perhaps, they may be rooted in the fear of side effects, but this assumption requires further investigation. There are other groups reporting the lower rates of radical prostatectomy use in African American, compared to Caucasian, men [53–56]. However, if African American patients do choose radical prostatectomy, there seemed to be equal timely access to the operating facility for men of any race and ethnicity, as reported by Banez et al [57]. The authors prospectively analyzed over 1500 patients (45% African Americans) treated with radical prostatectomy from 1988 to 2007, and no significant difference between the racial groups with regard to the time between biopsy and surgery was found in the equal-access centers.

Parsons et al [58] have reported yet another determinant for the PCa treatment choice: whether a clinic is a county or a privately operated hospital. The authors concluded that PCa patients received significantly different types of care at county hospitals compared to private providers. Although the study was not designed to specifically examine the racial determinant in treatment choice, the surprising and unexpected connection between the type of healthcare provider and PCa treatment choice may have implications on PCa racial disparity. The presence and nature of such implications is, in our opinion, a topic worthwhile of further research.

In conclusion, there are documented differences in the diagnosis and choice of primary treatment for PCa between African American and Caucasian men with similar risk profiles, which can have a significant impact on prognosis and quality of life. Whether all these differences are a consequence of the availability of African Americans to quality healthcare, fear of side effects, or personal emotional attitudes and cultural beliefs, remains an open question, sole existence of which emphasizes the need for personalized treatment and care plans for men of different racial and ethnic backgrounds.

2a. Disparities in treatment for earlier stages (Gleason score ≤ 7) PCa

Richert-Boe et al [59] reported that African American men were less likely to receive treatment with curative intent than Caucasian men for an early stage PCa. The authors reviewed medical records of 79 African- American and 158 Caucasian men (matched for age, stage, grade, and year of diagnosis) from the Kaiser Permanente Northwest Tumor Registry to identify all men diagnosed with local- or regional-stage PCa between 1980 and 2000. Not only was it found that treatment with curative intent was administered less often to African Americans than to Caucasians, but African American men were less likely to be offered treatment with curative intent by urologists (85% versus 91%, respectively).

Caucasian men were 71% less likely to receive androgen deprivation therapy than radical prostatectomy, compared with African Americans, for a low-risk disease (odds ratio 0.29). Caucasians also were less likely to receive radiation treatment than radical prostatectomy for a low-risk disease compared with African Americans. Although the last conclusion did not quite reach statistical significance, it might highlight a subtle difference in treatment of men of different races [51]. The authors noted that the disparities mentioned in their study were not explained by factors other than race.

A different conclusion was, however, reported by Hoffman et al [60] who examined whether there were racial differences in initial treatment for clinically localized PCa. Participants were selected from the SEER program, of which 884 were Caucasians and 430 were African Americans. The authors found that among the 71% of men with less aggressive cancers, African Americans and Caucasians were equally likely to receive either radical prostatectomy or radiation therapy (80.0% vs 84.5%). Therefore, among men with less aggressive cancers, there were no racial differences in undergoing radical prostatectomy or radiation therapy. The reasons for the conflicting evidence are currently unknown, and may include objective (African American men living in different areas may approach the treatment options differently) or subjective (selection bias) components. If these differences actually exist, they may negatively impact survival of African American men, treated for PCa. Additional research is needed to establish the reasons and causes for the racial differences and design interventions aimed to maximize the benefits of treatment and quality of life for every racial and ethnic group, including men of African descent.

