PREVENTION OF CERVICAL CANCER

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CONTENT TABLE

LIST OF ABBREVIATIONS

AGUS	Atypical glandular cells
AIDS	Acquired Immuno Deficiency Virus
ASC's	Atypical squamous cells
Ascus	Atypical Squamous cells of uncertain significance
Candida spp	All species of Candida
CIN	Cervical intra-epithelial lesion
DNA	Deoxyribonucleic Acid
HIV	Human Immuno Deficiency Virus
HPV	Human Papilloma Virus
Lletz	Large loop exicision of the transformation zone
OC	Oral contraceptive
PAP test	Cervical smear test, the Papanicolaou test
SIL	Squamous intra-epithelial lesion subdivided in LoSIL (low) and HiSIL (high)
TBS	The Bethesda System
VIA test	Visual inspection with Acetic Acid

INTRODUCTION

Worldwide, after breast cancer, cervical cancer is the second most common cancer that affects women. In 99.7% of all cases, cervical cancer results from a history of persistent infection by a 'high risk' subset of a family of viruses called human papilloma virus – or HPV. Some cancer-causing HPV types (particularly HPV-16) are also believed to cause a substantial number of other genital cancers, as well as some cancers of the mouth, throat and anus.

In Africa, which has a population of 267.9 million women aged 15 years or greater, it is estimated that 78 897 women are diagnosed with cervical cancer annually and 61 671 (78%) will die from the disease.

Lessons learned from countries that have successfully implemented mass organised screening programmes are that the cumulative reduction in cervical cancer incidence is achieved by selecting the appropriate target group for screening and by extending the coverage to 100% of targeted women. Coverage has been shown to be much more important than frequency of screening, and even by screening women infrequently, e.g. 10-yearly but with high coverage, a two-thirds reduction in cervical cancer can be anticipated.

Based on this information, the South African Health Department proposed screening women over the age of 30 years and offering asymptomatic women 3 free smears in a lifetime, 10 years apart. For women who had never been screened and who were over 50 years, one smear would be offered.

The natural history

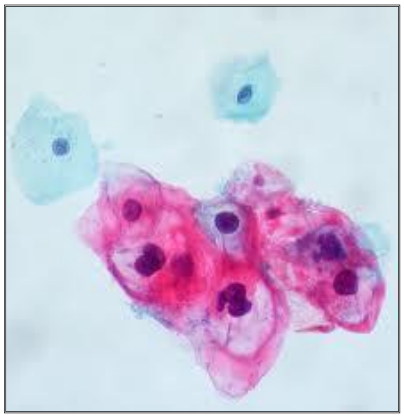
The natural history of cervical cancer has been extensively studied and there is now a substantial body of molecular, clinical and epidemiological evidence that persistent infection of the cervix with oncogenic types of human papillomavirus (HPV) is an essential event in the pathogenesis of cervical cancer. Over time, persistent infection leads to cervical cancer precursors, variously named mild, moderate or severe dysplasia, cervical intra-epithelial neoplasia (CIN) grades 1, 2 and 3 and, most recently, low- and high-grade squamous intra-epithelial lesions (SIL). Detecting cervical cancer precursors has traditionally been done through cervical cytology (papsmear) , and coupled with appropriate treatment this approach to cervical cancer prevention has reduced cervical cancer to a relatively rare disease in people where the system functions properly.

RISK FACTORS

Several risk factors increase the chances of developing cervical cancer. Women without any of these risk factors rarely develop cervical cancer. Although these risk factors increase the odds of developing cervical cancer, many women with these risks do not develop this disease.

Cervical cancer risk factors include:

Human papilloma virus infection



Abnormal smear, DNA HPV (human papilloma virus)

The most important risk factor for cervical cancer is infection by the human papilloma virus (HPV).
HPV is passed from one person to another during skin-to-skin contact and sex including vaginal intercourse, anal intercourse, and even during oral sex.

Many women become infected with HPV, but very few will ever develop cervical cancer. In most cases the body's immune system fights off the virus, and the infection goes away without any treatment. In some women the infection persists to cause cervical cancer.

HPV infections occur mainly in young women and are less common in women older than 30. Uncircumcised men are thought to be more likely to have the virus and be able to pass it on to someone else. HPV infection can be present for years without any symptoms.

Smoking

Women who smoke are about twice as likely as non-smokers to get cervical cancer. Smoking exposes the body to many cancer-causing chemicals that affect organs other than the lungs. These harmful substances are absorbed through the lungs and carried in the bloodstream throughout the body. Tobacco by-products have been found in the cervical mucus of women who smoke. Researchers believe that these substances damage the DNA of cervix cells and may contribute to the development of cervical cancer.

