Cancer Association of South Africa (CANSA)

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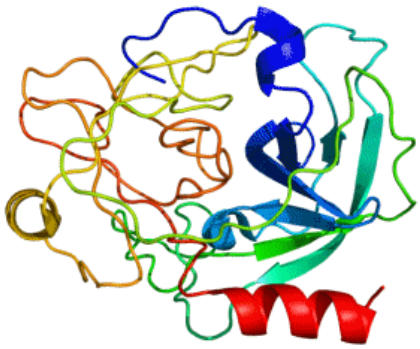
Fact Sheet on the Role of Prostate Specific Antigen (PSA) Screening on Prostate Cancer Diagnosis and Treatment

Introduction

Prostate Specific Antigen (PSA) is a glycoprotein enzyme exclusively produced by the epithelial cells of the prostate gland. PSA is a member of the kalllikrein-related peptidase family.

PSA is produced for the ejaculate, where it liquefies semen to allow sperm to swim freely. It is also believed to create the correct pH balance for sperm to survive and also instrumental in dissolving cervical mucus, allowing easy entry of sperm into the uterus.



[Picture Credit: PSA]

Incidence of Prostate Cancer in South Africa

According to the outdated National Cancer Registry (2017) known for under reporting the following number of prostate cancer cases was histologically diagnosed in South Africa during 2017:

Group - Males 2017	No of Cases	Lifetime Risk	Percentage of All Cancers
All males	8 937	1:16	22.37%
Asian males	229	1:25	23.27%
Black males	4 102	1:21	29.34%
Coloured males	1 018	1:14	21.34%
White males	3 588	1:10	16.78%

N.B. 'Histologically diagnosed' means that a biopsy (removal of a specimen of tissue) was performed and that a diagnosis of Prostate Cancer was confirmed by a qualified pathologist.

The frequency of histologically diagnosed cases of prostate cancer in South Africa for 2016 was as follows (National Cancer Registry, 2017):

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Group - Males 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	1	4	20	255	1 655	3 557	2 671	774
Asian males	0	0	0	4	32	100	78	15
Black males	1	4	18	145	828	1 692	1 979	66
Coloured males	0	0	1	29	206	408	306	68
White males	0	0	1	227	589	1 357	1 217	347

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Prostate cancer is caused by changes in the DNA of normal prostate cells. DNA makes up the genes, which control how cells behave. DNA is inherited from one's parents. It is estimated that a small percentage (about 5 to 10%) of prostate cancers are linked to these inherited changes.

Research shows that men with BRCA1/2 mutations are more likely than non-carriers to be diagnosed with advanced-stage prostate cancer or cancer that had already spread.

Prostate Specific Antigen

Prostate Specific Antigen (PSA) is a protein produced by normal prostate cells. This enzyme participates in the dissolution of the seminal fluid coagulum and plays an important role in fertility. The highest amounts of PSA are found in seminal fluid; some PSA escapes the prostate and can be found in the blood serum.

Rising levels of PSA in serum are associated with prostate cancer. The PSA level also tends to rise in men with benign prostatic hyperplasia (enlargement of the prostate) and is a good marker for prostate volume. PSA levels are usually also elevated in men with acute bacterial prostatitis (inflammation of the prostate).

David, M.K. & Leslie, S.W. 2020.

"The primary reason for the utilization of any screening exam should be that the procedure detects the premature stages of a pathologic condition and allows for early intervention, thereby preventing unnecessary morbidity or mortality, before any clinical signs or symptoms of the disease. For the detection of prostate cancer, an elevated serum prostate-specific antigen is the most common laboratory abnormality, as the majority of men with early prostate cancer have no symptoms. However, prostate-specific antigen, otherwise known as PSA, is clinically imprecise as benign and malignant processes both, can elevate the serum marker. Despite the risks and benefits of serum PSA screening, it is the most useful tool available for the detection of early prostate cancer, giving affected individuals the best chance for cure."

What Every Man Should Know About PSA screening

- Screening does not lower one's risk of having prostate cancer; it increases the chance that one will find out that one has it
- PSA testing can detect early-stage cancers that a digital rectal examination (DRE) would miss
- A "normal" PSA level of 4 ng/ml or below does not guarantee that one is cancer-free; in about 15% of men with a PSA below 4 ng/ml, a biopsy will reveal prostate cancer
- A high PSA level may prompt one to seek treatment, resulting in possible prevention of urinary and sexual side effects

- Conditions other than cancer – non-cancerous enlargement of the prostate (BPH) and prostatitis (inflammation of the prostate), for example, can elevate one's PSA level

PSA testing guidelines from the American Cancer Society emphasise discussing the pros and cons of prostate cancer screening with one's doctor, including one's individual level of prostate cancer risk, before having a PSA blood test.

