Researchers Seek Genetic Clues to High Prostate Cancer Incidence in African Americans

by Vickie Williams

Prostate cancer occurs in African-American men more often than in any other racial group in the world, and they die at two to four times the rate of other American populations. Why this happens is not understood, and cultural and historical barriers make finding an explanation more difficult.

Now two powerful institutions and their physician collaborators are trying to find patterns that will yield answers. Howard University in Washington, D.C., and the National Institutes of Health’s Human Genome Research Institute (HGRI) in Bethesda, Maryland, are studying genetic profiles to find a pattern that links African-American families to prostate cancer.

Helping them is Assistant Professor of Urology Curtis Pettaway, M.D., of the Department of Urology at The University of Texas M. D. Anderson Cancer Center. He and other researchers are recruiting African-American families to the study. The researchers provide the subjects; the institutions provide the funding, study coordination, and genetic analyses.

“If you have a group of individuals who appear to be predisposed to the early onset of prostate cancer, such as African Americans, then it seems that it would be prudent to study this population to get insights into what makes the cancer grow,” Dr. Pettaway said. “These insights may have widespread applicability for prevention, diagnosis, and therapeutic approaches to prostate cancer.”

(Continued on next page)
Search for Genetic Clues
(Continued from page 1)

“That’s my hypothesis, and that’s why I think this study is important,” he said.

About 10% of prostate cancer cases are familial, according to the American Cancer Society, and these are characterized by early onset and advanced stage at diagnosis.

The goal of the African-American Hereditary Prostate Cancer Study, according to Dr. Pettaway, is to isolate the gene or genes involved. Preliminary studies show that in a group of African-American men with familial prostate cancer an area on the long arm of chromosome 1 (1q24-25) may be involved. This same area was also previously reported to be associated with hereditary prostate cancer in other populations, but the association may be even higher for African-American families.

“Even though we have some evidence to support a role for chromosome 1 in this disease, researchers at the genome institute do not limit their testing to this area,” said Dr. Pettaway. “They conduct a genome-wide scan using markers that can identify areas on all chromosomes that might be associated with prostate cancer.” Scientists announced last fall that the X chromosome may also be involved in hereditary prostate cancer and that perhaps prostate cancer susceptibility could be passed from mother to son. Ultimately, researchers want to develop an early detection tool using genetic markers to identify men at high risk for familial prostate cancer.

The two-year, $3.5 million study is being conducted at seven sites across the country, including M. D. Anderson, where Dr. Pettaway is the study’s principal investigator. Each site has a goal of enrolling 14 families in which at least four men, preferably first-degree relatives under age 65, have been diagnosed with prostate cancer. Of these four, at least three must be alive. Once the patients are identified, four or five other family members (for a total of eight family members) must consent to undergo blood testing. The additional family members may consist of either men or women of any age and any degree of relationship, and they do not have to have cancer.

The study was initiated after an earlier genetic study in men with hereditary prostate cancer detected a strong association with the chromosome 1q24-25 region. Of the families studied only two were African American, but both showed the linkage to chromosome 1. This finding prompted researchers to organize the current study to recruit 100 African-American families with prostate cancer nationwide.

“Insights may have widespread applicability for prevention, diagnosis, and therapeutic approaches to prostate cancer.”

Using a questionnaire and interviews, Dr. Pettaway and Pamela Roberson Smith, a study coordinator, chart each family’s pedigree. If the pedigree suggests that multiple family members are affected in successive generations, the patients are recruited for the study.

“At this point,” Smith notes, “the real challenge begins.”

“Some African Americans are hesitant to participate in medical research,” Dr. Pettaway said, attributing their reluctance to cultural beliefs or frank distrust of the scientific community. “The Tuskegee Syphilis Study is a good example of the latter.”

In that study, 399 black sharecroppers in Macon County, Alabama, were denied treatment for syphilis from 1932 to 1972 so that researchers could study the natural course of the disease.

“I think that at least the older African Americans remember the Tuskegee experiment and how blacks were mistreated in that study,” Dr. Pettaway said. “And so, there are clearly fears and myths that have to be dispelled prior to gaining their participation in research. We are in a unique position for this because at every level of the study African Americans are involved—in planning, implementation, data collection, and analysis.” According to study organizers, this project is the first large-scale genetic study of African Americans conducted primarily by African-American investigators.

Dr. Pettaway believes organizing the study this way will rebuild trust and encourage participation. “We are hoping this factor will help us gain patients’ confidence and increase their comfort level,” he said.

