A literature review on cancer of the cervix

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1. Introduction

1.1. Burden of disease

Cancer of the cervix is a significant public health problem globally, especially in developing countries where it is the most common cancer in women. Developing countries bear a disproportionate burden of the disease, experiencing age-standardised mortality rate that are twice those experienced in developed countries. Every year, approximately half a million new cases of cancer of the cervix are reported globally, 80% of which occur developing countries, where the disease is also the leading cause of cancer-related death among women[1,2]. The huge disparities in morbidity and mortality between developed and developing countries exist largely because over the last few decades, developed countries have implemented effective programmes for the prevention of cancer of the cervix, in some countries reducing incidence and mortality by up to 80%[1,2,3].

Southern Africa has one of the highest reported age-standardised incidence rates of cancer of the cervix (higher than 40 per 100,000 women)[1] and existing data indicates that the incidence of disease is actually increasing in some parts of Sub-Saharan Africa[1]. In South Africa, cancer of the cervix causes significant cancer-related morbidity and mortality among women[4]. It has been estimated that 5000 new cases of the disease are reported annually, accounting for 16.7% of all cancers reported annually in the country[5]. Though the disease is the second most common cancer among all women, amongst black women it is the commonest[6]. Though easily preventable, it is the leading cause of cancer

death amongst women in South Africa[5,6], accounting for about 1500 deaths annually. However, death rates are differentially distributed in the different ethnic groups, the highest mortality occurring in Black women (25 per 100 000 women) and the lowest in White women (5 per 100 000 women)[7]. Though this data was reported in the late 1980's it is unlikely that these patterns have changed much over the last 20 years. These differences in mortality by race reflect past and present differential access to cancer of the cervix prevention programmes among the races in South Africa.

1.2. What is cancer of the cervix?

Cancer in general can be described as an abnormal growth of cells. Cancer of the cervix is a cancer involving the squamous cells of the cervix. Thus, cancer of the cervix means there is "abnormal growth" of the squamous cells of the cervix (commonly referred to as the mouth of the uterus). That is the squamous cells of the cervix start "behaving" in a way that they shouldn't – they grow at an abnormally fast rate, function differently and start looking different from the normal squamous cells of the cervix. At a more advanced stage, the cancer cells spread to surrounding tissue such as the bladder, and even spread to distant tissue such as bones and lungs, through the blood stream.

What causes cancer of the cervix?

The primary underlying cause of cancer of the cervix is Human Papilloma Virus (HPV)[8,9,10]. HPV is a common sexually-transmitted disease that does not always cause symptomatic disease in infected individuals. Existing evidence indicates that more than 97% of all cancers of the cervix are associated with persistent infection HPV.

Cancer of the cervix is a disease with a long latent period, which means it develops over a long period of time. The natural history of the disease is such that the disease is induced by HPV and persistent HPV infection progresses onto a pre-invasive (pre-cancer) stage, characterised by the presence of pre-cancerous cells in the cervix (broadly called dysplasia). Women are most commonly infected with HPV in their teens, 20s, or early 30s, but it may take as long as 15-20 years for the disease to progress from HPV infection through low-grade to high-grade dysplasia and finally to cancer of the cervix. High grade dysplasia is a precursor for cancer of the cervix. The natural history of the disease is illustrated in figure 1.

What are the main risk factors?

Age: Any woman who has ever had sex is at risk of developing cancer of the cervix, but the risk increases as a woman gets older. Currently, age is the most reliable predictor of risk for cancer of the cervix. The risk is greater in women over 35 years of age.

