WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

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PROSTATE GLAND CANCER IN MEN

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ABSTRACT

Prostate cancer is the most common cancer in men. Many people have prostate cancer without knowing it and will not experience any symptoms in their lifetime. However, when prostate cancer spreads, it can quickly become life-threatening. Prostate cancer develops in the prostate gland, a walnut-sized organ that sits deep in the pelvis. The prostate is located right beneath the bladder and in front of the rectum. It produces semen that nourishes and transports sperm. Most prostate cancers grow slowly and stay within the prostate gland at first. Some grow aggressively and spread quickly to other parts of the body.It's not yet clear what causes prostate cancer. Prostate cancer happens when genetic material in cells changes abnormally, and the cells grow out of control. When enough of these abnormal cells build up, they can form a tumor in the prostate that may be felt during an exam or seen on imaging.

KEYWORDS: Prostrate, Bladder, Gland, Rectum, Cells, Tumor.

DESCRIPTION

Prostate cancer is a disease in which abnormal cells develop in the prostate, part of the male reproductive system. In Australia, it is the most commonly diagnosed cancer in men, affecting up to 1 in 7 men by the age of 75. In men, prostate cancer is the most commonly diagnosed cancer and is the second leading cause of cancer death worldwide While high-grade prostate cancer spreads quickly and can be fatal, for most men it's a slow-growing disease.
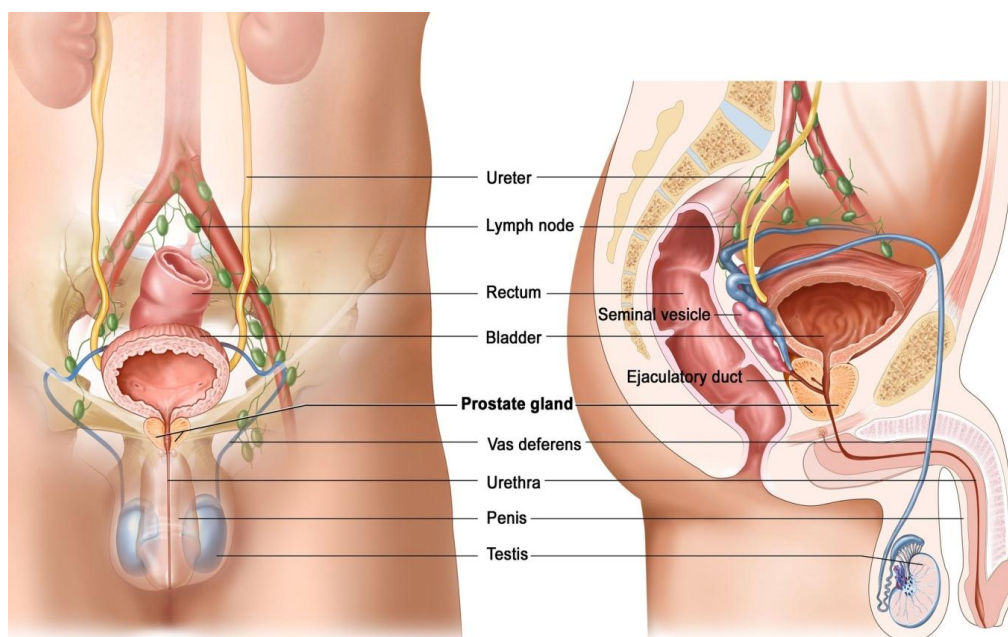
Fig. 1: Male Reproductive System.

