

How I Manage Prostate Cancer

Mark W. McClure, MD, FACS
Landmark Urology and Complementary Medicine, PA

As a board certified urologist, I offer men with prostate cancer state-of-the-art conventional cancer therapies. As a urologist board certified in holistic medicine, I also offer these men state-of-the-art complementary therapies.

Conventional Therapies

When I counsel men with prostate cancer I don two hats. When I don my conventional medicine hat, I recommend the latest conventional therapies for prostate cancer. These recommendations include:

- **Prevention.** I discuss prostate cancer prevention with all my male patients. Preventive measures are especially important for men with a family history of breast or prostate cancer because they're at increased risk, and for men with a current or past history of prostate cancer because preventive measures can slow the growth of prostate cancer or prevent its recurrence. I also share this program with women because they call the shots when it comes to family health care.
- **Early detection.** I advise routine *PSA screening* (digital rectal examination, PSA blood test, and a questionnaire about voiding symptoms) starting at age forty. However, anyone with a family history of prostate cancer or a family history of breast cancer should start screening at age 35 (a positive family history of either of these cancers increases the risk of developing prostate cancer). It's also important to calculate PSA doubling time since the PSA value can be in the normal range, but still be indicative of prostate cancer if it has an abnormal velocity or doubling time (a velocity of more than 0.75 ng/ml/year or a doubling time of less than 10-12 years. See www.prostate-cancer.org *PCRInsights*, October 2001 for further information). Also if the PSA value exceeds the expected PSA value for a given prostate gland size there is an increased risk of underlying prostate cancer. The gland size is determined by performing a prostate ultrasound. The expected PSA value due to BPH is calculated by multiplying the prostate volume by 0.12; for example a 30 gram gland equates to a PSA value of 3.6.

On the other hand, routine screening is discouraged by some professional organizations. They claim early detection doesn't influence prostate cancer mortality; it merely increases the risk of side effects – impotence and urinary incontinence – which adversely influence quality of life. I disagree and recommend screening because scientific studies have shown PSA screening detects prostate cancers that are clinically significant over 90% of the time – that is, if left untreated these cancers are likely to spread.¹ Prostate cancer is the second leading cause of death from cancer in men. Prevention, early detection, and appropriate therapies can reverse this statistic.

- **Accurate staging.** Staging involves a careful analysis of the prostate biopsy coupled with results of clinical staging studies - physical findings, blood studies, and imaging tests (ultrasound, x-rays, and nuclear medicine studies). The results of staging studies are used to predict the extent of the cancer. Special tables called nonograms correlate biopsy results with clinical staging studies. I refer the interested reader to the Prostate Cancer Research Institute web page (www.prostate-cancer.org) for further information. Accurate tumor staging prevents the inappropriate use of invasive therapies, when there is little chance for cure; that is, when the tumor has already spread to other parts of the body.

STAGING STUDIES

I. Digital rectal examination (DRE):

A simple office procedure that takes only seconds to perform; a DRE is performed by inserting a lubricated gloved finger inside the rectum. This allows your doctor to feel the outside surface of the prostate (called the peripheral zone). Since approximately seventy percent of prostate cancers arise from the peripheral zone, an abnormal DRE is often the first sign of prostate cancer. If the prostate feels abnormal, further investigation is warranted.

II. Transrectal prostate ultrasound (TRUS):

Consisting of a special probe that is inserted into (hence 'trans') the rectum, a transrectal ultrasound probe emits harmless sound waves from the end of the probe. These reflected sound waves are then displayed on a TV monitor that allows your urologist to 'see' the internal portions of the prostate. Biopsies (samples of prostate tissue) are taken by inserting a needle through a separate channel located within the probe.

III. Prostate Biopsy:

Before performing a prostate biopsy, numbing jelly is squirted inside the rectum to numb the lining of the rectum, and a special needle is used to deaden the nerves surrounding the prostate. Following this, a total of 12 biopsies are taken under ultrasound guidance. The biopsy tissue is sent to a laboratory for further evaluation.

A specialist, called a pathologist, examines the tissue under a microscope. If cancer cells are detected (a 'positive' biopsy), the pathologist's report will include information about the tumor volume (estimated by the number of positive biopsy specimens and percentage of cancer contained within each) and aggressiveness (based on the *Gleason* score).

Tumor cells are graded by their appearance under the microscope, and are given a 'score' called a Gleason score (named after the pathologist who originated the scoring classification) - the higher the score (range two to ten), the more aggressive the tumor. Aggressive tumors – tumors with a Gleason score of seven or above - are more likely to spread. (For an in-depth discussion of the Gleason score, visit the Prostate Cancer Research Institute's website, www.prostate-cancer.org, click on the tool bar under "insights", then click on January 2001, volume 4, number 1).

Let me address another issue before we move on. Some of my patients have refused to have a prostate biopsy because they've either read or been told that a prostate biopsy can spread cancer. It's true that a prostate biopsy can liberate benign and malignant prostate cells, but there isn't evidence that these liberated cells can set up shop outside the prostate. For one thing, our immune system is constantly destroying abnormal cells that stray into the blood stream. Furthermore, cancer cells must overcome another of other hurdles before they can survive elsewhere in the body. ²

IV. Tumor Staging For Positive Biopsies

a. Tumor Stage –

Before making a recommendation regarding treatment, other factors must be considered. These include the PSA level (the higher the PSA reading, the greater the risk for spread), tumor stage (extent of the cancer), and tumor volume among other things.

There are two types of staging- *clinical* staging (based on a correlation of the prostate biopsy findings, DRE, plus other blood and x-ray tests) and *pathological* staging (based on an examination of surgically removed tissue).

Clinical Staging

Clinical staging uses a system called *TNM*, which stands for **tumor (T), lymph nodes (N), and metastasis (M)**. The primary tumor stage is subdivided into four stages, designated T1 through T4. Cancers that are confined to the prostate are labeled as T1 -T2. Tumors that have spread outside the prostate, or into structures that surround the prostate, are designated as T3 - T4.

If the tumor has spread to the lymph nodes, it's designated as N+; if it has metastasized further, it's designated as M+. When there's a high likelihood that the tumor has spread beyond the prostate (for instance, when men have a prostate cancer with a Gleason score of seven or higher, or a PSA level that is greater than twenty), additional staging studies are usually ordered (e.g., ProstaScint scan, endorectal MRI, CAT scan – see the discussion below under imaging studies)

○ **Bloodwork –**

- **PSA:** Detected by a simple blood test, a 'total' PSA (usually referred to simply as a 'PSA' value or level) measures the total amount of PSA in the blood stream. Approximately ninety percent of the PSA in the blood is bound or stuck to another protein; the remaining portion is unbound.
- **Percentage-free PSA.** This modification of PSA measures the ratio between total PSA (bound and unbound) and the unbound or "free" PSA in the serum. This test is most useful for men with PSA levels between four and ten. According to some reports, the percentage-free PSA is more accurate than PSA alone in predicting the presence of prostate cancer.³ In prostate cancer, most of the 'free' PSA is bound to a protein in the blood called alpha-1-chymotrypsin so the percentage of free PSA is low.
- **Complexed PSA (cPSA)** This test measures the amount of PSA that is bound to protein in the blood (primarily alpha-1-chymotrypsin). This marker is more accurate than total PSA for values between 2.6 – 4.0 ng/dl (incidence of prostate cancer is as high as 26% in this range). The sensitivity is similar between total PSA (56%) and cPSA (63%) and %free PSA (64%) but the specificity is better for cPSA: 20% for cPSA vs. 9.8% for total PSA.⁴
- **PAP(prostate acid phosphatase).** If this marker is elevated it may indicate that prostate cancer cells have spread beyond the

prostate to done since tumor cells use this enzyme to hydrolyze phosphate in bone.

- **PCA3Plus** is a urine-based genetic for prostate cancer risk that tests for over expression of the PCA3 gene. The test is obtained by voiding into a specimen container after the prostate is massaged. The test is 75% specific for prostate cancer risk.
- **Neuroendocrine markers** are often generated by more aggressive tumors.⁵
 - ❖ **NSE (neuron specific enolase)** is increased in locally invasive disease
 - ❖ **CEA (carcioembryonic antigen)** If both NSE and CEA are elevated, cancer spread to liver and lungs is more likely.
 - ❖ **CGA (chromogranin A)** elevation may indicate aggressive disease if the level continues to increase, but if the level remains stable, the elevated blood level may simply be an indication of excessive bone resorption (loss).
- **Prolactin.** This hormone is made released by the pineal gland in the brain. If it is elevated it can make androgen receptors more responsive and increase prostate cancer growth.
- **Dihydrotestosterone (DHT).** Inside prostate cells, the enzyme 5-alpha reductase converts testosterone and the adrenal hormones DHEA-s and androstenedione into DHT. DHT is five to ten times more potent than testosterone. DHT binds with special receptors called *androgen receptors* inside prostate cells. The DHT-androgen receptor complex travels to the nucleus inside the cell with instructions that cause the nucleus to produce new DNA that causes benign and malignant cell growth.
- **Testosterone.** Made by the testicles and released into the blood stream, testosterone also binds to androgen receptors inside the cell. Inside prostate cells an enzyme called 5-alpha reductase converts testosterone into DHT.
- **Sex Hormone Binding Globulin (SHBG).** Made in the liver, SHBG is a protein that circulates in the blood and binds male and female hormones. The majority of sex hormones in our bodies are bound to SHBG. As such, bound hormones are unavailable to bind with receptors and influence cellular

activity. A small percentage of sex hormone, called the “free” fraction, are unbound; they’re free to bind with cellular sex hormone receptors. SHBG constantly regulates the concentration of “active” (free or unbound) male and female hormones in the blood. SHBG can also bind to the prostate cell membrane when it’s not bound to sex hormones and act as a second messenger – it can stimulate benign and malignant prostate cell growth. Similarly, mutations in the androgen receptor, increased androgen receptor concentration, and increased androgen receptor activity or sensitivity can allow other hormones, for instance, estrogen, progesterone, and prolactin, to promote benign and malignant cell growth.

