

Racial Differences in Prostate Cancer

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Prostate cancer is the most common non-cutaneous cancer diagnosed in American men and the second leading cause of male cancer deaths.¹ African American men suffer disproportionately with almost double the incidence of and death from prostate cancer. Many sociologic and biologic theories have been applied to solve this conundrum; however, there is still great contention over what the isolated causes of these racially divided outcomes are.

Epidemiology

United States Statistics

In 2006, it is estimated that 234,460 men will be diagnosed, and 27,350 men will die from prostate cancer.¹ Data from the Surveillance, Epidemiology, and End Results (SEER) database 1998-2002 revealed the median age at diagnosis for prostate cancer was 69 years of age. Approximately 0.0% were diagnosed under age 34; 0.5% between 35 and 44; 8.0% between 45 and 54; 26.1% between 55 and 64; 37.5% between 65 and 74; 23.2% between 75 and 84; and 4.7% at 85 years of age or greater.² The age-adjusted incidence rate from 1998-2002 was 173.8 per 100,000 men per year. SEER data from 1998-2002 also revealed the median age at death from prostate cancer was 79 years of age. Approximately 0.0% died under age 34; 0.1% between 35 and 44; 1.2% between 45 and 54; 6.3% between 55 and 64; 22.1% between 65 and 74; 42.3% between 75 and 84; and 27.9% at 85 years of age or greater. The age-adjusted death rate was 30.3 per 100,000 men per year.²

African Americans suffer a disproportionately high incidence of and mortality from prostate cancer compared to whites. Relative to whites, African Americans suffer from a 1.6 times higher incidence of prostate cancer. According to SEER 13 registries from 1998-2002, whites were diagnosed with prostate cancer at a rate of 169.0 per 100,000 men compared to African

Americans diagnosed at a rate of 272.0 per 100,000 men.² African Americans compared to whites also suffer from a 2.5 times greater mortality from prostate cancer. Whites died with prostate cancer at a rate of 27.7 per 100,000 men compared to African Americans who died at a rate of 68.1 per 100,000 men.²

North Carolina Statistics

In 2006, it is estimated that 7,120 men will be diagnosed and 830 men will die from prostate cancer in North Carolina.¹ The age-adjusted incidence rate for all races from 1999-2001 in North Carolina was 159.4 per 100,000 (United States 161.2 per 100,000).² The age-adjusted death rate from 1999-2001 for all races in North Carolina was 35.6 per 100,000 (United States 30.3 per 100,000).² More alarmingly, some North Carolina counties have the highest incidence of and death from prostate cancer in the world, irrespective of race (see Table 1 and 2). The etiology for such high prostate cancer incidence remains unknown.

Racial differences in the incidence of and death from prostate cancer persist when examined at the state-specific level. SEER data from North Carolina from 1999-2001 showed that whites had an incidence rate of 143.6 per 100,000 (United States white incidence in 2001 was 144 per 100,000) compared to African Americans who had an incidence rate of 238.5 per 100,000 (United States African American incidence in 2001 was 234.1 per 100,000).² During a similar time period (1998-2002),

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Table 1.
Ten Counties with the Highest Incidence of Prostate Cancer (per 100,000)
 (United States White Incidence 144 per 100,000/African American Incidence 234.1 per 100,000)

| | All | | White | | African American |
|--------------------|-------|--------------------------|-------|--------------------------|------------------|
| Lenoir County | 262.7 | <i>Lenoir County</i> | 213.6 | <i>Onslow County</i> | 464.7 |
| Onslow County | 247.8 | <i>Onslow County</i> | 212.4 | <i>Perquimans County</i> | 419.3 |
| Perquimans County | 245.2 | <i>Craven County</i> | 212.0 | <i>Lenoir County</i> | 376.2 |
| Hertford County | 243.0 | <i>Perquimans County</i> | 199.3 | <i>Craven County</i> | 334.7 |
| Craven County | 233.1 | <i>Hertford County</i> | 194.1 | Burke County | 319.0 |
| Pamlico County | 231.5 | Pamlico County | 192.0 | <i>Alamance County</i> | 316.8 |
| Pasquotank County | 216.7 | Transylvania County | 189.4 | Catawba County | 313.9 |
| Camden County | 212.8 | <i>Alamance County</i> | 187.1 | Cleveland County | 309.6 |
| Alamance County | 206.7 | Pasquotank County | 186.4 | <i>Hertford County</i> | 303.9 |
| Northampton County | 204.3 | Alleghany County | 186.3 | Chowan County | 298.9 |

