

Cervical cancer in Southern Africa: The challenges

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Introduction

Cervical cancer remains the second most common cancer among women worldwide and the most common cancer amongst black African women in South Africa.¹ Annually there are 500 000 cases of cervical cancer worldwide, of which the mortality is about 50%.² This is largely due to presentation at a late stage. Lack of availability of treatment facilities may be another factor contributing to this high mortality.

Ironically, cervical cancer is one of the few medical conditions with a precursor lesion, which if appropriately detected and treated, can result in a reduction of both the prevalence and mortality from cervical cancer. It turns out that southern Africa like so many other parts of the developing world, suffers from the same ills such as a lack of finances, lack of knowledge of the disease and a lack of political will to curb the prevalence of the disease. A significant amount of the health budget needs to be spent treating this disease every year.

There is now a large body of evidence implicating the oncogenic human papillomavirus (HPV) as a necessary agent in the pathogenesis of cervical cancer. To date, two commercial vaccines have been developed to curb the diseases caused by the high risk and low risk HPVs. However, similar to the problems of screening for cervical cancer, it remains a challenge to ensure that there will be sufficient dissemination of information about the vaccines to the community, uptake of the vaccine by women and the political will to implement a preventative vaccine strategy.

The burden of cervical cancer in southern Africa

Whilst cervical cancer is the sixth most common cancer in developed countries, in sub-Saharan countries it accounts for approximately 15% of all cancers.³ The true estimate of the prevalence of cervical cancer in southern Africa is difficult to establish as cancer registries are non-existent. About 83% of all cases of cervical cancer occur in developing countries such as southern Africa.⁴ Cervical cancer usually affects women in the fifth and sixth decades of life, but has been found to be more prevalent in the fourth decade of life for human immunodeficiency-virus (HIV)-infected women. This is the time of their lives when they are most productive and when they play a pivotal role in their families and society. A pathology-based cancer registry was initiated in South Africa in 1986 and collected information from the public and 80 private laboratories. In 1986, there were 2 897 (17.4%) histologically-confirmed cases of cervical cancer.¹

In 1992, although the proportion of reported cases had increased, the proportion of confirmed new cases remained stable at 17.8% (4 467). The age-standardised incidence rate (ASIR) of cervical cancer for the

period 1993–1995 in South Africa was 22/100 000. However, the ASIR for black African women was 27/100 000.⁵ It was reported that the lifetime risk of a black African woman developing cervical cancer was 1 in 34 compared to 1 in 93 for white women. This reflects the better socio-economic status and more frequent screening practices among white women. In contrast, in 1998, the ASIR of cervical cancer for black African women in South Africa was reported to be 34.4/100 000.⁶ The ASIR of cervical cancer for black African women in Durban, South Africa, for the period 1994 to 1999 was 45/100 000. It was also noted that 66% of women with cervical cancer had stage III and IV disease at presentation.⁷

The trend of cervical cancer being most prevalent among women in low-resource settings is not unique to Africa, but is also seen in other developing parts of the world (Haiti 93/100 000; Zimbabwe 52/100 000; Malawi 56/100 000; Swaziland 52/100 000).¹ In contrast, very low rates are seen in developed countries (Syrian and Arabic Republic 2.99/100 000; Finland 4.16/100 000).¹ Mortality and incidence of cervical cancer parallels the socio-economic environment. Mortality for black women was reported to be 5.9/100 000 compared with 2.6/100 000 for white women.⁸

Theoretically, cervical cancer is a disease that should be diagnosed at an early stage because of cervical cytological screening. However, in reality most patients in developing countries present in advanced stages when the symptoms of abnormal vaginal bleeding or an offensive vaginal discharge become a personal and social problem.

