Chapter 8
The Prevention of Cervical Cancer

Onome Ogueh and Olufunso Adebola Adedeji

Abstract There are 500,000 new cases of cervical cancer every year, and about 84% of them occur in developing countries. Fifty-six percent to ninety percent of these women present late with FIGO stage III or IV. All cervical cancers are attributable to genital Human Papilloma Virus (HPV) infection, and the introduction of HPV vaccine has raised the potential for significant reduction in worldwide incidence of HPV infection and cervical cancer. The HPV vaccines are bivalent (active against HPV 16 and 18) or quarivalent (active against HPV 6, 11, 16 and 18). HPV type 16 and 18 accounts for 75% of cervical cancer. In HPV naïve women, both vaccines are over 99% effective in preventing precancerous lesions and subsequently cervical cancer associated with HPV type 16 and 18. The objective of HPV immunisation programme is to provide three doses of the vaccine to girls before they reach the age when the risk of HPV infection increases, but vaccination programmes are very low and variable in sub-Saharan Africa. It is estimated that vaccination of 58 million 12-year old girls before the start of sexual activity worldwide will prevent 690,000 cases and 420,000 deaths related to cervical cancer at a cost of US$4 billion. Seventy percent of cancers prevented, and 75% of deaths, will be in low or lower middle income countries. Screening is essential, as early treatment of pre-cancerous lesions prevents up to 80% of cervical cancers in countries where screening is routine. However, screening implementation and utilisation is challenging in Africa because of poor infrastructure, long travel distances, lack of trained medical personnel, inadequate record keeping and delayed testing. Therefore, the WHO approved strategy for cervical screening in low resource countries is visual inspection with acetic acid (VIA) or with Lugol's iodine (VILI). Despite their limited specificity both VIA and VILI are useful screening tools for low-resource

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O.A. Adedeji (ed.), *Cancer in Sub-Saharan Africa*,
DOI 10.1007/978-3-319-52554-9_8

settings because they are economical, and they provide immediate results. Research is going on in SSA about the feasibility and utility of HPV-DNA testing for cervical cancer screening, but in the short to medium term, HPV vaccination and VIA secondary screening will save many lives in SSA.

Keywords HPV • Screening • Vaccination • Human papilloma virus • Cervical cancer • Sub-Saharan Africa

8.1 Epidemiology

Cervical cancer is the commonest female cancer in sub-Saharan Africa (SSA; Fig. 8.1) with an age standardised incidence rate (ASR) of 34.8/100,000 in 2012. In Europe, the ASR incidence was 11.4/100,000 ranking fifth after breast, colorectal, lung and corpus uteri. Cervical cancer was also the most common cause of cancer death in SSA with ASR mortality of 22.5 per 100,000 whereas in Europe, it ranked 10th with ASR mortality of 2.6 in 2012 (GLOBOCAN 2012, IARC).

Within SSA, there is a wide variation in cervical cancer age standardised rate (ASR) of incidence from the highest of 65/100,000 in Mozambique to the lowest of 7.9/100,000 in Sudan and the highest ASR of mortality of 49.8/100,000 in Malawi to the lowest of 5.3/100,000 in Sudan (GLOBOCAN 2012). Similarly, there is a sub-regional variation in the incidence of cervical cancer with the highest ASR

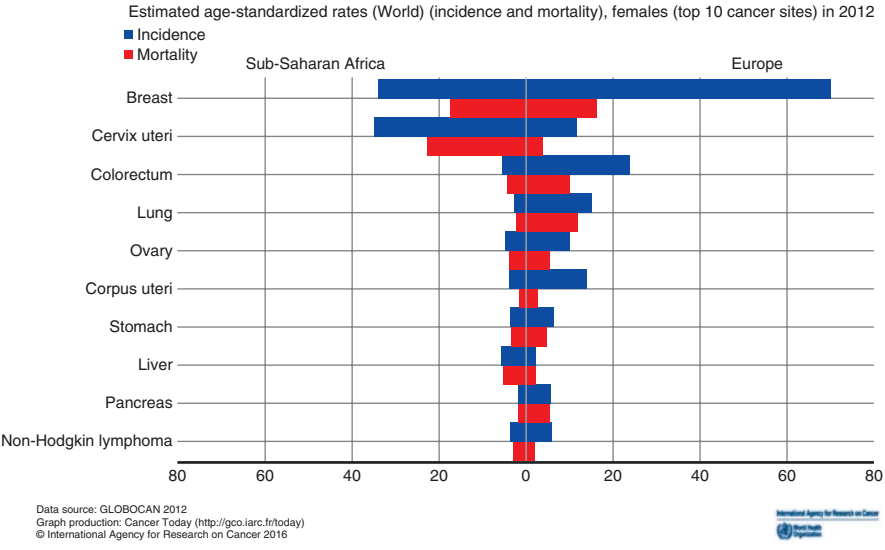

Fig. 8.1 Age standardised incidence and mortality of top 10 cancers in sub-Saharan African women compared to Europe in 2012 (GLOBOCAN 2012)

