Cervical cancer in South Africa: An overview of current status and prevention strategies

Cervical cancer is distressingly common in developing countries.

LYNETTE DENNY, ***MB ChB, MMed (O&G), PhD, FCOG (SA)***
Principal Specialist and Head of Department, Groote Schuur Hospital and University of Cape Town

Lynette Denny is Head of the Department of Obstetrics and Gynaecology, Groote Schuur Hospital and University of Cape Town. Her main research interest is in cervical cancer prevention in low-resource settings and she is currently conducting a randomised trial of the safety and immunogenicity of the bivalent vaccine in HIV-positive women. She is a gynaecological oncologist.

E-mail: lynette.denny@uct.ac.za

Current estimates are that 493 243 women are diagnosed with cervical cancer per year and 273 505 die from the disease.[1] Globally it is the second most common cancer in women and the most common in developing countries. 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, which is a significantly higher incidence to mortality ratio than found in developed countries (http://www.who.int/hpvcentre). There is some regional variation in age-standardised incidence rates (ASIR) of cervical cancer in Africa, with ASIRs of 42.7/100 000 reported in eastern Africa, 28/100 000 in middle Africa, 12.1/100 000 in northern Africa, 38.2/100 000 in southern Africa and 29.3/100 000 in western Africa.

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By contrast, in the USA, which has a population of 121.32 million women aged 15 years and older, 13 162 women develop cervical cancer per year and 5 214 (40%) die from the disease, where it is ranked the 4th most common cancer in women aged 15 - 44 years, but the 11th most common among all women. Current data for South Africa are lacking due to failure to maintain the pathology-based cancer registry. Between 1993 and 1995, an average of 3 387 new cases of cancer of the cervix were reported annually, with 1 497 deaths reported in 1994.[2] The South African Cancer Registry, which reported on cancer incidence in 1998 - 1999, recorded 6 061 and 5 203 new cases of cervical cancer respectively.[3] These data represented ASIRs of 34.3/100 000 and 28.7/100 000 respectively. Over 80% of the women diagnosed with cervical cancer were black African women who had ASIRs of 42 and 35/100 000 in the 2-year reporting period. Approximately 3 680 women died from cervical cancer each year, representing nearly 60% mortality. The ASIR of cervical cancer in the southern African region as a whole is 38.2/100 000, with ASIRs estimated to be 61.6/100 000 in Lesotho, 58.9/100 000 in Swaziland, 30.4/100 000 in Botswana and 22.2/100 000 in Namibia.

Data on cervical cancer incidence in South Africa have been unavailable since the 1999 Cancer Registry was published. The Medical Research Council, however, published a report in October 2007 of cancer incidence in selected municipalities of the Eastern Cape Province between 1998 and 2002.[4] The area of surveillance included 10 magisterial districts in the former Transkei area and covered a population of 1.4 million people. During the study period, 2 829 cases of cancer were reported of which 1 184 (41.8%) were in men and 1 645 (58.2%) were in women.

Table I shows the percentage of leading cancers in women from 1998 to 2002 in 10 magisterial districts in the Eastern Cape. Overall the ASIR of cancer was 59.1/100 000 in women and 72.8/100 000 in men. For cervical cancer the ASIR was 20.2/100 000, but the range was from 10 to 30/100 000 in different areas. Breast cancer was the third most common among women, with cervical cancer being about three times more common than breast cancer.

Table I. Percentage of leading cancers in women in 10 magisterial districts in the Eastern Cape

Site	Number	%
Cervix	552	33.8
Oesophagus	514	31.5
Breast	186	11.4
Ovary	24	1.5
Lung	20	1.5
Melanoma	19	1.2
Thyroid	15	0.9

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. This policy has been implemented in a fragmented and uncoordinated manner and has not yet had a significant impact on cervical cancer incidence, although accurate data on cervical cancer incidence and the impact of sporadic or current screening activity in South Africa are lacking.

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It is important to contextualise the issue of cervical cancer prevention in South Africa and other developing countries, with regard to overall socio-economic conditions, competing health needs and health care infrastructure. It is sobering to note that in Africa, for example, which had a population of 812 million (404 million men and 408 million women) in 2008, only 7.2% of the population was covered by medically certified causes of death and only 8.3% of the population was covered by population-based cancer registries. Throughout sub-Saharan Africa in 2008 there were an estimated 667 000 incident cancers diagnosed and 518 000 deaths recorded, i.e. 78% of all people diagnosed with cancer died (http://www.who.int/stats).

Cancer of the cervix also needs to be understood in the context of the HIV epidemic. In 2007, it was estimated that 33 million adults and children were infected with HIV globally, of whom 22 million (67%) were living in sub-Saharan Africa south, where 75% of the world's HIV-related deaths were recorded. While the expected increase in cervical cancer (which is considered an AIDS-defining illness by the Centers for Disease Control, USA) has not materialised in Africa, as more and more women infected with HIV survive due to access to and use of antiretroviral therapy, cervical cancer incidence is likely to be increased by the HIV epidemic.

