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Cervical Cancer Prevention and Treatment in Low-Resource Settings

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INTRODUCTION

In a recent analysis based on the 2008 worldwide estimates of cancer compiled by the International Agency for Research on Cancer (IARC, Lyon, France)[1], it was estimated that 529,512 women were diagnosed with cervical cancer corresponding to an age-standardized incidence rate (ASIR) of 15.4/100,000 and 274,967 women died of the disease, with an age-standardized mortality rate (ASMR) of 7.8/100,000[2]. The majority of the cases diagnosed (n = 453,032; 85.5%) were found in developing countries, as were the deaths (n = 241,818; 87.9%). 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. There is a striking disparity in the incidence of and mortality from cervical cancer in different regions of the world. Figure 1 shows the annual number of deaths from cervical cancer in developed and developing regions by age group, and it is evident that the number of deaths in developing countries is nearly 10 times greater than in developed regions.

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 over 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 all found in Eastern, Southern or Western Africa (Figure 2). In addition, there are marked variations within regions themselves as illustrated in Figure 3 for Southern Africa[1], where the highest incidence is found in Lesotho and Swaziland, two countries that have neither screening programs nor any anti-cancer treatment facilities and who have 1 and 2 doctors per 10,000 population, respectively (compared to 8/10,000 in South Africa and 27/10,000 in the USA)[3].

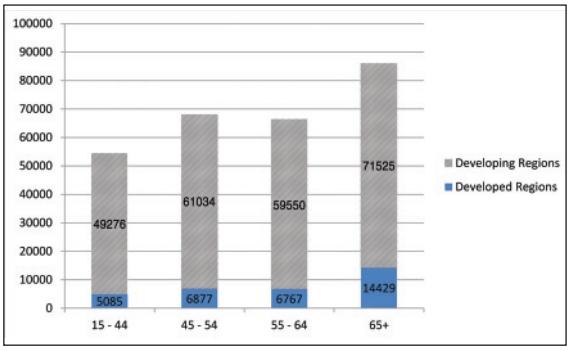

Figure 1 Annual number of deaths from cervical cancer by age group in developed and developing regions. Source: Globocan 2008[1], http://www.who.int/hpvcentre

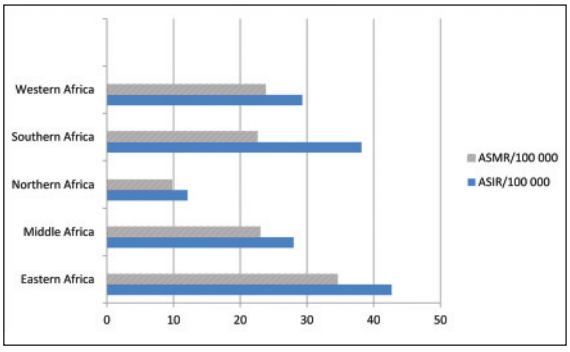

Figure 2 ASIR/100,000 and ASMR/100,000 in different regions of Africa. Source: Globocan 2008[1], http://www.who.int/hpvcentre

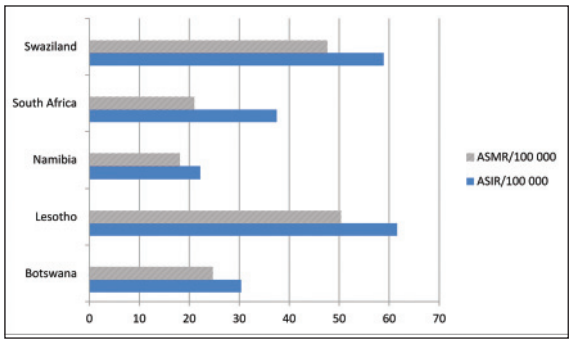

Figure 3 ASIR/100,000 and ASMR/100,000 in different countries within Southern Africa. Source: Globocan 2008[1], http://www.who.int/hpvcentre

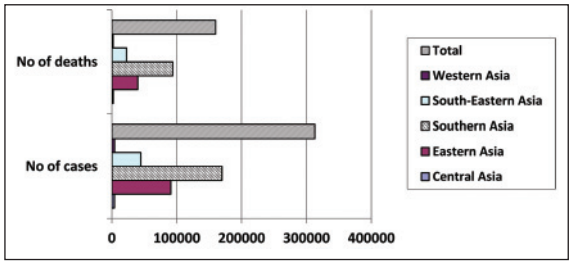

Figure 4 Incidence and mortality of cervical cancer in Asia. Source: Globocan 2008[1], http://www.who.int/hpvcentre

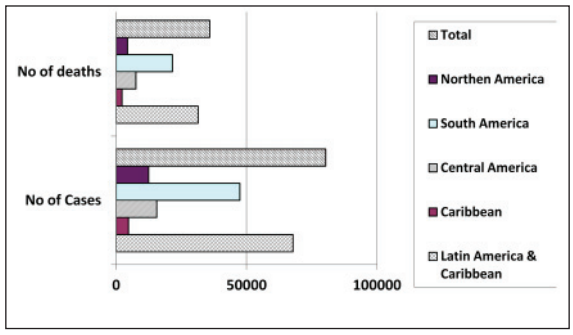

Figure 5 Number of cases and deaths due to cervical cancer in the Americas. Source: Globocan 2008[1], http://www.who.int/hpvcentre

Overall, Asia has a population of 1391.30 million women aged 15 years and older who are at risk of developing cervical cancer[1]. Cancer of the cervix is the second most common cancer among women in the Asia Pacific region (after cancer of the breast) with an estimated 312,752 cases diagnosed per year and 159,774 deaths recorded[1]. The distribution of cervical cancer cases in Asia varied significantly by region (Figure 4) with the highest incidence in Southern Asia (169,854; 54.3% of all cases in Asia) and lowest in Central and Western Asia.

The Asia Pacific region was estimated in 2000 to contribute 51.6% of the world's total cervical cancer cases and 50.3% of the deaths[4]. China and India provide 85% of the population of the region, and the estimated ASIR of cervical cancer in China (6.8/100,000) is low. However there is a wide variation within China with ASIR of 23.6/100,000 in Shanxi compared to 5.8/100,000 in Guanxi province[4]. India, Bangladesh, Nepal and Sri Lanka together contribute to around one-third of the global cervical cancer burden[5]. India has a population of 1.2 billion people and information on cervical cancer comes from 18 population-based registries, covering about 4% of the total population. ASIR range from 9–40 per 100,000 women in different regions of India.

The situation in Latin America and the Caribbean is similar to other parts of the developing world with the highest incidence and mortality found in Latin America and the Caribbean combined. Figure 5 shows the incidence and mortality from cervical cancer in different regions[1].

By comparison, in Europe, where there are 321.8 million women aged 15 years and older at risk, 59,931 women are diagnosed with cancer of the cervix and 28,812 die from the disease and cervical cancer ranks as the 7th most frequent cancer in Europe. America has a population of 336.5 million women aged 15 years and older and yearly 86,532 women are diagnosed with cervical cancer and 38,436 die from the disease. It ranks as the 4th most frequent cancer in women in America[1].

The huge difference in cervical cancer incidence in developing versus developed regions is a reflection of the absence of national cervical cancer screening programs in most developing countries. Where national organized screening programs have been implemented, as was achieved in many Scandinavian countries in the second half of the last century, cervical cancer incidence and mortality were significantly reduced[6,7]. There are many barriers to setting up national screening programs in developing countries, although in the last 15 years, new approaches and technologies have made the possibility of implementing secondary prevention screening programs in poor countries more feasible and currently there are demonstration projects in over 40 developing countries (www.iarc.org).

NATURAL HISTORY OF CERVICAL CANCER

The natural history of cervical cancer has been extensively studied in the past 30–40 years, and persistent infection of the cervix with certain high-risk types of human papillomavirus (HPV), a largely sexually transmitted infection (STI), has been well established as a necessary cause of cervical cancer. High-risk types of HPV are identified in nearly all carcinomas of the cervix and the relative risk of cervical cancer associated with infection with high-risk types of HPV is higher than the risk of lung cancer associated with smoking[7]. Munoz *et al.*[8] pooled data from 11 case–control studies involving 1918 women with histologically confirmed squamous cell carcinoma of the cervix and 1928 control women. The pooled odds ratio for cervical cancer associated with the presence of any HPV infection was 158.2 [95% confidence interval (CI) 113.4–220.6]. On the basis of the pooled data, 15 HPV types were classified as high risk (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82) and are considered carcinogenic.