- **Complete Blood Count (CBC).** If prostate cancer has spread to the bone marrow located inside the bone it can cause anemia (low blood count).
- **Liver profile.** Anti-androgen drugs (see discussion below) used to treat prostate cancer can damage the liver. A liver profile measures liver enzymes. Elevated liver enzymes may signify liver damage.
- **Leutinizing Hormone (LH).** Made by the pituitary gland in the brain and released in the blood stream, LH stimulates the testicles to make testosterone.
- **Immune function markers:** CD4 (T-helper cells), and CD4/CD-8 (T-supressor cell) ratio, and NK (natural killer cells) are markers of immune function.
- **Immunohistochemistry testing:** Prostate biopsy material can be analyzed for genetic abnormalities such as:
 - **DNA ploidy** Ploidy measures the chromosome makeup of cancer cells. Aggressive tumors usually exhibit an abnormal (aneuploid) pattern, whereas slow growing tumors predominantly exhibit a normal (diploid) pattern – two sets of chromosomes.

MOLECULAR PROGNOSTIC MARKERS⁶

- **Proliferative Antigens:**

1. **Ki-67** – nuclear antigen present throughout the cell cycle in dividing cells.
Overexpression (increased activity)
correlates with time to biochemical failure.

- **Aptosis-related proteins:**

2. **bcl2** is an integral membrane protein that inhibits apoptosis. Aggressive tumors have an over expression of high concentration of this proto-oncogene. *Bcl2* prevents cells from committing suicide (a process called apoptosis). Overexpression also correlates with increased risk of biochemical failure (see discussion under recurrent prostate cancer).
- **Growth factors:**
 3. **TGF-β1**: *Transforming growth factor beta* plays a role in the control of cellular proliferation (growth;), chemotaxis (movement in response to chemicals), angiogenesis (formation of new blood vessels), and cellular differentiation (as cancer cells become less differentiated, they are more aggressive). Loss of the inhibitory effects of TGF-β1 is associated with cancer progression. This molecular marker is measured by staining prostate tissue with a special chemical called a histochemical stain. It can also be measured by a blood test. Elevated levels are associated with an increased risk of invasion and metastasis.
 - **Adhesion molecules:**
 4. **E-cadherin** is a cell membrane protein that is involved in intercellular adhesion. It helps suppress invasion of cancer cells. Decreased levels increase the risk of locally invasive cancer or metastasis.
 5. **CD 44** is a cell adhesion molecule. Lower levels increase the risk for biochemical recurrence.
 - **Oncogenes:**
 1. **HER 2/neu** is a transmembrane tyrosine kinase growth factor receptor. It shares similar properties with epidermal growth factor receptor. Amplification of HER 2/*neu* is an adverse prognostic indicator

and is associated with advance disease and progression of androgen independent prostate cancer (discussed under recurrent prostate cancer)

▪ **Tumor Supressors:**

2. **p53** Also called guardian of the genome, *p53* is a pivotal tumor suppressor gene that blocks the cell growth cycle when there is DNA damage. This pause in the growth cycle allows time for the DNA damage to be repaired. Over 80% of prostate cancer cells, particularly more aggressive forms, have mutant (abnormal) *p53* genes. Mutations are associated with increased risk of biochemical failure and decreased survival.
3. **PTEN** is a phospholipid phosphatase that acts as a regulator in the PIP3/Akt signaling pathway that inhibits apoptosis and promotes cellular proliferation. Loss of PTEN increases cell growth.
4. **p27** or protein 27 (K1p1) inhibits an enzyme called cyclin-dependent kinase that affects cell cycle arrest and apoptosis. Absent or decreased levels are associated with an increased risk of biochemical recurrence.

Many of these tests are available in certain research centers: e.g., Bostwick Laboratories, www.bostwicklaboratories.com

• **Adrenal androgen precursors.**

- ❖ **Dihydroepiandrosterone –sulfated (DHEA-s).** In response to ACTH (adrenocorticotrophic hormone) released from the pituitary gland, the adrenal glands make a number of hormones from cholesterol. These adrenal hormones include two androgen precursors called DHEA and androstenedione. After being released into the blood, DHEA is sulfated (a sulfur molecule is attached) in the liver. Inside the prostate cell, DHEA can be converted to testosterone and DHT. DHEA also

increases the production of a potent cell growth promoter called insulin growth factor type-1 (IGF-1).

- ❖ **Androstenedione.** This androgen precursor can also be converted to testosterone and DHT inside the prostate cell.

- **Imaging Studies**

- **Bone Scan:** A bone scan is a nuclear medicine imaging study (“pictures” or images are taken). Performed as an outpatient, a tiny amount of nuclear material (called a tracer) is injected into a vein. Several hours later, after the tracer has had a chance to circulate throughout the skeletal system, a special camera is used to visualize any “hot spots” (a ‘positive’ scan) that light up in the bones. Although cancer may be the reason for a positive bone scan, other causes are more common, for instance, arthritis or previous bony fractures. Additional x-rays of suspicious areas will usually resolve the issue.

Men with a PSA level greater than twenty, or those with a Gleason score of 7-10 should have a bone scan. (Men with PSA values less than 20 have a less than 1% chance of having a positive bone scan.)

- **CAT scan:** A CAT scan (Computerized Axial Tomography) is a special type of x-ray study that uses a computer to cross sectional pictures of the body. Although helpful in certain circumstances, (for instance, to show the relationship and size of the prostate relative to surrounding structures when radiation therapy is planned) CAT scans are only 40-50% accurate in predicting if cancer has spread outside the prostate.
- **MRI:** The abbreviation MRI stands for **M**agnetic **R**esonance **I**maging. Using strong magnetic waves and radio frequency waves, a MRI obtains special computer generated images based on differences in tissue water composition. These images can be displayed three-dimensionally. Fancy as it sounds, MRI is even less accurate than a CAT scan at predicting spread of prostate cancer cells to the lymph nodes.

Several modifications of the MRI technology, though, have improved the accuracy of MRI scanning of the prostate. For instance, by using an additional coil called an **endorectal coil** (‘endo’ rectal means within the rectum) in addition to four external coils, a MRI scan can more accurately predict the stage of local prostate cancer. In fact, seminal vesical invasion by cancer cells as

well as spread of the cancer beyond the prostate capsule can be predicted in 96% and 81% respectively.

Another application of MRI technology, known as **MR spectroscopic imaging** (abbreviated MSRI) yields different pictures depending on the relative cellular concentrations of citric acid (citrate) within the prostate. The prostate normally makes large amounts of citrate, cancer cells don't. Based on research performed at University of California San Francisco, MSRI can be used to pinpoint the location of areas within the prostate that are suspicious for cancer. MSRI can also help detect cancer recurrence within the prostate. Read more about MSRI in *PCRInsights* (www.prostate-cancer.org August 2000 issue).

Ferumoxtran-10 high resolution MRI uses a special solution that contains ultra small super-paramagnetic iron oxide particles. A baseline MRI of the abdomen and pelvis is taken. Then the iron particle-containing solution is injected into a vein. A second MRI is taken 24 hours later. Normally lymph nodes take up the iron particle uniformly. When cancer is present in lymph nodes, the iron particles are not taken up evenly, which causes a moth eaten appearance. According to preliminary data, the sensitivity of the test is 90% and the specificity is 97%.⁷

- **ProstaScint scan** : –

ProstaScint is an antibody – a protein made by the immune system that seeks out and attaches itself to foreign proteins. One of these foreign molecules, called prostate specific membrane antigen, is expressed by normal prostate cells and even more so by prostate cancer cells. Made in the laboratory from the spleens of mice, ProstaScint is a special type of antibody called a monoclonal antibody. Monoclonal means all of the copies are exactly the same. ProstaScint antibodies are then tagged with radioactive material (In-111 capromabpendetide, PtostaScint®, Cytogen Corporation, Princeton, NJ) and injected into a vein. Once in the bloodstream, like a magnet, they are drawn to cancer cells and stick. A special camera called a gamma camera that uses single photon emission computed tomography (SPECT) to obtain different views (planar and cross sectional) looks for any radioactive hot spots.

The first scan, which takes about an hour, is taken 30 minutes after the ProstaScint has been injected. A follow-up scan

is taken 4 to 5 days later. This allows time for the tracer to seek out any cancer cells and decreases the false positive rate by allowing sufficient time for the isotope to washout of blood vessels and bowel. The second scanning session takes a bit longer, usually two and a half hours or so. The scanning procedure is harmless. The gamma camera doesn't emit radiation; it merely detects the presence of any tracer.

How accurate is the ProstaScint scan? Compared to a MRI or CAT scan, it's better at detecting cancerous lymph nodes. Nevertheless, the ProstaScint scan sensitivity ranges from 11-66% and specificity is less than or equal to 72%. Specificity is increased by 3-D MRI or CT fusion with the ProstaScint scan.⁸ (Sensitivity correctly predicts the presence of cancer; specificity correctly predicts the absence of cancer.)

The accuracy can be improved by combining ProstaScint with a CT scan or MRI (called a **Fusion CT or MRI-ProstaScint study**).

- **DEXA Scan:** is a study that measures bone mineral density. Loss of bone density occurs in up to 63% of men with prostate cancer. The rate is even higher when men are treated with medications that suppress male hormone. A baseline DEXA scan is recommended if men are going to be treated with androgen deprivation therapy (see discussion under prostate cancer recurrence) for longer than 12 months.
- **TRUS** Prostate size is measured as part of the transrectal ultrasound study. PSA density is determined by dividing the PSA value by prostate size. PSA density reflects tumor volume: As tumor volume increases, so does the risk of tumor spread outside the prostate.

Pathologic Staging

In addition to examining tissue under the microscope, the pathologic stage can be estimated by using special tables called **nomograms**. The best known of these tables, called the Partin nomogram, was devised by comparing the pathologic stage of thousands of surgical specimens with the preoperative clinical stage (DRE, Gleason score and PSA). Other nomograms integrate tumor volume and other parameters to predict tumor stage.

Nomograms can also predict the likelihood of tumor recurrence after surgery or radiation therapy. The Prostate Cancer Research Institute uses Neural Net Technology to evaluate and correlate disparate clinical and pathologic data (<http://www.prostate-cancer.org> , click on the tool bar under software, then click on [Prostate Cancer Tools II](#)). A prostate cancer prediction program by Memorial Sloan-Kettering Cancer Center is also helpful (<http://www.mskcc.org/mskcc/html/10088.cfm>)

- **Individualized treatment.** Factors that must be considered include a person's clinical stage (is the cancer confined to the prostate gland?), age and life expectancy (are they expected to live at least ten years?), and quality of life priorities (are they willing to trade a better chance for a cure, in exchange for an increased risk of complications such as urinary incontinence or impotence?).