The Prostate Specific Antigen Screening Debate

The purpose of screening is to detect prostate cancer at its earliest stages, before any symptoms have developed. Some men do experience symptoms that might indicate the presence of prostate cancer. These symptoms can also indicate the presence of other prostate diseases or disorders (such as non-cancerous enlargement of the prostate (BPH) or inflammation of the prostate), so these men will undergo a more thorough work-up.

Typically, prostate cancer that's detected by screening is in the very early-stages and can be treated most effectively. Physicians can screen for prostate cancer quickly and easily in their office using two tests: the PSA (prostate-specific antigen) blood test and the digital rectal exam (DRE).

The PSA Blood Test - PSA is a protein produced by cells within the prostate and released in very small amounts into the bloodstream. When there is a problem with the prostate—like the development and growth of prostate cancer—more and more PSA is released. It eventually reaches a level where it can be easily detected in the blood.

For a PSA test, a small amount of blood is drawn from the arm, and the level of PSA is measured:

- Levels under 4 ng/mL are usually considered "normal."
- Levels over 10 ng/mL are usually considered "high"
- Levels between 4 and 10 ng/mL are usually considered "intermediate."

PSA is not a perfect test. Levels can be elevated if other prostate problems are present, such as BPH or prostatitis (inflammation of the prostate). Some men with prostate cancer may even have low levels of PSA. PSA can also be diluted in men who are overweight or obese, due to a larger blood volume, and a prostate biopsy at a relatively lower number (i.e. 3.5 instead of 4) should be considered.

The Digital Rectal Examination - During a DRE, the physician inserts a gloved, lubricated finger into the rectum and examines the prostate for any irregularities in size, shape, and texture. Often, the DRE can be used by urologists to help distinguish between prostate cancer and non-cancerous conditions such as BPH.

[Picture Credit: Digital Rectal Examination]

Important to Note - Many men will be found to have cancer even with "normal" results from the PSA test and DRE.

The decision about what to do next in this circumstance is usually based on the patient's age, other risk factors, and the specifics of the type of cancer (grade, stage, etc).

Albertsen, P.C. 2020.
Objective: To evaluate the current prostate cancer screening and treatment paradigm in light of recently published long-term results of major screening and treatment trials.
Methods: Historical review of the evolution of the diagnosis and treatment of prostate cancer followed by a detailed summary of the findings and differences among the three major screening trials and the three major treatment trials.
Results: Prostate-specific antigen (PSA) testing can identify clinically significant prostate cancer and has produced a significant stage shift and is the likely explanation for the decline in prostate cancer mortality. Unfortunately, PSA testing predominantly identifies low-grade disease that is unlikely to progress during a patient's lifetime leading to substantial diagnosis of indolent disease. Treatment with radical prostatectomy (RP) appears to benefit primarily younger men (aged <65 years) with intermediate-grade disease. Too few men with low-grade disease benefit from RP to justify intervening in all. Unfortunately, high-grade prostate cancer often progresses despite surgery and radiation.
Conclusion: The primary PSA testing paradigm is wrong. Rather than attempting to identify all prostate cancers as early as possible, testing objectives should shift towards identifying men likely to harbour clinically significant disease. These are the men who appear to benefit from early diagnosis and intervention, including the earlier use of antiandrogen therapy prior to widespread metastases.

Institute for Quality and Efficiency in Health Care (IOWiG). 2020. Prostate cabcer screening with a PSA test: IQWiG Reports – Commission No. S19-01 [Internet]. Cologne (Germany): Institute for Quality and Efficiency in Health Care (IQWiG); 2020 Jun 10.
Research question: The objective of this investigation is to assess the benefit of prostate cancer screening with the prostate-specific antigen (PSA) test in participants without suspected prostate cancer in respect of patient-relevant outcomes.
Conclusion: With regard to all-cause mortality, there was no hint of any benefit or harm of prostate cancer screening with the PSA test in comparison with no such screening. With regard to prostate cancer-specific mortality, the studies using a PSA cut-off value below 4 ng/mL revealed an indication of a benefit of prostate cancer screening with the PSA test. For the other subgroup, there was no hint of any benefit or harm. Since opportunistic prostate cancer screening with the PSA test was common in the control groups of the 2 largest studies using a PSA cut-off value of 4 ng/mL or higher (i.e. high contamination), it is doubtful whether the PSA cut-off value is the actual characteristic which convincingly explains the difference between subgroups. With regard to the outcome of diagnoses of metastatic prostate cancers, there was an indication of benefit. With regard to the outcomes of health-related quality of life and adverse events as well as the consequences of false-negative screening findings, there was no hint of benefit or harm, albeit based on insufficient available data (no data at all). Proof of harm was found for the consequences of overdiagnoses as well as for false-positive screening findings.
Prostate cancer screening by PSA test causes harm to overdiagnosed men (men with prostate cancer which does not require treatment) as well as to men with false-positive screening results (men without prostate cancer). Much of screening-related harm arises at an early time and, in many cases, persists lifelong.
Prostate cancer screening with the PSA test benefits some men with prostate cancer by sparing them the distress caused by metastatic cancer or delaying the same. However, this benefit arises

