

PROSTATE CANCER PATIENT GUIDE

A comprehensive resource on diagnosis, treatment, side effects, and risk factors for patients and families with a history of prostate cancer.



**“Be vigilant, live healthy,
and don’t give up. This disease
can be conquered.”**

— FORMER COMBAT MARINE, KOREAN WAR

About this guide

There are no two ways about it: being diagnosed with cancer is hard and it is life-changing. Despite increasing optimism about treatment, today's cancer landscape can be challenging, as patients have access to an unprecedented amount of information. There are literally millions of cancer-related webpages, blogs, and videos available at your fingertips. But it's important to acknowledge that this isn't always a helpful thing. A cancer diagnosis can be disorienting, and for many, the overwhelming volume of information available can be more of a burden than an aid.

This guide focuses all of the information available about contemporary prostate cancer research, treatment, and lifestyle factors into one consolidated resource. It is for any man who has been newly diagnosed, who is in treatment, or is concerned about a rising PSA. Beyond that, it's for any loved one or caregiver who wants to cut through the information noise and get directly to need-to-know information for prostate cancer patient navigation. Lastly, as we are beginning to recognize the genetic underpinnings of cancer, this guide is for any family member who might want to understand how their shared genes affect their own short- and long-term risk factors—and whether they should be screened as well.

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This guide was originally released in 2017, and updated for print in 2019, by the Prostate Cancer Foundation (PCF). The Prostate Cancer Foundation is the world's leading philanthropic organization funding and accelerating prostate cancer research. Since its beginning in 1993, the Prostate Cancer Foundation has funded key research leading to many of the treatments used by doctors today to improve the lives of patients, with the mission that someday, soon, no man will die of this disease.

Subjects depicted are models and are used for illustrative purposes only. Prostate cancer standards of practice change regularly. For the most up-to-date information, please register for updates at [pcf.org](https://www.pcf.org).

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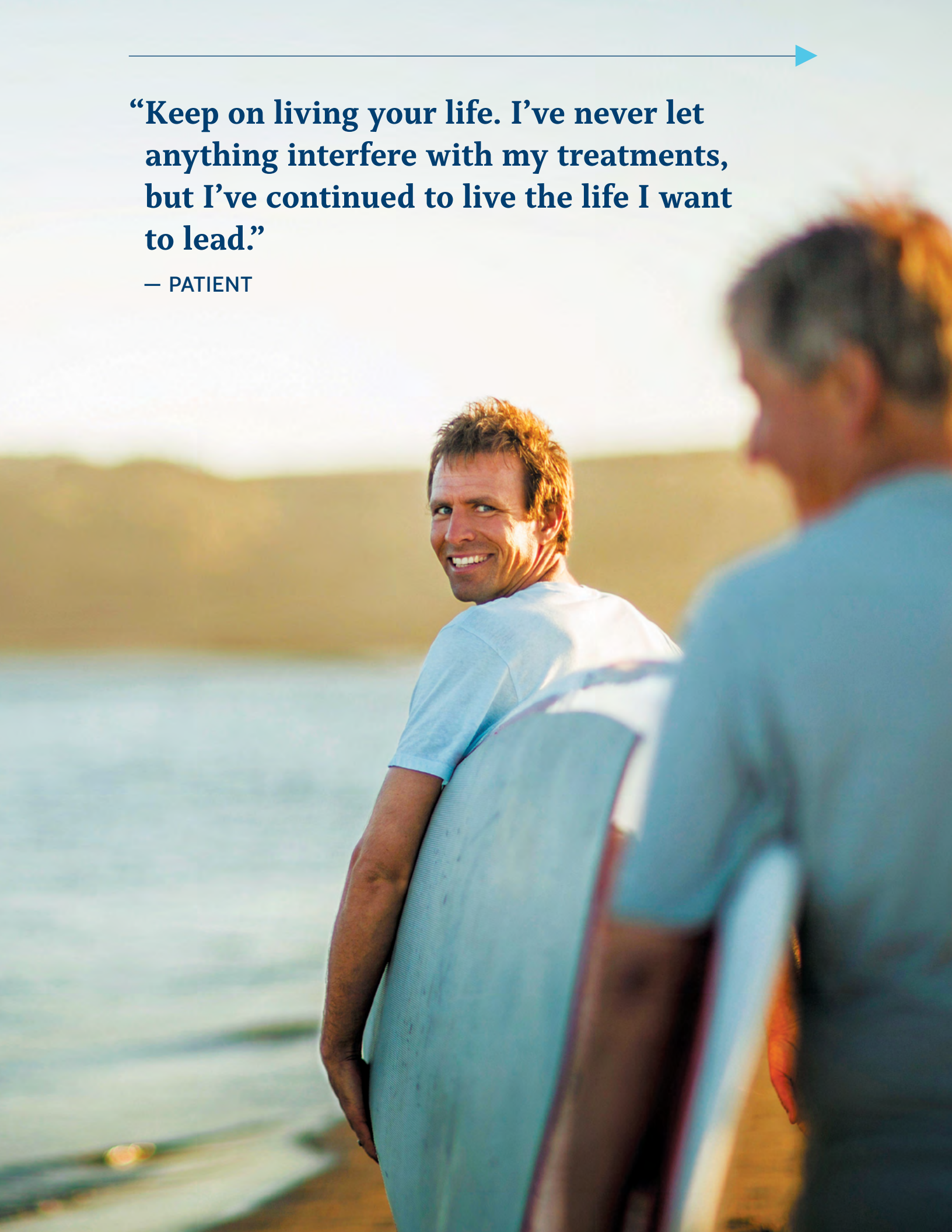
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“Keep on living your life. I’ve never let anything interfere with my treatments, but I’ve continued to live the life I want to lead.”

— PATIENT



GENERAL INFORMATION

What is Prostate Cancer?

In general, **cancer** is a condition in which a normal cell becomes abnormal and starts to grow uncontrollably without having the signals or “brakes” that stop typical cell growth. Prostate cancer starts in the prostate, a small gland located below the bladder that is responsible for secreting one of the components of semen. Prostate cancer cells form masses of abnormal cells known as **tumors**.

Prostate cancer, therefore, is when a normal prostate cell becomes altered and starts growing in an uncontrolled way.

In many cases, prostate cancer is relatively slow-growing, which means that it takes a number of years to become large enough to be detectable, and even longer to spread outside the prostate, or metastasize. However, some cases are more aggressive and need more urgent treatment.

Surviving Prostate Cancer

Approximately 95% of all prostate cancers are detected when the cancer is confined to the prostate, so treatment success rates are high compared to most other types of cancer in the body. **The 5-year survival rate in the United States for men diagnosed with prostate cancer is 99%.** In other words, the chances of the cancer spreading or men dying from their prostate cancer is generally low. However, prostate cancer comes in many forms and some men can have aggressive prostate cancer even when it appears to be confined to the prostate.

Amidst much optimism and progress in the last 10 years, it's important to keep in mind that prostate cancer is still a deadly disease for some men, and it is the second leading cause of cancer death among men in the US, with nearly 87 men dying from it every day.

In general, the earlier the cancer is caught and treated, the more likely the patient will remain disease-free. In fact, many men with “low-risk” tumors, which are the most common type of prostate cancer, can safely undergo active surveillance, in which they are monitored without immediate treatment (and treatment-related side effects) while still preserving their chance of long-term survival if the cancer becomes aggressive enough to require treatment.

Rates of Diagnosis

Prostate cancer is the third most prevalent type of cancer in the US and the fourth most common worldwide. Nearly 175,000 new cases are estimated in the US for 2019, and about 1.27 million men were diagnosed globally in 2018. Approximately one in nine men in the US will be diagnosed with prostate cancer at some point in their lives. The older you are, the more likely you are to be diagnosed with prostate cancer.

Although only about 1 in 437 men under age 50 will be diagnosed, the rate shoots up to 1 in 59 for ages 50 to 59, 1 in 22 for ages 60 to 69, and 1 in 13 for men 70 and older. Nearly 60% of all prostate cancers are diagnosed in men over the age of 65.

IS THERE A CURE FOR PROSTATE CANCER?

When people think about cancer treatment success, they often think of the word “cure.” Thanks to advances in treatment in the last 15 years, it is sometimes possible to say that a man has been “cured” of prostate cancer. However, more often statisticians think of “cure” as a function of time: is 5 years without a cancer recurrence equal to a cure? Or is it 10 years? Unfortunately, in some men, prostate cancers can recur even 10 years after treatment. So instead of using the term “cure,” doctors commonly use terms such as *biochemical control* (PSA levels kept at bay) or *freedom from developing metastatic disease* (the cancer has not spread to distant organs) to help quantify the success of prostate cancer treatment.

20 genes

that run in families have been discovered that have overlap from prostate cancer to other cancers.



Since 1993, deaths from prostate cancer have been cut in half.



If the prostate cancer is caught at an early stage, most men will not experience any symptoms.

99%

Prostate cancer is 99% treatable if detected early.

Prostate cancer has one of the highest survival rates of any cancer.

10 THINGS TO KNOW

A man of African descent is 76% more likely to develop prostate cancer.

76%

As men age, their risk of developing prostate cancer increases exponentially.

Thanks to emerging science, in the next 5 years, we may see an end to all incurable prostate cancer.



In the US, prostate cancer is the **most common** non-skin cancer in men.

2x

Men with relatives with a history of prostate cancer are twice as likely to develop the disease.

Prostate cancer is almost always diagnosed with a biopsy. The most common reason for a man to undergo a prostate biopsy is due to an elevated prostate-specific antigen level, or PSA, determined by a blood test. Recent changes in PSA screening recommendations have impacted the rates of prostate cancer diagnosis (see [Screening for Prostate Cancer](#), page 73).

Risk Factors

As indicated by the rates of diagnosis, **age** is the biggest—but not the only—risk factor for prostate cancer. Other important factors include family history, genetic factors, race, and lifestyle and dietary habits.

Genes that increase risk for disease can run in families. Genetic factors contribute to about 40% of all prostate cancers, which makes prostate cancer the most “inheritable” of all cancers. Men who have a relative with prostate cancer are twice as likely to develop the disease, while those with 2 or more relatives are nearly 4 times as likely to be diagnosed. The risk is even higher if the affected family members were diagnosed before age 65. Men may also be at increased risk of prostate cancer if they have a strong family history of other cancers, such as breast cancer, ovarian cancer, colon cancer, or pancreatic cancer. Because family members share many genes, there may be multiple genetic factors that contribute to the overall risk of prostate cancer in a family. However, there are also some individual genes that we now know increase the risk of prostate cancer, and men with these genes may need to undergo genetic counseling, be screened differently, or consider changes in treatment. For more on family risk, see [The Genetics of Risk](#), page 73.

It is still a scientific mystery, but African American men are 76% more likely to develop prostate cancer compared with white men, and 2.2 times more likely to die from the disease.

Prostate cancer appears to develop about 3 years earlier among African American men, on average, than among white men. Whether this phenomenon is due to environmental factors—such as diet, stress, and exercise; socioeconomic factors—such as those related to access

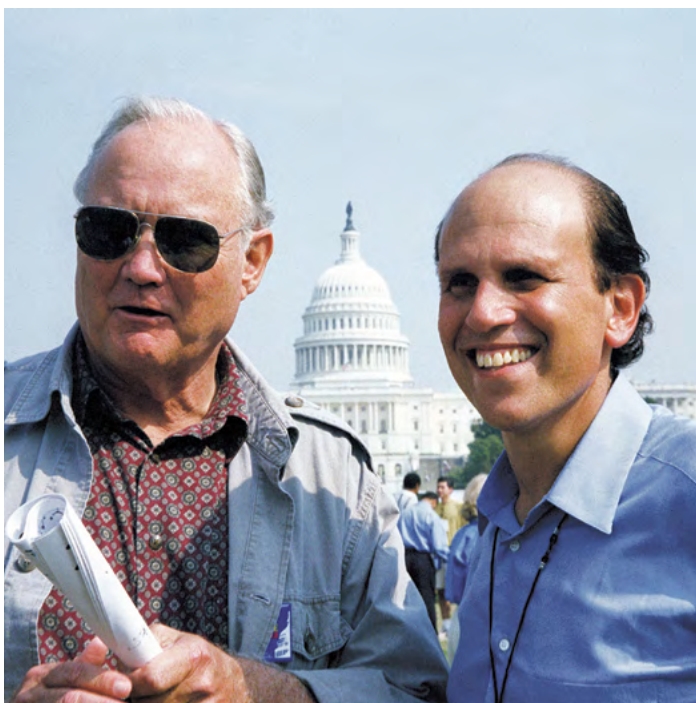
to healthcare; or genetic factors—such as genes that run in families, remains unclear. Improving understanding about the origins of risk will help inform better treatments and is an active area of research for the Prostate Cancer Foundation. In the meantime, it is important to keep in mind that not every African American man will get prostate cancer, and that all prostate cancer has a better chance of being managed effectively and cured if it is detected early.

Other risk factors for prostate cancer are [social and environmental factors](#)—particularly a high fat, high processed carbohydrate diet—and lifestyle. Men who are overweight or obese are at greater risk of ultimately developing an aggressive form of prostate cancer. Research has shown that in obese men, recovery from surgery tends to be longer and more difficult, and the risk of dying from prostate cancer can be higher.

Symptoms

If you've recently been diagnosed with prostate cancer, you may be asking yourself if there were warning signs or symptoms you should have noticed earlier. Unfortunately, there usually aren't any early warning signs for prostate cancer. The growing tumor usually does not push against anything to cause pain, so for many years the disease may be silent. That's why screening for prostate cancer is such an important topic for all men and their families. In rare cases, prostate cancer can cause symptoms that include:

- ▶ A need to urinate frequently, especially at night, sometimes urgently
- ▶ Difficulty starting or holding back urination
- ▶ Weak, dribbling, or interrupted flow of urine
- ▶ Painful or burning urination
- ▶ Difficulty in having an erection
- ▶ A decrease in the amount of fluid ejaculated
- ▶ Painful ejaculation
- ▶ Blood in the urine or semen
- ▶ Pressure or pain in the rectum
- ▶ Pain or stiffness in the lower back, hips, pelvis, or thighs



PCF founder and chairman Michael Milken is joined by General Norman Schwarzkopf in 1998 on the Mall in Washington for “THE MARCH: Coming Together To Conquer Cancer.”

Keep in mind that urinary symptoms don't necessarily mean you have cancer. Prostatitis and BPH (**Benign Prostatic Hypertrophy**, also known as enlargement of the prostate) are common and benign diseases that can cause similar symptoms.

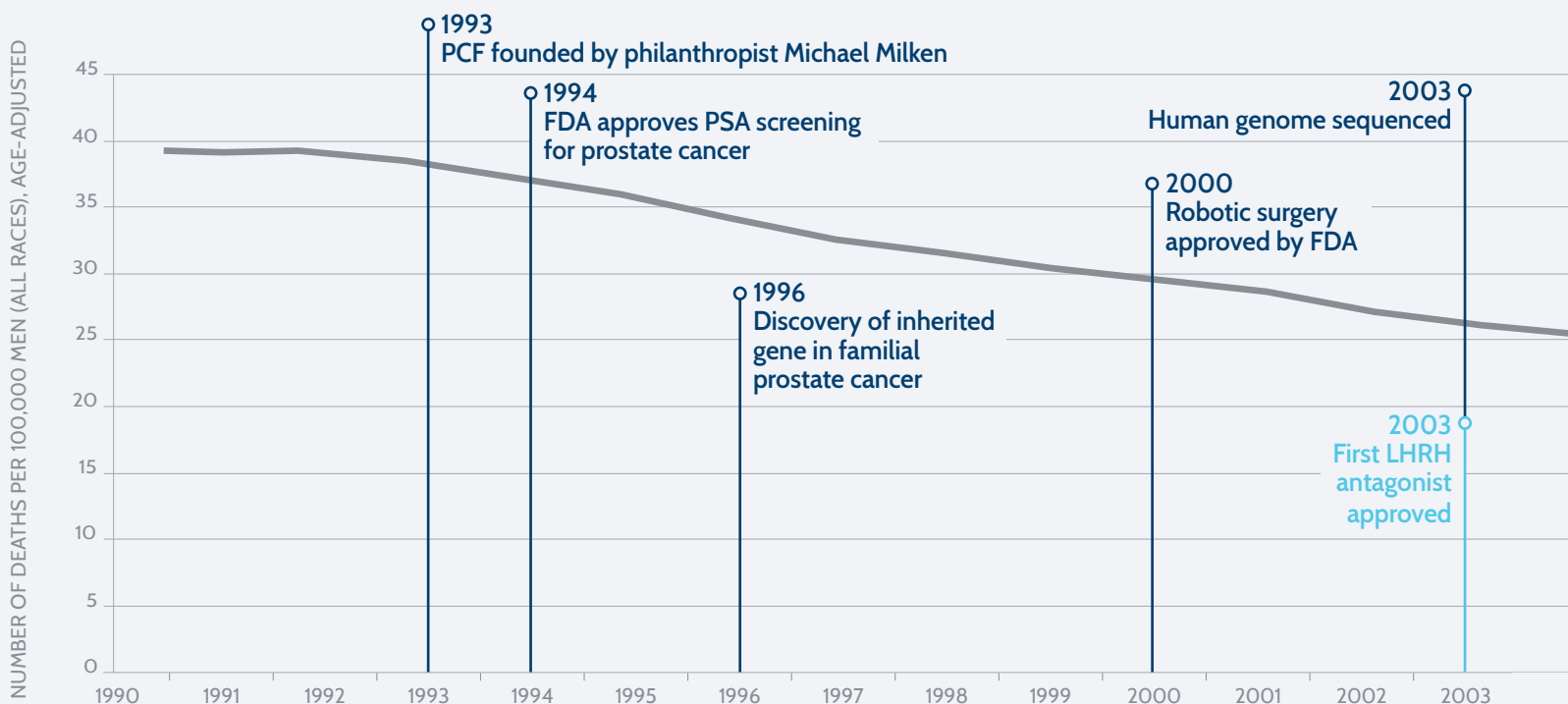
What about difficulty in having an erection? Again, this is most likely not caused by prostate cancer but by other factors such as diabetes, smoking, high blood pressure, cardiovascular disease, medications, or aging.

Remember: Symptoms are symptoms, and no matter what's most likely to be causing them, you should get them checked out by a doctor.

History & Progress

Modern prostate cancer research was framed in the 1940s by the discovery that **hormones**, primarily testosterone, were responsible for the growth of prostate tumors. Over the next 5 decades, various types of chemotherapy, radiation therapy, surgical options, and hormone therapy were refined.

Breakthroughs in Prostate Cancer Treatment and Practice



In 1994, the FDA approved the PSA blood test to detect prostate cancer in men without symptoms. Since cancer detected early is much easier to treat, use of the PSA test for screening has contributed to the subsequent increase in the number of patients diagnosed early enough to be cured with surgery or radiation, and has substantially contributed to a 52% reduction in deaths from prostate cancer over the past 2 decades in the U.S. However, the PSA test sparked concerns that it has led to over-diagnosis and over-treatment of non-aggressive, slow-growing prostate cancers that may never have caused harm to the patient.

Since 1993, when the Prostate Cancer Foundation began funding life-prolonging advancements in research, amazing strides have been made in finding therapies for treating advanced prostate cancer that are now part of an improved standard of care. There have been tremendous advancements, including:

- ▶ Imaging technology to help find prostate cancer
- ▶ Precision radiation therapy
- ▶ Development of robotic surgery
- ▶ Numerous new FDA-approved therapies that help men live longer

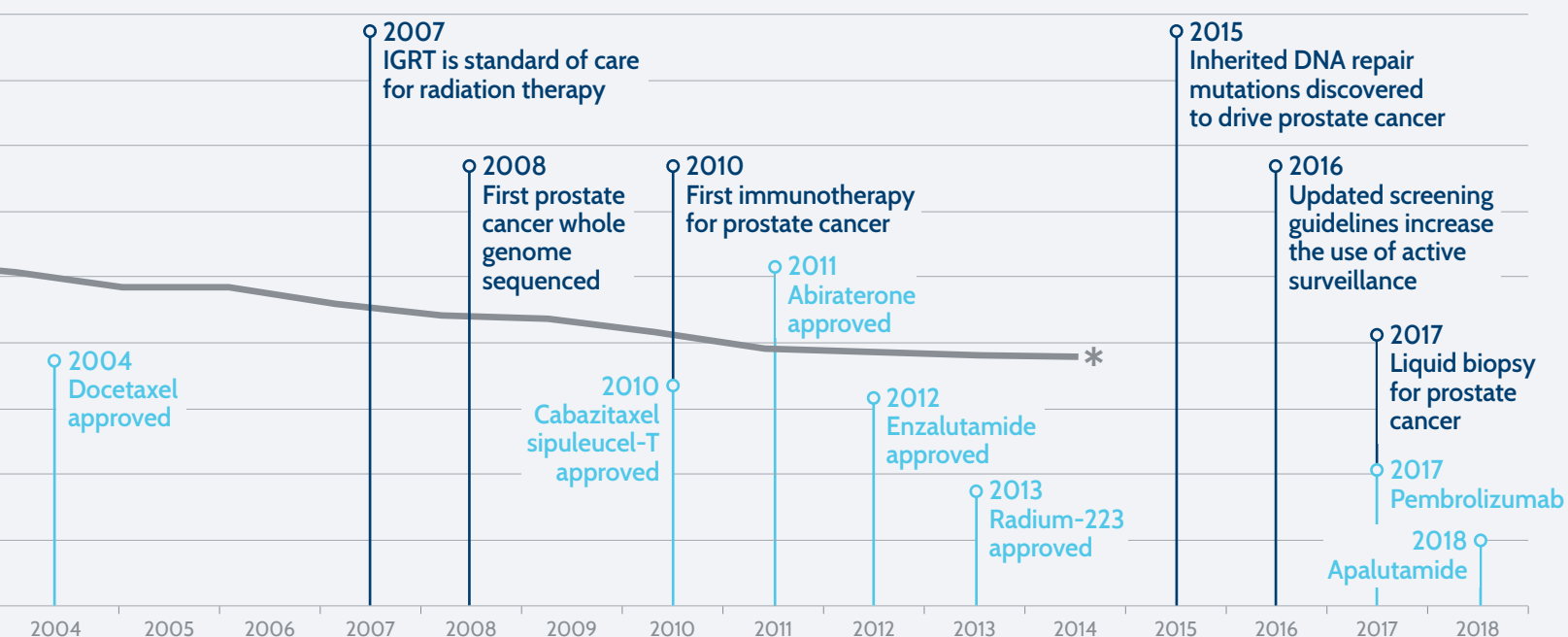
Because of these improvements and potentially other unknown factors, **since 1993, deaths from prostate cancer have been cut in half** (from 39.3 per 100,000 men in 1993, to 19.2 per 100,000 men in 2016).

Today, precision medicine, which involves matching the right drug to the right patient at the right time, is ushering in a new era in treatment for prostate cancer including DNA testing as a gold standard in cancer care. Furthermore, in localized prostate cancer, doctors are learning that a tumor's genetic signature may help to predict which patients may be at risk for aggressive disease in the future. Scientists are also exploring how **immunotherapy**—the process of using the body's own immune system to combat disease—can be used more effectively in treating and preventing prostate cancer.

MEDICAL BASICS

The more you know about the normal development and function of the prostate, where it's located, and what it's attached to, the better you can understand how prostate cancer develops and impacts a man's life over time—due either to cancer growth or as a result of treatment.

*Data available through 2014



The Anatomy of the Prostate

The **prostate** is a small, squishy gland about the size of a ping-pong ball. It sits under the bladder and in front of the rectum. The prostate is only present in men. It is important for reproduction, because it supplies the fluids needed for sperm to survive and it helps push out semen during ejaculation. Sperm are not made in the prostate; they are made in the **testes** and travel to the prostate through the vas deferens (the tubes which are cut in a vasectomy procedure).

The prostate is divided into several anatomic regions, or zones. Most prostate cancer starts in the **peripheral zone** (the back of the prostate) near the rectum. That's why examining the prostate via a gloved finger in the rectum, known as **digital rectal exam (DRE)**, is a useful screening test.