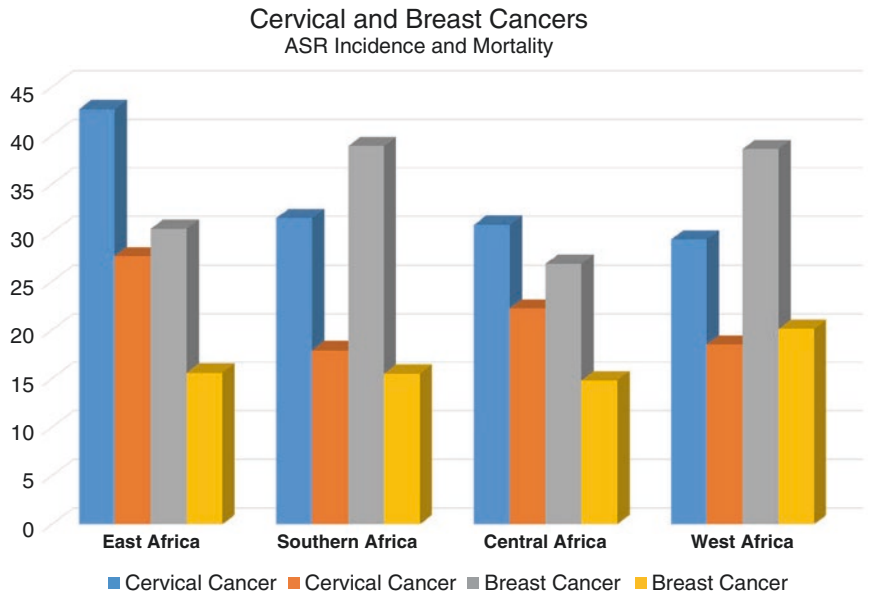

Fig. 8.2 Age standardised rate (ASR) of incidence and mortality per 100,000 of cervical and breast cancers in SSA by sub-regions

incidence and mortality in East Africa and, cervical cancer is less common than breast cancer in southern and western Africa (Fig. 8.2). In West Africa, unlike the other three sub-region, mortality from cervical cancer is less than that from breast cancer (GLOBOCAN 2012).

There are 500,000 new cases every year worldwide and about 84% of these occur in developing countries (Ferlay et al. 2012). However, new cases of cervical cancer is set to increase by 46.7% in SSA in 2025 from the 2012 level compared to an increase of only 1.7% in Europe (GLOBOCAN 2012, IARC). Most of the increases in SSA will be in women under 65 years of age.

Demographic shifts partially explains the increase in cervical cancer incidence, but other contributing factors include poor preventive measures. Human papilloma virus (HPV) infection is responsible for almost all cases of cervical cancers (Plummer et al. 2016) and despite the proven efficacy of vaccination, worldwide coverage is 1.4% (Lancet Editorial 2016). Across Africa, acceptability of HPV vaccination is high but awareness is low even among healthcare workers (Finocchario-Kessler et al. 2016). Furthermore, screening implementation and utilisation is challenging in Africa because of poor infrastructure, long travel distances, lack of gynaecologists and laboratory pathologists, indadequate record keeping and delayed testing results (Finocchario-Kessler et al. 2016).

In addition to the problems of prevention, late diagnosis is common across Africa with 56–90% of women diagnosed with stage III or IV cervical cancer

(Finocchario-Kessler et al. 2016). In a retrospective cohort study with a prospective follow up in North Central Nigeria, Musa et al. (2016) found that 72.3% of cases of invasive cervical cancer were diagnosed at advanced stages (Stage 2B and above) with an overall death rate of 79.8% (Musa et al. 2016). Early diagnosis is crucial and the 5-year survival for stage 1A is 95% but it is 20–30% for stage 4 disease.

8.2 Risk Factors

The risk factors for cervical cancer includes smoking, early age of onset of coitus, multiple sexual partners, early marriage and high parity, HIV/AIDS and marriage to a male whose sexual consorts had cancer of the cervix. It is now apparent that these factors are surrogate markers for genital HPV infection which is by far the most important predisposing factor for cervical cancer.

Genital HPV infection is the commonest sexually transmitted disease, and adolescents are at high risk of contacting the infection. An estimated 80% of sexually active women will be exposed to HPV by the age of 50, but peak exposure occurs in late teens and early twenties. There are more than 40 types of HPV that can infect the genital tract of both men and women. Most of these are symptomless and most infection will regress spontaneously after 6–12 months. There is no treatment that can eradicate the infection. Over time persistent genital infection can lead to cervical cancer and other HPV related diseases including genital warts, vulva intraepithelial neoplasia, vaginal intraepithelial neoplasia and cervical intraepithelial neoplasia (Madeleine et al. 1997; Clifford et al. 2003a, b, 2005; Sotlar et al. 2004).