Immunosuppression

Human immunodeficiency virus (HIV) damages the body's immune system and places women at higher risk for HPV infections. This may explain the increased risk of cervical cancer for women with AIDS. In women with HIV, a cervical pre-cancer might develop into an invasive cancer faster than it normally would.

Chlamydia infection

Chlamydia is a relatively common kind of bacteria that can infect the reproductive system. It is spread by sexual contact. Some studies have seen a higher risk of cervical cancer in women whose blood test results show evidence of past or current Chlamydia infection compared with women who have normal test results.

Diet

Women with diets low in fruits and vegetables may be at increased risk for cervical cancer. Also overweight women are more likely to develop adenocarcinoma of the cervix.

Oral contraceptives

There is evidence that taking oral contraceptives (OCs) for a long time increases the risk of cancer of the cervix. Research suggests that the risk of cervical cancer goes up the longer a woman takes OCs, but the risk goes back down again after the OCs are stopped.
In a recent study, the risk of cervical cancer was doubled in women who took birth control pills longer than 5 years, but the risk returned to normal 10 years after they were stopped.

Multiple full-term pregnancies

Women who have had 3 or more full-term pregnancies have an increased risk of developing cervical cancer. One theory is that these women had to have had unprotected intercourse to get pregnant, so they may have had more exposure to HPV. Also, studies have pointed to hormonal changes during pregnancy as possibly making women more susceptible to HPV infection or cancer growth. Another thought is that the immune system of pregnant women might be weaker, allowing for HPV infection and cancer growth.

Young age at the first full-term pregnancy

Women who were younger than 17 years when they had their first full-term pregnancy are almost 2 times more likely to get cervical cancer later in life than women who waited to get pregnant until they were 25 years or older.

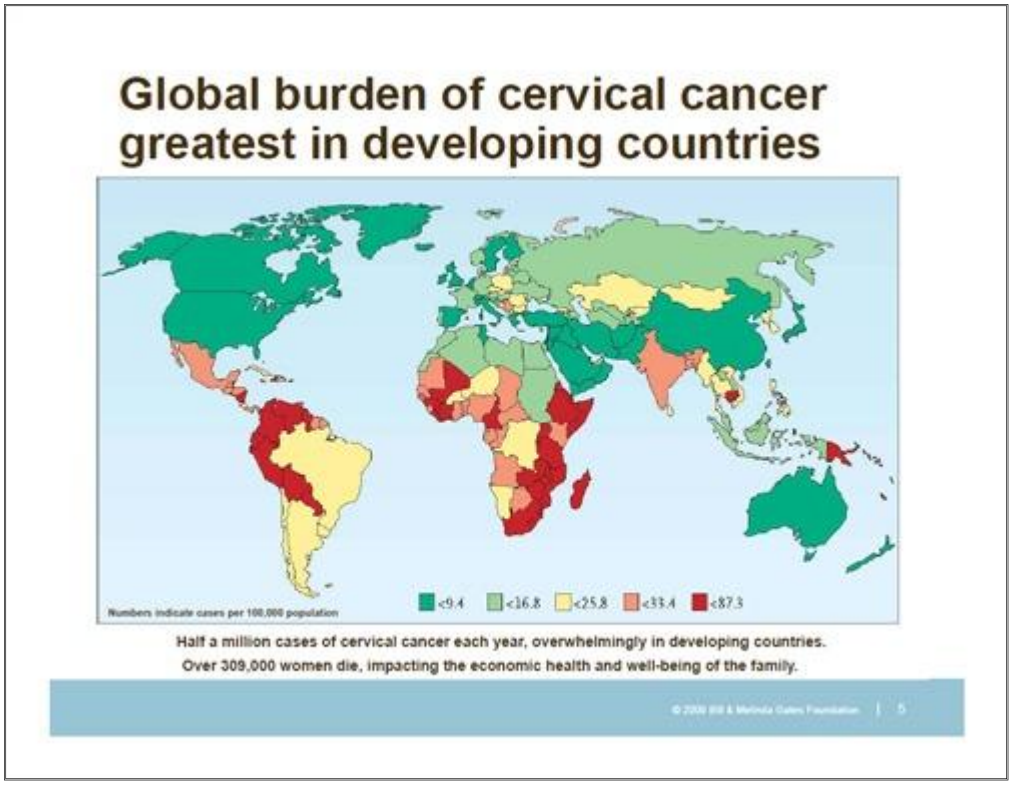
Family history of cervical cancer

Cervical cancer may run in some families. Some researchers suspect that some instances of this familial tendency are caused by an inherited condition that makes some women less able to fight off HPV infection than others. In other instances, women from the same family as a patient already diagnosed may be more likely to have one or more of the other non-genetic risk factors previously described in this section.