The problems of cervical cancer screening in southern Africa

Well-organised screening programmes are effective in reducing the incidence and prevalence of cervical cancer.⁹ Following the implementation of screening programmes in the Nordic countries, the mortality from cervical cancer showed a decreasing trend. The largest fall was in Iceland (84% from 1965 to 1982). The screening interval here was the shortest and the target age range the widest. In contrast, in Norway only 5% of the population was screened resulting in a reduction of only 11%.¹⁰ In order to produce a significant impact on the prevalence of cervical cancer, a minimum of 70% of the population needs to be screened. Although there have been no randomised controlled trials to determine the impact of cervical cancer screening, the evidence for a benefit derives from cohort and case-controlled studies.¹¹ The barriers to an effective screening programme in developing countries include: lack of awareness of the disease and the role of screening; failure of women to avail themselves of screening; low budget allocation for screening purposes; the demands of competing health needs such as HIV infection, tuberculosis and other common diseases; no consumer demand and therefore no political will to establish screening programmes; war and civil strife endemic in many African countries. It is estimated that the average yearly per capita expenditure on health in many African countries is about US \$3 compared with US \$500 in the United States of America.¹²

Cytology-based screening programmes require considerable infrastructure. It seems that in African countries, health care personnel simply do not counsel women about this important disease and the availability of smears to detect and prevent cervical cancer. It is quite possible that women who are screened never return for results of their smears and modes to communicate messages to patients do not exist. Referral of women with abnormal smears for colposcopy and treatment is deficient in many developing areas due to lack of availability of this expertise. Furthermore, conventional cytology is associated with a low sensitivity of approximately 50%. In a survey performed in Nigeria, 254 women were randomly assessed and asked about knowledge of cervical cancer.¹³ Only 15% had ever heard of cervical cancer and even less knew about cervical screening. Similarly, in a study done in an obstetric ward at Baragwanath hospital in Johannesburg, South Africa, 89 women were questioned about cervical smears¹⁴; only two of them had had cervical smears and four had heard about cervical screening. It appears that the discrepancy between developed and developing countries concerning rates of incidence and mortality of cervical cancer is paralleled by a similar discrepancy regarding education and knowledge of cervical cancer and its prevention. In a study of the knowledge and uptake of cervical cytology in Durban, South Africa, it was found that women from varying socioeconomic backgrounds did not avail themselves of screening, despite residing within a 10 km radius of a health care facility which either provides or could provide a screening service.¹⁵ 36.7% of women who had at least one cytological smear performed in their lives were not informed of the purpose of a smear. Further, only 14.7% of sexually active medical students had a cytological smear in their lifetime.

The problem of the HIV epidemic

The Centers for Disease Control (CDC), USA, labelled cervical cancer as an AIDS-defining illness in 1993.¹⁶ The issue, however, is complex and studies have not clearly demonstrated any significant increase in cervical cancer, especially in Africa. This is most likely due to the fact that many young HIV-infected women demise from AIDS-related illnesses prior to developing invasive cervical cancer.

In separate studies from Durban, South Africa, the effects of the HIV epidemic have been demonstrated.^{17,18,19} It can clearly be seen that rather than an increase in the incidence of cervical cancer, the total numbers of women with cervical cancer in the province of KwaZulu-Natal had declined over a period of time. KwaZulu-Natal has not only the largest population in South Africa, but also the highest HIV prevalence. Furthermore, HIV infected women with cervical cancer presented about 10–15 years earlier than their HIV non-infected counterparts. In a case-control study performed in South Africa, HIV-infected women were five times more likely to be infected with high-risk HPV compared to HIV non-infected women.²⁰ Also, HIV-infected women with high-risk HPV types were 40 times more likely to have a cervical cancer precursor lesion than women not infected with the HPV or HIV viruses. The above findings demonstrate the need to implement a different screening strategy for HIV-infected women. The CDC recommends that HIV-infected women should have a cytological smear performed and repeated six months later if the first smear is negative. Thereafter, smears should be performed annually. However, this will remain a challenge for many developing countries with other health care priorities.