In a meta-analysis of HPV types found in invasive cervical cancers worldwide[9] data on a total of 10,058 cases (which included squamous cell carcinomas, adenocarcinomas and adenosquamous carcinomas) confirmed the high prevalence of HPV in cervical cancers in different regions of the world, with HPV 16 (51%) and 18 (16.2%) being the commonest. However, more than 16 other types of HPV were also associated with cervical cancer, of which types 45, 31, 33, 58 and 52 were the most prevalent. Further, HPV type 16 was more prevalent in squamous carcinomas and HPV type 18 more prevalent in adenocarcinomas of the cervix. Overall, HPV prevalence differed little between geographical regions (83–89%) but was low compared to the almost 100% prevalence in studies that have used the most sensitive methods of detection for HPV.

A more recent publication evaluated HPV infection in paraffin-embedded samples of histologically confirmed cases of invasive cancer from 38 countries in Europe, North America, central South America, Africa, Asia and Oceania taken over a 60 year period[10]. A total of 10,575 cases of invasive cervical cancer were included in the study and 85% (n = 8977) were positive for HPV DNA. The eight most common types of HPV detected were 16, 18, 31, 33, 35, 45, 52 and 58 and their combined contribution to the 8977 positive cases was 91%. HPV types 16, 18 and 45 were the three most common types in each type of cervical cancer (squamous cell, adenocarcinoma and adenosquamous carcinoma).

There is good evidence that HPV infection precedes the development of cervical cancer by a number of decades and that persistent infection with HPV is necessary for the development of and progression of pre-cancerous lesions of the cervix, either to higher grades of pre-cancerous disease or to cancer[11]. Cervical cancer progresses slowly over decades from pre-invasive cervical intra-epithelial neoplasia (CIN) to invasive cervical cancer, a process that can take 10–30 years.

Kjaer *et al.*[12] studied a cohort of 8656 women who were screened twice 2 years apart in 1991 and 1993 with cervical cytology and HPV DNA analysis by hybrid capture 2 (Qiagen) and line probe assays. The women were followed up through the Danish Pathology Data Bank for cervical neoplasia for up to 13.4 years. They found that for women who had normal cytology but were positive for HPV 16 in 1993, the estimated probability of developing CIN 3 or worse within 12 years was 26.7% (95% CI 21.1–31.8%). The corresponding rate for those infected with HPV 18 was 19.1% (95% CI 10 4–27.3%), for HPV 31 was 14.3% (95% CI 9.1–19.4%) and HPV 33 was 14.9% (95% CI 7.9–21.1%). The absolute risk of developing CIN 3 or worse for high-risk types other than HPV 16, 18, 31 and 33 was only 6% and the risk of CIN 3 or worse if HPV DNA test was negative was 3% (95% CI 2.5–3.5%). For women who tested HPV 16 positive on two occasions the risk of developing CIN 3 or worse was 47.4% over 12 years.

Bruni *et al.*[13] reported on a meta-analysis of cervical HPV prevalence, HPV type and age-specific prevalence distribution restricted to women with normal cytological findings and included studies from January 1995 to May 2009. The analysis included 194 studies for a total of 1,016,719 women with normal cytology tested for HPV. These data show us that many women with normal Pap smears, harbor occult or undetected HPV infection. The estimated crude and adjusted HPV prevalences among women with normal cytological findings worldwide were 7.2 and 11.7%, respectively, 24% for sub-Saharan African regions, 16.1% in Latin America and Caribbean, 14.2% in Europe and 14% in Southeastern Asia. Of the global HPV burden,

22.5% of HPV infections were estimated to be produced by HPV 16. Further, they report that the prevalence of high-risk HPV is highest in regions with highest cervical cancer prevalences. It is important therefore to understand that normal cytology does not mean women are not at risk of cervical cancer.

UNDERSTANDING CERVICAL CANCER IN THE CONTEXT OF THE DEVELOPING COUNTRIES, USING SUB-SAHARAN AFRICA AS A CASE STUDY

Sub-Saharan Africa (SSA) consists of 53 countries almost all of which have the lowest ranked human development index (HDI) and highest human poverty indices (HPI)[14]. 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, i.e. 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 *et al.*[15] evaluated cancer survival for 341,658 people diagnosed with a variety of cancers from 1990 to 2001. Two of the cancer registries were in SSA, The Gambia and Uganda, where survival was the lowest. No cancer exceeded a 5-year survival of >22% in The 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 is 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 to 91% in Europe[15]. To illustrate the typical situation in Africa, Hanna and Kangolle[16] refer to the situation in Tanzania, which is a low-income country of 42.5 million people and where 21,180 new cases of cancer were diagnosed in 2008. Nationwide there is one medical oncologist, four radiation oncologists, two physicists and seven pathologists. There is no dedicated surgical oncology. There are two radiation machines in the country with an estimated need for 45.

The African continent has 130 medical schools located in 41 countries, but facilities for training in cancer diagnosis and management are found mainly in North Africa (Egypt, Morocco, Algeria) and South Africa with limited facilities in Nigeria, Libya and Zimbabwe. In 2007 it was estimated that the per capita expenditure on health in the USA was $6096 compared to $32 in SSA, most of which were donor dollars[14].

Further, there is a great shortage of trained healthcare personnel in Africa where there is also a very large 'brain drain' or exodus of trained personnel to other more attractive continents. 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 1000 population)[17]. In a study by Scheffler *et al.*, 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[18].

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 but a few) has been the HIV/AIDS epidemic, where 70% of the world's cases of HIV are diagnosed (www.unaids.org). 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[19]. Women infected with HIV have an increased risk of being infected with HPV and are therefore considered at higher risk for cervical cancer. However, the expected increase in women 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 anti-retroviral medication, this scenario is expected to change.

Studies have consistently shown higher prevalence of HPV infection, persistent infection with HPV, infection with multiple types of HPV and higher prevalence of cervical cancer precursors in HIV-infected women[20–22]. The Rwandan Women's Interassociation Study and Assessment (RWISA) is an observational prospective cohort study of 710 HIV-positive women and 226 HIV-negative Rwandan women, enrolled into the study in 2005[23]. The prevalence of HPV was significantly higher in the HIV-positive group and adjusted for age (25–34 years 75% vs 29%; 35–44 years 64 vs

7%; 45–54 years 57% vs 13% and >55 years 38% vs 0%). In addition, 46% of HIV-positive women had high-risk types of HPV and 35% were infected with multiple types and in turn, this was associated with higher risk of abnormal cytological findings.

Denny *et al*.[24] found that 68% of their cohort of HIV-positive women were infected with high-risk types of HPV, and 94% of these infections persisted over a 36-month period, with only 6% clearing infections. In another South African study of 5595 women aged 35–65 years of age followed for 36 months, 577 women were HIV positive at enrolment and subsequently 123 women seroconverted. Among women who underwent HIV seroconversion, HPV prevalence was 20.3% before seroconversion, 23.6% at seroconversion and 49.1% after seroconversion. HIV seroconversion was associated with newly detected HPV infection and increased risk of low-grade cytological abnormalities compared with HIV-negative women[25]. A recent article reported on a case-controlled study from Côte d'Ivoire of 132 women with invasive cervical cancer and 130 control women who had normal Pap smears. It demonstrated a positive association between HIV infection, cervical cancer and concomitant high-risk type of HPV infection with an odds ratio of 3.4 (95% CI 1.1–10.8)[26].

The situation in Latin America is very similar to that in Africa, where cervical cancer remains a serious public health problem. Despite declines of cervical cancer incidence and mortality in North America, the Pan American Health Organization (PAHO) reported in 2004 that in the preceding 40 years there had been no decline in cervical cancer incidence in Latin America and the Caribbean[27]. The highest mortality data were documented in Nicaragua, El Salvador and Peru, where ASMR of over 20/100,000 women were reported in all three countries in 2000. Similar to the situation in Africa, women present late, and the mortality to incidence rate is high due to lack of access, human and other resources to manage cancer. As in Africa, PAHO reported that there was little recognition among political structures of the extent of cervical cancer, resulting in cancer control receiving very limited resources.

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 prior to exposure to the type of HPV included in the vaccines.

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, PA, USA) vaccines have been tested in randomized placebo-controlled trials and shown to be safe, immunogenic and highly efficacious up to 6.5 years after vaccination[28–32]. The vaccines use HPV type-specific L1 proteins that self-assemble into virus-like particles (VLPs). The bivalent vaccine is delivered by intramuscular injection at 0, 1 and 6 months. The quadrivalent vaccine, is also given via intramuscular injection, at 0, 2 and 6 months.

Both vaccines work by inducing neutralizing serum antibodies (IgG). Studies consistently show that L1 VLPs induce high levels of serum-neutralizing IgG, that is presumed to transudate across the cervical epithelium in high enough concentrations to bind to virus particles and prevent infection. There is good evidence provided by randomized 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).

Both vaccines appear to offer full protection against types 16 and 18, which are estimated to cause >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 etiology of cervical cancer, thus increasing the projected protection from vaccination to 75–80%.

