Cancer Association of South Africa (CANSA)

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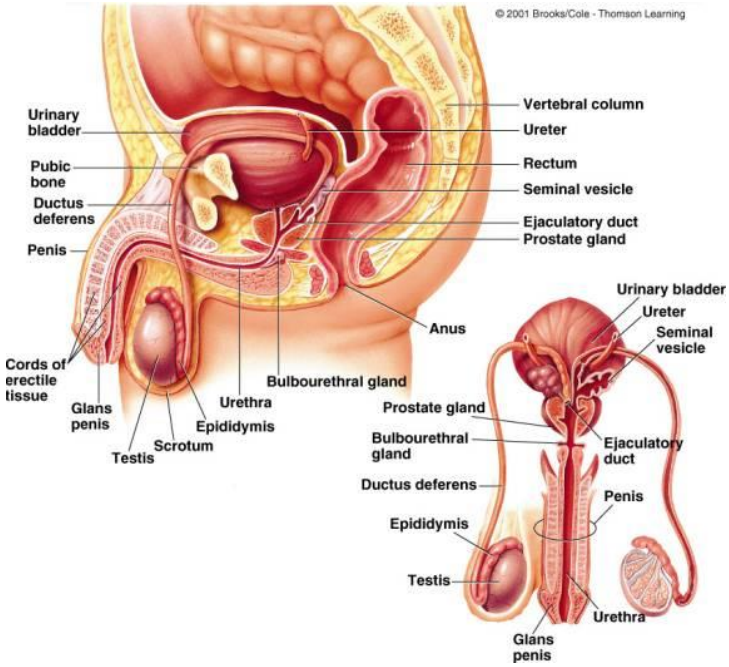
Fact Sheet on Testicular Cancer

Introduction

The testicles are two oval glands situated in the scrotum (sac) and are the male sexual organs that produce male sex hormones and sperm. They form part of the male reproductive system.

The epididymis is a soft tubular structure behind each testicle which collects, stores and carries sperm. It connects with the *vas deferens* that joins the urethra in the prostate gland.

The *Sertoli Cells* (germ cells) produce sperm while the *Leydig Cells* produce the male sex hormone *testosterone*.



[Picture Credit: Male Reproductive System]

Testicular cancer is a disease when one of the many kinds of testicular cells multiply uncontrollably, forming a mass in one or both testicles. Testicular cancer is not contagious and cannot spread from one person to another. This form of cancer is relatively rare when compared with other types of cancer. Testicular cancer accounts for approximately ½ percent of all cancers in men. In South Africa it is one of the most common male cancer in men between the ages of 15 and 49.

Darabos, K. & Hoyt, M.A. 2020.
"Coping through emotional processing (EP) with cancer-related circumstances can take several forms, including methods thought to be constructive (e.g., planning, meaning making) and unconstructive (e.g.,

rumination). These forms can have differential relationships with experiences of stress. Associations of coping through constructive and unconstructive EP in expressive writing with salivary stress biomarkers were examined among young adult testicular cancer survivors. Constructive processing was significantly associated with less overall daily cortisol output and smaller salivary alpha-amylase awakening response; unconstructive processing was also associated with lower daily cortisol output. These preliminary results from this exploratory study inform future research associating emotion-regulation coping and biological stress reactivity."

Wang, A.W. & Hoyt, M.A. 2020.
BACKGROUND AND OBJECTIVES: Perceiving benefit from a health-related stressor such as cancer has been associated with better psychological adjustment in various cancer populations; however, it has not been studied in the context of young adulthood or gender-related cancer threat. This study investigated the role of benefit finding in psychological adjustment among young adults with testicular cancer, and whether BF moderates cancer-related masculine threat.
DESIGN: This study utilizes a cross-sectional design with a diverse sample of young adult testicular cancer survivors.
METHODS: Men with a history of testicular cancer (*N* = 171; *M* age = 25.2, *SD* = 3.32) completed questionnaires of benefit finding, cancer-related masculine threat, and indicators of psychological adjustment.
RESULTS: Multiple regression analysis revealed that cancer-related masculine threat was associated with worse adjustment across indicators and that benefit finding was related to higher positive affect and lower depressive symptoms. Benefit finding attenuated the potentially adverse effect of cancer-related masculine threat on negative affect and depressive symptoms such that cancer-related masculine threat demonstrated a stronger association with negative affect and depressive symptoms for people with relatively low BF.
CONCLUSIONS: For young adult men with testicular cancer, finding benefit appears to promote well-being in the face of masculine cancer threat.