The **seminal vesicles** are rabbit-eared structures that store and secrete a large portion of the ejaculate. These structures sit on top of the prostate.

The **neurovascular bundle** is a collection of nerves and vessels that run along each side of the prostate, helping to drive erectile function. They travel from the lower spine all the way across the pelvis to the penis. Since

this bundle sits very close to the prostate, it is often disturbed during prostate cancer treatment, and is sometimes directly invaded by more aggressive cancers.

The **bladder** is like a balloon that gets larger as it fills up, holding urine until the body is ready to void. The **urethra**, a narrow tube that connects to the bladder, runs through the middle of the prostate and along the length of the penis, carrying both urine and semen out of the body. It is the hose that drains the bladder.

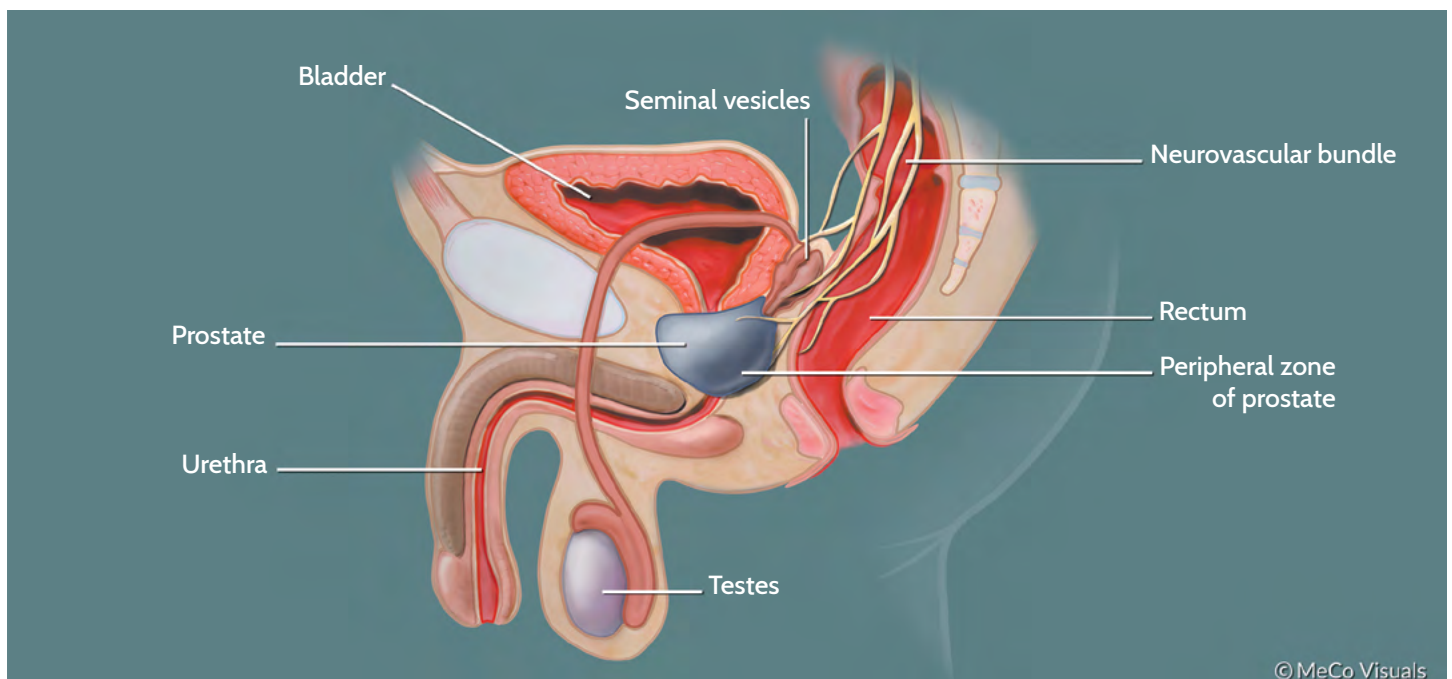
The **rectum** is the lower end of the intestines that connects to the anus, and it sits right behind the prostate.

The Biology of Prostate Cancer

To properly understand diagnosis and treatment options, it's important to understand how prostate cancer grows. A normal prostate uses **androgens** (including testosterone and dihydrotestosterone, or DHT) during its development and everyday function.

Once prostate cancer forms, it feeds on androgens and uses them as fuel for growth. This is why one of the backbones of treatment for men, especially with advanced prostate cancer, is to lower a man's androgen levels with drugs collectively termed "hormone therapy."

The Anatomy of the Prostate



ANDROGENS

Androgens are hormones that are important for many male characteristics and aspects of reproduction. A common androgen is testosterone.

GRADE

Grade is a measure of how abnormal the prostate cancer cells look under the microscope. It's used to predict how quickly they might grow or spread.

Prostate cancer occurs when a normal prostate cell begins to grow out of control. In many cases, prostate cancer is a slow-growing cancer that does not progress outside of the prostate gland before the time of diagnosis.

The rate of growth and spread of prostate cancer is reflected in the grade of the cancer, measured by either the Gleason score or the ISUP (International Society of Urological Pathology) grade group classification.

“High-grade” prostate cancers are those that are composed of very abnormal cells and are more likely to both divide and spread faster from the prostate to other regions of the body. Often, prostate cancer spreads first to tissues that are near the prostate, including the seminal vesicles and nearby lymph nodes.

Researchers have identified various biological and genetic subtypes of prostate cancer. It is possible for any given prostate cancer tumor to contain multiple subtypes of prostate cancer. Doctors and researchers are only just now beginning to use subtyping to guide treatment recommendations, thanks in part to active and ongoing research funded by the Prostate Cancer Foundation. For information on how to get your tumor genetically sequenced, visit [pcf.org](https://www.pcf.org).

Understanding Metastasis

Sometimes cancer cells will escape the prostate and grow quickly, spreading to nearby tissue. Nearby lymph nodes are often the first destination for a spreading cancer. If

prostate cancer has spread to your lymph nodes when it is diagnosed, it means that there is higher chance that it has spread to other areas of the body as well.

Metastasis refers to tumor cells leaving the prostate and forming tumors somewhere else in the body.

If and when prostate cancer cells gain access to the bloodstream, they can be deposited in various sites throughout the body, most commonly in bones, and sometimes in other organs such as the liver, lungs, or brain. Bone metastases are seen in 85% to 90% of metastatic cases.

Even if you are told your cancer is confined to your prostate gland, there is no way to know this with absolute certainty. New data from studies funded by the Prostate Cancer Foundation, using new types of molecular imaging, has shown that more than 10% of patients with high grade “organ-confined” prostate cancer actually have small deposits of metastatic disease. These technologies continue to be actively investigated.

“If my doctor tells me that I have prostate cancer metastases in my bones or my lungs, does that mean I have bone cancer or lung cancer?”

This does not mean you have “bone cancer” or “lung cancer,” since these tumor cells came from the prostate and did not develop from bone or lung cells. Your treatment would be focused on prostate cancer rather than bone or lung cancer.

What is PSA?

PSA, or **Prostate Specific Antigen**, is a protein produced by the prostate and found mostly in the semen, with very small amounts released into the bloodstream. It is used as a “disease marker” to represent prostate cancer. When there’s a problem with the prostate—such as the development and growth of prostate cancer—more PSA

is released. PSA eventually reaches a level where it can be easily detected in the blood. This is often the first indicator of prostate cancer.

During a PSA test, a small amount of blood is drawn from the arm, and the level of PSA is measured. Doctors look at the overall level of PSA, as well as its rate of rising (velocity) compared with prior test results. As the PSA number goes up, the chance that cancer is present increases. Men whose levels go above 3 or 4 are often recommended to undergo a biopsy; however, this PSA level does not mean that prostate cancer is definitely there, and some cancers may be present even when PSA levels are lower, particularly among younger men.

THE PSA DEBATE

PSA is not a perfect test to screen for prostate cancer. Elevated levels can be caused by other benign prostate diseases and problems, such as BPH (benign prostatic hyperplasia, an enlarged prostate) or prostatitis (an infection in your prostate). There is an active debate around prostate cancer screening. Some health care professionals are concerned that increased PSA screening is finding tumors that are so slow-growing as to pose no long-term threat to the patient. Some think this can lead to “overtreatment” in many men with low-risk cancers, causing unnecessary side effects and quality-of-life impact. However there is a lot of data to suggest that PSA testing has reduced the death rate from prostate cancer, because men with aggressive cancers are diagnosed earlier—often before the cancer has spread—and can be cured and/or more effectively managed by earlier treatment. If PSA screening is done well, its value is greatly increased. It is critical to test men at the appropriate age, repeat PSA tests once the baseline level is known, and reserve treatment for those with higher risk cancers. The Prostate Cancer Foundation is actively funding new research into better prostate cancer screening tests that are more specific and sensitive than the PSA test.

PSA screening decisions should be made in consultation with your doctor and based on a full examination of risk factors. See also, [The Genetics of Risk](#), page 73.

In men who have confirmed diagnosis of prostate cancer, rising PSA is a useful test to track prostate cancer growth, since it can be detected well before any clinical signs or symptoms. The PSA is also widely accepted as an invaluable tool for monitoring prostate cancer disease activity and recurrence of prostate cancer after treatment.

The Biology of Sex Steroids

Prostate cancer cells are just like all other living organisms—they need fuel to grow and survive. The main fuel for prostate cancer growth is the sex hormone testosterone.

The term **sex steroid**, or **sex hormone**, refers to the substances secreted by the testes and ovaries (**androgens** and **estrogens**, respectively) which are responsible for the function of the reproductive organs and the development of secondary gender characteristics (such as facial hair, muscle mass, and sex drive). Androgens and estrogens are present in both men and women, though at different levels. The most important androgen for male reproduction is **testosterone**. Testosterone is primarily made in the testes, but a smaller amount is made in the adrenal glands above the kidneys. The prostate typically grows during adolescence under the control of testosterone.

Since androgens—including testosterone—fuel prostate cancer growth, prostate cancer treatment regimens may include some amount of hormone therapy, which deprives tumor cells of androgens.

The prostate is not essential for life, but it is important for reproduction. It supplies substances that facilitate fertilization, sperm transit, and sperm survival. Enzymes like PSA (the same protein that is measured in the blood test) loosen up semen to help sperm reach the egg after intercourse. Sperm is made in the testes, and it travels through the prostate during its transit, picking up seminal fluid along the way.

The older term “medical castration” is sometimes used to describe a drug treatment regimen for controlling hormone levels. **Androgen deprivation therapy (ADT)**, in which medication is used to cut off the supply of testosterone to the prostate, is part of the treatment plan for metastatic prostate cancer and also for some patients with non-metastatic disease. ADT is associated with high rates of response, but it can have side effects, especially when used for long durations of time (i.e. years).

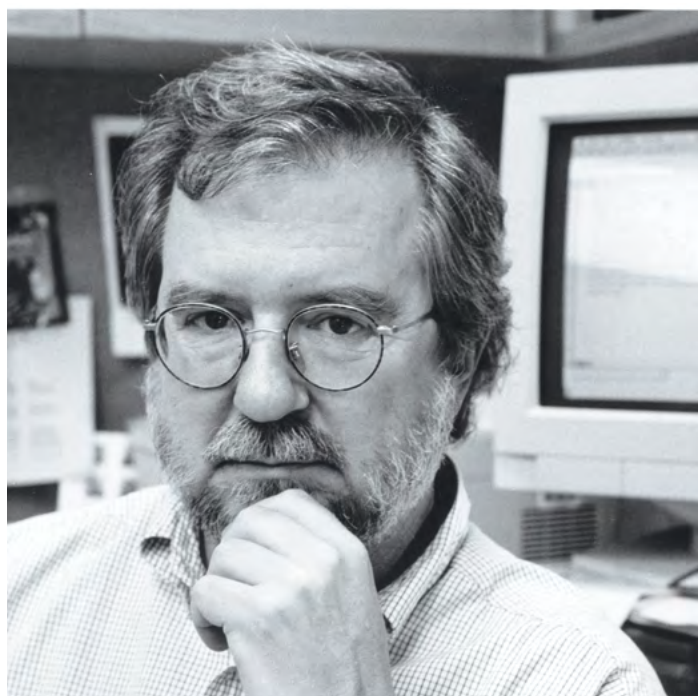
Precision Oncology

New knowledge is beginning to explain the decades-old question of why a treatment may work for one patient but not another. Cutting-edge technologies that allow clinicians to identify the mutations present in a patient's tumor cells have resulted in the emerging field of precision medicine, or customized treatments based on the unique biology of an individual's tumor. Precision medicine is an approach to disease treatment and prevention that takes into account individual variations in genes, immune function, environment, and lifestyle.

Doctors now know that each patient doesn't just have prostate cancer, they have their own particular form of prostate cancer.

The hope is that someday, all treatment will start with genetic tests of the cancer, followed by custom treatments. Currently, there are multiple commercial tests that are approved by Medicare and select private insurance companies to better understand the aggressiveness of a tumor. Studies suggest that these tissue-based genetic tests outperform grade or stage in predicting whether a cancer is likely to metastasize. The tests are currently approved for use in select patient cases. Also on the horizon is the concept of “liquid biopsy,” where doctors can use blood tests to identify cancer mutations and treatment options.

How can you find out if you are a candidate for a precision therapy? Right now, precision medicine is an emerging field, so many treatments have limited availability, but a good start for anyone with metastatic, recurring, or treatment-resistant prostate cancer is to ask your doctor about precision medicine clinical trials that may be appropriate.



PCF was the first prostate cancer research organization to fund Jim Allison's work in immunotherapy. Allison's work on using the body's own immune system to fight cancer earned him the 2018 Nobel Prize for Medicine.

Another exciting area of research in prostate cancer relates to the use of immunotherapy. Historically, the problem with curing cancer has been the uncanny ability of cancer cells to reprogram themselves after treatment and hide from the immune system. The promise behind immunotherapy is that doctors are able to program the body to be smarter than the tumor, and use the immune system to kill the cancer. Numerous ongoing clinical trials are being conducted around the world trying to optimize immunotherapy to treat prostate cancer.

Today, treatments for prostate cancer include many traditional forms of cancer therapy (surgery, radiation, and/or chemotherapy) and some forms that are very specific to the prostate (hormone therapy and precision medicines in clinical trials). Remember that all treatment regimens must be balanced against quality of life concerns, considering the potential side effects of each treatment, the aggressiveness of the cancer, and the overall life expectancy of the patient.

“My cell phone rang. It was the urologist. I stopped what I was doing and got the news. I still remember. He said, “There’s a little bit of cancer.”

— PATIENT



UNDERSTANDING YOUR DIAGNOSIS

No matter the exact words used to describe the results of your prostate biopsy, a diagnosis of prostate cancer can change everything. It can be confusing, frightening, and overwhelming. It is important to remember that the word “cancer” can refer to an extremely wide spectrum of biology and that, when detected early, prostate cancer tends to be less aggressive than many other cancers.

As a newly diagnosed patient, you might be torn by arguments favoring one treatment plan over another or you may feel ill-equipped to make the decisions that are being required of you. For family members and loved ones, there can be an ache to help and to comfort, but without knowing what a man's needs might be. One of the most important tools you have for managing your diagnosis, both physically and emotionally, is education. The information contained in the guide can help you feel satisfied that you have made an informed decision for you and your family.

DETECTION, DIAGNOSIS AND STAGING

The **PSA** blood test and Digital Rectal Exam (DRE) can be used to detect prostate cancer when no symptoms are present. They can help catch the disease at an early stage when treatment is thought to be more effective and potentially has fewer side effects. It is recommended that you abstain from strenuous exercise and ejaculation for 48 hours preceding your PSA, since these may artificially inflate PSA test results.

After your PSA test, your health care provider may perform a **DRE**, in which a gloved, lubricated finger is inserted into the rectum to examine the prostate for any irregularities in size, shape, and texture.

During a PSA test, a small amount of blood is drawn from the arm, and the level of PSA, a protein produced by the prostate, is measured. The majority of men have a PSA under 1 ng/mL. Historically, many physicians used a PSA of 4 as the borderline between “normal” and “abnormal.” We now realize this question is more complicated.

Assessment of a “normal” PSA must take into account:

- The patient's age
- Prostate size
- Previous PSA tests
- Other medical conditions, such as BPH or prostatitis
- Drugs that may artificially lower PSA, such as finasteride (Proscar® or Propecia®) or dutasteride (Avodart®)
- Infections and procedures involving the urinary tract that can elevate the PSA
- Use of various herbal supplements, such as saw palmetto

Making the Diagnosis via Biopsy

Although a high PSA may increase a doctor's suspicion of prostate cancer, a biopsy is almost always done to confirm a diagnosis. A PSA test is simply used to assess whether or not you should have further testing—usually in the form of a prostate cancer biopsy to determine the presence of cancer cells.

There are 3 main ways men are initially diagnosed:

- 1. TRUS-guided biopsy:** A Trans-Rectal Ultra-Sound-guided biopsy using local anesthetic is the most common way that prostate cancer is diagnosed in the US. An ultrasound probe is placed in the rectum to allow visualization of the prostate, then multiple needles are used to sample for cancer. If a patient had magnetic resonance imaging (MRI) before the biopsy, needles may be targeted into areas that looked suspicious on the MRI (the MRI itself provides useful information, but cannot diagnose prostate cancer).
- 2. Trans-perineal biopsy:** The prostate can also be biopsied under local anesthetic by placing a needle through the skin between the scrotum and anus (perineum).
- 3. Incidentally:** Some men are diagnosed when prostate cancer is found incidentally during an unrelated surgical procedure of the prostate or bladder.

Prostate tissue from the biopsy is then examined under a microscope by a pathologist to confirm the presence or absence of prostate cancer cells.

“Targeted” or “fusion” biopsies (sometimes referred to as an MRI fusion biopsy) are increasingly being offered at select centers that use MRI, in addition to the ultrasound, to better visualize tumors within the prostate and help guide biopsy needles to the most concerning areas. There is wide variation in quality of MRI; at this point in time, MRI and fusion biopsy should only be performed at a high-volume center with particular expertise in prostate radiology. Research on the continued improvement of this technology continues.

SIZE VS. GRADE

The size and grade of your tumor don't always predict its behavior over time. A small, high-grade cancer is much more likely to spread to other parts of the body than a large, low-grade cancer. In some cases, tumor DNA genetics and biomarkers may be better predictors of growth over time. Consult with your health care provider to find out if these options might be right for you.

PI-RADS (Prostate Imaging Reporting and Data System) is a structured reporting scheme for evaluating the prostate for prostate cancer based on an MRI scan. The PI-RADS score is for patients who have not yet undergone therapy. The scores are:

- ▶ PI-RADS 1: **very low**—clinically significant cancer is highly unlikely to be present
- ▶ PI-RADS 2: **low**—clinically significant cancer is unlikely to be present
- ▶ PI-RADS 3: **intermediate**—the chance of clinically significant cancer is neutral
- ▶ PI-RADS 4: **high**—clinically significant cancer is likely to be present
- ▶ PI-RADS 5: **very high**—clinically significant cancer is highly likely to be present

In summary, PI-RADS 4 or 5 lesions have a **high probability** for disease that warrants targeted biopsy for confirmation. PI-RADS 1-3 are unlikely to represent clinically significant cancer.

As previously noted, prostate MRI is still a developing technology and is ideally performed and interpreted at academic centers or other prostate sub-specialty centers.

Staging Your Disease

There are 5 main components to staging prostate cancer:

- ▶ Your PSA level
- ▶ The grade of your tumor (done via biopsy)
- ▶ The stage of your tumor (termed the “**T-stage**” for the prostate **tumor**)—for example, is the prostate cancer contained completely within the prostate?
- ▶ For some men, getting imaging to determine if the cancer has spread to lymph nodes (termed the “**N-stage**” for **nodes**) or bones or other organs (termed the “**M-stage**” for **metastasis**).
- ▶ The extent of the cancer revealed by the biopsy. For example, in a typical prostate biopsy which includes at least 12 needle core samples, a cancer found in 9 of the 12 cores is a higher risk than a cancer found in just 2 of the cores.

1. PSA: A blood test.

Your doctor should have your most recent PSA tests and, if outdated, may order a fresh one. PSA can also be considered in relation to the size of the prostate, since a bigger prostate will normally make more PSA. Your **PSA density (PSAD)** score is calculated by taking your PSA score and dividing by the volume (size) of your prostate in grams or milliliters. PSAD values under 0.15 (e.g., a PSA of 7.5 for a 50-mL prostate) are usually considered reassuring.

2. Grade: How aggressive the cancer looks.

If prostate cancer is found when looking at biopsied tissue under a microscope, the pathologist assigns a grade to the cancer. There are 2 grading systems currently in use, which can be confusing for patients.

The original grading system for prostate cancer is called the Gleason score, which ranges from 6 to 10 (6 is low grade, 7 is intermediate grade, and a score of 8 to 10 is high grade).

In 2014, the World Health Organization replaced the Gleason score with the simpler ISUP Grade Group system ranging from 1 (low) to 5 (very high).

Many hospitals report both the Gleason score and the ISUP grade group, but there may be hospitals that still report only the old Gleason system.

ISUP Grade Group and Gleason Score Comparison

| Risk Group | ISUP Grade Group | Gleason Score |
|--------------------------|------------------|------------------------|
| Low | Grade Group 1 | Gleason Score ≤ 6 |
| Intermediate Favorable | Grade Group 2 | Gleason Score 7 (3+4) |
| Intermediate Unfavorable | Grade Group 3 | Gleason Score 7 (4+3) |
| High | Grade Group 4 | Gleason Score 8 |
| High | Grade Group 5 | Gleason Score 9-10 |

3. Tumor staging (or T-stage): The extent of the prostate cancer.

The digital rectal exam (DRE) gives information on how extensive the prostate cancer is within the prostate area. In some cases, your practitioner may order a prostate MRI to give more information if the cancer extends outside the prostate. Staging is classified as follows:

- ▶ T1: The tumor was found solely by a biopsy done due to an elevated PSA (i.e. was not detectable by DRE or imaging) or was found incidentally during an unrelated procedure. T1 tumors can be divided into T1a-T1c subcategories, depending on how the tumor was found and its size.
- ▶ T2: The health care provider felt a nodule(s) on your prostate during the rectal exam. T2 tumors can be divided into T2a-T2c subcategories, depending on the tumor location and size.
- ▶ T3: The tumor extends out of the prostate capsule. If the tumor also extends into the seminal vesicles, this is referred to as T3b, if not, it's T3a.
- ▶ T4: The tumor invades into the rectum or bladder (advanced).

4. Evaluating for metastatic disease: Has the tumor spread beyond the region around the prostate?

Aggressive cancers (e.g. PSA >20, ISUP grade group 4 or 5 [Gleason score 8-10], or stage T3-4) usually warrant imaging scans to determine the presence of metastatic disease. Some men whose cancer has less aggressive features may benefit from further imaging and they should discuss this with their doctor. This is most commonly done with a computed tomography (CT) scan or an MRI and a bone scan, although newer and more sensitive imaging technologies are in development, such as molecular PET imaging (e.g. PSMA, Axumin, Choline). It is important for your doctor to know if your cancer has spread to lymph nodes, bones or other body sites since it will influence their treatment recommendations.

5. Biopsy cores: How many were positive?

One other aspect that your physician will look at on your pathology report in addition to the grade, is the number of biopsy needle cores that contain cancer divided by the total number of cores sampled. This is referred to as **percent positive cores**. The higher the percentage, the more aggressive the disease generally. For example, if 12 biopsies were taken, and 4 were involved with cancer, then you would have 4/12, or 33% positive cores.

GLEASON 3+3

Modern pathologists do not go below Gleason 3+3 (Gleason 6, or ISUP Grade Group 1) when scoring prostate cancer tumors. If you have detectable prostate cancer, the lowest Gleason score you will receive is a 6. Many, but not all, prostate cancers in this Gleason range may be slow growing and could be appropriate candidates for active surveillance. Consult your doctor or practitioner for more information.

SELECTING YOUR TREATMENT

There is no “one size fits all” approach for precise treatment of prostate cancer. For some men this feels liberating; for others, it can be confusing and frustrating.