However, both vaccines are prophylactic and should be administered to individuals prior to infection. HPV is most commonly transmitted through sexual activity and is known to be the commonest STI 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[33].

From a developing country point of view introducing the HPV vaccine into public health poses many challenges. The most obvious is cost, and the present price of both vaccines is unaffordable. However, cost is only one aspect. Firstly, no 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* and for this to happen, a great deal of political will needs to be generated. Unfortunately, no studies have 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.

Besides the need to create a new infrastructure, both vaccines require a cold chain, thus a reliable source of electricity, which is notoriously difficult in many developing countries, particularly in Africa. The need for three injections and therefore follow-up poses its own challenges, as does the necessity for intramuscular injection (skills, medical waste disposal). Furthermore, one is injecting a young girl to prevent a disease that will only manifest after 30 years or more. Developing a national strategy will require those familiar with vaccination (pediatricians, public health officials) to communicate with those who work in the adult oncology field (traditionally two worlds that never intersect). However, developing a pubescent or adolescent health platform may be highly desirable. Such a platform would be a unique opportunity to offer parallel services to young people, e.g. booster vaccination against hepatitis B and tetanus, possibly anti-HIV vaccination in the future, anti-helminthic medication, nutritional assessment, and education about drug, tobacco and alcohol use, pregnancy prevention and sexuality in general.

Whether or not countries introduce the vaccine into the public health sector will be determined by (1) the burden of HPV-associated disease in a particular country, (2) being able 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, (3) the creation of the appropriate infrastructure for the administration of the vaccine, and finally (4) the cost. Clearly, implementing anti-HPV vaccination involves a great deal more than getting the needle in the arm. Currently, in some countries mother–daughter projects have been started: the mother comes for cervical cancer screening and the daughter is vaccinated. In November 2011, the Global Alliance for Vaccines and Immunization (GAVI) announced a plan to vaccinate 2 million girls from nine developing countries by 2015, contingent on the manufacturers of the vaccine providing an affordable price[34].

MODERN APPROACHES TO SECONDARY 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 (for instruction manual on colposcopy, http://screening.iarc.fr/colpo.php) 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 to cytology[35], 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%, which is similar to cytology. 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 *et al.*[36] performed a meta-analysis of 26 studies in which VIA was performed on asymptomatic women who underwent confirmatory testing and the disease threshold was CIN 2 plus. They report a sensitivity of 80% and a 92% specificity 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 a reasonable alternative to cytology. However, in more recent randomized studies, VIA has performed poorly in terms of test characteristics and prevention of disease.

Denny *et al.*[37] conducted a randomized screening trial to evaluate the safety, acceptability and efficacy of screening women with different methods and treating those with positive tests without the intervention of colposcopy and histological sampling. A total of 6555 unscreened women, aged 35–65 years, underwent either testing for high-risk types of HPV DNA, or VIA performed by nursing sisters in a primary care setting. Group one was screened for HPV and all women with positive results were treated with cryotherapy. The second group was screened using VIA and received cryotherapy once VIA was positive, and the third group, the control group, was only screened and received no treatment for 6 months, regardless of the screening result. Women were followed up 6 monthly for a period of 36 months. The findings were that after 36 months there was a sustained significant decrease in the detection of CIN 2 or greater in group 1 (HPV testing and treatment) compared to the control group (1.5% vs 5.6%, respectively). In group 2 (VIA and treatment) the difference was 3.8% versus 5.6% in the control group. For every 100 women screened, the HPV testing and treatment strategy eliminated 4.1 cases of CIN 2 or greater compared to VIA and treatment which eliminated 1.8 cases. HPV testing proved to be more reliable in correctly diagnosing CIN 2 or greater than VIA. These data confirmed the superior performance of HPV DNA testing as a primary screening test coupled with treatment with cryotherapy compared to VIA.

In another landmark study Sankaranarayanan *et al.*[38] performed a cluster randomized trial of 131,746 women aged 30–59 years who were randomly assigned to one of four groups: (1) HPV testing, 2) cytologic testing, (3) VIA, or (4) standard of care which involved no screening as the control group. Women who had positive tests underwent colposcopy with directed biopsies and those with cervical cancer precursors were treated. The incidence rate of cervical cancer stage 2 or higher and death rates from cervical cancer were significantly higher in the cytologic and VIA groups compared to the HPV-testing group. In the HPV-testing group the hazard ratio (the probability that an incident happens in a certain time span as a comparison between two groups) for the detection of advanced cervical cancer (stage 2 or greater) was 0.47 (95% CI 0.33–0.83) compared with the control group which means that there was less advanced cancer in the HPV-testing group during the observation period. Further, the ASIR of invasive cancer among women who had negative test results on cytological or VIA testing was more than four times greater than 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 is not affordable to developing countries. However, new technology and more accessible and easier HPV DNA tests are being developed (http://www.qiagen.com/about/whoweare/qiagencares/the-carehpv-test.pdf) as are other molecular tests in an attempt to improve specificity and reduce the rate of overtreatment. In the meantime, it is recommended that very-low-resource settings develop the infrastructure for cervical cancer screening, initially using VIA as it is the most affordable and implementable mode of screening. Creating infrastructure to screen is critical to the success of any screening program regardless of the tests and approaches used. There are some excellent tools available on the internet to help you with the start of a screening program. Videos, on-line instructions and free-download books are available at http://www.iarc.fr/en/publications/pdfs-online/prev/index2.php. We strongly recommend you to go and visit that page.

Visual inspection with acetic acid and Lugol's iodine

A very good instruction book for VIA and visual inspection with Lugol's iodine (VILI) can be downloaded for free on: http://screening.iarc.fr/viavili.php?lang=1. There are three approaches:

'Screen-and-treat' approach

In this approach, treatment decisions are based on the results of the screening test, without a prior diagnostic test. Most screen-positive women can be treated with cryotherapy at primary healthcare level at the time of screening; this could reduce loss to follow-up and have an impact on cervical cancer

control. However, tissue will not be available for histological confirmation.

Colposcopy-based 'see-and-treat' approach

To address the issue of potential overtreatment with the screen-and-treat approach, an intermediate approach can be used. Patients with a positive screen (on Pap smear, VIA, VILI or HPV) can be examined with a colposcope. If a pre-cancerous lesion is detected, it can be treated immediately. If cryotherapy is the chosen treatment, colposcopically directed biopsies can be taken before treatment to confirm the diagnosis following the procedure. If loop electrosurgical excision procedure (LEEP) is used, tissue will be available as a result of the procedure. This approach is contingent on the availability of equipment and trained and experienced providers, as well as laboratories able to process the tissue provided.

'Opportunistic screening'

In healthcare facilities where speculum examinations are performed and no screening program has yet been implemented, healthcare workers can apply acetic acid (white vinegar) during each speculum examination that is performed for any other reason. Women with a positive acetic acid test should be treated with cryotherapy or LEEP, if the healthcare provider has been trained to perform these techniques safely and effectively.

Visual screening method[39]

In VIA we inspect the transformation or transition zone (between the columnar and the squamous epithelium of the uterine cervix). In a visual test, the provider applies acetic acid (in VIA) or Lugol's iodine solution (in VILI) to the cervix, and then looks to see if there is any staining. A VIA test is positive if there are raised and thickened white plaques or aceto-white epithelium; a VILI test is positive if there are mustard or saffron-yellow colored areas, usually near the squamous cell junction (SCJ). Either test is suspicious for cancer if a cauliflower-like fungating mass or ulcer is noted on the cervix. Visual screening results are negative if the cervical lining is smooth, uniform and featureless; it should be pink with acetic acid and dark brown or black with Lugol's iodine.

Note: visual methods are not recommended for use in postmenopausal women, because their transition zone is most often inside the endocervical canal and not visible on speculum inspection.

The following materials and equipment are needed for visual methods:

- Soap and water for washing hands.
- A bright light source to examine the cervix.
- A speculum, high-level disinfected (it need not be sterile).
- Disposable or high-level disinfected examination gloves (need not be sterile).
- Examination table covered by clean paper or cloth.
- Cotton-tipped swabs.
- Dilute acetic acid solution (3–5%) or white vinegar.
- Lugol's iodine solution.
- 0.5% chlorine solution for decontaminating instruments and gloves.
- Recording form.

Preparation:

1. Explain the procedure, how it is done, and what a positive test means. Ensure that the woman has understood and obtain informed consent.
2. Do a speculum examination.

