PROSTATE CANCER

An introduction to aging science brought to you by the American Federation for Aging Research
The prostate is a golf-ball-sized gland that sits below the bladder, surrounding the urethra, at the base of the penis. A doctor can examine it with his or her finger through the front of the rectal wall. The prostate gland secretes a fluid that is a component of semen.

Cancer can arise in the prostate gland. After skin cancer, it is the most common form of cancer diagnosed in men. The latest American Cancer Society estimates are that about 240,000 new cases will be diagnosed, and 33,720 men will die of, prostate cancer in 2011. It is the second leading cancer killer of men, after lung cancer. About 1 in 36 men will die of prostate cancer.

**RISK FACTORS FOR PROSTATE CANCER**

**Gender**
All men are at risk.

**Age**
The incidence of prostate cancer increases dramatically during the decade from age 60 to 70. However, younger men can and do have aggressive prostate cancer. The average man over 50 is at risk.

**Race**
African Americans are significantly more likely to develop prostate cancer than whites and other ethnic groups.

**Diet**
Although this is controversial, a high-fat diet may increase the risk, likely through increased obesity.

**Family history**
A history of prostate cancer in close relatives increases your risk.

**Hormones**
Also controversial is the idea that higher baseline testosterone levels may increase risk.

*Of note: A few years ago, reports linking previous vasectomy to an increased risk of prostate cancer were published. However, subsequent larger studies determined there was no association between vasectomy and the risk of prostate cancer.*
HOW DO DOCTORS DIAGNOSE PROSTATE CANCER?

Prostate cancer is diagnosed based on a combination of signs, symptoms, and a variety of tests.

Signs and symptoms
Like many cancers, early prostate cancer typically occurs silently. In fact, most prostate cancer diagnosed today is found by an abnormal prostate specific antigen (PSA) blood test, long before there are any symptoms at all.

Advanced prostate cancer can produce back pain, cause weight loss and fatigue, and it can affect urine flow by causing obstruction, which in turn can precipitate decreased urine flow, increased urine frequency, and/or a feeling of bladder fullness after voiding. However, the most common cause of symptoms of reduced urine flow is benign prostatic hypertrophy (BPH), which affects the central portion of the prostate gland, and is not related to cancer. Therefore, symptoms are an unreliable guide in the diagnosis of prostate cancer, especially when the cancer is in the earliest, curable stages.

Tests to screen for prostate cancer
The two most important tests for prostate cancer can detect it early, before it produces symptoms. They are:

- **The digital rectal examination (DRE)** This is done by a physician, who inserts a gloved finger into the rectum and feels the prostate gland through the rectal wall for masses, irregularities, or hard areas.

- **Prostate specific antigen (PSA)** This is a blood test that measures a substance released by the prostate gland into the circulatory system. All men have some circulating PSA; the blood level can rise in prostate cancer, urinary tract infections, and BPH. The “normal” value for PSA varies with age and ethnicity, with older men and African American men having higher values. The National Cancer Institute (NCI) and the American Urological Association (AUA) recommend that both DRE and PSA testing be performed annually on all men over 50. However, screening decisions are complex with conflicting results from the most recent large screening trials. One such trial showed a decrease in disease-specific mortality, while a second trial showed no mortality differences. As a result, guidelines recommend POSSIBLE screening with PSA only for men with a significant remaining life expectancy (RLE). The American Cancer Society, for instance, recommends that only men over age 50 with a RLE of at least 10 years should be considered for screening, and the AUA recommends that men over 40 with a RLE of 10 years be considered.

Another approach is to consider screening candidates on the basis of RLE alone, without regard to age. The American Geriatrics Society takes this. A reasonable approach for all clinicians is to educate their patients on the benefits and risks of prostate cancer screening, encouraging them to make informed decisions.

Tests to confirm the diagnosis of prostate cancer
A biopsy of the prostate gland, which can be done in a urologist's office, confirms the diagnosis of prostate cancer. An appropriate biopsy includes the insertion of 12 needles into the prostate to provide adequate gland saturation. After being diagnosed, prostate cancer is then graded and staged. The grade of a prostate cancer, called a Gleason score, assesses how aggressively the cancer is growing on a scale from 2 to 10. A Gleason score of 2 to 6 is considered “low grade,” 6 is “intermediate grade,” and 8 to 10 is “high grade” — the most aggressive type, with the worst prognosis.