With appropriate care, most men can live with prostate cancer for many years without serious consequences. Prostate cancer occurs when cells in a man's prostate gland grow in an unusual way to form an abnormal growth called a tumour.
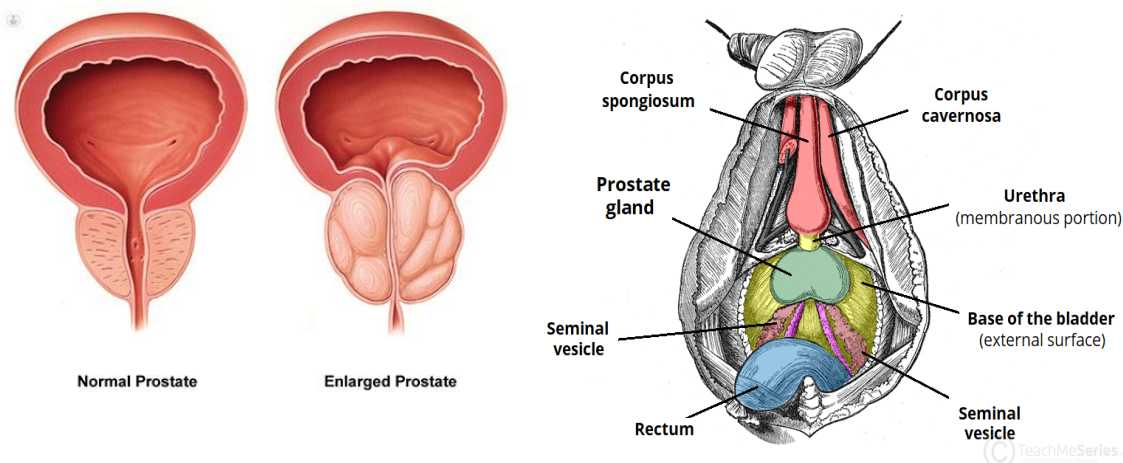

Fig. 2: Showing protrate gland.

The prostate, normally a golf ball-sized gland that sits below the bladder, helps produce the fluid in semen. There are different kinds of prostate cancer. While most grow slowly and cause no symptoms for many years, some spread aggressively and can cause serious illness and death.In men, prostate cancer is the most commonly diagnosed cancer and is the second leading cause of cancer death worldwide.[1] The only potentially modifiable risk factors identified to date are insulin-like growth factor-I (IGF-I) and free testosterone. Some evidence suggests that adiposity may be related to prostate cancer risk, but this association appears to vary by tumour subtypes; an inverse association has been observed between obesity and risk of overall prostate cancer and non-aggressive prostate cancer (slow-growing tumours), while obesity has been positively associated with risk for aggressive (fast-growing with lethal progression) prostate cancer, including dying from prostate cancer. However, it is unclear whether the association with aggressive forms of the disease is due to late detection (which may lead to poorer prognosis), is biologically driven, or is a combination of both. Studies investigating the association between adiposity and prostate cancer risk have mainly used body mass index (BMI), which does not distinguish between fat and muscle mass, as a surrogate of adiposity instead of a more accurate measure. Moreover, there is some evidence suggesting that while some individuals within the normal range of BMI may have excessive adiposity, some individuals within the overweight/obese range of BMI do not seem to have metabolic disturbances. However, it is unknown if these metabolic disturbances may be the mechanisms linking obesity to prostate cancer. A recent genome-wide association study (GWAS) has identified two clusters of genetic variants associated with higher adiposity: one associated with an 'unfavourable' metabolic profile (unfavourable adiposity, UFA) and another with a 'favourable' metabolic profile (favourable adiposity, FA), using body fat percentage and metabolic biomarkers [i.e. HDL cholesterol (HDL-C), sex hormone–binding globulin (SHBG), triglycerides (TG), aspartate transaminase (AST) and alanine aminotransferase (ALT)][6] to define the clusters. The UFA were associated with lower HDL-cholesterol and SHBG, and higher triglycerides and liver enzymes, and vice-versa for FA. In this GWAS, the adiposity-increasing alleles in both UFA and FA were associated with higher subcutaneous adipose tissue (SAT), BMI and C-reactive protein (CRP). The UFA alleles were associated with higher deposition of all fat depots including visceral fat and ectopic fat (i.e. liver and pancreas), and were associated with higher risk of cardio-metabolic disease, while the FA alleles were associated with lower liver fat and a lower risk of cardiometabolic diseases (e.g. Type 2 diabetes, heart disease, stroke).Mendelian randomization (MR) analyses, which use genetic variants as proxies for exposures,[7] may help to address reverse causation and confounding in observational studies, and therefore help to clarify the association between adiposity and prostate cancer. In this study, we sought to estimate the effects of UFA and FA on prostate cancer risk using a two-sample MR framework, updating previously published results on total prostate cancer risk based on 79,194 cases and 61,112 controls,[8] and for the first time describing associations with aggressive and early-onset disease. For this, we used genetic instruments identified from UK Biobank and genetic data from the PRACTICAL consortium (up to 85,554 prostate cancer cases [15,167 aggressive and 6988 early-onset subtypes] and 91,972 controls). For comparison of these new adiposity measurements with classic measurements of adiposity, our secondary aim was to investigate the association of BMI-related genetic variants with prostate cancer risk.

