Prostate cancer is the most common form of cancer found in males in the United States. The American Cancer Society predicts that approximately 218,890 new cases of prostate cancer will be diagnosed in the United States in 2007, and 27,050 men will die of this disease. In comparison, in 2004, there were 230,000 new cases diagnosed and 29,090 men died of prostate cancer.

The prostate is a walnut-sized gland located in front of the rectum and under the bladder that secretes the fluid that carries sperm. Prostate cancer occurs when cells grow abnormally in the prostate gland to form tumors.

Currently, thanks to increased awareness of the high incidence of the disease and regular, rigorous screening, 86 percent of all prostate cancers are found while they are still in or near the prostate. In the past 20 years, new techniques to diagnose prostate cancer early – many developed at Stanford University – have increased the survival rate of the disease from about 65 percent to almost 100 percent.

The Cancer Center’s individualized approach to diagnosis and treatment of prostate cancer begins with a comprehensive

**NERVE-SPARING RADICAL PROSTATECTOMY**

This technique saves the nerves that control a man’s ability to get and keep an erection. Research has shown that nerve-sparing surgery, which should be performed only by a specially trained, skilled and experienced surgeon, has a 60 to 85 percent chance of restoring a man’s sexual potency.

Stanford urologic surgeons Joseph Presti, Jr., MD, Professor of Urology and Director of the Urologic Oncology Program; James Brooks, MD, Associate Professor of Urology; and Harcharan Gill, MD, Associate Professor of Urology, are experts in performing this delicate procedure.

“It is well established that the surgeon’s experience is critical to ensure good outcomes with respect to being cured of cancer and maintaining quality of life.”

Urologic surgeons at the Stanford Cancer Center (http://cancer.stanford.edu/urologic/prostate.html) offer several promising treatment options for prostate cancer that enable many men to lead active, normal lives and resume sexual activity.
DEAR FRIENDS,

We welcome you to the second issue of the Stanford Cancer Center News. Although we have a number of exciting developments to report, we are greatly saddened at this time by the sudden and unexpected loss of Steven Leibel, MD, Ann and John Doerr Medical Director and Associate Director for Clinical Care and Research in the Center. Steve played such an important role in the development of our clinical research programs in cancer over the past four years, and in the ability of the Center to gain recognition from the National Cancer Institute.

Steve's dedication to building the very best interdisciplinary disease programs and his patient, understanding approach to solving problems were among his many attributes. He was also an individual of great accomplishments and stature in the field of radiation therapy for prostate cancer, and this issue on prostate cancer clinical care and research at Stanford is dedicated to him.

We will all miss him greatly.

The Cancer Center continues to move forward in its mission to integrate the best research with our clinical care and cancer prevention missions. While much of the emphasis is on clinical research into new therapies for cancer, there is also an increasing need to develop new diagnostic approaches and to identify biomarkers that reflect the behavior of specific cancers, that is, whether they will behave in a more benign or aggressive fashion.

Nowhere is this need more evident than in the field of prostate cancer. Earlier diagnosis and the overwhelming prevalence of this disease have made it imperative to identify which patients are in need of treatment as opposed to observation and, if treatment is required, which therapy has the most benefit in terms of quantity and quality of life.

Over 30 years ago, Dr. Thomas Stamey, Professor of Urology at Stanford, was first to report that levels of prostate-specific antigen, or PSA, in the blood could be used as a marker of prostate cancer. PSA has provided an excellent initial screening tool, but it is not specific for cancer. Furthermore, a number of prostate cancers will remain dormant over an individual’s lifespan. How can we identify these? How should they be followed?

Our interdisciplinary prostate cancer group led by Dr. Joe Presti, deals with these questions daily, and research has been directed at characterizing the biologic variants of prostate cancer in the hopes of developing new prognostic markers that will help to individualize patient decisions about treatment. Again, Stanford is leading the way in research and in therapeutic advances, such as the CyberKnife approach to delivering radiation therapy.

We look forward to a future where this disease can be reduced in its occurrence and where, once diagnosed, it will have a more predictable course that allows the optimal intervention with the fewest side effects available.

