Cancer Association of South Africa (CANSA)

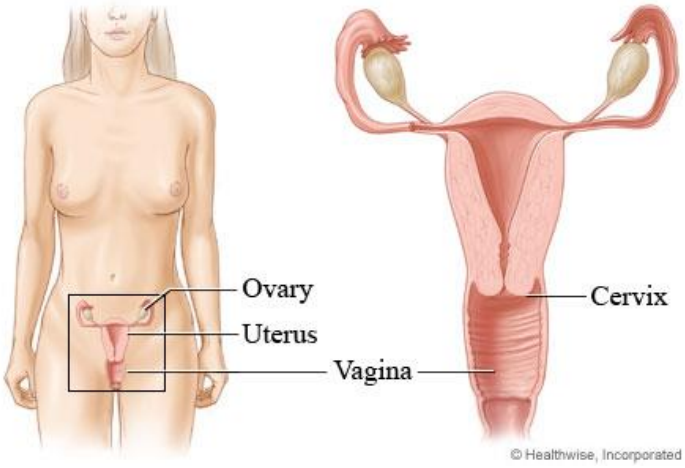
Research • Educate • Support

Fact Sheet
on
Cancer of the Vagina

Introduction

The vagina (from Latin *vāgīna*, literally 'sheath' or 'scabbard') is a fibromuscular tubular tract which is a sex organ and has two main functions - sexual intercourse and childbirth. In humans, this passage leads from the opening of the vulva to the uterus (womb), but the vaginal tract ends at the cervix. Unlike men, who have only one genital orifice, women have two, the urethra and the vagina. The vaginal opening is much larger than the urethral opening, and both openings are protected by the labia. (Wikipedia).

[Picture Credit: Female Reproductive System]



The vagina is a 7 ½- to 10-cm long tube. It is sometimes called the *birth canal*. The vagina goes from the cervix (the lower part of the uterus) to open up at the vulva (the external genitals). The vagina is lined by a layer of flat cells called *squamous* cells. This layer of cells is also called *epithelium* (or *epithelial lining*) because it is formed by epithelial cells.

The vaginal wall underneath the epithelium contains connective tissue, muscle tissue, lymph vessels and nerves. The vagina is usually in a collapsed state with its walls touching each other. The vaginal walls have many folds that help the vagina to open and expand during sexual intercourse or the birth of a baby. Glands near the opening of the vagina secrete mucus to keep the vaginal lining moist (American Cancer Society).

Incidence of Cancer of the Vagina in South Africa

According to the National Cancer Registry (2012) the following number of cancer of the vagina cases was histologically diagnosed in South Africa during 2012:

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	162	1:1 281	0,43%
Asian females	4	1:1 628	0,37%
Black females	122	1:1 227	0,74%
Coloured females	15	1:1 371	0,36%
White females	21	1:1 517	0,13%

The frequency of histologically diagnosed cases of cancer of the vagina in South Africa for 2012 was as follows (National Cancer Registry, 2012):

Group - Females 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	1	2	20	24	38	29	27	7
Asian females	0	0	1	0	0	1	1	1
Black females	0	2	19	26	29	16	22	3
Coloured females	1	0	0	5	3	3	2	1
White females	0	0	0	3	6	8	2	2

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.

Cancer of the Vagina

Secondary cancers in the vagina are more common than primary vaginal cancer, and usually come from the neck of the womb (cervix), the lining of the womb (endometrium) or from nearby organs such as the bladder or bowel.

There are several types of vaginal cancer:

Squamous cell carcinoma

About 70 of every 100 cases of vaginal cancer are *squamous cell carcinomas***.** These cancers begin in the squamous cells that make up the epithelial lining of the vagina. These cancers are more common in the upper area of the vagina near the cervix. Squamous cell cancers of the vagina often develop slowly. First, some of the normal cells of the vagina get pre-cancerous changes. Then some of the pre-cancer cells turn into cancer cells. This process can take many years.