When appropriate, I recommend definitive conventional therapies for prostate cancer – usually surgery or some form of radiation therapy - because prostate cancer can be cured 85% of the time when it's confined to the prostate gland.^{9,10}

Opponents of routine screening and aggressive management of prostate cancer argue that most men die with, not because of prostate cancer. However, they fail to mention that these statistics refer to latent or low-grade prostate cancer, not the more aggressive varieties. Prostate cancer is still the second leading cause of death in men. In the year 2001 alone, over thirty one thousand men died because of prostate cancer.

Although every man with prostate cancer is unique, there are still some basic principles that guide treatment decisions. Below I've listed a brief overview these principles and discuss management options for each stage of prostate cancer.

Organ-confined prostate cancer

A great summary of treatment options for organ-confined prostate cancer is outlined in *PCRInsights* (www.prostate-cancer.org August 2003 issue). A brief overview of options is listed below.

Active Surveillance

Active surveillance, just as the phrase implies, means that active surveillance rather than definitive treatment is planned. While active surveillance remains controversial, most researchers agree that under certain circumstances, it is appropriate. These situations include:

- ✓ Men who have life expectancy of less than 10 years, either due to serious medical problems or advanced age (usually over the age of 75).
- ✓ Patients over the age of 70 who have a low gleason score (6 or below) and a small volume of disease, such as incidental prostate cancer diagnosed on a TURP specimen (stage A1) or less than 10% of one biopsy core contains cancer. Men who fall into this category, if left untreated, have a life expectancy similar to that of men without prostate cancer.
- ✓ Tumors with a slow doubling time. Doubling time refers to tumor growth rate. Prostate cancer tumors can double as quickly as every 10 days, or take as long 10 years. The quicker the doubling time, the more dangerous the tumor. If left untreated, tumors with doubling times longer than 2.4 years are more likely to remain localized to the prostate, while those with doubling times less than 1.8 years have a greater risk of metastasizing. You can calculate your doubling time on the PCRI we site (www.prostate-cancer.org, [Prostate Cancer Tools II](#)).

During active surveillance, a PSA and DRE is checked every three months during the first year after diagnosis. A second restaging prostate biopsy is performed a one year after the initial prostate biopsy. The second biopsy is recommended to determine whether the prostate cancer has increased in volume or Gleason score. One third of the time, the repeat prostate biopsy doesn't show any prostate cancer. This doesn't mean that the cancer is gone, though, but it is a favorable finding. If the tumor hasn't increased in volume or Gleason score, the interval between evaluations can be changed to every six months. A repeat prostate biopsy is performed again in two to three years or sooner if a change is noted on DRE or the PSA significantly increases.

As part of the active surveillance protocol, I encourage men to incorporate the measures listed below under complementary therapies. A combination of healthy dietary and lifestyle changes coupled with selected

vitamins and supplements can often slow prostate cancer growth and delays the need for more aggressive therapies.

Active surveillance, though, isn't recommended for everyone. In particular, watchful waiting is not recommended for healthy men under the age of seventy with tumors confined to the prostate for the following reasons:

- ✓ **Tumor growth.** One dilemma is the certainty that *all* prostate cancers, if left untreated, will continue to grow.
- ✓ **Unpredictability.** Furthermore, despite careful observation, there is no way to accurately predict at what point a potentially curable cancer will spread beyond the prostate and become incurable.
- ✓ **Understaging** is another reason for caution. Understaging means that a tumor is more extensive or aggressive than suspected based on the biopsy report. Up to a third of prostate tumors are understaged.

Surgery

Developed around the turn of this century, surgical removal of the prostate, also called radical prostatectomy, is currently the most popular treatment for localized prostate cancer.

- *Procedures.* Two different surgical approaches are used to remove the prostate. One approach, called a *radical retropubic prostatectomy*, is performed through an incision made from the belly button to the pubic bone. Another approach, called a *radical perineal prostatectomy*, is performed through an incision made in the skin between the anus and scrotum. In both cases, the prostate and seminal vesicles are removed. Since prostate cancer can spread to the pelvic lymph nodes, this tissue is usually removed as well. The technique chosen depends on the surgeon's training. Both techniques work equally well. *Minimally invasive laparoscopic and robotic laparoscopic radical prostatectomy* is gaining momentum. Although the side effect profile is similar to open prostatectomy, the recovery is faster with a laparoscopic and robotic laparoscopic approach.
- *Hospital Stay.* Performed on the same day of admission to the hospital, the whole procedure takes two to three hours. With an open approach, men typically experience a two to three-day hospital stay. With a laparoscopic or robotic approach, men are usually discharged the day following surgery. With both types of surgery, a catheter remains in place for another seven (laparoscopic or robotic surgery) to

- fourteen days (open surgery). Depending on the situation, return to normal activity is usually possible within three to six weeks following open surgery and two weeks following laparoscopic and robotic surgery.
- *Advantages.* Surgery offers certain advantages that are not offered by the other therapies used to treat prostate cancer. These advantages include:
 - ✓ **Complete removal.** At least theoretically, surgery removes all of the cancer from the body.
 - ✓ **More accurate cancer staging.** Unlike non-surgical therapies for prostate cancer, tissue is examined under the microscope.
 - ✓ **Improved urination.** Men who experience difficult urination before surgery (due to an enlarged prostate) usually experience significant improvement in their voiding symptoms after surgery.
 - ✓ **Easier monitoring.** Without a prostate, the PSA should be non-detectable.
 - *Disadvantages.* In spite of its many advantages, radical prostatectomy has its complications. These complications can be divided into two main categories - early and late.
 - ✓ **Early complications** include blood loss and infection.
 - ✓ **Late complications** include urinary incontinence (loss of urine) and impotence (inability to get an erection). The risk of incontinence and impotence increases in older patients.
 - **Urinary incontinence.** Fortunately, urinary incontinence is usually temporary - over fifty percent of men regain continence by three months following surgery, and all but five percent of the remaining men regain control within a year. Men can speed the return of urinary control by practicing Kegel exercises. New modifications in surgical technique have also decreased the incontinence rate following radical prostatectomy. (For a detailed overview about the management of post-prostatectomy urinary incontinence visit our website at www.urolmd.com and click on health centers, and then articles, and then post-prostatectomy urinary incontinence.
 - **Impotence.** Following radical prostatectomy, more men are affected with impotence than urinary incontinence. Even so, when the nerves surrounding the prostate are 'spared', approximately sixty percent of men (who were potent

beforehand) maintain their potency after surgery.¹¹ (Note: It can take as long as 4 years for men to regain their potency following radical prostate surgery because the nerves are often bruised during surgery.) Even though impotence is common following radical prostatectomy, there are remedies.

- *Oral medications* (such as Viagra®) and injectable medications (such as prostaglandin E1) can restore potency in 40% of men that were potent before surgery..
- *vacuum tumescence pumps* (devices that cause penile swelling – ‘tumescence’ – by creating a vacuum) can correct impotence by increasing penile blood flow.
- Another device, called a *penile prosthesis*, bypasses the need for additional penile blood flow altogether. Performed as an outpatient surgical procedure, two silicone cylinders are positioned within the penis inside the space that normally expands with blood during an erection.
- *Cure Rate.* According to Johns Hopkins researchers, approximately eighty-five percent of men with stages T1 and T2, and forty-three percent of men with T3 tumors, treated with surgery are free of disease (cured) at ten years.

Radiation Therapy

First discovered in 1895, x-rays have been used to treat prostate cancer since 1910. Radiation therapy, (abbreviated RT) uses high-energy atomic particles (electrons, neutrons, protons and photons) to either directly or indirectly damage cellular DNA. The atomic particles carry excess energy that is deposited in target tissue, which displaces electrons (a process called ‘ionization’) and the released electron is a free radical that can directly or indirectly damage adjacent DNA. Tumor cells either stop growing or undergo apoptosis when their DNA is damaged.

- *Procedure.* Performed on an out patient basis, RT is delivered to the prostate by means of an external machine (hence the name ‘*external beam*’ therapy). Lasting fifteen to thirty minutes each; treatments are given daily for six to seven weeks. New modifications in equipment

and pretreatment planning have reduced side effects and improved outcome. For instance:

- Three-dimensional *conformal XRT* uses computer simulation to design a ‘forward’ treatment program that *conforms* to the prostate. Its accurate to within 7-10mm.
- *Intensity modulation (IMRT)* uses a special shield to modulate (vary) the emitted dose to maximize treatment to the prostate. Using ‘inverse’ treatment planning, IMRT sets dose for tumor and target volume and restricts dose to adjacent structures. Thousands of beamlets or ‘pencil beams’ of radiation coming from every conceivable direction create a radiation dose shape. IMRT is accurate to within 1-3 mm. Placement of gold markers into the prostate with a transrectal ultrasound procedure that is similar to a prostate biopsy improves the accuracy and safety of IMRT.
- Collectively, these two modifications minimize damage to surrounding tissues and permit higher doses of XRT to be safely given. Cure rates are increased with higher doses of radiation. Depending on the aggressiveness and stage of prostate cancer, doses range between 7200 – 8100 Gy (tumors with a high Gleason scores and those that extend beyond the prostate are treated with higher doses). The cure rate increases by 26% when the dose is increased from 6800 Gy to 7800Gy.
- Proton Beam therapy: Available since 1990, proton beam uses nuclear technology to shoot fast moving ions into prostate cancer cells, which promote apoptosis. This technology is expensive and it is only available in select locations in the US. The benefits of proton beam therapy versus IMRT are a matter of controversy.
- Cyberknife: The cyberknife uses a robot-directed arm to deliver radiation to prostate cancer and an image system that tracks the tumor in real time. Although early results are encouraging, long term follow-up studies are pending.

Furthermore, incorporating androgen withdrawal therapy (discussed later) for 2-3 months before radiation therapy and continuing it after therapy improves treatment outcome (the length of post treatment therapy is controversial and ranges from 3 months to 3 years). Withdrawing androgen kills cancer

cells, shrinks the size of the prostate, and makes radiation more effective because it has to kill fewer cancer cells. Androgen withdrawal also can kill cancer cells that have escaped to other parts of the body.

