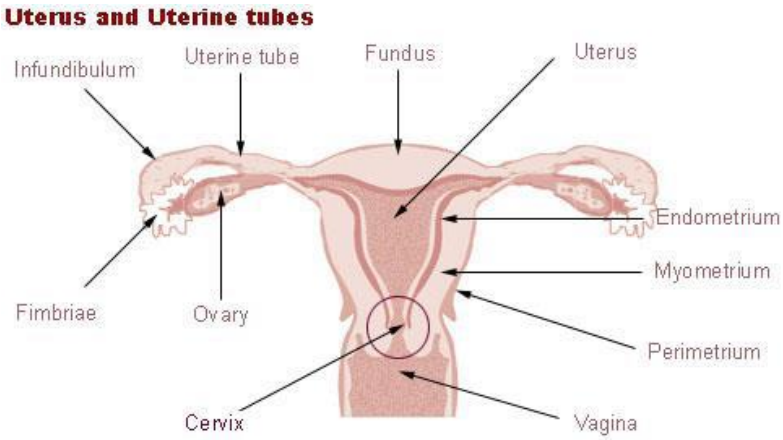
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Cervical Cancer

Introduction

The cervix is the lower, narrow end of the uterus (the hollow, pear-shaped organ where a foetus can grow). The cervix leads from the uterus to the vagina (birth canal) below. The cervix is sometimes referred to as the *uterine cervix*. The part of the cervix closest to the body of the uterus is called the *endocervix*. The part next to the vagina is the *exocervix*.



[Picture credit: Female Reproductive System]

Worldwide, cervical cancer counts among the top five (5) female cancers in the world (Globocan statistics 2018). It is much less common in developed countries like the United States of America because of the routine use of Pap smears by most women.

The top five (5) female cancers, worldwide, are:

- Breast Cancer
- Colorectal Cancer
- Lung Cancer
- Cervical Cancer
- Thyroid Cancer.

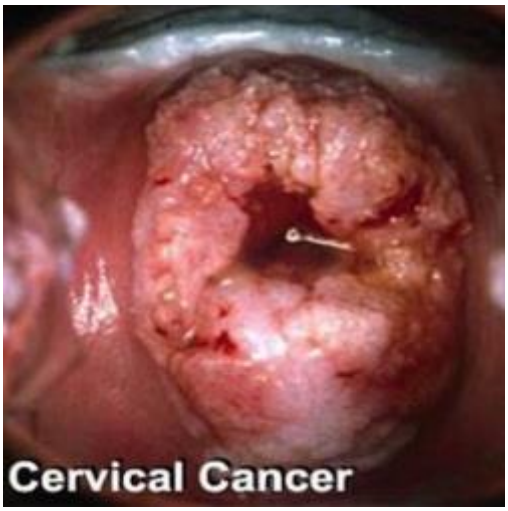
Cervical cancer tends to appear during midlife. Over half of the women diagnosed are between the ages of 35 and 55. It rarely occurs in women under 20 and only 20% of the infected women are over 65 years of age (CervicalCancer.org).

Cervical Cancer

Cervical cancer is a malignant neoplasm arising from cells originating in the cervix. Cervical cancer is a disease in which cells in the cervix become malignant (cancerous). The two main types of cells covering the cervix are *squamous cells* (on the *exocervix*) and *glandular cells* (on the *endocervix*). The

place where these two cell types meet is called the *transformation zone*. Most cancers start in the transformation zone of the cervix.

[Picture Credit: Cervical Cancer]



Cervical cancer is usually a slow-growing cancer that may not have immediate symptoms but can be found with regular Pap smear tests (a procedure in which cells are scraped from the cervix and looked at under a microscope). Cervical cancer is almost always caused by Human Papillomavirus (HPV) infection.

Cervical cancer starts as a pre-cancerous condition called dysplasia. This pre-cancerous condition can be detected by a Pap smear and is 100% treatable. That is why it is so important for women to get regular Pap smears done. Most women who are diagnosed with cervical cancer today have not had regular Pap smears or they have not followed up on abnormal Pap smear results.

Undetected pre-cancerous changes can develop into cervical cancer. From there is can spread to the bladder, intestines, lungs, and liver. It can take several years for pre-cancerous changes to turn into cervical cancer. Patients usually start experiencing problems when the cancer is already advanced and has spread.

Tumour Grade and Tumour Stage

Tumour grade and stage are terms used to describe the severity of a tumour, while tumour grade describes the appearance of cancerous cells in the tissue by examining them under a microscope.

Tumour stage encompasses:

- The location of the tumour.
- The size and/or extent of the original tumour.
- Whether cancer cells have spread to lymph nodes or anywhere else in the body.
- The number of tumours present.

Doctors use tumour grade, cancer stage, and a patient's age and general health to decide the course of treatment for the patient and determine prognosis. Prognosis describes all factors including the disease course, cure rate, chances of survival, and risk of recurrence of cancer.

<u>What are the cancer stages?</u>

Different systems of cancer staging are used to describe the types of cancer. Below is a common method in which stages are ranged from 0 to IV.

- Stage 0: The tumour is confined to its place of origin (in situ) and has not spread to nearby tissue.
- Stage I: The tumour is located only in the original organ, is small, and has not spread.
- Stage II: The size of the tumour is large but has not spread.

- Stage III: The tumour has become larger and may have spread to surrounding tissues and/or lymph nodes.
- Stage IV: The tumour has spread to other distant organs of the body, which is known as the metastasis stage.

TNM staging

Another common staging method used for cancer is the TNM system, which stands for tumour, node (which means spread of the tumour to lymph nodes), and metastasis. When a patient's cancer is staged using the TNM system, a number will be present along with the letter. This number signifies the extent of the disease in each category - tumour, node, and metastases.

Another system of cancer staging divides cancer into five stages, which include:

- In situ: Abnormal cells are present but have not spread to nearby tissue.
- Localized: Cancer is located only in the original organ and shows no sign of its spread.
- Regional: Cancer has spread to nearby lymph nodes, tissues, or organs.
- Distant: Cancer has spread to distant parts of the body.
- Unknown: The stage cannot be figured out due to a lack of enough information.