The medical term most often used for this pre-cancerous condition is *vaginal intraepithelial neoplasia* (VAIN). 'Intraepithelial' means that the abnormal cells are only found in the surface layer of the vaginal skin (epithelium). There are 3 types of VAIN: VAIN1, VAIN2, and VAIN3, with 3 indicating furthest progression toward a true cancer. VAIN is more common in women who have had their uterus removed (hysterectomy) and in those who were previously treated for cervical cancer or pre-cancer.

In the past, the term *dysplasia* was used instead of VAIN. This term is used much less now. When talking about dysplasia, there is also a range of increasing progress toward cancer - first, mild dysplasia; next, moderate dysplasia; and then severe dysplasia.

Adenocarcinoma

Cancer that begins in gland cells is called *adenocarcinoma*. About 15 of every 100 cases of vaginal cancer are adenocarcinomas. The usual type of vaginal adenocarcinoma typically develops in women older than 50. One certain type, called *clear cell adenocarcinoma*,

occurs more often in young women who were exposed to diethylstilbestrol (DES) in utero (when they were in their mother's womb).

Melanoma

Melanomas develop from pigment-producing cells that give skin its colour. These cancers usually are found on sun-exposed areas of the skin but can form on the vagina or other internal organs. About 9 of every 100 cases of vaginal cancer are melanomas. Melanoma tends to affect the lower or outer portion of the vagina. The tumours vary greatly in size, colour and growth pattern.

Sarcoma

A sarcoma is a cancer that begins in the cells of bones, muscles or connective tissue. Up to 4 of every 100 cases of vaginal cancer are sarcomas. These cancers form deep in the wall of the vagina - not on its surface. There are several types of vaginal sarcomas. *Rhabdomyosarcoma* is the most common type of vaginal sarcoma. It is most often found in children and is rare in adults. A sarcoma called *leiomyosarcoma* is seen more often in adults. It tends to occur in women older than 50.

Other cancers

Cancers of the vagina are much less common than cancers that start in other organs (such as the cervix, uterus, rectum or bladder) and then spread to the vagina. These cancers are named after the place where they started. Also, a cancer that involves both the cervix and vagina is considered a cervical cancer. Likewise, if the cancer involves both the vulva and the vagina, it is considered a cancer of the vulva.
(American Cancer Society; National Cancer Institute; MacMillan Cancer Support).

Causes and Risk Factors for Cancer of the Vagina

Scientists have found that certain risk factors make a woman more likely to develop vaginal cancer. But many women with vaginal cancer do not have any apparent risk factors. And even if a woman with vaginal cancer has one or more risk factors, it is impossible to know for sure how much that risk factor contributed to causing the cancer.

Age - Squamous cell cancer of the vagina occurs mainly in older women. Only 15% of cases are found in women younger than 40. Almost half of cases occur in women who are 70 years old or older.

Diethylstilbestrol (DES) - DES is a hormonal drug that was given to some women to prevent miscarriage between 1940 and 1971. Women whose mothers took DES (when pregnant with them) develop clear-cell adenocarcinoma of the vagina or cervix more often than would normally be expected. There is about 1 case of this type of cancer in every 1,000 daughters of women who took DES during their pregnancy. This means that about 99.9% of DES daughters do not develop this cancer.

DES-related clear cell adenocarcinoma is more common in the vagina than the cervix. The risk appears to be greatest in those whose mothers took the drug during their first 16 weeks of pregnancy. Their average age when they are diagnosed is 19 years. Since the use of DES during pregnancy was stopped by the FDA in 1971, even the youngest DES daughters

are older than 35 -- past the age of highest risk. But there is no age when a woman is safe from DES-related cancer. Doctors do not know exactly how long women remain at risk.

DES daughters have an increased risk of developing clear cell carcinomas, but women don't have to be exposed to DES for clear cell carcinoma to develop. In fact, women were diagnosed with this type of cancer before DES was invented.

DES daughters are also more likely to have high grade cervical dysplasia (CIN 3) and vaginal dysplasia (VAIN 3) when compared to women who were never exposed.