Of the over 40 genotypes of HPV that affect the genital tract, seven account for 85–90% of cervical cancers worldwide (Munoz et al. 2004), and types 16 & 18 are responsible for about 75% of cervical cancers in Europe (Clifford et al. 2003), while types 6 & 11 account for 90% of genital warts (Von Krogh 2001). In addition to cervical cancer, the oncogenic HPV also induces cancer of the anus, vulva, vagina, penis, mouth and throat. All cases of the approximately 530,000 new cases of cervical cancer annually worldwide, are induced by HPV infection compared to only 25% of vulva cancers, 88% of anal cancers and 31% of oropharyngeal cancers (Plummer et al. 2016).

8.3 Primary Prevention of Cervical Cancer

Genital HPV infection is sexually transmitted the only certain way of preventing infection is by abstaining from all sexual activities or for mutual monogamy in non-infected couples. For those who are sexually active condoms may lower the chance of getting HPV infection if used correctly all the time. However, the recent introduction of HPV vaccine has raised the potential for significant reduction in worldwide incidence of HPV infection and subsequently cervical cancer.

8.3.1 The HPV Vaccine

In a work that was initiated in the mid-1980s, the HPV vaccine was developed in parallel by researchers in Georgetown University Medical Center, University of Rochester, the National Cancer Institute in the USA, and the University of Queensland in Australia. In 2006 the U.S. Food and Drug Administration (FDA) approved the first preventive HPV vaccine, marketed by Merck & Co. under the trade name *Gardasil*, and by the second quarter of 2007, *Gardasil* had been approved in 80 countries. Another vaccine called *Cervarix,* marketed by GlaxoSmithKline, was licensed in Australia in June 2007, and it was approved in the European Union in September 2007. *Cervarix* was approved for use in the U.S. in October 2009.

The HPV vaccines are subunit vaccines made from major protein of the viral coat or capsid. These virus-like particles mimics the structure of the native virus but do not contain any viral DNA (Syrjänen and Syrjänen 2000). The vaccines elicit virus-neutralising antibody response that prevents initial infection with the HPV types represented in the vaccines.

Cervarix is a bivalent vaccine that protects against HPV type 16 and 18 that accounts for 75% of cervical cancer. *Gardasil* on the other hand is quadrivalent and protects against HPV type 6, 11, 16 and 18, and therefore in addition to protecting against cervical cancer, it also protects against genital warts. In clinical trials in HPV naïve women both vaccines are over 99% effective at preventing precancerous lesions and subsequently cervical cancer associated with HPV type 16 and 18 (Franco and Harper 2005; Sanofi Pasteur MSD Data on File 06/008). Current studies suggest that protection is maintained for at least 6 years, but based on immune responses it is expected that protection will be extended further. *Gardasil* is also 99% effective in preventing genital warts associated with HPV type 6 and 11. A summary of efficacy of the two cervical cancer vaccines is shown in Table 8.1 (Herrero and Franceschi 2014).

Table 8.1 Key findings from clinical trials of HPV VLP vaccines (Herrero and Franceschi 2014)

Study group	Outcome	Quadrivalent vaccine	Bivalent vaccine
Young women	Infection efficacy	Proven	Proven
	CIN2 + efficacy	Proven	Proven
	CIN3 efficacy	Proven	Proven
	VIN/VaIN 2/3 efficacy	Proven	Proven[a]
	Genital warts efficacy	Proven	Not a target
	Anal infection efficacy	Not proven[b]	Proven
	Partial cross-protection infection	Proven	Proven
	Partial cross-protection CIN2+	Proven	Proven
	Therapeutic efficacy	None	None
	Safety	No concerns	No concerns

(continued)

Table 8.1 (continued)

Study group	Outcome	Quadrivalent vaccine	Bivalent vaccine
Mid-adult women	Infection efficacy	Proven	Proven[a]
	CIN2 + efficacy	Proven	Not proven
	Immunogenicity	Proven	Proven
	Safety	No concerns	No concerns
Young men	Infection efficacy	Proven	Not proven
	Genital warts efficacy	Proven	Not a target
	Anal infection efficacy	Proven	Not proven
	AIN2 + efficacy	Proven	Not proven
	Safety	No concerns	No concerns
Children	Infection efficacy	Not proven	Not proven
	Disease efficacy	Not proven	Not proven
	Immunogenicity	Proven	Proven
	Safety	No concerns	No concerns

AIN2+ anal intraephithelial neoplasia, grade 2 or worse, *CIN* cervical intraepithelial neoplasia, *HPV* human papillomavirus, *VaIN* vaginal intraepithelial neoplasia, *VIN* valvular intraepithelial neoplasia, *VLP* virus-like particle

[a]Meeting abstract, not yet published

[b]"Not proven" indicates that no data have been reported

8.3.2 Vaccination Programs

The objective of HPV immunisation programme is to provide three doses of the vaccine to girls before they reach the age when the risk of HPV infection increases and they are subsequently at risk of cervical cancer. Hence in the United Kingdom vaccination is routinely recommended for all girls at 12–13 years of age. However, *Cervarix* is licensed for individuals from 10 years and *Gardasil* is licensed from 9 years. There is also evidence suggesting that HPV vaccines are effective in preventing cervical cancer in women up to 45 years of age especially if they had not already been exposed to HPV infection. The benefit-cost is however reduced in older women because of the lower incidence of lesions among women infected by HPV later in life (Herrero and Franceschi 2014) Three dose schedule of intramuscular injections, with flexible dosing intervals if necessary; *Cervarix*: 0, 1–2 and 6 months and *Gardasil*: 0, 1 and 4 months. Since the currently available vaccines offer protection against HPV type 16 and 18 that are responsible for only 75% of cervical cancer it is essential to also institute secondary preventive measures even in women who have been vaccinated.

