

**CERVICAL CANCER PREVENTION IN KENYA:
SPECIAL CONSIDERATIONS FOR
HIV-INFECTED WOMEN**

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Masters in International Health
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KIT (ROYAL TROPICAL INSTITUTE)
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CERVICAL CANCER PREVENTION IN KENYA: SPECIAL CONSIDERATIONS FOR HIV-INFECTED WOMEN

A thesis submitted in partial fulfillment of the requirement for the degree of
Masters of International Health

By

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ABBREVIATIONS

ACCP	Alliance for Cervical Cancer Prevention
AIDS	Acquired Immune Deficiency Syndrome
AOR	Adjusted Odds Ratio
ARR	Adjusted Relative Risk
CC	Cervical Cancer
CDC	Centers for Disease Control
CHW	Community Health Workers
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia
CIS	Carcinoma in situ
DALY	Disability Adjusted Life Years
FHI	Family Health International
GAVI	Global Alliance for Vaccines and Immunisation
GDP	Gross Domestic Product
FBO	Faith Based Organisation
HAART	Highly Active Anti-Retroviral Therapy
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HPV DNA	Human Papillomavirus Deoxyribonucleic Acid
HSV-2	Herpes Simplex Virus type 2
HSIL	High grade Squamous Intraepithelial Lesion
HR	Hazard Ratio
IARC	International Agency for Research on Cancer
ICC	Invasive Cervical Cancer
ICESCC	International Collaboration of Epidemiological Studies of Cervical Cancer
KDHS	Kenya Demographic and Health Survey
KNBS	Kenya National Bureau of Statistics
LEEP	Loop Electrosurgical Excision Procedure
LSIL	Low grade Squamous Intraepithelial lesion
MOH	Ministry of Health
MOMS	Ministry of Medical Services
MOPHS	Ministry of Public Health and Sanitation
NACADA	National Agency for the Campaign Against Drugs
NASCOP	National AIDS and STI Control Program
NGO	Non-Governmental Organisation
NHIF	National Health Insurance Fund
OR	Odds Ratio
PATH	Program for Appropriate Technology in Health
PapSmear	Papanicolaou's Smear
PEPFAR	President's Emergency Plan for AIDS Relief
RR	Relative Risk
SIL	Squamous Intraepithelial Lesion
SWAP	Sector Wide Approach
TB	Tuberculosis
UNDP	United Nations Development Fund

US	United States
VIA	Visual Inspection with Acetic Acid
VIAM	Visual Inspection with Acetic Acid with Magnification
VILI	Visual Inspection with Lugol's Iodine
WHO	World Health Organisation
WPP	World Population Prospects

GLOSSARY

Acetowhite: Well defined abnormal white lesions that appear on the cervix after application of 3-5% acetic acid.

Biopsy: The process of removing tissue samples for diagnostic purposes.

Carcinogenesis/Oncogenesis: The process of altering normal cells to cancer cells.

Cervix: The lower part or opening of the uterus (womb).

Cervical Transformation Zone: The area of the cervix where columnar type of epithelium is transformed to squamous type epithelium. This is part of the cervix where abnormal cells occur.

Cervical Intraepithelial Neoplasia: Abnormal changes in cervical epithelium diagnosed by microscopic examination of tissue (histology).

Cervical Precancer: Abnormal cervical lesions that have potential to progress to cervical cancer.

Colposcopy: The procedure used to examine the cervix using equipment (colposcope) that illuminates and magnifies the cervix.

Condyloma: A wart-like structure on the mucous membrane or skin

Cytology: A method of examining cells using a microscope

Dysplasia: Abnormal growth of body tissue

Histology/Histopathology: The examination of tissue under the microscope.

Metaplasia: The changing of one type of epithelium/tissue to another.

Squamous Intraepithelial Lesion: Cellular changes in squamous type of epithelium detected by microscopic examination of cells (cytology).