What are the cancer grades?

Cancer grades are based on examination of the suspected tissue sample under a microscope. This involves surgically removing a piece of the suspected cancerous tissue and sending it to the lab for analysis. The entire procedure is known as a biopsy.

A doctor who specializes in diagnostic tests (pathologist) examines the cells of the tissue and determines whether they are harmless (benign or noncancerous) or harmful (malignant or cancerous). They describe the microscopic appearance of the cells and assign a numerical "grade" to most cancers.

Generally, a lower grade indicates slow-growing cancer and a higher grade indicates fast-growing cancer.

The most commonly used grading system is as follows:

- Grade I: Cancer cells that look like normal cells but are not growing rapidly.
- Grade II: Cancer cells that don't look like normal cells with their growth being faster than normal cells.
- Grade III: Cancer cells that look abnormal and have the potential to grow rapidly or spread more aggressively.

Sometimes, the following system can be used:

- GX: Grade cannot be assessed (undetermined grade)
- G1: Well-differentiated (low grade)
- G2: Moderately differentiated (intermediate grade)
- G3: Poorly differentiated (high grade)
- G4: Undifferentiated (high grade)

Incidence of Cervical Cancer in South Africa

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

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	6 600	1:40	15,85%
Asian females	75	1:113	5,82%
Black females	5 641	1:33	30,29%
Coloured females	395	1:73	8,64%
White females	489	1:69	2,89%

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

Group - Females 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 females	10	149	1 162	1 087	1 619	1 026	513	234
Asian females	0	2	13	19	22	15	3	1
Black females	9	129	985	1 609	1 355	895	445	214
Coloured females	1	9	72	108	115	51	32	7
White females	0	9	92	151	127	65	33	12

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.

According to **Bruni, *et al*.,** (2019), the burden of cervical cancer for South Africa for 2018 is estimated as:

- Annual number of cervical cancer cases 12 983
- Annual number of cervical cancer deaths 5 595

Causes of Cervical Cancer

Almost all cervical cancers are caused by the Human Papilloma Virus (HPV). HPV is a common virus that is spread through skin-to-skin contact, body fluids and sexual intercourse. There are many different types of HPV. Some strains lead to cervical cancer. Other strains may cause genital warts, while others do not cause any problems at all.

Human Papillomavirus (HPV) is the most common sexually transmitted infection in the world. More than 100 HPV types have been identified, over 40 of which can infect the genital area. HPV types are classified by their association with cancer:

Non-oncogenic (low-risk HPV) – such as HPV 6 and HPV 11
It can cause:

- Benign or low-grade abnormalities of cervical cells
- Anogenital warts
- Recurrent Respiratory Papillomatosis – a disease of the respiratory tract

Ongonenic (high-risk HPV) – such as HPV 16 and HPV 18

It can cause:

- Intraepithelial neoplasia of the anogenital region
- Cervical cancer
- Vulva cancer
- Vaginal cancer
- Penile cancer
- Anal cancer
- Oropharyngeal cancers

Cervical cancer counts among the top five (5) cancers in women worldwide, with about 500 000 new cases and 250 000 deaths each year, according to the World Health Organization (WHO). Virtually all cases are linked to genital infection with HPV, the most common viral infection of the reproductive tract.

The top five (5) cancers are (Globocan 2018 statistics):

- Breast Cancer
- Colorectal Cancer
- Lung Cancer
- Cervical Cancer
- Thyroid Cancer

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 warts 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

CANSA's Position:

CANSA:

- is in favour of vaccinating all prepubescent girls against HPV
- commends and requests the South African Government, National Department of Health, and National Department of Basic Education to continue the HPV vaccination programme started in 2014 whereby every girl in Grade 4 (9 years) to be vaccinated against HPV at no cost
- CANSA further recommends that the HPV vaccination programme be extended to also include prepubescent boys

Signs and Symptoms of Common Gynaecologic Problems

Early on, cervical cancer may not cause signs and symptoms. Advanced cervical cancer may cause bleeding or discharge from the vagina that is not normal, such as bleeding after sex. If any of these signs are present, a medical doctor should be consulted. The cause may be something other than cancer, but the only way to know is to consult a medical doctor.

Gynaecologic Cancer Symptoms

Symptom	Cervical Cancer	Ovarian Cancer	Uterine Cancer	Vaginal Cancer	Vulva Cancer
Abnormal vaginal bleeding or discharge	▪	▪	▪	▪	
Pelvic pain or pressure		▪	▪		
Abdominal or back pain		▪			
Bloating		▪			
Having to pass urine often		▪		▪	
Itching or burning of the vulva					▪
Changes in vulva colour or skin such as a rash, sores or warts					▪

(Centers for Disease Control and Prevention)

Risk Factors for Cervical Cancer
Even though HPV infection is the major cause of cervical cancer, several risk factors are linked to the development of cervical cancer.

Risk factors for cervical cancer include:
- Having sex at an early age
- Having many sexual partners
- Having first sexual intercourse at a young age
- Smoking tobacco products
- Using oral contraceptives
- Having a weakened immune system
- Poor economic status (may not be able to afford regular Pap smears or have limited access to screening services)
- Sexual partners who have multiple partners or who participate in high-risk sexual activity
- parity – HPV is less common among women with decreased parity
- women who smoke are more susceptible to cervical cancer than women who do not smoke
- failure to always use barrier methods during sexual intercourse, and
- ineffective management and treatment of sexually transmitted infections (STI's)
- Women whose mothers took the drug DES (diethylstilbestrol) during pregnancy in the early 1960's to prevent miscarriage

Staples, J.N. & Duska, L.R. 2019.
"The Pap smear is the only proven screening intervention in the field of gynecologic oncology. Women should receive treatment for precancerous conditions of the cervix, vulva, vagina, and endometrial lining. Women with inherited conditions should consider having a risk-reducing surgery once they have finished childbearing. The human papilloma virus vaccination should be offered to all girls and boys aged 11 to 12 years, and can also be given as early as age 9 and through 26 years of age."

