Prostate Cancer

Prostate cancer is the third-leading cause of cancer deaths among men in the United States. Yet, when detected in its early stages, prostate cancer can be effectively treated and cured. What are its causes and symptoms? How is it diagnosed? The following information should help answer such questions.

What is the prostate?

The prostate gland is a small, walnut-sized gland in men. It is located below the bladder and surrounds the upper portion of the urethra. The prostate gland lies in front of the rectum, and its posterior surface can be felt during a rectal examination. The function of the prostate is to secrete a fluid that makes up part of the semen. The prostate gland may be a source of many health problems in men, the most common being benign prostatic hyperplasia (BPH), prostatitis and cancer.

What is prostate cancer?

Prostate cancer is a significant health-care problem in the United States due to its high incidence. It is the most common non-skin cancer in men affecting approximately 234,000 American men each year with approximately 27,000 of these men dying each year. Prostate cancer is different from most cancers in that an appreciable percentage of men, particularly older men with a shorter life expectancy, may have a silent form of this cancer—it will not cause symptoms or progress beyond the prostate gland during their lifetime. Sometimes this cancer can be small, slow growing and present limited risk to the patient. Clinically important prostate cancers can be defined as those that threaten the well-being or life span of a man.

What are the causes and risks associated with prostate cancer?

What causes prostate cancer is a subject of intensive research. It is likely that prostate cancer occurs due to many reasons. Predominately a disease of elderly men, the diagnosis of prostate cancer is rare before age 40 but increases dramatically thereafter. In the United States, it is estimated that one in 55 men between the ages of 40 and 59 will be diagnosed with prostate cancer. This incidence climbs almost to one in six for men between ages 60 and 79. This association is also reflected in mortality as prostate cancer accounts for about 10 percent of cancer-related deaths in men between the ages of 60 and 79 and nearly 25 percent in those over the age of 80.

Worldwide, prostate cancer ranks third in cancer incidence and sixth in cancer mortality among men. There is, however, a notable variability in incidence and mortality among world regions. The incidence is low (but rapidly increasing in recent years) in Japan and intermediate in regions of Central America and Western Africa. The incidence is higher in North America and Northern Europe. Although some of these differences may be accounted for by differences in screening for prostate cancer and the risk of other diseases among world regions, it is likely that they can be accounted for, in part, by genetic predisposition as well as diet and other environmental factors.

There are also ethnic determinants of risk. Blacks are in the highest risk group, with an incidence of more than 200 cases per 100,000 black men. The incidence in Caucasian and Asian men is slightly more than half that of blacks. In addition, blacks tend to present with more advanced disease and have poorer overall prognosis than Caucasian or Asian men.

Men with a family history of prostate cancer are at an increased risk of developing the disease. The risk correlates with the number of first-degree relatives (father, brother or uncle) affected by prostate cancer and the age at onset. Men with a family history of disease may have a risk of developing prostate cancer 2 to 11 times greater than men without a family history of prostate cancer.

There is also considerable evidence showing that prostate cancer is more common in men with a high intake of fat in their diets. The worldwide difference in prostate cancer incidence may be associated with dietary intake of soy proteins. In Asian countries such as Japan and the Republic of Korea where prostate cancer incidence and mortality are just a fraction of that in North America, soy consumption in the form of tofu, soymilk and miso is up to 90 times higher than that consumed in the United States. In a study of more than 40 nations, researchers found soy, on a per calorie basis, to be the most protective dietary factor. This

protective role may be associated with two of soy's components, genistein and daidzein that may act as weak estrogens or through other mechanisms. Estrogens are female hormones that inhibit prostate cancer growth. Some experts have suggested that the worldwide differences in prostate cancer incidence may also be explained by the high intake of green tea by residents of Asia.

