US TOO®
PROSTATE CANCER
EDUCATION & SUPPORT

HOT SHEET

APRIL 2004

5 IN 5: TAKE FIVE MINUTES FOR FIVE QUESTIONS ABOUT PROSTATE CANCER

Mark A. Moyad, MD, MPH

Empower Yourself in Five Minutes

Prostate cancer is the most common cancer diagnosed among American men. But this does not have to be intimidating, as more effective treatment options are available today than *ever* before. Whether you have recently been diagnosed with prostate cancer or you are currently or have been treated, asking the right questions will help you achieve the best possible result. Knowledge is power. To best evaluate your situation, gather information from a variety of credible resources. A great place to start is your doctor and other health care professionals. It only takes five minutes to ask five very important questions.

For Newly Diagnosed Men

Before determining a specific treatment, your doctor will determine your situation using several tests. For example, the results of your prostate-specific antigen (PSA) blood test(s), Gleason score pathology report (which determines how aggressive your cancer is), and cancer stage tests (which determines how far your cancer has spread) will all help to guide you to choose the best possible treatment.

After you receive the results of your tests, you should talk with your doctor(s) about your situation and the possible treatment options available, focusing on options that have been proven safe and effective for prostate cancer similar to yours.

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WE'RE LOSING THE WAR ON CANCER, REPORTS FORTUNE MAGAZINE; SPECIAL INVESTIGATION FINDS ALARMING SYSTEMIC FAULTS — AND SUGGESTS RADICAL SOLUTIONS

America is losing the war on cancer — and it is time to overhaul the battle plan, reports FORTUNE magazine in a groundbreaking special investigation. FORTUNE executive editor and Hodgkin's disease survivor Clifton Leaf reports that the percentage of Americans dying from cancer is about the same as it was in 1970, and reveals systemic problems that are making cancer so difficult to defeat. "It is like a Greek tragedy," says Intel Chairman and prostate cancer survivor Andy Grove. "Greek Tragedy is the perfect term for it. Heroic figures battling forces greater than themselves. Needless death and destruction — and it doesn't have to stay this way," writes Leaf, who offers a series of radical changes to turn the battle around. The story appears in the March 22 issue of FORTUNE.

Leaf begins by showing how, in the last three decades, researchers and scientists have amassed an enormous

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US TOO PUBLICATIONS

In addition to the Hot Sheet, ***Us TOO*** also publishes a FREE e-mail based news service providing updates on the latest prostate cancer related news. To subscribe or link to the archives simply visit the ***Us TOO*** Website: www.ustoo.org

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NEW MARKER FOR PROSTATE CANCER FOUND

Testing for a protein called EPCA that signals the early presence of prostate cancer could help doctors detect the disease up to five years sooner than it can now be diagnosed.

That good news is reported in the March issue of the Journal of Urology.

EPCA is a marker protein that indicates the earliest cell changes that occur during cancer development.

The study authors suggest that testing for EPCA could serve as an adjunct to the current diagnostic approach — repeat needle biopsies — used for men with elevated prostate-specific antigen (PSA) levels. PSA is a substance released by the prostate gland that can be detected in blood. PSA is commonly used to check for signs of prostate cancer and other prostate problems.

"One of the problems with testing for levels of PSA as an indicator of prostate cancer is that PSA levels often fluctuate up and down, making it difficult to know for certain whether a man has prostate cancer without performing multiple biopsies over time," study author Robert Getzenberg, a professor of urology, pathology and pharmacology at the University of Pittsburgh School of Medicine, says in a prepared statement.

"By testing for EPCA in men with high levels of PSA, we may be able to detect the presence of prostate cancer earlier, before it is discoverable by biopsy, saving patients the fear and stress of repeat procedures and enabling us to treat the disease sooner," Getzenberg says.

He and his colleagues compared 29 tissue samples from men with prostate cancer who had initial negative biopsies with tissue samples from 27 healthy men. They found the samples from the negative biopsies of men who were later diagnosed with prostate cancer expressed EPCA. They did not detect EPCA in the biopsy sample of men who remained free of prostate cancer.