Bold italic indicates counties with the highest incidence of prostate cancer shared by African Americans and whites.

Table 2.
Ten Counties with the Highest Mortality from Prostate Cancer (per 100,000)
 (United States White Mortality 27.7 per 100,000/African American Incidence 68.1 per 100,000)

| | All | | White | | African American |
|--------------------|------|----------------------|-------|----------------------|------------------|
| Caswell County | 62 | <i>Pender County</i> | 49.3 | Richmond County | 143.8 |
| Warren County | 61.1 | Franklin County | 41.8 | Catawba County | 141.6 |
| Pender County | 60.7 | Watauga County | 39.4 | Sampson County | 120.0 |
| Perquimans County | 58.9 | Lenoir County | 38.5 | Cleveland County | 115.8 |
| Granville County | 58.8 | Montgomery County | 38.5 | <i>Pender County</i> | 108.2 |
| Hoke County | 57.2 | Yancey County | 37.7 | Wayne County | 103.6 |
| Halifax County | 55.8 | Craven County | 36 | Duplin County | 99.8 |
| Richmond County | 55.2 | Carteret County | 35.9 | Caswell County | 98.9 |
| Northampton County | 55.1 | Granville County | 35.9 | Gaston County | 97.7 |
| Vance County | 55.1 | Halifax County | 35.9 | Northampton County | 97.1 |

Bold italic indicates counties with the highest incidence of prostate cancer shared by African Americans and whites.

whites in North Carolina had a mortality rate of 27.9 per 100,000 (United States white mortality rates 1998-2002 were 27.7 per 100,000) compared to African Americans who had a death rate of 79.3 per 100,000 (United States African American mortality rates 1998-2002 were 68.1 per 100,000).² African Americans in North Carolina suffer a 1.6 times greater incidence of and 2.8 times greater mortality from prostate cancer compared to whites. These differences are similar to differences seen on a national level.

Possible Explanations for Prostate Cancer Differences

Access and Allocation of Healthcare

Many studies have shown that minorities do not receive the same allocations of procedures as do whites who have the same

disease processes.³⁻⁵ Peterson et al. showed in a Veteran Affairs study of 33,641 men that African Americans with an acute myocardial infarction were 33% less likely than whites to undergo cardiac catheterization, 42% less likely to receive coronary angioplasty, and 54% less likely to receive coronary bypass surgery.³ Similar outcomes were demonstrated by Ayanian et al. who studied a retrospective cohort of 27,485 men and women from various hospital systems who underwent inpatient angiography for coronary heart disease in 1987.⁴ Results showed that whites are more likely than African Americans to receive revascularization procedures after coronary angiography. With regard to cancer care, Armstrong et al. studied 408 women with a family history of breast or ovarian cancer, of whom 217 underwent genetic counseling for breast cancer (BRCA1/2) testing (cases), and 191 women did not (controls).⁵ Results showed that African Americans were significantly less

likely to undergo genetic counseling for BRCA1/2 testing than were white women.

