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Cervical cancer prevention and early detection from a South African perspective

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The objectives of this chapter are to review the history of cervical cancer prevention and to discuss and evaluate new and novel approaches from a South African perspective. Methods for prevention and early detection of cervical cancer have been well established since the 1960s, yet implementation of appropriate policies and healthcare interventions have not occurred in the majority of low- and middle-income countries (LMICs). In these countries, cervical cancer remains a significant cause of premature death and is the second most-common cancer in women after breast cancer. Further, good-quality data on the true incidence and mortality of cervical cancer are lacking in many LMICs due to lack of cancer registries and national cancer-control programmes.

Alternatives to cytology-based cervical cancer prevention have been studied in the past 20 years. Testing for high-risk types of human papillomavirus (HPV) and linking positive tests to immediate treatment is a promising approach. This approach, known as screen-and-treat, provides treatment during the same visit as the screening visit, and overcomes many of the obstacles to widespread screening. Point-of-care tests for HPV are also now available in South Africa. Primary prevention of cervical cancer using HPV vaccination in young girls aged 9–15 years is predicted to reduce the cumulative incidence of cervical cancer by 70–80% over the long term and is likely to be effective in HIV-positive women. South Africa introduced a HPV vaccination programme in 2014 for girls aged nine years or older or in Grade 4. However, screening will need to continue for older women.

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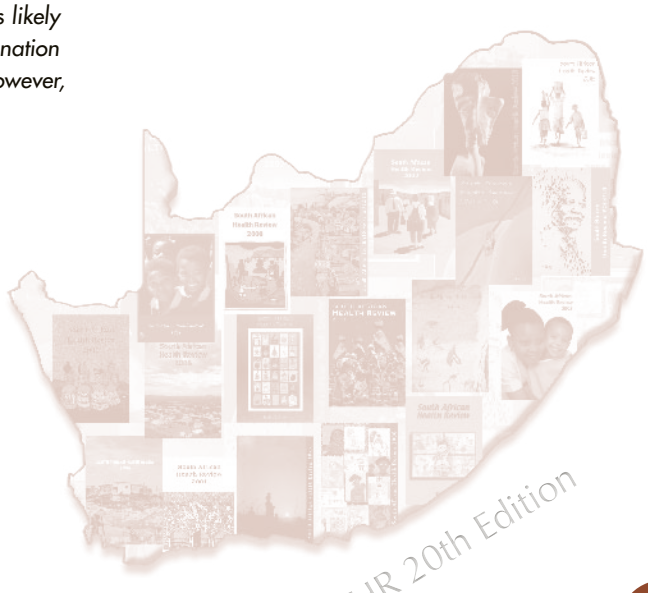

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Introduction

Cervical cancer is the fourth most-common cancer among women globally and the second most-common cancer in South African women. The GLOBOCAN 2012 estimates, which reported on cancer incidence and mortality rates by sex and age group for 184 countries using population-based cancer registries (PBCRs), suggested that 14.1 million new cancer cases and 8.2 million cancer deaths occurred worldwide in 2012.[1] Overall, lung cancer was found to be the most common cancer, followed by breast cancer. There were an estimated 528 000 new cases of cervical cancer in 2012, with around 85% of cases diagnosed in low- and middle-income countries (LMICs).[1] The highest-risk regions with age standardised incidence rates (ASIRs) of over 30 per 100 000 persons included Eastern Africa, Melanesia, and South and Middle Africa. Rates were lowest in Australia and New Zealand (5.5 per 100 000 persons) and Western Asia.[1]

Accurate interpretation and estimation of cancer incidence is hampered by the absence of PBCRs; for example, in 2006 only 21% of the world population was covered by PBCRs (8% in Asia and 11% in Africa).[2] Additionally, in 2014, Parkin et al. found that 20 out of 54 countries in Africa had no data on cancer and only seven countries had high-quality regional data coverage.[2]

According to 2012 estimations, 265 672 new cervical cancer deaths were reported globally in that year, with cervical cancer deaths ranking as the fourth leading cause of female cancer deaths in the world and the second most-common female cancer deaths among women aged 15–44 years.[3]

According to 2012 estimates, there were 4 248 cervical cancer deaths annually in South Africa that year, with cervical cancer ranking as the first cause of cancer deaths among women of all ages. The age standardised mortality rate was estimated at 18 per 100 000 women in South Africa, compared with 6.8 per 100 000 internationally.[3]

In developing countries, cancer receives significantly fewer resources than other diseases due to multiple competing health and social and environmental needs, specifically HIV, malaria and tuberculosis, lack of clean water, poor sanitation, civil strife, environmental stability and widespread poverty.

