US TOO® PROSTATE CANCER EDUCATION & SUPPORT

HOT SHEET

OCTOBER 2004

"HEDGEHOG" SIGNAL DISTINGUISHES LETHAL FROM LOCALIZED PROSTATE CANCERS

Source: Johns Hopkins Medical Institutions

Johns Hopkins researchers have discovered a possible way to distinguish lethal metastatic prostate cancers from those restricted to the walnut-size organ.

If future studies show their test — measuring the level of activity of a signaling pathway called Hedgehog — can predict which prostate cancers will spread, the results could revolutionize decision making processes for prostate cancer patients, the researchers say.

Most prostate cancers grow slowly, making "watchful waiting" a common alternative to immediate surgical removal of the prostate. However, there's no sure-fire way to tell whose cancer will stay put in the gland, and whose will be aggressive and spread — a development that despite aggressive treatment is usually fatal.

In the September 12 advance online edition of Nature, the Hopkins researchers report that only three of 12 localized prostate tumors obtained at surgery had detectable activity of the Hedgehog signaling pathway. In contrast, all 15 samples of metastatic prostate cancers, donated at patients'

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SPECIAL FOCUS: THE PSA CONTROVERSY CONTINUES

STUDY SUGGESTS SCREENING PROCESS FOR PROSTATE CANCER IS UNRELIABLE

San Jose Mercury News
September 9, 2004

The most common screening tool for detecting prostate cancer - the PSA test - can be unreliable at predicting cancer risk in many men, a new Stanford University study suggests.

The exam needlessly causes many men who wouldn't die from their slow-growing prostate cancer to have their prostates removed, surgery that often leads to incontinence and impotence, the researchers said.

The Stanford findings, published Friday in the Journal of Urology, are likely to intensify the already heated debate over whether men concerned about cancer should undergo the simple blood test.

Some medical groups such as the National Cancer Institute have neutral stances on the screening for prostate cancer, neither recommending for or against it. Others, such as the American Cancer Society, believe doctors should offer PSA tests to men 50 and older. But whether a man

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PSA TEST SAVES LIVES AND SHOULD NOT BE ABANDONED, URGE PROSTATE CANCER EXPERTS

Canada NewsWire
September 13, 2004

The Prostate Cancer Research Foundation of Canada, the leading national organization devoted solely to eliminating prostate cancer, warns that a study published in the October issue of the Journal of Urology may discourage men from taking advantage of the most important early warning device for prostate cancer — the PSA (or prostate specific antigen) test.

"The PSA test is the most valuable tool we have for early detection of prostate cancer," said John Blanchard, President and CEO of the Prostate Cancer Research Foundation of Canada, and a recent prostate cancer survivor.

"The PSA test is not perfect. Nor is it designed to say whether a man has prostate cancer or not. The majority of prostate cancer specialists rely on the PSA test for early detection and the 95% cure rates that early detection offers," says Blanchard.

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US TOO PUBLICATIONS

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REPORT ON HORMONE REFRACTORY PROSTATE CANCER DISEASE MANAGEMENT

Researchers from the University of California, Davis, reported on current approaches in hormone refractory prostate cancer management.

P.N. Lara and colleagues wrote, "Prostate cancer is the most common cancer diagnosed in American mates, and is the second leading cause of cancer-related deaths. Most patients who develop metastatic disease will initially respond to androgen deprivation, but response is invariably temporary.

"Most patients will develop androgen-independent (hormone-refractory) disease that results in progressive clinical deterioration and ultimately death."

"This progression to androgen independence is accompanied by increasingly evident DNA instability and alterations in genes and gene expression, including mutations in p53, over-expression of Bcl2, and mutations in the androgen receptor gene, among others," they reported.

Lara and coauthors continued, "Treatment options for hormone-refractory disease include intensive supportive care, radiotherapy, bisphosphonates, second-line hormonal manipulations, cytotoxic chemotherapy and investigational agents.

"A post-treatment reduction in the level of prostate specific antigen (PSA) by 50% has been shown to correlate with survival and has been accepted by consensus as a valid endpoint in clinical trials."

