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Genetics, Disparities, and Prostate Cancer

Editor's note: In 2005, more than 200,000 new cases of prostate cancer will be detected in the United States, and about 30,000 men will die from the disease. African American men are particularly hard-hit, dying from this disease at more than twice the rate of European Americans. The reasons for this racial/ethnic disparity are largely unknown, but probably involve an interaction among genetic, environmental, and social factors. This Issue Brief reviews current knowledge about the genetic basis of prostate cancer and summarizes ongoing research at Penn that investigates the role of genetics in prostate cancer treatment and outcomes.

Prostate cancer: age, race, and family history matter

In the U.S., one of every six men will be diagnosed with prostate cancer in his lifetime, with most men diagnosed after age 60. Three factors clearly increase the risk of developing prostate cancer: age, race, and having a family history of prostate cancer. Other factors, such as diet, lifestyle, and hormones are also likely to a role in prostate cancer risk and outcomes, although the contribution of these factors is not as well understood.

- The incidence of prostate cancer varies widely by geographic location and race. African American men have the highest prostate cancer rates in the world, and Asian men have the lowest. African American men have a 60% higher risk of getting prostate cancer than European Americans.
- Prostate cancer "runs" in certain families, although hereditary forms of prostate cancer account for only about 5%-10% of all prostate cancer cases. But even in the non-hereditary form, family history does matter: having a brother or father with prostate cancer (especially diagnosed at younger ages) increases a man's prostate cancer risk 2- or 3-fold.
- The widespread use of prostate cancer screening by prostate-specific antigen (PSA) tests and digital rectal examination has dramatically changed the detection of this disease. Screening detects tumors at earlier stages, which can lead to earlier treatment. But earlier treatment is not necessarily better. Screening can also detect tumors that would not cause a man any problems in his lifetime; screening could then lead to unnecessary treatments, which can have significant side effects such as impotence or incontinence. Thus, screening for prostate cancer remains controversial. The U.S. Preventive Services Task Force has concluded that evidence is insufficient to recommend for or against routine screening for prostate cancer.

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Genetic basis of prostate cancer is likely, but not well-understood

Genetic factors can influence prostate cancer at many stages. They can influence the likelihood of developing prostate cancer, the severity of the disease, and the response to treatment. Because there is controversy about widespread screening for prostate cancer, understanding how genetic variations affect the development and course of prostate cancer is critical for identifying men who might benefit from screening because they are likely to have a poor clinical outcome.

- Researchers have identified a handful of “susceptibility” genes that might be responsible for the hereditary form of prostate cancer, although the role of specific genes in causing prostate cancer is complex and not completely understood.
- One group of candidate genes are those involved in how the body processes male hormones, since testosterone is a major determinant of prostate growth. Another group of candidate genes are those involved in regulating the immune system’s response to tumors.
- Natural variations in some candidate genes differ substantially by race. It is likely that these genetic differences, interacting with environmental exposures and screening behaviors, could explain variability in prostate cancer risk and outcomes across racial or ethnic groups.

Decade-long studies of the causes of prostate cancer provide some answers

For the past decade, Rebbeck and colleagues have conducted a series of case-control studies at the University of Pennsylvania Health System (UPHS) to understand the role of genetics and family history in prostate cancer. Their ongoing work collects genetic information on “cases” (men diagnosed with prostate cancer) and compares them with “controls” (men without prostate cancer who were seen at UPHS for checkups or acute illness).

- The “cases” in these studies are recruited through urology clinics, and are not selected based on a strong family history. Thus, the vast majority of men in these studies are not members of hereditary prostate cancer families.
- The investigators also collect detailed information on family history, demographics, prostate cancer screening history, tumor characteristics, and cancer treatments to begin to understand how all of these factors affect prostate cancer outcomes.
- These studies include enough African American men to investigate the role of genetic factors in explaining racial and ethnic disparities in prostate cancer.

Family history may be related to clinical outcomes in men diagnosed with prostate cancer

Although family history affects a man’s risk of getting prostate cancer, it is not clear whether family history affects the outcomes of prostate cancer. Rebbeck and colleagues assessed this relationship in their cases. They compared tumor characteristics and other clinical features in men with and without a family history of prostate cancer.