We are also delighted to announce the awarding of a new Chair, the Ernest and Amelia Gallo Professor in the School of Medicine, to Dr. Phil Beachy, a Howard Hughes Investigator who has joined us from Johns Hopkins University. Dr. Beachy is working on a signaling pathway that is relevant to cell growth and cancer, the so-called Hedgehog pathway.

There is exciting evidence that this pathway is activated in metastatic foci of prostate cancer. Whether activation is causally related to metastasis is not clear, but this finding raises the possibility that chemical inhibitors of Hedgehog signaling may be effective in treating and possibly even in preventing advanced prostate cancer, a stage for which we are in great need of new therapies. We are very grateful to the Gallo family for creating this new endowed Chair.

As always, the Stanford Cancer Center is here to serve the needs of our patients, to educate and to find new solutions to the many problems posed by cancers. We are excited by the advances, but remain humble in the face of the many challenges remaining. Most importantly, we are grateful to the many friends and patients of the Stanford Cancer Center who contribute so much to what we are able to do.

Sincerely,

Beverly S. Mitchell, MD
Deputy Director

If you prefer not to receive the Stanford Cancer Center news in the future, please let us know via e-mail at ecrown@stanford.edu or in writing to: Elizabeth Crown, Stanford Cancer Center, 800 Welch Road, 2nd floor, Stanford, CA 94305-5796.
Promising Surgical Treatment for Prostate Cancer

CONTINUED FROM PAGE 1

with respect to being cured of cancer and maintaining quality of life. We perform hundreds of these procedures each year and achieve excellent cancer and quality-of-life outcomes in the vast majority of our patients. Most patients go home within two days of their surgery and can resume normal activities within four weeks,” Dr. Presti said.

DA VINCI ROBOTIC PROSTATECTOMY

Another advance in the treatment of prostate cancer is the da Vinci surgical robot (http://cancer.stanford.edu/male/RoboticRadicalProstatectomy.html). Drs. Gill and Benjamin I. Chung, MD, Assistant Professor of Urology, have completed additional training in minimally invasive techniques and are highly experienced in performing robotic prostatectomy.

ADVANTAGES OF ROBOTIC-ASSISTED SURGERY

Robotic-assisted surgery allows our surgeons to have a three-dimensional view of the surgical field, at a greatly increased magnification – up to 15 times greater than the human eye. Fine articulating instruments, under the command of the surgeon, are used to precisely remove the prostate and preserve the nerves responsible for maintaining erectile function.

Using robotic technology allows the surgery to be performed using very small incisions, greatly decreasing blood loss, and may enhance recovery time, speeding convalescence despite having undergone major surgery. Comparative studies between open and robotic surgery are ongoing.

HOW IT WORKS

The operating surgeon controls the da Vinci robot. The surgeon sits at a console specifically designed to allow for total control of the operation. The surgeon looks into a binocular eyepiece system that allows him/her to view the surgical field under 3-D vision. The instruments, which are placed through the small incisions, are maneuvered with hand controls that allow the operating surgeon extremely precise and fine control.

These “wristed” instruments are designed to allow for 90 degrees of articulation and seven degrees of freedom, which is more than the human hand is capable of performing. The prostate is detached from its surrounding structures and, when possible, the nerves controlling erectile function are delicately preserved.

“How you decide to have a radical prostatectomy or a robotic prostatectomy, the Stanford Cancer Center provides experienced surgeons who can provide to you the highest level of care,” Dr. Presti said.

For more information about these nerve-sparing prostate cancer procedures, or to make an appointment with a Stanford prostate cancer specialist, call the Urologic Oncology Program at (650) 725-5544.

patient evaluation designed to identify the disease in its earliest stages and determine whether the tumor is localized to the prostate or has spread to distant organs.

An annual prostate-specific antigen (PSA) test and digital rectal examination (DRE) are vital in the evaluation for prostate cancer. If either is abnormal, a biopsy is recommended to determine whether you have prostate cancer.

Our treatment approach is dynamic and interactive. A multidisciplinary team of Stanford physicians defines therapeutic goals for each patient and updates treatment programs if prostate cancer recurs. Our doctors guide patients through the sometimes-complicated therapeutic choices, including the option of watchful waiting, or “active surveillance.”

