Cervical cancer and human papillomavirus: South African guidelines for screening and testing

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South Afr J Gynaecol Oncol 2010;2(1):23-26

Introduction

Cervical carcinoma is still the most common cancer of women on the African continent. Mortality remains high – worldwide at 50% – mainly because of late presentation, advanced stage of disease and absence of a functioning screening process. The aetiological link between human papillomavirus (HPV) infection and cervical cancer has been well established and a number of high-risk HPV genotypes have been identified. HPV infection is the most common sexually transmitted infection (STI) in the world today – up to 80% of sexually active females will harbour HPV at some point in their lives. The majority of women will experience natural elimination of HPV infection because of an intact immune system. Persistent infection with a high risk type HPV puts women at high risk to develop precursors of cervical cancer or carcinoma itself. As part of a public health response to this serious problem, several HPV vaccines are under development. Use of vaccines still poses unanswered questions in many respects.

The precursors of cervical cancer can be detected and treated. The most important aspect of detection is screening of asymptomatic women. The Pap smear is generally used for this purpose. If this is used with wide coverage in a population, Pap smear screening has been shown to lead to a drastic reduction in the occurrence of cervical cancer in that population.

As more information becomes available about HPV and as tests for accurate detection of HPV have been developed, much of current discussion on cervical cancer and its precursors should centre on HPV, the role of HPV testing and the clinical use of these tests in South Africa.

Screening for cervical cancer

Objectives of screening

Screening programmes aim to reduce mortality and morbidity from cervical cancer and to decrease the number of patients suffering from cervical cancer. Through screening, the existence of precursor lesions of the cervix can be detected and managed. Basic screening programmes can lead to downstaging of cervical cancer which offers benefit for patients in its own right.

Current status of cervical screening in South Africa

The national policy on cervical screening allows for three smears in a woman's lifetime taken at 10 year intervals from 30 years of age. This policy has been implemented in some areas but not throughout the country. The National Health Laboratory Service, where cytology laboratories in the public sector are to be found, has not fully rolled out a programme to become a part of the process. Several initiatives for screening are starting or are in the planning stage: this includes initiatives from the National Department of Health, its Directorate of Maternal and Child Health and some provincial Health Departments. Over the years several proposals for screening made by academics and professional societies were rejected by policy making authorities, frequently on the basis of perceived high cost. The result is that currently there is no population-wide screening programme in South Africa. In several areas partial screening does take place. In the private sector opportunistic screening is commonly practised.

Current status of cervical screening internationally

In populations where coverage is wide enough to reach more than 70% of women, the maximum impact of decreasing the incidence of cervical cancer and cervical cancer deaths becomes apparent and reaches a plateau at 84% coverage. It is expected that the occurrence of cervical cancer can be reduced by 70% or more under such circumstances. In such programmes the frequent recall of women led to huge cost increases that in turn resulted in curtailment of the programmes in many areas. Current recommendations include that the first Pap smear should be taken at age 21 years or within three years of onset of sexual activity.

Thereafter smears should be taken annually until age 30 after which smears should be taken every three years, concluding the screening at age 65–70 years for those women who have had persistent normal smears.

In developing countries the objectives are very different. The WHO advocates one smear (at age 30–35 years) in a woman's lifetime as the least to be performed. Never having had a Pap smear remains one of the highest risk factors for the development of cervical cancer.

Obstacles and ideals

The Pap smear has a lower than expected sensitivity of only 54%. This is improved when liquid based cytology is used. Cost of a national population-based screening programme is a serious obstacle. Lack of capacity, lack of treating facilities and lack of knowledge in the patient population all prove to be huge obstacles. The HIV pandemic is a massive obstacle in several respects.

Ideals for cervical screening in South Africa include the achievement of wide enough coverage of the female population to impact on the health of the women of South Africa, the empowerment of women to expect and indeed demand proper screening programmes to be in place, and improved popular education and awareness. Better knowledge may lead to increased acceptance of screening requirements by women, including acceptance of the need for follow-up visits. The highest ideal is improved sexual health for the population. Other ways of screening should be developed and assessed to overcome the problems and impasse of the current programmes. Capacity for diagnosis and treatment must be increased.