Vaginal adenosis - Normally, the vagina is lined by flat cells called squamous cells. In about 40% of women who have already started having periods, the vagina may have one or more areas where it is lined instead by glandular cells. These cells look like those found in the glands of the cervix, the lining of the body of the uterus (endometrium), and the lining of the fallopian tubes. These areas of gland cells are called *adenosis*. It occurs in nearly all women who were exposed to DES during their mothers' pregnancy. Having adenosis increases the risk of developing clear cell carcinoma, but this cancer is still very rare. The risk of clear cell carcinoma in a woman who has adenosis that is not related to DES is very, very small. Still, many doctors feel that any woman with adenosis should have very careful screening and follow-up.

Human papilloma virus - Human papilloma virus (HPV) is a group of more than 100 related viruses. They are called papilloma viruses because some of them cause a type of growth called a *papilloma*. Papillomas - more commonly known as warts - are not cancers.

Different HPV types can cause different types of warts in different parts of the body. Some types cause common warts on the hands and feet. Other types tend to cause warts on the lips or tongue.

Certain HPV types can infect the outer female and male genital organs and the anal area, causing raised, bumpy warts. These warts may barely be visible or they may be several inches across. The medical term for genital warts is *condyloma acuminatum*. 2 types of HPV, HPV 6 and HPV 11, cause most cases of genital warts. These 2 types are seldom linked to cancer, and so are called *low-risk* types of HPV.

Other HPV types have been linked with cancers of the cervix and vulva in women, cancer of the penis in men, and cancers of the anus and throat (in men and women). These are known as *high-risk* types of HPV and include HPV 16, HPV 18, HPV 31, as well as others. Infection with a high-risk HPV may produce no visible signs until pre-cancerous changes or cancer develops.

HPV can be passed from one person to another during skin-to-skin contact. One way HPV is spread is through sex, including vaginal and anal intercourse and even oral sex.

Up to 90% of vaginal cancers and pre-cancers (vaginal intraepithelial neoplasia -- VAIN) are linked to infection with HPV.

Vaccines have been developed to help prevent infection with some types of HPV. Right now, 2 different HPV vaccines have been approved for use in the United States by the Food and Drug Administration (FDA): Gardasil® and Cervarix®.

Cervical cancer - Having cervical cancer or pre-cancer (cervical intraepithelial neoplasia or cervical dysplasia) increases a woman's risk of vaginal squamous cell cancer. This is most likely because cervical and vaginal cancers have similar risk factors, such as HPV infection and smoking.

Some studies suggest that treating cervical cancer with radiation therapy may increase the risk of vaginal cancer, but this was not seen in other studies, and the issue remains unresolved.

Smoking - Smoking cigarettes more than doubles a woman's risk of getting vaginal cancer.

Alcohol - Drinking alcohol might affect the risk of vaginal cancer. A study of alcoholic women found more cases of vaginal cancer than was expected. But this study was flawed because it did not look at other factors that can alter risk, such as smoking and HPV infection. A more recent study that did take these other risk factors into account found a decreased risk of vaginal cancer in women who do not drink alcohol at all.

Human immunodeficiency virus - Infection with HIV (human immunodeficiency virus), the virus that causes AIDS, also increases the risk of vaginal cancer.

Vaginal irritation - In some women, stretching of the pelvic ligaments may cause the uterus to sag into the vagina or even extend outside the vagina. This condition is called *uterine prolapse* and can be treated by surgery or by wearing a pessary, a device to keep the uterus in place. Some studies suggest that long-term (chronic) irritation of the vagina in women using a pessary may slightly increase the risk of squamous cell vaginal cancer. But this association is extremely rare, and no studies have conclusively proven that pessaries actually cause vaginal cancer.

Auto immune condition – a condition called systemic lupus erythematosus increases the risk for vaginal cancer.

Women who have had radiotherapy to the pelvic area - may also have a very slightly increased risk.