- *Advantages.* The chief advantage of RT is that surgery is not required. Most men can continue with their normal activities throughout therapy.
- *Disadvantages.* Similar to surgery, RT can also cause complications. For instance, RT can cause urinary complications such as difficulty voiding, or burning on urination; bowel complications such as diarrhea, or rectal pain; and impotence in sixty percent of men (who were potent beforehand). RT also increases the risk of bladder and rectal cancer. Even though the absolute number of men that develop bladder cancer is only one percent or so, the risk of developing bladder cancer increases as a function of time. Fortunately, natural therapies can decrease the risk of developing these radiation-induced cancers. For starters, men undergoing RT should take Selenium 200 micrograms daily, Green tea extract 500mg. twice daily, and drink enough water to make at least 2 quarts of urine daily.
- *Cure Rate.* As with surgery, the ‘cure’ rate following RT is determined by measuring the PSA value. Before starting RT, most patients have an elevated PSA level (greater than four). Following radiation therapy, the PSA level reaches its lowest level within eighteen months. Critz and colleagues report that eighty-eight percent of men are cured at ten years if the PSA level reaches 0.2 nanograms per milliliter or less and stays there. On the other hand, if the final PSA is 0.5 nanograms per milliliter or higher, only fifty-six percent of men are cured at ten years.¹² (Prostate cancer recurrences following RT are rare after ten years.)

Brachytherapy

Brachytherapy is an outpatient surgical procedure in which tiny radioactive seeds (usually Iodine 125 or Palladium-103) are implanted into the prostate gland. ‘Brachy’ means short – the radioactive seeds release their radiation over a short distance, as opposed to external beam RT, which affects a much broader area.

- *Procedure.* An outpatient surgical procedure, brachytherapy is performed under general anesthesia. A transrectal ultrasound probe is used to guide the placement of special needles – usually twenty-five

or so - into various areas of the prostate. These needles are poked through the skin isn't necessary. Measuring about the size of a rice grain, seventy to one in the perineum (the area between the anus and the scrotal sac) – a surgical incision hundred and fifty seeds are implanted throughout the prostate. The seeds give off intense radiation to an area measuring about the size of a dime. Although the seeds are permanent, they release most of their radiation within a year (ranging between three to twelve months, depending upon the type of seed that's used). The entire procedure takes about an hour. Normal activity can usually be resumed within a matter of a few days.

- *HDR brachytherapy.* This technique starts the same as traditional brachytherapy. Needles are placed through the perineum into the prostate using a special template as a guide. After a computer has determined the proper dose, a HDR machine is used to deliver intense radiation (Iridium-192) into each of the needles. A total of three treatments are given, each lasting about 5 to 8 minutes. The first treatment is given at the same time the needles are placed. The template and needles remain in place and the second and third treatments are given the following day, once in the morning and again in the afternoon. Following the last treatment, the template, needles and foley catheter are removed and the patient is discharged. Several weeks later, a series of twenty external beam treatments are given over a total of four weeks.
- *Advantages.* The chief advantage of brachytherapy is that it can be performed on as a single outpatient procedure. High-dose brachytherapy allows treatment planning and dose optimization before the implant, which allows adjustments to be made for abnormal anatomy. As a result, less radiation is given to the rectum and urethra.
- *Disadvantages.* Many of the same side effects associated with other therapies for prostate cancer are also encountered with brachytherapy. Furthermore, data on long-term cure rates are still preliminary.
- *Cure Rates.* Following brachytherapy, depending on the stage, between 65 to 80% of men are cured at ten years. (Cure is defined as a PSA less than 0.5 ng per milliliter.)

Cryotherapy

Cryotherapy, also called cryoablation (the prefix 'cryo' means to freeze and 'ablation' means to get rid of) was first used to treat prostate cancer in 1964. Like brachytherapy, modern cryotherapy has benefited from

advances in computer, x-ray imaging, and ultrasound technology. Delivered through special probes inserted into the prostate, liquid nitrogen or helium/neon is used to freeze the prostate. Cryosurgery is becoming more available. Even so, it has a steep learning curve (increased number of complications initially until the surgeon develops proficiency) and causes impotence in the majority of men treated because it can freeze the nerves that cause erection. Currently cryosurgery is usually reserved to treat men with high stage, high-grade tumors, and locally recurrent prostate cancer following XRT.

Focal Therapy: In an effort to decrease morbidity, researchers are experimenting with methods to localize prostate cancer tumors and restrict ablative therapies to the portion of the prostate that contains the tumor and spare the remainder of the prostate gland. Studies have shown that prostate cancer is located in multiple areas within the prostate 80% of the time, so until a better localization process is found and longer follow-up data is available, focal therapy should be considered experimental.

Androgen Deprivation Therapy as *Primary Treatment*

Androgen deprivation therapy (ADT) uses drugs and/or surgery to prevent androgen (male hormone) from stimulating prostate cancer cells. ADT is one of the mainstays for treating metastatic prostate cancer. Although ADT as primary treatment (instead of surgery or radiation therapy) is considered investigational, some oncologists and urologists are using ADT as first-line treatment for prostate cancer, especially for men who wish to delay more invasive options. Following prolonged ADT (one year or longer), researchers were surprised to discover that a small percentage of men's prostates no longer contained cancer cells when they were surgically removed. Unfortunately, though, there is no way of accurately predicting which men will fall into this category. Therefore, ADT should not be viewed as a cure for prostate cancer. Just the same, the use of primary androgen suppressive therapy (PAST) in men older than 80 years with localized disease increased from 3.7% in 1991 to 30.9% in 1999.¹³

In a prospective study of 276 men with clinically localized prostate cancer that received PAST (orchiectomy or LHRH-agonists with or without nonsteroidal antiandrogens), the overall survival at 5 years was 66% and the cancer specific survival was 91%.¹⁴ Four factors were associated with overall survival: age 75 years and older conferred twice the risk of death in five years; Gleason score 7 or greater was associated with a 4-fold increase

in death from prostate cancer; PSA greater than 20 ng/ml at diagnosis was associated with twice the risk of overall and cancer specific death within 5 years; and an abnormal DRE increased the risk of death within five years.

Orchiectomy:

Surgically removing the testicles (called a bilateral *orchiectomy*) effectively eliminates testosterone production, but it's not reversible. Therefore, orchiectomy is usually reserved to treat metastatic prostate cancer (discussed later). It is possible to remove the testicle without removing the epididymis (structure that is attached to the side of the testicle). This procedure, called a subcapsular orchiectomy, gives a better cosmetic appearance.

LHRH – agonists:

On the other hand, reversible “medical” castration is possible by using a medication called a LHRH (*Leutinizing Hormone Releasing Hormone*) agonist [stimulant]. Here's how it works: Under normal circumstances, a small gland located in the center of the brain called the hypothalamus regulates blood testosterone levels. It does this by releasing LHRH into a portal blood system that connects the hypothalamus and the adjacent pituitary gland. Inside the pituitary, the LHRH docks on special receptors to form a complex. This complex is broken down by a peptidase-enzyme, which releases LH into the systemic circulation leading to the rest of the body. The LHRH-binding complex in the pituitary is then free to bind additional LHRH.

Downstream, blood-borne LH targets testosterone-producing cells inside the testicles called *leydig* cells. LH stimulates leydig cells to make and release testosterone into the blood stream.

The hypothalamus is constantly monitoring hormone levels in the blood. If the levels are too high, the hypothalamus stops sending signals (e.g., LHRH) to the pituitary, which in response stops sending signals (e.g., LH) to organs (testicles) downstream. If, the levels are too low, the situation is reversed.

In the 1980's scientists formulated two LHRH agonists called Lupron® and Zoladex® that simulate natural LHRH made by the hypothalamus. The synthetic time-release medication is given intramuscularly (into a muscle) or subcutaneously (injected beneath the skin), once every month, three months, or four months depending on the formulation. A variety of new comers are now available, but all LHRH-agonists work in the same way.

Initially, similar to what occurs naturally, the testicles respond to the burst of LHRH-induced LH production by making more testosterone. This ‘flare’ response of testosterone production lasts only 5-12 days, but it must be blocked to prevent rapid prostate cancer growth. Starting oral medications called anti-androgens (e.g., Eulexin® and Casodex®, see discussion below) one week prior to administering LHRH agonist medication blocks testosterone’s ability to stimulate androgen receptor within prostate cells.

Within a matter of weeks after administering a LHRH-agonist, super normal levels of artificial LHRH ‘down regulate’ (make them less responsive) pituitary LHRH receptors. As a result, they no longer respond to LHRH and stop releasing LH. As a result, the blood testosterone level drops to a castrate level (20 ng/ml or less, same as removing the testicles) within a month of so.

Once the LHRH-agonist medication is stopped, the serum testosterone level gradually returns to normal. However, depending on the duration of ADT, it can take up to a year or longer for the testosterone level to normalize.

LH-RH antagonist: Arabinex® works differently than LHRH-agonists. It blocks the action of naturally produced LHRH. Due to reimbursement issues, it is currently only indicated in special situations.

Anti-androgens:

As mentioned earlier, the adrenal gland manufactures two androgen precursors called DHEA and androstendione. These two androgen hormones can be converted to testosterone inside the prostate cell. This process can be reversibly blocked at the level of the androgen receptor inside prostate cells by oral medications called *anti-androgens* (Eulexin® 125mg two pills three times daily or Casodex® at 50mg daily). High dose Casodex (150mg daily) is sometimes used when LHRH-agonists and ‘low’ dose antiandrogens have failed to suppress PSA and in patients with high risk prostate cancers (PSAs greater than 20 ng/dl, Gleason score greater than or equal to 7, and locally advanced prostate cancer).

5-alpha reductase inhibition:

In 1984, researchers discovered that an oral medication called finasteride (Proscar®) blocks the conversion of testosterone to dihydrotestosterone (DHT) by blocking the enzyme *5-alpha reductase*. DHT, you may remember, is five to ten times more potent than testosterone.

Proscar® 5mg is taken twice daily. (It should lower DHT level to $\leq 30\text{ng/dl}$)

Proscar® is traditionally used to treat benign prostate enlargement since it can shrink the prostate size by twenty percent or more. However, it can take up to six months to reach its maximum effect.