HPV infection: not all women who are infected with HPV develop cancer of the cervix and it is not currently possible to predict which women with HPV infection will actually develop cancer of the cervix. In fact, only about 5% of women infected with HPV go on to develop cancer of the cervix later in life[1]. However, in recent years, research has shown that particular types of HPV (high risk types), in association with other co-factors, such as smoking and immune suppression, are largely responsible for most cases of cancer of the cervix[8,9,10]. Thus, women who are infected with these high risk types of HPV are considered to be at higher risk of developing cancer of the cervix than women infected with the other low risk types of HPV. Furthermore, women with persistent HPV infection

who are over the age of 35 years are at greater risk of developing the precursor lesions of cancer of the cervix. A lot is not yet known about the exact nature of the role of HPV in the development of cancer of the cervix, but some facts are certain:

- HPV infection does precede high-grade dysplasia[8]
- Persistent infection with HPV plays a central role in the development of cervical dysplasia[11, 12]
- High risk HPV infection is a good predictor of subsequent high grade dysplasia in young women, and an even better predictor in older women.

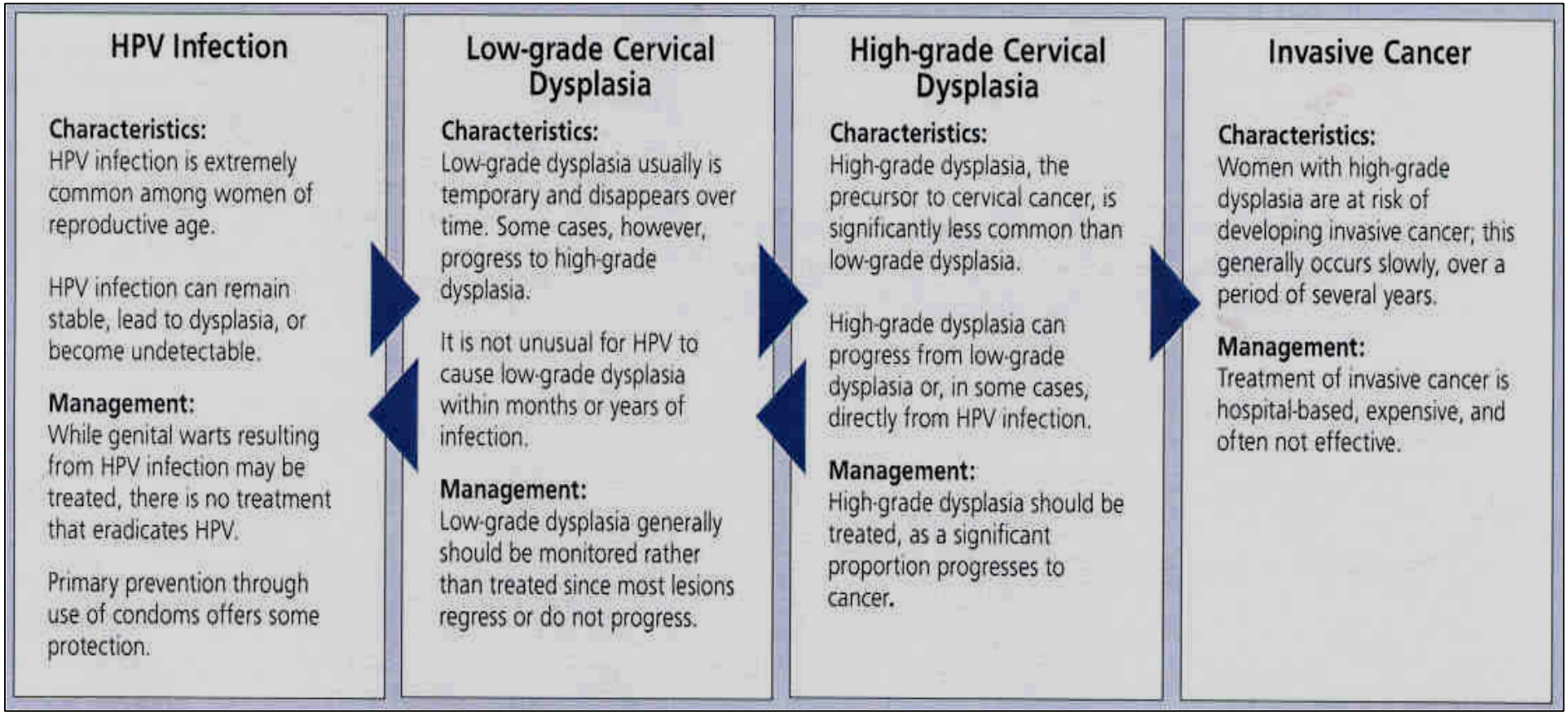
Smoking[1]: tobacco use may influence whether a woman with dysplasia is likely to develop cancer of the cervix.

