CANCER of the CERVIX and its PREVENTION

A FACT BOOK FOR HEALTH WORKERS
1.0 Introduction

The cervix is the lowest portion of a woman’s uterus (womb). It is located in the upper end of the vagina (Fig. 1).

Fig. 1: ANATOMY OF INTERNAL FEMALE GENITALIA

1.1 Burden of Cervical Cancer

Cervical cancer has a devastating effect on women’s health worldwide. An estimated 466,000 new cases of cervical cancer occur each year worldwide and there are 1.4 million women living with cervical cancer. The vast majority of these women are in developing countries. In developing countries, cervical cancer incidence is second only to breast cancer and it is the leading cause of female cancer deaths. Worldwide, cervical cancer takes the lives of 231,000 women annually, with over 80 percent of these deaths occurring in developing countries. These cases of invasive cervical cancer arise from approximately 7,000,000 cases of pre-cancer worldwide that could be identified through screening and treated effectively to prevent cancer (Parkin 2000; Ferlay, et al 2002).

The highest age-standardized incidence rates of cervical cancer have been reported in Asia, southern Africa, Central America, eastern Africa, and South America. In all of these regions, the rates are over 40 cases per 100,000 women. For example, a study in Zimbabwe found
an incidence rate of 54 per 100,000, the rates in Guinea were 46 per 100,000 and the rates in Uganda 45.6 per 100,000 (WHO 2006; Chonunga et al 2000; Koulibały, et al 1997). It is clear that the incidence of cervical cancer in Uganda is among the highest in the world. The incidence is rising, as the previous incidence rate for Uganda was 41.7 per 100,000 (Ferlay, et al 2002).

Cervical cancer is the most common reproductive health cancer among women in Uganda, accounting for up to 40 percent of all cancers recorded in the Kampala cancer registry, as well as for 80 percent of all female malignancies. By the time of diagnosis, up to 90 percent of cervical cancers are inoperable. Cases of cervical cancer occupy up to 30 percent of gynaecological beds at Mulago hospital and this trend is increasing; a study by PATH in April 2007 shows the bed occupancy for cervical cancer to be at 64.5 percent. In 2006, about 40 percent of all patients receiving radiotherapy had cervical cancer (Wabinga, et al 2000).

1.2 Definition of Cervical Cancer
Cervical cancer is the uncontrolled growth of abnormal cells in the cervix. The cervix has two types of cells, the columnar epithelium in the cervical canal and the squamous epithelium on the ectocervix. The abnormal cell growth begins at the junction (Squamo-columnar junction) between these two cell types. The vast majority of these cancers are squamous-cell carcinomas.

Invasive cancer means that the cancer affects the deeper tissues of the cervix and may have spread to other parts of the body. This spread is called metastasis. Cervical cancer usually spreads by direct invasion of neighboring tissues to involve the bladder, the vagina, and/or the rectum and later involve the intestines, ureters, liver, and kidneys.

1.3 Cause of Cervical Cancer
Almost all cervical cancers are caused by the human papillomavirus (HPV). HPV is a common virus that is spread through sexual intercourse. There are many different types of HPV, and many do not cause problems. However, certain strains of HPV actually lead to cervical cancer (types 16 and 18 cause over 70 percent of cervical cancer cases) and other strains may cause genital warts.

**Risk factors for HPV infection:**
- Early age at first sexual intercourse.
- Multiple sexual partners.
- Wives in polygamous unions.
- Parity.
- Smoking

1.4 Development of Cervical Cancer
The development of cervical cancer is very slow. It can take up to 20 years from infection with HPV to become cervical cancer. It starts as a precancerous condition called dysplasia. Cervical dysplasia is a term used to describe the appearance of abnormal cells on the surface
of the cervix. These changes in cervical tissue are classified as mild, moderate, or severe. While dysplasia itself does not cause health problems, it is considered to be a precancerous condition. Left untreated, dysplasia sometimes progresses to an early form of cancer known as cervical carcinoma in situ, and eventually to invasive cervical cancer (Fig. 2). Dysplasia is the earliest form of precancerous lesions recognizable by Pap smear or in a biopsy by a pathologist.

Like all cancers, cancer of the cervix is much more likely to be cured if it is detected early and treated immediately. The slow progression of cervical cancer provides opportunities for prevention, early detection, and treatment. These opportunities have caused the decline of cervical cancer over the past decades in countries with effective cervical cancer screening and treatment programs.

**1.5 Symptoms and Signs of Advanced Cervical Cancer**

Symptoms of cervical cancer tend to appear only after the cancer has reached an advanced stage, and may include:

- Irregular, intermenstrual or abnormal vaginal bleeding after sexual intercourse.
- Back, leg, and/or pelvic pain.
- Fatigue, weight loss, loss of appetite.
- Vaginal discomfort or odorous discharge which may be pale, watery, pink, brown, or bloody.
- Single swollen leg.