2b. Disparities in treatment for later stages (Gleason score ≥ 8) PCa

Lu-Yao et al [61] retrospectively analyzed over 9,000 men in the SEER database (1,200 African Americans) who died of metastatic PCa during 1991 – 2000. Compared with Caucasian men, higher proportions of African American men did not receive hormonal therapy before death of PCa (25% of Caucasians and 38% of African Americans). The author have noted, that because limited treatment options for advanced PCa are effective, tolerable or longevity-promoting, it is extremely important to take better advantage of using hormonal therapy for metastatic PCa to improve the quality of life and, in some cases, survival. Therefore, the reported difference in hormonal therapy use by race may be, in part, responsible for the PCa disparity, especially taking into consideration the findings, reported by Sassani et al [8]. The authors reported that African American patients had a significantly lower rate of treatment failure compared to Caucasian men, when treated with Leutinizing Hormone Releasing Hormone (LHRH) agonist therapy, which is a main (standard of care) treatment available for men with an advanced PCa. The study cohort included 692 patients (15.5% African American), and after controlling for all variables, the relative risk for treatment failure in African American vs. Caucasian was 0.66. The authors suggested that PCa in African American men may be more androgen sensitive, but the reasons for this are yet unknown.

Lowrance et al [62] explored the racial disparities in the treatment of 3,412 men (11% African American) with clinical stage T3 or T4 PCa. In this analysis of older men with locally advanced PCa, African American patients were significantly less likely than Caucasian patients to receive any treatment, and five-year survival rates by race were 61% for Caucasians, and 55% for African Americans. The difference in survival was statistically significant.

The same trend, described for a low-grade PCa, was also seen for a high-grade disease. In the study by Moses et al [7, 51], Caucasians were less likely to receive androgen deprivation therapy than radical prostatectomy compared with African Americans (odds ratio 0.52). Similar conclusion was drawn by Hoffman et al [40] who noted that among men with more

aggressive cancers (defined as PSA ≥ 20 ng/mL or Gleason score ≥ 8), African Americans were less likely to undergo radical prostatectomy than Caucasians (35.2% vs 52.0%), but more likely to receive conservative management (38.9% vs 16.3%). These treatment differences may reflect African Americans' greater likelihood for presenting with pathologically advanced PCa for which surgery has limited effectiveness. Whether this hypothesis is true or not remains yet an open question, however, there is a clear need to better address the limited treatment opportunities available for men with advanced PCa, especially in African American population where there are lower rates of curative interventions.

3. Disparities in Survival and the Quality of Life

According to the SEER Statistics data, five-year relative survival by race is 99.6% for Caucasian men and 95.9% for African American men [2, 63]. Moreover, age-adjusted PCa related mortality is two to three fold higher for African American, compared to Caucasian, men [1–2]. In addition to worse overall survival and higher mortality rates, African American patients treated for PCa exhibit diminished general outcomes and quality of life (QOL) after PCa treatment, compared to Caucasians [64–65]. The causes of this aspect of PCa racial disparity are obscure, and research evidence is conflicting. Some researchers attribute the racial disparities in survival to Socio-Economic factors. For example, Tewari et al [56] explored the effect of socioeconomic factors on long-term mortality in men with clinically localized PCa. In this study, African American patients were more likely to have lower incomes, a greater baseline PSA level, and greater comorbidities. In addition, African American men had significantly increased cancer-specific (hazard ratio 1.47) and overall (hazard ratio 1.29) mortality. However, after adjusting for health insurance status and SES, the differences disappeared (adjusted hazard ratios 1.04 and 0.96, respectively). The authors concluded that, in their cohort, socioeconomic factors were sufficient to explain the disparity in survival. Schwartz et al [54] explored the influence of race, SES, and treatment on survival of patients with PCa. In this study, a greater SES for both localized and regional stage PCa was associated with longer overall and cancer-specific survival in the African American population. Older age and poorly differentiated tumor grade predicted poor survival but did not explain the racial difference; however, the adjustment for SES eliminated much, if not all, of the racial difference in overall and cancer-specific survival among men with localized or regional stage PCa.