It is estimated by the World Bank that while developing countries account for 84% of global population and 90% of disease burden, they have access to 20% of the global domestic product (GDP) and 12% of global health expenditure. It is this inequity that is responsible for the high rate of cervical cancer in developing countries, where no country has managed to either sustain or initiate cervical cancer screening programmes.[5]

Natural history of cervical cancer

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 - 3 and, most recently, low- and high-grade squamous intra-epithelial lesions (SIL). Detecting cervical cancer precursors has traditionally been done through cervical cytology, and coupled with appropriate treatment this approach to cervical cancer prevention has reduced cervical cancer to a relatively rare disease where the system functions properly.

It has long been realised that HPV is sexually transmitted, and transmission occurs through mechanical abrasion of an infected epithelial surface with an uninfected epithelium. HPV DNA can be detected in vulval, vaginal, cervical, oral and anal tissues in women and on the penis, glans, foreskin, scrotum, mouth and anus of men. HPV infection in the majority of men and women is asymptomatic and transient without any clinical consequences. It is only in a minority that the infection becomes persistent, thus increasing the risk of dysplasia and subsequent progression to cancer.

Clearance of HPV infection requires an effective host immune response. The long duration of HPV infection in some individuals is attributed to the virus's ability to 'hide' from the host immune system. While antibodies play a limited role in HPV clearance (only 70% of incident HPV infections develop serum antibodies after 18 months of initial DNA detection), cytotoxic T cells appear critical to effect viral clearance. T-cell immune suppression has been shown to have a profound effect on the risk of HPV infection and persistence, particularly in HIV-positive women, who have at least double the prevalence of HPV compared with HIV-negative women who report similar risk profiles.[6]

Primary prevention of cervical cancer

Primary prevention of cervical cancer implies prevention of HPV infection *de novo*. Until recently primary prevention of cervical cancer relied on (*i*) abstinence, (*ii*) mutual monogamy of virgins or (*iii*) 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.

The development of vaccines against certain types of HPV has been a major breakthrough in the options available for the prevention of cervical cancer. Monovalent (against HPV 16), bivalent (against HPV 16, 18; Cervarix, GlaxoSmithKline Biologicals, Rixensart, Belgium) and quadrivalent (against HPV 6, 11, 16, 18; Gardasil, Merck and Co., Inc, West Point, Pennsylvania, USA) vaccines have been tested in randomised placebo-controlled trials and shown to be safe, immunogenic and highly efficacious up to 6.5 years after vaccination. The vaccines use HPV type-specific L1 proteins that self-assemble into virus-like particles (VLPs). In the bivalent vaccine, the L1 protein of each type is expressed via a recombinant baculovirus vector. The vaccine consists of purified L1 VLPs of HPV types 16/18 formulated on an ASO4 adjuvant comprising 500 µg of aluminium hydroxide and 50 µg of 3-dacylated monophosphoryl Lipid A. The vaccine is delivered by intramuscular injection at 0, 1 and 6 months.

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In the quadrivalent vaccine, the L1 protein for each HPV VLP type is expressed via a recombinant *Saccharomyces pombe* vector and the vaccine consists of purified L1 VLPs of HPV types 6/11/16/18 formulated on a proprietary alum adjuvant. The vaccine is also given via intramuscular injection, at 0, 2 and 6 months.

Both vaccines work by inducing neutralising serum antibodies (IgG). Studies consistently show that L1 VLPs induce high levels of serum-neutralising IgG that is presumed to transudate across the cervical epithelium in high enough concentration to bind to virus particles and prevent infection.

There is good evidence provided by

randomised placebo-controlled trials that these vaccines prevent both persistent infection with the types included in the vaccines, as well as pre-invasive lesions of the anogenital tract associated with the types present in the vaccines. In addition, the quadrivalent vaccine prevents the development of genital warts caused by types 6 and 11 (both associated with benign disease).[7-12] Both vaccines appear to offer full protection against types 16 and 18, which are estimated to cause over 70% of cervical cancers worldwide, and a slightly lower fraction of cervical cancer precursors. 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. As mentioned above, 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.

Goldie *et al.*[13] used modelling to predict that, assuming coverage of 70% of girls aged 9 - 12 years, vaccinating against types 16 and 18 will reduce the lifetime risk of cervical cancer by 43%. In addition, a combined approach of vaccinating young girls and screening women over the age of 30 years, at 70% coverage for both, will provide an estimated 53 - 70% reduction in the lifetime risk of cervical cancer. At coverage rates of 100% the expected cancer reduction with vaccination alone reaches 61%, but with the combination of vaccination and screening older women, the reduction is approximately 75%.