Adding to the complexity of detecting and treating cervical cancer is the impact of the HIV epidemic, which has diverted limited resources away from preventive health activities such as cancer screening. Additionally, it is well recognised that people living with HIV have higher rates of human papillomavirus (HPV)-associated disease, and in 1993, cervical cancer was classified as an AIDS-defining illness.[4]

Health inequity and cervical cancer

The incidence of cervical cancer is strongly related to health inequity. Ways to prevent and detect cervical cancer have been known since the beginning of the last century, yet the impact of these interventions has not migrated to developing countries and cervical cancer remains a leading cause of premature death and disability in women.[5] Disability-adjusted life years (DALYs) per 100 000 population among women with cervical cancer was found to be highest in sub-Saharan Africa at 641 per 100 000, compared with 355 per 100 000 in Latin America and the Caribbean, 243 per 100 000 in South-East Asia, 466 per 100 000 in India, and 58 per 100 000 in Australia and New Zealand.[5] Worldwide, 169.3 million years of healthy life were lost because of cancer in 2008. Soerjamataram et al. estimated that infection-related cancers (liver, stomach and cervix) in Africa contributed 25% to the total cancer burden. Using the Human Development Index (HDI), a composite indicator that includes life expectancy, education and gross domestic product per head, Bray et al. concluded that in 2008, a significantly greater proportion of the cancer mortality burden was seen in low and medium HDI areas.[6]

Cervical cancer in South Africa

South Africa's pathology-based National Cancer Registry (NCR) was established in 1986 and is the main source of the country's cancer statistics. It collates and analyses cancer cases diagnosed in pathology laboratories (public and private) and reports annual cancer incidence rates stratified by age, sex and population groups. The NCR was incorporated into the National Institute for Occupational Health (NIOH) in 2009 and receives data on about 80 000 cases per year, of which 60 000 are new cases.[7] In 2011, the NCR recorded 4 907 cases of cervical cancer and 5 627 cases of breast cancer. Of all cervical cancer cases diagnosed in South Africa, 82.7% were diagnosed in black women and 9% in white women. Overall, cervical cancer represented 15% of all cancers diagnosed in women compared with breast cancer, which accounted for 21%.

Data for 2003–2007, derived from a registry of 2 808 cancer patients living in a rural area of the Eastern Cape (EC),[8] indicated that most cancers were diagnosed in women (60.4%), with cervical cancer being the most common (34%), followed by oesophageal cancer, breast cancer, Kaposi's sarcoma and liver cancer.

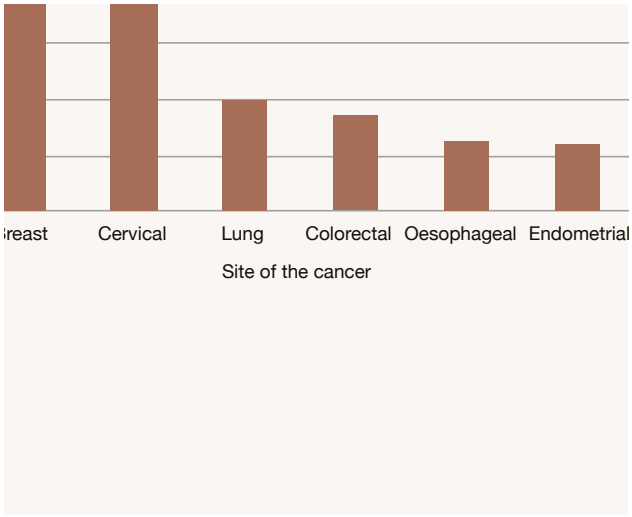
Further information on cervical cancer incidence was reported by the Institut Catalan d'Oncologia (ICO) Information Centre on HPV and Cancer in 2016.[9] Their data indicate that about 7 735 new cases of cervical cancer were diagnosed annually in South Africa in 2012, with cervical cancer being the most common cancer in women aged 15–44 years. The ASIR was estimated at 31.7 per 100 000 persons for South Africa compared with 14.0 per 100 000 persons globally. Figure 1 shows the ASIRs of cancer of the cervix compared with other cancer rates in women of all ages in South Africa using ICO Information Centre data.[9]