When used in combination with LHRH-agonists or anti-androgens, the side effects of Proscar® alone are hard to distinguish since the other medications cause similar effects.

Just the same, since Proscar® is occasionally taken alone, a brief discussion of its side effects is in order. Approximately five percent of men taking Proscar® experience impotence (the inability to obtain or maintain an erection), four percent complain of decreased sex drive, and less than one percent notice breast enlargement. In addition, about one third of men experience a reduction of seminal fluid. These side effects disappear once the medication is stopped. Although it's not considered to be a side effect, Proscar® can also increase hair growth for men with male pattern baldness. Finally, in men who have not been treated with androgen deprivation, it's important to know that Proscar® decreases serum PSA by up to fifty percent. Therefore, before starting Proscar®, these men should have a baseline PSA blood test, and a new baseline after taking the medication for six months.

Dutasteride® is newer *5-alpha reductase* inhibitor that blocks type 1 and type 2 alpha-receptors. Prostate cancer cells express both types of these receptors.¹⁵

Combination Therapy:

As stated above, when only one medication is used to block androgen it's called *monotherapy* (ADT1); when two or medications are used it's called *combination therapy*. When two medications are used together it's called androgen deprivation-2 (ADT2), and ADT3 when all three are used

Monotherapy usually implies some form of LHRH agonist medication is being used. However, in an effort to reduce the side effects of LHRH agonist medication, high dose Casodex (150mg daily) is occasionally used as 'monotherapy'.

Although data are conflicting, some experts recommend using combination therapy since each of these medications influences androgen stimulation at different levels. Just the same, a ten-year prospective randomized European study failed to show a survival benefit of using ADT2 versus ADT1.

Regardless of which therapy is used, though, the end result should be a serum testosterone level to $\leq 20\text{ng/dl}$.

Monitoring Treatment:

Baseline biomarkers discussed above (see staging) are measured prior to starting androgen deprivation therapy. Serum (blood) testosterone plus any other elevated biomarkers are measured monthly until they normalize. Serum PSA monitoring continues throughout therapy to detect any increase. The desired levels are a DHT ≤ 30 , serum testosterone $\leq 20\text{ng/ml}$, and PSA $\leq 0.05\text{ng/ml}$, and LH $\leq 1\text{ng.ml}$.

Normally, during androgen deprivation the serum PSA should remain non-detectable (less than 0.05 ng/ml using an ultra-sensitive PSA assay). If the PSA increases during ADT, other biomarkers may need to be checked again and further staging studies such as a bone scan may be indicated.

As an added benefit, the tumor's response to androgen deprivation can be used to predict the presence or absence of *androgen-insensitive* prostate cancer cells. If the PSA level drops quickly and stays non-detectable it suggests that the prostate cancer is *androgen-dependent*; that is, the cancer cells need male hormone to grow. Approximately eighty percent of prostate cancer cells fall into this category. This brand of prostate cancer is less dangerous.

On the other hand, androgen-insensitive prostate cancer (AIPC) cells don't need androgen to grow. Tumors with a high Gleason score (seven or above) usually contain some AIPC cells. If AIPC cells are present, the PSA takes longer to become undetectable in response to androgen withdrawal therapy, or the PSA remains elevated. Even if the PSA becomes undetectable (because of the death of androgen-sensitive cells), if AIPC cells are present, the PSA often starts to creep up again despite androgen withdrawal.

Reasons for an elevated PSA during androgen deprivation:

- The first thing that needs to be evaluated is the serum testosterone level. It should be $\leq 20\text{ng/ml}$. The androgen precursors DHEA-s and androstenedione and the **LH** level should also be checked.
- Certain blood pressure medications may interfere with androgen deprivation.¹⁶ Consider medication if men are taking calcium channel blockers (adalat, calan, cardizem, norvasc, Plendil, Procardia, Sular, Veilan) and use ace inhibitors instead.
 - **If the LH level is < 1 and the adrenal androgen precursors level is normal or increased:** the adrenal androgens can be suppressed with high dose ketokonazole plus prednisone. It's

most effective if it is started before the PSA is greater than 10. If a low PSA nadir is achieved, there is often a long remission. This combination works effectively in combination with chemotherapy (See *PCRInsights*, May 2004, for an in-depth discussion, www.prostate-cancer.org).

- If the **serum testosterone isn't $\leq 20\text{ng/ml}$** , the LHRH-agonists may not be doing their job. **If the LH level is > 1** , the LHRH agonist dosing interval can be switched from every 3 or 4 months to monthly. Alternatively, a LHRH antagonist can be used instead of a LHRH agonist.
 - If the patient taking a LHRH-agonist, but not an anti-androgen, an anti-androgen can be added.
- If the patient is on ADT2 or ADT3, and the androgen precursors are normal, **AIPC** is the probable cause.
- Protein phosphorylation: In order to bind DHT and testosterone effectively, the androgen receptor must be phosphorylated; that is, a phosphate molecule must be added. Additional phosphate groups are added to the DHT/Testosterone-androgen receptor complex to promote prostate growth. The start and stop signal for cell growth is also regulated by protein phosphorylation. AIPC induces abnormal protein phosphorylation - it tells cells to keep growing. In addition, abnormal protein phosphorylation allows prostate cancer cells to be stimulated by extremely low androgen levels. In other words, AIPC can grow despite androgen deprivation therapy because ADT doesn't totally eliminate androgen stimulation.¹⁷
 - ❖ An anti-inflammatory prescription drug called **Celebrex®** is a selective Cox-2 inhibitor that blocks genes that interfere with protein phosphorylation. Consequently, research is underway to determine if Celebrex® can prevent prostate cancer growth. Additionally, Celebrex® decreases the production of arachidonic acid (a special type of omega-6 essential fatty acid) metabolites that promote prostate cancer cell growth (see discussion in complementary therapies under dietary fat). Finally, Celebrex® blocks the action of IGF-1 and can improve the effectiveness of XRT and chemotherapy.¹⁸

- **High dose ketokonazole plus prednisone** is an alternative for treating AIPC. AIPC often contains genetic abnormalities such as mutant tumor suppressor gene p53, and oncogene bcl-2, both of which prevent apoptosis.
- **“Second line” hormone therapies** such as estrogen (DES 1mg by mouth plus low dose coumadin 1mg or 1 mg transdermal crème daily daily is sometimes effective for AIPC.
- **Chemotherapy** is also useful for treating AIPC and ARMs. (Visit the www.prostate-cancer.org web site for an in-depth discussion). The combination of Docetaxol and prednisone improved survival median survival by 2 months and significantly decreased pain, especially bone pain, and improved quality of life.¹⁹ Prostate cancer vaccines are also being evaluated.
- **Leukine (GM-CSF)** is used to reverse low white blood cell counts in patients receiving chemotherapy. Dr. Eric Small has used Leukine to treat men with advanced prostate cancer. Men were injected with 250 mcgs of Leukine subcutaneously (just under the skin) 14days out of 28 days. Cancer progression was slowed or even stopped.²⁰ Side effects are generally mild and consist of transient inflammatory reaction at the injection site and swelling. These side effects usually resolve within 72 hours of stopping the medication.
- **Natural therapies** are useful in AIPC:
 - ❖ **Melatonin** - Melatonin, a hormone made in the brain by the pineal gland, directly and indirectly inhibits the growth of prostate cancer cells. It does this by decreasing the production of prolactin and IGF-1, stimulating the anti-tumor immune system, and causing differentiation of cancer cells. According to one study, over half of the patients with hormone-resistant prostate cancer that took 20 mg. of melatonin at bedtime had their hormone sensitivity restored!²¹ Taking supplemental melatonin doesn't interfere with the brain's normal production of melatonin.²² Research has also shown that melatonin can enhance chemotherapy effectiveness.²³
 - ❖ **Milk Thistle** - Rich in antioxidant flavonoids known as silymarin, an extract of milk thistle seeds has been shown to inhibit prostate cancer initiation, promotion, and progression. Researchers report that milk thistle works by altering signaling molecules and adaptor proteins affecting epidermal growth factor receptor (a potent

stimulus of cell growth). As a result, prostate cancer cells, even AIPC, stop growing.²⁴ The protective effect of milk thistle is dose dependent. Therefore, take two hundred fifty milligrams (of a standardized extract containing seventy percent silymarin complex) four times daily with food.

- ❖ PC-SPES - A combination of eight Chinese herbs, the herbs within PC-SPES work synergistically to inhibit angiogenesis, stimulate the immune system, induce an estrogenic effect, and inhibit 5-alpha reductase.²⁵ PC-SPES also blocks the oncogene bcl-2. Consequently, PC-SPES inhibits the promotion and progression of both androgen-sensitive and androgen-insensitive prostate cancer. While treatment must be individualized, the usual dose is three 320mg capsules taken three times daily (available from Botaniclab, Brea, CA).

Although some patients take PC-SPES as primary treatment for prostate cancer, PC-SPES is not a cure for prostate cancer. Furthermore, since PC-SPES can cause serious side effects such as blood clots that can be fatal, therefore it should only be used under the supervision of a urologist or oncologist. Currently PC-SPES is unavailable because the manufacturer voluntarily ceased production because of contamination with other pharmaceutical medications including estrogens and coumadin.

- ❖ Green Tea - Green tea is rich in a group of flavonoid antioxidants called *catechins*. One of these catechins - *epigallocatechin gallate* (abbreviated *EGCG*) - has two hundred times the antioxidant power of vitamin E. Furthermore, EGCG kills hormone-insensitive prostate cancer cells.²⁶ Researchers theorize that green tea prevents cancer by preventing DNA strand breaks, inhibiting cell proliferation, decreasing the contact of carcinogens with cells, blocking cancer initiation, and slowing cancer progression. Since the protective benefit of green tea is dose dependent, I recommend taking five hundred milligrams of an herbal extract (standardized to contain eighty percent total polyphenol and fifty-five

percent EGCG) once daily for prevention, and twice daily for men with prostate cancer.

