

Review

Cervical Cancer in Africa

Lynette Denny¹ and Rose Anorlu²

Abstract

Cervical cancer is a relatively rare disease in countries that have instituted and maintained national screening programs, with call and recall of women at various intervals and built-in quality control with appropriate monitoring and evaluation. Unfortunately, this process has failed in most areas of the world where more than 80% of new cases of cervical cancer are diagnosed. Cervical cancer affects women in the prime of their lives causing premature and needless suffering and death in a critically important segment of the world's population, despite being one of the few cancers that can be prevented with simple testing. In the past 15 years innovative approaches to both primary and secondary prevention of cervical cancer have been subjected to a number of large scale, scientifically valid and applicable studies that have opened the way for new approaches. Treatment of cervical cancer in Africa is hampered by the lack of diagnostic and treatment facilities, lack of healthcare infrastructure and poor pathology services. Further, there is a significant brain drain of trained healthcare workers in Africa that exacerbates the problem. Cancer is becoming an increasingly important public health problem as more people live longer. It is time to develop programs for the prevention, early detection, treatment, and palliation of cancer sufferers in Africa. *Cancer Epidemiol Biomarkers Prev*; 21(9); 1434–8. ©2012 AACR.

Cervical Cancer

In a recent analysis based on the 2008 world wide estimates of cancer compiled by the International Agency for Research on Cancer (IARC, Lyon, France; Globocan 2008; ref. 1), it was estimated that 529,512 women were diagnosed with cervical cancer corresponding to an annual Age Standardized Incidence Rate (ASIR) of 15.4/100,000. An estimated 274,967 women died of the disease, with an annual Age Standardized Mortality Rate (ASMR) of 7.8/100,000 (2). The majority of cases ($n = 453,032$; 85.5%) and deaths ($n = 241,818$; 85.5%) were found in developing countries. Globally, cervical cancer was the third most common cancer ranking after breast (1.3 million cases) and colorectal cancer (0.57 million cases) and the fourth most common cause of cancer death ranking below breast, lung, and colorectal cancer. Figures 1 and 2 illustrate the distribution of cervical cancer incidence and deaths in the different regions of the world (1).

In Africa, which has a population of 267.9 million women aged 15 years and older at risk of developing cervical cancer, approximately 80,000 women are diagnosed with cervical cancer per year, and just more than 60,000 women die from the disease (1). However, cervical

cancer incidence in Africa also varies considerably by region. The highest rates in Africa (ASIR > 40/100,000) are found in Eastern and Southern Africa (Fig. 3; ref. 1). In addition, there are marked variations within regions themselves as illustrated in Fig. 4 for Southern Africa (1), where the highest incidence is found in Lesotho and Swaziland, 2 countries that have neither screening programs nor any anticancer treatment facilities and who have 1 and 2 doctors per 10,000 population, respectively (compared with 8/10,000 in South Africa and 27/10,000 in the United States; ref. 3).

Most women in developing countries present with advanced disease, often untreatable or suitable only for palliation. For instance, in Sudan where 197 women were diagnosed with cervical cancer in 2007, 141 (71%) had advanced stage disease (4). The Kampala population-based registry, estimated 5-year survival rates between 1993 and 1997 for various cancers and compared these to African-American cancer patients diagnosed during the same time period and registered in the Surveillance, Epidemiology, and End Results program of the National Cancer Institute of USA. The Kampala registry included a total population of 1.2 million people. The absolute and relative 5-year survival of women in Kampala was 15.9% and 18.2%, respectively, compared with approximately 60% in African-American women in the United States (5). Gondos and colleagues reported on the 5-year absolute and relative survival estimates for black Zimbabweans diagnosed with cancer in Harare, Zimbabwe between 1993 and 1997. The 5-year absolute and relative 5-year survival was 26.5% and 30.5%, respectively, compared with around 60% for African-American women during the same time period. These very low rates of survival were attributed to late presentation of disease (6).