Natural history of cervical cancer and prevention

Infection of the cervix with high-risk types of human papillomavirus (harp) is necessary for the development of cervical cancer. There is now strong epidemiological, clinical and biological evidence of the causal relationship between infection with one or more of the 14 hrHPV types and cervical cancer. The most commonly associated HPV types are types 16 and 18, which account for around 70% of all cervical cancer cases.[10]

Cervical cytology testing involves collecting exfoliated cells from the cervix and examining these cells microscopically. An analysis by the International Agency for Research on Cancer (IARC) performed on eight of the world's largest screening programmes in the

Figure 1: Age standardised incidence rate per 100 000 women for cervical and other cancers in women of all ages in South Africa



Source: Bruni et al., 2016.[9]

1980s showed that well-organised screening programmes were effective in reducing the incidence of and mortality from cervical cancer.[11] Following the introduction of nationwide screening in the 1960s, cumulative mortality rates of cervical cancer demonstrated a significant falling trend. The greatest fall was in Iceland (84% reduction from 1965 to 1982) where the screening interval was the shortest and the target age range the widest. The smallest reduction in cumulative mortality (11%) was in Norway where only 5% of the population had been part of organised screening programmes.[12]

Overall, cervical cytology screening programmes have not been successfully initiated, implemented or sustained in low- and middle-income countries (LMICs), largely because of the complexity of the infrastructure required. Cervical cancer screening either does not occur or occurs sporadically, with the consequence that the incidence of cervical cancer and mortality from the disease remains high in LMICs.

HPV DNA genotyping

Once the epithelium of the cervix is infected by harp, usually through sexual contact, persistent infection may develop into cancer precursors (known as cervical intraepithelial neoplastic (CIN) grades 1–3, or more recently, using the Bethesda system, low- or high-grade squamous intraepithelial lesions (LSIL and HSIL), respectively).[13] Left untreated, these lesions may evolve into invasive cervical cancer, of which HPV types 16 and 18 are the most commonly detected.[14]

If cervical cancer precursors are detected, they can be removed either by ablation or excision, preventing progression to invasive cancer.

Cervical cancer prevention in South Africa

South Africa has historically provided opportunistic screening for cervical cancer prevention, despite being one of the better-resourced countries in sub-Saharan Africa.[15] Hence there are different rates of cervical cancer according to age, race, urban and rural areas, and socio-economic status. For example, Fonn et al. estimated that only 20% of South African women had been screened in 2000,[16] and during the period 2002–2003, coverage in the general rural population was estimated at 9.6% and coverage in the general urban population at 17.3 %.[4]

In 2000, The National Department of Health (NDoH) recommended that screening should start at age 30 and then be done every 10 years for three decades for asymptomatic women. Further, they recommended that all women with high-grade cervical cancer precursors or malignant lesions be referred to appropriate facilities for evaluation and treatment. There are many challenges when setting up screening programmes, particularly considering the impact of the HIV epidemic, which has channelled health resources away from preventive interventions such as for cervical cancer, and thus increased the risk of women developing HPV-related cancers. The gap between screening and treatment is acknowledged to be very high in South Africa, although there are few published data to support this statement.[17]

According to the National Health Laboratory Service (NHLS), just under a million smears were performed in South Africa between 2013 and 2014, of which 601 066 were classified as normal (66.5%), 8.6% were classified as LSIL, and 2.2% as HSIL.[a] Table 1 shows the data by province.

Table 1: Number of cervical smears performed and laboratory results by province, 2013–2014

Province	Cases (n)	Low-grade intraepithelial lesions (%)	High-grade intraepithelial lesions (%)
Eastern Cape	70 377	5.1	3.8
Free State	52 107	7.2	2.0
Gauteng	156 851	18.7	7.0
KwaZulu-Natal	181 705	14.3	7.7
Limpopo	82 085	6.7	3.1
Mpumalanga	55 116	3.4	6.9
North West	64 270	5.9	3.6
Northern Cape	12 522	2.1	6.2
Western Cape	128 411	8.6	3.8
Total	903 657	8.6	2.2

Source: Personal Communication, 2017.[a]

In order to determine the most appropriate age to begin cervical-cancer screening in South Africa, the NDoH extracted data on the number of HSIL cases (Table 2) and cervical-cancer cases (Table 3) during 2013–2015. While the diagnosis of HSIL remained relatively constant, the number of cervical-cancer cases rose steadily. Of importance is that the vast majority of significant disease, both malignant and precancerous, was found in women over the age of 30 years, suggesting that this is likely to be the most cost-effective age to begin screening.

a Personal Communication: Dr Manala Makua, Director of Women's Health and Genetics, South African National Department of Health, 9 January 2017.