More severe symptoms may arise in the very advanced stages, including severe anaemia, renal failure, fistulae (rectal/vesico-vaginal), and lymphoedema.
A physical examination by a qualified medical doctor is performed to look for signs of advanced cervical cancer. Signs may include: appearance of abnormalities of the cervix with gross erosion, ulceration or fungating mass; pelvic metastasis manifested as indurations; lower limb oedema; or other tissue abnormalities extending to the vagina.

1.6 Stages of Cervical Cancer
If the woman is diagnosed with cervical cancer, the health care provider (Gynaecologist) will order more tests to determine how far the cancer has spread. This is called staging the disease. Tests used to determine the stage of cervical cancer may include (depending on the resources available in the health system):
- Examination under anaesthesia (EUA) for clinical staging.
- Cystoscopy and proctoscopy.
- Chest X-ray and CT scan.
- Intravenous pyelogram (IVP).
- Magnetic resonance imaging (MRI).

Examination under anaesthesia (EUA)
This procedure is done in theatre under anaesthesia by a gynaecologist. At this examination, the woman is put in lithotomy position and the bladder is emptied of urine using a metal catheter. This also helps to check if the bladder is involved.

Inspection of the vulva and vagina is done, then the cervix is examined after insertion of a self-retaining speculum. A biopsy is taken from any tumor tissue. The extent of tumor spread is determined by bimanual examination, and rectal involvement is determined by doing a rectal exam.

EUA can be followed by cystoscopy and proctoscopy to help rule out local invasion of the bladder and the colon (rectum), respectively.

Chest X-ray and CT Scan
A routine chest radiograph is obtained to help rule out pulmonary metastasis. A CT scan of the abdomen and pelvis is performed to look for metastasis in the liver, lymph nodes, or other organs and to help rule out extension to the ureters which would manifest as hydroureter or hydronephrosis. In patients with bulky primary tumor, barium enema studies can be used to evaluate extrinsic rectal compression from the cervix.

After the diagnosis is established, complete blood cell counts and serum chemistry for renal and hepatic functions should be ordered to look for abnormalities from possible metastatic disease. Then, a decision will be taken on whether surgery or radiotherapy will be done for the patient based on the findings of EUA, histology, and proctoscopy/cystoscopy.
1.7 Treatment

Treatment of precancerous lesions

Early cervical cancer can be cured by removing or destroying the precancerous or cancerous tissue. There are various surgical ways to do this without removing the uterus or damaging the cervix, so that a woman can still have children in the future. Women with an abnormal test are offered cryotherapy if they are eligible in the see-and-treat approach. Currently, this is the approach recommended by the Ministry of Health since it doesn’t require very highly-trained health personnel. In this approach, women with a positive visual inspection with acetic acid (VIA) test are treated at the same sitting to avoid loss to follow-up. Those with larger lesions are referred to a gynaecologist who will take a biopsy, loop electrosurgical excision procedure (LEEP), or do a cold knife cone biopsy. Women with high-grade lesions may be offered hysterectomy depending on the gynaecologist’s assessment.

Types of surgery for early pre-cancer include:
- **Cryotherapy**: freezes abnormal cells at very low temperatures and the cervix heals over a period of time and reverts to normal. This treatment can achieve cure rates for pre-cancer of up to 95 percent. Because of this, follow-up of the women is very important.
- **LEEP**: uses electricity to remove abnormal tissue and is good because tissues will be available for histology.
- **Laser therapy**: uses light to burn abnormal tissue.

Treatment of invasive Cancer

Treatment of cervical cancer depends on the stage of the cancer, the age and general health of the woman.

**Hysterectomy** (removal of the uterus but not the ovaries) is often performed for cervical cancer that has not spread. In more advanced disease, a radical hysterectomy may be performed. A radical hysterectomy removes the uterus and much of the surrounding tissues, including internal lymph nodes, and the upper part of the vagina. In the most extreme surgery, called a pelvic exenteration, all of the organs of the pelvis, including the bladder and rectum, are removed.

**Radiotherapy** may be used to treat cancer that has spread beyond the pelvis, or cancer that has recurred. This method can be a primary treatment option just like surgery. Radiotherapy is either external or internal. Internal radiotherapy uses a device filled with radioactive material, which is placed inside the woman’s vagina (intra-cavitory radiotherapy) next to the cervix. The device is removed when she goes home. External radiotherapy beams radiation from a large machine onto the body where the cancer is located. It is similar to an X-ray.