The study also found EPCA wasn't confined to the tumor in men with prostate cancer. The protein was also expressed throughout the prostate. That indicates that EPCA may be useful as a prognostic marker for prostate cancer.

Researchers are now conducting a multi-center study to further assess EPCA and its potential use as a biomarker for prostate cancer.

PHASE II PROSTATE TRIALS USE PRE-PROSTATECTOMY STUDY DESIGN TO IDENTIFY PROMISING PREVENTION AGENTS AND BIOMARKERS

NCI Cancer Bulletin
February 10, 2004

A short window of opportunity between the histologic diagnosis of prostate cancer and definitive treatment (prostatectomy) is being used in several phase II prostate cancer trials to identify promising prevention agents and biomarker end points. The goal is to obtain key information about the effects of novel study agents on intermediate end point biomarkers (IEBs) and about the distribution of the agent in prostate tissue.

Because prostate cancer has a long natural history, IEBs such as serum markers (e.g., prostate-specific antigen [PSA]), histopathological markers, or tissue-based markers are used to find preliminary evidence of efficacy or biologic activity in phase II trials. Evaluation of these agents may lead to the next generation of phase III chemoprevention trials for prostate cancer.

In this "pre-prostatectomy" trial design, men with early-stage prostate cancer are randomly assigned to receive the study agent or placebo for about 3 to 6 weeks between a diagnostic biopsy and a prostatectomy. Investigators have direct access to prostatic tissue from

transrectal ultrasound (TRUS)-guided biopsies and the entire gland following surgery, to systematically assess the biologic activity of agents in the target organ.

This clinical model has the advantage of allowing rapid screening of agents in relatively small, randomized, placebo- controlled pilot trials with 60 subjects or less and that are conducted within the standard of care of patients scheduled for radical prostatectomy, according to Dr. Ronald Lieberman, program director in NCI's Division of Cancer Prevention (DCP) Prostate and Urologic Cancer Research Group.

A variety of agents are being tested with this phase II trial design, including androgen receptor antagonists, antiinflammatory agents (selective COX-2 inhibitors), vitamin D analogs, and micronutrient antioxidants. (See table.)

"The phase II pre prostatectomy cancer prevention trials are a practical and efficient way to determine whether the chemopreventive agent concentrates in a man's prostate and has a biologic effect there. This is an important step in selecting agents for more definitive prostate cancer prevention trials," said DCP director Dr. Peter Greenwald.

Investigational Agents for Prostate Cancer Prevention Using Phase II Pre-Prostatectomy Trial Design

Category	Agent	Investigator
androgen receptor antagonists (antiandrogens)	bicalutamide	Donald Urban, *University of Alabama*
polyamine synthesis inhibitors	DFMO	Donald Urban, *University of Alabama*
selective estrogen receptor modulators (antiestrogens)	toremifene	Joel Nelson, *University of Pittsburgh Cancer Institute*
micronutrient antioxidants	vitamin E, selenium, lycopene	Jeri Kim, *M. D. Anderson Cancer Center* N.B. Kumar, *H. Lee Moffitt Cancer Center*
soy-derived agents	isoflavones, genistein	N.B. Kumar, *H. Lee Moffitt Cancer Center* Omer Kucuk, *Wayne State University*
anti-inflammatory selective COX-2 inhibitors	celecoxib	Michael Carducci, *Johns Hopkins University*
vitamin D analogs	doxercalciferol	George Wilding, *University of Wisconsin*
novel proapoptotic inducers	sulindac sulfone	Brad Leibovich, *Mayo Clinic*

One of these studies, for example, uses high-grade prostatic intraepithelial neoplasia (HGPIN) as a primary end point for toremifene. Since there is growing evidence that estrogens play a role in the development of prostate cancer, this study is evaluating the effects of toremifene, a selective estrogen receptor modulator. The trial is comparing the percent of HGPIN present in the radical prostatectomy tissue of patients with stage I or II adenocarcinoma of the prostate who were treated with toremifene orally once a day for up to 6 weeks, against the tissue of patients who received observation alone prior to prostatectomy.