EXECUTIVE SUMMARY

Cervical cancer (CC) is a preventable disease yet it is the leading cause of cancer-related morbidity and mortality among Kenyan women with over 2625 cases and 2111 deaths annually. HIV increases the risk of CC. In Kenya, over 840,000 women are infected with HIV but current estimates of CC in HIV-infected women are unknown.

Human papillomavirus (HPV), a sexually transmitted infection is the necessary but insufficient cause of CC. Multiple sex partners and early sexual debut are main risk factors for HPV infection. Key cofactors for CC in Kenya include coinfection with HIV and herpes simplex-2, infection with high-risk and multiple HPV types, smoking, polygamy, poverty and illiteracy among women and an inadequate health system. Sexual behaviour such as multiple partners common to both HIV and HPV transmission and associated HIV-induced immunosuppression make HIV-infected women susceptible to CC.

CC can be reduced through health education, sexual risk reduction, male circumcision, HPV vaccines and through screening and treatment of precancers. Low cost methods using visual inspection with acetic acid for screening and cryotherapy for treatment of pre-cancers are recommended for Kenya. These screening and treatment methods are equally effective in HIV-infected women but frequent screening is recommended for this population. Lack an organized screening program, inadequate financial and human resources, inadequate health infrastructure, low awareness of CC and sociocultural beliefs are barriers to CC prevention in Kenya.

An affordable CC prevention program is required for HIV-infected and uninfected women in Kenya with emphasis on more frequent follow-up for HIV-infected women.

Keywords: Cervical cancer, human papillomavirus, HIV, pre-cancers, cervical neoplasias, Kenya, prevention, screening, treatment, low-resource settings

CHAPTER 1

INTRODUCTION AND BACKGROUND

INFORMATION ON KENYA

1.1 Introduction

Cervical cancer is the second most common cancer worldwide and the most common in developing countries. Globally, 529,409 women are diagnosed and 274,883 women die from cervical cancer every year. Developing countries represent 86% of the new cases and 88% of deaths. Worldwide, Eastern Africa is the region that is most affected with cervical cancer with an age standardized incidence rate and mortality rate of 25.3 and 34.5 per 100,000 women per year respectively (WHO, 2010a).

The low cervical cancer rates in developed countries have largely been attributed to high quality cytology-based screening programs. However, these programs require robust health infrastructure and considerable financial and human resources. Therefore implementation of screening in developing countries is difficult (WHO, 2010a).

Infection with human papillomavirus (HPV) is the necessary but not sufficient cause for cervical cancer (Munoz, 2000). Other cofactors needed for progression of HPV infection to cervical cancer include HIV co-infection, high parity, smoking, long term oral contraceptive use, poor diet and co-infection with other STIs (Munoz et al., 2003).

In particular, studies have shown that compared to HIV negative women, HIV-infected women are at an increased risk for HPV infection and tend to be infected with multiple genotypes of HPV (Yamada et al., 2008, Strickler et al., 2005). Furthermore, HPV persists in the cervical cells as the virus is not cleared as efficiently by the body's impaired immune response (Moscicki et al., 2004). Consequently, they are at increased risk for HPV associated cervical pre-cancers (Yamada et al., 2008, Moodley et al., 2006) and cervical cancer (Palefsky et al., 2006, Frisch et al., 2000). Moreover, cervical cancer presents earlier in HIV infected women (Gichangi et al., 2003) and once established, presents in aggressive forms with poor survival rates (Gichangi et al., 2003). Based on these findings, the CDC declared cervical cancer an AIDS defining malignancy (CDC, 1992).

In Kenya, cervical cancer is the most frequent cancer and the leading cause of cancer-related death among women. Cervical cancer has an annual crude incidence rate of 16.5 per 100,000 women and a corresponding age-standardized incidence rate of 28.7 per 100,000 women (WHO, 2010). Like most developing countries, Kenya lacks the financial and human resources to implement a nationwide cytology based screening program (Gichangi et al., 2003).