Other factors - Other factor that may increase the risk of vaginal cancer inclue:

- Organ transplants.
- Having a history of abnormal cells in the uterus or cancer of the uterus.
- Having had a hysterectomy for health problems that affect the uterus.

(American Cancer Society; Cancer Research UK; National Cancer Institute; MacMillan Cancer Support).

High and Low Risk Human Papilloma Viruses

Most people infected with HPV never develop any symptoms, however, there are a number of conditions that can result from an HPV infection.

HPV Research Scientists have separated HPV types into those that are more likely to develop into cancer and those that are less likely. The so-called 'high-risk' types are more likely to lead to the development of cancer, while 'low-risk' viruses rarely develop into cancer.

The sexually transmitted varieties of 'high-risk' HPV types include:

HPV-16	HPV-18	HPV-31	HPV-33	HPV-35	HPV-39
HPV-45	HPV-51	HPV-52	HPV-56	HPV-58	HPV-59
HPV-68	HPV-69				

A few other HPV types are also sometimes included on this list. These 'high-risk' HPV types cause growths that are usually flat and nearly invisible as compared to the warts caused by types HPV-6 and HPV-11.

Up to 70% of cervical cancer cases are caused by HPV-16 and HPV-18.

'Low-risk' HPV types can cause no symptoms or may cause conditions such as genital warts, but do not cause cervical cancer. Warts can form weeks, months, or even years after sexual contact with a person who has genital HPV. It is also possible that wrts may never appear. In fact, most people with 'low-risk' HIV types never know they are infected because they do not get warts or any other symptoms.

The following table lists various conditions along with their associated types of HPV:

Disease	**HPV Type**
Cervical cancer	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58
Precancerous changes	16, 18, 34, 39, 42, 55
Laryngeal papillomas	6, 11, 30
Genital Warts	6, 11, 30, 40, 41, 42, 43, 44, 45, 51, 54
Common warts	1, 2, 4, 26, 27, 29, 41, 57
Flat warts	3, 10, 27, 28, 41, 49
Plantar warts	1, 2, 4

(eMedTV).

Signs and Symptoms of Cancer of the Vagina

Possible signs of vaginal cancer include pain or abnormal vaginal bleeding.

Vaginal cancer often does not cause early symptoms and may be found during a routine pelvic exam and Pap test. When symptoms occur, they may be caused by vaginal cancer or by other conditions. Check with your doctor if you have any of the following problems:

- bleeding or discharge not related to menstrual periods
- pain during sexual intercourse
- pain in the pelvic area
- a lump in the vagina
- pain when urinating
- constipation

(National Cancer Institute).

Diagnosis of Cancer of the Vagina
Screening healthy women for vaginal cancer - Vaginal cancer is sometimes found during a routine pelvic exam before signs and symptoms become evident.

During a pelvic exam, the doctor carefully inspects the outer genitals, and then inserts two fingers of one hand into the vagina and simultaneously presses the other hand on the abdomen to feel the uterus and ovaries. He or she also inserts a device called a speculum into the vagina. The speculum opens the vaginal canal so that the doctor can check the vagina and cervix for abnormalities.

The doctor may also do a Pap test. Pap tests are usually used to screen for cervical cancer, but sometimes vaginal cancer cells can be detected on a Pap test.

Tests to diagnose vaginal cancer - the doctor may conduct a pelvic exam and Pap test to check for abnormalities that may indicate vaginal cancer. Based on those findings, the doctor may conduct other procedures to determine whether a patient has vaginal cancer, such as:

- Inspecting the vagina with a magnifying instrument. Colposcopy is an examination of the vagina with a special lighted magnifying instrument called a colposcope. Colposcopy allows the doctor to magnify the surface of the vagina to see any areas of abnormal cells.

- Biopsy - removing a sample of vaginal tissue for testing. Biopsy is a procedure to remove a sample of suspicious tissue to test for cancer cells. The doctor may take a biopsy of tissue during a colposcopy exam. The doctor sends the tissue sample to a laboratory for testing.