The intake of other certain dietary factors may also reduce the risk of developing prostate cancer. Such substances include lycopene and selenium. Cooked tomatoes are rich sources of lycopene. Lycopenes are antioxidants that may protect cells from becoming cancerous. Several studies have shown that the likelihood of developing prostate cancer is reduced by high intake of lycopene. Researchers found that men ingesting two or more servings of tomato sauce per week had a 36 percent reduction in cancer risk compared to those who did not. Selenium intake has also been reported to lower prostate cancer risk. In a clinical trial designed to determine if selenium could lower skin cancer recurrences, men who took selenium had a 63 percent reduction in prostate cancer incidence compared to those who took a sugar pill (placebo). Attention has also focused on vitamin D's effect on the prostate. Epidemiologic evidence shows an inverse relationship between prostate cancer risk and ultraviolet radiation, the primary source for vitamin D production. This observation has led some to suggest that higher rates of prostate cancer in the elderly may be partly due to decreased sun exposure or a decline in the body's ability to make vitamin D with aging.

Finally, the correlation of vasectomy and prostate cancer risk remains controversial. Although some studies have suggested that men who have undergone a vasectomy are at an increased risk of developing prostate cancer, many other studies have failed to show such a correlation.

What are the symptoms of prostate cancer?

In its early stages, prostate cancer often causes no symptoms. When symptoms do occur, they may include any of the following: dull pain in the lower pelvic area; frequent urination; problems with urination such as the inability, pain, burning, weakened urine flow; blood in the urine or semen; painful ejaculation; general pain in the lower back, hips or upper thighs; loss of appetite and/or weight; and persistent bone pain.

How is prostate cancer diagnosed?

Currently, digital rectal examination (DRE) and prostate specific antigen (PSA) are used for prostate cancer detection. The age at which time screening for prostate cancer should begin is not known with certainty. However, most experts agree that healthy men over the age of 50 should consider prostate cancer screening with a DRE and PSA test. Screening should occur earlier, at age 40, in those who are at a higher risk of prostate cancer such as African-American men or those with a family history of prostate cancer.

DRE: The DRE is performed with the man either bending over, lying on his side or with his knees drawn up to his chest on the examining table. The physician inserts a gloved finger into the rectum and examines the prostate gland, noting any abnormalities in size, contour or consistency. DRE is inexpensive, easy to perform and allows the physician to note other abnormalities such as blood in the stool or rectal masses, which may allow for the early detection of rectal or colon cancer. However, DRE is not the most effective way to detect an early cancer, so it should be combined with a PSA test.

PSA Test: The PSA test is usually performed in addition to DRE and increases the likelihood of prostate cancer detection. The test measures the level of PSA, a substance produced only by the prostate, in the bloodstream.

This blood test can be performed in a clinical laboratory, hospital or physician's office and requires no special preparation on the part of the patient. Ideally, the test should be taken before a DRE is performed or any catheterization or instrumentation of the urinary tract. Furthermore, because ejaculation can transiently elevate the PSA level for 24 to 48 hours, the patient should abstain from sexual activity for two days prior to having a PSA test. A tourniquet or rubber strap is tied around the upper arm to mildly restrict the flow of blood and keep blood in the vein. Then, a needle with a tube-like container attached is inserted into a vein, usually in the bend of the elbow or the top of the hand. After a sufficient sample of blood is obtained, the needle is withdrawn, a bandage is placed on the puncture site and firm pressure is held until the bleeding stops. The entire test takes less than five minutes and produces only mild discomfort. After, the patient may experience slight bruising at the puncture site.