The American Cancer Society (ACS) recommends routine HPV vaccination for girls and boys starting from the age of 11 or 12. It can be started as early as 9 years of age (ACS 2016). It is also recommended for females aged 13–26 years old and males aged 13–21 year old who have not started or completed the series. HPV

vaccination is also recommended up to the age of 26 years for homosexual males and for those with weakened immune systems, including people with HIV, if they have not previously been vaccinated (ACS 2016). In an earlier recommendation, members of the Sub-Saharan Africa Cervical Cancer Working Group (2009) did not recommend male vaccination, however the group promised to review the decision when more evidence is available and high vaccination coverage of women had been achieved.

Vaccination programmes for HPV is very variable in sub-Saharan Africa and it is still very low, but with the support of public-private partnerships like the Global Alliance for Vaccines and Immunization (GAVI), some inroads are being made. With the cost of HPV vaccine reduced to US$5 per vaccine dose through the GAVI scheme, Rwanda in its first year under the programme achieved a three-dose vaccination coverage of 93.2% among an estimated 98,762 eligible girls in grade six (Herrero and Franceschi 2014). At this time by January 1, 2012, only Rwanda had a national HPV vaccination programme amongst GAVI eligible countries in SSA (Jit et al. 2014) and only South Africa in non-GAVI eligible countries had a programme (Kim et al. 2013). The Rwandan programme was possible because of initial 3-year donation of two million doses of quadrivalent vaccine Gardasil and 250,000 HPV screening test by Qiagen (Adefuye et al. 2013). After the 3 years, the vaccine was to be offered at a highly discounted price.

8.3.3 Economic Modelling

Using an economic model, Papilloma Rapid Interface for Modelling and Economics (PRIME), Jit et al. (2014) estimated the health and economic benefit of vaccination of girls against HPV before onset of sexual activity in GAVI eligible countries. They estimated that vaccination of 58 million 12-year old girls before the start of sexual activity worldwide will prevent 690,000 cases and 420,000 deaths related to cervical cancer at a cost of US$4 billion. Seventy percent of cancers and 75% of deaths prevented will be in low or lower middle income countries (Jit et al. 2014).

Another economic modelling, which is Excel-based, has projected that vaccination is cost-effective across SSA with 7.9–35.0 cervical cancer cases averted per 1000 vaccinations. Disability Adjusted Life Years (DALYs) projected to be averted, with HPV vaccination coverage of 70% and lifelong protection against HPV 16/18, ranged from 1.28 in Central African Republic to 80,100 in Nigeria (Kim et al. 2013; Table 8.2). HPV vaccine will be cost-effective in most SSA countries at a cost of five US dollars. This is the price currently offered by vaccine manufacturers to the GAVI alliance compared to the price of US$100 the vaccine costs in developed countries (Kim et al. 2013).

GAVI plans to aid vaccination of up to a million girls against HPV by 2015 in selected countries and up to 20 million girls and women in 30 countries by 2020 (Adefuye et al. 2013).

Table 8.2 Cervical cancer vaccination model

Country	Cancer incidence (ASR)	Cases averted per 1000 vaccinated	DALYs averted[a]
AFR D			
Angola	30	15.19	10,220
Benin	35	21.83	6620
Burkina Faso	28.6	15.01	9660
Cameroon	24	12.12	8030
Cape Verde[b]	34.9	21.66	260
Chad	19.9	10.12	4000
Comoros	51.7	31.84	650
Equatorial Guinea[b]	25	13.49	230
Gabon[b]	24.4	15	520
Ghana	39.5	23.66	17,270
Guinea	56.3	35.01	11,460
Guinea-Bissau	35.1	17.49	980
Liberia	41.8	24.7	3170
Madagascar	27.2	16.38	11,320
Mali	37.7	17.63	9820
Mauritania	35.1	20.39	2160
Mauritius	12.9	11.75	160
Niger	15.6	8.62	5450
Nigeria	33	16.18	80,100
Sao Tomé, Príncipe	23[c]	13.97	80
Senegal	34.7	19.21	9080
Seychelles[b]	12.9[c]	7.86	10
Serra Lone	41.9	19.91	4040
The Gambia	32.4	17.59	1300
Togo	30	19.65	3690
AFR E			
Bostwana[b]	22.2	11.03	440
Burundi	49.1	29.84	6960
Central Afr. Rep.	19.4	9.16	1280
Congo, Dem. Rep.	21.3	10.13	30,650
Congo, Rep. of (Brazzaville)	27.2	15.29	1800
Cote d'Ivoire	26.9	16.89	9240
Eritrea	12.9	8.15	1330
Ethiopia	18.8	10.26	27,770
Kenya	23.4	11.89	16,650
Lesotho	35	10.77	770
Malawi	50.8	22.32	14,780
Mozambique	50.6	19.41	17,710
Namibia[b]	15.8	8.94	410