Access to and allocation of healthcare alone cannot explain the racial differences in prostate cancer outcomes. Robbins et al. studied men insured within the Kaiser Permanente organization and found that African American men presented with higher stages and worse survival from prostate cancer compared to white men.⁶ This study showed that even in an equal access system, racial differences in prostate cancer outcomes still remained. In contradiction to the Kaiser study, Freedland et al. found an equal percentage of African American and white men presenting with clinically localized and metastatic prostate cancer in the Veterans Affairs system.⁷ No differences were found in patient age or clinical stage of prostate cancer between black and white men at the time of diagnosis, but African American men presented with higher median serum prostate-specific antigen (PSA) values (14.2 versus 9.4 ng/mL, $p = 0.0001$) and slightly higher median Gleason scores (6.2 versus 5.9, $p = 0.025$).⁷ More recent studies have shown that African Americans and whites, when matched by pathologic stage and grade after radical prostatectomy, have similar disease outcomes.⁸ Eastham et al. demonstrated that African American and white men with clinical T1c^a prostate cancer (diagnosed by PSA alone) have similar pathologic outcomes and PSA recurrence rates after radical prostatectomy, which further illustrates that in the modern era of PSA testing, stage for stage/grade for grade, African Americans and whites have similar outcomes.⁹ These data re-enforce the argument that African Americans should be screened aggressively and early (after age 40) if any survival benefit from treatment is to be shown.

Prostate Cancer Screening Participation

The frequency of incidental prostate cancer detection in African Americans and whites appears similar;¹⁰ however, African Americans are more frequently diagnosed with higher tumor volumes,¹¹ more advanced tumor stages,¹² more diffuse and greater volumes of high-grade prostatic intraepithelial neoplasia (HGPIN),^{13,14} higher Gleason grades,^{15,16} and higher PSA levels^{11,14,16,17} compared to whites. Several studies have shown that when African Americans and whites are matched for stage and grade and undergo radical prostatectomy, there are no differences in PSA recurrence or risk of death from prostate cancer.¹⁸⁻²⁰ In light of the disparity in the incidence and mortality statistics, it would be reasonable to think that African American men would participate in more prostate cancer screening when offered. Unfortunately, several studies have shown quite the contrary. Ashford et al. evaluated 404 African American men in Harlem, New York and analyzed those who received prostate cancer screening.²¹ Results showed that the prevalence of self-reported PSA screening in Central Harlem was lower than that reported for other populations, with only 24% of men 50-74 years of age ever having had a PSA test.

Choice of Definitive Therapy

Many studies have shown that African Americans compared to whites choose radical prostatectomy less often. Hoffman et al. studied 1,144 African American and white men with clinically localized prostate cancer and found that among men with more aggressive cancers (PSA greater than or equal to 20 ng/mL or Gleason score greater than or equal to 8), African Americans were less likely to undergo radical prostatectomy than whites (35.2% versus 52.0%), but more likely to receive conservative management (38.9% versus 16.3%, $p = 0.003$).²² Treatment differences may reflect the greater likelihood for African Americans to present with pathologically advanced disease. Yan et al. analyzed men that underwent PSA screening and followed outcomes of therapy in men subsequently detected to have prostate cancer.²³ Non-African American patients had a greater than four times likelihood of selecting radical prostatectomy versus watchful waiting compared to African Americans. In an analysis of SEER data from 1995-1999, Denberg et al. showed that African Americans received equal amounts of definitive therapy for curative intent; however, African Americans compared to whites were significantly more likely to choose radiotherapy versus radical prostatectomy.²⁴

Biologic Explanations for Prostate Cancer Differences

Androgen Axis: Steroids

In studies that would later win the Nobel Prize in Medicine, Charles Huggins and Clarence Hodges demonstrated that withdrawal of testosterone causes prostate cancer to go into remission, but that it is almost certainly to recur in its testosterone-insensitive form.²⁵ Since prostate cancer is an androgen-stimulated cancer, could racial differences in prostate cancer be attributable to differences in androgen levels? In a study by Ross et al., male college students (mean age 20 years) living in southern California had testosterone levels measured. Total testosterone and free testosterone levels were 15% and 13% higher, respectively, in African Americans compared to whites.²⁶ Ellis et al. also measured androgen levels in over 4,000 male Army veterans ranging from 31-50 years of age (mean 38 years), but found that African Americans had only a 3.3% higher mean testosterone level compared to whites.²⁷ Kubricht et al. reported serum testosterone levels were similar between 189 African American and 264 white men undergoing biopsy for prostate cancer.²⁸ Beyond 40 years of age, African Americans and whites appear to have similar testosterone levels. If there are any differences in androgen levels, it occurs earlier in life and not in the prostate cancer-risk group after age 40.