Stanford physicians offer the most advanced treatment options, including prostatectomy techniques that preserve the nerves that control erectile function, robot-assisted laparoscopic prostatectomy and non-invasive CyberKnife radiosurgery. Our clinical cancer program is complemented by a university-wide research effort, ensuring that promising laboratory advances are made available to patients in the shortest possible time.

For more information on the Stanford Cancer Center’s prostate cancer program, visit: http://cancer.stanford.edu/urologic/prostate.
It has become apparent that all cancers, including prostate cancer, are the product of changes in the genes present in normal cells. The outcome of these genetic alterations, which include mutations and the gain or loss of genetic material, is that critical genes get turned on or off. This, in turn, alters the normal growth patterns of cells and can make cancer cells more aggressive.

Currently, there are no genetic markers for prostate cancer that can be used in the clinic. This contrasts with breast cancer, for which several genes, such as the much-publicized HER2/Neu, have been identified. Scientists developed a drug called Herceptin, which inhibits production of HER2/Neu and improves survival of patients with breast cancer. In this instance, the genetic marker that serves as the “diagnostic” is also the therapeutic target, and the activity of the targeted protein in tissues or blood can be measured.

**GENE EXPRESSION PROFILING**

To identify proteins that will serve as new biomarkers of prostate cancer, several Stanford investigators are taking advantage of DNA microarray technology that allows simultaneous assessment of expression of over 40,000 genes. DNA microarrays were developed by biochemistry professor Patrick Brown, PhD, and his colleagues at Stanford.

Microarrays are microscope slides spotted with snippets, or sequences, of DNA. Microarrays reveal the signature of specific genes that are active in the cell being studied. With this technology, researchers can compare normal prostate cells with those in various stages of malignancy and then attempt to link any genetic alterations with diagnostic clues.

“Our studies from gene expression profiling have shown that, just as every individual is different, every tumor is different,” said urologist James Brooks, MD. Brooks, who has been collaborating with Brown on cancer gene marker research for 10 years, believes that genomic studies of prostate cancer will provide new prognostic markers for prostate cancer and may better define the appropriate treatment.

“Better methods to assess prognosis may dramatically change cancer therapy. Identification of new targets may lead to new therapies for prostate cancer,” he said.

Brown, Brooks, and imaging expert Sanjiv Sam Gambhir, MD, PhD, recently received a $7.5 million gift from Canary Foundation for cancer early detection research. These funds will allow Brown and Brooks to further their DNA microarray studies of prostate cancer and others cancers.

In the same vein, Brooks and Jonathan Pollack, MD, PhD, are developing a prostate cancer genome atlas. To date, the researchers and their lab groups have identified three molecular subtypes of prostate cancer. The subtypes apparently coincide with the behavior of the tumors; one indicates an aggressive form, one an intermediate form and a form that is less aggressive.

**FATHER OF VITAMIN D RESEARCH**

David Feldman, MD, Professor of Medicine, is one of the world’s foremost authorities on using vitamin D as a treatment for cancer, specifically prostate cancer. Feldman has been studying the mechanism of action of vitamin D for 25 years and has pioneered its potential use to treat malignancies. In addition to his work on vitamin D therapy for prostate cancer, Feldman, with Robert Carlson, MD, head of the Breast Cancer Oncology Clinic, and a team of clinical researchers, is currently exploring the use of vitamin D to treat breast cancer.

Feldman’s group has shown in the laboratory that the activated form of vitamin D, called calcitriol, limits the growth of prostate cancer cells and cancers in an animal laboratory model. Calcitriol is the hormonal form of vitamin D and is the metabolite created in the body after consumption of vitamin D – containing food or exposure to sunlight. Despite its name, calcitriol should really be considered a hormone and not a vitamin.

To determine the spectrum of genes regulated by calcitriol in prostate cancer cells, the researchers used a cDNA microarray. They discovered that many genes were regulated by calcitriol, but they chose to focus further research
on two genes that are critical in the production and breakdown of prostaglandins – local hormones that play a major role in inflammation. Inflammation is thought to be associated with cancer initiation, growth and progression.

Like calcitriol, NSAIDs such as ibuprofen and naproxen inhibit prostaglandins. Calcitriol inhibits expression of COX-2, the enzyme that synthesizes prostaglandins, while NSAIDs inhibit the activity of COX-2. Since the drugs inhibit synthesis of prostaglandins by different mechanisms, Feldman and Donna Peehl, PhD, wanted to determine whether combining calcitriol with NSAIDs could boost the action of calcitriol and synergistically achieve greater prostaglandin inhibition at even lower doses of the two drugs. They found significantly greater inhibition of prostate cancer growth using smaller doses of both drugs than using either drug by itself.