Testicular Cancer
Testicular cancer arises mostly (98,9%) in the germ cells of the testes in adults. Non-germ cell testicular tumours are uncommon and comprise a heterogeneous group.

Within the germ cell neoplasms tumours can be classified, based on pathologic and clinical features, into two broad histologic groups: seminomas and non-seminomas. Seminomas tend to grow more slowly and are very sensitive to radiation therapy, compared to non-seminomas which are more clinically aggressive and do not respond well to radiotherapy, Because these two types of cancers grow and spread differently, they are treated differently.

Incidence of Testicular Cancer in South Africa

Testicular cancer is not common. Internationally about 1 in 250 males will develop testicular cancer at some point during their lifetime. It occurs in young males. The average age of people at diagnosis is 33 years old.

The following South African statistics regarding histologically diagnosed cases of testicular cancer during 2017 are available from the outdated National Cancer Registry (2017), known for under reporting:

Group 2017	Actual No of Cases	Percentage of All Cancers	Estimated Lifetime Risk
All males	197	0,49%	1:1 737
Asian males	23	2,37%	1:554
Black males	29	0,20%	1:11 112
Coloured males	25	0,51%	1:1 169
White males	129	0,57%	1:246

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

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

Group 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	10	53	62	46	18	4	3	1
Asian males	1	12	9	1	0	0	0	0
Black males	6	6	8	6	2	0	0	0
Coloured males	2	9	1	10	2	0	1	0
White males	1	26	43	30	14	4	2	0

Comparison Between Global and South African Incidence of Testicular Cancer

Globally, testicular cancer is a rare tumour type accounting for 1% of malignancies in men. It is, however, the most common cancer in young men between ages 15 and 49, and mostly in Western populations. The incidence of testicular cancer is increasing globally, although a decline in mortality rates has been reported in Western countries.

Even though Testicular Cancer is increasing in incidence in many countries, mortality rates remain low and most men are cured.

Country	Incidence per 100 000 of the Population
New Zealand	7.8
United Kingdom	6.3
Australia	6.1
Sweden	5.6
United States of America	5.2
Poland	4.9
Spain	3.8
Colombia	2.2
China	1.3
South Africa	0.6
India	0.5

Causes of Testicular Cancer

The exact cause of testicular cancer is unknown. There are, however, several risk factors linked to testicular cancer.

A risk factor is something that affects a person's chance of getting a particular disease. Different cancers have different risk factors. Some risk factors, such as smoking, can be controlled. Others, like a person's age or race, cannot be changed. However, having a risk factor, or even several risk factors, does not mean that a person will get the disease. Not having any risk factors does also not mean that someone will not get the disease (American Cancer Society).

Risk Factors for Testicular Cancer

There is no way to prevent testicular cancer. Any person who believes that he may be at risk for testicular cancer should discuss this with his medical practitioner.

The following have been identified as risk factors for testicular cancer:

Having had an Undescended testicle(s) – before birth, the testicles normally develop in the belly of the foetus and then move down into the scrotum before the baby is born. It is estimated that in about 3% of boys, the testicles do not move down into the scrotum before birth (American Cancer Society). Sometimes the testicle or testicles stays inside the abdomen, while in other cases, it starts to move down, but gets stuck in the groin. Undescended testes is also known as *cryptorchidism*.

Men who have had *cryptorchidism* are several times more likely to get testicular cancer than those who did not have the problem. The risk is higher for men with a testicle in the belly as opposed to one that

has moved down at least part of the way. Among men with a history of this problem, most cancers start in the testicle that has not moved down.

Having had abnormal development of the testicles and/or other organs - men born with abnormalities of the testicles, penis and/or urethra (hypospadias), or kidneys, as well as those with inguinal hernia (hernia in the groin area, where the thigh meets the abdomen), may be at increased risk.

Having a personal history of testicular cancer – Men who have been cured of cancer of one testicle have an increased risk (about 3-4%) of getting cancer in the other testicle.

Having a family history of testicular cancer - A family history of testicular cancer increases the risk. If a man has the disease, there is a slight increased risk that his brothers or sons may also get it. Approximately 10% of testicular cancers appear to be genetically linked. It is believed that the genes do not cause testicular cancer, but rather make the man more susceptible to it.