The burden of HIV infection in Kenya is high. Among adults aged between 15 to 64 years, the HIV prevalence is 7.4% and out of this 60% of those infected are women (NASCO, 2007). This means that a large proportion of women in Kenya are at risk of acquiring cervical cancer.

In lieu of this, this thesis will focus on cervical cancer prevention strategies suitable for low resource countries with special consideration for HIV-infected women. Also to be covered in this thesis will be the determinants and natural history of cervical cancer; the association between HIV and cervical cancer; and the barriers facing cervical cancer prevention in Kenya. My interest in this area arose during my work as a medical doctor in a HIV treatment program in western Kenya that offered cervical cancer screening services to HIV-infected women enrolled in the program. The findings of this thesis will be used to advocate for the prioritization of cervical cancer prevention among HIV-infected women in Kenya.

1.2 Background information on Kenya

1.2.1 Socio-demographic indices

Kenya is a low income country located in East Africa. It is bordered to the south by Tanzania, to the west by Uganda, to the north by Sudan, to the northeast by Somali and to the south east by the Indian Ocean (KDHS, 2003) (See annex 1).

It covers a total area of 582,646 square kilometres and is divided into 8 administrative provinces. It is culturally diverse as there are about 42 ethnic communities in Kenya. The official language is English and the national language is Kiswahili. About 90% of Kenyans are Christians and 7% are Muslims (KDHS, 2003).

As at the year 2010, Kenya has a population of about 40.9 million people with about 21 % of the population residing in urban areas. The population pyramid is broad based with 42.8% of Kenyans being below 15 years, 54.6% being between 15-64 years and 2.6% being above 65 years of age (WPP, 2008). The burden on the economically productive age group is high as the child and old age dependency ratios are 78.5 and 4.8 respectively (UNDP, 2009).

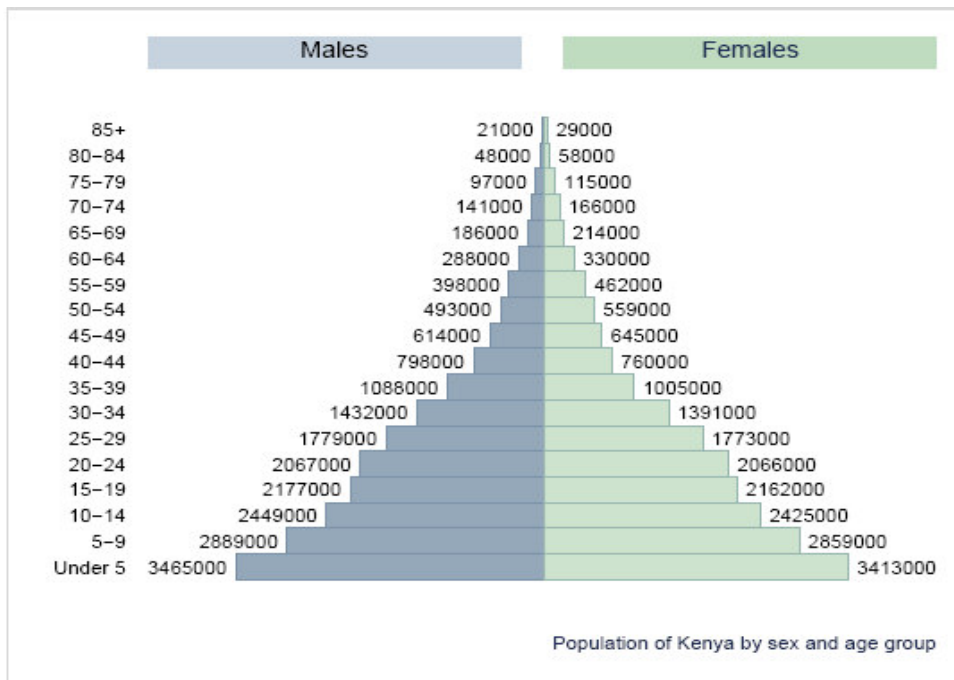


Figure 1: Population pyramid of Kenya as at year 2010; Source: (WHO, 2010b, WPP, 2008)