"Chemotherapeutic agents such as mitoxantrone, estramustine, and the taxanes have yielded improved response rates and palliative benefit, but not improved survival," they wrote.

"Therefore," the researchers concluded, "current efforts must be focused on enrolling patients onto clinical trials of investigational agents with novel mechanisms of action, and on using survival, time to progression, and quality of life as end points in routine clinical practice."

Lara and colleagues published their study in Annales D Urologie (Current strategies in the management of hormone refractory prostate cancer. Ann Urol, 2004;38(3):85-102).

For additional information, contact P.N. Lara, University California Davis, Center Cancer Davis, Service Hematology & Oncology, 4501 X St., Sacramento, CA 95817 USA.

PSA CAN BE UNRELIABLE

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undergoes the screening should be decided only after careful consideration of risks and potential benefits associated with it, the society believes.

The PSA test detects elevated levels of a protein called prostate-specific antigen in the bloodstream. In screening for prostate cancer, men with PSA levels of 4 or higher are generally told their results are abnormal. But a PSA level of between 2 and 10 is most commonly due to a benign enlargement of the prostate, rather than cancer, said Dr. Thomas A. Stamey, the lead author of the Stanford study. And when the test does help detect cancer, the disease is not always lethal.

As a prostate cancer screening tool, the "PSA causes more harm than good. It causes so many men to have their prostate out for a cancer that probably wouldn't cause their death," Stamey said.

"The PSA era is probably over for prostate cancer in the United States," the Stanford researchers concluded.

The PSA test was first approved by the Food and Drug Administration in 1986 to aid in the care of patients already diagnosed with the disease. In 1994, the agency allowed the test to be used to help diagnose the disease.

An abnormal PSA test does not mean prostate cancer is present. Rather, it suggests a man could have the disease. Physicians then usually remove some of their patients' cells

through a needle biopsy to make a cancer diagnosis.

But research published in the New England Journal of Medicine in May found that some men who had normal PSA levels still had cancer. And high PSA levels have not always been associated with the disease.

There has been little debate that the PSA test is an imperfect screening tool for prostate cancer. But researchers are hoping for scientific proof that the tool is helping to bring down prostate cancer death rates or at least extending patients' lives. That evidence does not yet exist.

"Screening will pick up the disease earlier when it's potentially more curable. That's enough to sell most people on the test," said Dr. Howard L. Parnes, chief of prostate cancer research in the NCI's prevention division. "What does that really mean? You're finding things that may not need to be cured. You're also finding things that can't be cured."

Indeed, one in six men will get prostate cancer during his lifetime, according to the American Cancer Society. Other researchers have placed that number even higher, perhaps as high as one in four.

For many men, the cancer will never cause any symptoms, let alone kill them. One research study of men in their 20s killed on the streets of Detroit found that 8 percent had invasive prostate cancer. Only one man in 32 with prostate cancer succumbs to the illness, according to cancer society statistics.

The Stanford researchers argue that the disease is so ubiquitous that if you look for prostate cancer in an older man, you will find it. PSA tests can therefore cause unnecessary psychological stress.

Many men do not realize that an abnormal PSA test, and even a positive biopsy, is not a death sentence - and not necessarily cause for undergoing aggressive treatment, said Robert Hamm, a professor in the clinical decision-making program at the University of Oklahoma Health Sciences Center. Hamm drafted patient brochures that discuss prostate cancer risk and potential benefits from treatments. The handouts are online at www.fammed.ouhsc.edu/robhamm/Prostate/balsheet.htm.

Men considering undergoing a PSA screening should discuss the potential benefits and risks with their physician, Parnes believes. Men should also get regular rectal exams, which detect some prostate cancers.

For some men, taking the test and then doing something about it can bring peace of mind.

Victor Eastman, an East Bay chemist, works in a laboratory where more than 1,200 PSA tests are carried out each day. On a lark, he had a co-worker draw his blood and check his levels over the years. By the time he was 49, they had reached abnormal levels. A biopsy confirmed he had the disease.