CANSA supports:

- all efforts to assist women to quit smoking or preferably never to start smoking
- promotion of the use of barrier methods during intercourse to prevent the spread of HPV and other sexually transmitted infections (STI's) including HIV
- the promotion of the postponement of sexual activity to older age
- the effective management and treatment of sexually transmitted infections (STI's) and
- decreasing parity.

Types of Cervical Cancer
There are two main types of cervical cancer: squamous cell carcinoma and adenocarcinoma. Each one is distinguished by the appearance of cells under a microscope.

- Squamous cell carcinomas begin in the thin, flat cells that line the bottom of the cervix. This type of cervical cancer accounts for 80 to 90 percent of cervical cancers.

- Adenocarcinomas develop in the glandular cells that line the upper portion of the cervix. These cancers make up 10 to 20 percent of cervical cancers.

Sometimes, both types of cells are involved in cervical cancer. Other types of cancer can develop in the cervix, but these are rare.

- Metastatic cervical cancer is cancer that has spread to other parts of the body.

Referral Criteria
For any primary health care service to operate effectively a referral system needs to be in place.

The referral system must make provision for:
- Clients with a normal Pap smear to be informed of their next Pap smear date
- Any client with a microscopically suspicious lesion, whatever the cytological result, should be referred for colposcopy

CANSA's Position:
CANSA supports the above referral criteria.

CANSA has an organised cervical screening programme that services many women in rural and previously disadvantaged areas in South Africa. This service is offered using mobile health clinics manned by professional nurses. They work in close collaboration with the National Department of Health (NDoH), National Health Laboratory Services (NHLS) and private laboratories on agreement.

Staging of Cervical Cancer
A very important factor in determining the prognosis (outcome) of cervical cancer is how early the cancer is detected to determine how far it has spread.

The various stages of cervical cancer also affect the chance of recovery or prognosis of the patient.

Cervical Cancer Survival Rates
There are many different factors that affect the prognosis (outlook) of cervical cancer including the stage of the cancer, the age of the patient, and general health of the patient.

Signs and Symptoms of Cervical Cancer
Early signs and symptoms of cervical cancer

In women who receive regular Pap screening, the first finding of the disease is usually an abnormal Pap test result.

Early symptoms that may occur can include
- Abnormal vaginal bleeding between periods, after intercourse, or after menopause

- Any bleeding after menopause
- Continuous vaginal discharge, which may be pale, watery, pink, brown, bloody or foul-smelling
- Periods becoming heavier and lasting longer than usual

Signs and symptoms of progressed cervical cancer
Some of the common symptoms observed during the later stages of cervical cancer are:

- Vaginal bleeding after sexual intercourse
- Pelvic pain
- Pain during sexual intercourse
- Offensive vaginal discharge may occur (pink, pale, brown, blood streaked, and foul-smelling)
- Abnormal bleeding between menstrual periods
- Heavy bleeding during menstrual period
- Increased urinary frequency
- Bleeding after menopause
- Painful urination
- Pelvic pain that is not related to the normal menstrual cycle
- Low back pain
- Leg pain
- Single swollen leg
- Bone fractures
- Weight loss
- Urethritis or urinary infection can be a sign of cervical cancer

Diagnosis of Cervical Cancer
The following procedures may be used:

Pap smear – This is a procedure whereby cells from the surface of the cervix are collected. The cells are viewed under a microscope, after staining, to find out if the cells are abnormal. This procedure is also called a Pap test. It is short for Papanicolaou (1947) with reference to George Nicholas Papanicolaou (1883-1962), a Greek-born United States anatomist who developed the technique of staining and examining collected cells to test for cervical cancer.

Er Güneri, S. & Şen, S. 2020.
Background: Abnormal Pap smear result means there have been cell changes on the cervix but are not cancer. Women with abnormal test result may be affected from this situation. What do women with abnormal Pap smear results experience from a biopsychosocial perspective?
Objective: This study aimed to explore the experiences of women with abnormal Pap smear results according to the biopsychosocial model.
Methods: This phenomenological study's data were collected in interviews with 12 women who had abnormal Pap smear test results. Data collection tool consists of two parts that are an "Women's Information Form (WIF)" identifying women and semi-structured "Interview Form". Interviews were done face-to-face by using in-depth interviews technique. Semi-structured interview was recorded in audio recording device. Thematic approach was used to assess the data.
Results: The average age of the women was 42.5 ± 3.64, their age at first sexual intercourse was 23.0 ± 2.8 years and all of them were legally married. Five main themes were determined, which were

grouped under the Biopsychosocial Model Domains. The Biological Domain themes were Perception of Health and Disease, and Cervical Cancer Risk Factors; the Psychological Domain themes were Positive Feelings and Negative Feelings; the Social Domain theme was Continuing Social Life.
Conclusions: It was concluded that the cultural beliefs, perceptions, emotions and practices of women with abnormal Pap smear results should be considered in the diagnostic and treatment processes. These characteristics of women's experience are also important to consider when developing strategies to address barriers to effective cervical screening, diagnosis and treatment.

Human Papillomavirus (HPV) Test – A laboratory test used to check DNA for certain types of HPV infection. Cells are collected from the cervix and checked to find out if an infection is caused by a type of HPV that is linked to cervical cancer. It is also called the HPV DNA Test.

Bhatla, N. & Sghal, S. 2020.
"Cytology-based cervical screening had unequivocal success in reducing the incidence and mortality of cervical cancer in the last century. The recognition of the role of human papillomavirus (HPV) as a necessary cause of cervical cancer led to the development of HPV testing. Gradually, there has been a shift from reflex HPV testing for mild cytological abnormalities, to co-testing with cytology and HPV, and lately to primary HPV screening, based on evidence from well-designed large randomized controlled trials and meta-analyses. Advantages of primary HPV screening include higher sensitivity to detect pre-neoplastic lesions, better re-assurance with a negative test, and safe prolongation of screening intervals. However, clinicians and policy makers must ensure the availability of clinically validated HPV assays and triage protocols of screen positive cases prior to implementation of primary HPV screening. This is likely to reduce potential harm from over-treatment as well as extra burden on the health care system."