Very little PSA escapes from a healthy prostate into the bloodstream, but certain prostatic conditions can cause larger amounts of PSA to leak into the blood. One possible cause of a high PSA level is benign (non-cancerous) enlargement of the prostate, otherwise known as BPH. Inflammation of the prostate, called prostatitis, is another common cause of PSA elevation, as is recent ejaculation. Prostate cancer is the most serious possible cause of an elevated PSA level. The frequency of PSA testing remains a matter of some debate. The American Urological Association (AUA) encourages men to have annual PSA testing starting at age 50. The AUA also recommends annual PSA testing for men over the age of 40 who are African-American or have a family history of the disease (for example, a father or brother who was diagnosed with prostate cancer), or for those who are interested in an early risk assessment. Some experts have suggested that men with an initial normal DRE and PSA level of less than 2.5 ng/ml can have PSA testing performed every two years. However, a disadvantage of infrequent testing is that it limits the ability to detect a rapidly rising PSA level that can signal aggressive prostate cancer. Recently, several refinements have been made in the PSA blood test in an attempt to determine more accurately who has prostate cancer and who has false-positive PSA elevations caused by other conditions like BPH. These refinements include PSA density, PSA velocity, PSA age-specific reference ranges and use of free-to-total PSA ratios. Such refinements may increase the ability to detect cancer and these should be discussed with your physician.

Currently, it is recommended that both a DRE and PSA test be used for the early detection of prostate cancer. It is important to realize that in most cases an abnormality in either test is not due to cancer but to benign conditions, the most common being BPH or prostatitis. For instance, it has been shown that only 18 to 30 percent of men with serum PSA values between 4 and 10 ng/ml have prostate cancer. This number rises to approximately 42 to 70 percent for those men whose PSA values exceeding 10 ng/ml.

Biopsy: Prostate biopsy is best performed under transrectal ultrasound guidance using a spring-loaded biopsy device coupled to the transrectal probe. The patient is prepared with an enema and an antibiotic. The lubricated ultrasound probe is inserted into the rectum. Some lubricating gels include a topical anesthetic. Patients are positioned on their side for this procedure. The physician will first image the prostate using ultrasound noting the prostate gland's size and shape and whether or not any other abnormalities exist, the most common of which are shadows which might signify the presence of prostate cancer. However, not all prostate cancers are visible. After the prostate gland has been anesthetized with an injection of a local anesthetic through a long fine needle that is passed through the probe, the physician performs the biopsy. Using the spring-loaded biopsy device attached to the ultrasound probe, the physician performs multiple biopsies of the prostate gland. Generally, 10 to 12 (or more, depending upon the size of the prostate gland and the prior PSA and biopsy history of the patient) biopsies will be performed. Each biopsy removes a cylinder of prostate tissue approximately 3/4 inch in length and 1/16 inch in width. The entire procedure takes 20 to 30 minutes. The biopsy tissue taken will then be examined by a pathologist (a physician who specializes in examining human tissue to determine whether it is normal or diseased). The pathologist will be able to confirm if cancer is present in the biopsy tissue. If cancer is present, the pathologist will also be able to grade the tumor. The grade indicates the tumor's degree of aggressiveness—how quickly it is likely to grow and spread. The Gleason grading system is the most widely used system. In this system, the majority tumor pattern is assigned a score from 1 to 5 and the minority pattern is similarly assigned a score, using the same scale. The majority and minority scores are added together to give a Gleason sum ranging between 2 and 10. Scores of 2 to 4 designate low aggressiveness, 5 to 6 mildly aggressive, 7 moderately aggressive and scores of 8 to 10 highly aggressive.

The transrectal ultrasound guided prostate biopsy is usually well tolerated. Injecting local anesthetics into the area before biopsy may minimize this discomfort. Blood in the ejaculate (hematospermia) and blood in the urine (hematuria) occur in most patients.. High fever is rare, occurring in only 1 to 2 percent of patients. The antibiotic is continued for at least 48 hours after the biopsy procedure.

Why is prostate cancer staged?

Once prostate cancer has been diagnosed by a prostate biopsy, the physician must stage the disease to determine the extent of the cancer (i.e., the "T" stage) and whether it has spread beyond the prostate gland to the surrounding tissues, the seminal vesicles, the lymph nodes and/or the bones. The T stage is determined by the DRE and other imaging studies of the prostate gland and surrounding tissues, such as the ultrasound scan, CT scan, MRI scan, or MR spectroscopy scan. The T stage is divided into the following categories:

T1: Doctor is unable to feel the tumor or see it with imaging (e.g., transrectal ultrasound)

T1a: Cancer is found incidentally during a transurethral resection (TURP) for benign prostatic enlargement. Cancer is present in less than 5% of the tissue removed and is low grade (Gleason < 6).