The overall total fertility rate is high at 4.9 live births per woman (KDHS, 2003). The fertility rate of rural women is higher (5.4) than that of urban women (3.3). The high fertility rates can be explained by the low use of family planning methods. The latest statistics show that only 28.4% of women in Kenya use any form of family planning method (KDHS, 2003).

Life expectancy levels are still low. The overall life expectancy at birth is 53.6 years with that of females (54.0 years) being slightly higher than that of males (53.2 years) (UNDP, 2009). These low levels are due to the high burden of both infectious and non communicable diseases coupled with poor health services.

Kenya's economy is mainly agricultural. The GDP in 2008 was US\$ 778.765 per capita (KNBS, 2008) and GDP growth rate was 1.7% (KNBS, 2009). The low rate in early 2008 was attributed to the post election violence that affected the country (MOF, 2009).

Poverty levels are unacceptably high. Between the years 2000-2006, 52% of the population was living below the national poverty line. Furthermore, inequity is high in Kenya as reflected by the Gini coefficient which was 47.7 between the years 1992-2007 (UNDP, 2009).

Literacy levels remain moderate. The adult literacy rate is 73.6%. Males are more literate than females with rates of 77.7% and 70.2% respectively. In 2006, only 57% of Kenyans had access to improved water source (UNDP, 2009). These factors further explain the high burden of diseases in the country (See annex 2 for demographic indicators).

1.2.2 The Kenyan health system

Organization of the health care system

The key stakeholders in health care system include the government, private sector and development partners. The government and private sector provides health services in 52% and 48% of the health facilities in Kenya respectively (Ngigi and Macharia, 2006).

The Government is represented by the Ministry of Medical services (MOMS) and the Ministry of Public Health and Sanitation (MOPHS), local government and parastatals. MOMS and MOPHS however, provide the bulk of health services. MOMS is responsible for overseeing the curative and rehabilitative services while the (MOPHS) is responsible for preventive and promotive services (MOH, 2009). The Ministry of Health was split into MOMS and MOPHS following the power sharing deal in government after the post election violence in 2008. This split has introduced challenges in managing the health care system due to duplication of roles and competition for control and resources (Wamai, 2009). (See annex 4 for roles of ministries)

The private sector mainly provides curative services and limited preventive services. In collaboration with the district health management team, this sector serves communities (NCAPD, 2004).

The health care system is organized into 6 levels of care in a hierarchical pyramidal fashion with the first level representing the dispensaries and health centres and the sixth level representing the referral hospitals (MOH , 2005) (See Annex 5).

To improve efficiency, the health sector has been decentralized with decision making and resources being transferred from the Ministry of Health to the provincial and district levels. Districts are the pillars of this system and are headed by the District Medical Officer of Health with support of the District Health Management Board (Wamai, 2009, MOH, 2005). Decentralization has however had limited success due to poor supervision and coordination and delayed transfer of funds from the headquarters (Wamai, 2009).

Financing and coordination

The health sector in Kenya is underfunded. For example, in fiscal year 2007/2008, the total expenditure on health was 7.3% of the total government expenditure (MOMS, 2008). This is well short of the 15% expectation as outlined in the Abuja declaration.

The major sources of health care financing include the government, households and donors. For example, in year 2001/2002 health

expenditure by major source included, government (29.6%), out of pocket/user-fees (53.1%), donors (16.3%), private for-profit (2.3%) and non-governmental organizations (0.6%) (Wamai, 2009).