Dihydrotestosterone (DHT) binds to the androgen receptor with affinity similar to testosterone, but DHT reduces androgen receptor degradation rates more than testosterone because of its slower dissociation.^{29,30} Small racial differences in DHT or 5-alpha

a Prostate cancer with a T1c stage is traditionally characterized as being early-stage disease and having the best prognosis.

reductase, which catalyzes the conversion of testosterone to DHT, may increase androgen receptor protein levels in African Americans compared to whites. Accordingly, Ross et al. studied serum DHT metabolites in 100 university students and 54 Japanese medical students.³¹ African Americans and whites, respectively, had 25% and 31% higher levels of the DHT metabolite A-diol-glucuronide compared to Japanese students. Four recent studies have reported serum levels of DHT, and none found differences between cases and controls; however, in each of these studies, African Americans were either not included or race was unspecified.³²⁻³⁵

The aforementioned studies measured serum androgens that may not accurately reflect the true androgenic environment within the prostate. Mohler et al. analyzed steroid hormones that were extracted from snap frozen prostate tissue obtained intraoperatively from radical prostatectomy specimens of 36 African Americans and 59 whites.³⁶ Although tissue levels of testosterone and DHT did not differ by race, African American men had higher tissue androstenedione (ASD) and sex hormone-binding globulin (SHBG) than white men.

Androgen Receptor Expression

Lubahn et al. at the University of North Carolina at Chapel Hill (UNC-Chapel Hill) was the first to isolate the androgen receptor in 1988.³⁷ Extensive androgen receptor research continues at UNC-Chapel Hill. Recently, Gaston et al. performed a study looking at archived radical prostatectomy specimens obtained from 25 white and 25 African American men who had androgen receptor protein antigen retrieved and immunostained.³⁸ Androgen receptor protein expression was 22% higher in the benign prostates and 81% higher in the cancerous prostates of African American men when compared with white men. Similar results were found in a study by Olapade-Olaopa et al. The Olapade-Olaopa study compared androgen receptor expression in benign prostatic hyperplasia (BPH) and prostate cancer tissue of non-American blacks and non-American whites and found a similar increased expression of androgen receptor in blacks compared to whites.³⁹ Accordingly, prostate cancer may occur at a younger age and progress more rapidly in African American men compared to white men due to racial differences in androgenic stimulation of the receptor.

Racial differences in androgen receptor gene polymorphisms have also been described in the literature. African Americans, compared to whites, have been shown to express more androgen receptor polymorphisms, which may increase the risk of developing prostate cancer.

Racial Polymorphisms in the 5-alpha Reductase

Reichard et al. described genetic polymorphisms in the gene encoding the 5-alpha-reductase type II enzyme and compared allelic frequencies between three major United States populations—African Americans, whites, and Asian Americans. The authors found three different allelic families [containing 87 base pairs (bp), 103-107 bp, and 121-131 bp].⁴⁰ Whereas 18% of African Americans exhibited the 121-131 bp alleles, these alleles were not found in white or Asian Americans.

Consequently, this 5-alpha-reductase type II enzyme polymorphism may result in more efficient conversion of testosterone to DHT within the prostate, and thereby may have a role in carcinogenesis.