Alternatives to conventional cytology in an African setting

Due to the complexity of implementing a successful cytology-based screening programme in developing countries, researchers have focussed on alternatives to conventional cytology. The aims were to reduce costs, and to simplify the process as a 'one-stop' procedure in a 'screen-and-treat' approach. Visual inspection of the cervix with acetic acid (VIA) has been evaluated in many cross-sectional studies

and results have shown that its sensitivity is similar to cytology (62–80%), but specificity is lower (77–84%) in its ability to detect high-grade cervical dysplasia.²¹ Testing for high-risk HPV using commercial test kits have demonstrated that HPV DNA testing has a higher sensitivity than cytology or VIA. HPV DNA testing with cryotherapy has the potential of 'screening and treating' women without the need for colposcopy and histology. In a study conducted in Cape Town, South Africa, HPV DNA testing followed by cryotherapy was twice as effective as VIA followed by cryotherapy in reducing histologically confirmed CIN 2 and 3 at six and 12 months of follow-up.²² However, adequate training and monitoring of testing is necessary to evaluate the quality of the visual test. HPV DNA testing is not viable in developing countries due to the prohibitive costs.

The current status of cervical cancer screening in South Africa

The current South African policy is to offer all asymptomatic women above the age of thirty years three smears at ten-yearly intervals. Based on mathematical models developed in the 1980s and assuming 100% coverage of the population, this practice is expected to reduce the cumulative incidence of cervical cancer by two-thirds.²³ Data from the Western Cape, South Africa, indicate that in 2005, of the 62 331 women screened, 45 997 women were over the age of 30 years (74%).¹ Abnormalities were detected in 7.3% of smears. Similar results were reported for other provinces of South Africa. In KwaZulu-Natal, 28 760 smears were performed in 2005, accounting for 26% of the targeted number of smears for 2006 and 2007. These data provide proof that a large number of women remain unscreened. The Department of Health has estimated that in order to achieve the 70% coverage of the population, over five million women would need to be screened over the next ten years. No data are available from the private sector of South Africa, although the impression is that women are generally over-screened and this practice represents the availability of medical aid insurance for less than 10% of the population.

Vaccination as primary prevention: is it a viable solution for the Southern African situation?

In view of the low sensitivity of Papanicolaou smears there is a need to screen frequently and cover a sufficient percentage of the population to make any significant impact on the reduction in the prevalence of cervical cancer. This, however, is not feasible as well as not cost-effective, especially in developing parts of the world where screening is most needed. Prevention must therefore be aimed at the primary prevention of intraepithelial neoplasia through vaccination.

It had been recognised that the L1 protein coat of HPVs could self-assemble into viral-like particles (VLPs) when expressed in recombinant eukaryotic systems. The two commercially developed vaccines include Cervarix™ (Bivalent HPV 16 and 18, GlaxoSmithKline Biologicals, Rixensart, Belgium) and Gardasil™ (Quadrivalent HPV 6, 11, 16 & 18, Merck and Co, Inc West Point, Pennsylvania, USA). It is reported that vaccinating against HPV types 16 and 18 could potentially prevent 70% of cervical cancer and vaccinating against the 8 commonest HPV types could protect against 95% of cases.²⁴ A number of randomised clinical trials of these vaccines have demonstrated an excellent efficacy (over 90%) against persistent HPV infection and 100% efficacy against CIN 2/3 lesions.²⁵ These vaccines have been introduced in some developed countries as a cancer-prevention programme and while there is no doubt that vaccines can prevent significant morbidity and mortality, the major challenge remains the financial cost of implementing such a preventative strategy in the public sector of South Africa. Again, as in the case of Papanicolaou smears, the uptake of vaccines will probably be a regular phenomenon for the private sector of South Africa, while the majority of women who need it the most will not be vaccinated as these vaccines will not be available in the public sector for some time.

Management of cervical cancer

The management of cervical cancer should be an individualised approach involving counselling of the patient, investigations, staging and definitive treatment according to the stage of the disease.