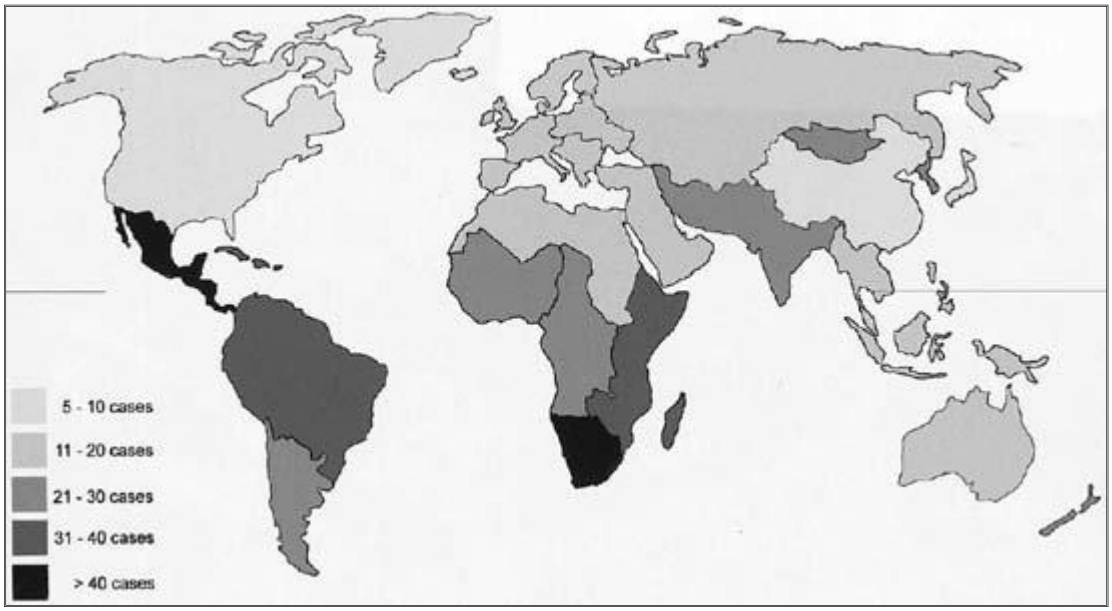
Poverty

Poverty is also a risk factor for cervical cancer. Many women with low incomes do not have ready access to adequate health care services, including Pap tests. This means they may not get screened or treated for cervical pre-cancers.

INCIDENCE OF CERVICAL CANCER



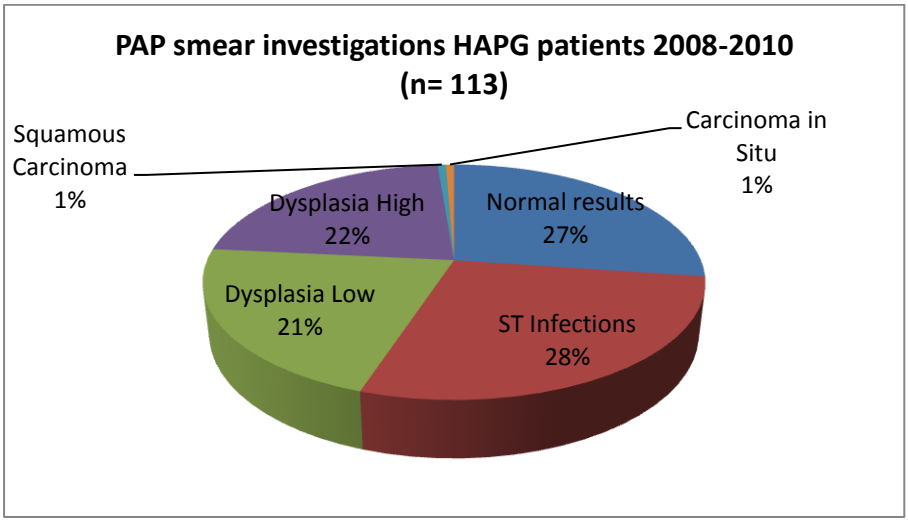
These countries have generally the lowest access to laboratory infrastructure where cytology tests can be performed.