Toremifene is the lead chemopreventive agent being developed by GTx, Inc., a Tennessee-based biotechnology company that focuses on men's health issues and is collaborating with DCP on this phase II study. Dr. Joel Nelson, principal investigator for the toremifene study at Hillman Cancer Center at the University of Pittsburgh Cancer Institute, noted that studies using this trial design are examining human tissues after defined exposure to a chemopreventive agent. The 4- week to 8-week lag time from diagnosis of prostate cancer until surgery provides a "unique window of opportunity to examine alterations in the prostate after exposure," he said.

Assuming that a chemopreventive agent will induce alterations after short exposure, the strategy is to identify those alterations and extrapolate to a longer exposure, according to Dr. Nelson. This is significantly easier and more cost effective, particularly in this case when there are so many compelling chemopreventive agents. But the challenges of the model, using alterations in tissues as evidence for chemoprevention, remain unproven, he noted. The studies are clearly hypothesis generating, yet they must start somewhere, he stressed.

Dr. Jeri Kim, assistant professor in the Department of Genitourinary Medical Oncology at The University of Texas M. D. Anderson Cancer Center, completed the first phase II trial using this model to study selenium and vitamin E, recruiting 48 patients in 18 months. (See "A conversation with…." on p8) The trial used the same regimen currently being used in the Selenium and Vitamin E Cancer Prevention Trial (SELECT) to see if researchers could identify potential surrogate end point biomarkers in that large study. The analysis is still ongoing.

Dr. Lieberman noted that the preprostatectomy clinical model provides a way to evaluate both the structure/ anatomy of the epithelial compartments (i.e., normal, precancer, and cancer) and the biology/function (specifically, the interface between the epithelium and stroma), which in turn allows investigators to assess the cellular, molecular, and biochemical effects of the experimental agent.

"Furthermore, effects on biomarker modulation can be correlated with changes in histology, proliferation, apoptosis, angiogenesis, and specific molecular targets related to the presumptive mechanism of action(s) of the agent," Dr. Lieberman added.

Evaluating agents for prostate cancer prevention is a major DCP research focus. For instance, the SELECT study has been enrolling a record number of participants to determine if these two dietary supplements can protect against the clinical diagnosis of prostate cancer and the phase III Prostate Cancer Prevention Trial (PCPT) has shown that finasteride can reduce the chances of getting prostate cancer by nearly 25 percent. ***(Also see "A conversation with Dr. Jeri Kim" on p8)***

WE'RE LOSING THE WAR ON CANCER

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amount of knowledge essential to the war on cancer. But after three months of intensive meetings with leading cancer specialists and top officials throughout the country, Leaf reports that a dysfunctional "cancer culture" has made the search for knowledge "an end unto itself rather than a means to an end." The result is a research and grant culture focused on finding the tiniest improvements to treatment rather than genuine breakthroughs.

Cancer research's focus on shrinking tumors in fatally ill patients is Leaf's most revealing example of this systemwide failure. The bulk of research money and energy is spent on this goal and not on understanding and arresting the process of metastasis — which kills an incredible 90% of patients. In fact, according to a FORTUNE examination of National Cancer Institute grants going back to 1972, less than 0.5% of study proposals focused on metastasis. Of nearly 8,900 NCI grant proposals awarded last year, 92% didn't even mention metastasis. Consequently, Leaf reports, "Pharma companies don't concentrate on solving the problem of metastasis (the thing that kills people); they focus on devising new drugs that shrink tumors (the things that don't)."

Leaf also points to the preclinical model for drug testing and development, which depends on lab mice, as another major flaw in the war on cancer. According to scientists, these models have very little predictive power for the treatment of human disease. Despite genetic and organ-system similarities, humans and mice have key differences in physiology, tissue architecture, metabolic rate, immune system function and molecular signaling. Tumors in mice can't mimic cancer's most maddening trait in humans, its quick-changing DNA — a characteristic that leads over time to staggering complexity in the most deadly tumors. And there is a very real possibility that reliance on this flawed model has caused researchers to pass over drugs that would work on humans.