T1b: Cancer is found after TURP but is present in more than 5% of the tissue removed or is of a higher grade (Gleason > 6)

T1c: Cancer is found by needle biopsy that was done because of an elevated PSA

T2: Doctor can feel the tumor when a digital rectal exam (DRE) is performed but the tumor still appears to be confined to the prostate

T2a: Cancer is found in one half or less of only one side (left or right) of the prostate

T2b: Cancer is found in more than half of only one side (left or right) of the prostate

T2c: Cancer is found in both sides of the prostate

T3: Cancer has begun to spread outside the prostate and may involve the seminal vesicles

T3a: Cancer extends outside the prostate but not to the seminal vesicles

T3b: Cancer has spread to the seminal vesicles

T4: Cancer has spread to adjacent organs, such as the urethral sphincter, rectum and/or wall of the pelvis

To determine if the cancer has spread to the lymph nodes or bones, the physician may order a CT or MRI scan of the pelvis. A bone scan may be obtained to rule out metastases to the bone. Sometimes follow-up imaging studies are needed to further evaluate abnormalities found on the bone scan. Some physicians order these scans only when the cancer is Gleason grade >7 or the patient has a PSA level > 10 ng/ml.

Prostate cancer represents a spectrum of disease. Although some cancers may grow so slowly that treatment may not be needed, others are a threat to life. Determining the need for treatment can be a complex decision. Initially, the need for treatment should be based on the stage and grade of the cancer as well as the age and health of the patient. Many physicians have sought to devise risk assessment schemes that predict the likelihood of disease recurrence if patients are treated and progression or significant growth of their cancer if they undergo initial surveillance or watchful waiting. By combining many types of information (i.e., serum PSA level, clinical stage, Gleason score, extent of cancer in biopsy specimens), patients can be advised of the likely aggressiveness of their cancer and the need for and types of treatment available. However, the longer the patient's life expectancy, the more uncertain the prediction becomes, as most prostate cancers progress with time. Imaging tests, such as a radionuclide bone scan, CT scan or MRI, and MR spectroscopy may help assess whether the cancer is still confined to the prostate or has spread elsewhere. When prostate cancer spreads (metastasizes) it is usually progresses in a cascade-like fashion to by perforating the capsule and extending into the periprostatic tissues, then to the seminal vesicles, then to the lymph nodes and finally to the bones, lungs, and other organs. With advanced prostate cancer, meningeal metastases are relatively common. Not all men with prostate cancer need to undergo imaging tests as the risk of spread to other organs can be estimated on the basis of serum PSA levels and cancer grade. It is reasonable to omit the bone scan in patients with newly diagnosed, untreated prostate cancer, who have no symptoms from their cancer, a Gleason score < 6 and have serum PSA concentrations less than 10 ng/ml and certainly in those with serum PSA concentrations less than15 ng/ml (unless the Gleason score is > 7 . Similarly, a pelvic CT scan or MRI may not be necessary in men with lower grade cancers, cancers still confined to the prostate and serum PSA values less than 10 ng/ml.

Frequently asked questions:

Can prostate cancer be prevented?

There is controversy about true prevention. Some physicians believe that antiandrogen drugs, such as finasteride and dutasteride, can prevent prostate cancer. However, others are skeptical, and some believe that antiandrogens can only slow the progression of well-differentiated elements but may allow higher-grade elements to emerge as the dominant elements in the tumor. Some physicians believe that general health measures might reduce the risk of prostate cancer, such as eating a healthy diet, being physically active and visiting the doctor on a regular basis. Clinical studies are ongoing which are testing the ability of some antioxidants, such as vitamin E and selenium to prevent prostate cancer. However, the preponderance of the current evidence suggests that vitamin E does not reduce prostate cancer risk.

What is the outlook for prostate cancer?