"I would say PSA saved my life," said Eastman, who at his doctor's encouragement underwent surgery to remove his prostate.

"Without that, how would I know I had prostate cancer?" he asked. "There were no symptoms. It's not like breast cancer - you can't have self-examination. You don't even know it's growing."

TOP PROFESSOR CALLS PSA TEST USELESS. OTHER EXPERTS DISAGREE. SO WHAT SHOULD MEN DO?

Daily Mail - *September 14, 2004*

WHAT ARE THE PROBLEMS WITH THE TEST?

RESEARCH at Stanford University Medical School questions whether the PSA test should be used as a test for prostate cancer, suggesting it indicates nothing more than the size of the prostate. Professor Thomas Stamey says: 'The PSA era is over.' UK experts have been voicing concerns about the PSA tests for years because around two out of three men with a raised PSA level will not have prostate cancer, and an elevated PSA can be caused by relatively harmless changes in the body such as an enlarged prostate, prostatitis or a urinary infection. Even when the PSA test is followed by a biopsy that shows there is cancer, it is impossible to judge whether the type of cancer you have is dangerous. Prostate cancer is thought by many to be the only cancer that can be in the body for years without causing problems. Many experts worry that people have unnecessary surgery and radiation, which can cause impotence. Others argue that the test can miss prostate cancer, and that it is possible to have prostate cancer even if PSA levels are normal.

WHAT ARE THE ALTERNATIVES?

MILLIONS of pounds are being spent on researching a more accurate indicator for prostate cancer, but nothing has gone beyond the experimental stage.

SHOULD YOU HAVE THE TEST?

IF YOU have problems passing water or have blood in your urine, you should go to your GP to ask for a test. However, you should be aware of the pros and cons. Taking a PSA test could reassure you, if the results come back normal. However, the PSA test can read normal when there is cancer, giving false reassurance. It can lead to anxiety, when you don't have cancer, and to an unnecessary biopsy. If you have cancer, neither the PSA test nor the biopsy will tell you whether it is of the type to give you problems. Treatment of early cancers may not help you live longer. And the treatments carry risks of incontinence and erectile dysfunction.

WHAT THE EXPERTS SAY

Chris Eden, Consultant Urologist at North Hampshire Hospital Basingstoke, says: 'Professor Thomas Stamey's comments are sensationalist, and declaring "the PSA era is over" could set back the early diagnosis of prostate cancer by decades. 'The reality is that the PSA test is flawed, but it is still the best marker of prostate cancer that we have. 'The PSA test is allowing lots of people to have their prostate cancer diagnosed early, giving them a window of opportunity to act before it is too late.'

Professor Colin Cooper from the Institute of Cancer Research says:

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HEDGEHOG

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deaths, had Hedgehog activity, which was 10 to 100 times higher than the highest levels seen in localized tumors. It remains to be seen whether Hedgehog activity in localized cancers will predict the ability to be metastatic.

The Hedgehog pathway produces a well-known growth and development signal during embryonic and fetal stages. It is also active in some cancers, including prostate, pancreatic and stomach cancers and the brain tumor medulloblastoma, but the researchers' study is believed to provide the first evidence of its role in cancer's spread.

"If we can use Hedgehog activity to predict whether a tumor will metastasize, we will have a great diagnostic tool, but manipulating the Hedgehog signaling pathway may also offer a completely new way to treat metastatic prostate cancer," says David Berman, M.D., Ph.D., assistant professor of pathology, urology and oncology at Johns Hopkins. "Right now nothing works very well — you can help temporarily by cutting off testosterone, but the cancer always comes back."

In experiments with mice, fellow Sunil Kahadkar, M.D., showed that blocking the Hedgehog signal with daily injections of either a natural plant compound called cyclopamine or an antibody slowed and even reversed growth of highly aggressive rat prostate tumors implanted into the animals. Without treatment, the aggressive cancers, from a collection established by Hopkins' John Isaacs, Ph.D., killed the animals within 18 days. A low dose of cyclopamine gave the animals an extra week to 10 days, but at a higher dose, these aggressive cancers not only didn't metastasize, they actually disappeared and didn't return.