"A fundamental problem which remains to be solved in the whole cancer research effort is that the preclinical models of human cancer, in large part, stink," Robert Weinberg, MIT biology professor and winner of the National Medal of Science tells FORTUNE.

All these failures come to a head, says Leaf, in the clinical trial — a rigidly controlled, three-phase system for testing new drugs and other procedures in humans. "The process remains the only way to get from research to drug approval — and yet it is hard to find anyone in the cancer community who isn't maddeningly frustrated by it," he reports.

In the end, Americans have spent — through taxes, donations and private R&D — approximately $200 billion to fight cancer since the war on cancer began in 1971. Yet even as research and treatment have intensified, cancer's annual death toll has risen 73% — over one and a half times the growth of the U.S. population. By contrast, deaths from heart disease and stroke have slowed dramatically.

The FORTUNE report concludes with a proposal for a radical overhaul in how America fights the war on cancer, including a transformation in the way the NCI funds research, a consolidation of the federal war chest into one bureaucracy, from five; and an overhaul of the FDA drug-testing and approval process. "For the nation to finally turn the tide in this brutal war, however, we have to collectively change the culture of the cancer community to one that embraces a coordinated assault on this disease," concludes Leaf. "Science now has the knowledge and the tools; we need to act."

YOU CAN HELP MAKE A DIFFERENCE TOWARD ELIMINATING THE SUFFERING AND DEATH DUE TO PROSTATE CANCER

Dr. Andrew von Eschenbach, Director, National Cancer Institute of the National Institutes of Health has asked for your opinion. This is what he has asked:

> For more than 30 years, we have been dreaming about eradicating cancer, while becoming progressively more frustrated by witnessing the toll that cancer takes. But we have stayed the course, and through our continued commitment of financial and intellectual capital, cancer is no longer mysterious. We have new insights into its vulnerability.
>
> We want to encourage you to provide input on any area in which you have knowledge , expertise or interest. We hope your suggestions will include responses to questions such as the following:
>
> - Where within this myriad of priorities and initiatives, are the most compelling opportunities for advancing toward our Challenge Goal?
> - Where are the largest research gaps within these priority areas that, if not filled, will prevent us from achieving our Goal?
> - If we cannot do it all, which efforts will be the most critical for moving toward our Goal?
> - What are some innovative ways in which we can increase synergism and leverage limited resources along the way to achieving out Goal?
>
> Today, we still may not be able to "cure" cancer, but we can now implement a comprehensive strategy to

preempt the onset and progression of the disease. Where previously we have failed, we can now succeed, not in the elimination of cancer but in the elimination of the outcomes of cancer - the suffering and death. To achieve this, we must plan for success. So, as director of the National Cancer Institute, I have issued a challenge: to eliminate the suffering and death from cancer, and to do so by 2015.

There is an initiative to identify public health and medical interventions that prevent, detect and predict cancer, and to promote the rapid and full adoption of these measures for the benefit of all. Another initiative is focused on overcoming the unequal burden of cancer that is borne by various population groups in our nation.

Finally, and most importantly, I will be releasing drafts of these initiatives early in 2004 and asking for input from the entire community. Together, we will find the common ground necessary to reach the challenge goal. A world in which the burden of cancer has been eliminated is no longer a dream; it is a vision taking shape as a plan. Let's work together to make that plan a reality.

Andrew C. von Eschenbach, M.D.
Director, National Cancer Institute

Respond by email not later than April 16, 2004 to bypassreview@mail.nih.gov

RE: NCI Challenge Goal to the Nation:
"Eliminating the suffering and death due to cancer by 2015"

As a knowledgeable prostate cancer survivor, the following are my suggestions on what it will take to help reach the NCI Challenge Goal:

(INSERT YOUR IDEAS HERE!)