While experts don't fully know all the causes, a factor that increases your risk is obseity, which also increases the risk of aggressive prostate cancer. Prostate cancer

becomes more common with age. It is also more common if a close relative (e.g. a father, brother or son) was diagnosed with prostate cancer before 65 years of age. Your ethnicity also affects your risk of getting prostate cancer. Men of Caucasian heritage are more likely to develop prostate cancer than Asian men, while men of African background experience the highest rates of death from prostate cancer. In 1% to 2% of cases, men inherit genes (BRCA1 or BRCA2) that increase the risk of developing prostate cancer. These are the genes that can also cause women to have an increased risk of breast or ovarian cancer. Confirmed prostate cancer is graded on a scale of 1 to 5 (known as a grade group system), based on how likely the cancer is to grow and spread to the rest of the body. Grade groups 4 to 5 are considered high risk.An older system of grading, known as the Gleason score, grades the cancer from 1 to 10. A Gleason score of 8 to 10 is considered high risk.

Radical Prostectomy
This is a surgical operation to remove the prostate gland and some of its surrounding tissue. It can be an open procedure or performed with a lproscope (keyhole surgery).

Radiation therapy involves doses of radiation being delivered to the prostate, either from the outside (external beam radiation therapy) or by using an internal implant (brachytherapy).

Medicine
Androgen deprivation therapy (ADT) is sometimes used together with radiotherapy if the cancer has spread to the rest of the body. ADT works by blocking the production of testosterone, a male hormone, or its effects. This will cause most prostate cancers to shrink or stop growing. However, after some time — the period is different for every man — the prostate cancer may become sensitive to remaining testosterone and re-grow (castrate-resistant disease.

The prostate is located under the bladder. The urethra, which is the tube that carries urine (pee) from the bladder to the penis, runs through the prostate.However, as you age, your prostate can get larger for many reasons. This can make it hard for you to urinate (pee).

Symptoms
The symptoms below do not mean you have prostate cancer but they can be signs of prostate cancer. Some symptoms of advanced prostate cancer include

Needing to urinate frequently or suddenly, finding it difficult to urinate (e.g. trouble starting, or being unable to urinate when the feeling is there or poor urine flow),discomfort when urinating,finding blood in urine or semen,pain in the lower back, upper thighs or hips.

Trouble starting or stopping urination (peeing).
- Slow urine stream.

- Painful urination or ejaculation.
- Dribbling of urine.
- Need to urinate more than is normal for you.
- Blood in your urine or ejaculate (semen).
- Waking up in the middle of the night with a need to urinate.

In advanced-stage prostate cancer, you may have these symptoms:
- Weight loss.
- Fatigue (extreme tiredness).
- Back pain or sciatica-like pain (sudden, "shooting" pain that goes from your lower back and down your leg).
- Swelling in your legs that does not go away.