Immune suppression[1]: exact role is not known, but immune suppression, especially related to HIV infection, also plays a mediation role.

Hormonal factors[1]: use of contraceptives, early age at first birth and high parity also play a role in mediating the disease.

Sexual behaviour[1]: younger age at first intercourse and having multiple sex partners have frequently been cited at risk factors for cancer of the cervix, but these are now thought to be indicators of exposure to HPV infection and are not independent risk factors.

Figure 1: Natural History of Cancer of the cervix[1]



Source: PATH

Prevention of cancer of the cervix

Cancer of the cervix is one of very few preventable cancers known in the health field. There are two main strategies that can be used for prevention:

1. Primary prevention

This involves preventing exposure to and transmission of HPV infection by means of safer sex practices. Strategies that promote behaviour change such as: abstinence from sexual intercourse, mutual monogamy, and the use of barrier methods (male or female condoms), are included in primary prevention. However, there is little evidence that infection with the HPV types that cause cancer of the cervix can be avoided by condom use[13]. Furthermore, because HPV infection is asymptomatic in most infected individuals and sexual behaviour is not easy to control, stemming transmission of HPV is a major public health challenge. In this regard, primary prevention is not an effective prevention strategy at a population level. It is an individual-based approach and thus would result in only a minor reduction in incidence of cancer of the cervix. However, such an approach can be integrated in existing behaviour-change programmes for STI/HIV prevention but must be complementary to population-based approaches (such as screening – see below).

Because of the limited effectiveness of behaviour change strategies, researchers are increasingly looking into the possibility of vaccines that could be used to prevent HPV infection. Most recently, researchers have shown success with HPV vaccine research[9]. They found that administration of an HPV vaccine to HPV-negative women reduced the incidence of HPV infection and of cervical dysplasia. This study

demonstrated the potential of HPV vaccines in reducing the incidence of cancer of the cervix, but more work is required as results need further evaluation.

2. Secondary prevention (cervical cancer screening)

Secondary prevention (early detection and treatment of disease) is the most effective and realistic strategy for prevention of cancer of the cervix. Secondary prevention of cancer of the cervix refers to early detection and treatment of precursors [high grade pre-cancerous lesions] of cancer of the cervix. Early detection of precursors of cancer of the cervix is achieved by cervical cancer screening. The point of cervical cancer screening is to screen women into two groups:

i) Those women that are more likely to develop cancer of the cervix (the presence of certain precancerous lesions in the cervix of these women indicates that they are more likely to develop cancer of the cervix). If these precancerous lesions are identified and treated early, these women will not develop cancer of the cervix.

ii) Those women that are less likely to develop cancer of the cervix.

Because cancer of the cervix has a long latent period and starts with a pre-invasive stage that is curable, it is possible to detect the disease early and take necessary steps to prevent progression to life-threatening incurable disease[10]. There are several cervical cancer screening methods that can be employed in cervical cancer screening programmes. The commonest and most well-established method is that of cervical cytology (Box 1), the method currently recommended for use in South Africa. Cervical cytology refers to the following process:

- Cells are scraped from the cervix by means of a simple test. The simple test that is employed to obtain cells from the cervix is called a Papanicolaou (Pap) smear.
- The cells are smeared and fixed onto a glass slide
- The slide is sent to a cytology laboratory to be examined under the microscope for precancerous lesions. Precancerous lesions may be of low grade or high grade.
- Women with high grade precancerous lesions are treated.