HPV and cervical cancer

HPV are mucosotropic DNA viruses that cause most of the malignancies of the anogenital tract. More than 100 HPV genotypes can be defined of which more than 40 infect the anogenital tract.

HPV infections are the most common sexually transmitted infections today. Based on research findings of the last two decades the firm conclusion has been reached that infection with a high risk HPV genotype is regarded as the primary cause of cervical cancer. Cervical carcinogenesis involves several cofactors – not all well understood or of equal importance – including cigarette smoking, poor nutrition, folate deficiency, HIV infection, genetic predisposition and the possibility of other genital infections such as with herpes simplex virus.

Certain high risk HPV types have been identified relating strongly to cervical carcinogenesis. Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 have been linked to cervical cancer. The virulence of these types differ. Some genotypes have been identified as of intermediate risk namely 23, 53 and 66. The low risk HPV types cause genital warts but not cancer.

HPV is easily transmitted but requires entry into the basal layer of the cervical epthelium at sites of micro- or macro-trauma. Most HPV infections are transient and persistent infection with a high-risk type of HPV poses a carcinogenic risk. When the cervix is infected with HPV mild cytological abnormalities are frequently present. Persistence of high risk HPV over time contributes to occurrence of random mutations leading to cervical cancer. Once HPV is integrated into the host genome severe cytological abnormalities are found and the histological diagnosis of cervical intraepithelial neoplasia (CIN) and eventually cervical carcinoma can be expected.

The different HPV types have been shown to have different viral persistence, different potential for viral integration and also different carcinogenic potential. The proportions of viral types in cervical cancer specimens therefore do not reflect the incidence of these viruses in the population, but rather their nature. Its is known that HPV type 16 alone causes about two-thirds of all cervical cancers worldwide and it is therefore the main pathogen.

Testing for high risk HPV

New assays able to detect high risk HPV DNA have recently been approved and are available for screening and diagnostic use.

Different tests

Currently available tests will detect the most common high-risk HPV viruses present in the sample. The different tests have subtle differences regarding the viral types included in the test battery. Commercially available tests in South Africa reflect active infection of the cells with HPV but do not test for viral integration into the genome, which is the carcinogenic event. The presence of HPV is therefore accurately established but not the state of the disease process.

Test results can be reported as either positive or negative for the presence of high risk HPV. Alternatively the list of high- and intermediate risk HPV types found in the sample can be reported. The clinical significance of presence of multiple HPV types or changes in the HPV types over time is not currently known. The list of viruses-type of result does not have any clinical importance or superiority above a simple positive or negative answer but may have useful research implications.

Sampling methods

HPV DNA can be isolated from various samples. Physician sampling has been performed over years. Recently patient self-sampling was developed.

Physician sampling with cervical swab or brush or spatula has been found adequate. It is not imperative to obtain the sample from the transformation zone and a sample taken from the posterior vaginal fornix or vaginal walls is adequate. Sampling in different areas of the vagina and cervix may render different results and different HPV types can be found. The prognostic

importance and clinical impact of these differences are not currently known.

Self-collection obviates the need for speculums, examination rooms and trained personnel and will have an important impact on the cost of screening. It has been found to be more acceptable to women than traditional Pap smear testing and the expectation is that this method will improve uptake. This has to be seen as a significant potential advantage. Self-collected samples for cervical cytology markedly decrease the sensitivity of the test unless the device is left inside the vagina for 10 minutes or longer. Some tampons need to be inserted for at least an hour. Vaginal swabs tipped with Dacron can be used with ease and collection with two consecutive brushes render better results than using a single one. Self-collected samples will render good results when DNA based testing is used.

Physician sampling and patient self-sampling have been extensively tested and both have been found to produce satisfactory and comparable results. The reason for this is that PCR (polymerase chain reaction) amplification of DNA makes the test method highly sensitive.

Transporting samples

Samples can be transported dry or in an essential buffer solution, depending on the sampling method and device used. When liquid based cytology is used, the same liquid used for cytology can be used for HPV testing.

Costs

The cost elements of HPV testing include the sampling device and transport method, the laboratory and personnel costs and the cost of the test kit used for DNA extraction, PCR and costs to read and report the result. The cost elements of screening also include the cost of the facilities and personnel to do initial sample collection, management of women with abnormal results and all c ommunication between the provider and the patient. It is complicated to calculate the cost of different screening programmes and to compare these, as large differences in collection methods and call back rates exist.