To add to the confusion, your doctor may not recommend treatment at all (also termed observation or “watchful waiting”), or might recommend putting you under “active surveillance,” with serial testing and a plan to offer curative treatment for the cancer only if it exhibits signs of progression. It’s important to learn as much as possible about the treatment options available and, in conjunction with your physicians, make a decision about what’s best for you.

Because men diagnosed with localized prostate cancer today may live for many years or decades, it is important to discuss not only cure, but also quality of life.

Your decision-making process will likely include a combination of clinical and psychological factors, including:

- ▶ The need for treatment
- ▶ Your family genetics
- ▶ Your level of risk based on biopsy and exam
- ▶ Your personal circumstances
- ▶ Your desire for a certain treatment option based on risks, benefits, and quality of life

For men who are sexually active, concerns about post-treatment potency are often top of mind. If preserving your ability to be intimate with a partner is a priority for you, make sure to discuss this with your doctor *before* selecting a treatment plan. It is also essential to realize, however, that many interventions are available to help with sexual function both before and after prostate cancer treatment.

FERTILITY OPTIONS

For men who are hoping to father a child in the future, it is vital to have a discussion on fertility preservation and sperm cryopreservation with your physician before you undergo any treatment. You can learn more about these issues in the Possible Side Effects: Fertility section on page 42.

The vast majority of prostate cancers are diagnosed by urologists, who perform the biopsies. A urologist will typically review treatment options, and should also offer consultation with a radiation oncologist. For men with more aggressive disease, or metastatic disease, patients should also have a consultation with a medical oncologist. A multidisciplinary prostate cancer care team will give you the most comprehensive assessment of the available treatments and expected outcomes, because each physician has expertise in different areas. Many hospitals and universities have multidisciplinary prostate cancer clinics that can provide a consultation on what team of doctors might be right for you.

In general, for nearly all cases of newly diagnosed localized prostate cancer, the chance of “cure” is about the same whether you have radiation therapy or surgery.

For men with metastatic disease, your doctor may now recommend genetic sequencing to determine if there is a targeted therapy for your type of disease. Talk to your doctor about whether tumor sequencing is right for you, or visit pcf.org for more information.

It is also important to remember that, often, physicians, books, blogs, and websites present only half of the story, favoring one treatment option. This leads to a great deal of misunderstanding. The best thing you can do is to read through this patient guide and make sure you seek the advice of a urologist, a radiation oncologist, and, based on the stage of your disease, a medical oncologist.

In the U.S. the 5-year survival rate for all men newly diagnosed with early stage prostate cancer is greater than 99%.

However, one treatment may be preferred for you based on the associated **side effects**. Your team of doctors will evaluate your type of prostate cancer to develop a treatment plan that may include surgery, radiation, some combination of both, or neither. The main difference between surgery and radiation therapy relates to quality of life and side effects. For many high-risk or aggressive cancers, often a combination of therapies offer the best chance of long-term disease control. Every patient has a different cancer and different priorities in regard to what aspects of **quality of life** are the most meaningful to them, so it's important to take time to understand and process your diagnosis as well as the therapy options available to you. Remember, it is always okay to get a second opinion, whether or not treatment is needed; if possible, chose urologists, radiation oncologists, and medical oncologists at high volume, prostate-focused cancer centers.

ASSEMBLING YOUR TEAM

Decisions about how to treat your prostate cancer can't be made in a vacuum. A new diagnosis can come with a lot of confusing information and feelings. Many aspects of this disease can affect the way you view yourself, the way you interact with others, and the way others interact with you. Yet at this chaotic time, you'll be asked to make some important decisions based on your doctors' recommendations. To help you along the way, it's prudent to work with your network of family, friends, and practitioners to align expectations and seek support as appropriate.

Doctors and Practitioners

Where possible, select a physician who specializes not just in cancer, but in the **nuances of your specific type of prostate cancer**. How do you find such a doctor? If you are newly diagnosed, start by consulting your diagnosing doctor, that is, the one who found your prostate cancer. He or she may be an expert in the field, or they may refer you to one or more doctors who are.

Other factors to consider when selecting a doctor:

- ▶ Are they affiliated with a reputable university or research hospital?
- ▶ Does their "bedside manner" align with your personality? Are they analytical? Compassionate? Do they seem interested in making you a partner in this process? Do they seem interested in what is important to you?
- ▶ Are they covered by your health insurance? If not, can you change insurance?

Remember:

- ▶ Take your time
- ▶ Get second or even third opinions
- ▶ Be careful of advice that seems highly opinionated, e.g. "surgery is the best" or "radiation is the best" or "eat this herb and your cancer will be cured." Avoid any health care provider who seems like he or she is "selling" something
- ▶ There are many books, websites, and blogs written by "experts" that claim their treatment is best: be cautious of these. For accurate information, use reputable websites like pcf.org and those that your doctor recommends
- ▶ Once you have committed, trust is key, but continue to be your own advocate: ask questions, do research, and remain curious

If you have a good relationship with your primary care provider, you may opt to stay in close touch about your diagnosis, treatment, and decision-making. Primary care providers can offer help to think about the big picture of your health, and can help you work through complicated decisions.

Family

Your family wants to support you. Feelings of powerlessness are a common concern around a cancer diagnosis; your loved ones want—or even need—to do something to feel like they are helping. Normally, this may feel like a fantastic offer. But after a cancer diagnosis, you may feel confused about how much support to accept, request, or reject. Keeping open channels of communication is key.

Tips for Spouses, Caregivers and Adult Children

- ▶ Agree on how you will make decisions
- ▶ Get ready for changes in routine
- ▶ Understand that there could be emotions from both sides around changes in ability
- ▶ Find out how treatments may affect moods, physical ability, and urinary, bowel, or sexual function
- ▶ It is normal to experience loneliness and fear—seek out support groups for spouses and caretakers

Tips for Young Children

- ▶ Keep children informed and treat them as part of the team
- ▶ Answer questions honestly, as age appropriate
- ▶ Be realistic but optimistic in your communications
- ▶ For older children, you might encourage them to join a support group. For younger children, consult your pediatrician or therapist for suggestions on how much information to share

Doctors and Practitioners Involved in Prostate Cancer Diagnosis and Treatment

Urologists specialize in problems affecting the urinary tract (kidney, bladder, prostate, urethra, penis, and related organs). They may treat only benign conditions (e.g. kidney stones, BPH) or may also treat cancer.

Urological Oncologists are urologists who specialize in surgery and treatments for prostate and other urological cancers.

Radiation Oncologists specialize in the use of radiation therapy to treat cancer.

Medical Oncologists specialize in treating cancer with medical therapies, such as chemotherapy, hormone therapy, and targeted therapies.

Radiologists and Nuclear Medicine Physicians specialize in interpreting imaging scans that you may have, and may also perform specialized biopsies or deliver radioactive medical therapies.

Pathologists specialize in interpreting the results from your biopsy or surgery to determine the type, extent, and grade of your cancer.

Nurse Practitioners (NPs) and Physician Associates (PA) are “physician extenders” who work closely with physicians to help you with your care. They often are the first line of response for your questions and concerns, and also manage some aspects of routine follow-up care.

Oncology Nurses administer treatment and monitor your vitals as you progress through the disease.

Dietitians and Naturopathic Doctors counsel patients on nutrition and wellness issues, including complementary medicine and mind-body awareness, related to cancer and treatment.

Physical Therapists create and execute rehabilitation programs to restore function and prevent disability following treatment.

Occupational Therapists work with patients to help them develop, recover, and improve the skills needed for daily living and working.

Genetic Counselors specialize in understanding and counseling you about inherited risks of cancer for you and your family.

Social Workers, Therapists & Counselors help patients and their families cope with the emotional, social, financial, and practical aspects of cancer.

Your Support Network

Outside of your immediate family, there may be many close friends and colleagues who care deeply about you, and have a strong desire to help. With friends and family who have volunteered their assistance, don't be shy about letting them know a few specific things that would be helpful to you. Examples might include rides to treatment, meals, caring for young children, or performing difficult chores during recovery. And when things feel overwhelming, don't be afraid to reach out for the support of family and friends. On the other hand, don't be shy about politely saying "no" to help you don't want, however generous. Many online resources exist for organizing volunteer resources during treatment, such as carecalendar.org or lotsahelpinghands.com.

Work with your network of family, friends, and practitioners to set expectations and seek support where appropriate.

Many friends and family choose to become active in the cancer community in order to diminish the common feeling of powerlessness that can come with a loved one's cancer diagnosis. For more info on getting involved, visit pcf.org/take-action.

You

Sadness, fear, sleeplessness, and anger are all normal early emotions after receiving a cancer diagnosis. Coping with these emotions isn't something you should take lightly. Seeking professional help, either from an online community, clergy, a church group, a cancer support group, or a private mental health professional isn't a sign of weakness. Taking care of your mental health is akin to the kind of psychological training that a quarterback goes through to make sure he can keep his head in the game: it's vital.

To join an online support group, please visit pcf.org/groups. For more information on counseling resources, visit cancer.org. To find a local prostate cancer support group in your area, visit ustoo.org.



"I needed and expected my spouse to be my advocate and help me hear the doctors. I needed my friends to listen and laugh, and not give me platitudes." – Patient

PROCESSING YOUR DIAGNOSIS

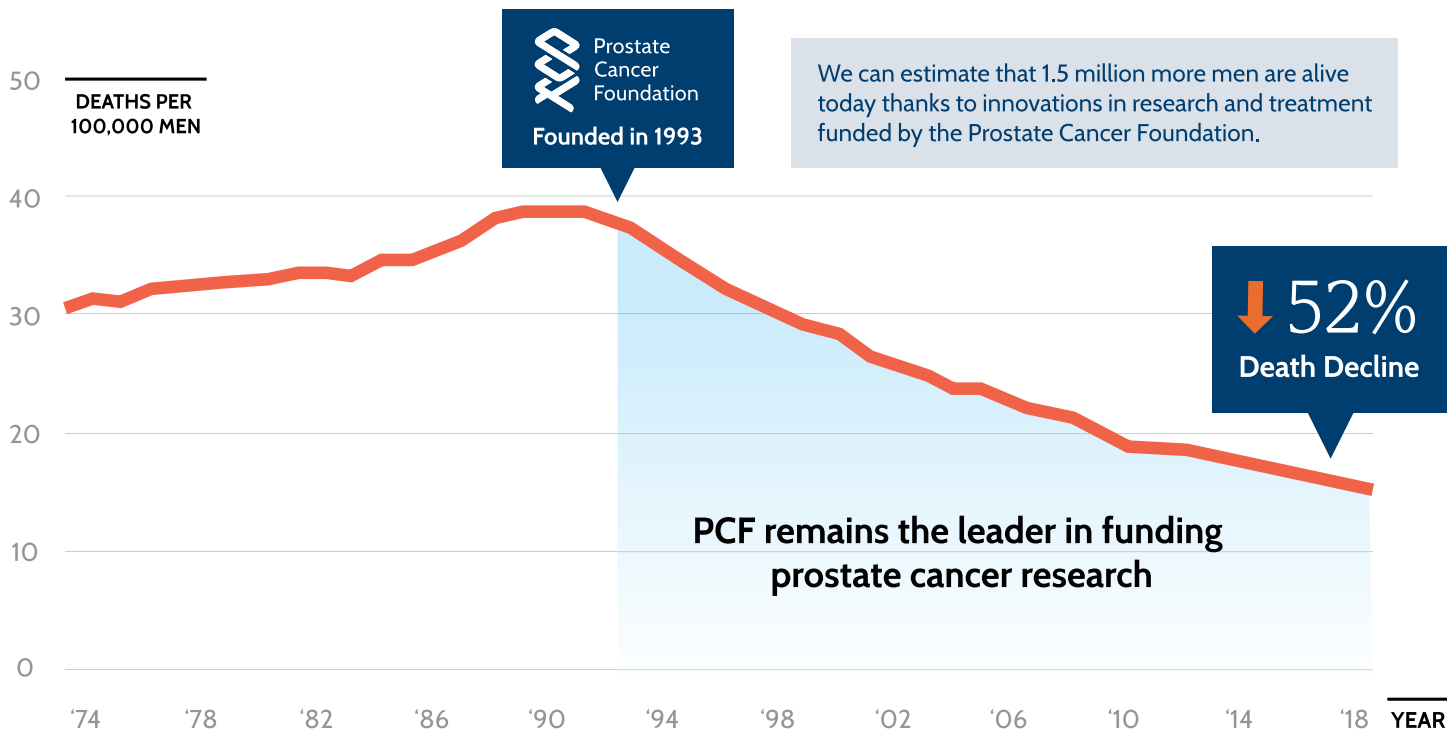
The final decision on treatment is yours and may be informed by a variety of psychological as well as clinical factors. Sometimes this decision process can be empowering, and sometimes it can be bewildering. For example, although the first instinct may be to choose a therapy from the first provider you see who promises to eradicate the disease, you should take your time to investigate your options. Depending on the features of your cancer, and your age, overall health, and personal family circumstances, [active surveillance](#) may be the right choice for you. [Side effects](#) of each treatment are also important to consider, and only you can know what potential outcomes are acceptable to you. Regardless of which treatment you choose, it's important to observe recommended [diet and lifestyle modifications](#) from the moment you are diagnosed.



Work with your network of family, friends, and practitioners to set expectations and seek support where appropriate.

For men who are sexually active, remember that stress can affect erectile function. In fact, a diagnosis of any type of cancer can disrupt sexual function for men and women. The maximum sexual function you could potentially regain after treatment will be based on your levels before diagnosis. Seek expert counsel for you and your partner on how to support each other through therapy and recovery.

In the end, after all of your research into different treatment types and side effects, different doctors, and different hospitals, the decision is going to come down to you. If there was one right answer that fit every man, we would tell you! The decision is very unique to each person; it may not be right for your brother, your friend, or any of the 20 other people you consulted, but it may be your best choice on the road to better health. Some people find the decision process liberating; others find it beyond their individual ability. Remember that it is okay to feel overwhelmed at first. Use this guide to begin to understand your options, but don't be afraid to rely on professionals, friends, and family to help you navigate your final treatment plan.



Thanks to recent advances in treatment, men who are diagnosed with prostate cancer today have many options available to them. It's important to understand the basics of prostate cancer and work with your medical team to identify what treatment options are right for you. Here are a few questions to help guide conversations with your treatment providers:

What is my PSA level? If multiple values over time have been collected, how fast has it risen, and what does this mean for me?

What is my prostate cancer grade/risk group? What does this mean in terms of our approach to my treatment?

Has my cancer spread beyond the prostate? Can it be cured?

Are there additional tests I need to have to gain the most precise understanding of the stage and aggressiveness of my cancer?

Can I avoid treatment at this time and be monitored under active surveillance? How does it work?

What treatment options exist for this stage of cancer? Which treatment do you think is better for me?

What side effects can I expect from the treatments available to me? Should I worry about impotence, urinary leakage, or rectal problems, and are the risks different with different treatments?

How do my baseline urinary, sexual, or bowel function affect my treatment decisions, if at all?

When will I see a radiation oncologist and/or medical oncologist to understand all of my options? If I speak to other specialists for second opinions before making a final decision on my plan of action, how do we coordinate it?

What is the effect of the treatments on my fertility? Should I consider sperm-banking or other measures before I undergo any treatments?

What will my pre/post-surgery rehabilitation plan look like?

Is my cancer likely to come back based on what you know today?

How can I improve the success of my therapy? Are there dietary changes I need to make? What about exercise?

Should I join a clinical trial?

Remember, you want to be a partner in your own care. The more educated and proactive you are, the better. Check in at pcf.org regularly for the latest research news and changes in practice.



“A lot of men are numbers guys. They know their Gleason score down to every biopsy core. I didn’t react that way. For me, it is what it is. Every man is different.”

— PATIENT



CHOOSING A TREATMENT OPTION

A man diagnosed with localized or locally advanced prostate cancer has 3 major treatment options: **active surveillance**, **surgery**, and **radiation therapy**. Choosing the best treatment for localized or locally advanced prostate cancer is generally based on age, the stage and grade of the cancer, the patient's general health, and an evaluation of the risks and benefits of each therapy option.

For men whose disease appears more aggressive, certain treatment combinations may be recommended. For example, radiation therapy is sometimes combined with hormone therapy; on the other hand, surgery is almost never combined with hormonal therapy, but may require follow-up radiation therapy, especially for men with more aggressive disease.

Remember, each first-line treatment for prostate cancer carries with it slightly different risks of **side effects**. It is critical that you ask your doctor to outline your risk for all possible outcomes of all possible treatment options before you select your path. For example, while one man might be more concerned about how fast he can get back to work, another man might be more interested in maintaining long-term erectile function.

THINGS TO WATCH OUT FOR

Primary hormonal therapy alone is not a standard treatment option for men with localized prostate cancer and should not be recommended.

Investigational treatment options for localized disease—such as cryotherapy and high-intensity focused ultrasound (HIFU)—have thus far not demonstrated the same long term success as surgery or radiation therapy in clinical trials, and both have been shown to be inferior as initial treatments. HIFU is not FDA-approved for the treatment of prostate cancer and often not covered by insurance. It is recommended that you only receive these treatments in the context of a clinical trial.

RISK GROUPS

Health care providers think about localized or locally advanced prostate cancer in terms of “risk groups,” which are assigned before the patient undergoes any treatment. There are 3 general risk groups based on the PSA, DRE, and biopsy, which can further be subdivided to better personalize treatment for each patient.

1. Low risk: Tumor confined to the prostate, the PSA is <10 and grade group 1 (Gleason 6). There is also a subset of extremely “slow-growing” tumors called “very low risk” in which the cancer is not detectable by DRE, has PSAD <0.15, and <50% of any core is involved with cancer.

2. Intermediate risk: Tumor is confined to the prostate, the PSA is between 10 and 20, or grade group 2 or 3 (Gleason 7). This category is often divided into a “favorable” and “unfavorable” intermediate risk.

3. High risk: Tumor extends outside the prostate, the PSA is >20, or grade group 4 or 5 (Gleason 8 to 10). There is also a subset of very aggressive tumors called “very high risk” in which the tumor has extended into the seminal vesicles (T3b), or the rectum or bladder (T4), or there are multiple biopsy samples with high grade cancer.

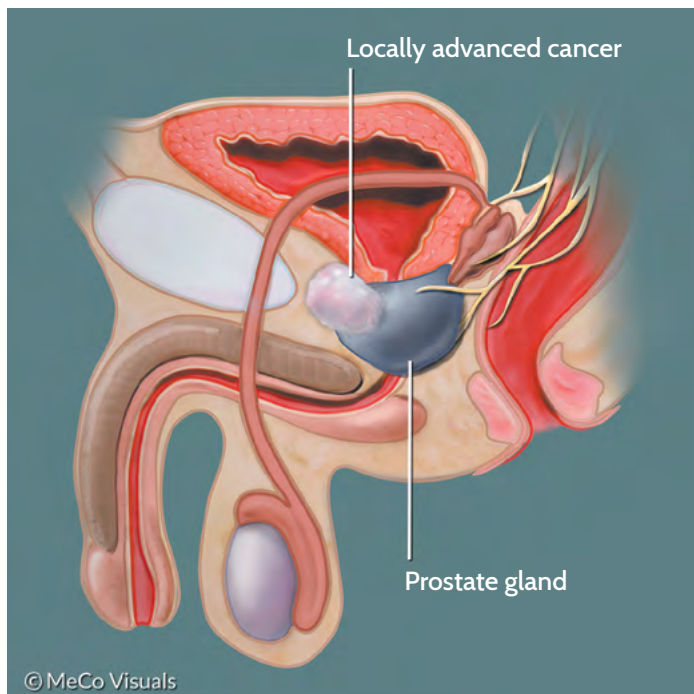
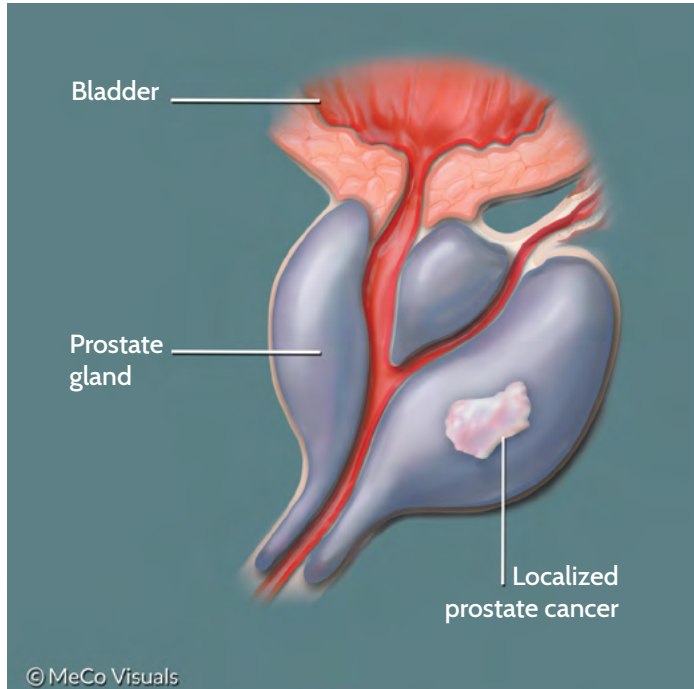
These risk groups are not perfect indicators of your risk for developing recurrent, aggressive prostate cancer. Currently, there are extensive, ongoing efforts to develop tests that can aid physicians in more accurately telling the difference between cancers that will become fatal and those that will sit in the prostate without spreading.

The treatment options for each risk group are very different and you should ask your doctor which risk group you belong to so you can better understand the most appropriate next steps.

How are Risk Groups Determined?

| Risk Group | Criteria | Treatments | Notes |
|---------------------|--|--|---|
| Low | | | |
| | T1 stage Grade group 1 PSA <10 ng/mL | Active surveillance or watchful waiting, depending on age | Certain patients with higher-volume low-risk disease, or strong family history of prostate cancers may be recommended definitive therapy |
| Intermediate | | | |
| Favorable | Any one of the following risk factors: T2b/c stage Grade group 2 PSA 10-20 Also, must have >50% of your biopsy cores negative for cancer | Surgery Radiation therapy | Active surveillance may be appropriate for select favorable intermediate-risk men Cure rates are similar between surgery and radiation therapy |
| Unfavorable | Grade group 3 or Can have any two of the following risk factors: T2b/c stage Grade group 2 PSA 10-20 >50% of your biopsy positive for cancer | Radiation therapy + short-term hormone therapy Surgery +/- post-operative radiation therapy | Cure rates are similar between surgery + post-operative radiation therapy vs. radiation therapy + hormone therapy |
| High | | | |
| | Any one of the following risk factors: Grade group 4 or 5 T3 or T4 stage PSA >20 | Radiation therapy + long-term hormone therapy Surgery +/- post-operative radiation therapy | Cure rates appear equal between surgery + post-operative radiation therapy vs. radiation therapy + hormone therapy |

Localized vs. Locally Advanced Prostate Cancer



Localized Prostate Cancer: the cancer has not spread outside the prostate.

Locally Advanced Prostate Cancer: the cancer has spread to nearby organs outside the prostate, but not to distant sites, such as lymph nodes or bones.

ACTIVE SURVEILLANCE

For men with low-risk disease who decide not to undergo immediate radical treatment for prostate cancer (radiation or surgery), active surveillance has emerged as the preferred standard of care.

Active surveillance is based on the concept that **low-risk** prostate cancer has not been shown to cause harm or decrease life expectancy. Over 30% of men have prostate cancers that are so slow growing that Active Surveillance is a better choice than immediate local treatment with surgery or radiation. Of the top 10 most common cancers, prostate cancer is the only one in which so many patients have a slow-growing tumor that does not require aggressive immediate treatment.

Active surveillance is not “no treatment,” but rather a strategy to treat you only if and when your cancer warrants treatment (some think of it as deferred treatment only if you need it).

Men with low-risk prostate cancer who have been on active surveillance for 10 to 15 years after diagnosis have remarkably low rates of their disease spreading or dying of prostate cancer. In fact, a Johns Hopkins study of men on active surveillance found that, 15 years later, less than 1% of men developed metastatic disease. This is an identical rate to what one would expect if all of these men were treated with surgery or radiation therapy. This is important because treatments used for localized prostate cancer—surgery and radiation—have side effects and costs that can alter a person’s quality of life.