Box 1: Cervical cytology – screening for cancer of the cervix

- A Pap smear is done to obtain cells to detect abnormalities in the cervix. Thus, it is a test that is predictive of disease and is not for making a diagnosis of cancer of the cervix.
- The aim of cervical cytology is to detect cancer of the cervix in the population at risk in its early asymptomatic form when it can be successfully treated.
- If these abnormalities are detected early, they can be treated, thus preventing morbidity and mortality associated with cancer of the cervix.
- Early detection is possible because the natural history of cancer of the cervix is such that it may take up to 20 years for the disease to progress from pre-cancer lesions to invasive cancer.

2. Cervical cancer screening Programmes

As previously mentioned, cancer of the cervix is a preventable disease. Concrete evidence exists demonstrating that well planned and instituted cervical cytology screening programmes can effectively reduce the incidence and mortality due to cancer of the cervix[14]. For example, the implementation of an organised national cervical cancer screening programme in Finland in 1963 decreased the incidence of cancer of the cervix to 5.5 per 100,000 women, one of the lowest incidents in the world[2]. On the other hand the large numbers of premature deaths due to cancer of the cervix in developing countries are attributed to the lack of effective cervical cancer screening programmes in those countries. Studies have shown that only about 5% of women in developing have had a Pap smear, compared to more than 40% of women in many developed countries.

The challenges involved in preventing cancer of the cervix in low resource settings are immense. In order to effectively reduce incidence and mortality from cancer of the cervix, a cervical cytology screening programme must target women most at risk (older women) and must have a number of essential components[1, 15]:

- Information, education and communication programme using culturally-appropriate field-based strategies targeted at both men and women in the community to ensure the appropriate age group for cervical cancer screening attends for the service
- Education and training of service providers – to increase awareness about the screening programme and upgrade their skills
    - Training service providers in technical skills

    - Training health providers in counselling skills – to enable them to provide appropriate information to women and allay fears and anxieties about the procedure
- Provision of cervical smears in appropriately equipped health facilities
- System for delivering specimens to cytology laboratories and reporting cytology results back to health facilities
- Mechanisms to ensure results of Pap smears are given to clients, including follow-up of women with abnormal results who do not return for results
- Setting up referral systems to ensure patients with abnormal Pap smear results are referred to the appropriate level of care for further tests and treatment
- Facilities for treatment of precursor lesions and cancer of the cervix must be in place
- Systems in place to collect statistics to enable monitoring and evaluation of the programme

No organised national screening programmes are in place in any of the Sub-Saharan African countries, most of which have female populations at high risk for cancer of the cervix[2]. Where cervical cancer screening services are available in the developing countries of Latin America, Africa and Asia, they have had limited impact if any, on incidence and mortality[1,2]. The reasons for this limited impact include[1,2,16]:

- Programmes are not organised and are mainly opportunistic. Opportunistic screening services usually target younger women, who are at low risk for precursors of cancer of the cervix. In addition, because it is less effective, opportunistic screening is more costly than organised screening programme.

- Pap smear testing is of poor quality due to inadequate training of screeners or poor quality laboratory services;
- Inadequate number of trained cytologists to examine specimens
- Poor utilisation of services by women due to lack of appropriate out-reach programmes to increase awareness, cultural barriers (gynaecological examination is cause of embarrassment or a taboo) or health service barriers.
- Inadequate investment of resources to maintain an organised screening service

It is evident from the above description of the components of a cytology-based cervical cancer screening programme that such a multi-faceted programme would be a challenge to implement in low-resource settings[17,18]. However, it is not an impossible task. In fact, guidelines for implementation in low-resource settings have been developed[1]. Furthermore, a study in East, Central and Southern African countries found that though the basic infrastructure for provision of cervical cytology was available, it was not optimally utilised and screening coverage remained extremely low[19].

Notwithstanding the limited resources and numerous competing priorities in developing countries, it undisputable that action must be taken to prevent the numerous premature deaths that occur due to cancer of the cervix annually. The consequences of not taking action are potentially grave, including:

- Impact on the health of women in society: increased morbidity and mortality. Social impact of loss of mothers, carers at a productive phase of their lives.