Mayer, P.J. & Poliak, M. 2020.
Background: Cytology-based screening has been a cornerstone of cervical cancer prevention for decades. Following extensive evidence demonstrating higher sensitivity and accuracy, lower variability and better reproducibility of human papillomavirus (HPV)-based screening compared with conventional or liquid-based cytology, recent European guidelines strongly recommend primary HPV-based screening over standard cytology-based screening. In addition, HPV-based screening offers the possibility of self-sampling and makes possible longer screening intervals in women with negative screening results.
Objectives: We summarize the current status of implementation of HPV-based screening in Europe, describe the real-life experience and challenges from countries already performing HPV-based screening, and briefly review immediate and long-term plans for screening implementation in selected European countries.
Sources: Data were obtained from peer-reviewed literature, personal communication with experts and authorities involved in formulating national recommendations and practical guidelines, and relevant national websites.
Content: As of July 2019, the Netherlands and Turkey are the only European countries with fully implemented national HPV-based cervical cancer screening. Italy, Sweden and Finland have already implemented HPV-based screening in several regions, and several other countries are at various stages of implementation. Some countries are considering transitioning from cytology-based to HPV-based screening, but are struggling with the suboptimal performance of current population-based programmes. Implementation of HPV-based screening has resulted in higher colposcopy referral rates, but also higher detection rates of CIN3+ lesions and cervical cancers requiring immediate

treatment. Cytology is mostly used as a triage test, although other strategies are under consideration in some countries.
Implications: HPV-based screening is best suited in organized population-based screening settings. In 2019, cervical cancer screening policies across Europe vary greatly. Experience in countries with national and regional HPV-based screening already implemented is generally very positive. Urgent action is needed in many European countries, especially those with suboptimal opportunistic cytology-based cervical cancer screening.

The cobas® HPV Test - is the only clinically validated, FDA-approved assay that simultaneously provides pooled results on high-risk genotypes and individual results on the highest-risk genotypes, HPV 16 and HPV 18. This test is a qualitative *in vitro* test for the detection of Human Papillomavirus (HPV) in patient specimens. The test utilises amplification of target DNA by the Polymerase Chain Reaction (PCR) and nucleic acid hybridisation for the detection of 14 high-risk (HR) HPV types in a single analysis.

The test specifically identifies (types) HPV 16 and HPV 18 while concurrently detecting the rest of the high risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) at clinically relevant infection levels. Specimens are limited to cervical cells collected in cobas® PCR Cell Collection Media (Roche Molecular Systems, Inc.), PreservCyt® Solution (Cytyc Corp.) and SurePath® Preservative Fluid (not approved in the US) (BD Diagnostics-TriPath).

Li, T., Wu, Z., Jiang, M., Zhao, Y., Yu, L., Qin, Y., Liu, B., Cui, J., Li, L., Pan, Q., Zhang, X., Liu, D., Chen, F., Qiao, Y. & Chen, W. 2020.
Objective: The Roche Cobas (Cobas) and BD Onclarity (Onclarity) human papillomavirus (HPV) assays are convenient, PCR-based, HPV DNA tests; currently, data on performance of Onclarity in Chinese women is limited. We aimed to evaluate the clinical performance of Onclarity for detecting cervical lesions in Chinese women.
Methods: In total, 1122 women were enrolled into this study. Exfoliated cervical cells were collected in PreservCyt medium and were tested using Cobas and Onclarity. Cytology and histology were interpreted by senior cytologists and a panel of pathologists, respectively, at Cancer Hospital, Chinese Academy of Medical Sciences.
Results: The assays showed excellent concordance for HPV16 (kappa = 0.91, 95% CI: 0.85-0.97) and for 12 other high-risk types (HPV31/33/35/39/45/51/52/56/58/59/66/68, kappa = 0.84, 95% CI: 0.78-0.90), and very good concordance for HPV18 (kappa = 0.75, 95% CI: 0.69-0.81). No difference for ≥CIN2 sensitivity was observed between Onclarity and Cobas (both 90.5%); and the <CIN2 specificity for detection was similar between Onclarity (84.2%, 95% CI: 81.6-86.4) and Cobas (80.4%, 95% CI: 77.6-82.8). When combined with cytology triage, the colposcopy referral rate point estimate was slightly lower for Onclarity (9.0%) than for Cobas (11.0%), with the same ≥CIN2 sensitivity of 75.0% (95% CI: 53.1-88.8) for Onclarity and Cobas.
Conclusions: Onclarity exhibited comparable screening performance and triage efficiency compared to Cobas in detection of cervical lesions in Chinese women.

Colposcopy – A procedure in which a colposcope (a lighted, magnifying instrument) is used to check the vagina and cervix for abnormal areas.

Schulmeyer, C.E., Stübs, F., Gass, P., Renner, S.K., Hartmann, A., Strehl, J., Mehlhorn, G., Geppert, C., Adler, W., Beckmann, M.W. & Koch, M.C. 2020.

Purpose: The current cervical cancer screening program in Germany recommends that the results showing suspected HPV infection should be further examined in specialized colposcopy units. This study aimed to correlate externally documented Pap smear results with in-house colposcopy-guided Pap cytology results and compare colposcopy-guided biopsy and postoperative histopathology results.
Methods: Clinical data were analyzed from 3627 examinations in 2844 patients who visited a university certified dysplasia unit from 2014 to 2017; 2212 patients underwent complete assessments, including Pap smear, colposcopy, HPV testing, colposcopy-guided biopsy, and/or surgery. The results were analyzed descriptively.
Results: External and in-house Pap results were consistent in 1054 ofthe 2212 patients (47.65%). Referral cytology showed a higher grade than in-house in 456 (20.61%) and a lower grade in 702 (31.74%). Using the histopathological findings as the gold standard, overdiagnosis in the referral cytology was noted in 180 patients (13.19%), underdiagnosis in 263 (19.27%), and concordant findings in 922 (67.55%). For in-house cytology, overdiagnosis was found in 133 patients (10.74%), underdiagnosis in 192 (15.51%), and accurate diagnosis with congruent cytology and histopathology findings in 913 (73.75%).
Conclusions: The rate of detection of cervical abnormalities differs significantly depending on whether the examination is performed routinely or in specialized units. Colposcopy-guided Pap smears correlate significantly better with histology than referral cytology results without colposcopic guidance. More severe lesions were also detected more accurately.
Keywords: Cervical cancer screening; Cervical intraepithelial neoplasia (CIN); Dysplasia; High-grade squamous intraepithelial lesion (HSIL); Low-grade squamous intraepithelial lesion (LSIL); Pap smear; Precancerous lesions of the cervix.