- ❖ Quercetin – Quercetin is a naturally occurring plant flavonoid found in onion, parsley, sage, tomatoes, and citrus fruits. Scientific research has shown that quercetin may inhibit the growth of androgen insensitive prostate cancer cells because it reduces the number of androgen receptors.²⁷ (Increased androgen receptor sites allow prostate cancer cells to grow at extremely low levels of androgen.) Quercetin is also available as a supplement. Take 250mg three times daily 20 minutes before meals along with equivalent amounts of bromelain (pineapple stem extract) to aid absorption.
- ❖ Indole-3 carbinol - Cruciferous vegetables (cabbage, broccoli, and cauliflower) contain this cancer-buster. Also available as a supplement, indol-3-carbinol decreases the activity of the oncogene bcl-2.²⁸

- If the androgen precursors DHEA-s and androstenedione are decreased, though, the PSA elevation may be due to an **androgen receptor mutation (ARM)**. Although the cause of ARMs varies, rapid tumor growth – the type seen with high-grade prostate cancers – increases the likelihood of genetic aberrations, including **ARMs**.

Normally the androgen receptor is finicky. Like a key in a lock, the receptor will only bind with DHT and testosterone. Androgen receptor mutations, though, change the shape of the receptor in such a way that it reacts with other substances. When ARMs are present, estrogen, progesterone, or even anti-androgen medication can stimulate prostate cell growth!

In fact, anti-androgens can even induce ARMs. Approximately 30% of men being treated with Eulexin® for several years develop androgen receptor mutations; but they're uncommon in men treated for less than one year.²⁹

- If the PSA is elevated because of an ARM, stopping the anti-androgen medication (called **Anti-Androgen Withdrawal**) will cause the PSA to drop.
- **Chemotherapy** is also useful for treating AIPC and ARMs. (Visit the www.prostate-cancer.org web site for an in-depth discussion).

- **Natural therapies** also have a role to play in combating ARMs. Over production of androgen receptors is one of the ways prostate cancers develop resistance to ADT. In laboratory studies, the following natural substances decrease androgen receptor concentrations³⁰:
 - ❖ Quercetin – see above
 - ❖ Green tea – see above
 - ❖ Resveratrol – found in grapes, red wine, Concord grape juice (16 oz, also increases HDL cholesterol and is higher in flavonoids and polyphenols than most red wines)³¹, and as a supplement (pure encapsulations® brand, 200mg capsule, take one daily). It activates P53 and blocks epidermal growth factor action.³²

(For more information on how to diagnose AIPC and ARMs, read *PCRInsights* October 1999, www.prostate-cancer.org).

Intermittant Hormone Therapy^{33, 34}: Assuming the PSA becomes non-detectable and remains so for a year, the LHRH-agonist and anti-androgen medication can be stopped, but Proscar® is continued since it can prolong the time men can stay off androgen deprivation by an average of 13 months.

PSA and testosterone levels are then followed monthly. Once the testosterone normalizes (≥ 150 ng/dl), continued monitoring is unnecessary. The time it takes for testosterone to normalize has prognostic implication. If it takes more than 4 months for the testosterone to normalize, men are usually able to stay off hormonal therapy for two years or more, whereas if it takes less than 4 months, androgen deprivation needs to be restarted much sooner - usually within 8 months after stopping the medication.

The indications for restarting androgen deprivation remain controversial. In general, treatment is resumed once the PSA reaches the pretreatment level or the PSA reaches 5, which ever is lower. If the PSA doubling time is less than 12 months, there is an increased risk of developing metastatic disease; therefore, treatment is often resumed earlier in this situation. Once ADT is restarted, the same routine is followed. In addition to reducing cost and improving quality of life, intermittent hormone therapy reduces the incidence of AIPC; after three years only 7% of men developed AIPC vs. 38.9% on continuous therapy.³⁵

Androgen Deprivation Syndrome: Although effective, androgen deprivation therapy can cause a number of unpleasant side effects, collectively known as the “Androgen Deprivation Syndrome” (see

www.prostate-cancer.org *PCRInsights*, January 1999 for details and preventive treatment strategies). Briefly these side effects include: anemia, muscle and joint aches, memory difficulties, frequent urination, impotence and loss of libido (sex drive), hot flashes (sudden sweating and flushing), fatigue, mood swings, breast enlargement, weight gain, liver damage, and osteoporosis.

In addition to the antidotes listed in *PCRInsights*, natural therapies discussed in *Smart Medicine for a Healthy Prostate* can be used to minimize some of these untoward side effects.

Treatments for Locally Advanced Prostate Cancer:

When the cancer has grown just outside the prostate, but nowhere else, it's called locally advanced prostate cancer (Stage T3N0M0). Unfortunately, other than surgery - where the tissue around the prostate can be microscopically examined - most tests are unreliable at predicting the presence or absence of cancer cells just outside the prostate gland. As a result, many tumors are under staged. In fact, after surgery, about fifty percent of men felt to have T2 disease (tumor confined to the prostate) are found instead to have T3 disease (tumor outside the prostate). Although the best management for locally advanced prostate cancer remains controversial, treatment often involves some type of surgery or radiation therapy. Androgen deprivation followed by brachytherapy and radiation therapy is one option. Chemotherapy is another consideration.

Treatments for Recurrent Prostate Cancer

In some cases, prostate cancer recurs even though the original therapy appeared to be curative. The best way to proceed in this situation is hotly debated among cancer specialists. Some favor immediate and aggressive treatment, others recommend conservative management (no treatment). Currently over sixty FDA-approved clinical trials are investigating options for treating recurrent prostate cancer. For more information on how to clinical trials visit the National Cancer Institute's web page (CancerNet @ <http://cancer.net.ncl.nih.gov/>) .

PSA recurrence only:

Many of my patients, particularly those who have had their prostates surgically removed, ask why they have to continue getting their PSA checked after treatment. It's important to monitor PSA because like radar, PSA can detect speeding cancer cells months or even years before they cause symptoms.

PSA elevation following therapy is also called a *biochemical failure*; that is, an elevated PSA *biomarker* implies that the treatment has failed.

- *After Surgery*: The PSA should become non-detectable (less than 0.05 ng/dl and ideally less than 0.01 ng/dl) within weeks after surgery and remain so. If the PSA elevation occurs early, especially within the first year or so following surgery, and the surgical margins were 'negative' (no sign of cancer outside the specimen), the recurrence is usually due to distant spread. Similarly, if the PSA doubling time is less than 9 months, or the pretreatment PSA was greater than 10, it also suggests there may be prostate cancer cells elsewhere in the body. An elevated PSA may be caused by persistent tumor if the surgical margins were "positive"; that is, cancer had spread beyond the prostate.

On the other hand, if the rise in PSA doesn't occur for years following surgery, the recurrence is usually local; that is, confined to the prostate 'bed' - area where the prostate used to reside. Most recurrences will declare themselves within seven years following surgery.

Either way, the workup is the same. Many of the same staging studies discussed earlier are repeated to determine where the cancer is located. If the studies show that the cancer is localized, radiation therapy is used to treat the pelvic region, focusing primarily on the prostate bed. Androgen deprivation is also part of the treatment plan. Clinical trials are also an option.

A 'salvage cure' occurs when the PSA becomes non-detectable following therapy and permanently remains so.

- After radiation therapy (XRT, brachytherapy). Ideally the PSA should decrease to 0.2 ng/ml or less within 18 months after therapy and remain there. A biochemical failure recurrence is defined as a PSA rise of at least 10% over baseline on three consecutive PSA determinations. Just the same, a bump in the PSA can normally occur during the first three years following radiation therapy. Prostatitis (prostate inflammation or infection) can also elevate the PSA level. Laboratory variation can also cause slight variations. Nevertheless, if the PSA continues to rise indefinitely, it signifies

recurrent prostate cancer. Patients with an increasing PSA following radiation therapy whose tumors were Gleason score 8 or above, and those whose tumor invaded the seminal vesicals or extended beyond the capsule are more likely to have distant disease.³⁶

If repeat staging studies don't show any sign of distant spread, treatment options including salvage radical prostatectomy or salvage brachtherapy (if XRT was used as primary treatment) can occasionally provide a "salvage" cure. Androgen deprivation and chemotherapy can also result in long-term survival. Clinical trials are also an option.

- Other options for slowing prostate cancer growth³⁷
 - Avodart® 0.5 mg or Proscar® 5 mg daily
 - Calcitriol (Rocaltrol®) 0.25 – 0.5 micrograms daily is the active form of vitamin D. It has anti-proliferative and anti-angiogenesis properties.
 - Dostinex – inhibits prolactin production by the pineal gland. Prolactin can stimulate the androgen receptor and thereby promote prostate cancer growth.
 - Celebrex 200mg daily
 - Leukotrine (Neupogen®) is a drug that stimulates white cell (leukocyte) production. It slowed or arrested prostate cancer in up to 50% of patients in one study.^{38 39}
 - Atacand is an angiotensin receptor blocker that may slow prostate cancer growth. Prostate cancer cells have angiotensin receptors on their cell surfaces.⁴⁰
 - Statin drugs such as Lipitor, Zocor, Pravacol, Lescol, and Crestor have anticancer effects and may slow the growth of prostate cancer cells. that lower cholesterol may slow the growth of prostate cancer cells.⁴¹
 - Mediterranean Heart Healthy Diet reduces the risk of heart disease and one study showed that it can reduce PSA doubling time.⁴²
 - Pomegranate Juice, 8 oz. daily or extract capsules that deliver an equivalent amount. One study showed that men with a median PSA doubling time of 13 months had their PSADT slowed to greater than 50 months by drinking 8 oz. pomegranate juice daily.⁴³
 - Mind-Body Medicine interventions (see below)

- Measures to slow PSA doubling time:

Supplements:

1. Vitamin D 1000 I.U. twice daily (increase dose if necessary to achieve a serum level between 50-100)
2. Lycopene 10mg one capsule three times daily (can take two with breakfast and one with dinner)
3. Selenium 200 micrograms daily
4. Soy isoflavones, 160 mg. Daily (www.revivalsoy.com)
5. Green tea extract 500mg daily
6. Quercetin 500 mg. Twice daily
7. Fish Oil, 4 grams daily in divided doses.

Metastatic prostate cancer:

When prostate cancer *metastasizes* it spreads to other parts of the body. Prostate cancer can spread by local extension, in the blood stream, or in the lymphatic system. When prostate cancer spreads locally, it invades surrounding structures in the pelvis. Although blood borne tumor cells usually spread to bone, they can involve other organs such as the brain, lungs, or liver. Lymphatic spread occurs via lymphatic vessels that drain the prostate.