- Impact on health services: it is much more costly to treat women with already established cancer (highly specialised health care are required, usually at tertiary or academic hospital level) than to treat early stages of disease that can be picked up by cervical screening. Cost analyses applied to the South African setting and elsewhere have established that treating only invasive cancer would cost 80% more than screening and early treatment of precursors[4].

In a bid to alleviate the cost of cervical screening programmes and identify more feasible screening strategies for resource-poor countries, researchers in South Africa and elsewhere are looking into alternatives to Pap smears and cytology-based cervical screening programmes. It is envisaged that less costly and less complex methods for cervical cancer screening (such as provision of screening services as a one-stop service) would be easier to implement and sustain in developing countries[18, 20].

3. Prevention of cancer of the cervix in South Africa

3.1. Historical context

Over the last three decades unsuccessful attempts have been made to introduce a cervical screening programme in South Africa. Various national policies were articulated, but rarely adequately implemented. These varied from the Department of Health's policy in the mid 70's of taking a Pap smear only if the cervix looked abnormal[4], to the Project Screen Soweto opportunistic screening, to the Western Cape policy in the mid 90's, focussing on family planning clinic attendees. Previously, cervical screening occurred in pockets around the country, often around academic health institutions in urban centres and invariably linked to family planning services[4]. Thus, those with good access to health care, who were also often at lower risk for cancer of the cervix, had greater opportunity to have Pap smears and were screened over and over, sometimes annually, while those without access and beyond the age group of the family planning clinic target group were often left out. Studies conducted in the late 1980s in Khayelitsha found that 55% of women in the study had never had a Pap smear[21] and a more recent multi-centre national study found that 80% of women had never had a Pap smear[22]. These findings indicate that historical cervical cancer screening services had a low population coverage and thus little impact on incidence or mortality. Furthermore, the inequity of access to this crucial health service produced and perpetuated disparities in morbidity and mortality between black and white women and between urban and rural women.

3.2. National policy for cervical cancer screening

In recent years, the National Department of Health (NDoH) has demonstrated political commitment to addressing this important public health problem by identifying cancer of the cervix as a national health priority[23]. During 1999, NDoH's National Cancer Control Programme (NCCP) was adopted as South African health policy, a component of which was a cervical cancer screening programme. The national cervical screening policy states that every woman is entitled to three free screening Pap smears (in the public sector) in her lifetime at 10-year intervals, starting at the age of 30 years. The policy decision to screen all women in South Africa over the age of 30 years was based on the best available epidemiological data, taking into account resource constraints. A recent national prevalence study found that occurrence of high grade dysplasia was highest in women in their late 30s, validating the NDoH rationale for commencing screening at the age of 30 years[22]. The policy decisions regarding cervical screening were subsequently articulated in the National Guideline for Cervical cancer screening Programme, which provides a broad national framework for a national cervical cancer screening programme[24].

These developments on the policy front pose a challenge to reproductive health programme managers. National and Provincial Health Department managers in Maternal, Child and Women's Health (MCWH) directorates are respectively tasked with developing a national strategy for and implementing the national cervical cancer screening programme. The MCWH Directorate at NDoH has led the process by establishing a cervical cancer screening advisory committee to advise on the development of a national strategy. A smaller task team is currently

working on shaping the strategy before broad consultation with stakeholders happens later this year. It is hoped the publication of a national strategy will facilitate the implementation of an organised national screening programme.

3.3. Programmes and services

Service provision

Though it is over two years since the National Guideline for a Cervical Cancer Screening Programme was published, not much implementation has happened on the ground in most provinces. Some commitment was however demonstrated in the Gauteng and Western Cape provinces, where the respective Provincial Governments earmarked funds for cervical cancer screening during 2001 and 2002. However, the extra injection of resources has not always translated into effective programme implementation and the impacts are yet to be assessed. Most of the other provinces have barely started preparing for provision of cervical cancer screening, and few have made some moves toward implementation, but there is clearly lack of uniformity across provinces. In the meantime, the Women's Health Project (WHP) and Women's Health Research Unit (WHRU) have been conducting a study in three districts (one each in Gauteng, Western Cape and Limpopo provinces) to assess the feasibility of implementing the national cervical cancer screening policy. Theirs and other work in the country have identified barriers to the provision and/or expansion of cervical cancer screening services, including:

- *Programmatic and health service barriers*: lack of management capacity to plan for service services, services not in place, limited access because services are only provided in urban centres or hospitals, lack of appropriate equipment and poor infrastructure,

inadequate treatment services, poor communication between health facilities and laboratories and between screening facilities and treatment centres inadequate health information system to monitor programme and failure to reach high-risk women (older women).