Table 2: Number of women with HSIL in different age groups, 2013–2015

Year	HSIL		
	20–25 years	26–30 years	31+ years
2013	2017	5 481	31 235
2014	1816	4 868	30 461
2015	1634	4 649	31 228

Source: Personal Communication, 2017.[a]

Table 3: Number of women diagnosed with cervical cancer by age group, 2013–2015

Year	Cancer of the cervix		
	20–25 years	26–30 years	31+ years
2013	6	42	1 809
2014	10	41	1 953
2015	14	39	2 011

Source: Personal Communication, 2017.[a]

Alternative screening approaches to cytology-based programmes

HPV DNA testing

Over the past 20 years, numerous studies have been designed to avoid the complexity and expense of cytology-based screening programmes. Specifically, these include using visual inspection with acetic acid (VIA) followed by treatment with cryotherapy, and HPV DNA testing as a primary screen followed by either treatment, colposcopy and histological sampling, and/or co-testing with cytology.

A randomised screening trial was conducted in Khayelitsha, Cape Town, to evaluate the safety, acceptability and efficacy of screening women and treating those with positive tests without the intervention of colposcopy and histological sampling. A total of 6 555 unscreened women, aged 35–65 years, underwent testing for high-risk types of HPV. HPV DNA testing and VIA testing were performed by nurses in a primary care setting.[18] The study found that the HPV screen-and-treat arm was associated with a 3.7-fold reduction in the cumulative detection of CIN 2 plus (i.e. CIN 2, CIN 3 or cancer) by 36 months, and VIA was associated with a 1.5-fold reduction. For every 100 women screened, the HPV screen-and-treat strategy eliminated 4.1 cases of CIN 2 plus (CIN 2, CIN 3 or cancer) compared with VIA-and-treat, which eliminated 1.8 cases.

HPV DNA testing has recently evolved from a laboratory-based test into a point-of-care test.[19,20] One of these tests utilises the same platform (GeneXpert) as used in testing for tuberculosis and sensitivity to rifampicin in the South African National Tuberculosis Programme. This technology to perform testing for HPV (14 high-risk HPV types) is identical to that used for tuberculosis (although the cartridges contain different reagents), and it is now available in approximately 250 sites in South Africa. The test does not require batching and gives a result within one hour. It can be performed by a non-laboratory-trained assistant, on site, thus providing the ideal algorithm for 'screening and treating' women in both rural and urban areas.

Xpert HPV has been evaluated in a number of studies, including in Cape Town, where just over 1 000 women (500 HIV-positive and 500 HIV-negative) were screened using this technology. Participants were recruited from among women attending a colposcopy clinic with a high likelihood of disease and from an unscreened group of women from the general population of Khayelitsha. When the number of genotypes was restricted to the eight most common types, a sensitivity of 85% was obtained for CIN 2+ in HIV-positive women, with a specificity of 82%. In the case of HIV-negative women, a sensitivity of 85% was obtained, with specificity for CIN 2+ of 93%.[21]

Primary prevention of cervical cancer through HPV vaccination

Given its strong aetiological association with high-risk HPV infection, cervical cancer provides an ideal opportunity for vaccination intervention. Two vaccines have been developed for the prevention of cancer, namely the HPV vaccine and the vaccine against hepatitis B, which is aetiologically associated with liver cancer. Genital HPV infection is very common in sexually active men and women globally. Not all those infected will seroconvert, but low levels of type-specific neutralising antibodies against the viral capsid (L1) occur in around 50–70% of women, providing partial protection against subsequent infection with that type.[22]

There are currently two commercially available HPV vaccines: the bivalent vaccine against types 16 and 18, known as Cervarix® (GlaxoSmthKline), and the quadrivalent vaccine against types 6, 11, 16 and 18, known as Gardasil® (Merck/MSD). Both are prophylactic vaccines and should be given to girls and/or boys prior to exposure to the virus. Vaccination against HPV types 6 and 11 prevents the development of genital warts. High-risk HPV infection is associated with anogenital cancers other than cancer of the cervix, including vulval, vaginal, anal, penile and oro-pharyngeal cancers. A nonavalent vaccine (Gardasil 9®, Merck/MSD) which provides additional protection against types 31, 33, 45, 52, and 58 is currently undergoing clinical testing and has been licensed by the Food and Drug Administration (FDA).[23]

Rigorous randomised clinical trials have shown that all three vaccines are safe, immunogenic and effective in preventing disease associated with the types contained in the vaccines, and that protection persists for at least nine years (except for the non-valent vaccine where long-term data are awaited).