The key to these successful numbers is making sure you are monitored regularly for signs of progression. A PSA blood test and digital rectal exam (DRE) are usually done once or twice per year, with a repeat biopsy of the prostate every 1 to 5 years. In carefully selected cases, MRI can potentially be used to avoid some of the follow-up biopsies.



Over 30% of men diagnosed with prostate cancer have slow growing or “lazy” tumors that are best monitored with active surveillance vs. immediate treatment.

If or when test results indicate that your cancer progression has begun to accelerate, treatment may be warranted and in a large majority of cases is still curative.

Who Should Choose Active Surveillance?

Some of the characteristics that might qualify you for active surveillance include grade group 1 (Gleason 3+3), PSA <10, cancer that is confined to the prostate and/or cancer that is very low volume when biopsied (see page 28 for a full comparison of risk groups). Selected cases with low-volume grade group 2 (Gleason 3+4) tumors may also be considered for active surveillance.

The ideal candidate for active surveillance has low-risk prostate cancer.

Often men wonder if they are the “right” age for active surveillance. There is no right answer to this question.

For younger men who have the potential to live for quite a long time after diagnosis, the question becomes one of preserving quality of life. If a man has a less aggressive form of cancer, he may be able to stay on active surveillance for many years, thus delaying side effects such as urinary incontinence, erectile dysfunction and others. On the other hand, it is important to keep in mind that younger men also have an overall lower risk of side effects after prostate cancer treatment.

For older men who might have a shorter life expectancy, either because of age or because of another medical condition, active surveillance may actually be too aggressive. For these men, watchful waiting may be more appropriate. **Watchful waiting** is a more passive strategy which avoids repeat biopsies and uses non-curative or palliative treatment only if the cancer spreads in a way that starts to cause symptoms. A man who is currently battling other serious disorders or diseases—such as significant heart disease, poorly controlled diabetes, or other cancers—should consult with his doctor about whether performing invasive tests or treatment would cause more harm than benefit.

For other men, as with any treatment for prostate cancer, shared decision-making with a physician is necessary. To that end, some physicians also administer commercial genetic tests—such as Decipher,[®] Oncotype Dx[®] GPS, and Prolaris.[®] Although some men may benefit from assessment through these tests, they are not routinely recommended to determine candidates for active surveillance. These tests are currently covered by Medicare and select private insurance companies, but check with your provider to confirm.

SURGERY

Removing the entire prostate gland and seminal vesicles through surgery, known as a **radical prostatectomy**, is a common option for men with intermediate or high-risk cancer that has not spread. Other surgical procedures may be performed on men with advanced or recurrent disease, such as removal of lymph nodes, which are initial landing spots for the spread of prostate cancer.

Open radical prostatectomy is the traditional way of surgically removing the prostate. In this procedure, the surgeon makes an incision in the lower abdomen in order to remove the prostate. The prostate may also be removed through the perineum, the area between the scrotum and the anus, although this technique is very uncommon.

In the last 10 years, robot-assisted **laparoscopic radical prostatectomy** has become very popular in the United States. This method requires small incisions to be made in the abdomen. A surgical robot's arms are then inserted into the incisions. With a robotic interface, the surgeon controls the robot's arms, which in turn control cameras and surgical instruments.

Compared with open surgery, robot-assisted surgery is associated with much less bleeding, a bit less pain, fewer short-term complications, and equivalent cancer cure rates. Preservation of urinary and sexual function recovery depends more on the surgeon's skill and patient factors than which method of surgery is chosen. Conversely, men with BPH symptoms (such as urinary frequency or urgency or a weak urine stream) may experience improvement in these symptoms after surgery.

Whether open or laparoscopic/robotic surgery is chosen, patients typically go home after an overnight stay in the hospital with a bladder catheter to help drain urine for 7 to 10 days. For a full discussion of side effects including those after surgery, see page 40.

SURGICAL MARGINS

After your doctor removes the prostate, a pathologist will examine the cells under the microscope. A final grade and stage will be determined at this point.

Your margins are **clear** if no cancer cells are seen at the outer edge of the tissue that was removed.

The margins are **positive** if the cancer extends all the way to the edge of the tissue that was removed.

Positive margins can imply that some cancer was left behind, and can be used to help determine the need for second-line therapy. But a positive margin isn't always a cause for alarm, especially in lower-grade cancers.

Patients with other problematic pathology features at surgery (e.g. extension of cancer beyond the capsule or invasion of the seminal vesicles or lymph nodes) may require complementary follow-up treatment of surgery or radiation. These decisions are usually made after the first PSA is checked 6 to 8 weeks after surgery.

Remember: make sure to request a copy of your pathology report; ask your doctor to explain it and to discuss options based on your results.



There are many different types of radiation therapy available today. Be sure to use this guide to talk to your physician about which option might be best for your prostate cancer.

There are three other complementary therapies that may be given in conjunction with surgery, based on your pathology report:

- ▶ Radiation therapy may be given to men with **high-risk** prostate cancer who have cancer that has penetrated through the prostate capsule, into the seminal vesicles, and/or who have positive margins after surgery. This may reduce the risk of recurrence, but may also increase the risk of side effects. You should discuss with your doctor the risks and benefits of radiation therapy once your pathology report is available.
- ▶ Another strategy is to use radiation only if PSA levels rise; this is referred to as **salvage radiation**, which should be done soon after the first PSA

becomes detectable. Hormone therapy may be given along with the radiation therapy. Genomic tests have been developed that may help you and your doctor decide if you would benefit from immediate radiation therapy instead of waiting to see if the PSA rises.

- ▶ Hormone therapy may also be recommended for men who have cancer found in their lymph nodes at the time of surgery; in this context, hormone therapy after surgery has been shown to help patients live longer.

Keep in mind that new treatment protocols are constantly improving, and you can always discuss with your doctor your eligibility to enroll in a [clinical trial](#) for patients who have had a prostatectomy.

RADIATION

Radiation involves the precise killing of cancer cells with ionizing radiation or photons. Radiation damages the cancer cells' **DNA** (the genetic material of the cancer cell), leaving them unable to survive, grow, or spread; subsequently, the cancer cells die. Radiation therapy, like **surgery**, is very effective at killing localized or locally advanced prostate cancer and has approximately the same cure rate as surgery.

Just as surgical skill can play an important role in determining outcomes from prostatectomy, the technical skill of your radiation oncologist can play an important role in radiation outcomes. When choosing a radiation oncologist, at a minimum, make sure he or she has broad experience with an assortment of approaches and can objectively help you decide on the best course of treatment. Ideally, seek a radiation oncologist who specializes in the treatment of prostate cancer.

External Beam Radiation Therapy (EBRT)

EBRT is the most common type of radiation therapy. In EBRT, CT scans and MRIs are used to map out the location of the tumor cells, and X-rays are targeted to those areas. Your “mapping” scan will help your radiation oncologist to locate the precise anatomy of your prostate, rectum, and bladder so that radiation technicians and physicists can work with sophisticated computer treatment systems to design a personalized radiation plan for you. There are many types of EBRT, each with its own advantages and disadvantages (see inset on the right).

Regardless of the form of external radiation therapy, it is done on an outpatient basis.

Since it is non-invasive, there is no down time or healing time. You can be physically and sexually active every day of treatment and in the months following. It is common to have mild increased frequency of urination or bowel movements during the weeks of treatment; 2 to 4 weeks after treatment completes, these symptoms generally begin to improve, though as with any treatment, a small percentage of men can have persistent problems with urinary and/or bowel function.

Many studies have shown that while surgery results in a more immediate loss of erectile function followed by a period of partial recovery, radiation therapy results in less and a slower loss of erectile function over time in men who had good erectile function before treatment. For more details, see [Possible Side Effects: Sexual Function](#) on page 42.

EBRT Types

3D conformal radiotherapy is a form of radiation therapy that targets the tumor effectively, but also affects a small amount of healthy tissue (such as the rectum or bladder). For this reason 3D conformal radiation therapy is less favored today over more modern techniques that result in very low side effects.

Intensity-modulated radiation therapy (IMRT) uses the power of modern computers and complex computer algorithms to modulate and shape the intensity of the doses and radiation beams in order to better target the radiation delivered to the prostate, while simultaneously delivering lower doses to the bladder and rectal tissue. This treatment is usually delivered in 20 to 44 treatments.

Image-guided radiation therapy (IGRT) is a form of IMRT, but is even more accurate. IGRT utilizes multiple ways to ensure that the tumor (and not the surrounding tissue) is being treated with high doses of radiation. These methods include placing gold markers or electromagnetic beacons that track radiation into the prostate.

Stereotactic body radiation therapy (SBRT) is a form of IGRT. However, what is unique is that treatment is given in just 5 treatments instead of the usual 20 to 44 treatments with classical IMRT/IGRT. SBRT is one of the newer forms of radiation therapy and it is not yet available at all treatment centers. Studies have shown it to be safe, just as effective, and have very low side effects, similar to the longer course of 9 weeks of radiation therapy. Talk to your doctor for more information.

Proton beam. Protons are similar to photons (X-ray technology) in many ways. Proton beam therapy has not been shown to improve cure rates or quality of life outcomes over other forms of radiation therapy and there are mixed reports of increased and decreased side effects. Protons for prostate cancer should largely be viewed as an area of active research, and you should talk to your doctor about them. Insurance companies often do not cover proton beam therapy (unless you are participating in a research study) and it is typically very expensive.

Treatment Durations

There are 3 common treatment durations, or number of treatments, that are used in EBRT:

- ▶ **Conventional:** For decades, radiation therapy has been delivered every day (Monday through Friday), for a total of 40 to 45 treatments over 8 to 9 weeks.
- ▶ **Moderate hypofractionation:** Recently, [clinical trials](#) that have shown that as few as 20 treatments in 4 weeks can have similar cure rates and side effects as conventional radiation over 8 to 9 weeks. In hypofractionation, the doses given each day are higher than conventional dose levels. This is considered by national guidelines to be the current standard of care.
- ▶ **Ultra-hypofractionation:** This is another name for SBRT, or treatment delivered in about 5 treatments. These doses are even higher than hypofractionated doses. This strategy is rapidly becoming more common because it has lower side effects, equal cure rates, and increased convenience. However, not all centers provide this treatment, and not all patients are good candidates, so make sure to consult your doctor. This type of radiation has been compared head to head with the traditional 8 to 9 week course of radiation and shown to have similar cure rates and side effects. Ongoing trials are assessing if it is superior to surgery.

Brachytherapy

Brachytherapy involves an invasive procedure under anesthesia to place radiation therapy “seeds” or temporary catheters inside the prostate that emit radiation at a very short distance.

Think of it as internal radiation therapy, rather than external radiation therapy. Radioactive seeds (LDR or low dose rate) or catheters (HDR or high dose rate) are inserted directly into the prostate while you are asleep under anesthesia. It is usually done in 1 to 4 treatment sessions depending on the method used. The seeds are permanently placed into your prostate, while

the catheters are only temporarily placed inside the prostate and then removed after treatment is done. LDR brachytherapy kills the cancer over many months as the seeds give off radiation to the immediate surrounding area, thus killing the prostate cancer cells. By the end of the year, the radioactive material degrades, and the seeds that remain are harmless.

Brachytherapy by itself is usually used only for [low-risk](#) or favorable [intermediate-risk](#) patients. It is usually combined with some form of external beam radiation and often hormone therapy for [higher-risk](#) patients. The success of brachytherapy, like surgery, is dependent on the skill of your practitioner. Ask your doctor to help you find an experienced radiation oncology team who can perform brachytherapy.

As the use of IGRT and SBRT have increased, brachytherapy is now less commonly used, but some patients prefer it because it doesn't require daily visits to the treatment center. Brachytherapy has shown higher rates of side effects in recent trials. Brachytherapy has been shown to increase urinary side effects by about 3-fold compared with external beam radiation therapy, and might also have worse rectal side effects. These side effects can include erectile dysfunction, urinary frequency, urinary obstruction with need for catheter use, and rectal injury with bleeding. Patients who have large prostates or those patients with a lot of urinary problems are usually poor candidates for brachytherapy. Additionally, patients will need to speak with their doctor regarding restrictions for holding infants in their lap after the procedure.

Hormone Therapy with Radiation

Hormone therapy is often given together with radiation therapy for localized disease (note: it is also used alone or in combination with other treatments for men with metastatic prostate cancer).

Hormone therapy usually consists of a shot that lowers your testosterone, given every 1 to 6 months, depending on the formulation, and sometimes a daily pill that blocks testosterone from reaching the cancer cells. Clinical trials show a benefit in patients who receive hormonal treatment with external beam radiation. Hormone therapy has been shown to improve cure rates of prostate cancer for men receiving radiation therapy and is part of the standard of care for men with certain types of intermediate-risk prostate cancer and nearly all high-risk prostate cancer. It is often given for intermediate-risk cancer for 4 to 6 months (called short-term hormone therapy), and for 1.5 to 3 years in men with high-risk localized prostate cancer.

Hormone therapy should not be given to men with low-risk prostate cancer and is not a standalone treatment for localized prostate cancer in any risk category.

COMPARING SURGERY AND RADIATION

In general, for nearly all cases of newly diagnosed localized prostate cancer, the chance of “cure” is the same whether you have radiation therapy or surgery.

The main difference between surgery and radiation therapy relates to **quality of life and side effects**. Every patient has different priorities in regards to what aspects of quality of life mean most to them, so it’s important to take time to understand and process your diagnosis as well as the therapy options available to you.

One treatment may be preferred for you based on the associated side effect profile, and your team of doctors will evaluate your type of prostate cancer and develop a treatment plan that may include radiation without surgery, surgery without radiation, some combination of both, or neither. In some cases, hormonal therapy is added.

EXPERIMENTAL THERAPIES FOR LOCALIZED PROSTATE CANCER

Surgery and radiation therapy remain the standard treatment for localized prostate cancer, but other emerging treatment options have recently become available. As time goes on and the benefits of these treatment options are better understood, it’s possible that they may be reasonable alternatives for certain patients.

For now, none of these are seen as standard treatment for localized prostate cancer because they lack support from randomized clinical investigations in comparison with radiation or surgery.

FOCAL THERAPY

“Focal” therapies are treatments that target just a region of the prostate thought to have the tumor, instead of treating the entire prostate gland. None of these therapies have yet been proven to have the same long-term success as surgery or radiation therapy in clinical trials, and are still considered experimental treatments. The likelihood of recurrence is high with focal therapy due to the fact that in over 60% of cases prostate cancer is actually “multi-focal”, meaning even if the biopsy and/or MRI showed the cancer to be in only one area, there is likely tumor in many areas of the prostate.

Cryotherapy

Cryotherapy, also known as cryosurgery or cryoablation, has been around for years, but is rarely used. With this approach, probes are inserted into the prostate through the perineum (the space between the scrotum and the anus), and argon gas or liquid nitrogen is delivered to the prostate, literally freezing the prostate cells to death.

Over the years, a number of modifications were made to avoid freezing damage to the nearby structures, but the rates for both erectile and urinary dysfunction



Be an informed patient: investigate all choices that apply to your cancer, compare treatment options and side effects, and discuss decisions with your family as appropriate.

remain high when it is applied to the entire prostate, and data on long-term outcomes are still limited. There is also investigation into treating only a portion of the prostate with cryotherapy, a type of treatment referred to as “focal therapy.”

Cryotherapy is also used as a secondary local therapy in men who underwent radiation therapy as initial treatment for localized prostate cancer. Side effects of this therapy include further urinary or sexual problems such as pain in urination (caused by scar tissue), erectile dysfunction, and an urgent need to urinate. Cryotherapy can result in injury to surrounding tissues such as the rectum or bladder, given the proximity of these structures to the prostate bed.

High Intensity Focused Ultrasound (HIFU)

HIFU has been recently approved by the FDA for prostate tissue ablation, but is not FDA-approved for the treatment of prostate cancer, and is thus experimental.

HIFU works exactly the opposite of cryotherapy: with HIFU, the prostate cells are heated to death. A probe is inserted into the rectum, from which very high-intensity ultrasound waves are delivered to the target area. Although this technique remains experimental in the United States, it has been used in Europe for a number of years. Side effects of HIFU are similar to those discussed above for cryotherapy and depend on the skill and experience of the surgeon using this technique. Serious side effects have also occurred after HIFU, despite it being “focal”. Most of the published literature has demonstrated relatively high recurrence rates with HIFU, and we are still learning how best to optimize and deliver this treatment.

Using HIFU to treat only the portions of the prostate thought to be cancerous instead of the entire prostate gland is an area that is being investigated.

Primary Hormone Therapy

Since testosterone serves as the main fuel for prostate cancer cell growth, it is a common target for treatment. **Hormone therapy**, also known as **androgen-deprivation therapy or ADT**, is designed to stop testosterone from being released or to prevent it from acting on the prostate cells.

Although ADT has always played an important role in men with advanced metastatic prostate cancer, it is also increasingly being used in combination with radiation therapy because studies have shown that this combination increases long term survival.

There is data to show that **hormone therapy alone is not an effective treatment strategy for men** with localized prostate cancer. Multiple large studies with very long follow-up have shown that survival is worse with hormone therapy alone compared with hormone therapy with radiation therapy. There are certain rare situations in which the other illnesses that a patient has, a patient’s overall health status, or advanced age may make the use of ADT alone a consideration, but this is the exception rather than the rule.

If you're a numbers guy, here's a place for you to record where you were at the time of initial diagnosis, and any notes from your doctor or outstanding questions about treatment options.

Age at diagnosis: _____

PSA #1: _____

Date: _____

PSA #2: _____

Date: _____

Grade: _____

Stage: _____

Number of positive cores in biopsy: _____

SHIM score before treatment: _____ (Go to pcf.org/SHIM to find your score)

Notes/questions about treatment options:



“I’m going to do everything I can do at each stage. Nothing heroic. Just whatever I can, I do.”

— PATIENT



IN TREATMENT: WHAT TO EXPECT

Mental Health

Your state of mind has played, and will continue to play, a critical role in your cancer journey. From staying positive to controlling your diet and exercise routine, your overall mental health is a cornerstone in the ongoing treatment and control of your disease.

Just as with your diagnosis, and regardless of which treatment option you choose, you may experience difficult feelings about your situation.

New feelings about treatment are normal. Remember, you do not have to face this alone.

Living with prostate cancer can affect the way you view yourself and it can affect your interactions with the world around you. As always, it's important to check in with yourself and seek help from **your team** of doctors, friends and family. Many patients choose to proactively attend support groups with other patients, or begin working with a mental health practitioner. Others feel more comfortable connecting one-on-one with another prostate cancer survivor. Everyone is different in terms of what he needs and how these needs can best be met. The most important thing is to prioritize yourself and reach out in ways that will work for you. Check with the hospital or cancer center where you received treatment for referrals to counseling services, often free, for patients living with prostate cancer.

Maximizing Quality of Life

As a man with prostate cancer, you may have significant concerns about the side effects of treatment. It is important to communicate with your doctor about your questions and concerns, both when choosing between treatment options, and when undergoing treatment. Find out from your treatment team whether they have recommendations for ways to modify behavior that can reduce or help you avoid specific side effects.

There are many misunderstandings about how often side effects may occur, how severe they really are or should be, and what can be done to manage them and counteract their occurrence. Many of the side effects that

men fear most following local treatment are less frequent and severe than they have been historically. This is due to:

- Technical advances in both surgery and radiation therapy
- Researchers persistently seeking new ways to help overcome side effects
- Improvements in treatment delivery methods

It's still important to understand how and why these effects occur, and to learn how you can minimize their impact on your daily life. It is important to have frank conversations with your doctors about the complications you most want to avoid, and consider treatment options in terms of the likelihood of the risks of these complications.

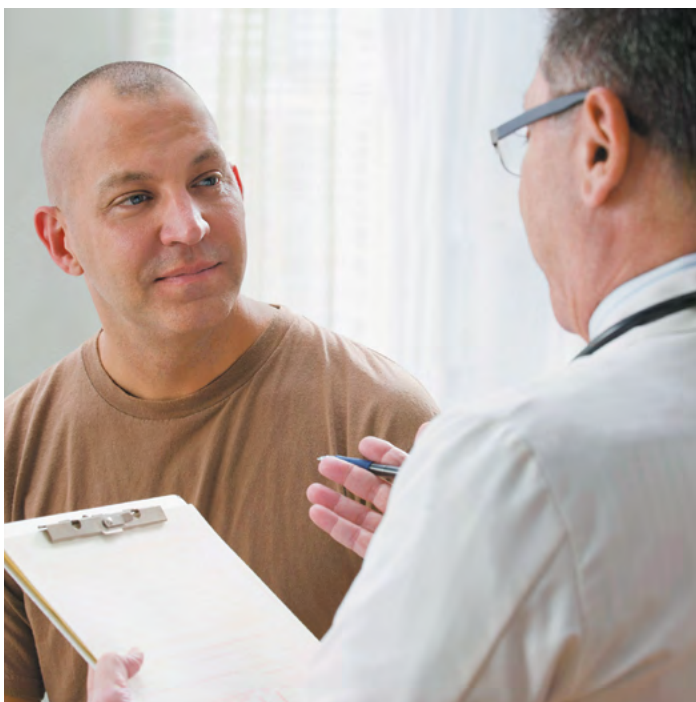
Early management of side effects has been shown to help patients live longer, better lives.

It is extremely important that you communicate with your doctors about the side effects that you are experiencing as you undergo treatment. Ongoing and proactive communication will enable your doctor to manage your side effects as early as possible to prevent worsening or development of downstream complications.

For resources surrounding mental and physical side effects from treatment, Us TOO is a non-profit organization providing local peer-to-peer support groups.

STATINS

A longitudinal study in Denmark has concluded that men with prostate cancer who are on statins live longer than men with prostate cancer who are not on statins. If you are on a statin, you should stay on it during your prostate cancer treatment. Statins have been associated with a 17% reduction in death from prostate cancer. At present, research has not indicated statin use exclusively for prostate cancer, but the bottom line is: if you're already on statins, stay on them during treatment. Statins include: atorvastatin (Lipitor®), fluvastatin (Lescol®), lovastatin (Mevacor®, Altacor™), pravastatin (Pravachol®), rosuvastatin (Crestor®), simvastatin (Zocor®), and pitavastatin (Livalo®).



When choosing a treatment option that is right for you, talk carefully with your doctor about which side effects are most tolerable for your lifestyle.

Monitoring for Recurrence

After initial treatment for localized or locally-advanced prostate cancer is complete, the next phase in the process is monitoring for a **recurrence**, or a regrowth of the cancer cells somewhere in your body. Monitoring for recurrence typically involves PSA testing, which is repeated every 3 to 6 months for the first 3 to 5 years, then yearly from that time on. If your PSA starts to rise, it could be a sign of your cancer returning, or it could be a sign of something else. The section on [What to Do If Your PSA Starts to Rise](#) (page 49) discusses all of the things that you should know about if this happens.

POSSIBLE SIDE EFFECTS

Because the prostate is close to several vital structures, prostate cancer and its treatments can disrupt normal urinary, bowel, and sexual functioning.

This section discusses side effects that might be experienced following surgery or radiation therapy for localized or locally advanced prostate cancer. For side effects related to advanced or metastatic prostate cancer, see [Side Effects from Treatments for Advanced Prostate Cancer](#) (page 63). Remember, before choosing any treatment, discuss worst possible side effects with your doctor.

Prostate cancer grows over years and decades, and requires a long-term perspective when you make treatment decisions. You should focus on long term cure and quality of life outcomes rather than short term “invasiveness”.

Urinary Function

Under normal circumstances, the **urinary sphincters** (bands of muscle at the base of the bladder and at the base of the prostate) remain tightly shut, preventing urine that's stored in the bladder from leaking out. During urination, the sphincters are relaxed and the urine flows from the bladder through the urethra and out of the body.