HIV Infection – Recent research has shown that there is some evidence that men infected with HIV (human immunodeficiency virus) have an increased risk of testicular cancer. This may be especially true for men who have Aids (Acquired Immunodeficiency Syndrome). No other infections have been shown to increase testicular cancer risk (Hentrich & Pfister, 2017).

Race – being white increases the risk of testicular cancer. White men are about 5 times more likely to get testicular cancer. The reason for this difference is not known.

Age – On average 9 out of 10 cases of testicular cancers occur in men between the ages of 15 and 49. However, this cancer can affect males of any age, including infants and older men.

Having fertility problems – studies have confirmed that men with fertility problems have an increased risk of testicular cancer. The problems they identified were low semen concentration, sperm that did not move around as much as normal, or a high proportion of abnormal sperm.

Occupation - Certain occupations (miners, oil or gas workers, janitors, leather workers, food and beverage workers, or workers involved in the manufacturing or application of pesticides) have an increased risk of testicular cancer.

Having a family history of breast cancer or malignant melanoma - men who have family members with breast cancer or malignant melanoma have an increased risk of testicular cancer.

Smoking marijuana – Studies from the University of Chicago have found that men who had smoked marijuana were twice as likely as men who had not to get an aggressive form of the disease (Callaghan, *et al*., 2017).

Body size – Some studies have shown that the risk of testicular cancer in somewhat higher in tall men, but other studies have not shown a link.

Having had a vasectomy - having had a vasectomy does not increase the risk of testicular cancer.

Having prior trauma to the testicles - Prior trauma to the testicles and recurrent actions such as horseback riding do not appear to be related to the development of testicular cancer.

Genetic risk factors - A new study looking at the genomes of more than 13 000 men identified four new genetic variants associated with an increased risk of testicular cancer, one of the commonly diagnosed type in young men today. The findings from this first-of-its-kind meta-analysis were reported online May 12 in *Nature Genetics* by researchers at the Perelman School of Medicine at the University of Pennsylvania.

Exposure to certain chemicals - Exposure to endocrine-disrupting chemicals (EDCs), such as bisphenol A, phthalates, heavy metals, polychlorinated biphenyls and organochlorines, have been linked to testicular cancer, but the evidence is inconclusive.

AlDybayan, S.H., Pyle, L.C., Gaqmulin, M., Kulis, R., Moore, N,D,m Taylor-Weiner, A., Hamid, A.A., Reardn, B., Wubbenhorst, B., Godse, R., Vaughn, D.J., Jacobs, L.A., Meien, S., Grgic, M., Kastelan, Z., Markt, S.C., Damrauer, S.M., Rader, D.J., Kember, R.L., Loud, J.T., Kanetsky, P.A., Greene, M.H., Sweeney, C.J., Kubisch, C., Nathanson, K.L., Van Allen, E.M., Stewart, D.R. & Lessel, D. 2019.

Importance: Approximately 50% of the risk for the development of testicular germ cell tumors (TGCTs) is estimated to be heritable, but no mendelian TGCT predisposition genes have yet been identified. It is hypothesized that inherited pathogenic DNA repair gene (DRG) alterations may drive susceptibility to TGCTs.

Objective: To systematically evaluate the enrichment of germline pathogenic variants in the mendelian cancer predisposition DRGs in patients with TGCTs vs healthy controls.

Design, Setting, and Participants: A case-control enrichment analysis was performed from January 2016 to May 2018 to screen for 48 DRGs in 205 unselected men with TGCT and 27 173 ancestry-matched cancer-free individuals from the Exome Aggregation Consortium cohort in the discovery stage. Significant findings were selectively replicated in independent cohorts of 448 unselected men with TGCTs and 442 population-matched controls, as well as 231 high-risk men with TGCTs and 3090 ancestry-matched controls. Statistical analysis took place from January to May 2018.

Main Outcomes and Measures: Gene-level enrichment analysis of germline pathogenic variants in individuals with TGCTs relative to cancer-free controls.