only after several years. Even these men might experience early treatment-related complications which persist lifelong. It is unclear whether screening leads to any life extension at all in these men. Considerably more men experience overdiagnosis-related harm rather than benefits from prostate cancer screening by PSA test. All things considered, the benefits of prostate cancer screening with the PSA test therefore do not outweigh the associated harms.

Actor Ben Stiller on PSA Testing

Actor Ben Stiller is crediting a prostate cancer screening test for saving his life, revealing today that he was diagnosed and treated for prostate cancer two years ago. But should all men get this screening test?

In an interview on The Howard Stern Show recently, Stiller revealed for the first time that he was diagnosed with prostate cancer at age 48. The actor, who is now 50, said doctors detected the cancer because Stiller had undergone a prostate-specific antigen test, or PSA test, which looks for levels of the protein PSA in the blood. Abnormally high levels of PSA in the blood can mean that a man has prostate cancer, but not always. In Stiller's case, a follow-up MRI and biopsy showed he had prostate cancer.

"This thing saved my life," Stiller said of the PSA test.

The PSA test is the main test used to screen for prostate cancer, but it is controversial. In 2012, the U.S. Preventive Services Task Force, or USPSTF (an expert panel that advises the federal government) recommended that men not undergo routine screening for prostate cancer with the PSA test, no matter their age.

The American Cancer Society have since changed their stance and now recommends that men have a discussion with their doctor about whether to start PSA screening at age 50 if they are at average risk for prostate cancer, and at age 40 to 45 if they have a family history of prostate cancer.

PSA Testing Saves Lives

An analysis of two influential studies of prostate cancer screening conducted in 2017 concludes that the much-debated PSA test “significantly” reduces deaths from the Prostate Cancer, suggesting that current recommendations against routine PSA screening might be steering men away from a lifesaving procedure (Bornman, 2015; Eetzioni, 2017).

Advantages of Prostate Specific Antigen Screening in South Africa

Studies related to increased prostate cancer incidence and associated mortality, decreased age at diagnosis and aggressive pathological/biochemical presentation has not sufficiently been studied in South Africa. Initiated in 2008, the Southern African Prostate Cancer Study (SAPCS) is a unique ongoing resource to investigate clinical presentation and risk factors within South African black populations. Data from this study suggest that lack of PSA testing, in particular the more rural localities, is contributing to aggressive presentation of prostate cancer at a late stage. The research

shows that men in Limpopo Province present almost 3 years later than what is found in other parts of the world.

The lack of PSA screening in remote areas results in lack of options for surgical intervention with less than 2% of the SAPCS being suitable for radical prostatectomy. The study further showed that there is a need for expansion to further elucidate the contributing factors driving aggressive disease. (Bornman, 2015).

The Nigeria experience – in a recent study by Akinremi, *et al*., (2014) in Nigeria, it was concluded that PSA screening is very important to better define the prostate cancer prevalence and characteristics in the population; otherwise political and economic circumstances will ensure that men still present late with aggressive prostate cancer.

Non-Cancer Causes of a Raised PSA Test

High PSA levels from prostatitis – "The PSA test is a good screening tool for prostate cancer, but it is not very specific," says Erik P. Castle, MD, FACS, an associate professor of urology at the Mayo Clinic. "Common causes of inflammation in the gland, called prostatitis, can cause high PSA levels." Prostatitis caused by bacteria can be treated with antibiotics. Another more common type of prostatitis, called nonbacterial prostatitis, can be harder to treat and last a long time. Prostatitis is the most common prostate problem for men younger than 50.

High PSA levels from medical procedures - "Anything that traumatically interferes with the architecture around the prostate gland can make PSA go up," says John Milner, MD, FRCS, an assistant professor of urology at Loyola University's Stritch School of Medicine in Chicago. "One of the most common causes of significantly high PSA from this type of trauma is the placing of a catheter into the bladder." Another cause is a prostate or bladder examination that involves passing a scope or taking a biopsy. "Since it takes about two to three days for PSA to go down by half, one should wait about two to three weeks after this type of trauma to do a PSA test."