Cancer can spread in the body, either in the bloodstream or through the lymphatic system. The lymphatic system is part of the body's defence against infection and disease. The system is made up of a network of lymph nodes (also called lymph glands) that are linked by fine ducts containing lymph fluid.

If the above tests show that the person has vaginal cancer, further tests may be necessary to find out whether or not any cancer cells have spread. The results of these tests will help the specialist to decide on the best type of treatment for you.

The patient may have any of the following additional tests:

- Chest x-ray and blood tests - These are necessary to assess general health and to check whether the cancer has spread to the lungs.

- CT (computerised tomography) scan - A CT scan takes a series of x-rays that build up a three-dimensional picture of the inside of the body. The scan is painless and takes 10-30 minutes.

- MRI (magnetic resonance imaging) scan - This test is similar to a CT scan but uses magnetism instead of x-rays to build up a detailed picture of areas of the body.

- PET scan (positron emission tomography scan): A procedure to find malignant tumour cells in the body. A small amount of radioactive glucose (sugar) is injected

into a vein. The PET scanner rotates around the body and makes a picture of where glucose is being used in the body. Malignant tumour cells show up brighter in the picture because they are more active and take up more glucose than normal cells do.

- Cystoscopy: A procedure to look inside the bladder and urethra to check for abnormal areas. A cystoscope is inserted through the urethra into the bladder. A cystoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue samples, which are checked under a microscope for signs of cancer.

- Ureteroscopy : A procedure to look inside the ureters to check for abnormal areas. A ureteroscope is inserted through the bladder and into the ureters. A ureteroscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease. A ureteroscopy and cystoscopy may be done during the same procedure.

- Ureteroscopy. A ureteroscope (a thin, tube-like instrument with a light and a lens for viewing) is inserted through the urethra into the ureter. The doctor looks at an image of the inside of the ureter on a computer monitor.

- Proctoscopy: A procedure to look inside the rectum to check for abnormal areas. A proctoscope is inserted through the rectum. A proctoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease.

(Mayo Clinic; MacMillan Cancer Support; National Cancer Institute).

Staging of Cancer of the Vagina

Knowing the stage helps the doctor to decide what kind of treatment is best and can help predict a patient's prognosis (chance of recovery). There are different stage descriptions for different types of cancer.

One tool that doctors use to describe the stage is the TNM system. This system judges three factors: the tumour itself, the lymph nodes around the tumour, and if the tumour has spread to other parts of the body. The results are combined to determine the stage of cancer for each person. There are five stages: stage 0 (zero) and stages I through IV (one through four). The stage provides a common way of describing the cancer, so doctors can work together to plan the best treatments.

TNM is an abbreviation for tumour (T), node (N), and metastasis (M). Doctors look at these three factors to determine the stage of cancer:

- how large is the primary tumour and where is it located? **(Tumour, T)**
- has the tumour spread to the lymph nodes? **(Node, N)**
- has the cancer metastasized to other parts of the body? **(Metastasis, M)**

Tumour. Using the TNM system, the ‘T’ plus a letter or number (0 to 4) is used to describe the size and location of the tumour. Some stages are divided into smaller groups that help describe the tumour in even more detail. Specific tumour stage information is listed below.

TX: the primary tumour cannot be evaluated.

T0: there is no evidence of cancer in the vagina.
Tis: the tumour is carcinoma in situ, an early cancer found only in one layer of cells that has not spread to nearby tissue.
T1: the tumour is in the vagina and has not spread through the vaginal wall or to other parts of the body.
T2: the tumour has spread through the vaginal wall and surrounding tissue, but not to the walls of the pelvis.
T3: the tumour has spread to the pelvic wall.
T4: the tumour has spread to the bladder, rectum, or other areas of the body.

Node. The 'N' in the TNM staging system stands for lymph nodes, the tiny, bean-shaped organs that help fight infection. Lymph nodes near the pelvis and groin are called regional lymph nodes. Depending on the exact location of the tumour (upper third, middle third, or lower third of the vagina), the lymph nodes near the hips or upper thighs may also be involved. Lymph nodes in other parts of the body are called distant lymph nodes.