- Fig. 1. Incidence of invasive cervical cancer in different countries around the world. (Adapted from information from the International Agency for Research on Cancer, Lyons, France.) - 2009

OUTCOMES OF INVESTIGATIONS DONE AMONG HIV PATIENTS IN HAPG, 2008 - 2010.

Investigations done between 2008 and 2010 in HIV patients in the HIV/AIDS Prevention Group gave the following outcomes:



Graph 1 – all HIV patients tested

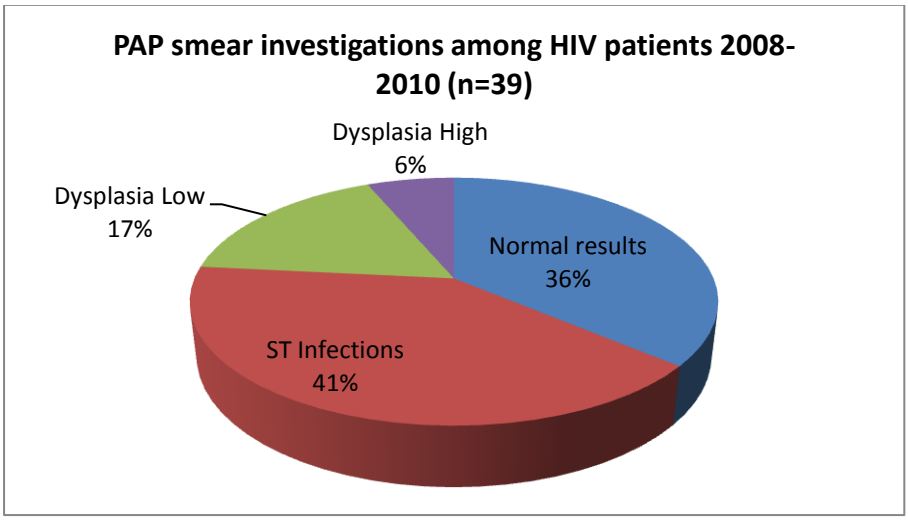
Results: PAP smear investigations among 113 HIV patients revealed that 27 % of the patients had normal results, while 28 % of the patients presented with sexually transmitted infections.

"Low dysplasia" (risk indicator) was found among 21 % of the population. "High dysplasia" amounted to 22%.

Squamous carcinoma and Carcinoma in situ has been identified in 1 % of the patients respectively.

Lletz was done for 34 patients.

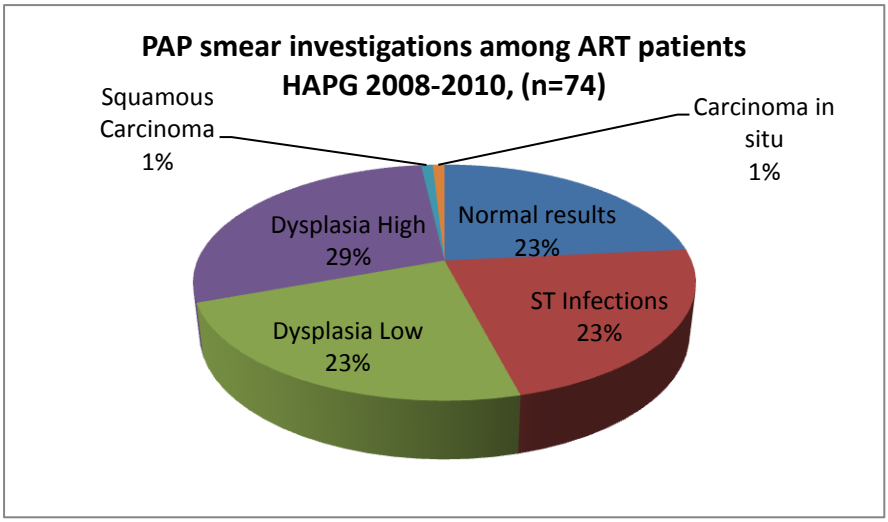
A breakdown among HIV patients with higher CD4's (not yet on ART) gave the following picture:



Graph 2 – Patients with higher CD4's

Results: Normal results were found in 36% of the patients and 41% of the patients presented with sexual transmitted infections. "Low dysplasia" was found in 17% of the patients and "high dysplasia" among 6% of the patients. Lletz was done for 2 patients.