Cross-protection with non-vaccine oncogenic types

Prevention of cervical cancer by vaccinating girls aged 9–14 years (recommended by the World Health Organization (WHO)) is likely to prevent 70–80% of cervical cancers in those vaccinated. Considerable cross-protection against infection with types 31, 33, 45 and 51 has been demonstrated for the bivalent vaccine.[24] In addition, the quadrivalent vaccine has shown partial protection against types 31 and 33. One study, in which 3 459 subjects were included in an intention-to-treat analysis, found that administration of the quadrivalent vaccine reduced the combined incidence of infection with types 31 and 45 by 31.6%, and the incidence of infection with types 31, 33, 45, 52, 58 by 17.7%.[25]

Table 4: Summary of South African national HPV vaccination campaigns, 2014–2016

Date and year	Dose 1 coverage (n)	Date and year	Dose 2 coverage (n)	Total dose (1 & 2) (n)
10 March–11 April 2014	419 589	29 September–31 October 2014	329 665	749 254
23 February–20 March 2015	356 228	11 August–4 September 2015	329 000	685 228
16 February–11 March 2016	432 987	2 August–6 September 2016	320 292	753 279
Total	1 208 804		978 957	2 187 761

Source: District Health Information System[1,4]

Impact of HPV vaccination

Countries that introduced the HPV vaccine soon after it was licensed in 2006 have had more time to measure the impact of HPV vaccination. An Australian study found that 29% of women tested for HPV in the years prior to the HPV vaccine programme were HPV-positive for the HPV types in the quadrivalent vaccine, but only 7% of women post-vaccination had a positive test.[26] There was also a reduction of HPV infection in unvaccinated women, suggesting some herd immunity.

Two versus three doses

A proof-of-principle study in Costa Rica included a group of women who did not receive all their vaccine doses and who were HPV-negative at baseline. The study reported that vaccine efficacy for women who received, one, two or three doses was similar in preventing persistent HPV infection. HPV 16 and 18 antibody titres in women receiving two doses at least six months apart were non-inferior to the three-dose group.[27] As a result of this and other studies, the WHO recommends two doses administered six months apart in girls younger than 15 years; however, the WHO still recommends three doses in HIV-positive individuals.[28]

HPV vaccination in HIV-positive women

Numerous studies have shown that HPV infection in HIV-positive women is more common than in the general population and that cervical cancer occurs 2–22 times more commonly in HIV-positive women.[29] Denny et al.[30] evaluated the safety and immunogenicity of the bivalent vaccine in HIV-positive women aged 18–25 years. HIV-positive women were randomised to receive the bivalent vaccine or a placebo at 0, 1 and 6 months, and a group of 30 HIV-negative women were recruited and vaccinated for comparison. The safety and immunogenicity profile of the bivalent vaccine was comparable in HIV-positive and HIV-negative women, and parameters such as CD4 counts and viral loads were not affected in either of the vaccinated or placebo groups. Serology in the HIV-positive vaccinated group was sustained through the 12-month period.

In 2014, Toft et al.[31] published a review of HPV vaccination trials in HIV-positive populations (men, women and children) and concluded that prophylactic HPV vaccination is safe, immunogenic and, by extrapolation, likely to reduce HPV-associated cancer in people living with HIV.