In a similar set of experiments using human prostate cancers implanted into mice, treatment with cyclopamine also caused those tumors to regress and not return — even months after treatment was stopped, the researchers report.

"Cyclopamine may not itself become an anti-cancer drug, in part because it's already in the public domain — it's been known since the mid 1960s as the cause of one-eyed sheep in the western U.S.," says Philip Beachy, Ph.D., professor of molecular biology and genetics in Hopkins' Institute for Basic Biomedical Sciences and a Howard Hughes Medical Institute investigator. "But our finding that cyclopamine inhibits Hedgehog signaling has provided the basis for drug companies' very active efforts to develop new mimics of cyclopamine."

Right now, prostate cancer is evaluated largely by levels of prostate specific antigen (PSA) circulating in the blood. However, the ranges associated with various potential diagnoses — non-cancerous growth, cancer, and aggressive cancer — are fairly rough guides. And even under a microscope, aggressive prostate cancer doesn't always look appreciably different from its wallflower counterpart.

In sharp contrast, levels of Hedgehog activity weren't even close between still-localized tumors removed during prostatectomies and those from lethal metastatic prostate cancers, which were collected as part of a research program run by G. Steven Bova, M.D., assistant professor of pathology, to try to figure out what makes them so deadly.

To investigate Hedgehog's role in metastasis, Karhadkar genetically engineered normal prostate cells to activate their Hedgehog signal. These cells then grew unchecked and formed aggressive tumors when implanted into mice, he found. He also discovered that triggering Hedgehog activity in a low-metastasizing rat prostate cancer line made it metastasize aggressively.

"Hedgehog isn't just making these cells grow and divide more, the signal is really converting them from being indolent to being highly invasive and dangerous," says Beachy.

Exactly how the Hedgehog signal is involved in other cancers, including pancreatic and stomach cancers and medulloblastoma, a childhood brain cancer, is still being worked out. Critical in normal embryonic development, the signal is supposed to be turned off when cells take on the "grown-up" identity of a differentiated cell type.

Karhadkar, Beachy and Berman — and a growing number of other scientists — point to the involvement in cancer of embryonic proteins and pathways like Hedgehog as evidence that aggressive cancer in particular might form not by accumulation of genetic errors in regular cells, but because a smaller number of errors occurs in a more primitive cell, what might be called a "stem cell," in the tissues. And it would be these "cancer stem cells" — transformed versions of the tissue's normal stem cells — that metastasize and travel through the body to form new tumors in distant places.

"Perhaps aggressive prostate cancers get started from a more primitive prostate cell or from a different initiating lesion than do prostate cancers that don't metastasize," says Beachy. "It's an idea we're exploring."

The research was funded by the National Institutes of Health, the Prostate Cancer Foundation, and the Howard Hughes Medical Institute. Authors on the paper are Karhadkar, Bova, Nadia Abdallah, Surajit Dhara, Anirban Maitra, John Isaacs, Berman and Beachy, all of Johns Hopkins; and Dale Gardner of the U.S. Department of Agriculture's Poisonous Plant Research Laboratory.

STUDY SHOWS IMPROVED 3-YEAR BIOCHEMICAL CONTROL OF RECURRENT PROSTATE CANCER

Cytogen Corporation announced the publication of a study evaluating the safety and efficacy of external beam radiation therapy aided by advanced molecular imaging with PROSTASCINT in recurrent prostate cancer patients following definitive surgical treatment.

Results from the study appear in the The Journal of Nuclear Medicine (Jani, AB. et al, "Radioimmunocintigraphy for Postprostatectomy Radiotherapy: Analysis of Toxicity and Biochemical

Control," The Journal of Nuclear Medicine, Vol. 45, No. 8, pp. 1315-1322).