Performing the test:

3. Adjust the light source in order to get the best view of the cervix.
4. Use a cotton swab to remove any discharge, blood or mucus from the cervix.
5. Identify the SCJ, and the area around it.
6. Apply acetic acid or Lugol's iodine to the cervix; wait a minute or two to allow color changes to develop. Observe any changes in the appearance of the cervix. Give special attention to abnormalities close to the transformation zone.
7. Inspect the SCJ carefully and be sure you can see all of it. Report if the cervix bleeds easily. Look for any raised and thickened white plaques or aceto-white epithelium if you used acetic acid or saffron-yellow colored areas after application of Lugol's iodine. Remove any blood or debris appearing during the inspection. For a schematic overview of the test, please see Figure 6. Figure 7 shows examples of

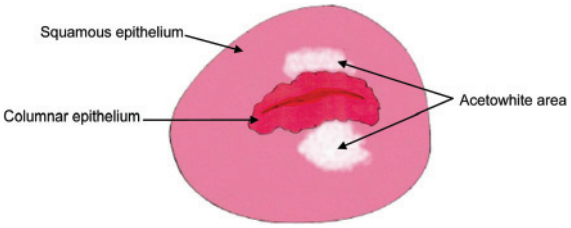

Figure 6 Schematic overview of the cervix and the aceto-white area. Courtesy of Screening Group (SCR), International Agency for Research on Cancer (WHO-IARC)

a negative and positive VIA tests and non-invasive cervical cancer.

8. Use a fresh swab to remove any remaining acetic acid or iodine solution from the cervix and vagina.
9. Gently remove the speculum.

After screening:

10. Record your observations and test result. Draw a map of any abnormal findings on the record form. A sample of a record form and map can be found at: http://screening.iarc.fr/doc/viaviliappendix.pdf and http://screening.iarc.fr/doc/cervicalcancergep.pdf (p. 124).
11. Discuss the results of the screening test with the patient. If the test is negative, tell her that she should have another test in 3 years. If the test is positive or cancer is suspected, tell her what the recommended next steps are. If she needs to be referred for further testing or treatment, make arrangements and provide her with all necessary forms and instructions before she leaves. If you can make the appointment immediately, do so.

Other diagnostic tests

Biopsy

Biopsy is the removal of small areas of the cervix for histopathological diagnosis. It should be done with a punch biopsy forceps (Figure 8); one or more small pieces of tissue (1–3 mm across) are removed from the abnormal areas of the cervix identified by colposcopy or VIA (see Chapter 1 on gynecological examination on how to do a biopsy). Bleeding is usually minimal. The samples are placed in a preservative, such as formalin, and the container labelled. This is then sent to a laboratory for precise histopathological diagnosis of the abnormalities,

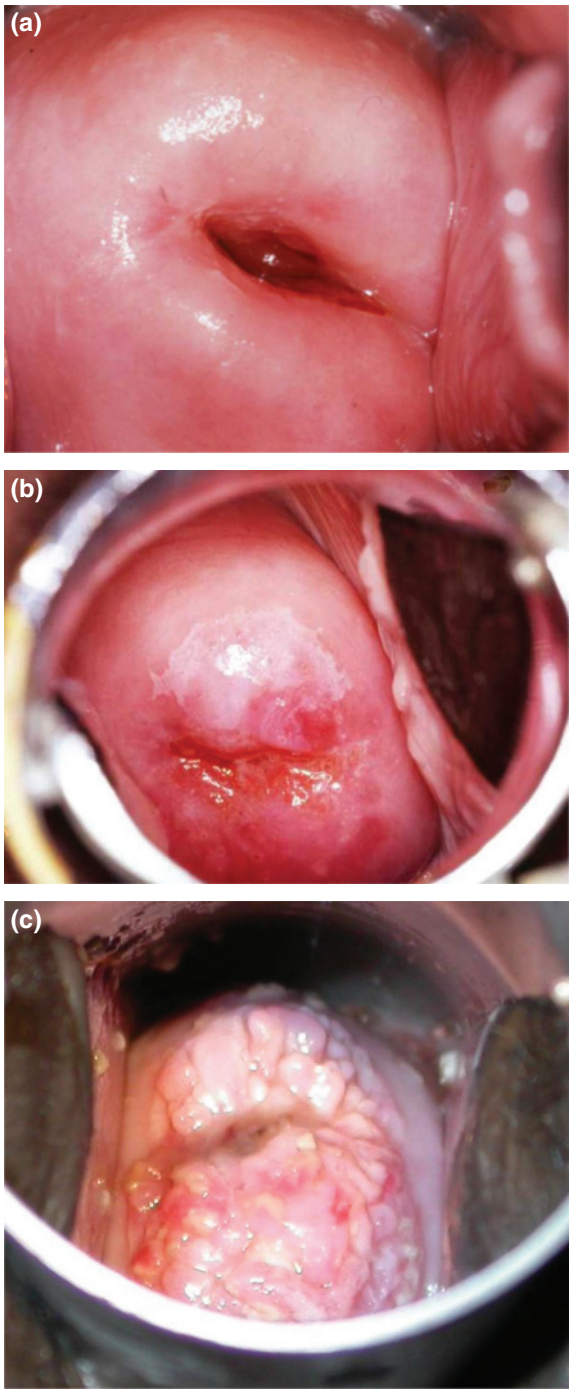

Figure 7 Examples of (a) negative (note no aceto-white areas seen) and (b) positive (note the well-defined opaque aceto-white lesion in the anterior lip arising from the SCJ) VIA tests and (c) non-invasive cervical cancer (note dense aceto-white area with irregular surface contour). Courtesy of Screening Group (SCR), International Agency for Research on Cancer (WHO-IARC)

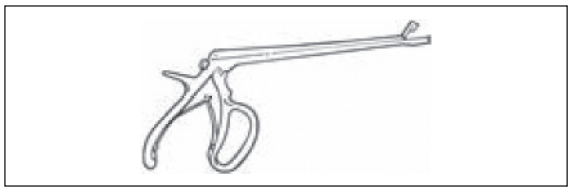

Figure 8 A cervical biopsy forceps. Source: Comprehensive cervical cancer control: a guide to essential practice. Geneva: WHO, 2006[39]

whether they are pre-cancer or cancer, and their severity and extent, so that treatment can be tailored to each case. A biopsy should be performed:

- On women with an abnormal screening test
- If suspicious lesions are seen on the cervix on speculum examination
- To map abnormalities before cryotherapy or LEEP.

Endocervical curettage

If a woman has a positive Pap test, but no abnormal areas are observed with colposcopy, there may be a lesion in the cervical canal. In this case, the endocervix can be examined with a special speculum and a sample of cells can be obtained with an endocervical curette for microscopic diagnosis. Endocervical curettage is a simple procedure, in which some of the surface cells are gently scraped from the cervical canal (See Chapter 1 on gynecological examinations). For more information and digital publications see http://www.iarc.fr/en/publications/pdfs-online/prev/index2.php.

TREATMENT OF PRE-MALIGNANT LESIONS

Pre-malignant lesions of the cervix can be treated with either cryotherapy, LEEP of cold knife conization. In this chapter we describe them with indications and contraindications. If you want thorough knowledge about the subject you can download the following publications for free: http://screening.iarc.fr/colpo.php and http://screening.iarc.fr/doc/cervicalcancergep.pdf.

Indications for treatment

All biopsy-confirmed CIN 2 and 3 lesions should be treated, because the majority of them persist and may eventually progress to invasive cancer. CIN 1 is more likely to resolve spontaneously; these patients can be followed up with colposcopy and cytology every 6 months until the lesion regresses to normal, or there is evidence of progression of the abnormality. If progression is noted, or in cases where follow-up is problematic, as well as in older women in whom spontaneous regression is less likely, immediate treatment should be considered.

Special considerations

Pregnancy

Women known or suspected to be pregnant should not be treated for pre-cancer; they should be advised to return at 12 weeks post-partum for further evaluation. If invasive cancer is suspected, the patient should be referred immediately to a specialist.

The woman is menstruating

Women who present for treatment during menstruation can be treated if the bleeding is slight. It is advisable to delay the procedure if menstruation is heavy and interferes with visualization of the extent of the lesion. However, it is important to remember that she may be bleeding because of cervical cancer, so an examination should not be deferred for longer than a week.

The woman has a cervical infection or pelvic inflammatory disease

- A cervical infection with no evidence of pelvic inflammatory disease (PID) (diagnosed clinically during speculum examination or with laboratory tests) can be treated with antibiotics concurrently with cryotherapy. If LEEP or cold knife conization is to be used, the infection must be treated before the procedure.
- If PID is suspected, a full course of appropriate antibiotic treatment should be completed prior to any treatment (see Chapter 17 on STI).
- Whenever a woman is treated for a cervical infection, with or without PID, her partner also needs to be fully treated to prevent reinfection. Until both have been fully treated, they should be advised to abstain from sexual intercourse or use condoms. Condoms and instructions on their use need to be provided to all such patients.