Introduction and coverage of HPV vaccination in South Africa

Data on South Africa's HPV vaccination programme, presented at the 31st International Papillomavirus Conference in 2017, indicated that planning for the HPV vaccination programme began in 2012 and involved wide consultation with relevant stakeholders, including school governing bodies, school principal associations and labour unions.[b] The intention was to use an integrated school-based health system. Budget was ring-fenced in 2013 to begin vaccination in 2014, and the aim was to vaccinate over 500 000 girls from just under 18 000 schools. Eligible girls were offered a two-dose regime with bivalent vaccine at month 0 and month 6. According to Dr Dlamini,1 208 000 girls have been vaccinated to date.[b]

The following factors were cited as being critical to the success of the programme: using the school health system, political will, ring-fenced funding, social mobilisation, integration (girls were offered deworming medication as part of the screening process), and reliable methods for monitoring and evaluation.[b]

Major challenges faced were staff shortages, lack of adequate transport, and lack of computer skills. Challenges have also been encountered in tracking school and learner coverage, and there is a need to develop a system to identify missed schools, vaccine-stock management and the management of adverse events.[b]

Data on coverage of Grade 4 girls from 2014 (Table 4) show that coverage has been consistently high, with good follow-up of girls requiring dose 2.

b Personal Communication: Dr NR Dlamini, Chief Director: Child Adolescent and Child Health, Department of Health, 15 March, 2017.

Conclusions

Cervical cancer is the second-commonest cancer diagnosed among women in South Africa and the commonest cancer among women aged 15–49 years. It is a preventable cancer, and where national screening programmes have been successfully implemented and sustained, cervical cancer incidence and mortality have been dramatically reduced. However, the complexity of the infrastructure required to implement cytology-based screening programmes has precluded LMICs from either initiating or sustaining effective national cervical cancer screening. This has prompted research in the past 20 years to find alternatives to cytology-based programmes, specifically VIA and molecular testing for hrHPV. Different algorithms and approaches have been recommended, the most popular being a 'screen-and-treat' approach, where women are tested for hrHPV and given a result at the same visit using a point-of-care test.

Primary prevention of cervical cancer using HPV vaccination has the potential to reduce cervical cancer by at least 70–80% in those vaccinated and is likely to have a major impact on HPV-associated disease in the long term. A major challenge, however, is to ensure that the vaccine is rolled out to the populations that need them most.

Recommendations

- The National Cancer Registry should be updated and upgraded to a population-based registry to enable more accurate data collection for planning, monitoring and evaluation.
- Where cytology-based programmes are functioning well, their resources should be consolidated. However, where no such programmes exist in South Africa, the NDoH should consider alternative algorithms for cervical cancer prevention, as defined in this paper.
- Cervical cancer screening in asymptomatic women should be free and provided at primary or district levels of care.
- Healthcare workers should be adequately skilled in all areas of cervical cancer control, and curricula at healthcare institutions should be relevant and aligned.
- The gap between abnormal screening results and referral for colposcopy and/or treatment must be closed.
- Where possible and feasible, consideration should be given to linking HPV vaccination of girls with screening of their mothers.
- Ongoing monitoring of coverage and uptake of HPV vaccination should be ensured and the programme should be adapted regularly to ensure high-quality implementation and the desired outcome, namely a major reduction in HPV-associated disease.

References

1 Ferlay F, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359–86.

2 Parkin DM, Bray F, Ferlay J, Jemal A. Cancer in Africa 2012. Cancer Epidemiol Biomarkers Prev. 2014;23(6):953–66.

3 Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.2. Cancer Incidence and Mortality worldwide. IARC CancerBase No. 11. Lyon, France, International Agency for Research on Cancer, 2013. [Internet] [cited January, 2017]. URL: http://globocan.iarc.fr

4 Castro KG, Ward JW, Slutsker L, et al. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR.1992; 41:1–19.

5 Soerjomataram I, Lortet-Tieulent J, Parkin DM, et al. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. Lancet. 2012;380(9856):1840–50.

6 Bray F, Jemal A, Grey N, et al. Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. Lancet Oncol. 2012;13(8):790–810.

7 National Cancer Registry. Cancer in South African 2012. Full report. [Internet]. [cited January 2017]. URL: http://www.nioh.ac.za/assets/files/NCR%202012%20results.pdf

8 Somdyala NIM, Bradshaw D, Gelderblom WCA. Eastern Cape Province Cancer Registry Technical Report. Cancer incidence in selected municipalities of the Eastern Cape Province 2003–2007. Cape Town: South African Medical Research Council; August 2013.

9 Bruni L, Barrionuevo-Rosas, Albero G, et al. ICO Information Centre on HPV and Cancer (HPV Information Centre). Human papillomavirus and related diseases in South Africa. Summary Report 15 December 2016.