Here are three sample suggestions from Bill Blair, Chair of the Us TOO Scientific Advisory Panel of the types of activities that might be proposed in response to Dr. von Eschenbach's request:

1. Explore the role of dietary modifications for cancer prevention, promotion and progression with publication of guidelines for the patient population.

2. Evaluate the efficacy of Herbal supplements that are percieved by Cancer patients as beneficial,ie PCPlus,Prostasol, Xyflamend etc.

3. Create a "Blue Ribbon" panel of experts made up of expert scientists, physicians and knowledgable patients to determine which of the many options available will meet the criteria for reduction of suffering and death in the immediate future with communication of their findings to the public.

OBESITY DRUG INHIBITS PROSTATE TUMOR GROWTH

The Burnham Institute's Jeffrey Smith, Ph.D., has discovered that orlistat, commonly prescribed as an anti-obesity drug, has a positive side-effect: it inhibits cancer growth. Dr. Smith made this discovery using an activity-based proteomics screening technique developed in his laboratory that makes it possible to identify active targets and simultaneously screen for their inhibitors. These results are published in the March 15 issue of Cancer Research.

The metabolism of a tumor cell is different from its normal counterpart cell. Scientists have long suspected that metabolism is connected to tumor progression. Dr. Smith and co-workers designed a proteomics screen based on monitoring the activity of a family of enzymes-serine hydrolyases-involved in metabolism. They used their screen to compare normal prostate cells with prostate cancer cells and discovered that the prostate cancer cells are affected by an increased activity of fatty acid synthase. Fatty acid synthase is the enzyme that converts dietary carbohydrate to fat.

The screen also identified orlistat, marketed by Roche as XenicalT, as an inhibitor of fatty acid synthase.

These discoveries, made in vitro, held true when tested in mice. When they administered orlistat to mice bearing prostate tumors, the Smith laboratory discovered that the drug was able to inhibit tumor growth. Further experiments confirmed that orlistat has no effect on normal prostate cells and no apparent side effects in the mice; it acts specifically on fatty acid synthase.

Additional screening of breast cancer and colon cancer cells revealed that fatty acid synthase activity is upregulated in these tumors, as well, presenting the possibility of designing new treatments for these cancers based on inhibiting the enzyme's activity with orlistat or a new drug based on orlistat's inhibitory activity.

Orlistat was originally developed as an inhibitor of pancreatic lipase. Pancreatic lipase is a member of the same enzyme family—the serine hyrdolases-used in Smith's screening. It is involved in processing of fats in the digestive tract, which is how the drug prevents adsorption of dietary fat.

The method developed by Dr. Smith represents a quantum leap in drug discovery. So-called "activity-based" proteomics screening is a new frontier in medical research, based on applying information gleaned from the human genome project. The ability to compile a comprehensive profile of a potential drug's activities, revealing unintended activities along with the intended behaviors targeted by the drug, offers a systematic way to simulate how a drug will work, before it is actually tested in animals and humans.

Given the time and cost inherent in developing new treatments, activity-

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FIVE MINUTES FOR FIVE QUESTIONS

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Question 1: What types of treatments are available for prostate cancer?
You and your physician will determine the best options based on a number of considerations, including the progression of your disease. Alternatives include:

Surgery — The goal of surgery is to remove the cancer. There are several different surgical options, appropriate for different stages of prostate cancer.

Radiation – Radiation therapy involves exposing cancer cells to high doses of radiation with the goal of killing the tumor. Two types of radiation (brachytherapy and external beam radiation) are most typically used to kill prostate tumors. External beam radiation therapy treats the prostate and other selected tissues with a carefully targeted beam of radiation administered from machines outside the body. Refined focus is even more available with 3-D Conformal Technique and Intensity Modulation (IMRT) radiation therapies. With brachytherapy, tiny radioactive seeds (each about the size of a grain of rice) are implanted into the prostate through a surgical procedure. Other less widely available types of radiation therapy – such as proton beam – may also be available to treat your prostate cancer.