The finding of substantial influence of SES on the survival and quality of life, however, was not supported by Dash et al [66] who examined an impact of socioeconomic factors on PCa outcomes in African American patients treated with surgery, in a cohort of 430 African American men. The authors concluded that there was minimal impact of income and/or education on PSA recurrence in their cohort. After controlling for race by studying a large and diverse cohort of African American men treated by radical prostatectomy, the primary finding was that neither income nor education had a statistically significant effect on recurrence-free survival. In further support of these findings, Halbert et al [67] examined the quality of life following PCa diagnosis in African American and Caucasian men when controlling for perceived stress and the level of religiosity. The sample consisted of 194 men: 66 African Americans and 128 Caucasians. The authors report no significant effect of the socioeconomic factors on emotional or physical functioning. However, several other important findings were noted: 1. African American men reported better emotional well-being compared with Caucasian men. The authors hypothesized that African American men are exposed to a greater number of adverse life events, and these experiences may reduce the threat of being diagnosed with PCa. 2. Religiosity did not have a significant effect on emotional or physical wellbeing of African American patients. This could be because the measure of religiosity did not evaluate whether the religious beliefs were actually used to

cope with the diagnosis. 3. Subjective stress had a significant adverse effect on emotional and physical well-being. The authors concluded that helping men to identify specific sources of stress and use coping strategies that are most likely to be effective at managing these issues may reduce levels of stress and enhance the quality of life. This finding was supported by Purnell et al [68] who have recently reported significantly higher levels of traumatic stress for African American PCa survivors compared to non-African American survivors. The authors analyzed 317 men (African American: $n = 30$, 9%; non-African American: $n = 287$, 91%) who were enrolled in the 24-months intervention trial, and found that racial disparity in traumatic stress persisted even after adjustment for all major covariates, indicating that this particular population may be under higher levels of psychological distress, which may negatively impact survival. In contrast to this last findings of Halbert et al [67] and Purnell et al [68], Hyacinth et al [69] reported no significant influence of stress on the QOL of PCa survivors in a cohort of 136 men (5% African Americans). The analysis revealed that survivors were experiencing low levels of stress which had only marginal influence on the overall quality of life. However, the study included only 5% African Americans, and it is possible that Caucasians and African Americans perceive stress differently. It is also possible that the time from the initial diagnosis to some extent alleviated the level of perceived stress, associated with PCa. Besides stress, which was insignificant in this study, the authors noted complaints of sexual, bowel and bladder problems in all races, including African Americans. It was not reported by Hyacinth et al [69] whether these problems are more pronounced in African American men, compared to Caucasians, however, Ukoli et al [70] have examined the cohort of African American men who underwent radical prostatectomy in the SEER historical database. The authors found that sexual and urinary symptoms, bone pain, fatigue and emotional distress all were significantly associated with radical prostatectomy in most African American men. It was concluded that expected benefits and side effects of radical prostatectomy, specifically tailored towards African American population, should be carefully weighed before the treatment decision is made. Similar results were also reported by Stanford et al [71]. These latter findings emphasize the need to conduct additional research among PCa survivors of African descent, aimed to tease out the benefits of a radical prostatectomy in terms of survivorship and longevity-promotion, versus possible significant side effects and substantially diminished quality of life following surgery in this particular population. In contrast to the findings reported by Halbert et al [67], Hamilton et al [72] and Zavala et al [73] emphasized on the exceptional role of the religious life and faith have on African American patients with PCa. The authors recommended that physicians and other medical personnel have to understand and support the unique relationship their African American patients may have with God, as this will improve both physical and emotional well-being and promote survival.

Penedo et al [42] have explored ethnicity and QOL after PCa treatment in a diverse sample of 204 men (85 Caucasian, 37 African American, and 82 Hispanic). In this sample, the relationship between ethnicity and QOL appeared to be significantly accounted for by sociodemographic, medical, and health behavior factors. Health behaviors related to sleep and physical activity demonstrated a robust association with QOL, suggesting that differences in these categories may be one of several mechanisms that may explain ethnic disparities in QOL. Ethnic group membership was related to QOL such that minority men had lower QOL than Caucasian men. Three variables - medical comorbidity, physical activity, and sleep functioning - remained significant and explained 37% of the variance in quality of life scores.