**Chemotherapy** uses drugs to kill cancer cells. Sometimes radiation and chemotherapy are used before or after surgery.
CERVICAL CANCER CAN BE PREVENTED THROUGH SCREENING

1.8 Screening for Cervical Cancer—Secondary Prevention

Cervical screening is not a test for cancer. It is a method of preventing cancer by detecting and treating early abnormalities which, if left untreated, could lead to cancer of the cervix. Special screening tests and tools are needed to detect cervical pre-cancer, often called dysplasia. Currently these include: the Papanicolaou (Pap) smear test, visual inspection with five percent acetic acid (VIA), Lugol’s iodine test (VILI), and the HPV-DNA test.

Pap Smear

The Pap smear is a technique that collects cells that are shedding off the cervix using a spatula or a brush. The cells are put on a glass slide, fixed with alcohol, processed, and read by a trained person (i.e., a cytotechnicians or pathologists).

Pap smears are the oldest method of cervical screening that have been used to screen for pre-cancers and cancer, but do not offer the final diagnosis. If abnormal changes are found, the cervix is usually examined under magnification using a colposcope. This process is called colposcopy, where the cervical glands and blood vessels are scrutinized and pieces of tissue are surgically removed (biopsy) and sent to a laboratory for histological examination. This test is done every three years beginning at age 25.

Newer low-cost technologies are now available especially for low-resource countries to screen for precancerous changes in the cervix. These tests include VIA and VILI.

VIA Test

In the VIA test a cotton swab soaked in five percent acetic acid is applied to the cervix and the result read after one minute. A positive test is shown by aceto-whitening (white patches) on the cervix (Fig. 3). This whitening occurs because the precancerous cells have increased protein in their nuclear material as a result of the abnormal growth. Normal cells do not change color; they remain pink after application of five percent acetic acid.

Fig. 3: FINDINGS ON VIA

| Normal Cervical | Cervical Pre-cancer | Extensive Tumor Mass |
VILI Test
In the VILI test the cervix turns a mustard yellow color if there is a precancerous lesion. This is because precancerous cells are devoid of glycogen and do not stain.

The VIA and VILI tests are done once every three to five years.

Once the abnormal test results are received, the patient should be referred to a gynecologist for colposcopy, biopsy, and treatment.

Other tests may be done to further evaluate the woman and these may include:
• Endocervical curettage to examine the opening of the cervix.
• Cone biopsy.

For secondary prevention, the best way to prevent cervical cancer is to provide well organised, systematic screening services to all women above 25 years in a routine manner and also ensure treatment services are available. Sexually active women should visit health facilities and request information on secondary prevention (screening) services.

1.9 HPV Vaccination—Primary Prevention

Introduction
Primary prevention aims to prevent women from acquiring HPV infection in the first instance, so there is no risk of an infection progressing to cervical cancer later in life. Since HPV is the causal agent and is sexually transmitted, lifelong sexual abstinence or vaccination prior to sexual debut are the two current primary prevention activities that offer the greatest protection against infection. Consistent and correct condom use reduces but does NOT eliminate the risk of infection with HPV. Because it is highly unlikely that most people will be able to abstain from sexual intercourse their entire lives, vaccination becomes the most practical primary prevention activity to prevent cervical cancer.

Major research has recently produced two HPV vaccines: they are the bivalent HPV-16/18 vaccine (Cervarix™) made by GlaxoSmithKline and the Quadrivalent HPV-6/11/16/18 vaccine (Gardasil®/Silgard®) made by Merck & Co. These vaccines have great potential and work well in young girls who have not been exposed to HPV and do not already have cervical pre-malignancy. Literature shows that there is no value to women who have been exposed to the virus types that the vaccine protects against or already have cervical pre-malignancy (Ferris D 2006). Consequently many women in Uganda will still remain at risk and will require screening.

Immunologic basis for vaccination
Normally, HPV infections induce strong, local, cell-mediated immunity that results in clearance of HPV-induced lesions and protects against subsequent infections with the same type of HPV virus, and this is for life based on currently available evidence.
Current HPV L1 virus like particle vaccines
Based on the current understanding of the body’s immune response to HPV viruses two vaccines have been developed using recombinant technology. The vaccines contain virus-like particles (VLPs). The VLPs are completely non-infectious and non-oncogenic. The VLPs are produced by cloning the major viral capsid genes. The recombinant proteins produced are purified and self-assembled into VLPs that look structurally similar to HPV viruses but do not contain any HPV-DNA or RNA. The VLPs are then mixed with adjuvant to produce the final vaccine product.