Smith takes what she calls a “shoot-from-the-hip” approach in recruitment: “It has been my experience that, culturally, African Americans are committed to family, and, historically, they are willing to take part in well-meaning causes,” she explained. “I felt that once they understood the value of the study, they would understand the value of their participation. So my approach has been to present the facts, which clearly outline the importance of this project.”

Dr. Pettaway and Smith agree that credit also must go to wives and mothers who persuaded husbands and sons to participate. “In many cases, the women have made the difference in whether a man finally agreed to participate in the study,” she said.

Other study sites include Michael Reese Hospital and Medical Center in Chicago, Howard University in Washington, D.C., Wayne State University in Detroit, Midtown Urology in Atlanta, Harlem Hospital Center in New York, and the College of Nursing at the University of South Carolina in Columbia.

For more information, contact Smith at (713) 792-4639 or by E-mail at proberso@mdanderson.org. For more information about the African-American Hereditary Prostate Cancer nationwide study, visit the web site at http://www.nihri.nih.gov/About_NHGRI/Dir/Prostate_Study/.
Prostate Cancer Clinical Trials

Clinical trials currently in progress at The University of Texas M. D. Anderson Cancer Center include the following for patients with prostate cancer.

- Phase I trial of weekly paclitaxel and doxorubicin in patients with androgen-independent prostate cancer (DM97-128). Physician: Shi-Ming Tu, M.D.

  To be eligible for this study, patients must have evaluable disease (a serum marker, such as a prostate-specific antigen or carcinoembryonic antigen measure, is acceptable), testosterone level of <50 ng/dL, and a performance status of ≤3 if compromised by cancer or ≤2 if compromised by comorbidity. Patients who have previously been treated with doxorubicin are eligible if the cumulative dose was <300 mg/m² and the patient is without evidence of clinically significant cardiac toxicity.

- Phase II study of gamma interferon in the treatment of androgen-independent prostate cancer (DM98-228). Physician: Shi-Ming Tu, M.D.

  Study participants must have histologic proof of prostate adenocarcinoma, evidence of osteoblastic metastases, and evidence of progression of disease. Conventional hormonal therapy and antiandrogen withdrawal must have failed. Patients cannot receive concurrent chemotherapy or radiotherapy, but previous treatment with chemotherapy and radiation does not affect eligibility.

- Phase II trial of gemcitabine combined with strontium 89 for the treatment of patients with androgen-independent prostatic carcinoma and painful bone metastases (DM96-216). Physician: Lance Pagliaro, M.D.

  Patients must have progressive disease despite androgen ablation and must have painful osteoblastic bone metastases with at least three sites of involvement. Participants may have received external beam radiation therapy ≥4 weeks before beginning the study and no more than one chemotherapy treatment. Exclusion criteria include brain metastases, serious intercurrent illness, and ingestion of calcium supplements or channel blockers two weeks before treatment.

- A randomized phase II trial of taxol/VP-16/estramustine vs. ketoconazole/doxorubicin/vinblastine/estramustine in androgen-independent prostate cancer (DM97-022). Physician: Randall Millikan, M.D., Ph.D.

  Patients with a PSA level of at least 4 ng/ml that rises (with an absolute change of at least 1 ng/ml) on at least two consecutive measurements are eligible for this study. Before study participation, at least 10 weeks must have elapsed since previous exposure to strontium 89, 8 weeks since exposure to mitomycin C, and 60 days since exposure to suramin. Eligible patients must be off antiandrogens and have no clinical history of heart disease. Previous exposure to any of the drugs listed in the study title, dependence on androgen therapy, undergoing more than one previous cytotoxic therapy, and an active second malignancy are criteria for exclusion.

- Phase II study of urethral sling procedure in patients undergoing radical prostatectomy (URL98-127). Physician: Louis Pisters, M.D.

  To be eligible for this study, patients must qualify to be a surgical candidate and undergo radical prostatectomy at M. D. Anderson Cancer Center. Study participants must either have a higher risk for urinary incontinence after radical prostatectomy or specifically request the sling procedure. Patients who have had a prostatectomy aborted for any reason are ineligible.

- A phase I study to investigate autologous interpositional saphenous nerve grafting of the cavernous nerves to preserve erectile function following radical retropubic prostatectomy (ID98-271). Physician: Christopher G. Wood, M.D.