"In this study, nuclear medicine physicians and radiation oncologists working together were able to show improved targeting of suspicious recurrent cancerous tissue in post-prostatectomy patients when PROSTASCINT imaging was used to guide radiotherapy treatment planning," said Michael J. Blend, PhD, DO, professor and director of the Section of Nuclear Medicine at University of Illinois at Chicago and coauthor of the study.

"PROSTASCINT was able to define a more precise clinical target volume without causing any significant increase to non-target tissue damage. These findings can serve as the basis for prospective studies in this area of investigation," continued Blend.

In this study, the records of 107 consecutive post-prostatectomy patients who received external beam radiotherapy were reviewed. From the original cohort of 107 patients, a group consisting of 54 patients was identified, which comprised patients for whom no PROSTASCINT scan was obtained (non- PROSTASCINT group). The remaining 53 patients had a PROSTASCINT scan (PROSTASCINT group).

The PROSTASCINT group was further subdivided into 40 patients for whom anatomical information derived from computed tomography (CT) imaging was fused with functional information obtained using single-photon emission computed tomography (SPECT) imaging with PROSTASCINT (PROSTASCINT fusion subgroup) and those 13 patients for whom no such fusion was performed (PROSTASCINT alone subgroup).

In both subgroups, a vessel registration technique developed at University of Chicago/University of Illinois was implemented to project the region(s) of prostate-specific membrane antigen (PSMA) expression as evidenced by uptake on the PROSTASCINT scan into the planning computed tomography (CT) scan to assist in defining the clinical target volume.

Biochemical failures (defined as two successive PSA rises to a level of greater than or equal to3D 0.2 ng/mL after a nadir) were identified to generate biochemical failure-free survival (BFFS) curves for each of the groups and subgroups. A small advantage in 3-year BFFS was observed in the PROSTASCINT group versus the non-PROSTASCINT group (80.7% vs. 75.5%); however, this advantage reached greater significance in the PROSTASCINT fusion subgroup versus the non- PROSTASCINT group (84.5% vs. 75.5%).

No significant differences in late toxicity were observed between any group or subgroup. However, acute gastrointestinal (GI) toxicity was higher in the PROSTASCINT group versus the non-PROSTASCINT group (P = 0.026), and acute genitourinary (GU) toxicity was higher in the PROSTASCINT alone subgroup versus the PROSTASCINT fusion subgroup (P = 0.050). Overall, most toxicity was grade 1 or 2; only one case of grade 3 toxicity and no cases of grade 4 or 5 toxicity were observed.

LYCOPENE CAN REDUCE LNCAP HUMAN PROSTATE CANCER CELL SURVIVAL

Lycopene can protect mammalian cells against membrane and DNA damage and might play a protective role against tumor promotion, study finds.

"We characterized the antioxidant and prooxidant effects of water solubilized lycopene at different concentrations using a prostate cancer cell line. Placebo was used as a control," scientists in the United States report.

"After 6, 24, and 48 hr incubation, LNCaP cells were harvested and used for each measurement. Cellular proliferation was determined using the MTT colorimetic assay. Lycopene inhibited cell growth in a dose-dependent manner and growth inhibition was 55% at 1 microM after 48 hr incubation," wrote E.S. Hwang and colleagues, University of Illinois, Department of Human Nutrition.

"The levels of 8-hydroxydeoxyguanosine/ deoxyguanosine (an oxidative DNA damage product) were significantly increased starting at 5 mcM lycopene after 24 and 48 hr incubation with no protection at the lower concentrations. Measurement of malondialdehye (MDA) for lipid peroxidation by HPLC system was significantly reduced at low concentrations of 0.1-1 microM," the researchers wrote.

"Clinically relevant concentrations of lycopene significantly reduced LNCaP cancer cell survival which can only partially explain by increased DNA damage at high lycopene concentrations of >5 mcM," they added.

The authors concluded, "Low concentrations of lycopene <5 microM acted as a lipid antioxidant but did not protect DNA. These results indicate that lycopene can protect mammalian cells against membrane and DNA damage and possibly play a protective role against tumor promotion associated with oxidative damage."