A prostate cancer’s stage refers to its spread in the body. Some doctors list the stages as A, B, C,
and D, while others refer to I, II, III, and IV. In A/I or B/II, the cancer is contained within the prostate gland; this is usually called “local disease.” In Stage C/III, it has spread outside the gland, but remains in the general vicinity of the gland; this is called “locally advanced disease.” In Stage D/IV, it has spread to distant parts of the body, such as the bone or other organs; this is called “metastatic disease.” Staging is determined through the use of imaging studies such as CT scans and bone scans.

Another way in which disease severity is assessed is by the degree of PSA elevation in the bloodstream. Patients with low PSA (10 or less) seem to do very well, while those with a higher PSA (10 to 20) do less well, and those with a very high PSA (greater than 20) tend to do poorly. This is called “biochemical” staging, and it can be used in combination with stage and grade to improve the accuracy of prognosis.

**CURRENT TREATMENT OPTIONS FOR PROSTATE CANCER**

A number of different treatment options exist for prostate cancer. Treatment choice will depend on the grade and stage of the disease, other co-existing medical conditions, the patient’s remaining life-expectancy, and the patient’s preferences.

As the descriptions of the various treatment choices below reveal, there is no one “right” treatment, and there is considerable controversy surrounding what the medical establishment considers the “best” treatment. Each patient must carefully confer with his doctor and family, weigh the treatment options, review their side-effects, and make a decision with which he is comfortable.

The current standard treatment options include:

**Watchful waiting and active surveillance**

Prostate cancer is often a slow-growing cancer that is not immediately life-threatening. Doctors and patients sometimes choose to follow its progress without immediately intervening, especially if the tumor is small and not causing symptoms, or if the patient is older and has other health problems that limit his life expectancy. Typically, PSA values are followed periodically, and a repeat biopsy is usually performed one year later. If the tumor does grow significantly, the Gleason grade increases, or if PSA levels rise quickly, more aggressive treatment (described below) is considered. Some men are appropriately concerned that the possibility of incontinence, sexual dysfunction, or both—common side-effects from treatment—outweighs the potential benefit of removing the tumor.

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Surgery
Radical prostatectomy, with or without robotic assistance, is typically offered to men with localized prostate cancer.

In this operation, the prostate gland and its surrounding tissue are completely removed through an incision. That incision is either made in the lower abdomen above the pubic bone or in the skin between the scrotum and the anus. The abdominal incision approach offers the doctor the option of trying to spare the nerves to the prostate if they are not involved in the cancer. This can often preserve sexual function. Complications from radical prostatectomy include urinary incontinence and impotence. Nerve-sparing surgery reduces, but does not eliminate, the risk of impotence.

Radiation therapy
Radiation therapy uses either X-rays (photons) or particles (protons) targeted at cancer cells. It is often the choice for prostate cancer that is confined to the gland (i.e. localized) or nearby tissue. Radiation therapy is as effective as surgery for localized cancer. The two main types of radiation therapy are external beam radiation therapy (XRT) and brachytherapy.

External beam radiation therapy (XRT) is more commonly offered to older men with localized prostate cancer. In this treatment, a machine delivers X-ray beams to the prostate gland. Treatments are typically given five days a week for several weeks. A new form of external radiation called conformal beam therapy, or intensity modulated radiation therapy (IMRT), uses computers and special equipment to very carefully focus the beam of radiation, so that more of the radiation reaches the tumor and less reaches and potentially damages the surrounding tissue. External beam radiation is often combined with androgen deprivation therapy (“hormonal therapy;” see below). Numerous randomized clinical trials have shown that for many patients the combination of XRT and hormones is more effective in eradicating prostate cancer than radiation alone. XRT is also frequently used for patients who have had a radical prostatectomy, but whose pathology report or post-surgical PSA suggests residual disease. This is called adjuvant or salvage radiation therapy. Common side-effects from external beam radiation include erectile dysfunction, radiation proctitis, nocturia, and increased urinary frequency.