Diet and Nutrition

Genetic differences cannot be the sole basis for difference of prostate cancer incidence. Epidemiological studies have demonstrated that as populations migrate from geographic areas with a low-incidence rate of prostate cancer to areas with higher-incidence rate, the migrating population begins to exhibit higher-incidence rates of prostate cancer. The incidence of prostate cancer varies throughout the world, yet African Americans have the highest incidence of prostate cancer in the world. The highest incidence of prostate cancer is in the United States, and the lowest is in Asia (as low as 0.5 per 100,000 in Qidong, China).⁴¹ Asia also has a low consumption of saturated animal fat and a high consumption of fiber and soy protein.⁴¹ Soy protein is abundant in the Asian diet, but is rarely consumed in the American diet. Soy has long been thought to have broad anti-neoplastic effects.⁴² There are two broad isoflavonoid components found in soy—genistein and daidzein, both of which may have mild estrogenic effects, which may cause apoptosis (cell death) of prostate cancer cells.⁴²⁻⁴⁴

Dietary fat intake is thought to be a major factor involved with the increased incidence of prostate cancer in the United States.⁴⁵⁻⁴⁸ Omega-6 fatty acids are thought to act as promoters of prostate cancer.⁴⁹ It is thought that at the cellular level, these fatty acids influence cellular proliferation, the immune system, and the potential for the tumor to invade locally and metastasize.⁴⁹ It is also thought that Omega-6 fatty acids (found in cereals, eggs, poultry, most vegetable oils, etc.) affect prostaglandin synthesis.⁴⁹ It has been shown that increased levels of prostaglandin E₂ increases oncogene Bcl-2 expression leading to carcinogenesis.⁵⁰ On the other hand, Omega-3 fatty acids found in fish oils, appear to be protective against prostate cancer.⁴⁹ These Omega-3 fatty acids are consumed in high amounts in Asia, whereas Omega-6 fatty acids are consumed in low amounts. The opposite occurs in the United States where Omega-3 fatty acids are consumed in low amounts and Omega-6 fatty acids are consumed at high amounts. Subsequent studies have shown that the African American diet contains the highest overall saturated fat and Omega-6 fatty acid content in the world.^{47,48}

Obesity may be an independent factor of prostate cancer progression. Amling et al. examined the relationship between obesity and race in predicting adverse pathological variables in patients undergoing radical prostatectomy.⁵¹ This was a multi-institutional retrospective analysis of the clinical and pathologic parameters on 860 patients with prostate cancer undergoing radical prostatectomy between 1992 and 1998. Obesity was defined as a Body Mass Index (BMI) greater than 30 kilograms/meter² (kg/m²). Obese patients presented with prostate cancer at younger ages, higher Gleason grades, and more advanced pathologic stages. These data suggest a racial correlate of prostate cancer because African Americans tend to have higher

grade prostate cancer and significantly higher average BMI compared to whites.

Insulin Growth Factor Pathways

Insulin-like Growth Factor 1 (IGF-1) stimulates cellular proliferation and inhibits apoptosis.⁵² IGF-1 is a stimulator prostate cancer growth factor and 95% circulates bound to specific high-affinity IGF binding proteins (IGFBPs 1–6).⁵³ Blood levels of IGFs in each individual are relatively constant with no apparent diurnal or circadian variation. Studies have shown that African Americans have low IGFBP-3 compared to whites.⁵⁴ This may allow for more free IGF-1 to stimulate neoplastic growth of the prostate. Abdominal obesity and hyperinsulinemia are associated with decreased serum levels of sex hormone-binding globulin, with a resultant increase in testosterone, lower serum levels of IGFBP-1, increased serum levels of IGF-1, and estrogenic compounds.⁵⁵⁻⁵⁸ Since African Americans have the highest BMI in the world, one can assume

these IGF pathways may directly affect carcinogenesis of the prostate.

Vitamin D

Vitamin D may have protective benefits against prostate cancer. Vitamin D is believed to decrease bcl-2 expression increasing apoptotic cell death.⁵⁹ Some have suggested that endogenous Vitamin D synthesis may be impaired in African Americans because of the darker skin pigmentation.⁶⁰

Conclusion

Striking differences in the incidence of and mortality from prostate cancer between African Americans and whites have persisted even after the advent of PSA testing. African Americans do not appear to fair worse than whites when matched by cancer stage and grade. More must be done to target this population for early and aggressive screening. **NCMedJ**

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