Hwang and colleagues published their study in Food Science and Biotechnology (Effect of lycopene on lipid peroxidation and oxidative DNA damage in LNCaP human prostate cancer cells. Food Sci Biotechnol, 2004;13(3):297-301).

For more information, contact P. Bowen, University of Illinois, Department of Human Nutrition, Chicago, IL 60612 USA.

MOLECULAR MARKERS AVAILABLE FOR DETECTION AND PROGRESSION OF PROSTATE CANCER

"Carcinoma of the prostate is the second leading cause of male cancer-related death in the United States. Better indicators of prostate cancer presence and progression are needed to avoid unnecessary treatment, predict disease course, and develop

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COMING SOON: NEW TOOL TO HELP PCA PATIENTS:

CAPSURE™ FOR PATIENTS TO LAUNCH THIS FALL

Dealing with prostate cancer is tough enough, but making decisions about treatment can often feel even tougher. Even with solid advice from a physician, decision-making can feel overwhelming. You may wonder about what other people in your situation have done and what they experienced. Or whether your experience is "normal." Yet, it's very difficult to find that type of information about more than a few friends, family or fellow support group members who have also been diagnosed.

That's how a unique program called CaPSURE' for Patients is aiming to help prostate cancer patients. Currently under development at the University of California, San Francisco, CaPSURE for Patients will make available to prostate cancer patients a database containing more than 11,000 prostate cancer case histories that physicians have been using for nearly a decade.

Established in 1995, CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) has been an important resource for urologists nationwide. It's a long-term, observational study that has amassed one of the most extensive sets of data available today on the treatment experiences of patients with prostate cancer. The database includes patients ranging from 40 years old to more than 90 who have been diagnosed with stage T1 to T4 prostate cancer offering a comprehensive picture of how urologists actually treat prostate cancer patients in the United States and the clinical and health-related quality of life outcomes that result.

CaPSURE was designed to support the decision-making processes of physicians, policy makers, and now patients by assembling and studying data that provide insight into:

- Patterns of clinical management across a broad patient sample
- The impact of prostate cancer on patients' well-being
- Real-world treatment outcomes in the care of prostate cancer
- New interventions, treatments, or technologies associated with improved outcomes in prostate cancer patients
- Benchmarks for treatments and outcomes on a national level
- Patient characteristics and treatment variables that are predictive of optimal or poor outcomes

The CaPSURE database offers an objective and realistic national picture of how urologists address prostate cancer and how their patients are benefiting from treatment decisions. Each case history contains:

- Comprehensive clinical assessment
- Method of diagnosis
- Clinical pathological staging
- PSA values at diagnosis and every patient visit
- Gleason score
- Positive margin status

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NEW CLUES ABOUT PROSTATE CANCER

Scientists have identified what may be the earliest step in the development of prostate cancer. The researchers bred mice lacking a single copy of a gene known to suppress tumors and found the animals developed a precancerous condition similar to the earliest stages of human prostate cancer. The study appears in the Sept. 1 issue of Cancer Research.

"We've known for a long time that a class of genes called tumor suppressor genes are usually inactivated or somehow their function is lost in cancers, including prostate," said study author Norman Greenberg, a professor of clinical research at the Fred Hutchinson Cancer Research Center in Seattle.

His team focused on a tumor suppressor gene called the Rb gene, known to be defective in a variety of cancer types, including up to 60 percent of human prostate cancers. The Rb and other tumor suppressor genes normally work to keep cells dividing at a healthy pace.

Traditional thinking has it that there are usually two copies of these tumor suppressor genes in each healthy cell, Greenberg said, and you would need to lose both copies for a tumor to appear. But the study with mice proved otherwise, he said.

Using genetically engineered mice, the researchers were able to show that lacking just one copy of the Rb gene was enough to give the mice a condition akin to the earliest stages of human prostate cancer, Greenberg said.

"If they lost the second copy it was no more severe," he said of the cancer that followed. "But losing one copy was enough to get it going."