Hormonal Therapy — Decreasing the production of testosterone slows cancer growth. This is the first line of treatment for patients with advanced prostate cancer and for those whose cancer has not responded to curative treatment options (radiation, surgery, etc…) Drugs called luteinizing hormone-releasing hormone agonists (LH-RHa) are prescribed to shrink the tumor, slow the spread of cancer and to alleviate symptoms. Anti-androgen drugs are also used to block the small amount of testosterone produced by the adrenal glands.

Chemotherapy – Chemotherapy is a common term used to describe cytotoxic drugs known to destroy cancer. These drugs typically target and destroy cells that divide rapidly, traits that define some cancerous cells but also some healthy ones. To destroy cancer cells while minimizing the harm to healthy ones, the drugs are carefully controlled in dosage and frequency. As with most therapies, chemotherapy also has some specific side effects which you should discuss with your doctor.

Cryotherapy / Cryoablation – The goal of 'Cryo' is destroying them – through the placement of several ultrasound-guided probes into the prostate and 'freezing' the prostate gland and surrounding tissues.

Watchful Waiting — Careful observation without other immediate treatment may be an appropriate option for men with less aggressive, typically slowly growing tumors.

Question 2: What are the side effects and risks associated with these treatment options?
Again, you and your doctor should discuss treatments that make sense for your situation. Ask about the specific advantages and disadvantages of all potential treatments. This should include side effects and other possible complications, how often they occur and if they can be effectively treated and how. Therapies for many side effects are widely available. In some situations your doctor may recommend combining treatments. If this is the case, you should always ask about the combined advantages and disadvantages of using more than one treatment.

Question 3: Is my current treatment making progress against my prostate cancer?
Ask your doctor if your current treatment is working or producing the expected results. If not, why? Has your cancer progressed or returned / recurred? Relying on treatments with a long history of being safe and effective against prostate cancer – and being sure to follow the treatment plan that you and your doctor have developed - can be a strong defense against the disease. Also be sure that you keep your physician informed of any medications you may be taking – including over-the-counter products and dietary supplements, and consider modifying your diet and exercise to a more 'heart healthy' program which can also benefit your fight against prostate cancer.

Question 4: Why are you considering changing therapies / treatments for me?
During or after your treatment, including hormonal therapy, your doctor may recommend changing or adding something else to your therapy. It is very important that you understand exactly why she or he is offering this recommendation.

There are lots of reasons your doctor may recommend a different therapy or treatment option. It may be to avoid side effects of the current treatment, or cancer may have spread to a point that requires a change or addition to the current treatment. Some changes may be suggested because of the personal experience or preference of the doctor. Again, ask your doctor about the specific reasons for this new recommendation and remember that the final decision on any treatment plan is yours. You need to feel comfortable that you understand what your doctor hopes to accomplish with the new therapy that the current one is not giving you. What other side effects can be expected with this new treatment?

Question 5: How is this therapy – or even this medication - different from my current therapy?
If your doctor recommends a change in your treatment plan, you should ask how this new treatment is similar to or different from your current one. Does it attack the prostate cancer in a different way? Are the side effects similar? What new side effects can be expected? What side effects can be reduced or eliminated? Your doctor may recommend a change such as going from radiation therapy to hormone therapy, or having radiation after surgery. However, your doctor may also recommend a not-so-obvious change, like simply changing the brand of your medication or the method in which it is administered. In every case you

have a right – and a responsibility – to understand and approve the change and the impact it will have on your treatment - and your quality of life.

For an objective overview of commonly available treatment options and therapies please visit the Us TOO website: www.ustoo.org.

Putting It All Together and Moving Forward

Remember, prostate cancer is treatable, and you ultimately are the person who controls your treatment decisions. While these five questions are a good start, don't limit yourself. You, your spouse or significant other along with your doctor are a team. Ask a lot of questions, even the difficult ones, to ensure you have the best chance of beating this disease. Remember – the final decision maker on the team is ultimately you, the patient. To best make that decision you need to be confident and well informed about the options and the reasons for the decisions being made. Make good use of your right to second opinions from expert specialists throughout your decision process.