Table 8.2 (continued)

Country	Cancer incidence (ASR)	Cases averted per 1000 vaccinated	DALYs averted[a]
Rwanda	34.5	19.27	6900
South Africa[b]	26.6	12.52	11,090
Swaziland[b]	50	17.24	550
Tanzania, Unit. Rep.	50.9	25.84	41,200
Uganda	47.5	23.52	32,180
Zambia	52.8	20.87	10,030
Zimbabwe	47.4	27.39	10,470
EMR D			
Djibouti	12.7	8.5	190
Somalia	20.3	10.89	3370
Sudan	7	4.68	4630

AFR D and *EMR D* high child and adult mortality, *AFR E* high child and very high adult mortality, *ASR* age standardised incidence rate per 100,000 people

[a]DALYs averted with HPV vaccination of 70% single cohort of 12 year-old girls in 2012 with 100% effective vaccine

[b]Countries not eligible for GAVI alliance support

[c]No country specific estimate available (Kim et al. 2013)

8.4 Secondary Prevention of Cervical Cancer

Secondary prevention involves early detection and treatment of the pre-invasive stages of the disease or identification of women at high risk of the disease for further testing and treatment if necessary. Treatment of cervical pre-cancerous lesions prevents up to 80% of cervical cancers in countries where screening is routine (Finocchario-Kessler et al. 2016). Established methods of screening include cervical cytology, visual inspection with acetic acid (VIA) or with Lugol's iodine (VILI) and HPV testing.

Cervical cytology is resource heavy, with medical, laboratory infrastructure and trained personnel unavailable in many SSA countries. There are poor patient tracking, return visits and where present, only in capital cities (Finocchario-Kessler et al. 2016). Only 1% of Ethiopian and 23.2% of South African women reported pelvic examination and pap test in the previous 3 years, with 40% of Tunisian to 94% of Malawian women having never received a pelvic examination (Finocchario-Kessler et al. 2016). Therefore, the WHO approved strategy for cervical screening in low resource countries is VIA or VILI.

From pooled analysis, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for VIA were 80% (range 79–82%), 92% (range 91–92%), 10% (range 9–10%) and 99% respectively although some studies showed a specificity of only 85% (Adefuye et al. 2013). However, some studies have shown that screening once at 35 years using VIA reduced life time risk of cervical cancer by 25–36% and relative cancer risk declined by additional 40% with

two screenings at ages 35 and 40 years (Adefuye et al. 2013). Screen-and-treat strategy has been found to be safe, acceptable and feasible in SSA and reduced loss-to-follow-up after a positive screening test although it has been criticised for lacking in evidence about safety and could compromise acceptability (Finocchario-Kessler et al. 2016). Despite the problems with VIA, it is affordable but it is operator dependent and its low PPV may result in overtreatment of some women (Denny et al. 2013).

8.4.1 Cervical Cytology

The conventional modality for obtaining cervical cytology was the Papanicolaou (pap) smear, but liquid-based cytology is now the standard modality in the United Kingdom as it offers improved sensitivity and reduction in the number of inadequate tests (NICE 2003). Cervical cytology based screening has reduced cervical cancer mortality in countries able to implement, sustain and financially support organised programmes that achieve broad coverage. Cervical cytology screening was introduced into the United Kingdom in 1967, and since then there has been a 50% decrease in invasive cervical cancer, and the screening programme is estimated to save approximately 4500 lives per year in England (Peto et al. 2004).

The United Kingdom has a very successful screening programme with 84% coverage in the last 5 years. It is free with established community based guidelines for call and recall of eligible women, and there is adequate arrangement for prompt response to a positive screening test including the provision of diagnostic test such as colposcopy and treatment.

Women are automatically invited for a cervical smear at the age of 25 years. They then have 3-yearly cervical smears until they are 49 years old, and from age 50 to 64 they have 5-yearly cervical smears. Women who are 65 years and over are only screened if they had had a recent abnormal test or if they had not been screened after age 50.

In contrast, screening in Nigeria is opportunistic and despite a high level of knowledge and positive attitude towards cervical screening, only 20.8% of health workers in Kano had previously had a pap smear (Kabir et al. 2005) and in Enugu State only 18% of female medical practitioners had had a cervical smear (Dim et al. 2009). Amongst female undergraduates in a Nigerian university only 5.2% had had cervical screening (Aniebue and Aniebue 2010). In a questionnaire survey in Ilorin, Nigeria, only 8.0% of the respondents had ever been screened for cancer of the cervix, and the proportion of women screened was significantly higher among those who demonstrated positive attitude to screening (81.5%, $p = 0.001$), those who were aware of the cervical cancer (100.0%, $p = 0.001$), and those who were aware of cervical cancer screening (88.9%, $p = 0.001$) (Idowu et al. 2016).