Brachytherapy is sometimes offered to men with localized, low-risk Prostate cancer. This is a form of internal radiation therapy, in which radioactive pellets about the size of grains of rice are inserted directly into the tissue of the prostate gland, using needles inserted through the skin between the scrotum and anus. They emit their radioactivity over several weeks and are left in place after they lose their radioactivity. In high-dose rate brachytherapy, radioactive needles are inserted into the prostate gland and left there for just one day. Brachytherapy is often combined with external beam radiation to give higher doses of radiation both inside and outside of the gland without damaging normal tissues.

Hormonal therapy (androgen deprivation therapy)
Male hormones or androgens, particularly testosterone and dihydrotestosterone, enhance the growth of prostate cancer; female hormones such as estrogen slow it. Thus, drugs that oppose male hormonal effects or mimic female ones are useful in controlling prostate cancer. These treatments are collectively called androgen deprivation therapy (ADT). ADT is considered in several situations:

- First-line treatment to older men with localized prostate cancer who are not candidates for surgery
- Combined treatment with external beam radiation therapy for localized prostate cancer
- Treatment for prostate cancer which has spread outside the prostate gland

ADT typically causes multiple toxicities that are especially worrisome for older adults. It increases fracture risk, age-related muscle loss, obesity, and frailty. ADT also increases the risk of developing diabetes, coronary artery disease, heart attacks, and strokes. These side-effects raise the concern for lowering quality of life and premature death from treatment effects on competing diseases.

The types of androgen deprivation therapies available include:

- **Orchiectomy**
  This is surgical removal of the testicles, eliminating the source of male hormones. Prostate cancers typically shrink after removal of the testes. However, over time, the cancer inevitably returns.

- **Luteinizing hormone-releasing hormone (LHRH) agonists**
  These injectable medications reduce the amount of testosterone the testicles make. The two most widely used in the United States are leuprolide and goserelin.
• **Antiandrogens**  
  Orchiectomy and LHRH agonists do not fully block the production of androgens. Antiandrogens block the effects of residual androgens and are often used in combination with orchiectomy and LHRH agonists in a process called dual androgen blockade. The standard antiandrogens available in the United States are flutamide, nilutamide, and bicalutamide.

• **Female hormones**  
  Di-ethyl stilbesterol (DES) is a synthetic estrogen sometimes used to treat prostate cancer. Progesterone is a “female” hormone, and it is sometimes useful when the other hormonal treatments fail. Megestrol acetate and medroxyprogesterone are the two used in this country. PC-SPES is a fairly new herbal blend that appears to contain highly estrogenic properties.

**Chemotherapy**  
Chemotherapy is used in patients whose cancer has spread beyond the prostate gland and surrounding tissues and who are no longer responding to ADT. Some of the medications used include docetaxel, estramustine, carbazitaxel, etoposide, vinblastine, and paclitaxel. They are given orally, intravenously, or by injection into the muscles. They have adverse effects and do not generally offer a cure, but rather help control the disease. Clinical trials are underway to look for more effective chemotherapeutic drugs. Other clinical trials are underway to investigate the role of chemotherapy in patients with a poor prognosis (high PSA, high Gleason’s score, or a lot of palpable disease) but localized (non-metastatic) disease. These patients’ cancers are rarely controllable with surgery or radiation, and it is hoped that the addition of chemotherapy will increase curability of these lesions.

**New options**  
Despite the multiple standard options for prostate cancer treatment, many have significant side effects such as incontinence, osteoporosis, or sexual dysfunction. New approaches are seeking to limit these and other side effects. For example, robotic-assisted laproscopic radical prostatectomy helps preserve sexual function in men under 60 by using newer nerve sparing approaches. In this procedure, the surgeon locates the bundle of nerves responsible for sexual response than run alongside the prostate gland. If those nerves are not involved in the prostate tumor, the surgeon makes every attempt to avoid cutting, removing, or damaging them during the surgical procedure. A recent study completed at Cornell showed that 90.7 percent of men younger than 60 with localized disease were able to maintain orgasmic and erectile function after the procedure. This method is not foolproof, because some of the nerves are hard to identify and protect. Despite the best efforts of their surgeons, most men who undergo prostate removal (radical prostatectomy) experience some postoperative sexual dysfunction, which often resolves over the next year.