The woman is HIV infected

HIV-positive women should be managed in the same manner as uninfected women. However,

HIV-positive women are known to have higher rates of persistence, progression and recurrence of disease after treatment. Women with HIV infection should therefore be monitored every 6 months after treatment, and promptly re-treated if persistent, progressive or recurrent high-grade lesions are detected. At present there is no clear evidence on whether treatment with highly active antiretroviral drugs modifies regression or progression of cervical pre-cancer and cancer.

Before any treatment, HIV-positive women should receive counseling to ensure that they understand the need for close follow-up, and the possibility of need for repeat treatments, as well as the potential for increased transmission and acquisition of STIs and HIV during healing. Abstinence from sexual intercourse is the best protection following treatment; if this is not feasible, condoms should be used consistently and correctly.

Treatment

Cryotherapy

Cryotherapy eliminates pre-cancerous areas on the cervix by freezing them. This relatively simple procedure takes about 15 min and can be performed on an outpatient basis. It involves applying a highly cooled metal disc (cryoprobe) to the cervix, and freezing its surface using carbon dioxide (CO_2) or nitrous oxide (N_2O) gas. The cryoprobe is applied to the cervix twice, for 3 min each time, with a 5-min thaw in between (double-freeze technique). A continuous supply of CO_2 or N_2O is required. The more expensive, bone-dry medical grade of gas is preferred, but industrial-grade gas can be used if that is what is locally available and affordable. Cryotherapy is highly effective for the treatment of small lesions, but for larger lesions the cure rate is <80%. Because the area of the cervix that is frozen has very few nerve endings, cryosurgery is generally associated only with some cramping or mild pain. It can, therefore, be done without anesthesia.

Cryotherapy can be performed at all levels of the healthcare system by a variety of trained providers (doctors, nurses, midwives) skilled in pelvic examination, and trained in cryotherapy as an outpatient procedure.

Performing cryotherapy

Before the procedure:

1. Explain the procedure, and why it is important to return for further management as requested. Ensure that the woman has understood and obtain informed consent.
2. Show her the cryotherapy equipment and explain how you will use it to freeze the abnormal areas on the cervix.
3. Prepare the patient for a gynecological examination, and perform a speculum.
4. If there is no evidence of infection, proceed with cryotherapy.
5. If there is a cervical infection, provide treatment (see Chapter 17 about STIs). You may proceed with the cryotherapy, or you may give the patient an appointment to return once the infection is cured.

Procedure:

6. Wipe the cervix with a saline-soaked cotton swab and wait a few minutes.
7. Apply acetic acid to outline the abnormality and wait a further few minutes.
8. Tell the woman she might feel some discomfort or cramping while you are freezing the cervix.
9. Wipe the cryoprobe surface with saline to ensure optimum effectiveness.
10. Apply the cryoprobe tip in the center of the os and make sure the probe adequately covers the lesion (Figure 9). If the lesion extends >2 mm beyond the probe, discontinue the procedure. Explain to the woman why you are doing this and what needs to be done for her as an alternative.
11. Ensure that the vaginal wall is not in contact with the cryoprobe or you may cause a freezing injury to the vagina.
12. Set the timer and release the gas trigger to cool the probe.
13. You will observe the ice forming on the tip of the cryoprobe and on the cervix (Figure 9). When the frozen area extends 4–5 mm beyond the edge of the cryoprobe, freezing is adequate. In some cases, the patient may have a vasovagal reaction, with fainting and plummeting blood pressure. If this happens, stop the treatment immediately and raise the patient's legs as much as possible.
14. Allow two cycles of freezing and thawing: 3 min freezing, followed by 5 min thawing, followed by a further 3 min freezing.

15. Once the second freezing is complete, allow time for thawing before attempting to remove the probe from the cervix. Removing it before it is fully thawed will pull tissue off the cervix.
16. Gently rotate the probe on the cervix to remove it. The area you have frozen will appear white.
17. Examine the cervix for bleeding. If bleeding is noted, apply Monsel's paste.
18. Do not pack the vagina.
19. Remove the speculum.

After the procedure:

20. Provide a sanitary pad.
21. Instruct the woman to abstain from intercourse and not to use vaginal tampons for 4 weeks, until the discharge stops completely. This is to avoid infection.
22. Provide condoms for use if she cannot abstain from intercourse as instructed. Teach her how to use them.
23. Invite her to return in 2–6 weeks to be checked for healing, and again in 6 months for a repeat VIA, Pap smear and possible colposcopy.
24. Inform her of possible complications and ask her to return immediately if she notes:
    a. fever with temperature higher than 38°C or shaking chills
    b. severe lower abdominal pain
    c. foul-smelling or pus-like discharge
    d. bleeding for more than 2 days or bleeding with clots.
25. Clean and disinfect the cryoprobe and decontaminate the cryogun, tubing, pressure gauge and gas tank:
    a. Decontaminate the cryotherapy unit, hose and regulator by wiping them with alcohol
    b. Wash the cryotip and the plastic sleeve with soap and water until visibly clean
    c. Rinse the cryotip and plastic sleeve thoroughly with clean water
    d. High-level disinfect the cryotip and plastic sleeve by one of the following methods: (1) boil in water for 20 min; or (2) steam for 20 min; or (3) soak in chemical disinfectant (0.1% chlorine solution or 2–4% glutaral) for 20 min and then rinse with boiled water
    e. It is critical that the hollow part of the cryotip is completely dry when next used, otherwise the water will freeze and the probe could crack or the treatment not work

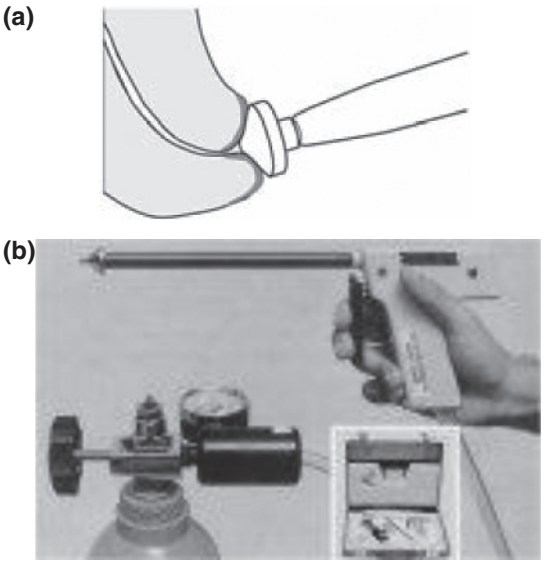

Figure 9 (a) Position of cryoprobe on the cervix and ice forming; (b) cryoprobe and equipment. Source: Comprehensive cervical cancer control: a guide to essential practice. Geneva: WHO, 2006[39]

    f. Either use a rubber cap to seal off the hollow part of the cryoprobe during processing, or thoroughly dry the cryoprobe before it is re-used
    g. If none of the high-level disinfection options are available, the cryotip and sleeve may be disinfected by soaking in 70–90% ethanol or isopropanol for 20 min. Allow to air-dry and then reassemble.

Follow-up:

26. Perform a pelvic examination to check for healing 2–6 weeks after the cryotherapy.
27. At 6 and 12 months, do a VIA, Pap test or a colposcopy and take a biopsy if necessary.

Indications and exclusion criteria for cryotherapy are shown in Table 1.

Loop electrosurgical excision procedure

LEEP, also called large loop excision of the transformation zone (LLETZ), is the removal of abnormal areas from the cervix using a thin heated wire (Figure 10). It requires an electrosurgical unit that produces a constant low voltage and transmits it to a wire loop device, which is used to remove the abnormal tissue. The loops are of very fine stainless steel or tungsten wire and come in different sizes

Table 1 Indications and exclusion criteria for cryotherapy

Eligibility criteria	*Exclusion criteria*
Positive screening test for cervical precancer	Evidence or suspicion of invasive disease or glandular dysplasia
Lesion small enough to be covered by the cryoprobe with no more than 2 mm beyond its edges	The lesion extends more than 2 mm beyond the cryoprobe edge
The lesion and all edges fully visible with no extension into the endocervix or onto the vaginal wall	Pregnancy
	PID (until treated)
	Active menstruation

PID, pelvic inflammatory disease

Table 2 Indications and exclusion criteria for loop electrosurgical excision procedure (LEEP)

Eligibility criteria	*Exclusion criteria*
A positive diagnostic test for precancer	Suspicion of invasive cancer or glandular dysplasia
Lesion extending <1 cm into the endocervical canal	Lesion extending >1 cm into the endocervical canal, or whose distal or upper extent is not visible (these lesions are treated by cold knife conization)
	Cervical infection or PID (until treated or resolved)
	Pregnancy or delivery within the last 12 weeks
	Bleeding disorders

PID, pelvic inflammatory disease

and shapes. The loop cuts and coagulates at the same time. LEEP aims to remove both the lesion and the entire transformation zone. The tissue removed can be sent for examination to the histopathology laboratory, allowing the extent of the lesion to be assessed. Thus, LEEP serves a double purpose: it treats the lesion, and at the same time, produces a specimen for pathological examination. The procedure also has the advantage that it can be performed under local anesthesia on an out-patient basis. It is successful in eradicating pre-cancer in >90% of cases. Treatment failure (i.e. persistent lesions at 6 or 12 months follow-up) is seen in <10% of women.