- *Barriers at provider level*: few providers trained to provide Pap smears, poor knowledge of cancer of the cervix and the rationale for screening, poor awareness of the screening policy, providers reluctant to provide the service as it is perceived as "extra work" and because they do not agree with the provisions of the screening policy – this results in missed opportunities for screening.

These problems highlight the need for a health systems development approach to implementing cervical screening programmes. From the above description, it is clear that a successful cervical screening programme requires a whole lot more than just "taking Pap smears". It is also important to ensure that there are health systems in place to support the screening programme.

It has been suggested that a substantial injection of resources and infrastructure would be required to implement and sustain a cervical cancer screening programme in this country, research has demonstrated that even with limited investment in health systems and infrastructure, it is possible to provide cervical smears and report results to clients[22]. To curtail excessive expenditure on infrastructure, cervical cancer screening services in this country should ideally be integrated within primary care clinics and community health centres, utilising existing infrastructure for provision of Pap smears.

Community mobilisation

An information, education and communication programme (IEC) that aims to increase awareness about cancer of the cervix and screening is an essential component of a cervical cancer screening service. The experience of Project Screen Soweto in the 1980s demonstrates this point as services were set up, but women did not attend due to lack of community education programmes[25]. Cervical cancer screening requires women who have no symptoms of disease to attend a health service for a procedure. This is a huge challenge because not many people like to attend a health service when they are not "sick". However, before women can even attend a clinic to demand a Pap smear they need to know about Pap smears and cancer of the cervix. Research conducted by the Medical Research Council in KwaZulu-Natal and by WHP and WHRU indicates that lack of awareness is one of the major barriers to women seeking cervical cancer screening services. Some other barriers include:

- Fear of the procedure
- Women feel embarrassed about gynaecological examinations, especially older women
- Socio-cultural barriers (it is considered to be "a woman's disease" that is not discussed openly so women are not "free" to request the service even when they know about it)
- Myths and stigmas (e.g. according to health care workers, communities associate Pap smears with HIV testing, though recent surveys have failed to demonstrate this)
- Poor communication between health providers and women attending health services – services not accessible to women

To bridge the information gaps and address these barriers requires a comprehensive and sustained IEC programme with extensive community

outreach. The purpose of this IEC programme would be to raise awareness about cancer of the cervix and the importance of screening as a preventive measure, to publicise the availability of screening services in the public sector at clinic level, and to encourage women to attend health services for screening according to the screening policy. Taking into account the gender and socio-cultural barriers, it is imperative that both women and men in the community are involved. From the experience of WHRU and WHP, it is recommended that the IEC programme should be developed and implemented in conjunction with community representatives and utilise culturally-appropriate outreach strategies, including:

Development and distribution of IEC materials: pamphlets and posters should be developed in appropriate languages. Currently, there are no national pamphlets and posters on cancer of the cervix other than the pamphlets developed by NGOs such as CANSA association and WHP and WHRU. IEC materials should include key messages that effectively inform women, such as:

- What is cancer of the cervix and what is a Pap smear?
- Who is at risk of acquiring the disease – women older than 35 years of age are more at risk of developing the disease
- The target age group that should be screened
- Cancer of the cervix can be prevented and early lesions treated
- Pap smears are done to prevent cancer of the cervix
- The Pap smear test is simple and painless
- How frequently screening should be done
- The importance of returning for results

Ideally any health information messages developed should be tested with members of the intended audience to ensure they are easily understood and are culturally appropriate. One of the big challenges for IEC programmes is how to provide information about cancer of the cervix that does not present it primarily as a sexually-transmitted infection (STI) and thus associated with promiscuity, and subject to stigma. It has been suggested that once communities link cancer of the cervix with STIs, they perceive Pap smears as a test for STIs and so women may not want to do the test. Thus, the IEC messages need to be presented in a manner that clearly highlights that all women are at risk, and age is the best predictor of risk. Some health education groups have steered clear of mentioning the role of HPV in development of cancer of the cervix, reasoning that not enough is known about the disease anyway. I am not entirely convinced this is ideal approach to the problem though.