In **prostatectomy**—the surgical removal of the prostate—the bladder is pulled downward and connected to the urethra at the point where the prostate once sat. If the sphincter at the base of the bladder is damaged during this process, some degree of urinary incontinence or leakage may occur. Nearly all men will have some form of leakage immediately after the surgery, but this will improve over time and with strengthening exercises. Most men regain urinary control within a

year; approximately 1 in 5 men will have mild leakage requiring the use of one or more pads per day, but this rate varies with surgeon experience. Pelvic floor muscle training with a physical therapist can help. In the case that incontinence persists past a year, a **urethral sling** or **artificial urinary sphincter** can potentially correct the leakage. Men with obstruction from BPH can expect their urinary stream to improve substantially after surgery.

Radiation therapy is targeted to the prostate. Advanced technology directs the dose of radiation away from the bladder and rectum. The urethra runs through the middle of the prostate, so it will receive radiation, but fortunately the urethra is very resistant to radiation therapy, and long-term urinary leakage is rare (less than 1 in 100). However, it can become irritated during and for months after radiation therapy, which usually manifests as a mild increase in urinary frequency and urgency. This can also cause **nocturia**, or waking up more at night to urinate.

Bowel Function

Solid waste that is excreted from the body moves slowly down the intestines, and, under normal circumstances, the resultant stool passes through the rectum and then exits via the anus. Damage to the rectum can result in bowel problems, including rectal bleeding, diarrhea, or urgency.

In **prostatectomy** it is very rare (less than 1%) for men to have altered bowel function after surgery. In rare cases of locally advanced prostate cancer where the cancer invades the rectum, surgery may result in rectal damage, but it isn't often used in these types of cases.

Since the rectum sits right behind the prostate, it may also receive some radiation during treatment. With modern **radiation therapy** (IMRT or IGRT), it is very rare

SURGERY VS. RADIATION THERAPY: MORE TO THINK ABOUT

Surgery causes more urinary incontinence (leakage) than radiation, and has more early impact on erection function. Radiation causes more urinary and bowel irritation, and can have a delayed impact on erection function. The truth is that today, well-selected patients can expect good long-term urinary and bowel function after both surgery and radiation therapy—as long as the treatment is done by experienced, high-volume physicians working in centers of excellence. Erectile function can be more variable, even in the best hands.

to have moderate or severe bowel problems (<3%), and with the use of a **rectal spacer** (see below) it is less than 1%. During **radiation therapy** you may experience softer stools or diarrhea (less than 10%). These symptoms typically resolve within a few weeks of completing radiation therapy. With modern radiation, only 2% to 3% of men will have bothersome rectal bleeding that may occur months or years after treatment, and with a rectal spacer this rate is reduced to less than 1%. Be sure to discuss with your doctor the types of radiation therapy that are appropriate for you, as older forms of radiation therapy (called 3D conformal) can increase rectal side effects significantly.

Since 2016, the FDA has approved a new device, called a rectal gel or spacer (SpaceOAR) to further reduce rectal side effects of radiation therapy. In a randomized trial it was shown that the rectal spacer reduces bothersome rectal side effects to 0%. Ask your physician if they offer SpaceOAR at their practice and if your insurance covers it.



Although some erectile function may be lost in some patients during treatment, many options exist for managing side effects (see inset on page 45).

Fertility

After any of the most common prostate cancer treatments—surgery, radiation therapy, or hormone therapy—you are unlikely to be fertile. As part of the surgical removal of the prostate, **the seminal vesicles and part of the vas deferens** are removed, disrupting the connection to the testes. Orgasm may still occur (without ejaculation) but natural conception will not be possible. Radiation similarly destroys the prostate and seminal vesicles; chemotherapy and hormone therapy are both harmful to sperm production.

If you are hoping to father a child in the future, discuss fertility preservation and sperm cryopreservation with your physician before you undergo any treatment.

Sexual Function

Regardless of whether the nerves were spared during surgery or whether the most precise dose planning was used during radiation therapy, **erectile dysfunction** remains the most common side effect after treatment. This is because the nerves and blood vessels that control the physical aspect of an erection are incredibly delicate, and any trauma to the area can result in changes. Other less common, treatable side effects that can influence function include scarring in the penis (Peyronie syndrome) and climacturia (releasing a small amount of urine during ejaculation). Fortunately, beyond short term side effects, there is also room for great optimism: many excellent treatments for managing erectile function (see inset on page 45) exist on the market today.

In fact, within 1 to 2 years after treatment, most men with intact nerves will see a substantial improvement. However, modern studies have shown that overall about 40% of men lose erectile function after surgery. The skill of your surgeon or physician can have a significant impact on this outcome, so it is very important to select your team carefully. Likewise, men with baseline erectile dysfunction and/or other diseases or disorders that impair the ability to maintain an erection, such as diabetes or vascular problems, will have a more difficult time returning to pre-treatment function. It's important to remember that your functionality after treatment can only be as good as it was before treatment. The best predictor of how you will be after treatment is how healthy you were going into treatment.

Four main components of erectile function may be affected by prostate cancer treatment:

1. Libido (sex drive) is most commonly affected by **hormone therapy**, or treatment that decreases your testosterone. You can have a low libido and still obtain an erection, but it is usually more difficult for men who have less interest in sex. This will return once your testosterone returns to normal after completing hormone therapy. Loss of libido can be a major concern for some patients and/or their partners and much less of an issue for others.

Diagnosis and treatment can bring about complex feelings that include sadness, anger, and anxiety. These are normal feelings that, when unmanaged, can likewise compromise your sex drive; don't be shy about seeking individual or couples counseling during treatment.

2. Mechanical ability is the ability to achieve a firm erection. It is controlled by the nerves and vessels that are intimately associated with the prostate and structures near the penis. Mechanical ability is most affected by surgery or radiation therapy.

3. Orgasm/climax can be more difficult after treatment, especially if libido is low or your erections are not as firm as they used to be. Also, sometimes there can be some discomfort initially after treatment when you climax. This usually is transient and will resolve. It is important to distinguish orgasm from ejaculation, as men will continue to have the pleasure sensation of orgasm without ejaculation.

4. The quantity of ejaculate may be minimal after treatment. The prostate and seminal vesicles which function to produce ejaculate are removed and/or irradiated during treatment, so it is common to have minimal or no ejaculate afterwards. So although you may be able to have an erection and reach an orgasm, nothing may come out.

Prostatectomy: Since the 1980s, most men with localized disease are treated with what is termed a “**nerve-sparing**” prostatectomy. The goal of the procedure is to take the prostate and seminal vesicles out while sparing the nerves adjacent to the prostate. Studies have shown that approximately 50% of men who have the ability to have an erection before surgery will maintain this ability long-term. This number varies tremendously with surgeon expertise, and can increase or decrease based on age, obesity, and the ability to spare the nerves. In general, men with lower-risk prostate cancer have higher rates than average of erectile function, given it is easier to spare the nerves. In contrast, it is more challenging to spare the nerves in high-risk prostate cancer, since the tumor may have invaded more tissue—leading to erectile function rates that are lower than average. If you receive radiation therapy after surgery your likelihood of erectile dysfunction will increase, since you are being exposed to the cumulative side effects of both treatments.

Radiation therapy: Similar to surgery, damage to blood vessels and nerves after radiation therapy can result in decreased erectile function over time. In general, radiation therapy has less of an impact on erectile function in the first 5 to 10 years after treatment compared with surgery, and approximately 70% of men who have baseline erectile function before treatment will keep erectile function after treatment. However, radiation therapy has a slower delay in erectile function decline than surgery; within 15 years after treatment, the rates are similar to those who underwent surgery.

In the long run, these rates do not appear to be affected by the use of short-term (4 to 6 months) hormone therapy, but will be affected by the use of long-term (18 to 36 months) hormone therapy.

Newer techniques in radiation therapy, termed “**vessel-sparing**” radiation therapy, have shown promising results for improving the preservation of erectile function, with close to 80% of men maintaining baseline function. Ask your radiation oncologist about vessel-sparing radiation therapy.

Management of Erectile Function

Oral medications such as sildenafil (Viagra®), tadalafil (Cialis®), and vardenafil (Levitra®)—a class of drugs known collectively as **PDE5 inhibitors**—relax the arteries in the penis, allowing blood to rapidly flow in. About 75% of men who undergo nerve-sparing prostatectomy or more precise forms of radiation therapy have reported successfully achieving erections after using these drugs. Consult your doctor to see if these medications might be right for you. Individuals taking medicines that contain nitrates, such as those for angina or heart problems, may not be candidates for these medications.

Alprostadil (MUSE®) is a medicated pellet about half the size of a grain of rice that is inserted into the urethra through the opening at the tip of the penis. Like oral medications, it also stimulates blood flow into the penis. About 40% of men have reported successfully achieving erections after using this drug, but the results are often inconsistent.

Alprostadil (Caverject®) uses the same drug that is in the MUSE pellets, but is delivered via an injection directly into the penis. Although nearly 90% of men using Caverject reported erections about 6 months after therapy, many men have a concern about injecting themselves regularly, so for this reason the treatment is sometimes used only after other approaches have not worked. However, it is one of the most consistently effective options after prostate cancer treatment.

Mechanical devices may be a solution for those unwilling or unable to use any form of medication to help improve erectile function, or as an adjunct to medications. The vacuum constriction device, or vacuum pump, creates an erection mechanically, by forcing blood into the penis using a vacuum seal. Because the blood starts to flow back out once the vacuum seal is broken, a rubber ring is rolled onto the base of the penis, constricting it sufficiently so that the blood does not escape. About 80% of men find this device successful, but it, too, has a high drop-out rate. Note that the constriction ring at the base of the penis is effectively cutting off fresh circulation. Because of this effect, it is crucial that the ring be removed immediately after intercourse, or the tissue can be damaged due to lack of blood flow.

A surgically inserted penile implant can be up to 100% effective, and about 90% of men remain satisfied with their implants even after 10 years. The implant consists of a narrow, flexible plastic tube, a small balloon-like structure and a release button. The penis remains flaccid until an erection is desired, at which point the release button is pressed and fluid from the balloon fills the plastic tube, pulling the penis up and creating an erection. Note that the surgical procedure is done under general anesthesia, so this option is not available to men who are not considered good candidates for surgery because of other health reasons.

WHAT'S ON THE ED TREATMENT HORIZON?

Neuro-protection therapies: We know that trauma to the body can cause tissue damage both in and around the trauma site. Fortunately, with prostate cancer surgery we know when the trauma is going to take place, and we know exactly what tissue area will be affected (unlike, say, in the case of a stroke). Therefore, researchers are looking into what preventative action we can take to strengthen and preserve the nerves around the penis before surgery.

Neuro-modulation therapy: Scientists are also using **regeneration biology**—e.g. using natural tissues like stem cells, umbilical tissues, and growth factors—to deliver protection before during and after surgery. Treatments like these have been successfully used in colorectal cancer and are now being applied to prostate cancer.

REMEMBER: ERECTILE DYSFUNCTION IS NOT A DISEASE STATE. IT'S NOT A DISEASE YOU HAVE GOTTEN. IT'S A SIDE EFFECT THAT NEEDS TO BE MANAGED.

Great strides have been made in the field of erectile dysfunction in the last 20-30 years. If you were a prostate cancer patient in the 1980s, your option was to take a single oral medication or get a penile prosthesis. Today, patients and doctors can choose between oral medications, injectable therapies, vacuum devices, penile prostheses, and erection-inducing suppositories.

In 2019, the name of the game for patients is shared decision-making. In 2018, the American Urological Association released 25 new guidelines for diagnosis and treatment of erectile dysfunction ranging from evaluation to diagnosis and treatment. The recommendations indicate that men should be informed of all options that are not contraindicated (e.g. harmful to their health); previously, some treatments were seen as first-line defense and others as second-line, regardless of the personal goals and characteristics of the patient.

In the recent past, oral medications such as Viagra®, Levitra®, Cialis®, or Stendra® were considered “first line of defense” for treatment. But now we appreciate that some men’s situation may dictate a better starting point. Here are two examples. If you are a man who had nerve-sparing surgery and you were potent before surgery, oral medications may be a

great starting point for you. On the other hand, if you are a man who had compromised erectile function before surgery (for any number of reasons), and your nerves were not spared during surgery, you may opt to go straight to a mechanical prosthesis. But here’s the thing that might be both frustrating and liberating: there’s no right answer we can give you as to which treatment fits you. It’s important to talk to your urologist to discuss your overall physical and mental health, as well as your ideal lifestyle outcomes. If you are in a long-term relationship, it could be helpful to also involve your sexual partner in these conversations.

If you have yet to go into treatment, make sure to take the SHIM (Sexual Health Inventory for Men) test. Your score from this questionnaire will provide a documented, realistic baseline to which you might return after surgery. It is important to keep in mind that while you might return to this baseline, prostate cancer treatment will never result in better erectile function than you had before. Visit [pcf.org/SHIM](https://www.pcf.org/SHIM) to get your score.

With all that said, remember that one of the issues with all current ED treatments is that they are not curative—they all provide varying degrees of temporary correction to the problem.

Consult your doctor as to which of these options might be right for you. Note: it is not necessarily the case that all men should start with oral medications. If you are a man with significant vascular disease or little to no intact nerve function, ask your doctor if you should go straight to a pump or injections, which have traditionally been considered “second-line” defenses. Just as the Prostate Cancer Foundation is a strong advocate for precision medicine, we believe in precision lifestyle treatments for men to live a full life after treatment. Make sure to discuss side effects and the pros and cons of each treatment with your doctor. Beware of over-the-counter treatments, supplements, or expensive experimental treatments that promise miraculous results.

PERMANENT UPGRADES TO HEALTHY LIVING

From the moment you are diagnosed with prostate cancer, it's important to make mindful decisions about your diet and lifestyle. Your everyday choices are vital to the success of your treatment and your recovery from the disease, and it's a great way to take back some of the control that cancer and its treatment may have had on your life.

There is growing scientific evidence that suggests healthy diet and lifestyle practices may actually slow the growth and progression of prostate cancer. Cutting-edge studies are starting to unpack some unexpected data on behaviors that may increase or decrease your risk for cancer. For example, a recent study in Italy found that drinking 3 or more cups of European-style coffee may cut your risk of prostate cancer in half. Another study suggests that the bacteria in your gut, known as your **microbiome**, may in fact alter your immune system's ability to respond well to cancer treatment. To stay up to date on the latest in lifestyle research, subscribe to the newsletter at [pcf.org](https://www.pcf.org).

Diet

Just a few simple changes in your daily eating habits can help support healthier living as you recover from prostate cancer, may decrease your time to return to normal function, and may even decrease risk of your cancer coming back or getting worse. All of these recommendations also apply to maintaining overall health, for you and your family. Research is ongoing, but the “anti-inflammatory” diet is heart-healthy and gives every prostate cancer survivor a better chance to maximize longevity through lifestyle.

1. Vegetables. Incorporate cooked tomatoes (preferably cooked with olive oil) and cruciferous vegetables (like broccoli and cauliflower) into many of your weekly meals. Certain fruits and vegetables contain large amounts of antioxidants. **Antioxidants** benefit the body by removing free radicals. Free radicals can attack healthy cells and permanently disrupt their operation.

2. Fat. Try to keep the amount of fat that you get from red meat and dairy products to a minimum. Several studies have reported that saturated fat intake is associated with an increased risk of developing advanced prostate cancer, while **long-chain omega-3 fatty acids** (the “good fat” found in fish such as salmon) are associated with lower risk. Avoid processed meats (lunchmeats) that contain nitrates and charred meat, which have been shown to have cancer-promoting properties. Choose fish, lean poultry, or plant-based proteins such as nuts and beans instead.

3. Vitamins. Try to get your vitamins from food sources, that is, eating a diet rich in vegetables and whole grains, rather than relying on vitamin supplements. In particular, avoid calcium substitutes. Rather, get your calcium from low-fat dairy foods and dark green leafy vegetables.

For more detailed information on nutrition, visit [pcf.org](https://www.pcf.org) and download our nutrition guides.

Exercise

Exercise is part of a healthy lifestyle for everyone. For prostate cancer survivors, exercise as much as you are physically able, at a pace which is maximal for your personal fitness. More and more research studies are emerging which indicate that exercise during cancer treatment can improve long-term outcomes when combined with traditional therapies. Exercise has been proven in multiple studies to both reduce prostate cancer risk and improve survival in patients, even with the most advanced forms of disease.

For those who are able to exercise vigorously, walk as briskly as you can (3 or more miles per hour), and try to add bouts of jogging. Vigorous exercise should include close to maximal effort, in which your heart beats rapidly and you are sweating. Such activity includes running, vigorous swimming, or fast bicycling.

Research suggests that exercise affects energy metabolism, inflammation, oxidative stress, immunity, and androgen signaling pathways, and is therefore beneficial for men with prostate cancer. Exercise reduces levels of inflammation. Several studies have shown that

vigorous exercise significantly reduced the risk of prostate cancer recurrence, compared with the same volume of exercise at an easy pace.

Lifestyle Changes

In addition to diet and exercise, several other lifestyle factors may be associated with prostate cancer risk and progression.

Smoking

Quitting smoking may reduce the risk of dying from prostate cancer, and reduces the risk of dying from any cause. **The health benefits from quitting begin on the first day after smoking ceases**, so it is never too late to quit. Recent evidence further suggests that smoking is associated with more aggressive prostate cancer at the time of diagnosis. Furthermore, smokers have a higher risk of prostate cancer progression, including recurrence and metastasis, as well as an increased likelihood of death. Importantly, when compared with current smokers, men who quit smoking more than 10 years ago had prostate cancer mortality risk similar to those who had never smoked. Quitting smoking is also associated with improved penile blood flow and erections.

Body Mass Index (BMI)

Body mass index is a measure of body fat calculated by dividing an individual's weight (in kilograms) by height (in meters)-squared. A BMI of 18.5 to 24.9 is considered a healthy weight, a BMI of 25 to 29.9 is considered overweight, and a BMI of 30 or higher is considered obese. High BMI is associated with increased risk of developing lethal prostate cancer, and growing evidence suggests that obesity (either before or at the



Maintaining a positive attitude along with healthy diet and regular exercise will help during recovery, as well as for the rest of your life.

time of diagnosis) is associated with increased risk for prostate cancer recurrence, progression and mortality. This may be due to biological mechanisms that involve insulin, altered levels of male hormones (androgens), and cellular activity in fat tissue. Furthermore, obesity has been shown to increase the rates of urinary incontinence after surgery. Eating a nutritious diet and keeping up your exercise routine will go a long way towards maintaining a healthy weight.



STOP

The next 2 sections are for men with rising PSA levels after initial treatment, or with Advanced Metastatic Prostate Cancer. If you are a newly diagnosed patient with local or locally advanced prostate cancer, we suggest skipping ahead to the section titled "For Our Sons, Daughters & Grandchildren," a discussion of the genetics of prostate cancer risk. Of course, feel free to proceed if you like.

“Six months after hormone therapy, my PSA started to rise. That’s when I got choked up. This was serious.”

— PATIENT



DETECTING RECURRENCE

At this point, your cancer cells have either been removed with surgery or killed with radiation.

But some prostate cancer cells might have been able to spread outside the treatment areas before they could be removed or killed. At some point these cells may begin to multiply and produce enough PSA that it can again become detectable by lab tests.

PSA monitoring after treatment is an important way of understanding whether or not all the prostate cancer cells have been destroyed. If you previously underwent surgery, your PSA should be undetectable. However, after surgery, since PSA is produced by all prostate cells, not just prostate cancer cells, there are often residual normal (benign) prostate cells that still make some PSA.

If your PSA begins to rise, your doctor will first try to determine where the cells producing PSA are located.

This involves imaging, such as a CT, MRI, or bone scan. However, in cases where PSA is still very low, imaging tests may not provide enough information to determine a further course of action. Newer **molecular imaging scans** can be done at select centers; these scans include C11-choline (performed in limited clinic centers), F18-fluciclovine (recently FDA-approved and available across the USA), F18-sodium fluoride (to evaluate for bone metastases, usually to confirm findings from bone scans) and PSMA-PET scans. It's important to note that all scans can have difficulty in finding tumors at low PSA levels. It's also important to note that some of these tests may not be covered by your insurance.

PSMA-PET is one of the new molecular imaging technologies that is more sensitive in detecting prostate cancer metastases in the body; although it is currently not FDA-approved in the USA, it is offered under research trials at select centers.

Whole body multi-parametric MRI (MP-MRI) is another emerging imaging technology for measuring sites and burden of metastatic disease that may be more sensitive than CT and bone scans. Its effectiveness is currently being tested in clinical trials.

To follow these and other evolving technologies, visit pcf.org/newsletter.

UNDERSTANDING THE NUMBERS

After prostatectomy, PSA drops to “undetectable levels,” (less than 0.1). This is effectively zero, but by definition can never get all the way to zero, given the sensitivity of the test and the fact that, at very low readings, other proteins may be misread as “PSA protein.” In contrast, because normal healthy prostate tissue isn't always completely killed during radiation therapy, the PSA level rarely drops to zero with this treatment. Rather, a different low point is seen in each individual, and that low point, called **nadir**, becomes the benchmark by which to measure a rise in PSA.

Because the starting point is different whether you had surgery or radiation therapy, there are 2 different definitions for disease recurrence as measured by PSA following initial therapy.

Following a prostatectomy, the most widely accepted definition of a **recurrence** is a confirmed PSA level ≥ 0.2 ng/mL. In the post-radiation therapy setting, the most widely accepted definition is a PSA that is seen to be rising from the lowest level (nadir) by at least 2.0 ng/mL. It's important to try to always use the same lab for all of your PSA tests because PSA values can fluctuate somewhat from lab to lab.

After radiation therapy, doctors need to look for confirmation from multiple tests because PSA can “bounce” or jump up for a short period, and will later return to its low level. If only one test was performed it's possible that it could have occurred during a bounce phase, and the results would therefore be misleading. PSA bounces typically occur between 12 months and 2 years following the end of initial therapy.

WHEN TO BE WORRIED ABOUT RISING PSA

Surgery Patients: PSA greater than 0.2 ng/mL

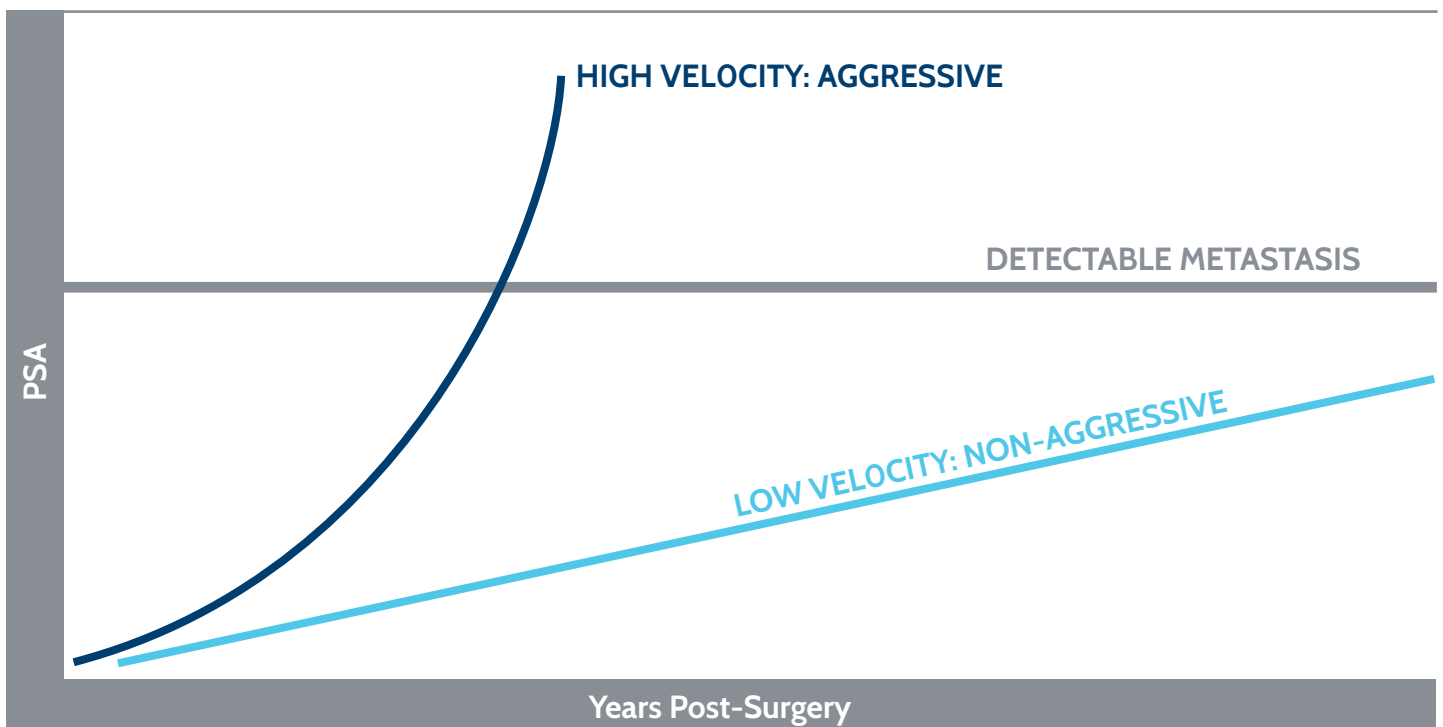
Radiation Patients: if your PSA is 2.0 ng/mL above your lowest reading after treatment (referred to as your “nadir” reading), as measured on 2 consecutive tests

If your PSA is rising but doesn't quite reach these definitions, your doctor might initiate further testing to assess the risk that cancer has come back. This is a gray area that requires a lot of input from your team, possibly including your urologist, radiation oncologist, and medical oncologist to help you decide on the best course of action.