Peay et al [53] have evaluated the health-related QOL after treatment for PCa in African American and Caucasian groups totaling 665 men (32% African American). It was found that at 12 months, African Americans who underwent external beam radiation had

significantly lower mean urinary function scores than Caucasians undergoing external beam radiation, while African Americans choosing surgery had significantly lower mean physical function scores than Caucasians undergoing surgery. The reasons for these preferences are not known. In addition, authors concluded that special attention should be paid to the reason for selection of external beam radiation among African American men and how this might impact long term urinary function.

Biochemical recurrence of PCa after radical prostatectomy, defined as a PSA of at least 0.4ng/ml followed by another increase, is an important determinant of survival and QOL, as rising PSA level is the first sign of ultimate progression to distant metastasis [74]. Hamilton et al [75] explored if African American men are at higher risk of biochemical PCa recurrence after radical prostatectomy. 1612 men (41% African American), were followed retrospectively for 50 months, and disease recurred in 488 men (31%), 265 of whom were Caucasian (29%) and 223 of whom were African American (34%). Although race was found to be significantly correlated with biochemical disease recurrence, with African American men being at an increased risk (hazard ratio 1.28), there was no significant difference noted with regard to the mean time to disease recurrence, and the PSA doubling time at the time of disease recurrence was found to be similar between the races. The authors concluded that continued work is needed to reduce the number of disease recurrences in the high-risk group of African Americans. Similar findings were also reported by Grossfeld et al [76] who examined a multiracial cohort of 1,468 patients following radical prostatectomy at the University of California. Overall, disease recurred in 21% of the patients, and African American race, serum PSA at diagnosis, biopsy Gleason score and percent positive prostate biopsies were independent predictors of recurrence. Estimated 5-year disease-free survival was 65% and 28% in Caucasian and African American men, respectively. However, when education and income were entered into the multivariate model, ethnicity was no longer an independent predictor, suggesting that socio-economic factors may be important contributors in the poorer outcomes among African American patients after radical prostatectomy.

Caire et al [77] explored the relationship between obesity and risk of pathological features and a greater risk of PSA recurrence in African American men in a cohort of 4196 consecutive patients who underwent radical prostatectomy from 1988 to 2008, retrieved from the Duke Prostate Center database. Obese African American men in this study had higher-risk disease characteristics and a greater risk of PSA recurrence despite controlling for PSA level and clinical tumor stage. SES might also play a role, as African American men might have limited access to healthcare and not attend for follow-up as frequently after diagnosis. Furthermore, a greater proportion of African American men were obese in the present cohort. Similar findings were reported by Spangler et al [78], who reported that obesity was associated with poorer tumor characteristics (OR 2.30, 95% CI 1.04–5.1), and greater likelihood of treatment failure and biochemical recurrence (adjusted hazard ratio 5.49, 95% CI 2.16–13.9) in African American, but not Caucasian men. Obesity is a modifiable risk factor that might be associated with more aggressive tumor biology, possibly mediated through increased leptin levels in obese men. Leptin is a protein hormone that is responsible for increased metabolism and decreased appetite. Leptin was reported to exhibit mitogenic effects on various cancer cell lines, including prostate [79], breast [80] and colorectal cancers [81] through MAPK and PI3-K pathways, thus promoting angiogenesis and facilitating proliferation. In addition to leptin, obesity may promote PCa progression through overexpressed markers of inflammation (IL-6, TNG-a), reduced plasma adiponectin levels (thus increasing the leptin/adiponectin ratio, favoring proliferation), and acquired insulin resistance [82]. Thus far, racial variations in systemic levels of mentioned above biomarkers and the degree of their implication in PCa disparity are still under exploration; however, taken together, the study suggests obesity might be responsible for the racial

disparity seen in PCa. In addition to obesity, dietary factors have been shown to correlate with PCa initiation and progression, with increased animal fat, cooked red meat and dairy consumption being the most studied dietary risk factors [83–84]. It was reported that African Americans tend to maintain high-fat diets more often than any other racial groups [12], thus possibly facilitating the disparity in PCa initiation, progression and survival. Extensive research aimed to explore the role of dietary patterns in overall PCa risk and its relation to disparity is currently ongoing.