  Study participants must be candidates for radical retropubic prostatectomy and have no discernible preoperative erection dysfunction (defined as the ability to have successful penetration on at least 75% of attempts). Other criteria include no peripheral neuropathy precluding procurement of a sural nerve

(Continued on page 4)
Matching the Medication to the Pain

Overcoming Barriers to Pain Relief in Hispanic and African-American Patients

by Dawn Chalaire

Teaching minority patients with cancer to talk about their pain may be the first step in ending the silent suffering of this largely underserved patient population, say researchers with the Pain Research Group at the University of Texas M. D. Anderson Cancer Center.

In a new study, the latest in a series that focuses on pain assessment and treatment of minority patients with cancer, investigators will evaluate the effectiveness of educational booklets and videos designed to teach African-American and Hispanic men and women how to take control of their own pain management.

“If you look at the research in how you change the way physicians practice, one of the strongest things you can do is make the patient more assertive. And not only make them more assertive, but help them clarify what they want to talk to their physicians about,” said study chairman Charles S. Cleeland, Ph.D., of the Pain Research Group.

“In our educational materials, we teach patients to use numbers for their pain severity. We teach patients to describe the kind of pain they’re having so the physician might think about what might be causing the pain, and we teach them to call back and ask for help if they’re not getting relief.”

In 1994, a study led by Dr. Cleeland and conducted through the Eastern Cooperative Oncology Group (ECOG) set out to document the presence and intensity of pain among 1,300 patients from across the country with metastatic or recurrent cancer. One finding that caught the researchers’ attention was that minority patients were three times more likely to be undertreated for pain than nonminority patients.

“That’s the first time we noticed that those coming from these large urban clinics, that are primarily African-American or Hispanic patients, were at greater risk. That set the whole thing in motion,” Dr. Cleeland said.

Subsequent studies looked in detail at the concerns and attitudes that African-American and Hispanic patients have about taking pain medication and talking to their physicians and nurses about pain. Research revealed that Hispanic patients are more likely to be concerned about becoming addicted to pain medications while African-American patients are less likely to take their pain medications as often as prescribed. Other, more universal, attitudes such as reluctance to admit that their cancer might be getting worse and fear of being viewed as a complainer were also identified.

Perhaps the most important barrier to adequate pain management is a lack of communication between doctors and their patients. According to Dr. Cleeland’s research, the greater the distance between the physician’s assessment of pain and the patient’s experience of pain, the more likely the pain will be inadequately treated. Several factors may figure into the discrepancy, including language differences, sex, culture, ethnicity, and time.

“I think the health care professionals that we surveyed in these institutions just don’t have the time.
Doing a good assessment of pain takes time. Often the patient is put in a bind. You’ve got five minutes on your follow-up visit. Are you going to talk about your pain or about your cancer?” said Dr. Cleeland.

Lack of staff time to attend to patients’ pain was one of the six top barriers to optimal cancer pain management reported by 59 physicians, nurses, and pharmacists involved in care of patients with breast cancer (see table). Others included inadequate pain assessment and patient reluctance to report pain. These findings were in line with those from an Eastern Cooperative Oncology Group survey of 1,177 ECOG physicians who ranked lack of proper assessment, patient reluctance to report pain, and patient reluctance to take analgesics as among the top four barriers to proper cancer pain management. The study was reported in the *Annals of Internal Medicine* 1993; 119:121–126.

Using information gleaned from these studies, the researchers developed four separate videos and booklets that are sex and heritage specific, one each for African-American and Hispanic men with prostate cancer and African-American and Hispanic women with breast cancer. The educational materials for Hispanic patients are available in Spanish.

“We developed our educational materials based on a lot of input from a lot of patients. And now we are doing the clinical trial to see how helpful they are,” said Karen Anderson, Ph.D., who is coordinating the intervention trial. Other investigators from M.D. Anderson Cancer Center include study cochairman, Rodger J. Winn, M.D., Department of Clinical Investigation; Vicente Valero, M.D., Department of Breast Medical Oncology; Arlene Nazario, M.D., Department of Clinical Investigation; and Danai Daliani, M.D., Department of Genitourinary Medical Oncology.

Researchers hope to recruit 240 outpatients with breast cancer and 240 outpatients with prostate cancer into two protocols for the multisite study that includes Houston’s M. D. Anderson Cancer Center, Lyndon Baines Johnson Hospital, and Ben Taub Hospital and sites in Los Angeles, Miami, and Chicago. Study participants meet with a bilingual research nurse who shows them the appropriate video, answers any questions they might have, and gives them a booklet to take home. Follow-up includes a phone call from the research nurse a few days later and three more visits. The trial is randomized to control for the effects of an educational intervention, with the control group receiving educational packets on nutrition.