A social national health insurance fund (NHIF) is in place but it has a low population coverage of only 25% and it neither covers out-patient fees nor caters for the poor and unemployed (MOMS, 2008). This has led to high out-of-pocket spending and placed financial burdens on Kenyans. It is estimated that 88% of people with insurance are covered by the NHIF, the rest are covered by private insurers (Wamai, 2009).

To improve coordination among key health stakeholders a health sector wide approach (SWAp) is in place. However commitment to its obligations by stakeholders including government is sub-optimal. Parallel financing is still present and only some funds are directed towards the agreed priority areas (MOMS, 2008).

Human resources for health

Though there has been an increase in health workers, Kenya still has a shortage of health workers. There were 204 health workers in 2009 compared to 169 health workers per 100,000 population in 2007. This is short of the WHO minimum recommendation of 228 health workers per 100,000 population. There were 18 doctors and 124 nurses per 100,000 population in 2007 (MOH, 2009).

Table 1: Registered health workers in Kenya, Source: (MOH, 2009)

Type of Personnel	2004	2004: Ratio / 100,000	2007	2007: Ratio / 100,000
Enrolled & Registered Nurses	40,081	122	44,105	124
Doctors	4,813	15	6,271	18
Clinical Officers	4,808	15	5,797	17
Pharmacists	1,881	6	2,775	8
Pharmaceutical Technologists	1,404	4	1,680	5
Dentists	772	2	931	3
Total	53,759		61,559	

Health workers are inequitably distributed. Many are concentrated in urban areas leaving rural and hard to reach areas understaffed. This is a problem considering only 21% of Kenyans live in urban areas. Between the years 2005-2007 the annual attrition rate from the Ministry of health was 4.5% with the main reasons of attrition being retirement, dismissal and resignation (MOH, 2009). (See fig 1).

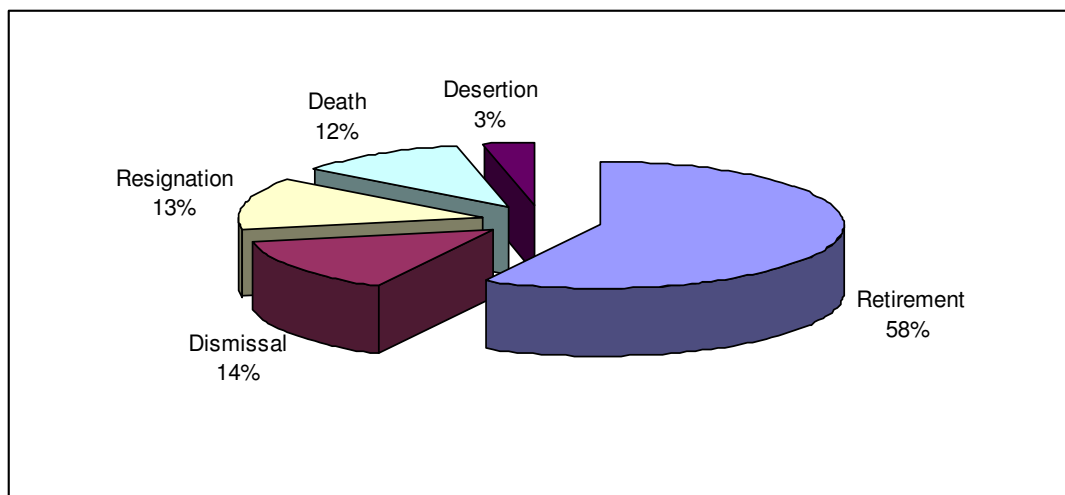


Figure 2: Reasons for MOH staff attrition between years 2005-2007. Source: (MOH, 2009)

Access and quality

The health sector is plagued by inequalities. For example, while 70% of urban dwellers have access to health facilities within 4km, only 30% of the rural population has a similar access (Ngigi A, 2006). About 44% of patients in Kenya do not seek health care services due to insufficient funds (MOMS, 2008). In addition, women's hospitalization costs are more than twice that of men yet women are less likely to be insured than men (Wamai, 2009).