PSA VELOCITY

The rate (or velocity) at which your PSA rises after prostatectomy or radiation therapy can be a very significant factor in determining how aggressive your cancer is, and can therefore be useful in determining how aggressively it might need to be treated.

PSA Velocity



When looking at PSA velocity in a few hundred men who had undergone either prostatectomy or radiation therapy, researchers found that men whose PSA doubled in under 3 months (fast velocity) had the most aggressive tumors and were more likely to die from their disease, whereas those whose PSA doubled in more than 10 months (slow velocity) had the least aggressive tumors and were less likely to die from their disease.

The faster your PSA rises, the more aggressive your disease is considered.

That said, measuring and using PSA velocity is not an exact science. There is no set number of times that your PSA has to be tested in order to determine the rate of rise, although most researchers would agree that more frequent tests over longer periods of time will likely give a better sense of how your tumor is growing.

Ultimately, PSA is just one of many factors that can influence the decision to pursue additional treatments. You and your doctors will need to weigh all of the different factors before deciding on the course that's right for you.

RISING PSA AFTER INITIAL TREATMENT

Questions to ask when your PSA is rising after initial treatment.

- ▶ What does it mean that my PSA level is rising?
- ▶ What is my PSA level now and how will we monitor changes over time?
- ▶ Am I a candidate for local “salvage” prostatectomy or radiation? Why or why not?
- ▶ Should I get an imaging scan to see if the cancer has spread to my bones or other organs?
- ▶ Should we add a medical oncologist to my treatment team to gain an additional perspective on treating my disease?
- ▶ If you recommend that I initiate androgen deprivation therapy (“hormone therapy”), how will this benefit me and slow down the growth of the cancer cells? When is the optimal time to initiate this treatment?
- ▶ Should my treatment plan also include abiraterone or docetaxel?
- ▶ What are the benefits and drawbacks/side effects of hormone therapy? Are there things that I can do to minimize the side effects?
- ▶ How long do the treatment effects of hormone therapy last?
- ▶ Should I consider joining a clinical trial?

LOCAL TREATMENTS FOR RECURRENT PROSTATE CANCER

In this section, we'll look at options for what to do when PSA first starts to rise after surgery or radiation therapy, and why a secondary local treatment might be right for you.

In general, the most common site of disease recurrence after surgery or radiation therapy is **local**, meaning in or near the prostate. For this reason, re-treating the prostate region may provide a second chance at cure. However, in some men, PSA may be produced by disease outside the pelvis, such as cancer in distant lymph nodes or bone.

This means that additional local therapy is not right for everyone. It's also important to keep in mind that a second form of local therapy has some degree of additional side effects.

Salvage Radiation Therapy Following Surgery

If your PSA starts to rise after you've undergone prostatectomy, “salvage” radiation therapy might be a good option to explore and is considered part of the standard of care. With this approach, EBRT is delivered to the area immediately surrounding where the prostate used to be (called the **prostate bed**) and sometimes to the pelvis, with the goal being to eradicate any remaining prostate cancer cells that have been left behind. Approximately 80% of men who have a rising PSA after surgery have residual disease in the prostate bed.

Note that this procedure is not for everyone. If there are obvious sites of metastatic disease outside of the pelvis, salvage radiation therapy is likely not the best choice, as it will only treat the prostate bed and potentially the nearby lymph nodes.

TIMING OF SALVAGE RADIATION

The best time to receive salvage radiation therapy is when your PSA first becomes detectable again, ideally when it is ≤ 0.2 ng/mL, and definitely below 0.5 ng/mL if possible. Once the PSA is above 0.5 ng/mL, cure rates with salvage radiation therapy alone start to fall off quickly. For some men with high-risk disease, hormone therapy is usually added to salvage radiation therapy, which has been shown to improve the cure rate.

The side effects that you suffer from salvage radiation therapy are directly related to the amount of side effects suffered from the surgery. In other words, if you had intact urinary control and erectile function after surgery, you are likely to have only mild side effects after radiation therapy. However, if you have some degree of urinary incontinence already or poor erectile function, salvage radiation therapy has the potential to worsen these to a more noticeable degree. In general, salvage radiation therapy (like all salvage therapies) is more likely to cause more side effects than upfront radiation therapy since the side effects may be additive to those previously experienced with surgery. These include rectal bleeding, incontinence (urinary leakage), strictures and difficulty urinating, diarrhea, and fatigue. Be sure to discuss potential side effects with your doctors before deciding on a course of therapy. In some cases, hormone therapy might be given in conjunction with radiation treatment, so it is also important to discuss the impact of that with your doctor.

Salvage Prostatectomy Following Radiation

In some cases, patients who have residual cancer in the prostate after radiation therapy may have improved results with “salvage” prostatectomy.

Even under the best of circumstances, post-radiation surgery is a very difficult operation to perform and can result in significant urinary effects and erectile dysfunction, so few surgeons across the country perform it regularly and successfully. If you talk with

your doctors about this treatment approach, be sure to carefully weigh all of the different factors that can play a role in determining whether this approach is right for you.

Brachytherapy Following External Beam Radiation

The use of radioactive seed implantation after EBRT has 5-year disease-free rates of around 50% (very similar to the success of salvage radiation therapy after surgery). Because this approach delivers radiation to very localized areas, it is not an optimal treatment for men with tumors that have spread beyond the prostate.

As with brachytherapy used as a primary therapy, side effects can sometimes be less frequent and less severe compared with other therapies, such as salvage prostatectomy. However, some studies have found high rates of urinary incontinence in men undergoing “salvage” brachytherapy, so careful consideration of existing urinary function and expected loss of erectile function should be discussed fully with your doctors before any decision is made.

Cryotherapy Following Radiation

Cryotherapy has been used as a secondary local therapy in men who underwent radiation therapy, and has shown 5-year disease-free rates around 40%. However, because the procedure does not completely destroy all remaining prostate cells, PSA generally does not drop to zero, so it is often difficult to determine complete success. Men with lower pre-cryotherapy PSA levels and lower-grade disease tend to fare better, while those who received hormone therapy in addition to radiation therapy tend to fare worse.

Side effects of cryotherapy tend to be milder compared with standard salvage prostatectomy. Nevertheless, rates for erectile dysfunction and urinary incontinence following this salvage procedure remain high, as do rates of pelvic or rectal pain. Because the severity of side effects tends to correlate with the amount of tissue that is frozen during therapy, better techniques are currently being studied that could improve outcomes over time.

Hormone Therapy Following Radiation

In select men who undergo surgery or radiation therapy, the best salvage treatment option may not be more local therapy, but rather hormonal therapy, which is a systemic therapy and therefore acts on tumor sites throughout the body. This has been shown to be beneficial especially in men who have lymph node involvement that was found at time of surgery. In addition, after radiation therapy, when the PSA is rising but there is no evidence of disease within the prostate via imaging or a repeat biopsy, initiation of hormone therapy alone may be most appropriate at the time when cancer spots are first seen on a scan or with a rapidly rising PSA. The next section provides more information on hormone therapy and other treatment options for advanced disease.

THERAPIES FOR ADVANCED (RECURRENT OR METASTATIC) PROSTATE CANCER

When a man experiences **PSA progression** after surgery or radiation, primary hormonal therapy is often given at some point, and often for many years. Some men will not require any therapy if their PSA doubling time is quite prolonged and no disease is present on scans.

Advanced disease refers to prostate cancer that has spread beyond the prostate and is unlikely to be cured with surgery or radiation alone.

Men diagnosed with **metastatic prostate cancer** (their disease has already spread beyond the prostate by the time of diagnosis), will often not undergo local treatments of the primary prostate tumor, such as surgery or radiation. Instead, their therapeutic journey will start in a similar way to men who were diagnosed at an earlier stage and had subsequent disease progression. Previously, the standard-of-care first-line treatment for metastatic prostate cancer was primary hormone therapy

INTERFERENCE EFFECTS

Many plant-based and complementary medicines can have estrogen-like properties and can interfere with the effectiveness of your hormone therapy, so be sure that your doctor has a complete list of all medicines—including the “non-traditional” ones—that you are taking, so that he or she can better monitor the effects of your therapy on the progression of your disease.

alone. However, recent clinical trials have found marked improvements in survival and other measures if abiraterone (a stronger form of hormone therapy) or docetaxel chemotherapy are started along with androgen deprivation therapy (ADT). It is important to discuss these treatment options with your doctor to determine which choice is right for you.

Primary Hormone Therapy

Primary hormone therapy (another name for ADT) is part of the standard of care for advanced and metastatic prostate cancer. ADT is designed to stop testosterone from being produced or directly block it from acting on prostate cancer cells. Although hormone therapy is effective at controlling prostate cancer growth, the loss of testosterone has side effects in nearly all men. These side effects range from hot flashes and loss of bone density to mood swings, weight gain, and erectile dysfunction. The timing of when to start primary hormone therapy once the PSA begins to rise is an individual decision and one that should be discussed with your doctor.

For a man starting primary hormone therapy, doctor visits are usually timed with the hormone therapy injections (which lower your testosterone), along with PSA and other lab checkups such as testosterone levels and liver and kidney function tests.



“There’s reason for hope. It’s realistic hope, not pie-in-the-sky hope.” – Patient

The majority of prostate cancer cells will die or stop growing following the removal of testosterone. However, in many men, some cells gain the ability to grow in the low-testosterone environment created by hormone therapy. As these **hormone therapy resistant prostate cancer** cells continue to grow, primary hormone therapies have less and less of an effect on stopping the growth of the tumor over time. This state is also referred to **castration resistant prostate cancer (CRPC)**. Despite this potential pitfall, ADT remains an important step in the process of managing advanced disease, and it will likely be a part of every man’s therapeutic regimen if he develops metastatic disease at some point during his fight against recurrent or advanced prostate cancer.

Types of Primary Hormone Therapy (Androgen Deprivation Therapy or ADT)

Orchiectomy: About 90% of testosterone is produced by the testicles. So orchiectomy—the surgical removal of the testicles—is an effective solution to blocking testosterone release. Because it’s permanent and irreversible, most men opt for drug therapy instead. The procedure is typically done on an outpatient basis in the urologist’s office. Since recovery tends to be quick and no further hormone therapy is needed, it is an option for men who prefer a low-cost, one-time procedure. It also may have a lower risk of cardiovascular complications and fractures compared with drug-based hormone therapy.

LHRH Agonist: LHRH, or luteinizing-hormone releasing hormone (also called GnRH, or gonadotropin-releasing hormone), is one of the key hormones released by the body that initiates the production of testosterone. Blocking the release of LHRH through the use of **agonists** (substances that initiate a response) is one of the most common hormone therapies used in men with prostate cancer. Drugs in this class, including leuprolide (Eligard[®], Lupron Depot[®], and Viadur[®]), goserelin (Zoladex[®]), and triptorelin (Trelstar[®]), are given as regular shots: once a month, once every 3, 4, or 6 months, or once per year. LHRH agonists cause a “testosterone flare” reaction, which is an initial transient rise in testosterone that happens over the first week or two after the first treatment. This can result in a variety of symptoms, ranging from bone pain to urinary issues. Fortunately, this can be prevented by co-treatment with anti-androgens.

LHRH Antagonists: These are a class of medications that can block LHRH (GnRH) from stimulating testosterone production without causing an initial testosterone surge. This class includes degarelix (Firmagon[®]), which is given monthly to men as an alternative to orchiectomy or LHRH agonists.

Anti-Androgens: Anti-androgens such as bicalutamide (Casodex®), flutamide (Eulexin®), and nilutamide (Nilandron®) can help block the action of testosterone in prostate cancer cells. They are often added to some hormone injections to prevent a temporary rise in testosterone.

Although the sexual side effects of the anti-androgens when given alone are typically fewer compared with hormone injections, anti-androgens might not be as effective as orchiectomy or hormone injections, and they are not the optimal choice for men with documented metastatic prostate cancer. Furthermore, when given alone, more than 70% of men experience breast tenderness or the formation/growth of breast tissue, termed **gynecomastia**.

When used in combination with LHRH agonists, anti-androgens tend to increase the risk of hot flashes, and in rare occasions can result in liver injury. Your liver function should be monitored while you take these medications. Fortunately, gynecomastia is rare when LHRH agonists and anti-androgens are used together.

In addition, nilutamide is known to cause visual light-dark adaptation problems and—rarely—cause inflammation and scarring in the lungs. If you develop a persistent cough or persistent shortness of breath while on nilutamide, you should contact your doctor.

Intermittent Hormonal Therapy

Over the years, researchers have explored different ways to minimize the [side effects of testosterone loss](#) while maximizing the therapeutic effect of hormone therapy. The most commonly explored strategy is to give LHRH intermittently, meaning that the drug is taken during “on” periods and skipped during “off” periods.

Intermittent hormonal therapy for the treatment of men with **PSA-only relapse** (biochemical recurrence or non-metastatic prostate cancer) has been found to be as effective as continuous hormone therapy. It is important to also recognize that it takes a while for testosterone to begin circulating again after LHRH agonists are removed, meaning that ADT injections are effective for weeks and sometimes months before testosterone rises again, and side effects are not immediately reversible.

With intermittent hormone therapy, the LHRH agonist is used for 6 to 12 months, during which time a low PSA level is maintained. If men reach a PSA below a threshold agreed upon by the patient and physician team, hormone therapy can be stopped until the PSA rises to a second agreed-upon threshold, at which point the drug is restarted.

During these “drug holidays” when hormone therapy is not being given, some men return to nearly normal levels of testosterone, potentially enabling sexual function and other important quality of life measures to improve before the next cycle begins again.

Intermittent therapy can be an attractive way to limit side effects from hormone therapy. However, at this time, we know that there are limitations to when we can use this approach to treatment, and that there are only certain men in whom intermittent therapy is appropriate. It is not right for all patients, especially those who have a rising PSA shortly after stopping hormone therapy. A patient-by-patient approach should be used based on response and tolerability to hormonal therapy.

Combination Treatments for “Hormone-naive” Metastatic Prostate Cancer

Abiraterone (Zytiga®) and taxane chemotherapy are two therapies that are typically used after cancer becomes metastatic and resistant to primary hormone therapy (see [Therapies for Hormone-Resistant Prostate Cancer](#) below for more information).

However, several recent clinical trials have found that in men with advanced prostate cancer who are just starting primary hormone therapy (“hormone-naive”), the addition of abiraterone or taxane chemotherapy significantly extends survival times and length of time before disease progression. In 2018, abiraterone became FDA-approved for high-risk hormone-naive metastatic prostate cancer patients who are initiating treatment with ADT. While ADT alone might still be the best choice for some patients, it is now recommended that patients with high-volume or high-risk hormone-naive metastatic prostate cancer should strongly consider the use of docetaxel or abiraterone in addition to ADT.

LHRH-Agonists plus Abiraterone

In 2017, results from 2 studies revealed that, in men who are just starting hormone therapy, the addition of abiraterone plus low-dose prednisone to the LHRH agonist Lupron delayed cancer progression by an average of 18 months and reduced the risk of death by 38%, compared with men being treated with Lupron only. Use of abiraterone in this situation was FDA-approved in February of 2018. Ask your doctor to discuss this approach with you if you are starting hormonal therapy for the first time.

Hormone therapy plus taxane chemotherapy

A recent clinical trial found that the addition of docetaxel extended overall survival by approximately 17 months in patients starting hormone therapy for the first time for metastatic disease, who also have a large volume of cancer. Whether the addition of docetaxel to ADT is beneficial in patients with low-volume disease is still unclear.

So which treatment is best for you? For patients with high-volume or high-risk hormone-naive metastatic prostate cancer, both of these combinations appear to have similar benefits on cancer outcomes. Studies have clearly found that the addition of docetaxel to ADT is beneficial in patients with high-volume metastatic disease, and the addition of abiraterone to ADT is beneficial in patients with high-risk metastatic disease. The benefit of these treatments in addition to ADT in low-volume or low-risk metastatic disease, respectively, is still unclear. Benefits, risks, side effects, costs and other issues should be considered with your doctor. For instance, patients who are older or less healthy may not be able to tolerate docetaxel, and abiraterone may be the only viable choice. On the other hand, those who can tolerate docetaxel may want to consider it, as the treatment length is far shorter (6 treatments given every 3 weeks for docetaxel, versus daily treatment until disease progression for abiraterone), and far less expensive.

THERAPIES FOR HORMONE-RESISTANT PROSTATE CANCER

It is important to note that the treatment landscape for advanced prostate cancer is rapidly changing. Treatments that were previously only given to patients after ADT has begun to fail are now being given upfront, at the time of ADT initiation. Thus, as you read the following sections, please keep in mind that optimal treatment choices are dependent on what treatments have previously been prescribed, and are best discussed with your doctor.

After a few years, prostate cancer cells often evolve ways to thrive despite the low androgen environment produced by primary hormone therapy, and become “castration-resistant.” For instance, tumors may evolve to produce their own androgens, prime the pump of the androgen receptor, or acquire alterations in the androgen receptor that allow sufficient activity with little or no androgens. In these cases, because prostate cancer cells still rely on the androgen receptor pathway to survive and grow, a number of “secondary” hormone therapy approaches can be used to keep the tumor from spreading.

TERMS TO KNOW

- ▶ Castration-resistant prostate cancer (CRPC)
- ▶ Hormone-resistant prostate cancer
- ▶ Hormone-refractory prostate cancer

All of these terms refer to the same status: the prostate cancer has learned to adapt and thrive in a low-hormone environment, thus primary hormone therapy is no longer an option and other treatment options should be considered, including second-line hormonal therapies which are even more effective at blocking androgen activity, as well as non-hormonal therapy options and emerging near-term therapies.

For many men who were using an anti-androgen in combination with an LHRH agonist, stopping the anti-androgen is the most common first step in secondary hormone therapy. About 10% to 30% of men will respond to anti-androgen withdrawal, which lasts on average 3 to 5 months. However, inevitably, additional therapies will need to be added even if this withdrawal response occurs. Switching to a different anti-androgen might also be able to offer an extra few months of benefit before other therapeutic approaches are required.

THERAPIES FOR NON-METASTATIC CRPC

Non-metastatic CRPC is a clinical state in which men receiving ADT begin to see their PSA levels rise (indicating the cancer is developing resistance to ADT), but the sites of cancer are not yet apparent on CT or bone scans.

In 2018, the FDA-approved two drugs for use in men with non-metastatic CRPC: apalutamide and enzalutamide, both of which are taken in addition to continuing ADT. The men who were treated on the clinical trials that led to these FDA approvals had rapidly rising PSA levels, with a PSA doubling time of less than 10 months.



New life-saving and life-extending therapies are constantly being tested and approved through clinical trials. Visit [pcf.org](https://www.pcf.org) and subscribe for the latest medical updates.

Prior to 2018, there were no FDA-approved treatments for non-metastatic CRPC, and these patients typically continued to receive ADT alone, despite evidence of a diminishing benefit. Today, thanks to research funded by the Prostate Cancer Foundation, men with non-metastatic CRPC have two treatment options which significantly delay metastatic disease.

As of press, it is still too early to know if the addition of either enzalutamide or apalutamide to ADT in non-metastatic CRPC improves overall survival. If you are a man with rising PSA levels and negative CT or bone scans, talk to your doctor about whether one of these drugs may be right for you.

Enzalutamide (Xtandi®), is an anti-androgen that acts by blocking the activation of the androgen receptor by testosterone, and is given orally. Side effects are mild but include fatigue, diarrhea, hot flushes, headache, frailty, falls, memory cloudiness and, very rarely, seizures. Enzalutamide has been FDA-approved for non-metastatic CRPC in combination with ADT, and for metastatic CRPC.

Apalutamide (Erleada®), is an oral anti-androgen medication that blocks the activation of the androgen receptor by testosterone. Apalutamide is very similar in chemical structure to enzalutamide and acts through the same mechanisms. The most common side effects include fatigue, hypertension, rash, diarrhea, nausea, weight decreased, arthralgia, fall, hot flush, decreased appetite, fracture, and peripheral edema. Apalutamide is only FDA-approved for the treatment of non-metastatic CRPC, in combination with ADT.

Abiraterone (Zytiga®, Yonsa®) is a pill taken by mouth that blocks the production of testosterone and other androgens, thereby stopping testosterone from stimulating prostate cancer growth. Abiraterone is administered in conjunction with prednisone, a corticosteroid, in order to minimize the adverse effects of abiraterone on other steroid pathways. Although a regimen of abiraterone + prednisone is generally well-tolerated, side effects may include fatigue, high blood pressure, and electrolyte or liver abnormalities, and patients need to be monitored regularly. Zytiga has been FDA-approved for metastatic hormone-naïve prostate cancer in combination with ADT, and for metastatic CRPC. Yonsa is a new formulation of abiraterone that was FDA-approved in 2018 for the treatment of metastatic CRPC.

THERAPIES FOR METASTATIC CRPC

Metastatic CRPC is a clinical state in which men who have previously received hormone therapy see their tumors begin to grow, and sites of metastatic disease can be found on imaging scans.

Second-line Hormone Therapies

There are 2 major androgen pathway blockers that are used for the treatment of hormone-refractory metastatic prostate cancer: abiraterone and enzalutamide. These therapies have exhibited similar survival benefits in similar clinical settings. Therefore, which one is initially prescribed is often driven by its side effect profile combined with other medical issues the patient may have. For example, enzalutamide is preferred if a patient has diabetes to avoid the prednisone that is given alongside abiraterone, and abiraterone is preferred if a patient has memory concerns, seizure disorders, or frailty related to age. Often when there is no medical necessity, insurance coverage and clinical trial options can help inform which agent is used first.

When treatment with either abiraterone or enzalutamide begins to fail, patients may be switched to the other drug. However, recent studies have indicated that patients who stop responding to abiraterone will have poor responses to enzalutamide and vice versa.

Researchers are actively investigating optimal strategies for patients whose cancer has become resistant to enzalutamide or abiraterone—for example, whether the next treatment should be chemotherapy or an investigational therapy. Clinically available blood tests which determine the presence of AR-V7, a biomarker, can help to indicate whether a patient is more likely to benefit from a second-line hormone therapy (abiraterone or enzalutamide) versus docetaxel chemotherapy.

NON-HORMONAL THERAPY OPTIONS

The therapies described in this section are typically used in patients whose cancer has progressed after treatment with hormonal therapy (ADT). However, clinical trials are continuing to test whether it is useful to introduce each of these treatments even earlier in the course of disease progression.

Taxane Chemotherapy

Currently, taxane chemotherapy, given with prednisone, is a standard of care for men with metastatic prostate cancer that has spread and is progressing despite hormone therapy. Taxane chemotherapy agents approved for the treatment of advanced prostate cancer include docetaxel (Taxotere®) and cabazitaxel (Jevtana®).

Taxane chemotherapy is also effective in prolonging life in patients who have a high burden of cancer on scans when starting hormonal therapy for the first time for metastatic disease. Taxanes kill rapidly dividing prostate cells by disrupting the protein structures required for cells to divide.