Together with Sandy Srinivas, MD, who treats prostate cancer patients, Feldman initiated a clinical study to test this hypothesis in men with early recurrent prostate cancer. The preliminary findings of the study indicate that the combination of calcitriol and naproxen slows the rate of rise of PSA in most patients and in some cases significantly reduces PSA levels.

Since PSA is the best surrogate marker of prostate cancer cells, especially in patients whose prostates have been removed, the reduction of this biomarker is a hopeful sign that the rate of prostate cancer progression has been slowed by the therapeutic drug combination.

**ALTERING EXPRESSION OF THE ANDROGEN RECEPTOR**

Prostate cancer is dependent on androgen (male sex hormones) to grow. One of the initial treatments of metastatic prostate cancer is to remove those hormones from the bloodstream. While this results in the arrest in cancer growth initially, eventually the cancer cells become resistant to the manipulation.

Zijie Sun, PhD, Associate Professor of Urology, is developing methods of making the “hormone-resistant” cancer cells responsive to these manipulations. In cell lines and animal models, he has demonstrated that the resistant cancer cells can be made sensitive once again to hormonal levels by altering their expression of the androgen receptor.

**HEDGEHOG, LOX AND OTHER DEVELOPMENTS**

Another gene that appears to make prostate cancer cells more aggressive is called Hedgehog. The Hedgehog protein signals cells during fetal development, and is especially important in directing developing organs to their appropriate location.

Stanford researcher Philip Beachy, PhD, has discovered that, in some circumstances, Hedgehog causes a number of cancer cells, such as those in prostate tumors, to become highly aggressive. Beachy, who is Ernest and Amelia Gallo Professor in the School of Medicine, has advanced the study of the molecular pathways that control growth of normal cells in the developing embryo and of cancer stem cells.

In landmark experiments, Beachy showed that inhibiting the Hedgehog protein reduced growth of prostate cancer cells, as well as cancers of the lung and gastrointestinal tract.

With Dr. Srinivas, Beachy will be studying the use of other drugs that block the Hedgehog pathway in patients with advanced prostate cancer.

Amato Giaccia, PhD and his lab study hypoxia (low oxygen), a condition associated with metastasis, resistance to chemotherapy and radiation therapy and poor survival. Giaccia is Jack, Lulu and Sam Willson Professor of Radiation Oncology and Director of Radiation and Cancer Biology.

According to Giaccia, a low-oxygen environment acts as a “rheostat that dials up a tumor’s ability to spread” by triggering adaptive genetic and metabolic responses that allow cancer cells to survive and establish new blood vessels, or to move from an oxygen-poor to an oxygen-rich environment.

His lab team has identified several markers of hypoxia – most recently, a gene called lysyl oxidase, or LOX, that has been shown to predict tumor recurrence and survival in head and neck, breast and pancreas cancers. They are currently exploring the potential role of LOX in prostate cancer.
Legacy of Prostate Cancer Research

“The discoveries from this group form the backbone of how patients and their physicians all over the world assess prognosis in prostate cancer.”

The Stanford Cancer Center pioneered comprehensive diagnosis and treatment for prostate cancer. Vital screening and systematic biopsy techniques were first developed and refined by Stanford doctors and became integral to the standard of care for prostate cancer.

World-renowned surgeon Thomas Stamey, MD, and pathologist John McNeal, MD, carried out a series of landmark studies that defined tumor grade and volume as predictive of outcome and dramatically improved use of Gleason scoring, a widely used method for classifying prostate cancer tissue.

Dr. McNeal painstakingly collected and catalogued over 1,300 malignant prostates that had been removed by urologists and developed a quantitative analysis of the microscopic tissues to improve the accuracy of diagnosis and prognosis following prostatectomy. Dr. McNeal’s recognition and description of the three anatomical zones of the prostate changed the way physicians worldwide view the prostate gland.