Secondary prevention of cervical cancer

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. This approach has proven very effective where the infrastructure to sustain it has been successfully maintained. As mentioned before, however, no developing countries have managed to initiate and sustain such a system.

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. The test characteristics of VIA have been evaluated in a number of cross-sectional studies in developing countries, summarised by Sankaranarayanan *et al.*[14,15] These studies have included nearly 150 000 women and have reported sensitivities of VIA for high-grade intraepithelial lesions which have ranged from 49% to 96% with specificities between 49% and 98%.

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.

Denny *et al.*[16] performed a randomised controlled trial of 6 555 women aged 35 - 65 in Cape Town, South Africa. This trial evaluated three 'screen and treat' strategies: (*i*) screening with VIA followed by cryotherapy if positive; (*ii*) screening with HPV DNA testing using Hybrid Capture II followed by cryotherapy if positive; and (*iii*) delayed treatment in a control group for 6 months regardless of the result of the screening tests (VIA and HPV DNA testing). The prevalence of high-grade cervical cancer precursors (defined histologically) was significantly lower in the two 'screen and treat' groups 12 months post randomisation compared with the delayed evaluation group. HPV DNA testing followed by cryotherapy was twice as effective in reducing high-grade lesions compared with VIA followed by cryotherapy.

Recently Sanakaranarayanan *et al.*[17] reported on a cluster-randomised trial performed in 114 clusters in Dindigul district, India. Fifty-seven clusters or areas were randomised to one round of VIA by trained nurses followed by treatment with cryotherapy if positive, and 57 to a control group (no screening). This study was the first to report on a reduction in cervical cancer incidence in the intervention versus the control group (all other VIA studies have used intraepithelial lesions as the outcome). This study showed a reduction of 25% in cervical cancer incidence and a 35% reduction in mortality compared with the control group in this trial located in South India.

In another study[18] the same group reported on a cluster randomised trial involving 52 clusters of villages, with a total of 131 746 healthy women between the ages of 30 and 59 years. The groups were randomised to undergo screening by HPV testing, cytological testing, VIA or standard of care (no screening). Women with positive screening tests were referred for colposcopy and biopsy and for treatment if lesions were detected. The hazard ratios for the incidence of advanced cancer and death in the HPV testing groups were 0.47 (95% CI:0.32 - 0.69) and 0.52 (95% CI: 0.33 - 0.83) respectively, as compared with the control group. There were no significant reductions in the numbers of advanced cancers or deaths observed in the cytological testing and the VIA group compared with the control group. These data represent 8 years of follow-up and this is the second study to use cancer diagnosis as an endpoint. In this study, a single round of HPV testing was associated with a significant reduction in the numbers of advanced cervical cancers and deaths from cervical cancer, and neither VIA nor cytology were, compared with the control group. The reason for the evidence of reduction of cancer in the first but not the second trial is not clear, but may be due to the higher incidence of treatment in the former trial.

These studies show that alternative strategies to cytology are effective in reducing cervical cancer precursors and cervical cancer. While current methods used for HPV DNA testing are prohibitively expensive, a new rapid HPV DNA test, called careHPV, is currently in clinical trials and is expected to be available in 2011. careHPV tests for 13 high-risk types of HPV, gives a result within 2 hours and can be performed at district level. It is estimated that it will cost $5 per test.

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In a nutshell

- The possibilities for cervical cancer prevention have never been as accessible and affordable as they are at present.
- While the current cost of the vaccines is excessive, there are worldwide attempts to ensure availability of the vaccines in developing countries and these efforts are likely to bear fruit.
- Meanwhile high-level research studies have shown the clinical effectiveness of screen-and-treat approaches using VIA and HPV DNA testing, and up-scaling these approaches needs to be encouraged.

Single Suture

Antidepressants only effective against severe depression

A new meta-analysis confirms that patients with severe depression get more benefit from antidepressant drugs than those with milder forms of the disease. Drug treatment worked little better than placebo for adults with mild or moderate depression in a reanalysis of patient level data from 6 selected placebo-controlled trials.

The trials included adults with baseline scores from 10 to 39 on the Hamilton depression rating scale, the most commonly used measure of symptom severity. Drugs became more effective as baseline scores increased, and the benefits were clinically relevant only for adults with baseline scores of 25 or more. Scores of that size indicate very severe depression, say the authors. Most adults taking antidepressants in clinical practice score well below 25 at presentation.

The authors found many more trials in their original search but had to exclude most of them because patient level data were unavailable. They also excluded trials that mentioned a placebo washout period, a common device to weed out patients susceptible to placebo effects. After other exclusions, the authors were left with just 6 trials of 2 drugs – paroxetine and imipramine. This limited analysis is broadly in line with results from at least two bigger meta-analyses, however. All 3 show greatest benefits for the most severely depressed adults, say the authors.

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