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OBESITY DRUG & PCA

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based proteomics screening opens up a new route for finding effective treatments based on monitoring basic cell behaviors, such as metabolism or respiration.

Proteomics screening is an efficient way to determine proof of concept needed before a potential treatment can be refined for clinical trials: in a matter of weeks, Dr. Smith was able to glean the initial discovery that linked excessive fatty acid synthase activity with flawed metabolism in cancer cells, and identified orlistat as its inhibitor.

"This discovery with orlistat has given us a very nice wedge with which we can go in and perturb tumor cells and ask the question, 'What are the active targets, what are the other changes that take place when you inhibit fatty acid synthase?'", says Dr. Smith, "and that will give us good insights into the mechanism, which we anticipate will reveal a whole swath of additional drug targets along this pathway. This is a big advance in the sense that we have an approved drug-approved for one indication—that has another target and another potential disease indication, prostate cancer."

Dr. Smith is Associate Scientific Director for Technology at The Burnham Institute and Associate Professor in the Institute's NCI-designated Cancer Center.

Co-authors contributing to this study include Drs. Steven J. Kridel and Fumiko Axelrod, postdoctoral fellows at The Burnham Institute, and Dr. Natasha Rozenkrantz of Activix Biosciences in La Jolla.

This research was supported by grants from the National Cancer Institute and the Department of Defense's Prostate Cancer Program.

PREOPERATIVE IMAGES OF PROSTATE CANCER VASCULARITY HAVE PROGNOSTIC VALUE

According to new research from Germany, "the aim of this study was to correlate quantitative dynamic contrast-enhanced MRI (DCE MRI) parameters with microvessel density (MVD) in prostate carcinoma. Twenty-eight patients with biopsy-proven prostate carcinoma were examined by endorectal MRI including multiplanar T2- and T1-weighted spin-echo and dynamic T1-weighted turbo-FLASH MRI during and after intravenous Gd-DTPA administration. Microvessels were stained on surgical specimens using a CD31 monoclonal antibody."

"The MVD was quantified in hot spots by counting (MVC) and determining the area fraction by morphometry (MVAF). The DCE MRI data were analyzed using an open pharmacokinetic two-compartment model," H.P. Schlemmer and colleagues, University of Heidelberg, University Hospital, Mannheim explained.

"In corresponding anatomic locations the time shift (Delta t) between the beginning of signal enhancement of cancer and adjacent normal prostatic tissue, the degree of contrast enhancement and the contrast exchange rate constant (k21) were calculated."

"The MVC and MVAF were elevated in carcinoma ($p<0.001$ and $p=0.002$, respectively) and correlated to k21 ($r=0.62$, $p<0.001$ and $r=0.80$, $p<0.001$, respectively). k21-values of carcinoma were significantly higher compared with normal peripheral but not central zone tissue. Delta t was longer in high compared with low-grade tumors ($p=0.025$)," scientists indicated.

"The DCE MRI can provide important information about individual MVD in prostate cancer, which may be helpful for guiding biopsy and assessing individual prognosis," researchers concluded.

Schlemmer and colleagues published the results of their research in European Radiology (Can pre-operative contrast-enhanced dynamic MR imaging for prostate cancer predict microvessel density in prostatectomy specimens? Eur Radiol, 2004;14(2):309-317).

NEW VIEW OF RECURRENT PROSTATE CANCER PROPOSED

Results of a study at Roswell Park Cancer Institute (RPCI) support taking a revised view of prostate cancer and how best to treat it.

Almost all advanced prostate cancer responds well at first to androgen deprivation therapy but the cancer recurs with a poor prognosis. This study suggests that these cases might need to be managed in a different way.

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RECURRENT PCA

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The research was led by James L. Mohler, MD, chair of the department of urologic oncology at Roswell Park Cancer Institute (RPCI), and involved colleagues at the University of North Carolina. The results were published in Clinical Cancer Research.