10 de Sanjose S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010;11(11):1048–56.

11 International Agency for Research on Cancer (IARC) Working Group on Cervical Cancer Screening. Summary chapter. In: Hakama M, Miller AB, Day NE, editors. Screening for Cancer of the Uterine Cervix. Lyon, IARC; 1986.

12 Laara E, Day NE, Hakama M. Trends in mortality from cervical cancer in the Nordic countries: Association with organised screening programmes. Lancet. 1987; May 30:1247–9.

13 Nayar R, Solomon D. Second edition of 'The Bethesda System for reporting cervical cytology' – atlas, website and Bethesda interobserver reproducibility project. Cytojournal 2004 (1):4.

14 Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12–9.

15 Kawonga M, Fonn S. Achieving effective cervical screening coverage in South Africa through human resources and health systems development. Reprod Health Matters. 2008;16(32):32–40.

16 Fonn S, Bloch B, Mabina M, et al. Prevalence of pre-cancerous lesions and cervical cancer in South Africa: a multicentre study. S Afr Med J. 2002;92(2):148–56.

17 Moodley J, Kawonga M, Bradley J, et al. Challenges in implementing a cervical screening program in South Africa. Cancer Detect Prev. 2006;30(4):361–8.

18 Denny L, Kuhn L, Hu CC, et al. Human papillomavirus-based cervical cancer prevention: long-term results of a randomized screening trial. J Natl Cancer Inst. 2010;102:1–11.

19 Einstein MH, Smith KM, Davis TE, et al. Clinical evaluation of the cartridge-based GeneXpert human papillomavirus assay in women referred for colposcopy. J Clin Microbiol. 2014;52(6):2089–95.

20 Toliman P, Badman SG, Gabuzzi J, et al. Field Evaluation of Xpert HPV Point-of-Care Test for Detection of Human Papillomavirus Infection by Use of Self-Collected Vaginal and Clinician-Collected Cervical Specimens. J Clin Microbiol. 2016;54(7):1734–7.

21 Kuhn L, Saidu R, Boa R, et al. Optimizing Point-Of-Care HPV testing for cervical cancer prevention in South Africa. EUROGIN 2016; Saltzburg Austria, June 15–18, 2016.

22 Wentzensen N, Rodriguez AC, Viscidi R, et al. A competitive serological assay shows naturally acquired immunity to human papillomavirus infections in the Guanacaste Natural History Study. J Infect Dis. 2011; 204(1):94–102.

23 Joura EA, Guiliano AR, Iverson O-E, et al. for the broad spectrum HPV Vaccine Study. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015; 372:711–23.

24 Wheeler CM, Castellesgue X, Garland S, et al and the HPV PATRICIA Study Group. Cross protective efficacy of HPV 16/18 ASO4-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4 year end of study analysis of the randomised double-blind PATRICIA trial. Lancet Oncol. 2012; 13:100–10.

25 Wheeler CM, Kjaer SL, Sigurdsson K, et al. The impact of Quadrivalent Human Papillomavirus (HPV; Types 6, 11, 16 and 18) L1 Virus-Like Particle Vaccine on Infection and Disease Due to Oncogenic Nonvaccine HPV types in sexually Active Women aged 16 – 26 years. J Infect Dis. 2009;199:936–44.

26 Tabrizi SN, Brotherton JM, Kaldor JM, et al. Assessment of herd immunity and cross protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study. Lancet Infect Dis. 2014;14(10):958–66.

27 Kreimer AR, Rodriguez AC, Hildesheim A, et al and the CVT Vaccine Group. Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV 16/18 vaccine. J Natl Cancer Inst. 2011;103:1444–51.

28 World Health Organization. Human papillomavirus vaccines: WHO position paper, October 2014. WER. 2014;89:465–91.

29 Forman D, de Martel, Lacey CJ, et al. Global burden of human papillomavirus and related diseases. Vaccine. 2012;30(S5):F12–23.

30 Denny L, Hendricks B, Gordon C, et al. Safety and immunogenicity of the HPV-16/18 ASO4-adjuvanted vaccine in HIV-positive women in South Africa: a partially-blind randomised placebo-controlled study. Vaccine. 2013;31:5746–53.

31 Toft L, Tolstrup M, Storgaard A, et al. Vaccination against oncogenic human papillomavirus infection in HIV infected populations: review of current status and future perspectives. Sex Health. 2014;11:511–23.