Results from phase I-III trials
Both vaccines are highly immunogenic (100 percent of study participants seroconverted) when administered parenterally in humans and they produce high-levels of neutralizing antibody up to 11 times above natural infection levels.

The vaccine is highly effective too. In Phase II trials, both vaccines reduced the HPV-related infection and pre-cancer by 100 percent compared to placebo recipients. The bivalent vaccine (Cervarix™) shows cross-protection against HPV 45/31 with a 55 percent reduction in infection.

The safety of these two vaccines in phase III trials has been excellent with only 0.1 percent of vaccine recipients discontinuing due to adverse experiences. The most frequently experienced problems were injection-site discomfort ranging from mild to moderate, and some fever.

HPV vaccines

- HPV vaccines are prepared from virus-like particles (VLPs) using recombinant technology.
- VLPs are non-living antigens, normally very safe.
- Both vaccines protect against oncogenic HPV-16 and -18; one also protects against HPV-6 and -11 that cause genital warts; both vaccines exhibit cross-protection against certain other oncogenic types.
- Both vaccines are highly efficacious in females unexposed to HPV-16 and/or HPV-18; not efficacious in previously infected females.
- Both vaccines provide protection for at least five years, likely much longer.

Vaccination age groups
Both HPV vaccines prevent persistent HPV infections and the development of HPV associated lesions best before the recipients become exposed to the virus. The vaccines are therefore prophylactic rather than therapeutic and are best administered prior to natural exposure to HPV infection.

The age group for HPV vaccines varies from country to country but, by and large, it is determined by a number of factors, including, average age at first sexual intercourse in that country or first exposure to HPV, HPV epidemiology. Because of the success in Universal Primary Education (UPE) in Uganda, school based vaccinations to the appropriate age group is the vaccination platform expected to achieve best coverage rates.
These two factors, age and school, ensure achieving maximum benefit to the girls and maximum coverage. The vaccine is not useful for those already exposed to the HPV type targeted by the vaccine. Women who are HPV-negative and older virgin girls could benefit from the vaccine but establishing that they are virgins, with certainty, is a big challenge at present. HPV testing is not available routinely and establishing virginity is not easy in a public-health setting.

For Uganda, initially the vaccine will be given to girls in primary five (P.5) in Ibanda District and to girls aged ten years in Nakasongola District.

**Vaccinating males: Is it worth it?**

There are no data documenting the efficacy of HPV vaccines in males regarding prevention of HPV infections in females or preventing cervical pre-cancer, although the vaccine is highly immunogenic in males. Secondly, the disease burden in males (penile, oropharyngeal, and anogenital cancers or warts) is considerably much less than the burden of cervical cancer in females.

With variations in risk, sexual behaviour, and the high vaccination coverage of females the benefits of vaccinating males is predicted to be limited for the purpose of cervical cancer prevention and may, therefore, not be cost-effective. Current computer modeling (London and Harvard Universities) suggests that it is more cost-effective to first focus resources on maximizing coverage among females, rather than both males and females. Data collected through phase 4 effectiveness studies will help answer this question.

**Vaccinating Males**

**Advantages:**

- HPV-16 and -18 cause cancers that affect men, these including penile, anal and oral cancers. These can be prevented through vaccination.
- There may be some additional indirect “herd immunity” benefit to immunizing males, since females are infected by male sexual partners.

**Disadvantages:**

- Doubles the programme cost and resource requirements.
- Magnitude of indirect protection through “herd immunity” is uncertain.

**The need for booster doses**

Currently the levels of neutralising antibodies are 11 times higher than in natural infections and for the duration of the studies (five years) they have remained high with no indication of tapering off. This suggests that boosters may not be required, although studies are ongoing and will continue surveillance over the next ten years or more to monitor antibody levels and vaccine efficacy.

HPV vaccines have been developed through high-quality research designs using the best technology currently available. The vaccines have been shown to be safe as there are only minor side effects; usually pain at the injection site. The vaccines are highly immunogenic up to 11 times the usual clinical immune response. They are effective in preventing cervical pre-cancer. According to currently available information, the immune response is uniformly high for at least five years with no evidence of antibody levels tapering off, suggesting that a booster dose later in life may not be needed.
1.10 Conclusions

- Cancer of the cervix is the leading cause of death among women in Uganda.
- Human papillomavirus (HPV) is sexually transmitted and is the underlying cause of cervical cancer.
- Cervical cancer can be prevented.
- For women already sexually active, early detection through screening using simple, effective tests, for example, VIA or VILI, can prevent cervical cancer (secondary prevention).
- For girls who are not yet having sex, vaccination with the HPV vaccine can protect girls from being infected later in life.
- HPV vaccines are safe, effective, approved by the government of Uganda, and do not make girls infertile.

1.11 References