These are tests that can help diagnose prostate cancer
- **Digital rectal examination (DRE):** a doctor or nurse practitioner puts their finger through your anus (opening to your bum) and into your rectum. Your rectum lies right behind your prostate. This allows the doctor or nurse practitioner to feel for any irregular texture (such as a lump) in your prostate. A lump may be a sign of cancer. Your doctor or nurse practitioner may recommend this exam if you have symptoms of a prostate problem.
- **PSA blood test:** this measures the amount of Prostate Specific Antigen (PSA) in your blood. Normal levels of PSA are between 4 and 7 ng/mL (nanograms per millilitre). You may need a PSA test if your DRE is suspicious for cancer. If you are over 40 years old, you may want to ask your doctor or nurse practitioner if they recommend you get this test.
- If the DRE or PSA blood test is suspicious for cancer, your doctor or nurse practitioner may then refer you to a urologist. A urologist is a doctor who specializes in the urinary system.
- **Transrectal ultrasound (TRUS):** a doctor puts an ultrasound transducer (a probe that uses sound waves to give an image) through your anus into your rectum. This lets the doctor look at your prostate and the tissues around it. An ultrasound is also used during a prostate biopsy to guide the needle that will take small pieces of tissue from your prostate.
- **Biopsy:** a doctor uses an ultrasound transducer to guide a needle to your prostate. The needle will be put into your prostate 10-12 times to take tiny pieces of the prostate. These pieces will be checked for cancer by a specialist (pathologist). Your doctor will give you some local anesthetic (numbing agent) to help with the discomfort during the biopsy.

If any of these tests are suspicious for cancer or find cancer, you may need more tests. These tests are only done if your cancer is high risk (see risk types below).
- **Bone scan:** this is a type of imaging that checks to see if cancer has spread to your bones. You will have this scan if your PSA is more than 10 ng/mL or

if your biopsy shows a high risk cancer (a cancer that is growing more quickly and is more likely to spread).

- **CT (computed tomography) scan:** this is a type of imaging that checks to see if your cancer has spread outside of your prostate into tissues or organs in your chest, abdomen or pelvis.
- More than 95% (95 out of 100) of prostate cancers are adenocarcinomas. These are cancers that start in gland cells. In the prostate, gland cells make mucus and prostatic fluid.

The other types of prostate cancer are rare and they start in other cells of the prostate.

Risk groups
Prostate cancer is divided into three risk groups: low risk, intermediate risk and high risk. The risk groups are based on:

- **PSA(Prostate specific Antigen)Test**
- **Gleason score**: This describes the cancer based on how it looks and acts. A pathologist gives a number after looking at the prostate cancer biopsy. The number can be 1, 2, 3, 4 or 5. The lower the number, the closer the cancer cells look and act like normal cells. The higher the number, the more they look and act like cancer cells The pathologist will give a number for each pattern of cells they see in the biopsy.
- The first number is the most common pattern they see. The second number is the second most common pattern they see. The pathologist will add the two scores to give the total Gleason score. Higher scores mean the cancer is higher risk.

For example, if the most common pattern is 3 and the second most common pattern is 4, the Gleason score is 3 + 4 = 7.