The decision on when to start chemotherapy is difficult and highly individualized based on several factors:

- ▶ What other treatment options or clinical trials are available
- ▶ How well chemotherapy is likely to be tolerated
- ▶ What prior therapies you have received and how you responded to them
- ▶ If radiation is needed prior to chemotherapy to relieve pain quickly



Although chemotherapy has a historically “bad rap,” prostate cancer chemotherapy drugs can actually help manage pain in patients with metastatic disease.

Often chemotherapy is given before pain starts, with the goal of preventing the cancer from spreading further to other sites. Discuss the use of chemotherapy with your medical oncologist early and often, and keep an open mind despite your concerns about chemotherapy’s “bad reputation.” Docetaxel can extend life, reduce pain, and improve quality of life. Clinical trials of docetaxel combinations and other promising therapies are a high priority for researchers.

Many men who are suffering from their cancer will experience symptomatic improvement after starting chemotherapy. For example, pain is often reduced in men starting docetaxel, and quality of life is generally better for men with cancer-related symptoms who receive chemotherapy as compared with no therapy.

Platinum Chemotherapy

Platinum-based chemotherapy agents including carboplatin (Paraplatin®), cisplatin (Platinol®), and oxaliplatin (Eloxatin®), are used for the treatment of various cancer types. Platinum chemotherapy is not yet FDA-approved for the treatment of prostate cancer; however, it is sometimes used in very advanced prostate cancer patients who have exhausted all other treatment options or in patients who have certain genetic subtypes of prostate cancer. Patients with advanced disease who are not responding to standard therapy can talk with their doctor about whether they may be candidates for platinum chemotherapy.

Sipuleucel-T Immunotherapy

The immune system has the remarkable ability to kill cells considered dangerous, such as infected cells or cancer cells. However, in most patients with progressing cancer, anti-cancer immune responses either never developed or have been turned off by the cancer. One way to turn on anti-cancer immune responses is the use of **therapeutic cancer vaccines**, which stimulate the immune system to recognize and fight cancer cells.

Sipuleucel-T (Provenge®) is a cell-based prostate cancer vaccine that has been approved by the FDA for men with metastatic hormone-resistant prostate cancer. This treatment is meant for men with minimal or no pain, and is most commonly given before chemotherapy, although it appears to be effective in some men even after chemotherapy. Some data suggest that the greatest benefit from sipuleucel-T is realized when it is used early (i.e., at a lower PSA level).

The treatment process involves filtering out your immune cells, stimulating them in a lab to fight prostate cancer, and then reinfusing those cells back into you intravenously (IV). This process is repeated every 2 weeks for a total of 3 treatments. The goal is to stimulate your own immune system to fight the cancer cells. This immunotherapy does not typically

lower PSA, treat symptoms, or delay disease progression—however, it has been shown to prolong life. There are ongoing studies attempting to clarify exactly how this treatment works. Sipuleucel-T should only be considered in cases where the patient has a slow-growing tumor and does not need urgent cancer shrinkage (which can be achieved more effectively with other agents).

This treatment can only be given in certain centers, and you should discuss with your doctor whether this treatment is appropriate for you.

The side effects of sipuleucel-T are usually limited to the few days after infusion of the stimulated cells. You can sometimes experience a flu-like illness with fever, chills, nausea, and bone/muscle aches. This generally resolves within 3 days and can be treated with acetaminophen.

Pembrolizumab

Pembrolizumab (Keytruda®) is a type of “immune checkpoint inhibitor,” which are a class of immunotherapies that block immune-suppressive signals and activate tumor-killing immune cells. Pembrolizumab was approved by the FDA in 2017 for the treatment of all solid tumors, including prostate cancer, that have mutations in **mismatch repair genes (MMR)** and/or exhibit **microsatellite instability (MSI)** in the tumor. Patients who qualify for this therapy must have progressed on prior treatment and have no satisfactory alternative treatment options. Hence, pembrolizumab would typically be considered after other available effective treatments (such as sipuleucel-T, abiraterone, enzalutamide, docetaxel, cabazitaxel, radium-223, etc.) have been used or deemed inappropriate.

Studies suggest that about 5% of metastatic prostate cancer patients have evidence of MMR mutations and/or MSI in their tumors. Some of these mutations may be inherited, and may be associated with **Lynch syndrome**, a condition which predisposes individuals to higher risks

WHAT IS MMR?

Mismatch repair (MMR) genes are proteins that work to proofread and edit DNA to prevent mistakes that can lead to mutations and cancer. Defects in MMR gene function can be detected through laboratory-based tumor testing of microsatellite instability (MSI).

of developing certain cancers such as colorectal cancer. At present, regardless of family history, MMR deficiency and MSI are identified by genetic tests performed on biopsies or tumor material from prostate surgery.

Pembrolizumab is delivered intravenously once every 3 weeks. The most common side effects are fatigue, cough, shortness of breath, nausea, constipation, itching, rash, and decreased appetite. Because it works by modifying the immune system, there are rare but serious side effects related to overactive immune responses which are typically treated by stopping the drug and, in some cases, starting steroid medications to suppress the immune reactions.

Radium-223

Radium-223 (Xofigo®) is a calcium-like radioactive element that is used to treat men with hormone-refractory prostate cancer that has metastasized to the bones. Because of its calcium-like chemical properties, radium-223 is used in place of calcium to build and fix bones, and is more likely to be taken up in places where the bone has been damaged and is undergoing repair, particularly sites of growing metastases.

Radium-223 has demonstrated both life-prolonging benefits as well as quality-of-life benefits, with more time free of the debilitating complications of advanced prostate cancer (such as bone fractures or spinal cord compression).

It is important to discuss with your doctor the proper sequence of available therapies. Studies have shown that patients with predominantly bone-only metastatic

disease do better when radium-223 is given earlier in the course of the disease than when it is given after many lines of therapy (enzalutamide, chemotherapy, abiraterone, etc.), given that it is more likely that patients have cancer spread beyond the bones by this time. Radium-223 should not be given in combination with abiraterone acetate and prednisone/prednisolone as this combination has been found to increase risk for bone fractures and death.

Radium-223 is delivered intravenously once every 4 weeks. The most common side effects are nausea, vomiting, diarrhea, swelling of the lower legs and hands (peripheral edema) and low blood counts. Your white and red blood cells and platelet counts may temporarily decrease as well.

External Beam Radiation

Radiation therapy can be used in multiple ways in men with metastatic prostate cancer. The most common reason to receive radiation therapy is to manage pain from prostate cancer spreading to bone. Radiation therapy is very effective at reducing cancer-related pain and about 70% to 80% of patients will experience some degree of pain relief after palliative radiation therapy. Usually the radiation therapy is delivered across 1, 5, or 10 treatments. Since this is a pain relief strategy, a low/moderate dose of radiation therapy is used and there are usually very few side effects.

Another indication for radiation therapy is progressive disease within the prostate causing urinary obstruction or bleeding. Radiation therapy is usually given over 1 to 4 weeks in these settings, and is highly dependent on whether you have had previous radiation therapy to the prostate. Less common indications include relieving pain from spinal cord compression. EBRT is also used successfully to treat painful bone metastases. This can either be given as a 1-time dose or over 1 to 2 weeks of daily radiation treatments and can significantly improve symptoms. Sometimes radiation therapy may be recommended if there is an area of the bone (typically in the hip or leg) that looks like it may easily break, even if it is not currently painful. The goal in that case is to



“My PSA came back high. It was disturbing, but it also was a wake-up call that I had to live my life.” – Patient

reduce the risk of developing a fracture. This kind of radiation targeted to sites of painful metastases can usually be safely given, even if you received radiation to treat your initial prostate cancer. More recently **SBRT** has been used (high dose, ultra-precise radiation therapy, sometimes using only 1 dose).

Given the many uses of radiation therapy in advanced prostate cancer, talk to your medical oncologist and consult with a radiation oncologist to see if radiation therapy may be an option for you.

Other Bone-Targeting Treatments

Bones are the most common site of prostate cancer metastasis, occurring in 85%–90% of patients with metastatic prostate cancer. Bone metastases

interfere with the bone's normal health and strength, and if they grow large enough can lead to bone pain, fracture, or other complications that can significantly impair a man's health.

Early detection of bone metastases can help determine the best treatment strategy. It can also help ward off complications. Because men with prostate cancer bone metastases often experience painful episodes, pain management and improving quality of life are important aspects of all treatment strategies.

Treatment with bisphosphonates or denosumab (Xgeva® and Prolia®) can help prevent complications related to bone metastases, like fractures.

Bisphosphonates are drugs that are designed to help reset the balance in the bone between bone growth and bone destruction that is disrupted by the prostate cancer metastases.

Zoledronic acid (Zometa®) is a bisphosphonate that can delay the onset of complications associated with prostate cancer bone metastases and relieve pain. It is typically given once every 3 weeks as a 15-minute infusion. Less frequent schedules are sometimes used as well, depending on your individual circumstance and risk.

Denosumab is a different type of bone-targeting drug which is given as an injection, rather than an infusion, and may be used instead of a bisphosphonate.

There are some risks with both classes of bone-targeted agents, including something called osteonecrosis of the jaw, that can occur after deep dental procedures and extractions or sometimes spontaneously. This can result in jaw pain and poor healing of your teeth. Certain laboratory assessments must be monitored with regular use of either medication. Daily calcium and vitamin D supplements are needed, and you should discuss this with your doctor.

Current Treatment Options for Advanced Prostate Cancer

| Disease Stage | Treatments to Consider Once This Stage is Reached |
|---|---|
| Rising PSA but no detectable tumors on imaging (no previous hormone therapy) | Hormone therapy Radiation to prostate bed if prior surgery Surveillance Clinical trials |
| Hormone-naïve metastatic disease | Hormone therapy Hormone therapy + abiraterone Hormone therapy + docetaxel Clinical trials |
| Non-metastatic castration-resistant prostate cancer (Rising PSA but no detectable tumors on imaging in patients who had previous hormone therapy) | Hormone therapy + apalutamide Hormone therapy + enzalutamide Clinical trials |
| Metastatic disease; resistant to primary hormone therapy (castration-resistant prostate cancer) | Sipuleucel-T (if minimal symptoms) Abiraterone or enzalutamide Radium-223 (for treatment of bone metastases) Taxane chemotherapy (docetaxel or cabazitaxel) Clinical trials |
| Patient has exhausted all therapeutic options | Platinum chemotherapy Pembrolizumab (if MMR-deficient or MSI-high) Clinical trials |
| Bone protection | Denosumab Zoledronic acid Clinical trials |

SIDE EFFECTS FROM TREATMENTS FOR ADVANCED PROSTATE CANCER

This section will discuss the side effects of common therapies used to treat patients with advanced prostate cancer, including hormone therapy and chemotherapy. For a review of side effects from therapies for localized disease, such as surgery and radiation therapy, please refer to [Possible Side Effects](#) on page 40. And remember, **early management of side effects has been shown to help patients live longer, better lives.** Communicate with your doctor as soon as you experience any side effect of treatment.

It is important to understand how and why these side effects occur, so you can minimize their impact on your daily life.

Side Effects of Hormone Therapy

Testosterone is the primary male hormone, and plays an important role in establishing and maintaining typical male characteristics, such as body hair growth, muscle mass, sexual desire, and erectile function, and contributes to a host of other normal physiologic processes in the body. The primary systemic treatment for prostate cancer, ADT, lowers testosterone and causes side effects related to reversing all of the normal functions of testosterone.

Although most men may experience only a few of these symptoms, the list of potential effects of testosterone loss is long: hot flashes, decreased sexual desire, loss of bone density and increased fracture risk (osteoporosis), erectile dysfunction, fatigue, increased risk of diabetes and heart attacks, weight gain, decreased muscle mass,

anemia, and memory loss. “Bad” cholesterol levels rise, particularly LDL and total cholesterol, and muscle tends to get replaced by fat, especially around the abdomen.

Current research indicates a weak link between prolonged ADT and increased risk of dementia; in a subsequent study, no increased risk was shown between ADT and Alzheimer’s. While substitute therapies for ADT are an active area of research for the Prostate Cancer Foundation, ADT is currently a part of the standard of care. While it’s important to be aware of the possible side effects, it should not affect your decision to receive life-extending care.

At this time, it is not possible to predict how severely any individual will be affected by lowering testosterone with hormone therapy, but work is being done to find ways to help predict who might be affected by which effects.

Changes in [diet and exercise](#) have been shown to relieve many of the side effects of ADT. Before beginning hormone therapy, every man should discuss the effects of testosterone loss with his doctor and nutritionist, so he can alter his lifestyle to accommodate or head off the changes.

Because hormone therapy is used to treat nearly every man with advanced prostate cancer, it is important to think about ways to prevent, reverse, or identify these effects so that men can live their best lives.

One important approach is considering lifestyle measures that can reduce some of these effects. Eating a [heart-healthy diet](#) low in red meat and high in vegetables and fiber, and maintaining [physical activity](#) through daily weight-bearing exercise can reduce weight gain and maintain bone and muscle mass. Men should also discuss the increased risk

of diabetes, heart disease, weight gain, and high cholesterol with their primary care physicians so that they can undergo screening and, if necessary, treatment for these other illnesses throughout the course of treatment for prostate cancer. When making these changes, it is important to talk with a doctor to ensure that you are planning lifestyle modifications that are safe for you. There are also some strategies that can decrease the hot flashes, including medications and acupuncture.

It is important to check bone mineral density around the time of starting hormonal therapy and every 1 or 2 years following, to assess the loss of bone density. There are medications that can be used to reduce the risk of fracture if early signs of bone loss are found.

Side Effects of Chemotherapy

Chemotherapy drugs are powerful and can take a toll on the body. Reactions to drugs can vary widely from patient to patient, so it’s important to pay attention to any side effects that you experience, expected or otherwise.

The chemotherapy drug docetaxel is well tolerated, and many men are surprised to find that disease-related symptoms (pain, fatigue, loss of energy) are improved after starting this therapy. However, docetaxel does have some side effects to be aware of. For example, between 5% and 10% of men will experience a fever with a low white blood cell count that will require medical attention and can be life threatening. The risk can be reduced through the use of **white blood cell growth factors** (Neulasta®); note that the use of this supportive medication is at the discretion of the physician who must weigh the benefits of Neulasta against its side effects. Despite use of Neulasta, there is still a risk of serious infection. About 50% of men will experience significant fatigue at some point in their therapy, usually for the first week of each cycle. About one-third of men

will experience numbness or weakness in their toes or fingers that may interfere with function (**neuropathy**). This side effect is not always reversible, but in most cases resolves slowly over time. There are no treatments available to prevent neuropathy, but reducing the dose of docetaxel, delaying the next dose, or stopping treatment can slow neuropathy and potentially prevent it from progressing. It is important to talk with your doctor if you are developing neuropathy so that you can speak together about how to best handle further cycles of docetaxel.

Other side effects of docetaxel include low platelets which can result in bleeding (1%), anemia (5%), reduced heart function (10%), hair loss (65%), diarrhea (32%), nail changes (30%), loss of appetite (20%), shortness of breath (15%), and fluid retention (10% to 20%). Most of these are mild, reversible, and treatable, and should not be a reason to avoid chemotherapy if you need it.

Cabazitaxel, which affects blood counts, is almost always given with Neulasta to boost infection-fighting white blood cells because life-threatening infection due to a depressed immune system is the most serious side effect associated with this medication. A blood transfusion is sometimes necessary to treat anemia to combat the fatigue and shortness of breath related to low blood counts. Other possible side effects include: fatigue (37%), neuropathy (13%), shortness of breath (12%), headache (8%), hair loss (10%), abdominal pain (17%), diarrhea (6%), and low blood pressure (5%). Fortunately, recent data suggests that the side effects of cabazitaxel may be reduced, and the drug equally effective, if it is given at a lower dose than was initially approved. Talk with your doctor about whether the reduced dose of cabazitaxel from the recently reported FIRSTANA trial may be a better option for you than the initially reported and FDA-approved dose.



Reducing red meat and increasing daily consumption of cruciferous vegetables can help during ADT and beyond.

Regardless of the type of chemotherapy you are receiving, you will be monitored very closely by doctors, nurses, and pharmacists to make sure that all side effects are being addressed. Many of these side effects, especially fever and inability to keep food/drink down, need to be addressed right away—don't wait until your next appointment to tell your provider.

“There’s no way for me to pay back the people who have gotten us this far, and I can’t accept that. I have to pass it on. For me, that’s clinical trials.”

— PATIENT

A grid of test tubes is shown against a blue background. The tubes are arranged in rows and columns, receding into the distance. The tube in the center foreground is filled with a vibrant, swirling liquid in shades of orange, yellow, and red, contrasting with the otherwise empty and clear tubes.

WHAT IS PRECISION MEDICINE?

Precision medicine uses new diagnostic tests to treat the right patient with the right medicine at the right time based on the genetic make-up of that patient's cancer. The promise of precision medicine is this: someday, there will be no trial and error for prostate cancer drugs.

Precision diagnosis is the process of looking at the genetic and molecular characteristics of your unique tumor (uniquely mutated genes and uniquely expressed proteins), and using this information to identify the tumor's weaknesses—think of it like taking your cancer's fingerprint. Once that level of identification is possible, custom selected treatments have the potential to be effective with less guess work. Since cancer is a “genomic” disease, that is, most cancers involve mutations of various genes, it makes precision oncology one of the most exciting fields in research today.

Because every cancer fingerprint can be different, each cancer needs a custom treatment.

By example, if you have advanced prostate cancer and conventional hormonal therapy is no longer working, you might be helped by a new treatment regime—but you might not. Now, instead of wasting precious time, money and experiencing the side effects of therapies that will not benefit you, you can find out ahead of time if you should take one of these drugs by tests that use either tumor biopsies or your blood to evaluate the genome and molecular make-up of your cancer.

DID YOU KNOW?

Approximately one-third of metastatic prostate cancer patients have been found to have mutations in genes that repair damaged DNA (known as DDRs or DNA damage repair genes). These mutations have likely contributed to the tumor's development by allowing cells to accumulate more and more mutations, until they become cancer. New drug development for patients with DNA repair mutations is an active area of research for the Prostate Cancer Foundation.

Here's one example of just how precise the right treatment can be. Thanks to research funded by PCF, scientists have discovered a simple test to indicate whether your prostate cancer may be fueled by hormones outside of the testes, therefore decreasing the effectiveness of hormone therapy alone for you. Patients with the *HSD3B1*(1245C) gene variant are likely to become more quickly resistant to hormone therapy. Having the *HSD3B1*(1245C) gene variant may also affect how well you respond to abiraterone. Talk to your doctor about ordering genetic testing of your tumor to find out if you qualify.

Every day, more and more precision therapies are coming to [clinical trials](#), and hopefully, soon to market. Someday, the hope is that your cancer treatment will be 100% designed for your cancer, and it will be 100% effective. Unfortunately, some treatments may be so new that even your doctor isn't up to date on their availability. For the very latest information on emerging precision therapies, please visit pcf.org.

EMERGING NEAR-TERM THERAPIES

There are over 1,000 ongoing [clinical trials](#) in prostate cancer just in the US that are testing new therapies and therapeutic strategies. Worldwide, there are many more emerging therapies being tested in patients. Only a few of these will lead to practice-changing solutions for prostate cancer patients, new therapies, or improved ways to use therapies that have already been approved. There are however, several emerging therapies that have demonstrated highly promising results in clinical trials for the treatment of prostate cancer and should be noted. Consult your doctor to find out about getting into a clinical trial or to check the status of FDA approval.

PARP Inhibitors

PARP inhibitors, which include rucaparib (Rubraca[®]), olaparib (Lynparza[®]), niraparib (Zejula[®]), and others, are a class of precision medicine treatments that are effective against cancers with mutations in genes that repair damaged DNA. These “DNA damage repair” (DDR) genes include the breast and ovarian cancer risk genes BRCA1 and BRCA2. Approximately one-quarter of metastatic prostate cancer patients have these mutations in their tumors and may be candidates for treatment with PARP inhibitors.

PARP inhibitors are not yet FDA-approved for the treatment of prostate cancer, but several are now being tested in phase 3 trials (for more information on trial phases see [Clinical Trials](#) on page 71). If phase 3 trials are successful and PARP inhibitors receive FDA approval, screening of metastatic prostate cancer patients to identify those who have DDR mutations and may benefit from treatment with PARP inhibitors will likely become a common practice.

Notably, about 10% of men with metastatic prostate cancer have inherited DDR gene mutations. Men with metastatic prostate cancer should strongly consider [genetic testing](#) and counseling, as inherited DDR mutations may have treatment implications, and may be associated with an increased risk of other cancers. In addition, this information may be critically important for blood relatives, because they may also have inherited the same cancer risk gene.

There are options for early detection and prevention for some cancers including prostate, breast, ovarian, pancreatic, and colon.

Inherited gene mutations can cross many forms of cancer—including but not limited to prostate, breast, ovarian, colon and pancreatic. For this reason, it is very important to both learn and share with your doctor what cancers have occurred in other members of your family. It is also important to talk with your family about your own diagnosis, if you feel comfortable. See also the section on [Prostate Cancer Genes in Families](#) on page 75.

THE FUTURE LANDSCAPE OF PROSTATE CANCER PRECISION THERAPY

A few of the most exciting emerging therapies, which are currently being tested in clinical trials, are discussed below.

Precision Screening

The advent of precision medicine will enable patients to have their tumors profiled for mutations that render them sensitive to certain therapies. Clinical trials are being conducted to test therapies that target mutations in genes including PTEN-loss, PIK3C, AKT, RAF, Wnt, CDK12, IDH1, RB, and others. Investigations into the

efficacy of therapies targeting these mutations are only just getting started, and many of these investigational agents will only be offered at select treatment centers—typically academic institutions.

All men with metastatic prostate cancer are now encouraged to speak with their physician about [screening](#) to determine whether they may carry one of these inherited mutations.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are a class of immunotherapy that activate tumor-killing immune cells. Checkpoint immunotherapy alone (not in combination with other treatments) may only work for a subset of prostate cancer patients, and studies are underway to determine how best to identify these men. In 2017, the FDA-approved the checkpoint inhibitor pembrolizumab (Keytruda®), for patients with solid tumors that have mutations in mismatch repair genes (MMR) and/or exhibit microsatellite instability (MSI). Recent studies suggest that advanced prostate cancer patients whose tumors have lost both copies of the CDK12 gene may respond to checkpoint immunotherapy. Many studies are underway in prostate cancer to test other checkpoint inhibitors, including pembrolizumab, ipilimumab (Yervoy®), nivolumab (Opdivo®), durvalumab (Imfinzi®), atezolizumab (Tecentriq®), and avelumab (Bavencio®) alone and in combination with various therapies including PARP inhibitors, cancer vaccines, and radiation therapy.

PSMA Radionuclide Therapy

PSMA, prostate membrane-specific antigen, is a protein that is found at high levels on the surface of prostate and prostate cancer cells. PSMA radionuclide therapy is a new type of treatment consisting of radioactive molecules injected into your bloodstream that specifically seek out and destroy prostate cancer cells



Everything about you—from your cancer to your immune system to the bacteria that inhabit your body—is unique. More and more, scientists are thinking of cancer treatment as a personalized plan.

using PSMA to target the cancer. These agents (referred to as “radiopharmaceuticals”) are available in clinical trials in the US, Australia and Canada. The beauty of PSMA radionuclide therapy—in contrast to traditional radiation—that the radiation can be targeted exclusively to the site of metastasis, such that only the prostate cancer cells are destroyed and the surrounding normal tissue is spared.

CAR T Cells

CAR T cells (“chimeric antigen receptor”) are T cells taken from a patient and genetically engineered to target and kill tumor cells. CAR T cells targeting prostate cancer began testing in phase 1 clinical trials in 2017.

PROSTVAC

There are many strategies to activate the immune system to target and kill prostate cancer. One strategy is the use of **cancer vaccines**, which instruct immune cells to identify and kill cells that express certain prostate cancer-associated proteins. PROSTVAC is a vaccine that activates the immune system to target prostate specific antigen (PSA), a protein specifically expressed by prostate cancer cells (same PSA as in the PSA test). PROSTVAC has not shown efficacy as a single agent in clinical trials, but is currently being tested in combination with other therapies.