Androgen deprivation therapy as discussed above, is used to treat metastatic prostate cancer. Early treatment reduces the incidence of serious complications, such as bone fractures, and paralysis due to spinal cord compression. Furthermore, if the metastatic disease is minimal, early treatment also improves survival.⁴⁴

Chemotherapy also has a role to play. When most people think of chemotherapy (medicine used to treat cancer), they think of the horror stories they've heard about or witnessed. Although chemotherapy can have serious side effects, modern chemotherapy is currently one of the most promising areas in prostate cancer research. Surprising, as it may seem, these recent advances are not the result of revolutionary new drugs. They're the result of using existing drugs in novel ways. (See *PCRInsights*, August 2001 for an in-depth discussion, www.prostate-cancer.org). The combination of Docetaxol and prednisone improved survival median

survival by 2 months and significantly decreased pain, especially bone pain, and improved quality of life.⁴⁵

Finally, regardless of the stage, complementary therapies for prostate cancer discussed below should be part of every treatment protocol.

Complementary Therapies

When I don my other hat, I recommend complementary therapies to all of my patients with prostate cancer, including men being observed without treatment (so-called “watchful waiting”), and men that have been advised to undergo definitive conventional cancer therapies, but choose not to do so. These recommendations are based on scientific research, not hearsay or advertising hype. Michael Lerner, author of the book *Choices in Healing*, lends further support. After spending ten years researching complementary and alternative cancer therapies from throughout the world, he made the following observation: “Patients [that use complementary and alternative therapies] achieve a higher quality of life, respond better to most conventional cancer therapies, experience fewer side effects of treatment and fewer symptoms of disease, control pain better with less need for medication, experience more lasting or partial remissions and, if they die, experience better deaths.”⁴⁶

In addition, scientific research has shown selected complementary therapies can prevent the onset, promotion, and progression of prostate cancer, even for men with a genetic risk for developing prostate cancer.^{47, 48} Furthermore, complementary therapies may even prevent prostate cancer recurrence or progression in men with a current or past history of prostate cancer.⁴⁹ That’s why I recommend complementary therapies even though prostate cancer has been treated (and I hope cured). It’s important to change the soil that allowed cancer to grow in the first place.

Unfortunately, this information is news to just about everybody - including urologists. That’s why I have written a book called *Smart Medicine for a Healthy Prostate* to spread the good news. Here’s a condensed version of my program:

Prevention:

Prostate cancer doesn’t occur overnight, it’s a dynamic process that is constantly evolving and potentially reversible. Healthy choices can prevent or favorably modify the biology of prostate cancer, whereas unhealthy choices have the opposite effect. That’s why I counsel all of my male

patients, especially those with prostate cancer or a family history of prostate cancer, to adopt the prostate cancer prevention program listed below. Furthermore, it's never too soon to start: Autopsy studies have shown that a small percentage of teenagers harbor latent prostate cancer cells, and the incidence increases steadily thereafter.⁵⁰

Diet:

Establishing healthy eating habits is one of the best ways to prevent prostate cancer. You can immediately start lowering your risk of prostate cancer by adhering to the following list of do's and don'ts.

Do:

- Eat plenty of *fruits and vegetables*, at least five to nine servings daily. Packed with cancer-fighting vitamins and minerals, fruits and vegetables dramatically lower the risk of developing prostate cancer.⁵¹ For instance, eating ten servings of tomatoes weekly (one serving equals a medium sized tomato or one glass of tomato juice) lowers the prostate cancer risk by forty percent, and a substance found in cruciferous vegetables (e.g., broccoli and cauliflower) called indole-3 carbinol decreases the chance of developing and dying from prostate cancer.^{52 53 54}
- Eat at least twenty-five to thirty grams of *fiber* daily. Dietary fiber (plant material that isn't digested) decreases the risk of prostate cancer by binding with and eliminating excess fat and hormones from the body.⁵⁵
- Add *soy protein* to your diet. Derived from soybeans, and rich in cancer-fighting substances called *isoflavones* (most notably genistein), soy protein dramatically inhibits prostate cancer cell growth.⁵⁶ Among other things, soy protein inhibits prostate cancer by blocking tyrosine-specific protein kinase - a potent cancer cell growth promoter, and preventing cancer cells from forming new blood vessels (called angiogenesis).

Don't:

- Eat excess *fat*. Limit your fat intake to 20% of total calories or less, and limit consumption of saturated animal fat – the type found in meat, dairy, and fast food products. Meat-based diets double the risk of developing prostate cancer by stimulating excess production

of an essential fatty acid called arachidonic acid.⁵⁷ Arachidonic acid byproducts stimulate prostate cancer growth and prevent apoptosis, plus they enable prostate cancer cells to evade the immune system, inactivate natural killer cells and cytotoxic T cells (cells that attach themselves to prostate cancer cells, and kill them), form new blood vessels, and invade surrounding tissues.⁵⁸ With the exception of olive oil, and to a lesser degree canola oil, most cooking oils increase arachidonic acid production, and therefore prostate cancer risk. Olive oil actually reduces prostate cancer risk.⁵⁹

Cooking red meat at high temperatures, especially when the meat becomes charred, increases the formation of a variety of cancer-promoting chemicals. One chemical called PhIP (2-Amino-1-methyl-6-phenylimidazo [4,5-b] pyridine) reacts with DNA and may increase the risk for prostate cancer. Bacon, hamburgers, and cured meats, particularly when cooked at high temperatures, increase carcinogen formation. On the other hand, white meat forms less PhIP during cooking. Eating cruciferous vegetables, resveratrol (found in red wine and concord grape juice), garlic, soy isoflavones, virgin olive oil, and tea polyphenols may reduce the risk of meat carcinogens.⁶⁰

- Eat *excessive calories*. When it comes to cancer prevention, researchers have discovered that the amount of calories consumed per meal may be even more important than the type of food eaten.⁶¹ A steady diet of excess calories can be dangerous. Obese men are two and a half times more likely to develop prostate cancer and three and a half times more likely to die as a result.⁶² Therefore, limit your caloric intake to five hundred calories per meal and one hundred calories or less per snack (adjusted for body mass and level of activity). Losing weight, even a little bit, also lowers prostate cancer risk.

Refined sugar also creates problems because it depresses the immune system, elevates insulin levels, and stimulates tumor growth by increasing arachidonic acid production.⁶³ Maintaining a protein to carbohydrate ratio of 3:4 slows the uptake of sugar thereby moderating the release of insulin.

NOTE: Patients undergoing chemotherapy or radiation therapy have special nutritional requirements. Avoid malnutrition by eating a balanced diet, and consume at least 1-2 grams of protein per kilogram (one kilogram equals 2.2 pounds).

I highly recommend a cookbook by Snuffy Myers that is entitled *Eating Your Way to Better Health* (Myers, CE, Rivanna Health Publication, Charlottesville, VA, 2002). You can order it online at www.prostateforum.com or by calling 1-800-305-2432.

Lifestyle

Lifestyle –how we live– can either increase or decrease the risk of prostate cancer. Decrease your risk by:

- Decreasing Stress. Although not specific for prostate cancer, stress can increase the initiation, growth, and metastasis of tumors. I've outlined a variety of stress busters in my book and on my web page under *Nursing & Patient Education*.
- Eliminating Unhealthy Habits. Smoking (even second-hand smoke) increases the risk of developing a more aggressive prostate cancer. Drinking excessive alcohol -more than 96 ounces of alcohol weekly (about 10 drinks) - triples the risk.^{64, 65} On the other hand, red wine consumption in moderation can be beneficial. Drinking 4 oz. of red wine 4 times weekly decreased prostate cancer in 50% of patients in one study.^{66, 67}
- Exercising. Regular exercise can reduce the risk of prostate cancer by forty percent.⁶⁸ It does this by reducing stress, improving immune function, and enabling the body to use insulin more effectively thereby decreasing the production of insulin growth factor type 1 (IGF-1). Men with IGF- 1 levels in the highest quartile are eight time more likely to develop prostate cancer compared to men with levels in the lowest quartile.⁶⁹
- Avoiding Toxins. Environmental estrogens found in pesticides, herbicides, and man-made chemicals increase the risk of prostate cancer.^{70, 71} Avoid them.

Vitamins, Minerals, Herbs, and Nutritional Supplements

Contrary to popular belief, scientific research has shown that the following items can favorably influence the incidence and progression of prostate cancer.

- Vitamins reduce prostate cancer risk by decreasing carcinogen formation, improving detoxification of harmful substances, decreasing cancer cell growth, improving cellular communication,

and controlling cellular differentiation and the expression of cancer.⁷²

- The Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study is a randomized, double-blind, placebo-controlled primary prevention trial. A total of 13 017 French adults (7876 women aged 35-60 years and 5141 men aged 45-60 years) were included. All participants took a single daily capsule of a combination of 120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of beta carotene, 100 µg of selenium, and 20 mg of zinc, or a placebo. Median follow-up time was 7.5 years. The results showed that men who consumed a multivitamin near the reference daily intake experienced a 31% decrease in cancer overall and a 48% reduction in prostate cancer.⁷³

On the other hand, reanalysis of the data showed that men with an elevated PSA had an increased risk of developing prostate cancer.⁷⁴ During the follow-up, 103 cases of prostate cancer were diagnosed. Overall, there was a moderate nonsignificant reduction in prostate cancer rate associated with the supplementation (hazard ratio = 0.88; 95% CI = 0.60-1.29). However, the effect differed significantly between men with normal baseline PSA (< 3 µg/L) and those with elevated PSA ($p = 0.009$). Among men with normal PSA, there was a marked statistically significant reduction in the rate of prostate cancer for men receiving the supplements (hazard ratio = 0.52; 95% CI = 0.29-0.92). In men with elevated PSA at baseline, the supplementation was associated with an increased incidence of prostate cancer of borderline statistical significance (hazard ratio = 1.54; 95% CI = 0.87-2.72). The supplementation had no effect on PSA or IGF levels. The authors concluded that their findings supported the hypothesis that chemoprevention of prostate cancer can be achieved with nutritional doses of antioxidant vitamins and minerals.