LEEP is a relatively simple surgical procedure, but it should be performed only by a well-trained provider with demonstrated competence in the procedure and in recognizing and managing intraoperative and postoperative complications, such as hemorrhage. LEEP is best carried out in facilities where back-up is available for management of potential problems. In most resource-poor countries, this will limit LEEP to second-level (district hospital) facilities. Videos of LEEP can be seen at http://screening.iarc.fr/movieleeptheory.php and http://screening.iarc.fr/movieleeppractical.php.

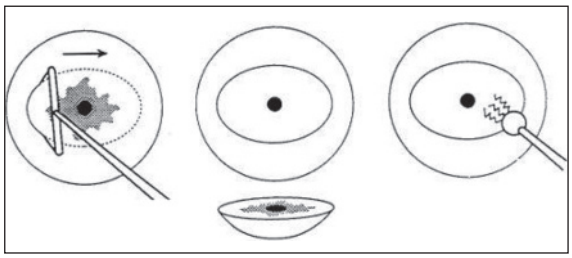

Figure 10 Excision of an ectocervical lesion with one pass. Source: Comprehensive cervical cancer control: a guide to essential practice. Geneva: WHO, 2006

Indications and exclusion criteria for LEEP are given in Table 2.

Cold knife conization

Cold knife conization is the removal of a cone-shaped area from the cervix, including portions of the outer (ectocervix) and inner cervix (endocervix). Conization is recommended for the treatment of dysplasia when out-patient treatment is not

feasible or not accessible, and to rule out invasive cervical cancer. It is a rather extensive operation, involving removal of a large area of the cervix with a scalpel, and is usually done under general or regional (spinal or epidural) anesthesia. It takes less than one hour. The patient may be discharged from hospital the same or the next day. Because of possible side-effects, cold knife conization should be reserved for cases that cannot be resolved with cryotherapy or LEEP excision. The extent of the conization will depend on the size of the lesion and the likelihood of finding invasive cancer. The woman's desire to have more children also has to be taken into account, as conization may result in cervical stenosis or incompetence in a few women. The tissue removed is sent to the pathology laboratory for histological diagnosis and to ensure that the abnormal tissue has been completely removed.

Cold knife conization should be performed only by providers with surgical skills, in an equipped surgical facility. Providers are usually gynecologists or surgeons trained to perform the procedure and to recognize and manage complications.

Procedure After informed consent, the patient receives general or spinal anesthesia and is put in lithotomy position. An Auvard speculum and an anterior wall speculum are inserted and the cervix is grasped with a tenaculum. The cervix is colored by acetic acid and Lugol's iodine to see the extent of the pre-malignancy. On both lateral sides of the cervix strong hemostatic sutures can be applied (from 2 to 4 o'clock and from 8 to 10 o'clock) to facilitate hemostasis. A Hegar dilator size 4, 5 or 6 is applied in the external os. With a scalpel, the entire abnormality of the cervix is removed in a cone shape, using the Hegar to facilitate stability of the cervix. The conus is marked at 12 o'clock with a marking suture and sent for histology. With cauterization hemostasis is applied. An intravaginal pack and bladder catheter may be applied for hemostasis.

Indications and exclusion criteria for conization are given in Table 3.

Management of complications of conization After cold knife conization, bleeding is the most common complication; it can occur immediately (primary bleeding) or up to 14 days after the procedure (secondary bleeding). In either case, the patient needs to return to the surgical facility. Secondary hemorrhage is usually related to local infection and, along with measures to stop the bleeding (like suturing, vaginal packing, cauterization), treatment with antibiotics should be prescribed. Local application of hemostatic gauzes (gauzes drenched in tranexamic acid, Surgigel etc.) may be useful.

CERVICAL CANCER

Over 80% of the world's cases of cervical cancer are diagnosed in countries without screening programs, and in developed countries, the women who do develop cancer are either screen-detected or women who have not been screened. Most women in developing countries present with advanced disease, often untreatable or suitable only for palliation. At a large tertiary institution in Cape Town, between 1984 and 2000, 3098 women with cervical cancer were seen of whom 571 were stage IIB (18%), 1425 were stage IIIA and B (46%) and 343 (11%) were stage IV (personal communication, Dr Leon Van Wijk, Department Radiation Oncology, Groote Schuur Hospital, Cape Town, South Africa). The revised International Federation of Gynecology and Obstetrics (FIGO) 2009 staging is shown in Table 4[40,41]. This staging has eliminated stage 0 (carcinoma *in situ*), and stage IIA has been sub-divided into IIA1 and IIA2 with a cut-off of 4 cm, as there are sufficient data to support that

Table 3 Indications and exclusion criteria for conization

Eligibility criteria	*Exclusion criteria*
Screen or diagnostic test suspicious for microinvasive cancer	Untreated cervicitis or PID
Endocervical glandular neoplasia	Pregnancy or childbirth within the past 12 weeks
Abnormal endocervical curettage	Obvious invasive cancer
Positive screen showing need for excisional procedure and outpatient procedures, such as LEEP, are not feasible	Contraindications to anesthesia
Stage 1A1 cervical cancer (see treatment of cervical cancer)	

PID, pelvic inflammatory disease; LEEP, loop electrosurgical excision procedure

Table 4 FIGO staging of carcinoma of cervix uteri, 2008

Stage 1	The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded)
1A	*Invasive carcinoma, diagnosed microscopically, with deepest invasion ≤5 mm and the widest diameter ≤7.0 mm*
1A1	Measured stromal invasion of ≤3.0 mm in depth and extension ≤7 mm
1A2	Measured stromal invasion of >3 mm and not >3 mm with an extension of not >7.0 mm
1B	*Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage 1A**
1B1	Clinically visible lesion ≤4.0 cm in greatest dimension
1B2	Clinically visible lesion >4.0 cm in greatest dimension
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
II A	*Without parametrial invasion*
IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension
IIA2	Clinically visible lesion >4.0 cm in greatest dimension
IIB	*With obvious parametrial extension*
Stage III	The tumor extends to the pelvic side wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney†
III A	Tumor involves lower third of the vagina, with no extension to the pelvic side wall
III B	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

*All macroscopically visible lesions – even with superficial invasion – are allotted to stage 1B carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.0 mm and a horizontal extension of not >7 mm. Depth of invasion should not be >5 mm taken from the base of the epithelium of the original tissue – squamous or glandular. The depth of invasion should always be reported in millimeters, even in those cases with early (minimal) stromal invasion (1 mm). The involvement of vascular/lymphatic spaces should not change the stage. †On rectal examination there is no cancer-free space between the tumor and the pelvic side wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause

maximum tumor diameter has an impact on prognosis as it has in stage 1B cancer of the cervix[40]. Cervical cancer remains a clinically staged disease, largely because other means of staging are not available in many developing countries where the majority of cases are diagnosed. The use of diagnostic imaging to assess the size of the primary tumor is encouraged but not mandatory[42]. For those institutions with access to magnetic resonance imaging or computed tomography scanning, radiological tumor volume and parametrial extension should be recorded. Other investigations, e.g. examination under anesthesia, cytoscopy, sigmoidoscopy and intravenous pyelography are no longer mandatory, but optional. Figure 11 gives a diagrammatic illustration of the spread of cervical cancer[42].

Prognostic factors for cervical cancer

Patient-related factors include age, degree of anemia and smoking[43]. Tumor-related factors include stage, tumor size, nodal involvement, cell type and hypoxia[43]. Radiation treatment-related factors include overall treatment time, dose, use of brachytherapy and concurrent chemotherapy, all of which improve survival[44].