Dr. Stamey, who was the first Chairman of the Department of Urology at Stanford, is best known outside the university for his 1987 study that defined prostate-specific antigen (PSA) levels as a useful diagnostic and prognostic marker in prostate cancer and for developing global standards and guidelines for PSA use. Dr. Stamey also implemented the use of ultrasound to guide needle biopsies of the prostate.

“The discoveries from this group form the backbone of how patients and their physicians all over the world assess prognosis in prostate cancer,” said Joseph Presti, Jr., MD, Professor of Urology and Director of Stanford’s Urologic Oncology Program.

Building on their legacy of prostate cancer research, Drs. Stamey and McNeal, with their colleague Donna Peehl, PhD, Professor of Urology, established one of the world’s best-characterized prostatectomy tissue and serum banks. Dr. Stamey has banked several thousand frozen prostate tissues and almost 54,000 serum samples.

Dr. Peehl is also considered a world expert on establishing cell cultures from prostate tissues. Recently, she developed a breakthrough culture technique that keeps prostate cancer tissues alive for several days after surgery. During this period, researchers can study in real time how prostate cancer cells – which retain all of their structure and function – behave in their surrounding environment in the body and respond to experimental therapies.

Dr. Peehl and her laboratory team are also attempting to identify genes that may play a role in prostate cancer. One of these genes, called monoamine oxidase A (MAO-A), which is associated with neurological disorders such as depression and Parkinson’s Disease, may cause prostate cancer cells to become more aggressive.

Results of these studies raise the possibility that antidepressive drugs that block activity of MAO-A (called MAO-A inhibitors) could possibly be used either for prostate cancer therapy or to prevent progression of prostate cancer to the aggressive stage.

SUN, VITAMIN D AND PROSTATE CANCER

Mounting studies, including many from the Stanford Cancer Center and its partner, the Northern California Cancer Center, support the hypothesis that vitamin D reduces the risk of prostate cancer. The major source of vitamin D is casual exposure to sunlight.

A recent study from the NCCC may help confirm that hypothesis. Epidemiologist Esther John, PhD, and Jocelyn Koo of the NCCC, with colleague Gary Schwartz, PhD, of Wake Forest University, showed that men who are born in sunny climates and those who spend a lot of time in the sun while growing up have half the risk for developing prostate cancer as those who do not. This group of men also has a lower risk for developing fatal than non-fatal prostate cancer.

The study additionally showed a 53 percent reduced risk of prostate cancer in men who have frequent recreational sun exposure.

The researchers cautioned men not to sunbathe excessively because of the risk of developing melanoma and other skin cancers. They noted that it usually takes only a few minutes of sun exposure for skin to produce large quantities of vitamin D. The safest way to increase vitamin D levels is from supplements.

These study results were published in a recent issue of the journal Cancer Epidemiology Biomarkers & Prevention.

The study examined the effect of early-life versus adult sun exposure on prostate cancer risk in the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study, a nationwide prospective study of men and women spanning a wide range of residential sun exposure. The researchers previously published an study on sun exposure and breast cancer risk that was based on data from NHANES I.
Your Options for Prostate Cancer Treatment

Technology developed and perfected at Stanford University was crucial in the development of the Da Vinci surgical robot.

Active surveillance: Also called watchful waiting, active surveillance means monitoring a patient’s condition and treating if the cancer shows signs of progression. If a patient’s prostate cancer is not advanced and is slow growing, he may not need immediate treatment. Active surveillance often is used in older men with additional medical problems or in men with small, low-grade (slow-growing) cancers. Cancer Center researchers will be investigating the use of vitamin D in patients in active surveillance.

Surgery: Surgeons remove the prostate (radical prostatectomy) as well as some tissue surrounding it, and usually remove a sample of the lymph nodes in nearby tissue to determine whether the cancer has spread beyond the prostate.

Advances in engineering and computer technologies have enabled urologists to remove the prostate without making large incisions – called minimally invasive surgery. Stanford’s urologists are specially trained to perform minimally invasive laparoscopic prostatectomy, which uses a small telescope with a built-in magnification mechanism and a variety of long, thin surgical instruments placed through three to five tiny incisions.

Robotic prostatectomy is a more-refined laparoscopic approach. Technology developed and perfected at Stanford University was crucial in the development of the Da Vinci surgical robot. Our surgeons have completed fellowships in minimally invasive techniques and several are highly experienced in performing robotic-assisted prostatectomy.