- Antioxidants work better in combination; therefore, I recommend taking a high potency multivitamin. In addition, if the concentration of vitamins contained in your multivitamin falls short in the following categories, take supplemental vitamins (in divided doses) to achieve a daily intake of:
 - 400 I.U. vitamin E (mixed tocopherols)⁷⁵ (daily intake of vitamin E > 400 IU may increase the risk of premature death, albeit the actual risk is quite low. Although the news media hyped a report that taking vitamin E can more than

double the risk of premature death, the actual risk was less than ½ of 1 %)

- 1000 I.U. vitamin D twice daily⁷⁶ (monitor your serum 25-hydroxyvitamin D3 level to ensure that it is between 50-100 ng/ml)^{77, 78, 79, 80}
- 5,000 I.U. vitamin A⁸¹ (doses > 5000 IU daily increase the risk of osteoporosis)
- 25,000 I.U. beta carotene⁸²
- 1000 mg. vitamin C⁸³

➤ Minerals:

- Selenium⁸⁴ - According to a landmark study reported in *The Journal of the American Medical Association*, men who supplemented their diet with the trace element selenium reduced their risk of developing prostate cancer by two thirds. In addition, selenium also decreases prostate cancer promotion and progression.⁸⁵ Other researchers noted an inverse relationship between blood selenium levels before the diagnosis of prostate cancer and the risk of advanced prostate cancer, especially in men with a PSA \geq 4 ng/ml.⁸⁶ Take at least 200 micrograms of yeast-derived selenium daily. (Taking up to 600 micrograms daily is usually well tolerated.) The SELECT Trial was terminated prematurely because Vitamin E and Selenium were not shown to decrease the risk of developing prostate cancer. The study was stopped after only 4 years, though. It may take much longer to demonstrate the benefit of Selenium supplementation. There was also a non-significant increase (less than 1% over placebo) of diabetes, which is unlikely to be problematic.
- Zinc - While not specific for prostate cancer, researchers have recently discovered that the essential micronutrient zinc inhibits the growth of prostate cancer cells and enhances apoptosis.⁸⁷ Take thirty to sixty milligrams of zinc daily.

➤ Herbs: Although not specific for prostate cancer, scientific research suggests that the following herbs may help prevent the initiation, promotion, and/or progression stages of prostate cancer. **The mechanism of action for each of the following herbs is described in my book.**

- Green Tea⁸⁸ - 500mg extract once daily for prevention and twice daily for men with prostate cancer.
- Curcumin⁸⁹ - A potent antioxidant, curcumin is the major ingredient of curry powder. Take four hundred to six hundred milligrams, three times daily.
- Frankincense (*Boswellia serrata*)⁹⁰ – Take four hundred milligrams of a standardized extract (containing sixty percent boswellic-acid), taken three times daily.

➤ Nutritional Supplements A variety of safe and cost effective supplements play a vital role in decreasing the incidence and modulating the promotion and progression of prostate cancer.

- Lycopene⁹¹ – Derived from tomatoes, take a ten-milligram oil-based lycopene capsule twice daily with meals for prevention, or three times daily, if there is a family history of prostate cancer, or if prostate cancer is present.
- Genestein⁹² - Although the optimal preventive dose is unknown, I recommend supplementing with at least forty milligrams of genistein daily for prevention, and eighty milligrams daily for patients with prostate cancer. Researchers found that men taking 100mg of soy isoflavones twice daily slowed prostate cancer growth by 84% and AIPC was slowed by 35% (www.novasoy.com, www.revivalsoy.com soy bars such as Apple Cinnamon Celebration contain 160mg of soy flavones, 16 grams protein, 33 grams carbohydrates, and only 3 grams of fat (220 calories), and sweetened or unsweetened soy powder can be used to make a shake; each packet contains 160 mg of soy isoflavones per packet; adding to regular soy milk will bring the total isoflavones to 200 mg daily).⁹³ Increasing daily consumption of soy in your diet will also increase your daily intake of isoflavones.
- Fish Oil⁹⁴ - Fish oil is rich in an essential omega-3 fatty acid called *eicosapentaenoic acid (EPA)*. Take up to six grams a day with meals in conjunction with gamma linolenic acid (GLA). (see below). Strive for a ratio of 5:1 EPA to GLA.
- Bicalin (Chinese skullcap, *Scutellaria baicalensis*) can inhibit the formation of inflammatory arachidonic acid byproducts by blocking cyclooxygenase and lipoxygenase enzymes.^{95, 96} It is available from practitioners of traditional Chinese Medicine.

- Itis-Care®- is a proprietary blend of anti-inflammatory supplements. It is manufactured by Dr. Narula and is available at Whole Foods. Take as directed.
- Zyflamend® is an herbal anti-inflammatory supplement that is comprised of 10 herbs (barberry, Chinese goldthread, ginger, green tea, holy basil, hu zhang, oregano, rosemary, *Scutellaria baicalensis* Georgi, and tumeric. Researchers at Columbia University Medical Center, New York, studied twenty nine men with high grade PIN (age 40 – 75 years). The men took one Zyflamend orally three times daily with food and without other nutritional supplements. There was no significant toxicity. After 18 months, the PSA values decreased more than 10% in 12 men (46%), and more than 50% in seven men (27%). In nine men (35%) the PSA increased and in 4 men (15%) there was no change in PSA level. Of 35 biopsies from 21 patients, 31 (89%) were negative for cancer. Four Gleason grade 6 cancers were detected in 4 men in 5% of all cores. Initial results showed that high grade PIN was reduced.⁹⁷

➤ But **AVOID** the following Hormones and Supplements:

Although useful in other contexts, the following items can promote prostate cancer. Therefore, men with prostate cancer and those in the high-risk category should refrain from taking:

- DHEA – Although promoted for everything from anti-aging to cancer prevention, DHEA can promote prostate cancer since it boosts serum IGF-1 levels.⁹⁸
- Human Growth Hormone – The same precautions apply for HGH since it promotes IGF-1 production.
- Chondroitin Sulfate - This popular supplement is used to treat arthritis. Three studies have suggested a possible link between chondroitin sulfate and the spread of prostate cancer.⁹⁹
- Testosterone - Male hormone promotes prostate cancer cell growth. Its use is contraindicated in men with untreated prostate cancer. It's use in properly selected patients with symptomatic hypogonadism that have been treated for prostate is controvertial.

Men taking prescription medication (especially chemotherapy) should check with their physician or pharmacist before using either of the following items:

- St. John's Wort – This popular herb is used to treat depression, a common problem for cancer patients. Caution is advised, though, since St. John's Wort can either increase or decrease the blood level of drugs metabolized in the gut by cytochrome CYP 3A. More than half of all currently used oral drugs fall into this category.¹⁰⁰
- Grapefruit juice – Although a good source of antioxidant vitamins, grapefruit juice also affects drugs metabolized in the gut by cytochrome CYP 3A.¹⁰¹

Mind-body Medicine

Scientific studies have shown that mind-body medicine techniques (such as prayer, hypnosis, progressive muscle relaxation, Yoga, meditation, mental visualization, and imagery, to name a few) restore hope, and improve immune function, quality of life, and survival of cancer patients.^{102, 103, 104} Consider the following:

Researchers compared the survival and quality of life among twenty-nine men with early stage prostate cancer. Men who attended at least five out of six specially designed support group meetings were compared against a matched group of sixty-five men who didn't attend these meetings.

Attendees at the support meetings discussed seven different topics: (1) The effect of one's beliefs, feelings and attitudes on health; (2) mental relaxation and imagery techniques; (3) nutrition and exercise; (4) stress management; (5) self-esteem and spirituality; (6) receptive imagery/intuition and problem solving, and; (7) creating a personal health plan/goal setting. The men attending the meetings were also given an audiotape on guided imagery and were encouraged to read several books on the same topic.

The results were astounding. The treatment group not only enjoyed a better quality of life - they lived twice as long as the control group. That's why I recommend mind-body techniques for all of my patients. I also encourage men to explore the deeper meaning of prostate cancer. As a starting point, I suggest reading an article listed on our web page (www.urolmd.com). Click on the heading of '**Health Centers**' on the home page ⇒ Holistic Medicine ⇒ Mind/Body/Spirit ⇒ "Spirituality and Prostate Cancer".

Dr. Snuffy Myers published a book entitled *Survivor Stories* (Myers, CE, Rivanna Health Publication, Charlottesville, VA, 2002) that chronicles survivor stories of men with prostate cancer. You can order the book online at www.prostateforum.com or by calling 1-800-305-2432.

Dean Ornish and colleagues conducted an innovative pilot trial, which showed that healthy dietary and life style changes plus mindfulness meditation and group support sessions can favorably change the expression of hundreds of genes. The lifestyle interventions started with a 3-day residential retreat followed up with weekly one-hour support sessions. A low fat diet consisting of 10% fat content was provided for each of the 30 men in the study. The men walked 30 minutes daily for 6 days each week and practiced daily stress management for 60 minutes. After 3 months, researchers found favorable changes in more than 500 genes!¹⁰⁵

Immune System Support

Finally, optimal immune function is vital for prostate prevention and every step of prostate cancer care. The measures discussed above are a good start, but additional measures are necessary if you want to achieve optimal immune support. This is particularly important for men with prostate cancer. Although space doesn't allow for an adequate discussion of this vital topic, I suggest reading a book written by immunologist Jesse Stoff, MD, called *The Prostate Miracle* (NY: Kensington Books, 2000).

Other Benefits of Complementary Therapies

In addition to prevention, I combine complimentary therapies with conventional cancer therapies to decrease the incidence and severity of side effects, improve their effectiveness, enhance quality of life, and prolong survival. Please refer to my book for specific recommendations.

Conclusion:

In conclusion, I recommend prostate cancer prevention for all men, starting as soon as possible, and PSA screening for men in the appropriate age groups. I also recommend conventional therapies for organ confined prostate cancer since they can cure prostate cancer 85% of the time. Even when cancer has spread beyond the prostate, conventional therapies can decrease morbidity and increase survival.

Just the same, I firmly believe complementary therapies should be a part of every treatment plan. Scientific research has shown that complementary therapies can prevent the initiation, promotion, and progression of prostate cancer. Complementary therapies also improve the efficacy of conventional therapies and reduce the incidence of treatment-related side effects, improve quality of life, and prolong survival.

As the field of complementary and alternative medicine continues to expand, I encourage all physicians to maintain an open mind and evaluate new research as it becomes available. We owe it to our patients.

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