The quality of health services particularly in the public sector is often low due to insufficient financing, equipment, supplies and staff. Furthermore, regulatory standards are poorly developed to ensure high quality services (Ngigi and Macharia, 2006).

Health priorities

Kenya like most developing countries has a double burden of disease. Infectious diseases like HIV/TB and malaria continue to place an enormous burden on the health system. For example malaria is the leading cause of out-patient morbidity and there were 70,000 new HIV infections and, 117, 000 new TB cases in 2007 (MOH, 2009). The burden by non-communicable diseases is increasing in Kenya especially in urban areas due to changing lifestyles. In 2007, 33% and 67% of the total mortality was attributed to communicable and non-communicable diseases respectively. However, the true burden of non-communicable diseases is unclear due to poor prioritization, low awareness and funding and more donor driven focus on communicable diseases (Maina, 2009).

CHAPTER 2

PROBLEM STATEMENT, STUDY OBJECTIVES AND METHODOLOGY

2.1 Problem statement

Cervical cancer is a preventable disease yet it is the leading cause of cancer related morbidity and mortality among women in Kenya with 2625 cases and 2111 deaths being annually. If no intervention is carried out, cervical cancer cases and deaths are expected to rise by 55% and 36% respectively by the year 2025 (WHO, 2010b). However these figures are most likely an underestimate as there is no national cancer registry in Kenya hence most cases and deaths are not reported (Musibi, 2008). In general, there is limited data on the patterns and distribution of cervical cancer in Kenya as little research and reporting have been done.

As mentioned in the previous chapter, HIV-infected women are at an increased risk of developing cervical cancer. This is important to note as more than 1.4 million people in Kenya are living with HIV/AIDS and 60% of this population are women (NASCOP, 2007). This means that over 840,000 women have an elevated risk of cervical cancer. Due to limited reporting the current national cervical cancer rates in HIV infected women are unknown.

Despite this large disease burden, the platform for cervical cancer prevention is largely underdeveloped in Kenya. To start with, there is currently no clear policy that offers guidelines for cervical cancer prevention among women including those who are HIV infected (Gichangi et al., 2003). Furthermore a national cervical cancer screening program does not exist. Screening is opportunistic and offered in an uncoordinated fashion (Huchko, personal communication). A situation analysis of cervical cancer screening and diagnostic services in East Africa showed that most screening in Kenya is carried out in family planning clinics. This is ineffective as a majority of women attending family planning clinics in Kenya are below 25 years of age and therefore considered low risk for cervical cancer (Chirenje et al., 2001).

The overall cervical cancer screening coverage is unacceptably low in Kenya. It is estimated that only 3.2% of all eligible women aged between 18-69 years are screened every 3 years. The screening coverage of urban women is higher than that of rural women (4% vs. 2.6%) (WHO, 2010). As cervical cancer is more prevalent in poor communities who do not have access to screening services, this distribution is inequitable. This is attributed to the fact that rural women are more impoverished and less educated (KDHS,2003) hence are likely to lack the financial means to seek screening services and to be unaware of cervical cancer and methods of preventing it (Gatune,2005).

For HIV-infected women specifically, cervical cancer screening is only done by a few donor-supported HIV programs such as the United States Government President's Emergency Plan for AIDS Relief (PEPFAR). These programs are only present in selected districts and even in these districts their coverage is limited and they only screen women enrolled in their programs (Odek, Huchko, personal communication). As a result, many HIV-infected women don't know of their increased risk of cervical cancer and don't have adequate access to screening services.

Treatment of HIV-infected women is challenging. They are more prone to treatment complications unlike HIV negative women (WHO, 2006). In addition, unlike other AIDS related malignancies, HAART has not shown any clear beneficial effect on regressing cervical cancer disease (Magure, 2005). This means the prognosis of cervical cancer in this population is poor hence more focus should be channelled towards prevention.