Results: Among 205 unselected men with TGCTs (mean [SD] age, 33.04 [9.67] years), 22 pathogenic germline DRG variants, one-third of which were in *CHEK2* (OMIM 604373), were identified in 20 men (9.8%; 95% CI, 6.1%-14.7%). Unselected men with TGCTs were approximately 4 times more likely to carry germline loss-of-function *CHEK2* variants compared with cancer-free individuals from the Exome Aggregation Consortium cohort (odds ratio [OR], 3.87; 95% CI, 1.65-8.86; nominal $P = .006$; $q = 0.018$). Similar enrichment was also seen in an independent cohort of 448 unselected Croatian men with TGCTs (mean [SD] age, 31.98 [8.11] years) vs 442 unselected Croatian men without TGCTs (at least 50 years of age at time of sample collection) (OR, >1.4; $P = .03$) and 231 high-risk men with TGCTs (mean [SD] age, 31.54 [9.24] years) vs 3090 men (all older than 50 years) from the Penn Medicine Biobank (OR, 6.30; 95% CI, 2.34-17.31; $P = .001$). The low-penetrance *CHEK2* variant (p.Ile157Thr) was found to be a Croatian founder TGCT risk variant (OR, 3.93; 95% CI, 1.53-9.95; $P = .002$). Individuals with the

pathogenic *CHEK2* loss-of-function variants developed TGCTs 6 years earlier than individuals with *CHEK2* wild-type alleles (5.95 years; 95% CI, 1.48-10.42; *P* = .009).
Conclusions and Relevance: This multicenter case-control analysis of men with or without TGCTs provides evidence for *CHEK2* as a novel moderate-penetrance TGCT susceptibility gene, with potential clinical utility. In addition to highlighting DNA-repair deficiency as a potential mechanism driving TGCT susceptibility, this analysis also provides new avenues to explore management strategies and biological investigations for high-risk individuals.

Signs and Symptoms of Testicular Problems
Like any other part of the boy, the testicles can be affected by various conditions and diseases, which can lead to symptoms. The most common cancer signs and symptoms in the testicles and scrotum include:

- Lumps (masses)
- Swelling
- Pain

Cancer is only one of the possible causes of testicular symptoms. More often the symptoms are caused by injury, infection, or something else.

The symptoms of testicular cancer include:

- Uncomfortable feeling in a testicle
- Presence of a painless lump on a testicle – the lump can sometimes be as small as a grain of rice and feel like hard rubber
- An enlarged or swollen testicle
- Significant shrinking of a testicle
- A change in the consistency of a testicle
- A heavy or aching feeling in the back, lower abdomen, groin, or scrotum
- Any painless lump on a testicle that does not respond promptly to antibiotic treatment
- If the cancer has already spread to the lungs, problems like shortness of breath, chest pain, or cough (even coughing up blood) may develop
- In rare cases, testicular cancer spreads to the brain and can cause headaches and confusion
- Enlargement of breasts with tenderness in cases of testicular germ cell tumours
- In Leydig cell tumours, oestrogen-producing tumours can cause loss of sexual desire or make the male's breasts to grow
- Also in Leydig cell tumours, androgen-producing tumours can cause growth of facial and body hair at an abnormally early age in boys

Diagnosis of Testicular Cancer

The diagnosis of testicular cancer is done on the presence of symptoms followed by a physical examination and biopsy with confirmation by a qualified pathologist in an approved laboratory. These tests may include:

- Blood tests that measure the levels of tumour markers like alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (βHCG), and lactate dehydrogenase (LDH)
- Ultrasound – a test in which high-frequency sound waves are bounced off the testicles. The echoes produce a picture called a sonogram which can show the presence and size of a mass in the testicle
- Biopsy (microscopic examination of testicular tissue by pathologist) to determine whether cancer is present
- If testicular cancer is found, more tests are needed to find out if the cancer has spread from the testicle to other parts of the body. Determining the stage of the cancer helps the planning of appropriate treatment

Tumour markers according to tumour type

Tumour type	Tumour markers
Non-seminomas	Raised alpha-fetoprotein (AFP) and/or human chorionic gonadotropin (HCG) levels
Pure seminomas	Occasionally raised HCG levels but never AFP levels.
Choriocarcinoma	Raised HCG
Embryonal carcinoma	Raised HCG Raised AFP
Yolk sac tumour	Raised AFP
Widely spread tumour of type seminoma or non-seminomatous germ cell tumours (NSGCTs)	Raised lactate dehydrogenase (LDH) levels
Teratoma	Raised AFP

Cryopreservation of Semen

A diagnosis of testicular cancer is a situation where depositing of semen in a long-term storage bank is something that each patient should consider. Long-term storage of sperm offers options for future preservation of semen and peace of mind. Circumstances can change and the affected person may want to father a child after treatment for his testicular cancer.