Biopsy – A sample of tissue is cut from the cervix and viewed under a microscope by a pathologist to check for signs of cancer, often referred to as *cone biopsy*.

Mascilini, F., Quagliozzi, L., Moro, F., Moruzzi, M.C., De Blasis, I., Paris, V., Scambia, G., Fagotti, A. & Testa, A.C. 2020.

Background: Ultrasound-guided biopsy is an easy technique for obtaining tissue samples. It is commonly used for different types of tumors, such as breast and prostate cancers, in order to plan early and adequate treatment.
Objective: To evaluate the indications, adequacy, and safety of transvaginal ultrasound-guided biopsy in women with pelvic lesions suspected of gynecologic malignancy.
Methods: A retrospective study including all patients who had undergone transvaginal ultrasound-guided biopsy between April 2015 and May 2018 was carried out at the division of gynecologic oncology. Inclusion criteria were the presence at imaging of abdominal or pelvic tumors in patients considered not ideal candidates for primary gynecological surgery, or the origin and/or nature of the tumor was unclear and further management required histological verification. Patients with planned surgery were excluded from the study. Transvaginal biopsies were performed with a 18 G/25 cm core-cut biopsy needle and histology was obtained. Tru-cut biopsies were performed using an automatic bioptic gun with a 18 G/25 cm core-cut biopsy needle. Results are presented as absolute frequency (percentage) for nominal variables and as median (range) for continuous variables.
Results: A total of 62 women were analyzed. An adequate sample for histological analysis was obtained in all cases. Histopathological examinations showed 24 (38.7%) benign lesions (fibrosis, inflammation, uterine or ovarian myoma) and 38 (61.3%) malignant tumors, distributed as follows: 34 (89.5%) malignant gynecological lesions and 4 (10.5%) non-gynecological malignant tumors. Among the malignant lesions, there were 12/38 (31.6%) primary tumors, 24/38 (63.2%) recurrent

tumors, and 2/38 (5.3%) metastases from non-genital cancer. Ten patients eventually underwent surgery. Final histology was not in agreement with the results from transvaginal ultrasound-guided biopsy in 2 of 10 patients (20%); in particular, benign disease at transvaginal ultrasound-guided biopsy was malignant at final histology (two cases of recurrence of cervical cancer). Three patients (4.8%) had pain during the procedure, which was controlled by oral analgesic therapy and lasted for no longer than 10 min. No major complications were registered.
Conclusions: Transvaginal ultrasound-guided biopsy is a minimally invasive method to obtain adequate material for histological diagnosis and could avoid unnecessary surgical procedures, costly CT-guided procedures, or prolonged waiting times.

Endocervical curettage (ECC) - to examine the opening of the cervix

Zou, T., Dave, S., Adler, R.N., Manning, M.J., Scott, M.P., Strock, C., Kandil, D., Cosar, E. & Fischer, A.H. 2020.
Introduction: Colposcopic endocervical brushing cytology (CEB) is more sensitive than endocervical curettage (ECC) for detecting squamous intraepithelial lesions. There are no data on performance of CEB for detecting endocervical adenocarcinoma.
Materials and methods: A total of 151 patients were identified in a word search for "endocervical adenocarcinoma" in surgical pathology reports from January 2007 to June 2019. To measure sensitivity, reports of CEB or ECC samples within 1 year preceding the first surgical pathology diagnosis of at least endocervical adenocarcinoma in situ (AIS+) were examined. Specificity was measured in a cohort in which at least atypical glandular cells (AGC+) was reported in CEB or ECC.
Results: Seven CEB preceding diagnosis of AIS were identified: 6 of 7 were positive or suspicious for AIS+. One of 7 was negative and it was negative on re-review. Three of 6 positive CEB cases used cell blocks with immunohistochemistry. Seventy ECC samples preceding diagnosis of AIS were identified: 40 of 70 were diagnosed as AGC+. The sensitivities of CEB and ECC for detecting AIS+ at a threshold of AGC+ are 86% and 57% (too few patients for statistics), respectively. For specificity, 12 of 18 CEB and 9 of 25 ECC reports with AGC+ were false positive by follow-up surgical pathology. The specificities of CEB and ECC are 99.4% and 99.9%, respectively.
Conclusion: Sensitivity of CEB for detecting AIS+ (86%) is at least as high as ECC (57%). Specificity of CEB is similar to ECC. Addition of a cell block to CEB may be useful. CEB appears to be an appropriate test for follow-up of atypical glandular cells reported on Papanicolaou tests.
Keywords: Colposcopic endocervical brushing (CEB); Endocervical adenocarcinoma; Endocervical curettage (ECC); Endocervical sampling; Glandular.

Pelvic Examination – An examination of the vagina, cervix, uterus, fallopian tubes, ovaries, and rectum.

Million, E., Yvon, A., Oude-Engberink, A., Mares, P., Serayet, P., Pavageau, S., Clary, B. & Lognos, B. 2020.
Background: French general practitioners (GP) and gynaecologists can make use of recommendations when performing a patient's first pelvic examination. The indications and techniques for this examination are clear. The relational aspects and experience of the patients have been dealt with little.
Objectives: To analyse and understand the experience of French women during their first pelvic examination to propose practice recommendations based on their experiences.