As with surgery, the technological revolution is also advancing the field of radiation therapy. Perhaps the fastest developing area is in Intensity Modulated Radiation Therapy (IMRT). Previously, the prostate could only be irradiated by four to six beams coming from a limited number of angles. These beams often traversed (and thereby damaged) adjacent normal tissues like the bowels and bladder, leading to proctitis and cystitis. The calculations and 3-D imaging necessary for any more beams were beyond the range of standard treatment-planning computers. Modern computers have helped surmount this limitation. IMRT uses thousands of tiny beams (each of which carries a negligible amount of radiation) to bombard the prostate from many different angles in three dimensions. The point at which all of these tiny beams intersect (the prostate) is “zapped” with a high enough dose to destroy the cancer while the dose in the surrounding structures is small. Clinical studies continue to explore this technique’s efficacy and side effects and larger clinical trials are underway.

**PROSTATE CANCER AND AGING**

More than 80 percent of men diagnosed with prostate cancer are over age 65. The older a man becomes, the greater his risk of developing prostate cancer. About 20 percent of all American men will be diagnosed with prostate cancer, and about four percent will die from it. Given the indolent nature of the disease, most older men with prostate cancer will die with the disease rather than from it.

The decision to screen, diagnose and treat prostate cancer is complex, especially for older men, since they are more prone to toxicities from diagnosis (i.e. biopsy) and treatment. As mentioned above, a reasonable approach might be to base screening and treatment decisions on a patient’s remaining life expectancy (RLE). Easy to use geriatrics tools can
help assess RLE. These tools assist clinicians in individualizing treatment options to offer patients and family members.

**LATEST RESEARCH**

Research is showing that certain aspects of diet, exercise, and lifestyle may influence the risk of developing prostate cancer.

**The role of diet**

A diet lower in fruits, vegetables, and vitamin D may contribute to an increased risk of prostate cancer. Milk is the only dairy product associated with increased prostate cancer risk. This is likely because dairy products are rich in calcium and phosphorus. High calcium and phosphorus intake causes changes in the body’s metabolism of vitamin D, resulting in a lower level of circulating active vitamin D.

Fructose, a plant sugar, is associated with a lower risk of prostate cancer, probably because it increases levels of circulating active vitamin D. A study from Harvard Medical School of nearly 1,800 men with prostate cancer found that those with the highest consumption of dairy products had a three-fold higher risk of having advanced prostate cancer and a five-fold higher risk of having metastatic prostate cancer at the time of diagnosis. High intake of foods containing fructose (fruits and vegetables, mostly), on the other hand, was associated with a lower risk of having advanced prostate cancer at the time of diagnosis. In addition, higher consumption of legumes, nuts, finfish/shellfish, and alpha-tocopherol cause a decrease in prostate cancer risk.

A series of studies have evaluated the role of dairy products and prostate cancer. The Physician Health Study, consisting of a cohort of 12,000 men, reported a higher risk of prostate cancer among men with higher intake of dairy products. These results were similar to a study done in males in Sweden with high intake of dairy products. Based on the results from these epidemiologic studies, a correlation between long-term, high intake of dairy products and increased risk of prostate cancer, has been found. However, further studies are needed to confirm these results.

Some men choose to drink soy milk rather than cow’s milk. An epidemiologic study of 12,395 Seventh-Day Adventists revealed that those who drank soy milk more than once a day had a 70 percent reduction in their risk of prostate cancer. Soy milk contains isoflavones, and the authors of the study speculated that these could be the protective factor in soy milk. They recommended further studies to confirm their results.

Studies that have looked at vitamin A intake and prostate cancer have been conflicting, with some finding a higher risk for men with high intakes and other studies finding a reduced risk. Vitamin A belongs to a category of nutrients known as carotenoids, a class of antioxidants. The largest study to date (29,104 men), examining the association between exposure to retinol and prostate cancer incidence, showed that men with higher retinol levels at baseline were more likely to develop prostate cancer.

Numerous small epidemiological studies exploring the risk of certain food groups with prostate cancer have been published. A large case-control study, conducted in Cleveland Clinic, looked at 982 men with prostate cancer. In summary, this study showed that prostate cancer was inversely associated with increased intake
of leafy and high carotenoid vegetables, cooked greens (spinach, mustard greens, or collards), bean soups, and fruits (berries, orange, melon). On the other hand, foods with high glycemic index like dark breads (bagel, rolls), French fries, potato chips, chocolate, and soft drinks, were associated with increased risk of prostate cancer. However, these findings are inconsistent and relationships need to be explored further.