There are no immediate practical applications to the research, Greenberg said. But the hope is that eventually tests can be developed to distinguish between men who have only Rb mutations and those who have additional genetic defects associated with prostate cancer, such as the loss of the p53 tumor suppressor gene. That knowledge could help doctors decide when or whether aggressive treatment is needed, he said.

Hudak Recognized for Outstanding Service To The Prostate Cancer Community

Jane Hudak, RN, DNSc, recently received the Us TOO citation for distinguished service as Patient Counselor/Educator at the Center for Prostate Disease Research at Walter Reed Army Medical Center. Dr. Hudak was recognized for her expert and empathatic support of men diagnosed with prostate cancer and their families. As advisor to the Walter Reed Chapter, she was largely rsponsible for increasing the chapter's meeting schedule from four per year to 28 per year with a total annual attendance of 700 persons. She also developed and expanded a lending library regarding prostate cancer that is an important source of information to chapter members. Furthermore, she has developed a cadre of chapter volunteers who provide outreach education support to the local community. Congratulations to Jane Hudak on the occasion of Us TOO recognition of her sterling efforts in the fight against prostate cancer.

L to R: Dr. David McLeod, Director, Center for Prostate Disease Research, Jane Hudak, Vin McDonald ,WRAMC Us TOO

"We think this [loss of the single copy of the Rb gene] may be the earliest genetic lesion," Greenberg said. "It may in fact represent one of the earliest changes."

Based on what is known now, for instance, if a man had only an Rb lesion, "watchful waiting could be a good course," Greenberg said, referring to the decision not to perform treatment on prostate cancer because it appears to be slow growing.

Dr. Len Lichtenfeld, deputy chief medical officer for the American Cancer Society, said the new finding could prove promising. "It's fair to say they have honed in on a genetic change that appears to play a role. We have to emphasize that this experiment they did was in mice, not men."

Even so, Lichtenfeld said, the idea that the development of prostate cancer is a series of steps, not a single genetic malfunction, parallels what has been discovered about colorectal cancer. The new finding about prostate cancer "has to be taken forward and studied more, to see if we can develop a practical test to see if the change can be detected," he said.

But one of the treatment challenges, particularly for prostate cancer, is to determine which cancers will be aggressive and which won't, Lichtenfeld added. Focusing on the genetic changes might someday help doctors do that better, he said.

Molecular Markers

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more effective therapy," investigators in the United States report.

"Numerous molecular markers have been described in human serum, urine, seminal fluid, and histological specimens that exhibit varying capacities to detect prostate cancer and predict disease course. However," wrote J.V. Tricoli and coworkers, "to date, few of these markers have been adequately validated for clinical use."

"The purpose of this review," said researchers, "is to examine the current status of these markers in prostate cancer and to assess the diagnostic potential for future markers from identified genes and molecules that display loss, mutation, or alteration in expression between tumor and normal prostate tissues."

The authors continued, "In this review we cite 91 molecular markers that display some level of correlation with prostate cancer presence, disease progression, cancer recurrence, prediction of response to therapy, and/or disease-free survival.

"We suggest criteria to consider when selecting a marker for further development as a clinical tool and discuss five examples of markers (chromogranin A, glutathione S-transferase pi 1, prostate stem cell antigen, prostate-specific membrane antigen, and telomerase reverse transcriptase) that fulfill some of these criteria."

"Finally," Tricoli concluded, "we discuss how to conduct evaluations of candidate prostate cancer markers and some of the issues involved in the validation process."

Tricoli and colleagues published their study in Clinical Cancer Research (Detection of prostate cancer and predicting progression: Current and future diagnostic markers. Clin Cancer Res, 2004;10(12 Part 1):3943-3953).

For additional information, contact J.V. Tricoli, NCI, Diagnostic Research Branch, Cancer Diagnosis Program, 6130 Execut Blvd., Execut Plaza N, Suite 6044, Rockville, MD 20852

WHAT SHOULD MEN DO?