Microbiome

The microbiome is the collection of microorganisms living in your body and, in particular, your gut. So, what's that got to do with cancer? New research is revealing that it could be a lot. Studies suggest that the gut microbiota can affect the immune system and may influence how well patients respond to certain cancer treatments. Doctors now think that for your body to stay healthy and cancer fighting, it's important to have the right diversity of bacteria in your gut, but there's still a lot to learn about how this translates to improved patient outcomes. Exploring the relationship between your microbiome and cancer is an active area of research for the Prostate Cancer Foundation.

CLINICAL TRIALS: HOW TO GET INVOLVED

Finding new treatments, and how to best use new treatments, is the work of clinical trials. As just one example, the first 500 men cured of what was thought to be incurable advanced prostate cancer are likely to be cured on a new clinical trial, even before it is FDA-approved.

Clinical trials are the place where patients go to “be there for a cure.”

In clinical trials, researchers test the hypothesis that a certain treatment may be effective for patients, under certain conditions. Clinical trials bring life-extending and curative new treatments to cancer patients. Clinical drug trials play a vital role in moving new treatments to patients who need them most, securing data so that FDA approval can be obtained and new drugs can move into widespread clinical practice.

Moreover, for all the promising treatments that have emerged in cancer research in the last several years, there's still a huge task of figuring out exactly the right way to use them. For example, what are the best doses for optimum response? At what time during disease progression and treatment do we insert a drug into the regimen?

There are currently over 140 phase 3 trials and more than 650 phase 1 and 2 trials related to prostate cancer treatment in progress in the United States alone. These trials focus on the full breadth of the prostate cancer experience, looking at everything from better treatments for localized prostate cancer, to life-prolonging drugs for advanced disease, to lifestyle and prevention changes which can improve the lives of patients and their families. Treatments that are approved will further improve outcomes for patients and join the multiple life-extending and life-improving therapies that are already in use.

Drugs for Advanced Prostate Cancer

There are currently at least 20 drugs FDA-approved for the treatment of advanced prostate cancer. As an example of the efficacy of clinical trials, remember that all 20 of them had to go through Phase I, II, and III clinical trials in order to receive FDA-approved

designation. Of the 20 drugs, 8 were developed with direct early stage support from the Prostate Cancer Foundation. To support life-saving cancer research, you can make a donation at pcf.org.

| Treatment | Approved for Treatment of Prostate Cancer |
|---------------------------|---|
| Estramustine | 1981 |
| Leuprolide Acetate | 1985 |
| Flutamide | 1989 |
| Bicalutamide | 1995 |
| Mitoxantrone + prednisone | 1996 |
| Nilutamide | 1996 |
| Goserelin acetate | 1998 |
| *Zoledronic acid | 2002 |
| *Docetaxel | 2004 |
| Degarelix | 2008 |
| Cabazitaxel | 2010 |
| *Sipuleucel-T | 2010 |
| *Abiraterone | 2011 |
| *Enzalutamide | 2012 |
| *Radium-223 | 2013 |
| *Denosumab | 2013 |
| Pembrolizumab | 2017 |
| *Apalutamide | 2018 |

*PCF supported

GET INVOLVED!

Patients who participate in clinical trials become citizen scientists, providing an invaluable service both to treatment science and fellow patients.

For more prostate cancer clinical trial information, visit the Prostate Cancer Clinical Trials Consortium at www.pcctc.org or www.clinicaltrials.gov.

If you are considering a clinical trial, speak to your doctor about the potential benefits of participating in a trial so you can make an informed decision that is best for you. **Remember: A common misconception about clinical trials is that the “placebo” group gets no treatment at all; in fact, they often still receive the minimum standard of care.**

Clinical Trials

To achieve FDA approval, all new treatments must typically pass through 3 phases of testing.

Phase 1: Test a new agent on a small number of subjects for overall safety and to find the appropriate dose that can be safely given with acceptable side effects.

Phase 2: Determine if a therapy has any activity against the cancer and can prevent tumor growth, progression, extend a patient’s life, or relieve symptoms.

Phase 3: Compare promising treatments from Phase 2 against standard treatments to determine if the test treatment works better and has fewer or more manageable side effects. Phase 3 trials are typically large (hundreds of patients), randomized (each patient is randomly assigned to the standard treatment or the test treatment), and sometimes blinded (the patient and/or doctors are not told which treatment the patient is getting as a way to control for the “placebo effect”).

Phase 4: Approved drugs are continually monitored for safety and efficacy.

“I needed my children to be well and live their lives happily, while at the same time being aware of what was going on.”

— PATIENT



THE GENETICS OF RISK

In the last 25 years, several **hereditary mutations** (genetic mutations that run in families) have been discovered that may increase the risk of developing certain cancers. The most famous that you may have heard of are the *BRCA1* and *BRCA2* mutations that increase risk for breast and ovarian cancer.

Prostate cancer has long been recognized to have a familial component. In fact, of all human cancers, prostate cancer is the most common among family members, with 40% of prostate cancer attributable to genes that run in families. If you have received a prostate cancer diagnosis, it's important to speak with your family about risk, prevention, and screening. Having a father or brother with prostate cancer increases a man's risk of developing prostate cancer. The genes that cause this risk have been extensively studied and are complex.

SCREENING FOR PROSTATE CANCER

If you're reading this guide, it's probably because you've already been diagnosed with prostate cancer.

Because we now know so much about the relationship between genetics and risk, it is our hope that readers will immediately consider these issues in consultation with their extended family.

Should My Family Members Be Screened?

The question of screening is a personal and complex one, which may be further complicated by family history. It's important for each man to talk with his doctor to assess at what age prostate cancer screening might be appropriate.

Revisiting Family Risk

If a family history of prostate cancer or genetic predisposition exists, it is all the more important that your family understand the full picture of risk related to prostate cancer. There are 4 major factors that influence one's risk for developing prostate cancer. Since prevention can hinge on appropriate **screening**—neither too early, nor too late—it's important to understand your personal risk profile.

Age: The risk of prostate cancer increases with age. The average age at diagnosis of prostate cancer in the United States is 69 years, which is likely reflective of recommended screening patterns.

Race: African Americans are more likely to develop prostate cancer and have more than twice the risk of dying from it.

Family history: A man with a father or brother who developed prostate cancer has a twofold-increased risk for developing it. This risk is further increased if the cancer was diagnosed at a younger age (less than 55 years of age) or affected 3 or more family members. You should discuss with your doctor if you have a family history of not only prostate cancer, but also breast cancer, ovarian cancer, colon cancer, or pancreatic cancer.

Where you live: Consider this: The risk of developing prostate cancer for men who live in rural China is 2%, and is 17% for men in the United States. When Chinese men move to the US, their risk increases substantially. Men who live north of 40 degrees latitude (north of Philadelphia, Pennsylvania, Columbus, Ohio, and Provo, Utah) have the highest risk for dying from prostate cancer of any men in the United States—this effect may be mediated by inadequate sunlight which reduces vitamin D levels. Similar results were found in Sweden, which is also a high-risk country for prostate cancer: immigrants to Sweden had a lower risk compared with native-born Swedes but, interestingly, the difference diminished the longer they were in Sweden.

Most risk factors are hard or impossible to change. As mentioned, prostate cancer is over 8 times more common in Western culture than in Asia; moreover, when Asian men migrate to western countries the risk of prostate cancer increases over time. Why? Genetics, environment and lifestyle factors, and screening protocols may all play a role. Researchers are now looking at **prevention strategies** which may shed light on this mystery.

There is ongoing debate about the risks and benefits of prostate cancer screening. Benefits include early detection that could offer a better chance to cure the disease if your cancer warrants treatment. It also may inform you that you don't need your prostate cancer treated at all.

On the other side of the argument is concern with overtreatment. Because most prostate cancers grow very slowly, the side effects of diagnosis (a prostate biopsy) and treatment of low-risk prostate cancers could outweigh any benefit that might be gained.

The US Preventative Services Task Force (USPSTF) is an independent panel of experts that issues recommendations on disease screening. In 2018 the USPSTF issued an updated recommendation for prostate cancer screening, which recommends shared decision-making about PSA screening. Since the potential benefits and harms of PSA-based screening are closely balanced in men ages 55 to 69 years, the decision to screen should be an individual one. For men age 70 years and older, USPSTF continues to recommend against screening for prostate cancer, with the rationale that potential benefits do not outweigh the harms. For more info on the latest US Preventative Services Task Force recommendations visit [pcf.org/uspstf-faqs/](https://www.pcf.org/uspstf-faqs/).

Other professional organizations, such as the American Society of Clinical Oncology and the American Urological Association, also recommend shared decision-making about PSA screening. They maintain that PSA screening should be considered in the context of a man's life expectancy, family history, ethnicity, and other medical conditions. Experts agree that there is no role for PSA screening in men expected to live less than 10 years, since the rigor of some treatments and side effects can actually lessen life expectancy as well as quality of life.

BEGIN TO TALK TO YOUR DOCTOR ABOUT SCREENING AT AGE

- 40 ▶ If you have a family history of lethal prostate cancer
- 45 ▶ If you have African ancestry
- 50 ▶ If you have no history and you are not African American
- 55-69 ▶ Discuss with your doctor
- Over 70 ▶ Screening not proven to save lives

When to Start—and Stop—Screening

Regardless of your age, the Prostate Cancer Foundation recommends that you practice “precision screening,” and consult with your doctor to come up with a personal screening plan that's right for you. Go to [pcf.org/screen](https://www.pcf.org/screen) and use the screening tool as a guide to start a conversation with your doctor.

Be proactive: there is no “one-size-fits-all” approach to screening,

For men with a family history of lethal prostate cancer in a first-degree relative, begin a conversation with your doctor at age 40. For men of African American descent with no prior family history, talk to your doctor as early as age 45. For average-risk men, screening is typically recommended starting at age 50. Between 55 and 69 years, practice shared decision-making with your physician about when to begin screening. For most men over the age of 70, the USPSTF recommendation to discontinue screening may be appropriate. But if you are a healthy man over 70, be sure to discuss continued screening with your doctor. Research is ongoing to further illuminate the benefits and harms associated with screening in men above the age of 70.

Screening and Biopsy Review

PSA screening may reveal results that prompt a doctor to recommend a biopsy. However, the result may create more confusion if the PSA is mildly elevated. Fortunately, there are many other supplementary tests and considerations that can help a man who is undergoing screening decide whether a biopsy is necessary, including:

- ▶ Free PSA test (<25% Free PSA indicates greater risk of having cancer)
- ▶ PSA velocity or the rate of rise over time (faster increases mean more risk)
- ▶ PSA density, or the PSA per volume of prostate (higher density means more risk)
- ▶ Digital rectal exam results
- ▶ PSA-based markers (for instance the prostate health index, 4K score)
- ▶ Other markers, a urinary PCA3 or SelectMDx test
- ▶ MRI of the prostate

It should be noted that these recommendations apply only to screening—testing of healthy men without symptoms. Once the diagnosis of prostate cancer is confirmed by biopsy, PSA is used for monitoring the status of the cancer, and the interpretation of results depends on how the cancer is managed. Discuss these individual tests with your doctor to make screening decisions that are best for you.

PROSTATE CANCER GENES IN FAMILIES

For most patients, it is thought that multiple genes together lead to the highest risk. However, we have recently learned that there are certain relatively rare genes that run in some families that, when present,



We now know: some of the same genes that are responsible for prostate cancer are also responsible for cancers in daughters.

may increase a man's risk of developing prostate cancer; in some cases, these genes lead to the more aggressive forms of prostate cancer. In 2016, a PCF-supported study of men with metastatic prostate cancer found that more than 10% have inherited cancer risk genes such as *BRCA1*, *BRCA2* and at least 18 other newly-discovered genes that may be important to risk of prostate cancer and other types of cancer.

Over 20 different genes have been identified that run in families with prostate cancer (hereditary prostate cancer).

Because many of the genes and cancer pathways that cause prostate cancer occur across other cancers, PCF's work now has overlap in at least 67 other cancers (see chart on page 78). This is important because it highlights that men should be aware of their family history of all cancer—i.e. not just prostate cancer, but also breast, ovarian, pancreatic, leukemia, and other cancers.

Having a sister with breast cancer diagnosed at an early age (for example, in her 40s or younger) may be valuable information for a man to know and share with his doctor. Conversely, your prostate cancer may imply a high cancer risk for both your male and female family members.

There can also be other mutations that occur after birth, resulting from environmental and lifestyle factors. Scientists have identified a full 97 of these “somatic mutations” implicated in prostate cancer.

Do You Carry A Genetic Mutation?

All men with metastatic prostate cancer are now encouraged to speak with their physician about determining whether they carry an inherited cancer risk mutation. Talk to your doctor about a referral to a genetic counselor if you have any of the following risk factors that may indicate the presence of a hereditary cancer-risk mutation:

- ▶ Personal history of metastatic prostate cancer
- ▶ Blood relative with a known cancer risk gene (eg, *BRCA1*, *BRCA2*, Lynch syndrome, etc)
- ▶ Two or more family members with prostate cancer at Gleason ≥ 7
- ▶ One male relative with metastatic prostate cancer and/or who died from prostate cancer
- ▶ Three or more family members, on the same side of the family, with one or more of the following cancers: breast cancer diagnosed at <50 years old, ovarian cancer, pancreatic cancer, colon cancer, or multiple other cancers

WHAT DO WE KNOW ABOUT PROSTATE CANCER GENES?

Researchers are beginning to categorize genes for prostate cancer by whether they increase your risk of getting the disease or they increase the aggressiveness of advanced disease.

“CASCADE” GENETIC TESTING

Different from standard PSA screening for prostate cancer, cascade genetic testing is a form of screening that identifies whether family members share a genetic mutation. For example, if a man discovers that he is a carrier of an inherited mutation in the *BRCA1*, *BRCA2*, or other genes that increase risk for prostate cancer, this has critical implications for all his family members. If male family members have inherited the same mutation, they may be at increased risk for prostate cancer and other cancers such as male breast and pancreatic cancer. And if female family members have inherited these mutations, they may be at increased risk for pancreatic, breast, ovarian, and endometrial cancer. These mutations may also increase risk for other cancers, depending on the gene.

Men who find they are gene mutation carriers should encourage “cascade” (i.e. setting off a cascade of events) genetic counseling and testing for male and female family members, to assess whether they, too, are carriers of the mutation and are at risk for certain cancers.

Family members who learn that they are carriers need to discuss their findings with genetic counselors and their doctors to better understand their cancer risks, options for early detection, and how to reduce risk for various other forms of cancer.

Certain gene mutations may have enough information known about them to recommend more frequent screening for specific cancers in family members. Other gene mutations may have less known about them and/or tests can identify variants of uncertain significance. These may require further discussion with a genetic counselor and patients/families with these may consider participating in research registries to help doctors and researchers learn more about those specific variants.

For some genes which are better studied, there may be clear screening recommendations and risk-reduction strategies, such as medications and/or preventative surgeries for women at increased risk for breast and ovarian cancers. However, these decisions must be made with a well-informed genetic counselor and physician. While this information can have important benefits, it can also cause unnecessary worry and/or medical procedures if the family members or doctors are not fully informed. Early detection and management of cancer risk is a very specialized field and it is strongly recommended that families consider consulting doctors at a top-tier or academic medical center that is actively engaged in the latest research and treatments to get the most updated information, recommendations and the best medical plan if they are found to have a cancer risk mutation.

THE NUANCES OF GENETIC SCREENING

Many genetic testing companies are offering services to find hereditary mutations in cancer-associated genes. It is critical to be aware that the risk for any given cancer associated with any given mutation is not always clear. There are several well-studied mutations that researchers believe are more often present in patients with cancer. However, there are many more mutations that are less well studied, but have been observed in cancer patients, and therefore have some association with risk that is not yet well understood. Importantly, there are many more mutations of “unknown significance,” though “mutated,” we do not

WHAT'S THE DIFFERENCE BETWEEN GENETIC SEQUENCING AND TUMOR SEQUENCING?

Genetic testing (also known as germline genetic testing) looks only for hereditary mutations—those that you inherited from your mother or father that may increase your risk for developing cancer.

Tumor sequencing is performed on cancer samples obtained from biopsies, surgery, or blood tests and is designed to identify mutations that cancer cells acquired during disease progression—usually for the purpose of treatment decision-making. Note that tumor sequencing also has the potential to suggest presence of the germline (hereditary) mutations mentioned above. It is important to consider whether knowing more about inherited cancer risk is important to you, in which case you should have dedicated testing for this purpose.

yet know whether they confer a change in the gene that is sufficient to increase cancer risk.

How To Get Genetic Counseling and Testing

If you or someone in your family has been treated for prostate cancer, your family's urologist or oncologist may have a recommendation for a local genetic counselor and testing center. You can also find a list at the National Society for Genetic Counselors: www.nsgc.org.

If your genetic testing returns a positive result—that is, you have one of the genes implicated in prostate cancer risk or growth—it is important to consult with your doctor and seek genetic counseling. Remember, new clinical trials and studies are emerging regularly to find new treatments that might be relevant for you. Go to pcf.org for more information on the latest research and drug approvals.



The same gene errors that PCF is researching for prostate cancer apply to 7 of the top 10 pediatric cancers (so far).

THE FUTURE LANDSCAPE OF CANCER

For years, doctors focused on cancer as an organ-site disease, e.g. you had breast cancer, or colon cancer, or prostate cancer, etc. Thanks to some significant discoveries funded by PCF, we now know cancer is too complex to be studied in a single site in the body. Cutting-edge research is now targeting the mechanisms cancer uses to grow, which may be shared across many cancer types. In treating prostate cancer, PCF will likely impact hundreds of forms of disease, including most major forms of cancer in children.

For more information visit impact.pcf.org.

PCF'S IMPACT ACROSS ALL CANCERS

It is important to look at cancer risk across your whole family. Particularly for men with advanced or aggressive disease—that is, whose disease is most resistant to standard treatment—gene targeted therapies may be unusually effective. PCF believes that gene targets and pathways are the bridge to unlocking treatments for all cancer, not just prostate cancer.

- ▶ Brain
- ▶ Eye
- ▶ Lip
- ▶ Neck
- ▶ Thyroid
- ▶ Esophagus
- ▶ Thymus
- ▶ Lung
- ▶ Liver
- ▶ Stomach
- ▶ Gallbladder
- ▶ Pancreas
- ▶ Kidney
- ▶ Colon
- ▶ Bladder
- ▶ Rectum
- ▶ Skin
- ▶ Nerve
- ▶ Blood
- ▶ Sarcoma
- ▶ Prostate
- ▶ Testicle
- ▶ Breast
- ▶ Cervix
- ▶ Ovary
- ▶ Uterus
- ▶ Childhood brain cancer
- ▶ Childhood blood cancer
- ▶ Childhood kidney cancer

CASE STUDY: MSI

In prostate cancer, we currently have experimental treatments in the works for dozens of genes, but only one treatment that is FDA-approved based on a mutation found in tumors—pembrolizumab (Keytruda®) for microsatellite instability (MSI) or mutations in mismatch repair (MMR) genes. While only about 5% of advanced prostate cancer patients have MSI, approximately 15% of colon cancer patients do. Since testing for MSI was first developed and optimized for colon cancer, not all MSI tests may detect all prostate cancer with MSI; talk to your doctor about more precise testing.

PREVENTION

The ultimate goal is to prevent men from ever developing prostate cancer. Although significant progress has been made, the evidence is not strong enough to form conclusive recommendations on how to prevent prostate cancer. Note that screening does not lead to prevention, but only to earlier detection.

Improvements in diet and exercise are among the most commonly accepted strategies for prevention. This remains an active area of investigation with numerous ongoing studies examining the impact of medications, supplements, diet and exercise on prostate cancer risk.

As a critical prevention strategy, it is important to share these diet and exercise tips with family members who may be at risk.

DIET AND EXERCISE

For those with a family history of prostate cancer, it's important to make some preemptive, permanent lifestyle changes to maintain the best possible health.

Beyond genetics, diet and exercise are believed to be two of the major risk factors for prostate cancer. There is much hope on the horizon for men with prostate cancer



Fish, berries, cooked tomatoes, broccoli, and green tea are five of the top anti-inflammatory foods for protecting your prostate health.

and their families. Continuing to be prudent with regard to risk factors, screening recommendations, and diet and exercise changes can help men with prostate cancer live longer and better lives.

In closing, although living a healthy lifestyle and eating right are good for you, they will not eliminate your risk of prostate cancer, nor will they cure you by themselves if you are diagnosed with prostate cancer. If you are age 50 or over, if you are age 40 or over and African American or have a family history of prostate cancer, regular exercise and a good diet are even more critical for reducing risk; consider regular rectal examinations and PSA tests, and discuss the risks and benefits of these screening procedures with your doctor.

Remember: Every patient is unique. Be sure to take these general guidelines and discuss all available options, information, and questions with your physician.

► CHECKLIST: LIFESTYLE CHANGES FOR PROSTATE CANCER PREVENTION

- Adopt an “anti-inflammatory diet,” low in red-meat fat and dairy products, and high in foods that fight inflammation, like some of those listed below.
- Eat fewer calories AND exercise more to maintain a healthy weight. Vigorous exercise, within the bounds of safety for your personal physical fitness, has been shown to reduce a man’s chance of developing lethal forms of prostate cancer.
- Watch your calcium intake. Do not take supplemental doses far above the recommended daily allowance. Some calcium is okay, but avoid taking more than 1200 mg of calcium a day.
- Eat more fish—evidence from several studies suggest that fish can help protect against prostate cancer because they have “good fat” particularly omega-3 fatty acids. Avoid trans fatty acids (for example, margarine, microwave popcorn, packed baked goods).
- Try to incorporate cooked tomatoes, whose high lycopene content has been shown to prevent prostate cancer.
- Cook with extra virgin olive oil. A recent study indicated that 4 tablespoons per day is ideal. Make sure you use the first pressed “extra virgin” oil.
- Incorporate cruciferous vegetables (like broccoli and cauliflower) into many of your weekly meals. Recently, a study found that eating broccoli can help shift your intestinal flora away from the types of bacteria that are related to prostate cancer.
- Soy has been a topic of some health debate, but for anyone at risk for prostate cancer, adding soy to your diet can be beneficial.
- Green tea’s high antioxidant properties may be beneficial in warding off cancer.
- Avoid smoking for many reasons. In particular, a recent study revealed that men who smoked during prostate cancer treatment had a higher likelihood of metastasis.
- Drink alcohol in moderation. If you do drink, try one glass of red wine per day. Red wine contains resveratrol which has been shown to possibly have cancer fighting properties.
- Drink coffee. Wait, is that a typo? Nope. Recent studies have shown that drinking 3 cups per day of unfiltered “Italian style” coffee can lower your risk for prostate cancer.
- Seek medical treatment for stress, high blood pressure, diabetes, high cholesterol, and depression. Treating these conditions may save your life and will improve your survivorship with prostate cancer.
- Avoid over-the-counter supplements. Too many vitamins may “fuel the cancer.” While a multivitamin is not likely to be harmful, you probably don’t need it if you follow a healthy diet with lots of fruits, vegetables, whole grains, fish, and healthy oils. Ask your doctor about herbal supplements as some may harm you or interfere with treatment.
- Relax and enjoy life. Studies have show that the stress hormone cortisol can interfere with cancer cell death. Reducing stress in the workplace and home will improve your survivorship and lead to a longer, happier life.

Basic Sofrito Recipe

Sofrito is a tomato-based sauce that is used as a base in cooking in many cultures. The lycopene in cooked tomatoes has long been known to ward off prostate cancer add that to the latest research on olive oil and you’ve got a great cancer-fighting food.

This base recipe can be multiplied or modified with different herbs and spices, to transport it across the globe.

- 1 pound of tomatoes
- 1 medium onion
- 1 red pepper
- 3 cloves of garlic
- 1/3 cup of extra-virgin olive oil
- Fresh herbs to taste
- Salt, to taste

Finely chop all ingredients. Heat oil and add everything at once to the pan. Cook 20-30 minutes. Cool, refrigerate, or freeze.







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