However, the picture changes when investigating patients with lower CD4's who are already on ART:



Graph 3- ART patients with lower CD4's

Results: fewer patients are presenting with normal results (23%) as well as sexually transmitted infections (23%). In the same group of patients we found “low dysplasia” in 23 % and “high dysplasia” in 29 % of the patients.

Squamous carcinoma and Carcinoma in situ was also found in this group of patients.

These findings warrant that PAP smear investigations need to be done at regular intervals in immuno-suppressed individuals.

Lletz was done for 32 patients.

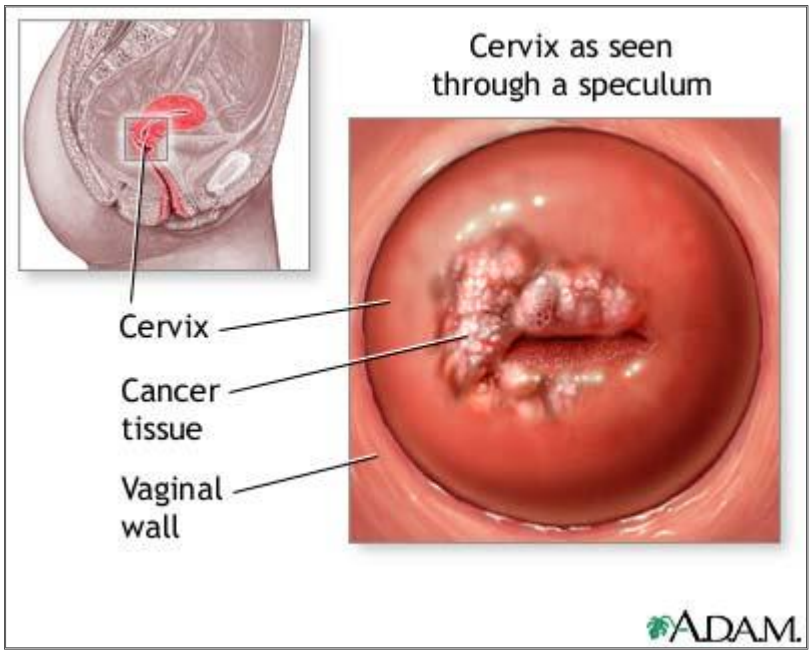
SIGNS AND SYMPTOMS OF CERVICAL CANCER

Women with early cervical cancers and pre-cancers usually have no symptoms.

Symptoms often do not begin until the cancer becomes invasive and grows into nearby tissue. When this happens, the most common symptoms are:

1. Abnormal vaginal bleeding, such as bleeding after sex (vaginal intercourse), bleeding after menopause, bleeding and spotting between periods, and having (menstrual) periods which are longer or heavier than usual. Bleeding after douching, or after a pelvic exam is a common symptom of cervical cancer but not pre-cancer.
2. An unusual discharge from the vagina -- the discharge may contain some blood and may occur between your periods or after menopause.
3. Pain during intercourse.

These signs and symptoms can also be caused by conditions other than cervical cancer. For example, infections can cause pain or bleeding.



PREVENTION OF CERVICAL CANCER

Primary prevention

Primary prevention of cervical cancer implies prevention of HPV infection. Until recently, primary prevention of cervical cancer relied on abstinence, mutual monogamy of virgins or condoms (which provide at best around 70% protection against transmission). Recently, however, two vaccines against HPV have become commercially available, providing us with the first really effective means of preventing infection with HPV and, ultimately, the development of cervical cancer.

Primary prevention of pre-cancers includes:

Avoid exposure to HPV

Certain types of sexual behaviour increase a woman's risk of getting HPV infection, such as:

· having sex at an early age

· having many sexual partners

· having a partner who has had many sex partners

· having sex with uncircumcised males

Delay sex

Waiting to have sex until older age can help avoid HPV. It also helps to limit the number of sexual partners and to avoid having sex with someone who has had many other sexual partners.

Use condoms

Condoms do provide some protection (70%) against HPV, but they cannot completely protect against infection. This is because HPV can still be passed from one person to another by skin-to-skin contact with an HPV-infected area of the body that is not covered by a condom - like the skin in the genital or anal area. Still, condoms can help the body get rid of an HPV infection faster.

Don't smoke

Not smoking is another important way to reduce the risk of cervical pre-cancer and cancer.

Get vaccinated

There are some data that the immune response to vaccination against types 16 and 18 provides some cross protection against types 45 and 31, both important in the aetiology of cervical cancer, thus increasing the projected protection from vaccination to 75 - 80%.