Various authors have calculated cost of HPV-based screening and compared it with existing cytology testing. HPV testing as a primary screening method may be cost effective when compared with existing protocols but these analyses are highly situation- and protocol-specific.

An attempt will be made by the Board to do cost analysis on the three recommended screening protocols (see annexures) and the results will be communicated at a later stage.

Clinical uses of HPV testing

Primary screening of a low risk population

High risk HPV testing offers several potential advantages over conventional cervical cytology in the setting of primary screening but also has many limitations.

High sensitivity

HPV testing is significantly more sensitive than cytology to predict cervical cancer and its precursors. The sensitivity of the test approaches 100% due to the ability of PCR to detect HPV DNA even when present in minute quantities. This high sensitivity and the long interval between infection and invasive cancer mean that HPV negative women can safely have a considerably longer screening interval than when using a cytology-based screening programme. The recommended screening interval will differ between countries and will depend to a large extent on available resources. In many countries even a once-in-a-lifetime screening with the much less sensitive cytology test is still to be reached! Most cytology based screening programmes compensate for the low sensitivity of a single test by repeating cytology every three to five years. This strategy leads to a high sensitivity of the screening programme but is expensive to implement.

It is apparent that HPV testing seems to be a much better test to use in any programme with once-in-a-lifetime testing or with long screening intervals (> 5 years). Longer screening intervals are more cost-effective overall.

Technical aspects

HPV testing is a more automated test than cytology. The margin for human error is much smaller as is the need for trained personnel.

When is HPV testing not indicated?

Certain subgroups of the population are NOT suited to HPV screening due to a very high prevalence of HPV. This includes women under the age of 30–35 years where HPV has been reported to be present in up to 80% of women and where its presence is mostly transient. In immune compromised women the incidence of HPV is also high but the high negative predictive value can be useful as a triage method.

Cost and availability

HPV testing is currently more expensive than cytology and is only available in certain specialised laboratories.

Need for education

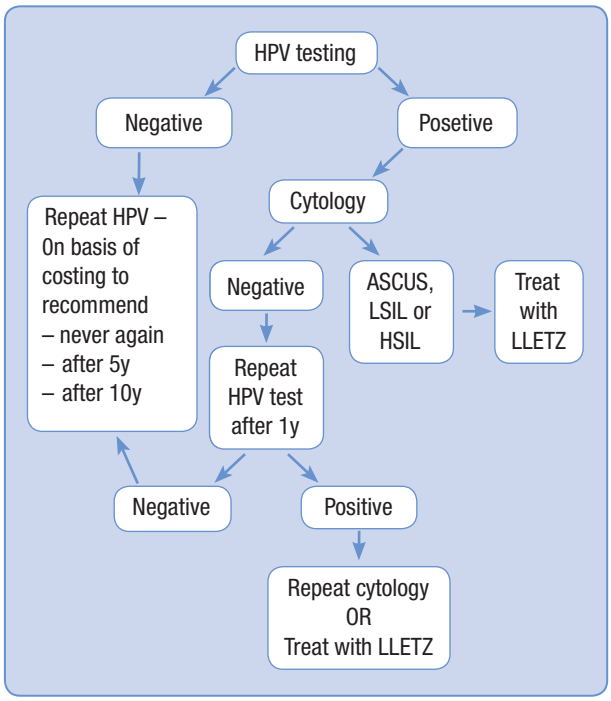
A large proportion of women already know about Pap testing, while HPV testing is new. The diagnosis of HPV infection may have a negative psychological impact on the woman. There is also a potential for confusion with HIV in the mind of the patient.