Thompson et al [85] have used the data from 288 African American and 975 Caucasian men in the randomized phase III trial that compared orchiectomy with or without flutamide in men with metastatic PCa, to determine if race was an independent predictor of survival. After adjustment for the most important prognostic variables (more extensive disease, younger age and higher Gleason score in African Americans), the hazard ratio for all cause mortality for African American men versus Caucasian men was 1.23. Disease extent, presence of bone pain, Gleason score of 8–10, and the general health status measures all were statistically significant, independent predictors of overall survival. After adjustment for these measures, African- American race was determined to be associated with even higher risk of death (hazard ratio 1.39).

The influence of co-morbid conditions on post-treatment QOL and PCa related mortality in men of different races was examined by Holmes et al [86]. The authors reported that African American men usually present with a greater comorbidity index (9% vs 4.6% Caucasian men). This factor contributes to worse treatment outcomes and racial disparity in survival ; when comorbidities are controlled for, these disparities disappear (hazard ratio = 0.98; confidence interval 0.94–1.03). It was also noted that, despite marked race-related differences in treatment, adjusting for this difference has little effect on survival. Putt et al [87] have examined the influence of comorbidities on the survival of elderly Medicare PCa patients in the sample of over 55,500 men. For both races, greater comorbidity was associated with decreased survival rates; however, the effect among African Americans was smaller than in Caucasians, and racial disparity in survival decreased with increasing number of comorbidities. Adjusting for treatment had little impact on these results. Racial disparities are most pronounced between African American and Caucasian men with no or few comorbidities and are not evident at higher levels of comorbidity. The reasons for this effect are unknown, however, the authors suggested that either African Americans with greater comorbidities may have died before PCa diagnosis (which is usually made in the 60s or 70s), or if PCa is more aggressive in African Americans, they are more likely die of it rather than of co-morbid conditions. A larger competing risk of death from PCa among African American men than Caucasian men could result in a smaller effect of comorbidities on overall survival. It is also possible that African American men are overall less susceptible to death caused by co-morbid conditions, compared to Caucasian men, and therefore at higher levels of co-morbidities, the rate of PCa attributed death in African American men is balanced by the rate of death in Caucasian men, caused by co-morbid factors, unrelated to PCa. Such “balancing” may be responsible for an overall alleged reduction in PCa racial disparity. While intriguing, these rationales are yet speculative and require additional transdisciplinary research, involving clinicians, epidemiologists, biostatisticians, behavioral scientists, and psychologists to rule out the definite conclusion.

The worse overall outcomes in African American men with PCa result in increased healthcare resource use and cost, as reported by multiple works published by Jayadevappa et al [88]. It was found that not only do African American patients have higher care cost for PCa at all levels (except the terminal phase where no substantial difference was noted), but that also the incremental cost of PCa care was higher for the African American group. In addition, African American men were more likely to have emergency room visits, while

Caucasian men utilized mostly outpatient visits, and the mean length of hospital stay was longer among African American men during all phases of care. In addition, African American men receiving treatment in the medium size hospitals were found to accrue higher cost (odds ratio = 1.53 compared to Caucasian men), but worse immediate post-treatment outcomes as defined by increased complications (odds ratio = 1.39 compared to Caucasian men) and greater co-morbidity [89]. Interestingly, this association was not observed for big and small hospitals, and is attributed to the limited amount of resources and lack of diversity that may be observed in a medium-sized hospitals. The authors concluded that any health-policy measures aimed at effectively reducing racial and ethnic disparity in care should address the issues related to variation in health resource usage and associated cost.