These physician-scientists are assessing robotic data critically and comparing it to the Cancer Center’s open prostatectomy data. In addition, the Department of Surgery has just opened the Goodman Simulation Center that will encourage virtual training and simulation technology and refine minimally invasive surgical techniques for treating prostate cancer.

Radiation therapy: This technique uses high-energy rays (similar to x-rays) to kill cancer cells and decrease their ability to divide. Radiation is often used to treat prostate cancer that is still confined to the prostate gland or has spread only to nearby tissue. If the cancer is more advanced, radiation may be used to shrink the size of the tumor and to provide relief from symptoms.

Radiation oncologists Steven Hancock, MD, and Christopher King, MD, PhD, are at the forefront of developing radiotherapy technology, and our patients have access to some of the most advanced radiological treatments in the world.

The Department of Radiation Oncology uses state-of-the-art computer systems and treatment-planning software that allow our physicians to visualize a patient’s anatomy in three dimensions. This information enables our specialists to “conform” radiation dose more closely to the shape of an individual’s tumor by creating specially tailored blocking devices and/or fine-tuning the directions from which radiation is administered.

Such planning improves accuracy, reducing the radiation received by healthy tissues and increasing coverage of tumors. In some cases, the conformal method enables doctors to deliver radiation to body regions that would have been difficult or impossible to treat in the past.

The CyberKnife, which was invented at Stanford, uses image-guided radiotherapy and robotic technology to deliver highly precise, high-dose radiation over the course of days rather than several weeks. Three tiny gold “seeds” are placed within the prostate and are used by the image-guidance system to accurately locate and track the position of the prostate during delivery of radiation.

Dr. King led the effort at the Stanford Cancer Center, which is the first institution in the world to use the CyberKnife to treat prostate cancer. Stanford has the most experience using the CyberKnife to treat prostate cancer and other solid tumors.

Systemic and hormonal therapies: The goal of hormone therapy is to lower the level of male hormones, particularly testosterone, in the body. Hormonal therapy is often used in combination with radiation and surgery.

Chemotherapy: Oncologists often use drugs to treat cancerous cells. Often, chemotherapy is not the primary therapy for prostate cancer, but may be used when the disease has spread outside the prostate gland, or in combination with other therapies.

Higher-risk prostate cancer patients treated at Stanford have special access to clinical trials – new treatments that build on chemotherapies and on our understanding of the disease.

For more information on Stanford’s Prostate Cancer Program, visit http://cancer.stanford.edu/urologic/prostate/.

Pictured above: Sandhya Srinivas, MD, Associate Professor of Medicine – Oncology, specializes in the treatment of prostate cancer.
The prostate develops tumors more frequently than other organs, although these tumors are generally slower growing than others. This means that a man could live for years with prostate cancer and die of another cause. Research has shown that every man will develop some degree of prostate cancer if he lives long enough. Autopsy studies have shown microscopic evidence of prostate cancer in 15 to 30 percent of men over 50 years and in 60 to 70 percent of men who reach 80 years. Although over 200,000 new cases of prostate cancer were diagnosed in the United States in 2007, fewer men died of the disease. This suggests that treatment is effective but also that many cancers are detected that pose no threat to longevity of the patient.

The use of prostate-specific antigen (PSA) has dramatically increased our ability to detect prostate cancer. However, research has shown that the PSA test, which is still the most common test for prostate cancer, may be inconsistent. Often, elevations of PSA result from non-cancerous causes, such as benign prostatic hyperplasia (BPH) and inflammation. Still, Joseph Presti, Jr., MD, who directs Stanford’s Urologic Oncology Program, believes that the PSA test is a useful screening tool. “While PSA is not perfect, it has revolutionized our ability to detect prostate cancer,” Presti said.

In a recent study, Presti and co-researchers showed that PSA performs better in detecting high-grade (more aggressive) cancer. In addition, adjusting the PSA level according to the size of the prostate (PSA density) greatly enhanced the performance of the test.

In a prior study, Drs. Presti and Christopher King showed that the rate of change of PSA in the one to three years before diagnosis, as opposed to a single determination, can help researchers distinguish between aggressive and non-aggressive cancers.