Media: community radio stations to air programmes or make public announcements and local and national newspapers to publish articles about cancer of the cervix and screening. Our study found that more than 75% of women attending health services listen to the radio and the radio was the commonest source of information about these topics.

Peer educator training: training appropriately selected members of the community on cervical cancer screening so that they in turn conduct workshops and give talks on cancer of the cervix within their communities, while also distributing pamphlets.

Drama and photo-comic: these methods have been employed in the Khayelitsha Cervical cancer screening Project. More information about these is available from the project.

Most of these IEC strategies may improve knowledge, but ultimately the aim is to see a change in practices, i.e. to see more women attending services for Pap smears. However, very little work has been done to evaluate the impact of various IEC strategies on women's attendance for screening. Thus it is difficult to determine which strategy works best. However, a study in RSA found that pamphlets and even photo-comics are not as effective as peer educator programmes.

4. Some key debates

- Is an organised cytology-based screening programme a reality?

Screening involves substantial costs and many poor countries cannot afford to set up a screening programme, especially a cytological-based programme. There are on-going debates questioning the feasibility of an organised cytology-based screening programme in this country. However, evidence based on modelling shows it is achievable.

- Impact of HIV

There have been calls from clinicians for revision of the national screening guidelines: to commence screening at an earlier age, or develop an alternative screening schedule for HIV positive women. This is in light of recent research suggesting the impact of HIV on dysplasia and cancer of the cervix (early lesions of Cancer of the cervix are more persistent in HIV + women; cancer of the cervix affects HIV + women at younger age, is more aggressive and early lesions are more likely to recur after treatment)[26].

- Alternative screening strategies

What is the most appropriate cervical screening method for this country? Is the Pap smear the best way to go? What about other "one-step" methods that, unlike cytology-based screening, do not require repeated visits to health facility? There are no answers but work is on-going on this issue. Dr L Denny is the best resource person for more information on this issue.

5. Key stakeholders

Some of the main actors in this area, at service provision, policy, academic, non-governmental and community levels include:, including a brief description of their activities. Some national actors include:

- CANSA association – mainly involved in health promotion activities, including large scale production and dissemination of IEC materials (pamphlets and posters).
- GAP - health promotion on various gender and reproductive health topics, including cancer of the cervix
- Khayelitsha Cervical cancer screening Project, University of Cape Town – have worked on cancer of the cervix in the area for years. Running a comprehensive screening service in the area, including development of photo comic called "Nokwezi's story", which has been made into a video and development of edu-drama. The group are also conducting research looking at alternative strategies for screening.
- National Department of Health, Maternal Child and Women's Health (Women and Genetics Division) – spearheading the development of a national strategy for cervical cancer screening in order to give guidance for implementation to provinces, regions and districts.
- PPASA – health promotion, community education: running a project looking at ways of involving men in cervical screening.
- Women's Health Project, University of the Witwatersrand – conducting research looking at the ways of implementing the screening policy, also involved in national strategy development.

- Women's Health Research Unit (in society), University of Capetown - conducting research to inform implementation of the screening policy and involved in national strategy development.

Concluding remarks

There is certainly an urgent need for advocacy to place cancer of the cervix high on the programme planning agenda at provincial and regional levels. Currently, breast cancer receives a lot of coverage in the media, and yet cancer of the cervix causes significantly more deaths. There is a lot of room for greater media involvement to increase the profile of cancer of the cervix among policy makers, managers, service providers and communities at large.

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