Cervical cancer diagnosis and treatment in Africa

Cervical cancer has a range of presentations from asymptomatic screen-detected micro-invasive disease, to abnormal vaginal bleeding, malodorous vaginal discharge, pelvic pain or symptoms of more advanced disease such as vesico-vaginal or recto-vaginal fistulae or metastases (most commonly to lung, bone or liver). Cervical cancer spreads by direct invasion into the cervix, body of the uterus, vagina and parametrium, or by hematogenous or lymphatic permeation to distant sites. In most African countries women present with advanced

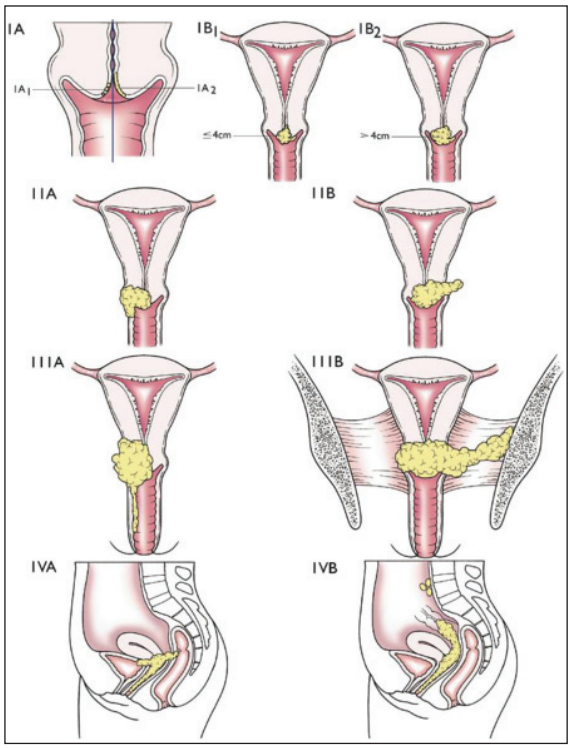

Figure 11 Diagrammatic representation of cervical cancer spread according to FIGO stages[42]

disease and even in those countries with radiation facilities, survival is poor.

Treatment of early stage disease (stage 1 or stage 2A) is generally surgical unless there are contra-indications to surgery, in which case primary radical radiation is the treatment of choice. Surgery ranges from a cone biopsy (see conization above) for early stage 1A disease to a radical hysterectomy (uterus, cervix, parametria, vaginal cuff) with bilateral pelvic lymph node dissection of external iliac, internal iliac, obturator and common iliac lymph nodes. A radical hysterectomy with pelvic lymph node dissection should only be performed by a well-trained gynecologist/gynecological oncologist or surgeon with expertise in this kind of surgery.

Performing radical hysterectomy

The most important first steps to take prior to performing radical hysterectomy include:

- Correct staging and ensuring the indication for the procedure is correct.
- The patient is fit for surgery and at minimal risk of anesthetic complications.
- Adequate thromboprophylaxis is given.
- The patient is well informed.

The skin incision can be vertical or transverse but must be adequate for a thorough exploration of the abdomen. Once the abdomen is entered careful palpation of the whole abdomen is mandatory with particular attention to the following:

- Presence of palpable pelvic and/or para-aortic lymph nodes.
- Evidence of extra-cervical disease.
- The ability to reflect the bladder and rectum in order to remove a cuff of vagina.

Once the feasibility of proceeding with surgery has been established, the round ligaments are ligated and cut and the surgeon should then immediately identify the ureter placed on the medial aspect of the broad ligament. The ureteric fascia should be opened, and the ureter traced to its insertion into the bladder bilaterally. The bladder should be reflected to allow for at least 2 cm of anterior vaginal cuff to be removed. The uterine artery should be separately identified and ligated either at the site where the ureter runs beneath it (type 2 modified radical hysterectomy) or at its origin from the internal iliac (hypogastric) or superior vesical artery (type 3 modified radical hysterectomy). The peritoneum between the utero-sacral ligaments is then opened and the rectum reflected to allow 2 cm of posterior vaginal cuff. The utero-sacral ligaments should be ligated as close to the sacrum as possible. The final step is removal of the parametria (created by the deflection of the ureters and bladder, rectum and utero-sacral ligaments) with a 2 cm vaginal cuff.

Removal of ovaries at the time of surgery is not mandatory and in younger women is not recommended; however, lifting the ovaries out of the potential radiation field may be useful in some patients. The final step is the removal of pelvic lymph nodes up to the level of the common iliacs. Lymph nodes should be removed from the obturator fossa, the external and internal and common iliac nodes. Routine postoperative drainage is not mandatory nor is closure of the peritoneum. However, suprapubic drainage of the bladder for 6–7 days postoperatively is recommended to prevent urinary retention in an atonic bladder (caused by

denervation due to reflection of the bladder). More complex approaches to radical hysterectomy are described, particularly nerve-sparing procedures in reference 45.

Other surgical options

Increasingly, fertility-sparing surgery has been used in the surgical treatment of early-stage disease, such as trachelectomy or radical trachelectomy for selected cases and with good results[46] but this type of surgery is generally not available in most African countries, nor is laparoscopic surgery. A new development is neoadjuvant chemotherapy in high-stage cervical cancer; reduction of tumor size may facilitate surgery and reduce the request for radiotherapy in low-resource countries[47]. We have to wait for results from currently ongoing studies.

Radiotherapy

Most women with cervical cancer in Africa will be treated with primary radiation therapy, either with curative or more commonly, palliative intent. Based on GLOBOCAN data from 2002 Barton *et al.*[48] 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[49]. 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 five radiation facilities for a population of over 150 million people[50]. In most cases radiation is delivered using cobalt machines which are a lot cheaper and easier to maintain than linear accelerators[49]. The median costs of radiotherapy using linear accelerators has been estimated at $11 compared to $4.87 for cobalt machines[51]. A survey of 72 low and middle income countries found that 24 countries with populations >1 million people did not have any radiotherapy service and the majority of these countries were in Africa[52]. Radiotherapy is still considered to be high-technology medicine in Africa and where facilities do exist, e.g. South Africa, Ethiopia (one machine for a population of >60 million), Madagascar, Nigeria, Tanzania, Uganda, Sudan, Kenya, Ghana, Senegal, Zimbabwe and Cameroon, they are located in tertiary institutions or in the private sector and are often non-functional or poorly maintained.

Radiation is an effective treatment for cervical cancer and randomized trials have shown a significantly improved survival with the addition of concomitant chemotherapy. A meta-analysis of 15 trials involving 3452 women reported on survival when women were treated for cervical cancer with concomitant chemotherapy: the majority of trials used cisplatin as the chemotherapeutic drug, and the minority used 5-fluorouracil, mitomycin C or a combination of both[52]. The review found that there was convincing evidence that adding chemotherapy to radiotherapy improves both overall survival and disease-free survival. Implementing this type of protocol in most African countries is unlikely to be feasible, even in South Africa, most units cannot afford to co-administer chemotherapy to women being treated with radiation for cervical cancer due to critical lack of resources. For information on radiotherapy and chemoradiation for cervical cancer see http://www.glowm.com/?p=glowm.cml/section_view&articleid=234.

In terms of survival, data from a gynecology oncology unit are shown in Figure 12 (personal communication, Dr Leon Van Wijk). This graph shows that early-stage disease has a good prognosis, but for women with stage 3 disease, only 30% are alive 5 years after diagnosis.

Palliative care

Palliation for women with advanced disease is also extremely limited in most low-resource countries, where for instance, oral morphine is only available in 11 countries[53]. Palliative care is a large subject on its own but the options for management range from providing emotional/psychological and spiritual support to women, to good quality pain control and to the judicious use of anti-cancer therapies,

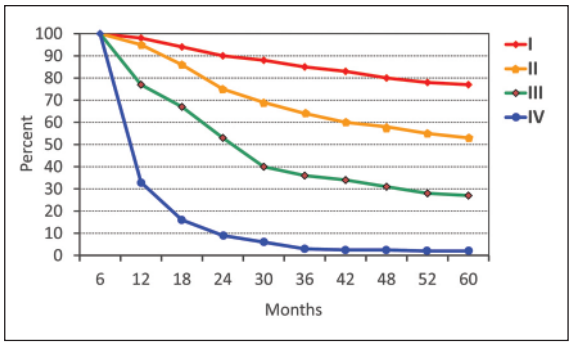

Figure 12 Five-year survival of women treated at Groote Schuur Hospital, 1984–2006 by stage

including diversion surgery for women with urinary and rectal fistulae. However, there are very few palliative care resources in most developing countries, and even fewer healthcare professionals adequately trained to provide good-quality care. However, there are possible synergies with national HIV care and treatment programs as they emphasize the continuum of care and include home-based care (HBC) programs as well. It is stated that HBC is not only for people living with HIV/AIDS (PLWHA) but with all chronic diseases. Including HBC for cancer patients into those programs would make a better use of resources and would take away the stigmatizing effect of being a client of such a service for PLWHA.

CONCLUSIONS

Cervical cancer is a preventable disease yet remains the commonest cause of cancer death among women in poor countries. 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 immediate treatment using cryotherapy significantly reduces both cervical cancer precursors and cervical cancer. In addition to new approaches to secondary prevention of cervical cancer, the recent availability of two highly effective vaccines against HPV infection has major implications for future prevention: the bivalent vaccine targets HPV types 16 and 18 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 towards molecular detection of cervical cancer precursors which should overcome many of the deficiencies associated with cervical cytology-based screening and programs.