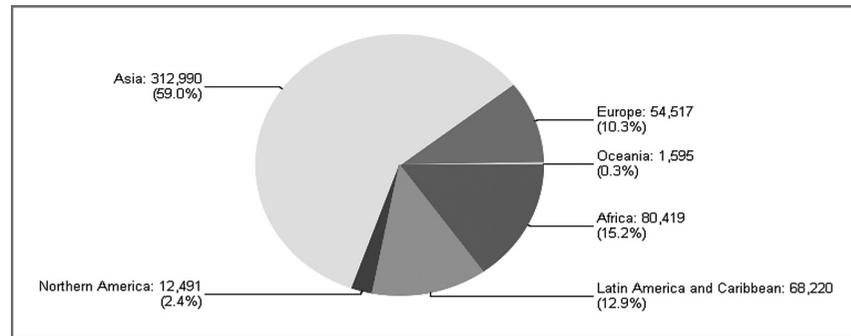
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Figure 1. Cervix uteri. Estimated number of cancer cases, all ages. Incidence of cervical cancer, all ages in different regions of the world. Globocan 2008: <http://globocan.iarc.fr/> (1).



Understanding Cancer Diagnosis and Management in the Context of the African Continent

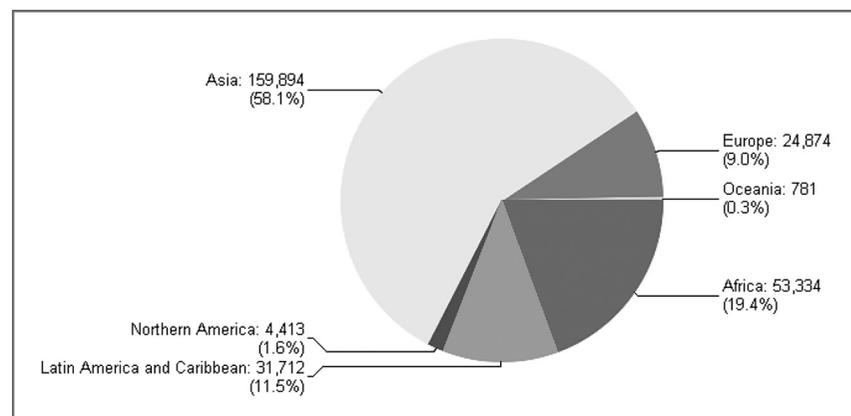
Sub-Saharan Africa (SSA) consists of 46 countries almost all of which have the lowest ranked Human Development Index (HDI) and highest Human Poverty Indices (HPI; ref. 7). With a total population estimated in 2008 of 812 million (404 million men and 408 million women), only 7.2% were covered by medically certified causes of death and 8.3% by population-based registries. It was estimated in 2008 that there were 667,000 incident cancers diagnosed and 518,000 cancer deaths recorded, that is 78% of those diagnosed with cancer died from the disease, however reliable data on cancer are difficult to find in the African context (1). Sankaranarayanan and colleagues (8) evaluated cancer survival for 341,658 people diagnosed with a variety of cancers from 1990 to 2001. Only two of the cancer registries that had data of sufficient quality to include in the analysis were located in SSA, Gambia and Uganda. Cancer survival as recorded in these 2 registries was the lowest of all countries surveyed in this study. No cancer exceeded a 5-year survival of greater than 22% in Gambia, and in Uganda the similar figure was 13% except for breast cancer where survival was 46% at 5 years. Moreover, access to anti-cancer therapies are very limited in almost all African countries and a World Health Organization (WHO) study in 2001 found that only 22% of African countries had access to anti-cancer drugs, compared with 91% in Europe (9, 10).

Further, there is a great shortage of trained healthcare personnel in Africa where there is also a "brain drain" or

exodus of trained personnel to other more attractive continents. The reasons for the exodus of African healthcare workers are various and include: poor salaries in State institutions, lack of career advancement, poor institutional support in terms of infrastructure, equipment, staff, access to training, and modern technologies such as medical equipment, access to electronic libraries, internet, among others. Further, developed countries often offer many of these benefits that are lacking in many African countries. WHO estimated in 2006 that Africa has a needs-based shortage of 818,000 healthcare professionals (meaning doctors, nurses, and midwives) based on a country needing 2.28 healthcare professionals per 1,000 population (9). In a study by Scheffler and colleagues, they estimated that for 31 SSA countries in 2015 the shortage of healthcare professionals will be 792,000 and the estimated wage bill necessary to eliminate the shortage is approximately \$2.6 billion (11).