Basic investigations include: full blood count, renal function, HIV status and CD4 count where relevant, chest X-ray and ultrasound of the abdomen. Patients who are due to receive chemoradiation will need a formal assessment of renal function with either a 24 hour creatinine clearance or an isotope glomerular function test if available. Staging is best performed in theatre and includes an examination under anaesthesia, cystoscopy, proctoscopy and biopsy where relevant.

In principle, early stage disease is best treated with surgery while locally advanced disease is treated with concurrent chemoradiation. Advanced disease requires individualised care consisting of either palliative radiotherapy or palliative chemotherapy and symptomatic treatment for the terminally ill patient.

Management of patients with cervical cancer in the Southern African regions poses numerous challenges. The state sector bears the burden of patients diagnosed with cervical cancer. This often leads to long waiting times for the clinical assessment of such patients and unacceptable surgical dates. Further, since high-care or intensive care facilities are shared with other surgical disciplines, high-care beds may be unavailable at the time of surgery. Nursing shortages and large patient workload lead to poor monitoring of surgical patients which may compromise outcomes in comparison to that of developed countries. Pathology laboratory services are usually overloaded with work leading to delays in obtaining reports and commencement of adjuvant therapy, where necessary. In many developing countries there is a lack of radiotherapy machines or appropriate staffing to administer radiotherapy. Often the number of radiotherapy machines available to treat the population is inadequate, resulting in unacceptable waiting lists. This often results in patients defaulting treatment and presenting later with more advanced disease. Due to the long waiting times to commence radiotherapy, patients with better performance statuses may be selected for radical treatment and others referred for palliative treatment. Many patients present with advanced stage disease and renal function is often noted to be impaired at the time of initial assessment. Administration of cisplatin-based chemotherapy becomes a problem in this situation. The HIV epidemic has resulted in many patients presenting in poor general condition leading to the prescription of palliative radiotherapy or just symptomatic care.

The management of the HIV-infected patient with cervical cancer presents difficult challenges. The performance status of the patient and CD4 count are crucial in tailoring treatment. Patients with CD4 counts of less than 200 cells/ μ L require referral for anti-retroviral treatment and improvement of nutritional status prior to definitive treatment. Although the extent of surgery for early stage disease varies, it has been shown that patients with CD4 counts above 200 cells/ μ L and good performance status have good outcomes with minimal morbidity following radical hysterectomy and pelvic lymph node dissection.²⁶ Frequent treatment interruptions, skin reactions and bone marrow toxicity have been reported with chemoradiation.

In general, survival rates vary between the developed and developing countries. Higher 5-year survival rates are reported for the United States (71%), Canada (72%) and Europe (59%) compared to developing countries such as the Philippines (29%) and India (40%).^{27,28} According to the Surveillance, epidemiology and end-results (SEER) data from the United States, survival rates are higher for white women (72.9%) compared to black women (61%).²⁹ In a retrospective analysis of patients treated with radiotherapy, the one, two and three year survival probabilities for

seropositive patients compared with seronegative patients were 67%, 40%, 27% and 89%, 62% and 51%, respectively.³⁰ By the fourth year the survival probabilities had fallen to 0% for the seropositive patients and 46% for the seronegative patients.

In a study performed in Kenya, HIV-infected patients experienced multisystem toxicity of the skin, gastrointestinal tract and genitourinary system seven times more commonly than HIV non-infected patients.³¹ Being HIV-infected was found to be an independent risk factor for treatment interruptions. Residual disease post external beam radiotherapy was also found to be 6-fold greater in HIV-infected women. Though data is limited it would be prudent to treat HIV-infected patients with caution.

Way forward?

Many aspects of the cervical cancer problem in southern Africa require research and evaluation in order to determine the most cost-effective preventative strategy. This will include measures such as on-site screening and immediate treatment of pre-invasive lesions, research to address the best methods of treating pre-invasive and invasive cervical lesions amongst HIV-infected women. What will be needed most is the political will to implement a long-term vaccine strategy.

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