8.4.2 *Visual Inspection Acetic Acid (VIA) or* Lugol*'s Iodine (VILI)*

Visual inspection of the cervix can be performed with 5% acetic acid or Lugol's iodine (Fig. 8.3) to identify pre-cancerous lesions. Visual inspection of the cervix with Lugol's iodine was the first method of cervical cancer screening, and was introduced in the 1930s by Schiller (Schiller 1938). With VIA pre-cancerous lesions appear opaque white (aceto-white change) with clearly demarcated borders at the squamo-columnar junction (transformation zone). With VILI abnormalities appear as well defined, thick mustard or golden yellow areas touching upon the squamo-columnar junction. Visual inspection with acetic acid and VILI are usually performed together; VIA first as the iodine used for VILI stains the cervix.

Despite their limited specificity both VIA and VILI are useful screening tools for low-resource settings because they are economical and provide immediate results.

Women with pre-cancerous lesions may be treated with cryotherapy or referred for colposcopy. However, in the absence of cervical cytology colposcopy may also be used as the primary method of screening for cervical cancer. Colposcopy involves microscopic inspection of the cervix using a colposcope that illuminates and magnifies the cervix up to 6–40-fold. Most clinicians will apply 5% acetic acid with or without Lugol's iodine at the time of colposcopy.

At colposcopy biopsies can be taken and treatments of precancerous lesions performed under local anaesthetic thus preventing progression to invasive disease. Treatments for pre-cancerous lesions include ablation with loop electrical excision, cryotherapy or large loop excision of transformation zone. These treatment strategies are well accepted in SSA (Finocchario-Kessler et al. 2016). Treatment for invasive cancer include surgery, radiotherapy and combined radio-chemotherapy but there is a dearth of research on these in SSA and 22% of 54 African countries have no access to any form of anti-cancer therapies (Finocchario-Kessler et al. 2016).

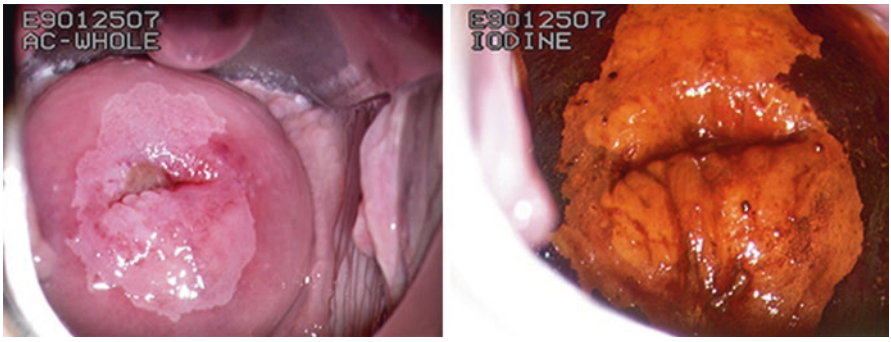

Fig. 8.3 *Left* visual inspection with acetic acid and on the *right* with Lugol's iodine

8.4.3 HPV-DNA

While research is going on in SSA about the feasibility and utility of HPV-DNA testing (Lince-Deroche et al. 2015; Finocchario-Kessler et al. 2016), it is not widely used because it is expensive (Lince-Deroche et al. 2015; Denny et al. 2013). In a study of HIV patients screened for HPV in Johannesburg, South Africa, VIA was the most cost-effective per true positive case of Cervical Intraepithelial Neoplasia 2 (CIN2) detected at a cost of US$17.05 (Table 8.3) compared to the standard PAP test (US$130.63) and HPV-DNA testing (US$320.09) (Lince-Deroche et al. 2015).

Table 8.3 Cost-effectiveness for screening for CIN2+ based on maximum number of cases achievable in an 8-hour day Pap 1 used standard criteria for positivity (high grade SIL, atypical squamous cells cannot rule out high grade lesion and squamous cell carcinoma). Pap 2 included all of Pap1 and any non-negative results (Lince-Deroche et al. 2015)

	Pap 1	Pap 2	VIA	HPV DNA
Sensitivity and specificity (95% Cl)				
Sensitivity	75.8% (70.8–80.8)	94.8% (90.5–99.2)	65.4% (59.7–71.1)	91.9% (88.5–95.3)
Specificity	83.4% (80.9–85.9)	35.6% (32.2–38.9)	68.5% (65.3–71.1)	51.4% (48.0–54.8)
Test results (n = 1193)				
Total positive (95% Cl)	431 (430–431)	888 (879–898)	509 (506–512)	750 (736–764)
TP (95% Cl)	298 (278–318)	373 (356–390)	257 (235–279)	361 (348–375)
FP (95% Cl)	133 (113–153)	515 (489–542)	252 (226–278)	389 (362–416)
Missed cases (FN'S) (95% Cl)	95 (75–115)	20 (3–37)	136 (114–158)	32 (18–45)
Screening costs (US$)				
Initial screen	9750 (7313–12,188)	9750 (7313–12.188)	4383 (3287–5478)	64,826 (48,619–81,032)
Colpo for all positive cases[b]	29,165 (21,891–36,427)	60,115 (45,609–74,373)	0.00 (0.00–0.00)	50,784 (38,791–62,309)
Total costs[c]	38,915 (29,204–48,615)	69,865 (52,922–86,561)	4383 (3287–5478)	115,610 (87,410–143,341)
% of total cost spent on colpo. For FP's	23.10%	50%	0.00%	23%
Cost per TP case detected	130.63 (104.95–153.09)	187.53 (148.79–222.02)	17.05 (14.01–19.61)	320.09 (251.31–382.71)