Patients fill out a baseline questionnaire before the intervention begins and a second questionnaire at the first follow-up visit. The main outcome measure is a Brief Pain Inventory, which rates the patient’s pain and the degree to which it interferes with daily activities. Researchers will also compare quality of life, functional status, and the degree of control that patients feel over their pain, as well as the degree of agreement between the physician’s ratings of pain and the patient’s ratings of pain.

“We’re hoping that by educating patients and helping them communicate better with their health care providers about their pain and also getting rid of any myths or fears about taking pain medication, that they’ll get better pain control and feel that there’s something they can do to help,” Dr. Anderson said.●
“Got Milk?”
Say Yes to Calcium’s Benefits

“Got milk?” asks current advertising. It answers with photographic evidence that celebrities not only have it, they drink it. At the same time, research is suggesting that a milk mustache could do more than make you look as cute as a celebrity: calcium, a major constituent of milk, may help prevent colon cancer.

Researchers say the evidence is significant but not conclusive, so a number of studies are investigating calcium’s role in chemoprevention of colon cancer, building on earlier studies in animals that suggested calcium’s cancer-protective abilities. Chemoprevention is the use of natural or synthetic agents to prevent cancer by preventing or treating early precancerous abnormalities of tissue.

The Research

One such study in the New England Journal of Medicine reported that taking calcium supplements may help stop colon polyps from recurring. Polyps are abnormal growths in the colon that are usually benign but may turn cancerous. They are often removed to prevent cancer from developing.

In the study, 930 patients who already had a polyp removed were assigned to take either 1,200 mg of calcium a day or a placebo. Nine months later, and then again after 36 months, doctors examined the patients’ colonoscopy. They determined that the risk of polyps reappearing was 17% lower in patients who took the calcium supplements and their average number of polyps was 24% lower.

Another study published in the Journal of the American Medical Association divided into two groups 70 people who’d had colon polyps removed. One group increased daily calcium to about 1,500 mg by consuming low-fat dairy products while the second group maintained normal diets. The researchers studied a variety of “biomarkers”—laboratory measures of human fluid or tissue samples—that are thought to be associated with tumor progression in the colon. They determined that the group that increased calcium consumption had a modest but significant change of the markers toward a more normal state. The addition of low-fat dairy foods, the researchers concluded, may be helpful as part of a comprehensive dietary regimen for chemoprevention in people at risk for colon cancer.

The Requirements

Calcium is important for maintaining bone strength. Calcium also helps muscles (including the heart) to contract, blood to clot, and nerves to send messages. Getting enough calcium, either through food or calcium supplements, can help prevent osteoporosis-related fractures, which number about 1.5 million per year in the United States.

But how much calcium do we need? A National Institutes of Health Consensus Panel recommends optimal daily calcium intake of 800–1,200 mg for children 1–10 years old, and 1,200–1,500 mg for young adults 11–24 years old. Adult men should have 1,000 mg daily up to age 64, and 1,500 mg daily at age 65 and over. Adult women should also have 1,000 mg daily, but should shift to 1,500 mg at 50 years of age and beyond. Women who are pregnant or lactating need 1,200–1,500 mg daily.

How Much Calcium Do YOU Need?

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<th>Group</th>
<th>mg/day</th>
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<tr>
<td>Children 1–10 years</td>
<td>800–1,200</td>
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<tr>
<td>Young adults 11–24 years</td>
<td>1,200–1,500</td>
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<tr>
<td>Adult men to age 64</td>
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<tr>
<td>Men age 65+</td>
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<tr>
<td>Adult women to age 50</td>
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<td>Women age 50+</td>
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<tr>
<td>Pregnant/lactating women</td>
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The Sources

Milk is probably the best dietary source of calcium because of the lactose (milk sugar) naturally in milk and the vitamin D added to it to enhance absorption of calcium through the gut. Yogurt is also an excellent source of calcium, though it contains no vitamin D. One cup of milk contains 300 mg of calcium, while one cup of nonfat plain yogurt contains 400 mg. Other calcium-rich foods are hard cheese, ricotta cheese, canned sardines, and vegetables such as kale, collard greens, Chinese cabbage, and broccoli.

Although obtaining calcium through food is preferable, calcium supplements are an option for increasing dietary calcium. While more research needs to be done to document the role of calcium in preventing colon cancer, the benefits of adding more calcium to our diets are many.

For more information, contact your physician or contact the M. D. Anderson Information Line:

(800) 392-1611 within the United States, or

(713) 792-6161 outside the United States.