A brief study at the Duke University Medical Center looked at the effects of flaxseed and a low fat diet on prostate cancer. Twenty-five prostate cancer patients followed a low fat diet with supplements of flaxseed. The flaxseed, indigestible when whole, was ground and the men sprinkled it on cereal or mixed it into juice or applesauce. At the end of a month, the men had lower cholesterol levels and lower testosterone levels as well. In men with less aggressive cancers, the diet was associated with a small decrease in PSA levels, but in those with aggressive disease, the PSA levels continued to rise. Biopsies of their tumors revealed that the flaxseed, low fat diet resulted in lower rates of cancer cell division. The scientists cautioned that the study was too small and too short to draw conclusions but suggested expanded studies were in order.

A study from the Karolinska Institute in Stockholm, Sweden, reported that men who consumed higher levels of fatty fish, such as salmon, herring, and mackerel, reduced their risk of developing prostate cancer. Over 30 years of study revealed that men who ate large amounts of such fish, which contain omega-3 fatty acids, had a two-to-three times lower risk of developing prostate cancer than men who ate no fish.

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Other risk factors
Researchers from the Health Professionals Follow-up Study also looked at the relationship between height and weight and the risk of prostate cancer. Men who were tall as adolescents had a higher risk of metastatic prostate cancer (and this might be related to earlier exposure to male hormones, as reflected in their younger achievement of adult height). Interestingly, men who were obese in their youth had a lowered risk of advanced prostate cancer. Obese males have somewhat lowered levels of male hormones and experience some conversion of their hormones to estrogen (a female hormone). Thus, adolescent hormonal levels might be related to older adult risk of developing prostate cancer.

Adult hormonal levels are also likely to influence the risk of developing prostate cancer. Diabetes can reduce the levels of testosterone a man has. The Health Professionals Follow-up Study has found that men who have had diabetes for at least five years have a lower risk of prostate cancer, and their risk falls even lower after ten years of diabetes. On the other hand, the Cancer Prevention Study performed by the Centers for Disease Control and Prevention found a higher incidence of prostate cancer in men who had diabetes for more than five years. The relationship between diabetes and prostate cancer needs to be further explored.

Smoking has been associated with a number of cancers, but the evidence linking it to prostate cancer has been weak. A study of over 1,000 men conducted in Utah, where a great many people belong to the Mormon Church (and thus do not smoke, drink alcohol, or use caffeine) found that none of those lifestyle choices played a role in the risk of developing prostate cancer. Though not a randomized study, the Health Professionals Follow-up Study has followed nearly 50,000 male physicians ages 40 to 75 for decades. Nearly 1,400 of them were found to have prostate cancer. Although no link was found between smoking and the occurrence of prostate cancer, a correlation was found between smoking and the occurrence of fatal prostate cancer.
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at PMSA. Early trials involving
such a vaccine have been report-
ed. Researchers in Seattle have
followed 19 patients who were
given an anti-PMSA vaccine for
up to 2 years. Reductions in tumor
activity were observed in men with
metastatic prostate cancer for an
average of 149 days after vaccine
administration and 187 days for
those with only local disease. An
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tigators in Maryland revealed that
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responded to the vaccine, some
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ses and a drop in PSA levels. The
next phase of trials has begun.

Antigens are proteins or other
substances that are typically
found on the surfaces of our cells.
Sometimes, our bodies generate
antibodies, immune proteins that
fit with those antigens like locks
and keys, specifically matched to
one another. Among the antigens
found on prostate cells is the well-
known prostate specific antigen,
or PSA, which is used as a marker
for the disease. Researchers in
Minneapolis have created a medi-
cation that combines the immune
response to PSA with a chemo-
therapeutic drug. Using cancer-
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BONE DENSITY AND PROSTATE
CANCER TREATMENT

Like women, men need their hor-
mones to maintain the density of
their bones. Men who lose andro-
gens, male hormones, are at risk
of developing osteoporosis and
osteoporotic fractures. The medi-
cal goal is to prevent the loss of
bone both during aging and for
treatment of prostate cancer. Since
late 1990s, research of agents
which protect men on androgen
depression therapy from develop-
ing osteoporosis, led to the use
of the use of bisphosphonates, in
particular zolendronic acid. Men
with widely spread prostate cancer,
had a reduction of bony fractures,
and other skeletal complications
when placed on intravenous zolen-
dronic acid at the time they started
androgen deprivation therapy.