Methods: Qualitative semi-structured interviews was conducted with 13 French women aged 18-30 years recruited from the surgery of a general practitioner using the snowball method. The data were analysed using an inductive method.
Results: The first pelvic examination was considered an indispensable rite of passage into adulthood and the life of a woman. They wanted a preparation for a consultation devoted to the first pelvic examination, with a time that is adapted to each woman. A patient-centred practitioner was more important than the pelvic examination itself.
Conclusion: Women requested for a general practitioner or a gynaecologist with a deeper understanding of a woman's experience to perform their first pelvic examination. We propose practical recommendations: the following 3 phases for the consultation: before the pelvic examination where the women and the practitioners may get to know one another; during the examination, which would involve the technical aspects and the associated procedures; and after the examination, where the patients and the practitioners review the experience and discuss prevention.

Once a woman is diagnosed with cervical cancer, the medical practitioner may order more tests to determine how far the cancer has spread. This is part of staging and may include:

- Chest X-ray
- Computed Tomography (also called Computerised Axial Tomography or CT scan)
- Cystoscopy
- Intravenous Pyelogram (IVP)
- Magnetic Resonance Imaging (MRI)

CANSA's Position Regarding Pap Smears
CANSA believes that it is ideal to have a Pap smear done 10-20 days after the start of the last period. It is not recommended to plan one's Pap smear during a period. Menstrual fluid and blood may make it difficult for the pathologist to interpret results. However, if the flow is light, some doctors will perform a Pap smear. Newer, liquid based Pap smears can separate cervical cells from mucus and blood, allowing a more accurate reading.

If a woman has started her period unexpectedly or finds that she has scheduled a Pap smear during a time when she may have her period, she should call her doctor's office. Ask to speak to a nurse or the doctor and inform them that the Pap smear will coincide with her period. It is best to reschedule an appointment.

Staples, J.N. & Duska, L.R. 2019.
"The Pap smear is the only proven screening intervention in the field of gynecologic oncology. Women should receive treatment for precancerous conditions of the cervix, vulva, vagina, and endometrial lining. Women with inherited conditions should consider having a risk-reducing surgery once they have finished childbearing. The human papilloma virus vaccination should be offered to all girls and boys aged 11 to 12 years, and can also be given as early as age 9 and through 26 years of age."

CANSA's Position:
CANSA Supports the *Cervical Cancer Prevention and Control Policy* of the National Department of Health regarding Screening Intervals for Pap Smears in the Public Health Sector:

Women in the Low Risk Target Group

- Women in the low risk target group will be offered screening three (3) times in their lifetime, assuming no abnormalities were found during screening.
- Screening will be offered first at age 30 and then at 10-year intervals (i.e. at ages 40 and 50).
- If a woman is first screened at an age older than 30, her last screen may be after age 50.
- All low risk women who are found to have an abnormality during routine screening should subsequently be screened at 3-year intervals until the screen result is negative.
- When the result is negative, the woman will return to the 10-year schedule.
- Pregnancy will not preclude screening for cervical cancer as screening can be safely performed up to 20 weeks of gestation to avoid missed opportunity.

Women who Fall into the High Risk Population or who are HIV+.

- Women who are recipients of organ transplants are considered to be at high risk.
- All women with immunosuppressive disease are also considered to be at high risk.
- All women on chronic immune suppressing treatment are also considered to be at high risk.
- Screening for HIV+ women will be done irrespective of CD4 count and antiretroviral (ARV) treatment and will be screened annually as per below.
- All HIV+ women are considered to be at high risk for cervical cancer whether they are receiving antiretroviral (ARV) treatment or not.
- All HIV+ women will be screened immediately for cervical cancer at diagnosis.
- All HIV+ women will be subsequently screened annually if the screening test is positive.
- All HIV+ women will be subsequently screened every 3 years if the screening test is negative.
- Because of the high incidence of HIV among younger women and girls, screening services will be provided routinely to younger women (i.e. younger than 30 years) from the time that HIV diagnosis is confirmed provided that the young women have previously had sex (i.e. putting them at risk of acquiring HPV).

CANSA further suggests that women avoid having anything in the vagina 24-48 hours prior to a Pap smear.

This includes:

- sexual intercourse
- spermicides, foams, or jellies
- douching
- vaginal inserts
- tampons

All of the above can make it difficult for the pathologist to accurately interpret results.

CANSA further believes that:

- every eligible woman should preferably have a Pap smear at least every 3 years
- it is better to have a Pap smear at a less-than-optimal time than not at all
- routine cervical screening is not required for women under 18 years of age, even if they are sexually active as there is no evidence to support encouraging women under 18 years of age to have a Pap smear
- all women who have ever been sexually active should start having Pap smears between the ages of 18 and 20 years, or two years after first having sexual intercourse, whichever is later
- a decision to screen a woman below the age of 18 years is at the discretion of the clinician and would depend on the individual circumstances of the patient
- Pap smears may cease at the age of 70 years for women who have had two normal Pap smears within the last five years
- Women over 70 years who have never had a Pap smear, or those who request a Pap smear, should be screened

Treatment of Cervical Cancer
Treatment of cervical cancer depends on:

- The stage of the cancer
- The size and shape of the tumour
- The woman's age and general health
- The woman's desire to have children in the future

Treatment of early-stage cervical cancer may include:
- Cervical Conisation – it involves removing a cone-shaped piece of tissue from the cervix and cervical canal. The overall size of the tissue removed will vary depending on the severity of the cancer
- Loop Electrosurgical Excision Procedure (LEEP) – use is made of a thin, low-voltage electrified wire loop to cut out abnormal tissue
- Cryosurgery – used for cervical dysplasia or abnormal cells on the cervix. If left untreated, these abnormal cells may develop into cervical cancer. Cryosurgery kills pre-cancerous and cancerous cells by freezing them
- Total hysterectomy (removal of the uterus)
- Internal Radiation Therapy (Brachytherapy)

Treatment for more advanced cervical cancer may include:
- Radical hysterectomy – where the uterus and much of the surrounding tissues,, including lymph nodes and the upper part of the vagina is removed surgically
- Pelvic exenteration – an extreme type of surgery in which all of the organs of the pelvis, including the bladder and rectum, are removed surgically

Radiation Therapy may be used to treat cancer that has spread beyond the pelvis, or cancer that has returned:

- Internal radiation therapy
- External radiation therapy

Chemotherapy
The treatment of cancer by means of cytotoxic and other drugs.