NX: the lymph nodes cannot be evaluated.
N0: cancer has not spread to the regional lymph nodes.
N1: cancer has spread to the regional lymph nodes.

Distant metastasis. The 'M' in the TNM system indicates whether the cancer has spread to other parts of the body.

MX: metastasis cannot be evaluated.
M0: the cancer has not spread to other parts of the body.
M1: the cancer has spread to another part of the body.

Cancer Stage Grouping of Cancer of the Vagina
Doctors assign the stage of the cancer by combining the T, N, and M classifications.

Stage 0:
The tumour is called carcinoma in situ. In other words, the cancer is found only in the first layer of cells lining the vagina, not in the deeper tissue (Tis, N0, M0).

Stage I:
The tumour has not spread through the vaginal wall or to other parts of the body (T1, N0, M0).

Stage II:
The tumour has spread through the vaginal wall, but not to the walls of the pelvis (T2, N0, M0).

Stage III:
Vaginal cancer is called stage III in either of these conditions:
Cancer has spread to the lymph nodes in the pelvis (T1, T2, or T3; N1, M0).
Cancer has spread to the pelvic wall (except the bladder), but not the lymph nodes (T3, N0, M0).

Stage IVA:
Cancer has spread to the bladder, rectum, or beyond the pelvis. The lymph nodes may or may not be involved (T4, any N, M0).

Stage IVB:
Any cancer that has spread to a distant part of the body (any T, any N, M1).

Recurrent:
Recurrent cancer is cancer that comes back after treatment. If there is a recurrence, the cancer may need to be staged again (called re-staging) using the system above.

Grading
Tumour Grade (G). In addition to the TNM system, doctors also describe a primary tumour by its grade, which is determined using a microscope to examine tissue from a tumour. The doctor compares the tumour tissue with normal tissue. Normal tissue contains many different types of cells grouped together, which is called differentiated. Tissue from a tumour usually has cells that look more alike, called poorly differentiated. Generally, the more differentiated the tissue, the better the prognosis.

GX: the tumour grade cannot be evaluated.
G1: the tumour cells are well differentiated (contain many healthy-looking cells).
G2: the tumour cells are moderately differentiated (more cells appear abnormal than healthy).
G3: the tumour cells are poorly differentiated (most of the cells appear abnormal).
G4: the tumour cells are undifferentiated (the cells barely resemble healthy cells).

FIGO Staging of Cancer of the Vagina
Stage 0 - carcinoma in situ and intraepithelial carcinoma
Stage I - limited to vaginal wall
Stage II - involved subvaginal tissue but not to pelvic wall
Stage III - extended to pelvic wall
Stage IV - beyond true pelvis or involved mucosa of bladder or rectum
Stage IVa - adjacent organs or direct extension beyond true pelvis
Stage IVb - distant organs
(Cancer.Net; ObGyn Knowledge Bank).

Treatment of Cancer of the Vagina
Treatment options for vaginal cancer depend on several factors, including the type of vaginal cancer and its stage. Treatment for vaginal cancer typically includes surgery and radiation.

<u>Surgery</u>
Types of surgery that may be used in women with vaginal cancer include:

Removal of small tumours or lesions. Cancer limited to the surface of your vagina may be cut away, along with a small margin of surrounding healthy tissue to ensure that all of the cancer cells have been removed.

- Removal of the vagina (vaginectomy). Removing part of the vagina (partial vaginectomy) or the entire vagina (radical vaginectomy) may be necessary to remove all of the cancer. Depending on the extent of the cancer, the surgeon may recommend surgery to remove the uterus and ovaries (hysterectomy) and nearby lymph nodes (lymphadenectomy) at the same time as the vaginectomy

- Removal of the majority of the pelvic organs (pelvic exenteration). This extensive surgery may be an option if cancer has spread throughout the pelvic area or if the vaginal cancer has recurred. During pelvic exenteration, the surgeon may remove many of the organs in the pelvic area, including the bladder, ovaries, uterus, vagina, rectum and the lower portion of the colon. Openings are created in the abdomen to allow urine (urostomy) and waste (colostomy) to exit the body and collect in ostomy bags.