Adding to the complexity of the challenges facing SSA (ranging from environmental disasters to competing health needs, endemic civil strife, war, lack of safe water, and sanitation to name a few) has been the HIV/AIDS epidemic, where 70% of the world's cases of HIV are diagnosed (12). It has been well known that HIV infection increases the risk of developing certain cancers and Kaposi Sarcoma, Non-Hodgkin Lymphoma, and Cervical cancer have been classified as AIDS defining diseases since 1993 (13). Women infected with HIV have an increased risk of being infected with HPV, of persistent infection with high-risk types of HPV, of developing cervical cancer precursors and are therefore considered at higher risk for cervical cancer (14, 15). However, the expected increase in women

Figure 2. Cervix uteri. Estimated number of cancer deaths, all ages. Mortality from cervical cancer in different regions of the world. Globocan 2008: <http://globocan.iarc.fr/> (1).



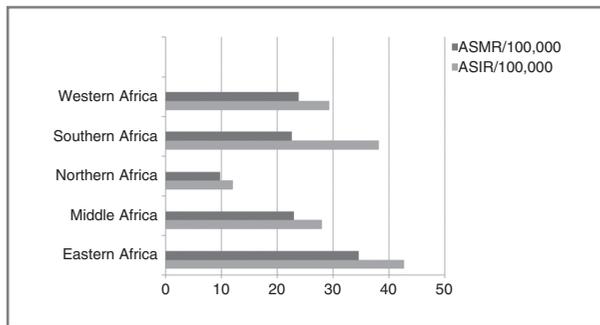


Figure 3. ASIR/100,000 and ASMR/100,000 in different regions of Africa. Globocan 2008: <http://globocan.iarc.fr/> (1).

diagnosed with cervical cancer in Africa during the HIV pandemic has not been convincingly observed, most likely due to most at-risk women dying from other opportunistic infections prior to developing cervical cancer or its precursors. In the era of antiretroviral medication, this scenario is expected to change.

Cervical cancer diagnosis and treatment in Africa

Women who are fortunate enough to access treatment for cervical cancer in Africa will most often receive radiation therapy, either with curative or more commonly, palliative intent. Based on GLOBOCAN data from 2002, Barton and colleagues (16) estimated that 55% (range 47–61%) of new cases of cancer diagnosed in Africa had an indication for radiotherapy. Radiation facilities are not available at all in 15 African countries (17). In those countries where radiation facilities do exist, there is usually one machine per several million people—for example, in Nigeria in 2007 there were only 5 radiation facilities for a population of more than 150 million people (18). In most cases, radiation is delivered using cobalt machines that are a lot cheaper and easier to maintain than linear accelerators. The median costs of radiotherapy using linear accelerators have been estimated at \$11 compared with \$4.87 per patient for cobalt machines (19). A survey of 72 low- and middle-income countries found that 24 countries with populations greater than 1 million people did not have any radiotherapy service and the majority of these countries were in Africa (20). Radiotherapy is still considered to be

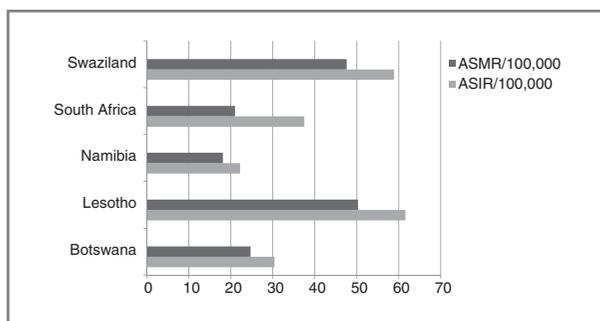


Figure 4. ASIR/100,000 and ASMR/100,000 in different countries within Southern Africa. Globocan 2008: <http://globocan.iarc.fr/> (1).

high-technology medicine in Africa and where facilities do exist [e.g., South Africa, Ethiopia (one machine for a population of more than 60 million), Madagascar, Nigeria, Tanzania, Uganda, Sudan, Kenya, Ghana, Senegal, Zimbabwe, Cameroon]. They are located in tertiary institutions or in the private sector and are often nonfunctional or poorly maintained.