However, bone breakdown from
prostate cancer is different from
bone breakdown in other cancers.
To treat bone loss caused by pros-
tate cancer, researchers at Johns
Hopkins University developed a
drug they call Denosumab. A study
comparing zolendronic acid to
denosumab in men with prostate
cancer with body-wide spread,
showed denosumab to be more ef-
fected in preventing fracture, spinal
cord compression in men with
hormone-resistant prostate cancer.

THE FUTURE OF PROSTATE
CANCER RESEARCH

Researchers will continue to try to
piece together the prostate cancer
puzzle, seeking better modes
of prevention, screening, and
treatment.

Prevention

While at this time, there is no
definitive knowledge about how
to prevent prostate cancer, a large
clinical trial of finasteride (Proscar),
a drug that has been used to treat
BPH, is being tested as a preven-
tive measure. Finasteride reduces
levels of dihydrotestosterone (DHT),
a male hormone that is important
in normal and abnormal prostate
growth. DHT plays a key role in
benign prostate enlargement and
is also believed to be involved in
the development of prostate can-
cer. Although Finasteride delays
the appearance of prostate cancer,
men on finasteride had a higher risk
for more aggressive cancer.
Several studies are also looking at antioxidants and dietary supplements as possible chemopreventive substances.

**Screening**
Another question under investigation is when and whom to screen. Researchers are looking at genetic markers that could suggest more accurately which men need to be screened earlier. In addition, geriatric assessment tools are being developed to assess RLE, in order to establish whether screening will benefit older men.

And research is also underway to test other, more finely calibrated screening measures that can help doctors better predict aggressive disease and when to do biopsies or not. These include Percent-Free PSA, Age Specific PSA, PSA Density and computer models that can incorporate multiple factors such as age, gland size, family history, race, and other factors.

**Diagnosis**
Clinical researchers are seeking to improve biopsy technique and yield. For example, they are studying Image Directed Biopsies, in which CT Scans, MRI-MR Spectroscopy, and Nuclear Medicine technologies are used to improve the accuracy of biopsies and to provide additional clues on who is more likely to develop cancer and who is not.

**Treatment**
The National Cancer Institute is currently supporting studies to compare surgery to active surveillance in the management of prostate cancer and to assess the quality of life of patients undergoing treatments.

Even after surgery to remove the prostate, some patients suffer from residual disease (e.g., elevated PSA levels indicating biochemical recurrence of disease). Researchers, therefore, are testing surgery with and without follow-up radiation to prevent relapses. Another way to improve the odds of surgical eradication is to add hormones to surgery, and this too is being evaluated in clinical trials.

On the radiation side, radiation-hormone combinations are being tested, as are improvements in radiation techniques that will shorten treatment time and produce more accurate radiation beam delivery. Researchers are also looking at the efficacy of new chemotherapeutic approaches plus radiation for high-risk prostate cancer, as well as more accurate ways of placing radioactive pellets using MRI techniques. Others are seeking genetic methods for targeting antibodies to cancer cells.

In patients who have had surgery and/or radiotherapy but have persistently elevated PSA, doctors know that cancer remains but are unable to find where it is and eradicate it. Researchers are exploring the development of an injectable monoclonal antibody (molecules produced in the laboratory that are designed to attach to specific defects in your cancer cells) that would effectively find prostate cancer cells and give off a kind of homing signal. This signal would then guide doctors to the residual cancer cells.

In castrate-resistant prostate cancer patients, three treatment choices exist, namely docetaxel, sipuleucel-T, and cabazitaxel. Increased survival from all treatments is less than five months. Other novel targeted therapies are being studied.

Finally, untangling the genetics of prostate cancer is a major research area. Developing genetic biomarkers of aggressive cancer would improve the information available through biopsy and drive treatment options/choices. Ultimately, developing ways to “turn off” the responsible genes could provide a way to stop pre-cancerous or even cancerous lesions or cells and prevent the disease from spreading.