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'THE PSA test is a useful indicator, but it is hard for men to know what to do with the results. Don't assume a high PSA level means cancer, and if you do have cancer you must think carefully about whether to have treatment because of the side-effects. 'It is too much of an overstatement to say "the PSA era is over", but we do desperately need a second test that will indicate which prostate cancers are life-threatening and which aren't.'

PROSTATE CANCER MOLECULAR TEST MAY ADDRESS LIMITATIONS OF TRADITIONAL TESTING

Molecular testing for a new, highly specific prostate cancer marker may help address some of the well-known limitations of current prostate cancer detection, according to a 517-patient study published in the Sept 1 issue of the journal UROLOGY.

In the multi-center study, an investigational molecular test called uPM3 gave a correct positive or negative result for the presence of prostate cancer 81% of the time. The uPM3 test detects the presence of a new prostate cancer gene marker called PCA3 in urine. In contrast, traditional prostate cancer detection by measuring total prostate specific antigen levels, or tPSA, had an overall accuracy of 43% or 47% in the study, depending on the cut-off level used.

"The uPM3 test is an exciting new urine test to help men make critical decisions regarding early detection for prostate cancer," said Alan Partin, MD, PhD, professor of urology at Johns Hopkins Medical Institute. Partin was not involved in the study.

In the UROLOGY study, the researchers collected urine samples following a digital rectal exam from 517 men undergoing prostate biopsies. The uPM3 test had a positive predictive value of 75%, compared to 38% for tPSA. This means that 75% of patients actually had prostate cancer (as confirmed by biopsy) when the uPM3 test was positive.

In addition, the uPM3 test had a negative predictive value of 84%, compared to 80% for tPSA at a cut-off of 4.0 ng/ml, which means that 84% of patients did not have cancer when the test was negative.

David Bostwick, medical director of Bostwick Laboratories, and a noted expert on the pathology of prostate cancer, stated: "Previous studies have shown that the PCA3 gene is one of the most specific genes yet found to be associated with prostate cancer. It is over-expressed in 95% of cancers tested, at a median level 66 times greater than in adjacent non-cancerous tissue."

"This study shows that identifying this gene in cells from the urine of men undergoing biopsy may be an important new tool for determining which men have this all-too-common disease," Bostwick continued.

PSA SAVES LIVES

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"The PSA test is a very accurate indicator of cancerous growth in the prostate," said Dr. Laurence Klotz, Chief of Urology, Sunnybrook and Women's College Health Sciences Centre in Toronto, and Chair of the Foundation's Scientific and Medical Advisory Committee. "The PSA test provides physicians with an early indication of the cancer, and leads to other tests for the disease, including ultrasounds, biopsies and the Gleason score which evaluates how aggressive the cancer is."

"With this diagnostic tool, we can catch the cancer earlier and increase our number of treatment options," said Klotz.

CAPSURE FOR PATIENTS

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- Initial and secondary treatments used
- Results of all lab tests including digital rectal exams, biopsies, and other diagnostic tests

In addition to the clinical data provided by physicians, patients contribute data about their quality of life and satisfaction with care. The patient questionnaires cover quality of life questions such as urinary and sexual function, lifestyle modification needed after diagnosis or treatment of prostate cancer, and questions about the patient's satisfaction with his medical care.

CaPSURE for Patients (CFP) will feature a web site designed to provide prostate cancer patients with access to this wealth of information and tools to help them use it to make informed decisions about their treatment. Patients will be able to access the rich CaPSURE dataset to understand treatment norms and will also have the ability to securely enter and track their own outcomes data for comparison against CaPSURE benchmarks.

According to the team developing this new patient resource, CaPSURE for Patients should be launching in the upcoming months.

For more information about CaPSURE, please visit the Web site at http://www.capsure.net.

The CaPSURE project is managed by the Urology Outcomes Research Group of the UCSF Department of Urology, San Francisco, Calif..

The CaPSURE web application and database are managed by Secure Outcomes of Santa Clara, Calif. The entire CaPSURE effort is underwritten by TAP Pharmaceutical Products Inc.