Immunotherapy
Treatment or prevention of cancer that involves the stimulation, enhancement, suppression, or desensitisation of the immune system.

Naumann, R.W. & Leath 3rd, C.A. 2020.
Purpose of review: Novel therapies are needed for the treatment of recurrent cervical cancer. The best chemotherapy regimen to date has a response rate of 48% with an overall survival of 17 months, with limited options for second-line chemotherapy. Immunotherapy can induce a strong immune response in cervical cancer due to retained viral antigens and is reviewed in this article.
Recent findings: Current clinical trials include treatment with Listeria that elicits an immune response against the E7 oncoprotein and active vaccines against the E7 oncoprotein. Although the response rates to programmed cell death 1 (PD-1) inhibition alone have been modest, the landmark survival reported in these trials suggests the activity of these agents may not be measured by RECIST criteria. The KEYNOTE-158 trial has led to the approval of pembrolizumab in recurrent programmed cell death ligand 1 (PD-L1) positive cervical cancer. Combinations of programmed cell death 1 and anticytotoxic T-lymphocyte-associated protein 4 inhibitors (CTLA4) inhibitors have shown promising and durable activity. There is active research with new combinations of checkpoint inhibitors, as well as combinations of these drugs with chemotherapy and radiation, and other novel approaches.
Summary: Immune therapy has broad activity in cervical cancer. Responses to immunotherapy can be dramatic and durable. Continued work to find the optimal combination and setting for immunotherapy is ongoing.

Therapeutic Vaccines
Utilising a patient's own immune system to fight an existing disease rather than immunising for protection against future disease.

Adoptive Cell Therapy
T cells are collected from a patient and grown in the laboratory. This increases the number of T cells that are able to kill cancer cells or fight infections. These T cells are given back to the patient to help the immune system fight disease. Also called cellular adoptive immunotherapy.

Monoclonal Antibodies
An antibody produced by a single clone of cells. Monoclonal antibodies can be made in large quantities in the laboratory and are a cornerstone of immunology. Monoclonal antibodies are increasingly coming into use as therapeutic agents.

Follow-up Treatment
Follow-up checks will continue for some years after treatment. At first follow-up checks may be conducted every few months, becoming gradually less and less frequent.

Follow-up checks may include:

- Having a physical examination by the medical practitioner
- Pap smear
- Colposcopy
- Blood tests for tumour markers
- X-rays
- CT Scan or MRI scan

Lowering the Risk for Cervical Cancer
Cancer prevention is action taken to lower the risk for getting cancer. The risk for cervical cancer can be lowered by:

- Having regular Pap smear tests – Current guidelines recommend that women should have a Pap test every 3 years beginning at age 21. These guidelines further recommend that women aged 30 to 65 should have HPV and Pap co-testing every 5 years or a Pap test alone every 3 years. Women with certain risk factors may need to have more frequent screening or to continue screening beyond age 65
- Having a Human Papilloma Virus (HPV) test - In women older than age 30, the Pap smear may be combined with a test for human papillomavirus (HPV) — a common sexually transmitted infection that can cause cervical cancer in some women
- Getting an HPV vaccine before becoming sexually active
- Not using tobacco products
- If smoking, to quit smoking
- Not having unprotected sexual intercourse
- Limiting the number of sexual partners
- Not becoming sexually active at a young age

Clark, K.T. & Trimble, C.L. 2020.
"The accumulating successes of immune-based treatments for solid tumors have prompted an explosion of cancer clinical trials testing strategies to elicit tumor-specific immune effector responses, either alone, in combination with immune checkpoint blockade, or with conventional cancer treatment modalities. However, across the board, clinical responses have been achieved in only a limited subset of cancer patients, underscoring a critical need to identify mechanisms and biomarkers of response, as well as mechanisms of resistance to therapy. Cancers caused by human papillomavirus (HPV) are driven by two viral oncoproteins, E6 and E7, both of which are functionally required for cellular transformation, thereby providing non-'self', tumor-specific antigenic targets. Immune responses that are specific for either or both of these oncoproteins can be used to follow the magnitude and kinetics of immune responses to therapeutic interventions. Moreover, identifying neoantigens is not a concern in early-stage disease - since HPV cancers are driven by HPV oncoproteins, the somatic mutational load in early disease is low, particularly in comparison to non-

HPV-related squamous cancers arising in the same organ site [1,2]. Cancers caused by HPV are a model clinical setting in which to test principles of immunotherapies, and to discover mechanisms of interactions between tumors and their attendant immune milieu. In this review, we will use examples of insights gained from studies of HPV disease to illustrate major themes of immune-based therapeutic strategies."

Lei, J., Ploner, A., Elfström, K.M., Wang, J., Roth, A., Fang, F., Sundström, K., Dillner, J. &, Sparén, P. 2020.

Background: The efficacy and effectiveness of the quadrivalent human papillomavirus (HPV) vaccine in preventing high-grade cervical lesions have been shown. However, data to inform the relationship between quadrivalent HPV vaccination and the subsequent risk of invasive cervical cancer are lacking.

Methods: We used nationwide Swedish demographic and health registers to follow an open population of 1,672,983 girls and women who were 10 to 30 years of age from 2006 through 2017. We assessed the association between HPV vaccination and the risk of invasive cervical cancer, controlling for age at follow-up, calendar year, county of residence, and parental characteristics, including education, household income, mother's country of birth, and maternal disease history.

Results: During the study period, we evaluated girls and women for cervical cancer until their 31st birthday. Cervical cancer was diagnosed in 19 women who had received the quadrivalent HPV vaccine and in 538 women who had not received the vaccine. The cumulative incidence of cervical cancer was 47 cases per 100,000 persons among women who had been vaccinated and 94 cases per 100,000 persons among those who had not been vaccinated. After adjustment for age at follow-up, the incidence rate ratio for the comparison of the vaccinated population with the unvaccinated population was 0.51 (95% confidence interval [CI], 0.32 to 0.82). After additional adjustment for other covariates, the incidence rate ratio was 0.37 (95% CI, 0.21 to 0.57). After adjustment for all covariates, the incidence rate ratio was 0.12 (95% CI, 0.00 to 0.34) among women who had been vaccinated before the age of 17 years and 0.47 (95% CI, 0.27 to 0.75) among women who had been vaccinated at the age of 17 to 30 years.