High PSA levels from BPH – Benign prostate hyperplasia (BPH), is an enlargement of the prostate gland, but it is not prostate cancer. "BPH means more cells, so that means more cells making PSA," explains Dr. Castle. BPH may not need to be treated unless it is causing frequent or difficult urination. BPH is the most common prostate problem in men over age 50. One's doctor may be able to tell the difference between BPH and prostate cancer by doing a digital rectal exam. BPH usually causes abnormal PSA tests in the 4 to 10 range.

High PSA levels from a urinary tract infection - "Any infection near the prostate gland, including a urinary tract infection, can irritate and inflame prostate cells and cause PSA to go up," says Dr. Milner. If you've been diagnosed with a urinary tract infection, be sure to wait until after the infection has cleared up before getting a PSA test. In men, most urinary tract infections are caused by bacteria and respond well to antibiotics. Be on the alert: BPH increases your risk for a urinary tract infection.

High PSA levels as one gets older - Even without any prostate problems, your PSA levels can go up gradually as you age. "At age 40, a PSA of 2.5 is the normal limit," says Milner. "By age 60, the limit is up to 4.5; by age 70, a PSA of 6.5 could be considered normal." Even so, a study done in Sweden and reported in the medical journal *BMJ*found that a low PSA at age 60 is especially welcome news. In

1,167 men who were followed from age 60 to age 85, those with a PSA at or below 1 ng/ml at age 60 had only a 0.2 percent chance of dying from prostate cancer.

High PSA levels after ejaculation - "Ejaculation can cause an elevation of one's PSA level, and so can having a digital rectal exam (DRE)," explains Milner. "These types of PSA elevations are usually not enough to make a significant difference unless one's PSA is borderline. PSA should return to normal in two to three days." Doctors will usually draw blood for a PSA level before doing a rectal exam. Ask your doctor if you should avoid ejaculation for a few days before a PSA test.

High PSA levels from riding one's bike - There have been occasional studies that link prolonged bike riding to an increase in PSA levels, but others haven't found such a connection. "You would probably have to be a Lance Armstrong-type bike rider to worry about bike riding and a significant rise in your PSA," says Castle. "The most important thing to know about PSA is that it is still a really important screening test for prostate cancer, and prostate cancer is still the number two cancer killer behind lung cancer for men." (Every Day Health).

To Have a PSA Screening Test or Not

Making the decision to have a PSA test depends on a variety of factors. Here are some tips that can help in making a good decision.

Cancer screening tests - including the prostate-specific antigen (PSA) test to look for signs of prostate cancer - can be a good idea. Prostate cancer screening can help identify cancer early on, when treatment is most effective. And a normal PSA test, combined with a digital rectal exam, can help reassure one that it is unlikely one has prostate cancer. But getting a PSA test for prostate cancer may not be necessary for some men, especially men 75 and older.

Professional organisations vary in their recommendations about who should - and who should not - get a PSA screening test. While some have definitive guidelines, others leave the decision up to men and their doctors. Organisations that do recommend PSA screening generally encourage the test in men between the ages of 40 and 75, and in men with an increased risk of prostate cancer.

Ultimately, whether one has a PSA test is something one should decide after discussing it with one's doctor, considering one's risk factors and weighing one's personal preferences. A simple test, not-so-simple decision - there are a number of pros and cons to the PSA test.

Pros of PSA Screening	Cons of PSA Screening
PSA screening may help one detect prostate cancer early	Some prostate cancers are slow growing and never spread beyond the prostate gland.
Cancer is easier to treat and is more likely to be cured if it is diagnosed in the early stages of the disease.	Not all prostate cancers need treatment. Treatment for prostate cancer may have risks and side effects, including urinary incontinence, erectile dysfunction and bowel dysfunction.
PSA testing can be done with a simple, widely available blood test.	PSA tests are not fool proof. It is possible for one's PSA levels to be elevated when cancer is not present, and to not be elevated when cancer is present.
For some men, knowing is better than not knowing. Having the test can provide one with a certain amount of reassurance – either that one probably do not have prostate cancer or that one does have it and can now have it treated.	A diagnosis of prostate cancer can provoke anxiety and confusion. Concern that the cancde3r may not be life-threatening can make decision making complicated.

The number of deaths from prostate cancer has gone down since PSA testing became available.	It is not yet clear whether the decrease in deaths from prostate cancer is due to early detection and treatment based on PSA testing or due to other factors.

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