CI confidence interval, *TP* true positive, *FP* false positive, *FN* false negative, *Colpo.* colposcopic biopsy

[a]All costs are presented with a range of 25% higher and lower

[b]Considers the colposcopic biopsy costs for true positives plus false positives. Not clinically relevant for VIA

[c]For initial screen plus colposcopic biopsy when indicated. Excludes colposcopic biopsy for VIA because not clinically relevant

Most of the costs incurred in the various aspects of the test were largely due to laboratory and transport costs (Table 8.4) which accounted for 63% of the total cost of PAP, and over 90% of the costs of HPV DNA and coloposcopy biopsy (Lince-Deroche et al. 2015).

In order to ameliorate the substantial of transport and laboratory costs, Singh and Badaya (2016) have proposed tele-cytology. This will involve the use of mobile vans and satellites to transmit prepared cytological slides of PAP smears to central laboratories for analysis. This will reduce the cost of transportation, access to centralised cytological services amd reduce the number of patients lost to follow-up amongst other advantages (Singh and Badaya 2016). This proposal will need a cost-effectiveness comparison to the use of VIA in sub-Saharan Africa.

Table 8.4 Average estimated procedure costs for each scenario (USD 2013)

	Cost (range)[a]	% of total
Pap		
Personnel	1.43 (1.08–1.79)	17.6
Supplies	1.03 (0.77–1.29)	12.6
Equipment	0.50 (0.37–0.62)	6.1
Lab/Transport	5.21 (3.91–6.51)	63.7
Total	8.17 (6.13–10.22)	100
VIA		
Personnel	1.56 (1.17–1.95)	42.5
Supplies	1.24 (0.93–1.55)	33.7
Equipment	0.88 (0.66–1.09)	23.8
Lab/Transport	0.00 (0.00–0.00)	0
Total	3.67 (2.76–4.59)	100
HPV DNA		
Personnel	1.39 (1.04–1.73)	2.5
Supplies	0.76 (0.57–0.95)	1.4
Equipment	0.46 (0.34–0.57)	0.8
Lab/Transport	51.74 (38.80–64.67)	95.2
Total	54.34 (40.75–67.92)	100
Colposcopic biopsy		
Personnel	2.10 (1.58–2.63)	3.1
Supplies	1.50 (1.12–1.87)	2.2
Equipment	1.00 (0.75–1.25)	1.5
Lab/Transport	63.11 (47.33–78.89)	93.2
Total	67.71 (50.79–84.64)	100

[a]Range represents 25% lower and higher than base case (Lince-Deroche et al. 2015)

8.5 Conclusion

New cases of cervical cancer is set to increase by 46.7% in sub-Saharan Africa by 2025 and despite the fact that it is a preventable disease, more work needs to be done to combat it. Within the financial support of private-public enterprises like GAVI, it has been shown that programs can achieve over 90% vaccination. With the GAVI target of aiding the vaccination of 20 million girls and women worldwide by 2020, there is an opportunity for policy makers in SSA to extend the programs beyond the short and medium terms and the limited coverage.

There are many encouraging research work adapting research questions to tackling SSA specific problems with regards to infrastructure and finance and best treatment pathways within such constraints. However, these difficulties aside, awareness and engagement with preventive programs continue to be problems. Public education is essential to tackle these. Elevating primary and secondary prevention of cervical cancer in the context of Millennium Development Goal 5b (i.e Universal Access to Reproductive Health) as advocated by Denny et al. (2013) will go a long way to addressing this and making it visible to policy makers. In the short to medium term, HPV vaccination and VIA screening will save many lives in SSA and achievable targets are needed on a country wide or sub-regional levels.

References

Adefuye PO, Broutet NJ, de Sanjose S, Denny LA. Trials and projects on cervical cancer and human papillomavirus prevention in sub-Saharan Africa. Vaccine. 2013;31(S5):F53–39.

American Cancer Society. Infections that can lead to cancer. 2016. http://www.cancer.org/acs/groups/cid/documents/webcontent/002782-pdf.pdf

Aniebue PN, Aniebue UU. Awareness and practice of cervical cancer screening among female undergraduate students in a Nigerian university. J Cancer Educ. 2010;25(1):106–8.