May 1999

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Prostate Cancer Initiatives: Progress Through Collaboration

The multidisciplinary Prostate Cancer Research Program at M. D. Anderson was founded in 1995 by Andrew C. von Eschenbach, M.D., professor of urology, to encourage collaboration between researchers from different departments who are studying prostate cancer.

Research is divided into three areas: developmental therapy, headed by Department of Genitourinary Medical Oncology chair Christopher J. Logothetis, M.D., and Department of Urology chair David A. Swanson, M.D.; biology, headed by Department of Cancer Biology chair Isaiah J. Fidler, D.V.M., Ph.D.; and epidemiology/genetics, headed by Department of Epidemiology chair Margaret J. Spitz, Ph.D. A pathology core resource program is led by Timothy J. McDonnell, M.D., Ph.D., and Patricia Troncoso, M.D.

Developmental Therapy

Because prostate cancer preferentially metastasizes to bone, Drs. Logothetis and Swanson have focused on strategies that use combination chemotherapy and radiopharmaceutical agents to preferentially transport drugs to the bone marrow. These studies have been completed and have established a foundation for a comprehensive strategy of specific bone targeting therapy in prostate cancer. Further research on the biology of metastatic prostate cancer cells is being conducted by Dr. Fidler, David J. McConkey, Ph.D., Robert Radinsky, Ph.D., Nora M. Navone, M.D., Ph.D., Christos N. Papandreu, M.D., and Curtis A. Pettaway, M.D. Ann McNeill Killary, Ph.D. and Sue-Hwa Lin, Ph.D., are studying the role of tumor suppressor genes in prostate cancer.

Dr. Logothetis and Department of Urology Assistant Professor Louis Pisters, M.D., are testing intraprostatic therapies that rely on transrectal ultrasonography to identify the optimal target sites for treatment and guide the intraprostatic placement of gene vectors. In a recently completed phase I trial, 26 men received injections of a vector used to transport the tumor suppressor gene p53 directly into the prostate tumor. Of interest was the observation that after six weeks, 27% of the study participants had at least a 25% decrease in tumor size. In other work, Dr. Pisters and Radiation Oncology Associate Professor Alan Pollack, M.D., Ph.D., and Radiation Oncology Faculty Associate Lewis G. Smith, M.D., are employing transrectal ultrasonography for brachytherapy to plan uniform-dose distribution of radioactive seeds in the prostate. Dr. Pollack is also the principal investigator in a phase III randomized study comparing the efficacy of an intensity-modulated external beam radiotherapy boost with an iodine-125 implant boost following conformal radiotherapy for patients with prostate cancer.

Biology

In the Department of Cancer Biology, Dr. Fidler, Zhongyun Dong, M.D., Ph.D., and others reported recently that human prostate cancer cells engineered to produce interferon-beta by infection with a retroviral vector containing murine interferon-beta cDNA suppressed angiogenesis, tumor growth, and metastasis of human prostate cancer cells in nude mice by inhibiting tumor angiogenesis and activating host effector cells. In addition to the study of interferon-beta, funded by grants from the American Cancer Society and National Institutes of Health, the researchers have also applied for grants to fund prostate cancer therapy studies involving multiple cytokine genes and a combination of suicide genes and interferon-beta genes.

Epidemiology/Genetics

Research led by Dr. Margaret Spitz includes an ongoing study of the risk factors associated with prostate cancer progression. Preliminary analyses of data collected from 318 white men with prostate cancer that had extended beyond the capsule of the gland and 158 men with prostate cancer that had not extended beyond the gland capsule indicated that greater current weight and early adult weight gain, along with having less education, being unmarried, and having no prior prostate cancer screening, were significantly associated with increased risk of being diagnosed with high-volume disease. The data also suggest that measures of body circumference and the percentage of body fat could provide clues to understanding prostate cancer progression. A study led by Sara Strom, Ph.D., and funded by the U.S. Department of Defense is examining the role of DNA repair capacity and microsatellite instability in determining prostate cancer risk and susceptibility. An initial investigation of the association between DNA repair capacity and prostate cancer risk revealed that patients with prostate cancer have reduced expression of five DNA-repair related genes when compared with age- and ethnicity-matched controls. Using a newly developed phytoestrogen database, members of the Department of Epidemiology analyzed dietary intake data collected from 83 patients with prostate cancer and 107 healthy controls. The group with prostate cancer reported consuming more calories and saturated and total fat than the control group. While both groups consumed similar amounts of fruits and vegetables, the control group consumed larger amounts of foods containing phytoestrogens, such as refried beans, imitation bacon bits, cranberry juice, onions, and apples.

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