Palliation for women with advanced disease is also extremely limited in most SSA countries, where for instance, oral morphine is only available in 11 countries (21). It is estimated that 80% of cancer deaths require pain treatment lasting an average of 3 months. In 2008, the actual procurement of morphine and equivalent opioids reported by governments in SSA to the International Narcotics Control Board was 10% of the quantity required to treat terminally ill patients with cancer and HIV.

Modern Approaches to Prevention of Cervical Cancer

Historically, cervical cancer has been prevented by performing cervical cytology within the context of national screening programs, referring women with abnormal cytology for colposcopy and treatment and follow up thereafter. Initiating and sustaining such programs have proved to be prohibitively complex for most developing countries. In the past 15 years alternatives to cytology-based screening programs have been investigated in developed and developing countries. The most tested approaches have been Visual Inspection with Acetic Acid (VIA) and HPV DNA testing either as primary screening tests, in combination with cytology or adjunctive to cytology. Thousands of women have participated in these trials. Cross-sectional studies have shown promising sensitivity of VIA compared with cytology (22) and the sensitivity of VIA to detect high-grade cervical cancer precursor lesions and cervical cancer has varied from 49% to 96% and the specificity from 49% to 98%. However, many of these studies suffered from verification bias, where the true status of disease in test negative women was unknown. In a more recent publication, Sauvaget and colleagues (23) carried out a metaanalysis of 26 studies in which VIA was carried out on asymptomatic women who underwent confirmatory testing and the disease threshold was CIN 2 plus. They report a sensitivity range of 80% (range 79–82%) and 92% specificity (range 91–92%) for VIA, with a positive predictive value of 10%. They conclude that in very low resource settings where the infrastructure for laboratory-based testing is not available, VIA is reasonable alternative to cytology. However, in more recent randomized studies VIA has carried out poorly in terms of test characteristics and prevention of disease.

Denny and colleagues (24) conducted a randomized screening trial to evaluate the safety, acceptability, and efficacy of screening women and treating those with positive tests without the intervention of colposcopy and histologic sampling. A total of 6,555 unscreened women,

aged 35 to 65 years, underwent testing for high-risk types of HPV DNA (using Hybrid Capture 2) and VIA, done by nurses in a primary care setting. This study found that HPV and treat "screen and treat" arm was associated with a 3.7-fold reduction in the cumulative detection of CIN 2 or greater by 36 months and VIA was associated with a 1.5-fold reduction. For every 100 women screened, the HPV and treat screen and treat strategy eliminated 4.1 cases of CIN 2 or greater compared with VIA and treat that eliminated 1.8 cases.

In another landmark study Sankaranarayanan and colleagues (25) carried out a cluster-randomized trial of 131,746 women aged 30 to 59 years who were randomly assigned to 1 of 4 groups: (i) HPV testing, (ii) cytologic testing, (iii) VIA, or (iv) standard of care that involved no screening as the control group. The incidence rate of cervical cancer stage 2 or higher and death rates from cervical cancer were significantly higher in the cytologic, VIA, and control groups compared with the HPV testing group. Further, the ASIR of invasive cancer among women who had negative test results on cytologic or VIA testing was more than 4 times greater the rate among HPV negative women.

These data suggest that primary screening with HPV DNA, followed by treatment will be associated with a significant reduction in cervical cancer and cervical cancer precursors. HPV DNA testing however remains a laboratory-based test and current tests are not yet affordable in developing countries. The ideal test for HPV DNA detection would provide a result at the time of examination and screening, that is a point-of-care test that has not yet been developed. New technologically more accessible and easier HPV DNA tests are being developed such as careHPV (Ref. 26; Qiagen), which is able to detect 14 high-risk types of HPV in around 2.5 hours at a much lower cost compared with current commercially available HPV DNA tests. Other tests being developed include detection of high-risk E6/E7 mRNA that have the potential to greatly increase the specificity of HPV DNA testing and reduce the rate of overtreatment (27, 28).