The number of men diagnosed with prostate cancer remains high. However, 5-year relative survival rates have increased dramatically and there has been at least a 25% reduction in the age-specific prostate cancer mortality rate since the beginning of the PSA era. It is estimated that 99 percent of men diagnosed with localized or regional prostate cancer survive at least five years, while only 33% of those with metastases at diagnosis survive 5 years.

What are the current treatment options for men with localized prostate cancer?

Surgery (Radical Prostatectomy)

Surgery remains the primary option for many men with localized prostate cancer. Compared to other treatment methods such as radiotherapy and cryotherapy, a radical prostatectomy has an advantage of providing accurate local staging as well as assessment of pelvic lymph nodes through a detailed pathologic analysis. For patients with prostate cancer pathologically confined to the prostate, the chance of cure with surgery alone at 10 years (undetectable PSA) is more than 90 percent. The risk of cancer progression in men with extracapsular disease (cancer beyond the capsule of the prostate gland) and/or positive surgical margins is much higher ranging from 30 to 50 percent, and these patients may benefit from additional therapy such as external radiotherapy or androgen ablation. Although the incidence of surgical complications is quite low, the main postoperative issues remain urinary incontinence (5 percent) and erectile dysfunction (20 to 50 percent).

Open Radical Prostatectomy: In radical prostatectomy, the entire prostate gland is removed as a unit with the seminal vesicles and the nearest portions of the vas deferens. There are several different surgical techniques in performing a radical prostatectomy. The retropubic approach utilizes a midline incision below the umbilicus and allows simultaneous access to the prostate and pelvic lymph nodes. Based on precise anatomical delineation, the prostate gland can be safely removed with limited blood loss and preservation of the neurovascular bundles, which are responsible for maintaining erectile function. With the surgical steps clearly defined, the retropubic approach remains the most popular technique used by practicing urologists.

In perineal approach, the prostate is removed through a small semi-lunar incision in the perineum. By avoiding the pelvic vein complex, which can lead to significant bleeding in the retropubic approach, bleeding is usually minimal. Other advantages include precise urethra-vesical anastomosis (re-attaching the urethra to the bladder), a smaller incision, a shorter hospital stay and faster overall recovery. The main disadvantages are a higher incidence of rectal injury, difficulty of preserving the neurovascular bundles and a separate incision for pelvic lymphadenectomy. Typically, the perineal approach is preferred in obese individuals or those with prior lower abdominal surgery.

Robotic Assisted Laparoscopic Radical Prostatectomy: With recent advances in minimally invasive surgery and computer technology, the prostate gland can now be removed through a small one- to two-inch incision in the patient's abdomen. Introduced in 2001, robotic prostatectomy utilizes a surgical robotic system—named the da Vinci Robot (Intuitive Surgical, Inc., Sunnyvale, CA)—to remove the prostate gland through laparoscopic access in which surgeons make keyhole openings rather than a single 6 to 8-inch midline incision. The da Vinci Surgical System is the first surgical robotic system approved by the Food and Drug Administration for performing robotically assisted, minimally invasive surgery.

The system incorporates a surgeon's console and four interactive, robotic arms equipped with a camera and miniaturized surgical instruments. A surgeon controls the da Vinci's arms from a remote console that precisely translates his hand, wrist and finger movements to the robotic arms inside the patient's body while

providing a three-dimensional view of those movements; the enhanced views offered by the da Vinci mean less chance of damaging surrounding nerves and tissue and a reduced risk of scarring. As a result, the incidence of postoperative erectile dysfunction and urinary incontinence appear to be much less than that of open radical prostatectomy. Furthermore, these small skin incisions result in less pain, less blood loss, faster catheter removal and a shorter hospital stay, with some patients returning to work as early as two weeks after the procedure. Patients who undergo this surgery generally leave the hospital the next day, and their overall recuperation time is reduced by half compared to that of standard open radical prostatectomy.

Despite its promising clinical results of robotic prostatectomy, the main caveat of this procedure is a steep learning curve in acquiring the surgical skills by the practicing urologists. It is estimated that the surgeon typically needs to perform 50 to 100 robotic prostatectomies before becoming facile with this approach.