If the most common pattern is 4 and the second most common pattern is 3, the Gleason score is 4 + 3 = 7. However, this cancer is a higher risk than the cancer above because the most common pattern (first number) is a higher grade than the second number.
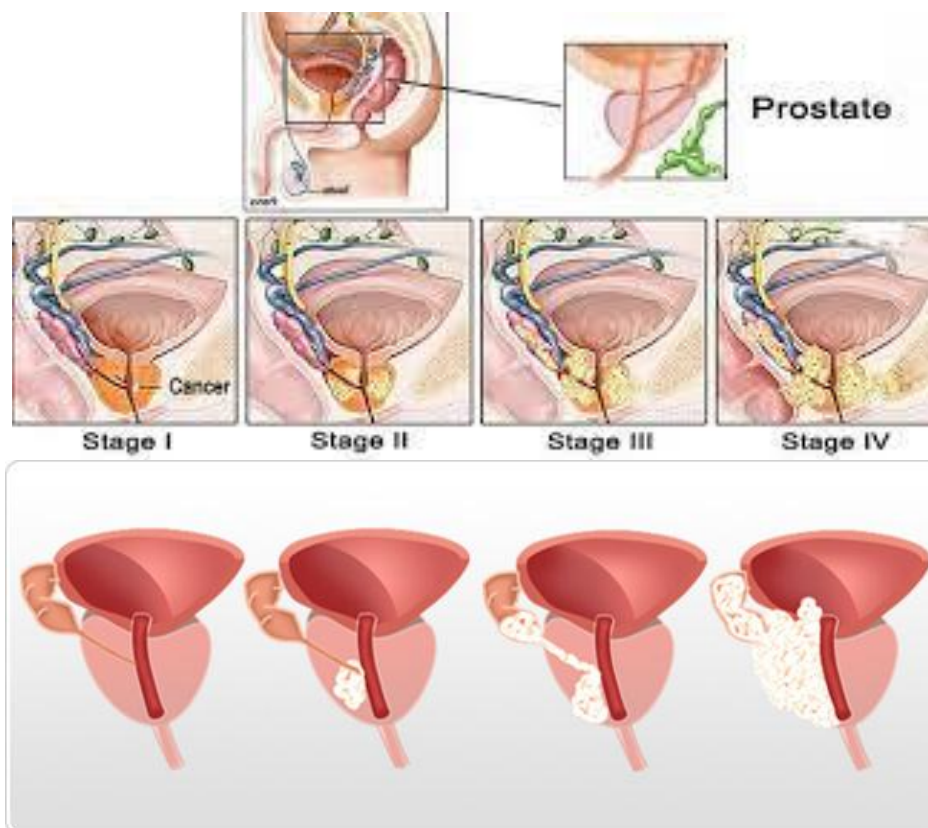

Fig. 2: Stages of prostate cancer.

Stage: Staging is based on how much cancer is in the body, where it was first diagnosed, if the cancer has spread and where it has spread to.

The stage of the cancer can help your health care team plan your treatment. It can also tell them how your cancer might respond to treatment and the chance that your cancer may come back (recur).

- **Stage T1:** doctor cannot feel the tumour during a digital rectal exam.
- **Stage T1a:** cancer is found in 5% or less of the tissue removed from the prostate.

o **Stage T1b:** cancer is found in more than 5% of the tissue removed from the prostate.
o **Stage T2:** doctor can feel a nodule (lump) during digital rectal exam. Cancer is only in the prostate.
▪ **Stage T2a:** tumour is in half or less of one side of the prostate.
▪ **Stage T2b:** tumour is in more than half of one side of the prostate.
▪ **Stage T2c:** tumour is in both sides of the prostate.
o **Stage T3:** tumour has grown through the capsule (outside layer) of the prostate.
▪ **Stage T3a:** tumour has grown outside of the prostate but not grown into the seminal vesicles (glands that make fluid that is added to semen).
▪ **Stage T3b:** tumour has grown outside of the prostate and into the seminal vesicles.
o **Stage T4**: tumour has grown outside the prostate and into nearby organs such as the bladder, rectum, pelvic muscles or pelvic wall.

Your PSA, Gleason score and stage determine your risk group. Your risk group helps your health care team plan your treatment.

Low risk - must have **all** of the following:
• PSA less than or equal to 10 ng/mL
• Gleason score less than or equal to 6
• Stage T1 or T2a

Intermediate risk - Not low or high risk, any of:
• PSA more than 10 ng/mL
• Gleason score is 7
• Stage 2B

Highrisk –has **any** ofthefollowing:
• PSA more than 20 ng/mL
• Gleason score is higher than or equal to 8
• Stage T3a or higher

Prostate Cancer Stages
When your care team determines your diagnosis, they also assess how advanced the cancer is, also called its stage. Your prostate cancer stage depends on how quickly the tumor has grown, whether the cancer spreads, and where it spreads. To help assign a stage, pathologists who specialize in analyzing cancer tissue examine the structure of cancer cells under a microscope.