The latter was also supported by Keating et al [90], Haas et al [91] and Smith et al [92], who reported an underuse of hospice services by African Americans with any cancer, including PCa, at the end of life. This aspect of the racial disparity is of particular concern, because the hospice use is associated with the reduced number of emergency room visits, decreased pain and suffering, and enhanced overall emotional and physical well-being of PCa patients at the end of life. The reasons for this disparity are not well understood and require further research, which should also explore the ways of promoting the hospice use among African American men and men of other minority groups, dying of PCa.

In contrast to previous reports, Klein et al [93] in their recent review come to a conclusion that if localized PCa is treated adequately and appropriately, patients do equally well across all stages, regardless of race or ethnicity. Survival outcomes were equivalent between Caucasians and African Americans when treatment was assigned in a uniform manner without regard to race. A similar conclusion was drawn by Merrill et al [94], who examined PCa data from the SEER Program. The authors reported no differences in PCa related mortality between races after adjusting for differences in stage and grade, age, number of primary cancers, and treatment. It was concluded that later stage at diagnosis is the primary reason for the higher likelihood of PCa mortality among black men compared to white men. Resnick et al [95] retrospectively reviewed the database of 2407 patients who underwent radical prostatectomy and concluded that no significant difference was found in PCa-specific measures of disease control, risk of disease upgrading, estimated tumor volume, or recurrence-free survival between Caucasian and African American men. The authors noted that, despite the well-documented racial disparities in PCa epidemiology and outcomes, no evidence exists that clinically-determined low-risk African American patients are at increased risk of advanced disease at radical prostatectomy.

Although studies demonstrate significant racial disparities of biological and socio-cultural nature, affecting PCa survivors of African descent, additional research is needed to establish their causes and outline intervention aimed to minimize them.

4. Summary, Conclusions and Future Directions

In summary, significant documented racial disparities exist at all stages of PCa management, from differences at presentation through treatment to progression-free survival, stable disease or death (Table 1). These disparities seem to be complex in nature involving biological, socio-economic and socio-cultural determinants. These mounting results highlight an urgent need for future clinical, scientific and socio-cultural research involving transdisciplinary teams to elucidate the causes for these racial disparities. Subsequently, these studies may also identify modifiable risk factors to guide evidence-based, targeted interventions aimed at helping eradicate the increased burden of PCa among the African American population.

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Table 1

Summary of documented disparities in African American men with PCa, using Caucasian men as a reference group.

At presentation	Overall disease management	Early disease	Advanced disease	Survival and QOL
Age: on average 3 years younger [13–14]	Decision making: Fewer options supplied, more unaddressed concerns remain [9]; fear of side effects [47]; family shared decision making is low [49];			Survival: generally shorter [2, 63, 85, 87]
Tumor: Increased volume [15–17], faster growth [19], advanced disease – OR 2.04 – 1.21 [20–22]	Staging: increased risk of not being staged [41]			QOL: generally lower [64–65]
PSA: Increased levels [16–18, 22]	Definitive treatment: surgery - overall less likely [7, 21, 50–51, 53–56]. EBRT - more likely for an early disease [53]			Increased side effects of treatment: urinary, bowel, sexual dysfunctions, sleep disturbances, pain and traumatic stress [42, 53, 68–71]
Seminal vesicle involvement increased. Organ confined disease decreased [22]				
Educational attainment, SES: lower [20, 40–41], [20, 40–42]. Health insurance: greater likelihood of being underinsured [43–45].	Non-definitive treatment (hormonal therapies, radiation): overall more likely, even for a low-grade disease [7, 51, 53].			PSA recurrence: increased risk [72–73, 77]
Marital status: Greater likelihood of being unmarried [20, 40–41]	ADT therapy for an advanced disease: less likely [61]			Mortality: increased both cancer-specific (1.47) and overall (1.29) [56]
				Healthcare cost: increased [88]
				Hospice use: lower [90–92]