Conclusions: Among Swedish girls and women 10 to 30 years old, quadrivalent HPV vaccination was associated with a substantially reduced risk of invasive cervical cancer at the population level. (Funded by the Swedish Foundation for Strategic Research and others.).

Wang, R., Pan, W., Jin, L., Huang, W., Li, Y., Wu, D., Gao, C., Ma, D. & Liao, S. 2020.

"Cervical cancer is one of the most common cancers threatening women's health, and the persistent infection of high-risk human papillomavirus (HPV) is closely related to the pathogenesis of cervical cancer and many other cancers. The carcinogenesis is a complex process from precancerous lesion to cancer, which provides an excellent window for clinical prevention, diagnosis, and treatment. However, despite the various preventions and treatments such as HPV screening, prophylactic HPV vaccines, surgery, radiotherapy, and chemotherapy, the disease burden remains heavy worldwide. Currently, three types of prophylactic vaccines, quadrivalent HPV vaccine, bivalent HPV vaccine, and a new nonavalent HPV vaccine, are commercially available. Although these vaccines are effective in protecting against 90% of HPV infection, they provide limited benefits to eliminate pre-existing infections. Therefore, new progress has been made in the development of therapeutic vaccines. Therapeutic vaccines differ from prophylactic vaccines in that they aim to stimulate cell-mediated immunity and kill the infected cells rather than neutralizing antibodies. This review aims at systematically covering the progress, current status and future prospects of various vaccines in development for the prevention and treatment of HPV-associated lesions and cancers and laying foundations for the development of the new original vaccine."

Eun, T.J. & Perkins, R.B. 2020.
"The most effective strategy for cervical cancer prevention involves vaccination to prevent human papillomavirus (HPV) infections during adolescence followed by screening to detect HPV infections during adulthood. HPV vaccination before sexual debut can prevent HPV infections, precancers, and cancers. HPV vaccination of sexually active populations does not prevent cancer. Screening with HPV testing is the most effective method of detecting precancers and cancers between ages 25 and 65. Ensuring adequate screening around the age of menopause may be the key to preventing cervical cancer among elderly women. Most cervical cancers at all ages occur among unscreened or underscreened women."

Staples, J.N. & Duska, L.R. 2019.
"The Pap smear is the only proven screening intervention in the field of gynecologic oncology. Women should receive treatment for precancerous conditions of the cervix, vulva, vagina, and endometrial lining. Women with inherited conditions should consider having a risk-reducing surgery once they have finished childbearing. The human papilloma virus vaccination should be offered to all girls and boys aged 11 to 12 years, and can also be given as early as age 9 and through 26 years of age."

Individuals Often Ask Whether a "Booster" HPV Vaccine is Required

The answer is "yes" depending on the following. In a 2-dose schedule of HPV vaccine, the recommended interval is 6–12 months, and the minimum interval is 5 months between the first and second dose. If the second dose is given earlier than 5 months, a third dose should be given.

HPV Vaccine Schedule and Dosing

If an HPV vaccine is given to individuals between the ages of 9 and 14 years of age, a 2-dose schedule is advised.
If and HPV vaccine is given to individuals between the ages of 15 and 26 years of age, a 3-dose schedule is advised.
Immunogenicity studies have shown that 2 doses of HPV vaccine given to 9–14 year-old individuals at least 6 months apart provided as good or better protection than 3 doses given to older adolescents or young adults.

Current studies have followed HPV vaccinated individuals for ten years, and the results show that there is no evidence of weakened protection over time.

According to the US Centers for Disease Control and Prevention (CDC) HP Vaccine Recommendations are:

- HPV vaccine is recommended for routine vaccination at age 11 or 12 years. (Vaccination can be started at age 9.)
- ACIP also recommends vaccination for everyone through age 26 years if not adequately vaccinated previously. HPV vaccination is given as a series of either two or three doses, depending on age at initial vaccination.

- Vaccination is not recommended for everyone older than age 26 years. However, some adults ages 27 through 45 years may decide to get the HPV vaccine based on discussion with their clinician, if they did not get adequately vaccinated when they were younger. HPV vaccination of people in this age range provides less benefit, for several reasons, including that more people in this age range have already been exposed to HPV.
- For adults ages 27 through 45 years, clinicians can consider discussing HPV vaccination with people who are most likely to benefit. HPV vaccination does not need to be discussed with most adults over age 26 years.

Keep in mind that HPV vaccination prevents new HPV infections but does not treat existing HPV infections or diseases. HPV vaccine works best when given before any exposure to HPV.

Most sexually active adults have already been exposed to HPV, although not necessarily all of the HPV types targeted by vaccination. At any age, having a new sex partner is a risk factor for getting a new HPV infection. People who are in a long-term, mutually monogamous relationship are not likely to get a new HPV infection.

Cervical Cancer and HIV

There are approximately 5,7 million HIV+ people in South Africa of which 60% are women. They are at higher risk of HPV infection and persistence. Research shows that they are infected with a broader range of HPV strains. Research has also found that those who are treated with Highly Active Antiretroviral Therapy (HAART), have a longer lifespan and are at a significantly higher risk to develop cancer of the cervix.

CANSA's Position:

CANSA supports a non-discriminating approach and calls for the equal treatment of all individuals.

CANSA further supports:

- The education of health personnel concerning the importance of cervical screening;
- The training of health personnel in the correct taking of Pap smears;
- The training of professional nurses in cytology so that they can be used for the staining and screening of Pap smears;
- Ensuring that good records are kept concerning the quality and outcome of Pap smears, including a client recall system;
- Effective follow-up and referral of clients;
- Educating the community about the importance of vaccination of all girls against HPV.

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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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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