TNM Staging
We use a system called TNM staging to describe how much prostate cancer has grown or spread within the body. In TNM staging, each letter describes an aspect of the cancer:

Tumor size, which tells your doctor how large the tumor has grown and how likely it is to have spread

Nodes, meaning whether cancer is present in nearby lymph nodes and, if so, how may

Metastasis, meaning whether the cancer has spread elsewhere in the body, such as the bones.

After each letter, an "X" or a number tells you about each aspect. "X" means the aspect can't be measured, while the numbers describe the extent of the cancer. Higher numbers indicate more advanced cancer. T ranges from TX-T4, N ranges from NX-N1, and M ranges from MX-M1. For example, you may see a stage written as T1N0MX.

Gleason Score
Pathologists also assign a Gleason score to prostate cancer. They add up subscores of specific cancer characteristics for a total Gleason score ranging from 6 to 10. A low Gleason score (6) means the prostate cancer is not aggressive, suggesting a better outcome. A Gleason score of 7 indicates a cancer with intermediate aggressiveness. A higher Gleason score (8-10) means the prostate cancer is more aggressive, suggesting a poorer prognosis.

Cancer Stages 1-4
Prostate cancer can also be assigned a stage from Stage 1 through Stage 4. These groups take into consideration TNM staging, Gleason score, and PSA levels to describe cancer in a simpler way. A lower stage means the cancer is confined within the prostate gland, and the Gleason score and PSA levels remain low. Higher stages describe more aggressive cancer that has spread. In these cases, the Gleason score and PSA levels are high.

Prostate Cancer Symptoms
In its early stages, prostate cancer does not cause symptoms. As the cancer grows or spreads to other parts of the body, you may experience

Bone pain, Pain in the pelvic area,Unexplained weight loss.

Symptoms such as a need to urinate frequently or trouble urinating are not usually signs of prostate cancer. Rather, these symptoms suggest an enlarged prostrat. An enlarged prostate often develops with age and can be treated with medications.

Prostate Cancer Types
Almost all prostate cancers are adenocarcinomas (a cancer that develops in glands). Rarer types of prostate cancer include sarcomas, small cell carcinomas, and transitional cell carcinomas.

Doctors also classify prostate cancer based on its location
Localized prostate cancer is contained in the prostate.
Metastatic prostate cancer has spread beyond the prostate to other parts of the body.

Prostate Cancer Risk Factors

Risk factors are things that increase your chance of having prostate cancer. Prostate cancer risk factors include:

Age: As you get older, your likelihood of developing prostate cancer increases.

Family history: You face an increased risk if you have a close relative with prostate cancer (father or brother), particularly prostate cancer that developed at an early age. Having a strong family history of breast, ovarian, colorectal, or pancreatic cancer also increases your risk of prostate cancer.

Race: African Americans are at a greater risk for aggressive prostate cancers and developing prostate cancer at a younger age.

Our genetic counseling services can assess your risk for prostate cancer based on your genes. We'll develop a care plan for you and your family. Learn more about our Cancer Genetics Program.

Prostate Cancer Screening

Prostate cancer screening can lead to early identification and treatment to prevent aggressive cancers from spreading. Screening is especially important if you have a family history of prostate cancer.

Prostate cancer screening tests include

Cancer Stages 1-4

- **Digital rectal Exam: (DRE):** Your doctor inserts a gloved, lubricated finger inside your rectum to feel your prostate for abnormalities in texture, shape, or size.
- **Prostate-specific antigen (PSA) test:** This blood test evaluates the amount of a prostate-specific substance in your bloodstream. A high PSA can be a sign of prostate cancer, although other non-cancerous conditions such as infection, inflammation, or an enlarged prostate may also increase the PSA level.