Clifford GM, Smith JS, Aguado T, et al. Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis. Br J Cancer. 2003a;89:101–5.

Clifford GM, Smith JS, Plummer M, et al. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. Br J Cancer. 2003b;88(1):63–73.

Clifford GM, Rana RK, Franceschi S, et al. Human papilloma genotype distribution in low-grade cervical lesions: comparison by geographical region and with cervical cancer. Cancer Epidemiol Biomark Prev. 2005;14(5):1157–64.

Denny L, Sankaranarayanan R, De Vuyst H, et al. Recommendations for cervical cancer prevention is sub-Saharan Africa. Vaccine. 2013;31(S5):F73–4.

Dim CC, Ekwe E, Madubuko T, et al. Improved awareness of Pap smear may not affect its use in Nigeria: a case study of female medical practitioners in Enugu, Southeastern Nigeria. Trans R Soc Trop Med Hyg. 2009;103(8):852–4.

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 GLOBOCAN 2012 v1.1.

Finocchario-Kessler S, Wexler C, Maloba M, et al. Cervical cancer prevention and treatment research in Africa: a systematic review from a public health perspective. BMC Womens Health. 2016;16(1):29.

Franco EL, Harper DM. Vaccination against human papilloma virus infection: a new paradigm in cervical cancer control. Vaccine. 2005;23(17–18):2388–94.
Herrero R, Franceschi S. Vaccination. In: Stewart BW, Wild C, editors. World cancer report. Lyon: International Agency for Research on Cancer; 2014. p. 314–21.
IARC (International Agency for Research on Cancer). GLOBOCAN. 2012. http://globocan.iarc.fr/Pages/online.aspx
Idowu A, Olowookere SA, Fagbemi AT, Ogunlaja OA. Determinants of cervical cancer screening uptake among women in Ilorin, North Central Nigeria: a community-based study. J Cancer Epidemiol. 2016;2016:6469240. doi:10.1155/2016/6469240. Epub 2016 Jan 6.
Jit M, Brisson M, Portnay A, Hutubessy R. Cost-effectiveness of female human papilloma vaccination in 179 countries: a PRIME modelling study. Lancet Glob Health. 2014;2:e406–14.
Kabir M, Iliyasu Z, Abubakar IS, Mahboob S. Awareness and practice of cervical cancer screening among female health professionals in Murtala Mohammed Specialist Hospital. Niger Postgrad Med J. 2005;12(2):179–82.
Kim JJ, Campos NG, O'Shea M, et al. Model-based impact and cost-effectiveness of cervical prevention in sub-Saharan Africa. Vaccine. 2013;31(Suppl 5):F60–72.
Lancet Editorial. HPV vaccination: a decade on. Lancet. 2016;388(10043):438.
Lince-Deroche N, Phiri J, Michelow P, et al. Cost and cost effectiveness of three approaches for cervical cancer screening among HIV-positive women in Johannesburg, South Africa. PLoS One. 2015;10(11):e0141969.
Madeleine MM, Daling JR, Carter JJ, et al. Cofactors with human papillomavirus in a population-based study of vulvar cancer. J Natl Cancer Inst. 1997;89:1516–23.
Munoz N, Bosch FX, Castellsague X, et al. Against which human papillomavirus types shall we vaccinate and screen? The international perspective. Int J Cancer. 2004;111(2):278–85.
Musa J, Nankat J, Chad J, et al. Cervical cancer survival in a resource-limited setting-North Central Nigeria. Infect Agent Cancer. 2016;11:15. doi:10.1186/s13027-016-0062-0. Published online 2016 Mar 24.
National Institute for Health and Clinical excellence (NICE) Guidance on the use of liquid-based cytology for cervical screening. Technology appraisal guidance [TA69] 2003.
Peto J, Gilham C, Fletcher O, Matthews FE. The cervical cancer epidemic that screening has prevented in the UK. The Lancet. 2004;364(9430):249–56.
Plummer M, De Martel C, Ferlay J et al. Global burden of cancers attributable to infections in 2012: A synthentic analysis. Lancet Glob Health. 2016. http://dx.doi.org/10.1016/S2214-109X(16)30143-7
Schiller W. Leucoplakia and cancer of the cervix. Am J Obstet Gynecol. 1938;35:17.
Singh S, Badaya S. Tele-cytology: an innovative approach for cervical cancer screening in resource-poor settings. J Cancer Res Ther. 2016;12:481–5.
Sotlar K, Diemer D, Dethleffs A, et al. Detection and typing of human papillomavirus by E6 nested multiplex PCR. J Clin Microbiol. 2004;42:3176–84.
Sub-Saharan Africa Cervical Cancer Working Group. Model HPV vaccine recommendations for sub-Saharan Africa. Clin Mother Child Health. 2009;6(1):1047–52.
Syrjänen K, Syrjänen S. Papillomavirus infections. In: Human pathology. Chichester: Wiley; 2000. p. 11–46.
Von Krogh G. Management of anogenital warts (condylomata acuminate). Eur J Dermatol. 2001;11(6):598–603.