Cryopreservation of human spermatozoa - introduced in the 1960's - has been recognised as an efficient procedure for management of male fertility before therapy for malignant diseases, vasectomy or surgical infertility treatments, to store donor and partner spermatozoa before assisted reproduction treatments and to ensure the recovery of a small number of spermatozoa in severe male factor infertility.

[Picture Credit: Cryopreservation]

Sperm cryopreservation is an important component of fertility management and much of its successful application seems to affect the reproductive outcome of assisted reproduction technologies (ART): appropriate use of cryoprotectants before and sperm selection technologies after cryopreservation seem to have the greatest impact on preventing DNA fragmentation, thus improving sperm cryosurvival rates.

<u>Reasons why men should consider semen cryopreservation</u>

- Before undergoing cancer therapies – therapies such as surgery, chemotherapy and radiation can cause permanent sterility and infertility
- Before having prostate or testicular surgery – damage can be caused to a man's reproductive organs during testicular surgery and prostatectomy
- Before having a vasectomy – to preserve fertility and prevent the need for reversal surgery if personal circumstances change
- High risk occupations – men exposed to things like chemicals, radiation and extreme heat can experience infertility
- Professional sportsmen (especially cyclists) – strenuous and consistent impact from the sport may possibly lead to infertility

<u>How semen is stored</u>

The semen is stored in small straws in liquid nitrogen in a cryogenic storage tank. Storage of 2-3 semen ejaculates is optimal, but this does depend on the volume of the ejaculate, the initial sperm count and forward progression of the sperm. The storage facility will analyse the sperm and will advise the client if more ejaculate is needed to be stored to ensure maximum reproductive success in the future.

<u>Using cryogenically preserved semen for reproduction</u>

Human semen has been cryogenically stored since the 1960's and due to ongoing research throughout the years, the process and techniques of cryopreservation have become more refined. In addition, birth defects among children 'conceived' using cryopreserved semen is no different to children 'conceived'

using a fresh semen sample. However, there are concerns around this if the semen was produced after chemotherapy – this is why it is crucial to preserve fertility prior to cancer therapies. Many pregnancies are achieved with Artificial Reproductive Technologies (ART) using cryogenically preserved semen samples but the success rate also depends on the female partner's fertility status and age.

Levi-Setti, P.E., Negri, L., Baggiani, A., Morenghi, E., Albani, E., Dioguardi, C.M.C., Specchia, C. & Patrizio, P. 2020.

OBJECTIVE: To assess rates of successful testicular sperm retrieval and intracytoplasmic sperm injection (ICSI) outcome in cancer survivors affected by non-obstructive azoospermia (NOA) or retrograde ejaculation (RE)/failure of emission (FOE).

METHODS: A retrospective analysis of cancer survivors who did not cryopreserve sperm prior to treatment undergoing testicular sperm extraction (TESE). Non-cancer NOA patients and neurologic RE/FOE were the control group.

RESULTS: A total of 97 cancer survivors were offered TESE and 88 (91%) accepted. Sperm was retrieved and cryopreserved in 34/67 patients with NOA (50.7%) and in 21/21 patients affected by RE/FOE (100%). Sperm retrieval rates were similar in the control group (44.9% in NOA and 100% in RE/FOE). The ICSI cumulative pregnancy rate (60%) and live birth rate (40%) per couple in 30 NOA men did not differ from controls (50.0 and 46.5%, respectively; p = 0.399/0.670). The cumulative pregnancy rate (66.7%) and live birth rate (55.6%) in 18 RE/FOE men did not differ from the control group (38.9 and 33.3%, respectively; p = 0.181/0.315). The cancer type and the resulting infertility disorder (NOA or RE/FOE) were not associated with ICSI outcomes. Female partner age was inversely related to the cumulative live birth rate, being fourfold lower (11.5%) in women ≥ 40 years and 48.8% in younger women (p = 0.0037).