Prostate Cancer Stages

When your care team determines your diagnosis, they also assess how advanced the cancer is, also called its stage. Your prostate cancer stage depends on how quickly the tumor has grown, whether the cancer spreads, and where it spreads. To help assign a stage, pathologists who specialize in analyzing cancer tissue examine the structure of cancer cells under a microscope.

Gleason Score: Pathologists also assign a Gleason score to prostate cancer. They add up subscores of specific cancer characteristics for a total Gleason score ranging from 6 to 10. A low Gleason score (6) means the prostate cancer is not aggressive, suggesting a better outcome. A Gleason score of 7 indicates a cancer with intermediate aggressiveness. A higher Gleason score (8-10) means the prostate cancer is more aggressive, suggesting a poorer prognosis.

Stage	
Stage I	- the cancer is small and only in the prostate
Stage II	- the cancer is larger and may be in both lobes of the prostate but is still confined to the prostate
Stage III	- the cancer has spread beyond the prostate to close by lymph glands or seminal vesicles
Stage IV	- the cancer has spread to other organs such as the bone and is referred to as metastatic cancer. If prostate cancer spreads, or metastasizes, to the bone, you have prostate cancer cells in the bone, not bone cancer

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Diagnostic tests may include

A radiologist will interpret your imaging results to understand the precise location and size of a tumor. Imaging tests may include.

Multiparametric Magnetic Resonance Image

Prostate-Specific Membrane Antigen (PSMA) PET/CTScanor PET/MRI ScanTransrectal\ Ultrasound Bone scan CT scan

Prostate biopsy, including

Core (transrectal) biopsy: We most frequently perform a core biopsy. This procedure uses a thin, hollow needle to take a tissue sample from your prostate. Your doctor numbs the area and accesses your prostate through the wall of your rectum.

Transperineal biopsy: With this procedure, your doctor accesses your prostate through your perineal skin (the area between the scrotum and anus) rather than going through your rectum. Your rectum may contain bacteria that can enter your prostate on the needle, which poses a risk to people with a history of infections or a weakened immune system. By avoiding your rectum, this approach significantly reduces your risk of infection.

Image-guided biopsy: We specialize in this approach (also called targeted prostate biopsy) for both transrectal and transperineal biopsies. Your MRI images show us the exact location of abnormal tissue. Guided by ultrasound imaging during the procedure, we target that abnormal tissue for a more accurate biopsy.

Prostate Cancer Blood Test
Blood lab tests can provide a variety of information about your blood cells, organ function, and the spread of cancer. During a blood test, a provider draws your blood so it can be tested at a lab. The results help your doctor establish a diagnosis and plan your course of prostate cancer treatment.

Conclusion: In men, prostate cancer is the most commonly diagnosed cancer and is the second leading cause of cancer death worldwideWhile high-grade prostate cancer spreads quickly and can be fatal, for most men it's a slow-growing disease. With appropriate care, most men can live with prostate cancer for many years without serious consequences.

REFRENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, 2021; 71: 209- 249.
2. Watts EL, Perez-Cornago A, Fensom GK, et al. Circulating free testosterone and risk of aggressive prostate cancer: prospective and Mendelian randomisation analyses in international consortia. *Int J Cancer*, 2022; 151: 1033- 1046.
3. Watts EL, Perez-Cornago A, Fensom GK, et al. Circulating insulin-like growth factors and risks of overall, aggressive and early-onset prostate cancer: a collaborative analysis of 20 prospective studies and Mendelian randomization analysis. *Int J Epidemiol*, 2022; 52: 71- 86.
4. Perez-Cornago A, Dunneram Y, Watts EL, Key TJ, Travis RC. Adiposity and risk of prostate cancer death: a prospective analysis in UK biobank and meta-analysis of published studies. *BMC Med*, 2022; 20: 143.
5. Perez-Cornago A, Appleby PN, Pischon T, et al. Tall height and obesity are associated with an increased risk of aggressive prostate cancer: results from the EPIC cohort study. *BMC Med*, 2017; 15: 115.
6. Martin S, Cule M, Basty N, et al. Genetic evidence for different adiposity phenotypes and their opposing influences on ectopic fat and risk of cardiometabolic disease. *Diabetes*, 2021; 70: 1843- 1856.
7. Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*, 2003; 32: 1- 22.
8. Martin S, Tyrrell J, Thomas EL, et al. Disease consequences of higher adiposity uncoupled from its adverse metabolic effects using Mendelian randomisation. *eLife*, 2022; 11: e72452.
9. Wu L, Wang J, Cai Q, et al. Identification of novel susceptibility loci and genes for prostate cancer risk: a transcriptome-wide association study in over 140,000 European descendants. *Cancer Res*., 2019; 79: 3192- 3204.
10. Conti DV, Darst BF, Moss LC, et al. Trans-ancestry genome-wide association meta-analysis of prostate cancer identifies new susceptibility loci and informs genetic risk prediction. *Nat Genet*, 2021; 53: 65- 75.
11. Censin JC, Peters SAE, Bovijn J, et al. Causal relationships between obesity and the leading causes of death in women and men. *PLoS Genet*, 2019; 15: e1008405.
12. Schumacher FR et al. Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci. *Nat Genet*, 2018; 50: 928- 936.
13. Burgess S, Bowden J. Integrating summarized data from multiple genetic variants in Mendelian randomization: bias and coverage properties of inverse-variance weighted methods. *arXiv Preprint*, 2015; Xiv: 1512.04486.
14. Verbanck M, Chen C-Y, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet*, 2018; 50: 693- 698.
15. Burgess S, Foley CN, Allara E, Staley JR, Howson JMM. A robust and efficient method for Mendelian randomization with hundreds of genetic variants. *Nat Commun*, 2020; 11: 376.
16. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-egger method. *Eur J Epidemiol*, 2017; 32: 377- 389.
17. Hemani G, Zheng J, Elsworth B, et al. The MR-base platform supports systematic causal inference across the human phenome. *eLife*, 2018; 7: e34408.
18. Genkinger JM, Wu K, Wang M, et al. Measures of body fatness and height in early and mid-to-late adulthood and prostate cancer: risk and mortality in the pooling project of prospective studies of diet and cancer. *Ann Oncol*. 2020; 31: 103- 114.
19. Watts EL, Appleby PN, Albanes D, et al. Circulating sex hormones in relation to anthropometric, sociodemographic and behavioural factors in an international dataset of 12,300 men. *PLoS One*, 2017; 12: e0187741.
20. Harrison S, Tilling K, Turner EL, et al. Systematic review and meta-analysis of the associations between body mass index, prostate cancer, advanced

prostate cancer, and prostate-specific antigen. *Cancer Causes Control*, 2020; 31: 431- 449.

21. Jochems SHJ, Stattin P, Häggström C, et al. Height, body mass index and prostate cancer risk and mortality by way of detection and cancer risk category. *Int J Cancer*, 2020; 147: 3328- 3338.

22. Freedland SJ, Platz EA, Presti JC, et al. Obesity, serum prostate specific antigen and prostate size: implications for prostate cancer detection. *J Urol*., 2006; 175: 500- 504.

23. Ma J, Li H, Giovannucci E, et al. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. *Lancet Oncol*, 2008; 9: 1039- 1047.

24. Albanes D, Weinstein SJ, Wright ME, et al. Serum insulin, glucose, indices of insulin resistance, and risk of prostate cancer. *J Natl Cancer Inst*., 2009; 101: 1272- 1279.