Primary Prevention of Cervical Cancer

The recent availability of vaccines against certain types of HPV has altered the landscape of possibility for prevention of cervical cancer. Both are prophylactic vaccines and need to be given to subjects before exposure to the type of HPV included in the vaccines.

Monovalent (against HPV 16), bivalent (against HPV 16, 18; Cervarix, GlaxoSmithKline Biologicals) and quadrivalent (against HPV 6, 11, 16, 18; Gardasil, Merck and Co., Inc.) vaccines have been tested in randomized placebo-controlled trials and shown to be safe, immunogenic, and highly efficacious (29–34). A recent publication reported on follow-up to 8 years after vaccination (35).

There is good evidence provided by randomized placebo-controlled trials that these vaccines prevent both persistent infection with the types included in the vac-

cines, as well as preinvasive 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).

From a developing country point of view introducing the HPV vaccine into the public health arena poses many challenges. The most obvious is cost, and the present price of both vaccines is unaffordable, although GAVI recently announced that it will subsidise the implementation of HPV vaccination in those countries that can show the ability to distribute the vaccine, and dependent on a price to be negotiated with the commercial companies (36). However, cost is only one aspect. Firstly, few developing countries have established pubescent/adolescent health platforms or school health systems from which to vaccinate young girls (and possibly boys). This infrastructure will have to be created *de novo* in many countries and for this to happen, a great deal of political will, along with resource allocation, needs to be generated. Unfortunately, no studies have yet included infants, so neither vaccine will be approved for integration into the Extended Program for Immunization (EPI) that has been successfully introduced into many developing countries, with high coverage. EPI is believed to save 3 million young lives per year.

Whether or not countries introduce the vaccine into the public health sector will be determined by (i) the burden of HPV-associated disease in a particular country, (ii) the ability to convince politicians and health officials (particularly those who work with children and vaccination) that it is worthwhile to invest in vaccinating children to prevent a disease of adulthood, (iii) the creation of the appropriate infrastructure for the administration of the vaccine, and finally (iv) the cost in relation to competing health priorities in individual countries.

Conclusion

Cervical cancer is a preventable disease yet remains the commonest cause of cancer death among women in poor countries (1). Recent research into alternative approaches for the secondary prevention of cervical cancer offers new possibilities for more affordable and implementable programs, particularly "screen and treat" programs that have been tested in randomized trials in South Africa and India and shown that HPV-based screening coupled with treatment using cryotherapy significantly reduces the incidence of cervical cancer precursors and cervical cancer (24, 25). In addition to new approaches to secondary prevention of cervical cancer, the recent availability of 2 highly effective vaccines against HPV infection has major implications for future prevention: the bivalent vaccine targets HPV types 16 and 18 (aetiologically associated with 70% of cervical cancers) and the quadrivalent vaccine targets types 6 and 11 (responsible for genital warts) and types 16 and 18. Further, a great deal of current research is aimed at finding accurate methods for the molecular detection of cervical cancer precursors. Once developed

these tests have the potential to overcome some of the deficiencies associated with cervical cytology-based screening and programs.

Disclosure of Potential Conflicts of Interest

L. Denny has received honoraria for appearing on various educational and speaker fora for both GlaxoSmithKline (GSK) and Merck/MSD. The author is the principal investigator for a randomized trial of the safety and efficacy of the bivalent HPV vaccine in HIV positive women sponsored by GSK and for a study on HPV genotyping in women with cervical cancer in Africa. In addition she has received funding from MSD/Merck for a study on genotyping in women with genital warts.

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Development of methodology: L.A. Denny
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L.A. Denny
Writing, review, and/or revision of the manuscript: L.A. Denny, R. Anorlu
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L.A. Denny
Study supervision: L.A. Denny

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