Both vaccines are prophylactic and should be administered to individuals prior to infection. HPV is most commonly transmitted through sexual activity and is known to be the commonest sexually transmitted infection in the world. Thus the vaccine should ideally be administered to girls (and possibly boys) prior to the onset of sexual activity, which varies considerably from country to country and in different cultures. Vaccination of girls

aged 9 - 12 years of age with high coverage is most likely going to be the most clinically effective and cost-effective strategy for cervical cancer prevention.

Secondary prevention

Secondary prevention of cervical cancer relies on the detection of cervical cancer precursors, and this has historically been performed using cervical cytology or the Papanicolaou smear. Women with abnormal smears are referred for colposcopy and once the diagnosis is confirmed either colposcopically or histologically, the transformation is removed either by excision or ablation.

The VIA test

The challenges posed by cytology-based screening programmes in resource restricted environments have prompted the search for alternative, technologically more appropriate and more affordable screening methods. Visual inspection with acetic acid, known as VIA, involves examination of the cervix after the application of 3 - 5% acetic acid, using the naked eye aided by a bright light source. Cases with suspected lesions are sent for further studies.

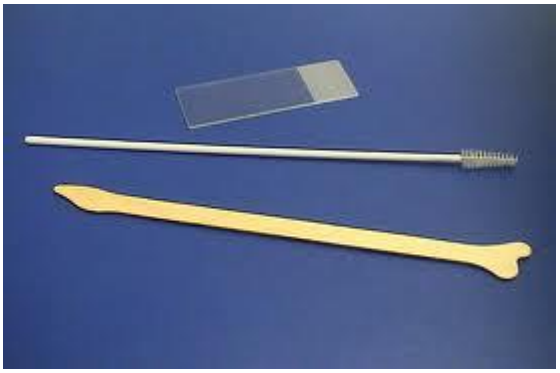
THE PAPANICOLAOU SMEAR

Dr Papanicolaou (1883-1962)

George Papanicolaou was born in Kyme, Greece in 1883. He obtained a medical degree from the University of Athens at the age of 21. Worked in Germany and France before immigrating to America where he worked at the Department of Anatomy at New York's Cornell Medical school from 1913. In 1939 the re-evaluation of the vaginal smear for cancer detection began. In 1943 his findings and conclusions were published in the famous monograph: "Diagnosis of uterine cancer by the vaginal smear." This diagnostic procedure was named the PAP test in 1954. Dr Papanicolaou died on the 18th of February 1962 of heart failure and pulmonary oedema and is buried in New Jersey

What does a Pap test involve?

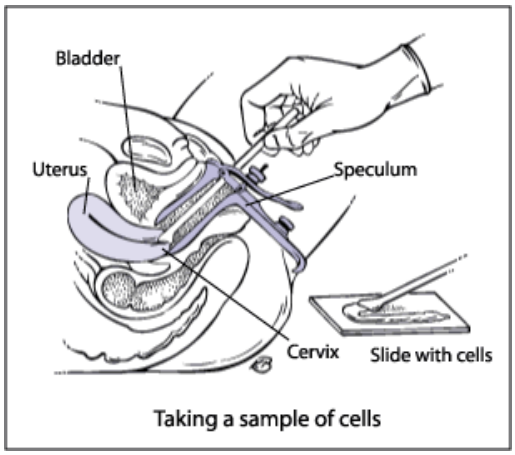
The following instruments are used to perform a pap smear:

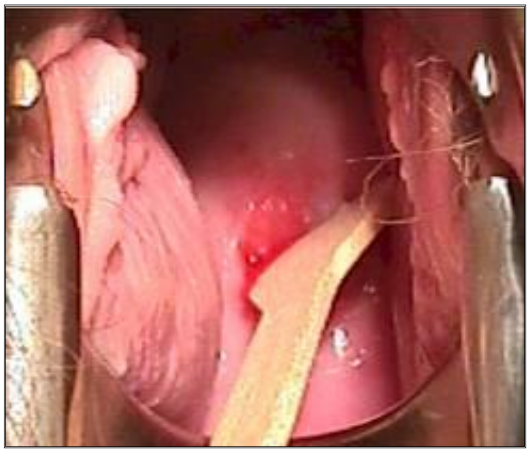


Picture 1: pap smear kit

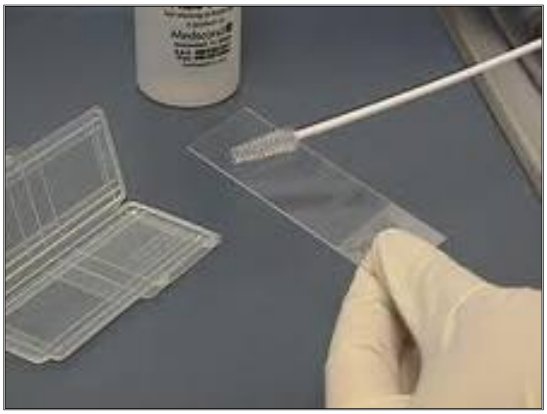
Picture 2: Vaginal specula

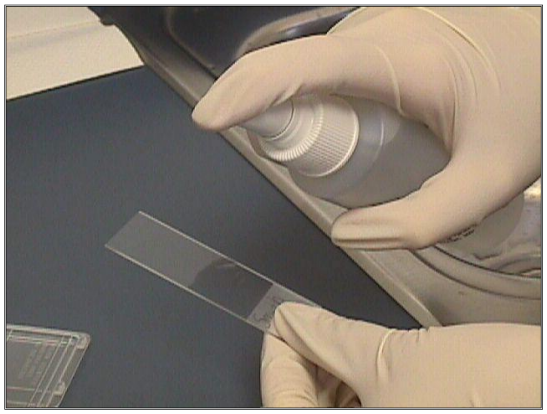
1. Performing a vaginal speculum exam during which a health care provider takes a sample of cells from a woman's cervix using a small flat spatula or brush.





2. Smearing and fixing cells onto a glass slide.





3. Sending the slide to a cytology laboratory where it is stained and examined under a microscope to determine cell classification.

4. Transmitting the results back to the provider and then to the woman.

How Pap test results are reported?

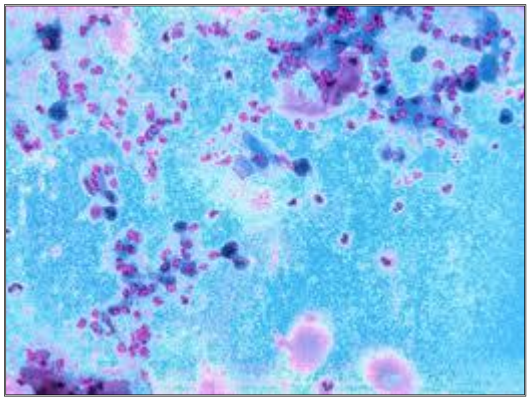
The most widely used system for describing Pap test results is The Bethesda System (TBS).

The general categories are:

- Negative for intraepithelial lesion or malignancy,
- Epithelial cell abnormalities, and
- Other malignant neoplasm's (not described in this paper)

Negative for intraepithelial lesion or malignancy

This first category means that no signs of cancer, pre-cancerous changes, or other significant abnormalities were found. Some specimens in this category appear entirely normal. Others may have findings that are unrelated to cervical cancer, such as signs of infections with yeast, herpes, or *Trichomonas vaginalis* (a microscopic parasite), for example. Some cases may also show reactive cellular changes, which is the way cervical cells respond to infection or other irritation.



Color enhanced trichomonas Protozoa PAP smear

Epithelial cell abnormalities

The second category, epithelial cell abnormalities, means that the cells of the lining layer of the cervix show changes that might be cancer or a pre-cancerous condition. This category is divided into several groups for **squamous cells** and **glandular cells**.

The epithelial cell abnormalities for **squamous cells** are called:

- Atypical squamous cells (ASCs);
- Squamous intraepithelial lesions (SILs);
- Squamous cell carcinoma

Atypical squamous cells:

This category includes atypical squamous cells of uncertain significance (ASCUS). This term is used when there are cells that look abnormal, but it is not possible to tell (by looking at the cells under a microscope) if the cause is infection or irritation, or if it is a pre-cancer. Most of the time, cells labelled ASCUS are not pre-cancer.

Squamous Intraepithelial Lesions (SILs):

These abnormalities are divided into low grade SIL and high-grade SIL.

Low-grade squamous intraepithelial lesions (LSIL) or cervical intraepithelial neoplasia (CIN) 1:
These are mild, subtle cell changes, and most go away without treatment.

High-grade squamous intraepithelial lesions (HSIL) or CIN 2 or 3:
Moderate and severe cell changes which require further testing or treatment.

Squamous cell carcinoma:

This result means that the woman is likely to have an invasive squamous cell carcinoma.
The epithelial cell abnormalities for **glandular cells** are called:

- Atypical glandular cells
- Adenocarcinoma

Atypical glandular cells (AGUS):

When the glandular cells do not look normal, but have features that do not permit a clear decision as to whether they are cancerous, they are called *atypical glandular cells*.