Establishing National Cancer Control Programs (NCCPs) is a critical next step for cancer control in developing countries. For resource allocation, countries must adopt policies at national level. NCCPs have four pillars: prevention, early detection through diagnosis, treatment and palliation. Political will is an important element in putting diseases such as cervical cancer on the health agenda.

WHO has established a cancer control program which has published some interesting materials on the establishment of control programs which you can download at: http://www.who.int/cancer/modules/en/index.html.

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REFERENCES

1. GLOBOCAN 2008. Cancer Incidence MaPWi. Available from: http://globocan.iarc.fr/ and http://www.who.int/hpvcentre
2. Arbyn M, Castellsague X, de Sanjose S, *et al*. Worldwide burden of cervical cancer in 2008. *Ann Oncol* 2011;22:2675–86
3. WHO. World Health Statistics. WHO Library Cataloguing-in-Publications Data. Geneva: WHO, 2010
4. Parkin DM, Louie KS, Clifford G. Burden and trends of type-specific human papillomavirus infections and related diseases in the Asia Pacific region. *Vaccine* 2008;26 (Suppl. 12):M1–16
5. Sankaranarayanan R, Bhatla N, Gravitt PE, *et al*. Human papillomavirus infection and cervical cancer prevention in India, Bangladesh, Sri Lanka and Nepal. *Vaccine* 2008;26 (Suppl. 12):M43–52
6. Hakama M, Louhivuori K. A screening programme for cervical cancer that worked. *Cancer Surveys* 1988;7:403–16
7. Walboomers JM, Jacobs MV, Manos MM, *et al*. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189:12–19
8. Munoz N, Bosch FX, de Sanjose S, *et al*. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003;348:518–27
9. Clifford GM, Smith JS, Plummer M, *et al*. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. *Br J Cancer* 2003;88:63–73
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;11:1048–56
11. Wright TC, Kurman RJ, Ferenczy A. Precancerous lesions of the cervix. In: Kurman RJ, ed. *Blaustein's Pathology of the Female Genital Tract*. NY: Springer-Verlag, 2002

12. Kjaer SK, Frederiksen K, Munk C, Iftner T. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. *J Natl Cancer Inst* 2010;102: 1478–88
13. Bruni L, Diaz M, Castellsague X, *et al*. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. *J Infect Dis* 2010;202:1789–99
14. Independent Evaluation Group Studies. Annual Review of Development Effectiveness: Achieving Sustainable Development. Washington, DC: World Bank, 2009
15. Sankaranarayanan R, Swaminathan R, Brenner H, *et al*. Cancer survival in Africa, Asia, and Central America: a population-based study. *Lancet Oncol* 2010;11:165–73
16. Hanna TP, Kangolle AC. Cancer control in developing countries: using health data and health services research to measure and improve access, quality and efficiency. *BMC Int Health Hum Rights* 2010;10:24
17. WHO. Working Together for Health: the World Health Report 2006. Geneva: WHO, 2006
18. Scheffler RM, Mahoney CB, Fulton BD, *et al*. Estimates of health care professional shortages in sub-Saharan Africa by 2015. *Health Aff (Millwood)* 2009;28:w849–62
19. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep* 1992; 41:1–19
20. Ellerbrock TV, Chiasson MA, Bush TJ, *et al*. Incidence of cervical squamous intraepithelial lesions in HIV-infected women. *JAMA* 2000;283:1031–7
21. Harris TG, Burk RD, Palefsky JM, *et al*. Incidence of cervical squamous intraepithelial lesions associated with HIV serostatus, CD4 cell counts, and human papillomavirus test results. *JAMA* 2005;293:1471–6
22. Palefsky JM, Minkoff H, Kalish LA, *et al*. Cervicovaginal human papillomavirus infection in human immunodeficiency virus-1 (HIV)-positive and high-risk HIV-negative women. *J Natl Cancer Inst* 1999;91: 226–36
23. Singh DK, Anastos K, Hoover DR, *et al*. Human papillomavirus infection and cervical cytology in HIV-infected and HIV-uninfected Rwandan women. *J Infect Dis* 2009;199:1851–61
24. Denny L, Boa R, Williamson AL, *et al*. Human papillomavirus infection and cervical disease in human immunodeficiency virus-1-infected women. *Obstet Gynecol* 2008;111:1380–7
25. Wang C, Wright TC, Denny L, Kuhn L. Rapid rise in detection of human papillomavirus (HPV) infection soon after incident HIV infection among South African women. *J Infect Dis* 2011;203:479–86
26. Adjorlolo-Johnson G, Unger ER, Boni-Ouattara E, *et al*. Assessing the relationship between HIV infection and cervical cancer in Cote d'Ivoire: a case–control study. *BMC Infectious Dis* 2010;10:242
27. Lewis MJ. A situational analysis of cervical cancer in Latin America and the Caribbean. Washington DC: PAHO, 2004
28. Garland SM, Hernandez-Avila M, Wheeler CM, *et al*. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med* 2007;356: 1928–43
29. Harper DM, Franco EL, Wheeler C, *et al*. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004;364:1757–65
30. Harper DM, Franco EL, Wheeler CM, *et al*. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet* 2006;367:1247–55
31. Koutsky LA, Harper DM. Chapter 13: Current findings from prophylactic HPV vaccine trials. *Vaccine* 2006;24 (Suppl. 3):S3/114–21
32. Villa LL, Costa RL, Petta CA, *et al*. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol* 2005;5:271–8
33. Goldie SJ, O'Shea M, Campos NG, *et al*. Health and economic outcomes of HPV 16,18 vaccination in 72 GAVI-eligible countries. *Vaccine* 2008;26:4080–93
34. GAVI Alliance. GAVI takes first steps to introduce vaccines against cervical cancer and rubella, 17 November 2011. Available at: www.gavialliance.org./library/news/press-releases/2011
35. Sankaranarayanan R, Gaffikin L, Jacob M, *et al*. A critical assessment of screening methods for cervical neoplasia. *Int J Gynaecol Obstet* 2005;89 (Suppl. 2):S4–12
36. Sauvaget C, Fayette JM, Muwonge R, *et al*. Accuracy of visual inspection with acetic acid for cervical cancer screening. *Int J Gynaecol Obstet* 2011;113:14–24
37. 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;102:1557–67
38. Sankaranarayanan R, Nene BM, Shastri SS, *et al*. HPV screening for cervical cancer in rural India. *N Engl J Med* 2009;360:1385–94
39. WHO. Comprehensive cervical cancer control: a guide to essential practice. Geneva: WHO, 2006. Available from: http://screening.iarc.fr/doc/cervicalcancergep.pdf
40. Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. *Int J Gynaecol Obstet* 2009;105:107–8
41. FIGO. Annual Report on the Results of Treatment in Gynaecological Cancer. London: FIGO, 2010
42. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet* 2009;105:103–4
43. Monk BJ, Tian C, Rose PG, Lanciano R. Which clinical/pathologic factors matter in the era of chemoradiation as treatment for locally advanced cervical carcinoma? Analysis of two Gynecologic Oncology Group (GOG) trials. *Gynecol Oncol* 2007;105:427–33
44. Stehman FB, Bundy BN, DiSaia PJ, *et al*. Carcinoma of the cervix treated with radiation therapy. I. A multivariate analysis of prognostic variables in the Gynecologic Oncology Group. *Cancer* 1991;67:2776–85

45. Hacker NF, Friedlander M. Cervical cancer. In: Hacker BA, ed. *Gynecological Oncology*, 5th edn. Philadephia, USA: Wolter Kluwer, 2009;341–95
46. Abu-Rustum NR, Sonoda Y. Fertility-sparing surgery in early-stage cervical cancer: indications and applications. *J Natl Comp Cancer Netw* 2010;8:1435–8
47. Colombo N, Peiretti M. Critical review of neoadjuvant chemotherapy followed by surgery for locally advanced cervical cancer. *Int J Gynaecol Obstet* 2010;20 (11 Suppl. 2):S47–8
48. Barton MB, Frommer M, Shafiq J. Role of radiotherapy in cancer control in low-income and middle-income countries. *Lancet Oncol* 2006;7:584–95
49. Ashraf H. Poor nations need more help to slow growing cancer burden: the International Atomic Energy Agency asks donors to provide millions of dollars to buy radiotherapy equipment. *Lancet* 2003;361:2209
50. Van Der Giessen PH, Alert J, Badri C, *et al*. Multinational assessment of some operational costs of teletherapy. *Radiother Oncol* 2004;71:347–55
51. Levin V, Tatsuzaki H. Radiotherapy services in countries in transition: gross national income per capita as a significant factor. *Radiother Oncol* 2002;63:147–50
52. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clinical Oncol* 2008;26:5802–12
53. Anorlu RI. Cervical cancer: the sub-Saharan African perspective. *Reprod Health Matters* 2008;16:41–9