Recommendations for HPV testing in primary screening

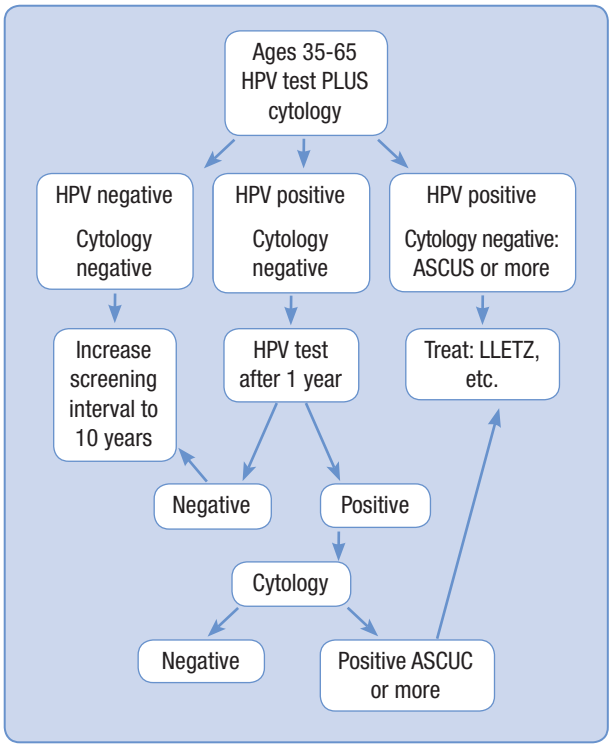
The following options for HPV testing as a primary screening test may include:

- Alone as a once-in-a-lifetime test between the age of 35 and 65 years in low resource settings (see Flow Diagram A).
- Alone or in combination with cytology in women over the age of 30 years to safely increase screening interval in negative women (see Flow Diagram B).

Flow Diagram A



Flow Diagram B



HPV testing as a management tool

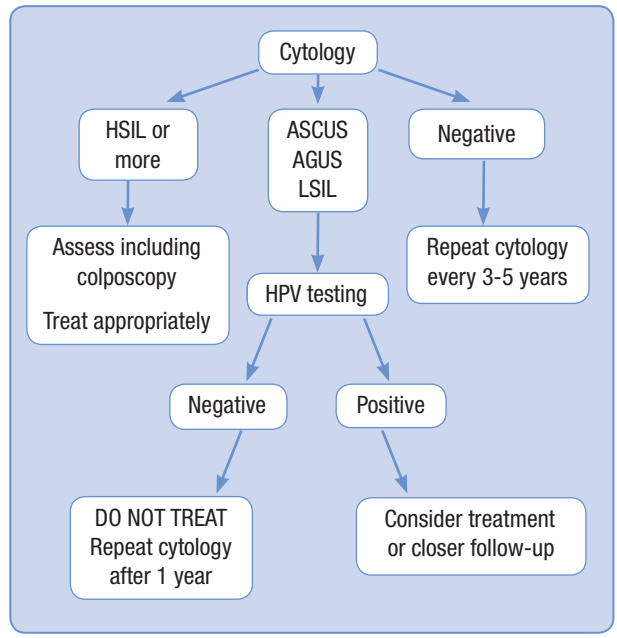
HPV testing is a very good indicator of prognosis in several clinical situations and can therefore successfully be used to triage patients. The absence of high risk HPV accurately predicts a very low risk for cervical carcinoma and absence of this disease for many years to come. This finding can be used to discharge patients from strict follow-up in various clinical circumstances. In a patient after the age of 30 years a finding of negative HPV plus negative cytology is regarded as highly predictive of no CIN lesions or cervical cancer and this patient needs very few screening episodes in her life (the "Super test").

On the other hand HPV positivity can predict future disease with some accuracy even in patients who are cytologically negative. Persistent HPV strongly correlates with future disease and is an indication for strict follow up or even for treatment.

The current role of HPV testing in triage

- Ambiguous or low risk abnormal cervical cytology
  If a patient had a low risk abnormal cytology result, HPV testing can identify those who test HPV negative who can be followed up with a relatively long interval of up to 10 years, and those who test HPV positive who can be offered treatment or close follow-up (see Flow Diagram C).

Flow Diagram C



- Follow-up after treatment for pre-invasive and invasive cervical disease
  Women who test positive for HPV during follow-up after LLETZ or similar treatment for CIN lesions have a much increased risk for recurrent disease. Specific follow-up protocols have not been evaluated and most reports refer to the first follow-up visit. The most likely implication is a recommendation for a tight follow-up schedule for HPV positive patients.

Immune compromised women

Women found to be HPV negative can be screened with normal screening intervals, while HPV positive woman must have increased surveillance or treatment.