Adenocarcinoma:

Cancers of the glandular cells are reported as adenocarcinomas. In some cases, the pathologist examining the cells can suggest whether the adenocarcinoma started in the endocervix, in the endometrium or elsewhere in the body

MANAGEMENT OPTIONS

For women with **low-grade squamous abnormalities** (ASCUS, LSIL or CIN 1), it's recommended repeating the Pap smear test after 6 months until the abnormality resolves and a referral for colposcopy/biopsy in persistent lesions after one repeat.

HPV DNA test could be used to decide whether or not to do a colposcopy/biopsy. If a high-risk type of HPV is detected, a colposcopy/biopsy is indicated.

Women with **HSIL, AGUS or CIN 2 and 3** are referred for colposcopy/biopsy in order to remove or destroy the abnormal cells. Treatment can cure all pre-cancer and prevent true cancer from developing.

Treatment modalities include Large Loop Excision of the Transformation Zone (LLETZ), Cone excision, Ablation, Histerectomy, etc.

Cases with **Squamous cell carcinoma** and **Adenocarcinoma** are referred for histological confirmation before commencing treatment by a gynaecologic-oncologist.

RECOMMENDED MANAGEMENT PROTOCOL

Repeat smear every 10 years (every 1 to 3 years if AIDS) to the following reports:

- No malignant cells
- Doderlein Bacilli
- Reparative changes
- Squamous metaplasia
- Atrophic Smear

Repeat smear with proper technique to the following:

- Poor fixation
- No endocervical cells (No need to repeat if the same on second smear)
- Blood stained

STI treatment as per protocol and repeat smear every 10 years to the following reports:

- Trichomonas vag

- Candida SPP
- Herpes virus
- Gardnerella Vaginalis
- Bacterial infection
- Inflammatory

Repeat smear in 6 months to the following:

- HPV
- LoSIL, CIN 1 (Consider LLETZ if AIDS)
- ASCUS (May need treatment if due to infection or atrophic changes)

Refer for Colposcopy/LLETZ/Gynaecology Clinic in case of the following reports

- Dysplastic or Malignant cells
- AGUS, HiSIL, CIN 2, CIN 3 or Carcinoma In Situ
- Persistent LoSIL, ASCUS or CIN 1 after repeated smear
- Endometrial hyperplastic cells
- Endometrial cell (normal or abnormal) if above 40 years
- Cervical carcinoma/Endometrial carcinoma or malignant cells (Refer to Gynae-Oncology after biopsy histological confirmation)

Management after LLETZ (Histology result)

- HiSIL or CIN 2 - 3 adequately removed: Pap smear every 6 months (for 1 year)
- HiSIL or CIN 2 - 3 "incompletely removed": Repeat LLETZ after 3 months
- Consider Histerectomy if second LLETZ also "incompletely removed"
- Cervical carcinoma on histology report: refer to Gynaec-Oncology.

Management after Histerectomy due to HiSIL or CIN 2 - 3

Repeat Pap smear from vaginal vault after 1 year following Histerectomy, thereafter according to the program.

SA guidelines for Cervical Cancer screening programme dated 1999 are the latest guidelines available. A review of these guidelines might be essential to deliver the required management and prevention of cervical cancer in HIV positive women. **SURGICAL TREATMENT ON HIV POSITIVE WOMEN**

Treatment of HSIL, CIN 2 and 3 or AGUS is difficult because of the higher likelihood of recurrence after excisional or ablative therapy. Second or third therapeutic procedures to manage CIN 2 or 3 are often required. Hysterectomy is not advocated, as there is a 50% recurrence rate at the vaginal cuff.

In 1993, the CDC included invasive cancer of the cervix as an AIDS-defining illness. The association of HIV infection with rapid progression of cervical squamous cell carcinoma has clearly been established by several studies.

Patients with invasive cervical cancer should be treated in the same way as HIV-negative patients. If the CD4 count is low, patients should be treated with antiretroviral therapy. The prognosis appears to be worse than in non-infected women.

For Lay Health Care workers information about the above can be found from the following website:

www.power-surge.com/educate/abnormalpaps_treatments.htm

The information is for personal use only and may not be reproduced without written permission. It is advisable for any lay worker to consult this web page. (copy the URL in your browser to find the page)

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DOCUMENTATION AND LAY OUT

CECILE MANHAEVE