Radiotherapy

Traditionally, radiotherapy has been reserved for an elderly population (over 70 years), men with locally advanced prostate cancer, and those with a short life expectancy (less than 15 years). Recent retrospective studies have shown that radiotherapy and surgery can offer comparable long-term outcomes up to 10 years, and as a result, the applicability of radiotherapy is no longer limited to the traditional indications. It is estimated that an equal number of patients undergo radical prostatectomy and radiotherapy at the present time.

Radiotherapy for prostate cancer can be divided into two modalities: external beam radiation (EBRT) and brachytherapy (PB). In external beam radiotherapy, a small amount of radiation is delivered incrementally to the prostate over a course of 6 to 7 weeks. The total radiation dose received is usually over 70 Gy. Currently, three-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT) is used to deliver high-dose radiation to the prostate while minimizing toxicity to the surrounding normal structures such as the bladder and rectum.

Prostate brachytherapy is a method in which radioactive seeds are implanted directly into the prostate. The seeds are delivered percutaneously into the prostate via the specially designed needles under real time ultrasound imaging. Both low-dose rate (but high-dose) permanent prostate seeds and high dose rate (HDR) temporary implants can be used to treat the gland successfully. PB is typically performed in an outpatient setting under either general or regional anesthesia. The procedure is usually well tolerated with minimal perioperative morbidity.

The relative effectiveness of EBRT and PB appear to be similar for early stage prostate cancer. Some patients are offered the combination therapy in which both EBRT and PB are utilized. For those with locally advanced cancer and/or highly aggressive cancer, androgen deprivation is also added to optimize cancer control.

The main side effects of radiotherapy include bladder and rectal toxicities which can result in urinary and bowel dysfunction. The incidence of erectile dysfunction also appears to be similar to that of surgery, ranging in 20 to 50%. The long-term effects of radiation to normal tissues remain unknown though an incidence of secondary malignancy appears to be higher in this population.

Cryotherapy

Cryoablation of the prostate is a treatment in which prostate cancer is eradicated by freezing the prostate gland. Cryotherapy has a similar setup to that of prostate brachytherapy in that special needles called "cryoprobes" are placed into the prostate transperineally under the guidance of transrectal ultrasound. Argon gas is then used to create an "iceball" which results in instant cell death within the predefined area. Real time ultrasound monitoring of cryoablation combined with the use of thermocouples prevents cryo injuries to the surrounding normal tissues. Although prostate cryotherapy is most commonly offered after failed radiotherapy, there is emerging data supporting its use as a single treatment option in men with newly diagnosed prostate cancer. Cryotherapy currently has a limited role as an initial therapy in newly diagnosed men. In addition, cryotherapy should only be employed in men with erectile dysfunction as virtually all patients experience impotence following cryotherapy.

Androgen Ablation Therapy

Prostate cancer is androgen sensitive in early stages. As such, androgen ablation can result in a dramatic reduction in cancer burden in the vast majority of cases. Unfortunately, most prostate cancers eventually progress despite effective medical or surgical castration and become androgen independent. In the management of localized prostate cancer, the role of androgen ablation is usually limited to a neoadjuvant or adjuvant setting. Two most common scenarios are 1) to reduce the prostate size prior to prostate brachytherapy and 2) to sensitize malignant cells to radiation during EBRT. For patients who are at high risk for cancer recurrence, a prolonged use of androgen ablation (up to 3 years) combined with EBRT has resulted in improved survival compared to EBRT alone.

Watchful Wait or Expectant Management

Prostate cancer is often a slowly progressive disease, and many men with prostate cancer will die from causes other than prostate cancer. Several nomograms (decision charts) have been established in order to distinguish men with clinically significant cancers from those with clinically indolent tumors. In general, older men with a limited life expectancy and those with low-grade, small-volume disease may benefit from expectant management, and a therapeutic intervention should be reserved for those demonstrating clinical progression.