If the vagina is completely removed, the patient may choose to undergo surgery to construct a new vagina. Surgeons use pieces of skin, sections of intestine or flaps of muscle from other areas of the body to form a new vagina. With some adjustments, a reconstructed vagina allows the patient to have vaginal intercourse. However, a reconstructed vagina is not the same as an original vagina. For instance, a reconstructed vagina lacks natural lubrication and creates a different sensation when touched due to changes in surrounding nerves.

Radiation therapy

Radiation therapy uses high-powered energy beams, such as X-rays, to kill cancer cells. Radiation can be delivered two ways:

- External radiation. External beam radiation is directed at your entire abdomen or just your pelvis, depending on the extent of your cancer. During external beam radiation, you're positioned on a table and a large radiation machine is maneuvered around you in order to target the treatment area. Most women with vaginal cancer receive external beam radiation.

- Internal radiation. During internal radiation (brachytherapy), radioactive devices — seeds, wires, cylinders or other materials — are placed in your vagina or the surrounding tissue. After a set amount of time, the devices may be removed. Women with very early-stage vaginal cancer may receive internal radiation only. Other women may receive internal radiation after undergoing external radiation.

  Radiation therapy kills quickly growing cancer cells, but it may also damage nearby healthy cells, causing side effects. Side effects of radiation depend on the radiation's intensity and where it's aimed.

Other Options

If surgery and radiation cannot control the cancer, the patient may be offered other treatments, including:

- Chemotherapy. Chemotherapy uses chemicals to kill cancer cells. It isn't clear whether chemotherapy is useful in women with vaginal cancer. For this reason, chemotherapy generally is not used on its own to treat vaginal cancer. Chemotherapy may be used during radiation therapy to enhance the effectiveness of radiation.

- Clinical trials. Clinical trials are experiments to test new treatment methods. While a clinical trial gives one a chance to try the latest treatment advances, a cure is not guaranteed. Discuss available clinical trials with the doctor to better understand the options.

(Mayo Clinic; American Cancer Society).

About Clinical Trials

Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer.

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People

who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for

a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or "trial arms": (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

<u>Use of Placebos</u>

The use of placebos as comparison or "control" interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial
The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial
The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials
In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over
After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the

study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

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Resources and References

American Cancer Society
http://www.cancer.org/cancer/vaginalcancer/detailedguide/vaginal-cancer-what-is-vaginal-cancer
http://www.cancer.org/cancer/vaginalcancer/detailedguide/vaginal-cancer-risk-factors
http://www.cancer.org/cancer/vaginalcancer/detailedguide/vaginal-cancer-treating-by-stage

Cancer.Net
http://www.cancer.net/cancer-types/vaginal-cancer/staging

Cancer Research UK
http://www.cancerresearchuk.org/cancer-help/type/vaginal-cancer/about/risks-and-causes-of-vaginal-cancer

eMedTV
http://hpv.emedtv.com/hpv/types-of-hpv.html

Female Reproductive System
http://www.webmd.com/women/vagina

MacMillan Cancer Support
http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Vagina/Vaginalcancer.aspx

Mayo Clinic
http://www.mayoclinic.com/health/vaginal-cancer/DS00812/DSECTION=tests-and-diagnosis
http://www.mayoclinic.com/health/vaginal-cancer/DS00812/DSECTION=treatments-and-drugs

National Cancer Institute
http://www.cancer.gov/cancertopics/pdq/treatment/vaginal/Patient/page1
http://www.cancer.gov/cancertopics/pdq/treatment/vaginal/Patient/page2
http://www.cancer.gov/clinicaltrials/learningabout/what-are-clinical-trials

ObGyn Knowledge Bank
http://www.nuthalapaty.net/kb/creog_display.asp?y=all&q=6-3-D-2

Wikipedia
https://en.wikipedia.org/wiki/Vagina