Advanced prostate cancer is often treated by hormonal treatment or surgical castration, either of which effectively removes the testicles to deprive the body of androgens (male hormones produced by the testicles). After remissions of months to several years, almost all prostate cancer recurs as what is currently called androgen-independent disease. Researchers have believed that these secondary tumors no longer require androgens to grow and have attempted to develop therapies based on that assumption, often with little success.

However, this research by Mohler and colleagues indicates that these recurrent prostate cancers have found a way to make the equivalent of testicular androgens directly from cholesterol or from weaker androgens made by the adrenal glands. "These findings will cause everyone in the field of prostate cancer to re-evaluate how they think about advanced prostate cancer," said Mohler. "We suggest that these advanced prostate cancers still depend on androgens for growth and they should be called recurrent and not androgen-independent."

The study compared prostate cancer specimens from 22 men whose prostate cancer recurred locally after surgical castration to samples from benign prostate specimens from 48 men who had received no prior treatment.

The researchers used immunohistochemistry and image analysis and found evidence of androgen receptor protein stabilization and high levels of tissue androgens - testosterone and dihydrotestosterone -in the samples with recurrent prostate cancer. "We believe that these androgens also activate the androgen receptor since we found that the tissue also contained high levels of the classic androgen-regulated gene product, prostate specific antigen or PSA," continued Mohler. The prostate-specific antigen (PSA) serum test - pioneered at Roswell Park Cancer Institute in the late 1970s - revolutionized prostate cancer detection and management. Elevated PSA levels are suggestive of cancer development.

"Novel therapies that target the androgen receptor directly and prevent the formation of androgens within prostate cancer tissue may offer the most effective approach to prolonging remission or reinducing remission of recurrent prostate cancer," noted Mohler (Mohler JL, Gregory CW, Ford OH 3rd, et al., The androgen axis in recurrent prostate cancer. Clin Cancer Res, 2004;10(2):440-8).

A Conversation with Dr. Jeri Kim

Assistant Professor in the Department of Genitourinary Medical Oncology
at The University of Texas M. D. Anderson Cancer Center

What makes this group of studies important to the broader research effort aimed at prostate cancer prevention?
The pre-prostatectomy model is important in studying the biological effects of chemopreventive agents in tissue.We have access to the entire organ and therefore the ability to study in detail the effects of a drug in different zones (areas) of the prostate. We can also study differential effects of a drug in normal tissue, in prostate intraepithelial neoplasia, and in prostate cancer. Since most prostate cancer occurs in the peripheral zone of the prostate, we are interested in effects there. If a drug of interest has no effect in the peripheral zone, it may not be useful.

How would you describe the novelty of searching for cancer prevention agents using the pre-prostatectomy model?
We are using the pre-prostatectomy model to study the biological effects of such agents as selenium and vitamin E to complement the national effort already under way to determine whether these agents can prevent prostate cancer. In this process, we will not only confirm the known mechanisms of action of these agents in prostate tissue, but we will also discover new mechanisms of action that may serve as new targets for chemoprevention or therapy for prostate cancer. Additionally, there needs to be a close collaboration among investigators from the laboratory and the clinic so new insights gained from *in vitro* and *in vivo* studies can be confirmed in the clinic and the questions raised from the clinic can be investigated in the laboratory.

What are the advantages and disadvantages of using this pre-prostatectomy cohort for studying novel agents such as selenium and vitamin E?
I think the major advantage, as mentioned, is the fact that we have access to the entire organ for correlative studies. On the other hand, there are disadvantages. Recruiting patients to a pre-postatectomy study using chemopreventive agents is difficult because patients who already have prostate cancer may not directly benefit from these agents and may be reluctant to participate in the study. Also, because chemoprevention studies in prostate cancer use biopsy as an end point (just as in the Prostate Cancer Prevention Trial, or PCPT), biomarkers studied in sections of the prostatectomy specimen will be compared with biopsy specimens of the prostate.