CONCLUSIONS: The rate of successful TESE and the ICSI outcome in cancer survivors with NOA and RE/FOE is the same as non-cancer azoospermic patients. Female partner age (older than 40 years) was associated with a significant reduction in live birth rates after TESE-ICSI procedures.

Treatment of Testicular Cancer

The treatment for testicular cancer may include:

<u>*Surgery*</u> – to remove the affected testicle. This is usually done through an incision in the groin and is called a radical inguinal *orchidectomy*. This usually does not affect the man's ability to get an erection and to produce sperm (unless both testicles have been removed). For cosmetic purposes, a prosthesis (artificial testicle) can be placed in the scrotum at the time of the operation, or at any time afterward.

<u>*Radiation therapy*</u> – which is also referred to as radiotherapy. Use is made of high-energy rays to kill cancer cells and shrink tumours. Radiation therapy affects normal as well as cancerous cells. The side effects depend mainly on the treatment dose.

<u>*Chemotherapy*</u> – use is made of anticancer drugs to kill cancer cells. When chemotherapy is given to testicular cancer patients, it is usually given as adjuvant therapy (after surgery) to destroy cancerous

cells that may remain in the body. Chemotherapy may also be the initial treatment if the cancer is advanced (has already spread outside the testicle).

Follow-up Treatment

Regular follow-up treatment is very important as testicular cancer can recur and affect the remaining testicle. The person should consult his medical doctor for regular blood tests to measure tumour marker levels.

Reducing the Risk for Testicular Cancer

There is no way to prevent testicular cancer. Unfortunately, testicular cancer is a type of cancer that cannot easily be prevented. There are simply no proven prevention methods.

Even though with Testicular Cancer there is very little one can do regarding the risk of age, race, and conditions occurring at birth, the following may contribute towards risk reduction:

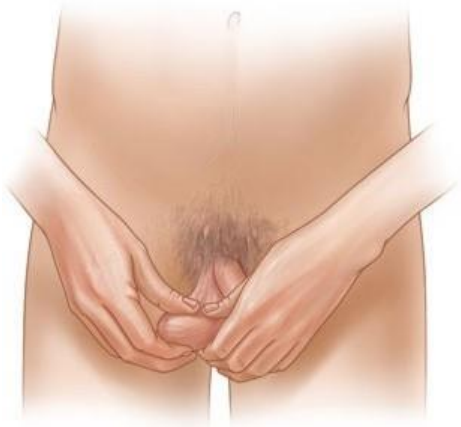
- By six months of age, boys with undescended testicles should be evaluated by a paediatric urologist who can assist with diagnosis and treatment
- Doing regular monthly testicular self-examinations and consulting with an urologist in the event of any abnormality which may be found

Testicular Self Examination (TSE)

The testicular self-examination (TSE) is an easy way for guys to check their own testicles to make sure there aren't any unusual lumps or bumps — which can be the first sign of testicular cancer.

Although testicular cancer is rare in teenage guys, overall it is the most common cancer in males between the ages of 15 and 49. It's important to try to do a TSE every month so you can become familiar with the normal size and shape of your testicles, making it easier to tell if something feels different or abnormal in the future.

[Picture Credit: RevolutionHealth]



Here is what to do:

- It is best to do a TSE during or right after a warm shower or bath. The scrotum (skin that covers the testicles) is most relaxed then, which makes it easier to examine the testicles
- Examine one testicle at a time. Use both hands to gently roll each testicle (with slight pressure) between the fingers. Place the thumbs over the top of the testicle, with the index and

middle fingers of each hand behind the testicle, and then roll it between the fingers

- One should be able to feel the epididymis (the sperm-carrying tube), which feels soft, rope-like, and slightly tender to pressure, and is located at the top of the back part of each testicle. This is a normal lump
- Remember that one testicle (usually the right one) is slightly larger than the other for most guys — this is also normal
- It is also normal for the testicles to hang at different heights – the left testicle usually hangs lower than the right testicle
- When examining each testicle, feel for any lumps or bumps along the front or sides. Lumps may be as small as a piece of rice or a pea
- If one notices any swelling, lumps, or changes in the size of a testicle, a change in the colour of the scrotum, or if one has any pain or achy areas in the groin, contact a medical practitioner
- Lumps or swelling may not be cancer, but they should be checked by a doctor, preferably an urologist, as soon as possible. Testicular cancer is almost always curable if it is caught and treated early.

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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CANSA Support

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