- Of the 684 men with prostate cancer in this study, 66% reported no family history of prostate cancer and 34% reported prostate cancer in a brother, father, uncle, or grandfather.
 - In men diagnosed before age 60, a positive family history was associated with a higher staged (more advanced) tumor. These men were twice as likely to have more advanced tumors than men without a positive family history. In men diagnosed at or after age 60, family history was not associated with tumor stage.
 - In men undergoing a prostatectomy as treatment for prostate cancer, post-surgery measurement of PSA can predict survival. After accounting for other factors, such as age, race, and tumor stage, men with a positive family history were 2.5 times as likely to have measurable PSAs after surgery.
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Susceptibility genes may affect cancer progression and severity, but in complex ways

In another study, the investigators analyzed 16 variants in three “susceptibility” genes in their cases and controls. These genes were previously identified in family-based studies, but their role in non-hereditary prostate cancer, and in African Americans, was not known. The investigators evaluated these issues in a study involving 1019 cases and 636 controls. Nearly 13% of cases were African American.

- The results indicate that the frequency of these genetic variants differ by race. Some rare variants were found in only one racial group.
- None of the variants was associated with the overall risk for non-hereditary prostate cancer in both races. However, a number of variants were associated with the risk of prostate cancer in subsets of men separated out by family history and severity of the disease. One variant was associated with prostate cancer in African Americans, but only in those men with a positive family history and more advanced tumors.
- Other results indicate that two of the genes may influence the severity or progression of prostate cancer, and that this effect may vary by racial background and family history of prostate cancer.

Testosterone genes influence prostate cancer risk

Genetic variants that affect how the body uses testosterone are thought to influence the development of prostate cancer, but no clear relationships have emerged from prior studies. Rebbeck and colleagues comprehensively evaluated variants by race/ethnicity and tumor characteristics to better understand whether these genes are related to the occurrence and severity of prostate cancer. The study involved 622 cases and 396 controls.

- Their results indicate that the genetic basis of prostate cancer is complex, may involve multiple genes interacting with one another, and may be different in different ethnic groups.
- For example, one variant is associated with a reduced risk of prostate cancer in European Americans but not African Americans; another variant is associated with nearly six times the risk, but only in men with a positive family history of prostate cancer.
- Combinations of genetic variants differ by race/ethnicity and may magnify the effects on risk. For example, one combination of variants appears in 4% of European Americans, and 35% of African Americans in this study. That combination is associated with an increased risk of prostate cancer, particularly for men diagnosed under age 60.

Ongoing work will study complex interactions of predictors of prostate cancer outcomes

Rebbeck and colleagues continue to study the interaction among genetic factors, family history, exposures, and screening behavior on prostate cancer outcomes.

- The ongoing study will include 500 African American men and 500 European American men in the cases and the same number in controls (2000 men in total). The investigators will study a broad group of candidate genes previously associated with prostate cancer.
- They will evaluate whether these genetic variants predict prostate cancer severity and outcomes, whether this prediction adds to the information available from tumor characteristics, and whether these effects differ by patterns of screening behavior and race/ethnicity.

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POLICY IMPLICATIONS

As these studies indicate, the genetics of prostate cancer is important, although poorly understood. It is likely that multiple genes, interacting with each other, combine with environmental and behavioral factors to cause prostate cancer. The impact of genetic variations on the severity and progression of prostate cancer is even less understood, but potentially more important to the 200,000 men in the U.S. diagnosed with prostate cancer each year.

- A large proportion of detectable prostate cancer may never cause a man any harm, and the treatments for prostate cancer, including surgery, radiation, and drugs, can produce more harm than benefit. Genetic information may help identify men for whom prostate cancer screening, or its treatment, is more clearly useful.
- Given that African Americans are at highest risk for prostate cancer, genetic studies that involve this racial group are critical. Barriers to African-American participation in research—from distrust of medical research to fear of discrimination to communication gaps—must be acknowledged and overcome.
- In the past, genetic studies have stigmatized racial/ethnic minorities and have led to discriminatory treatment. Indeed, it is now clear that there is more genetic variability within races than across races. The results of all genetic results must be communicated with sensitivity to past and present abuses, and presented in the context of current understandings of race, ethnicity, and biology.
- For all racial or ethnic groups, an important goal remains to identify those patients who have the most to gain from early detection and treatment of prostate cancer.

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