Moreover, HIV management in itself is already a major financial burden to both the health system and the infected individuals (MOH, 2009). An added burden of cervical cancer in HIV-infected women will create more strain to the health system.

Preventing the onset of cervical cancer is more cost effective than treating it. A World Bank study showed that screening and treatment for precancerous lesions is more cost effective than treatment or palliative care of cervical cancer. In this study, screening was estimated to cost US\$ 100 per DALY compared to treatment and palliation which was estimated at US\$ 2600 per DALY (Jamison et al., 1993).

Organized cytology based screening strategies have been responsible for significantly reducing the cervical cancer rates in developed countries. However, Kenya being a low income country lacks the necessary financial and human resources to establish similar programs. With this, low cost and effective cervical cancer prevention strategies are urgently needed.

2.2 Objectives

Overall objective

To explore the strategies appropriate for cervical cancer prevention with special considerations for HIV-infected women and make recommendations that will be adopted in the cervical cancer prevention policy in Kenya.

Specific objectives

- To analyze the determinants of cervical cancer
- To analyze the influence of HIV on cervical cancer
- To explore the cervical cancer prevention strategies suitable for low resource settings
- To discuss the barriers facing cervical cancer prevention in Kenya

- To formulate recommendations that can be adopted by the cervical cancer prevention program in Kenya

2.3 Study questions

This thesis sets to answer the following study questions:

- What are the determinants of cervical cancer?
- How does HIV influence the progression of cervical cancer?
- Which cervical cancer preventive strategies are suitable for low resource settings?
- What challenges face cervical cancer prevention strategies in Kenya?
- Which recommendations can be adopted by the cervical cancer prevention program in Kenya?

2.4 Methodology

This thesis is a literature review of peer reviewed journal articles, PhD dissertations and policy documents.

Articles were obtained using the search engines PUBMED, Google and Google scholar. Articles were also obtained from the websites of the Kenya National Bureau of Statistics (KNBS), World Health Organization (WHO), Centres for Disease Control (CDC), United Nations Development Program (UNDP), Program for Appropriate Technology in Health (PATH), International Agency for Research in Cancer (IARC), Family Health International (FHI) and Ministry Of Health Kenya. The reference lists of identified articles were also searched.

Lastly, experts in cervical cancer prevention in Kenya were contacted for additional information.

The key search terms used and combinations included "cervical cancer " "human papilloma virus" "cervical intraepithelial neoplasias" "cervical dysplasias" "epidemiology", "risk factors" "natural history", "HIV", "prevention", "policy", "vaccine", "screening" , "cost effectiveness", "low-resource settings" "Kenya"

Study limitations

There was language bias in this review as only articles written in English were reviewed. It was difficult analyzing the current state of cervical cancer and its prevention in Kenya as data on cervical cancer in Kenya is limited.

CHAPTER 3

DETERMINANTS OF CERVICAL CANCER

HPV is the necessary but not sufficient cause of cervical cancer (zur Hausen, 1976, Munoz, 2000). Other cofactors are required to facilitate progression of cervical HPV infection to cervical cancer. This chapter reviews HPV and the cofactors for cervical cancer.

3.1 HPV characteristics

HPV structure

HPV is a non-enveloped double stranded DNA virus with a genome of 8000 base pairs. Its genome codes for both early proteins (E1, E2, E4-E7) and late proteins (L1, L2) which are expressed in the early and late phases of the cell cycle respectively (Munoz et al., 2006).

E6 and E7 are the primary proteins responsible for malignancy. They modify the cell cycle by binding to the key host proteins involved in the control of the cell cycle. E6 binds and weakens the tumour suppression gene (p53), thereby preventing apoptosis (cell destruction) of infected epithelial cells and E7 binds the retinoblastoma protein leading to stimulation of proteins essential for DNA replication (Munoz et al., 2006, Hebner, 2006).

HPV types

There are more than 100 types of HPV with 40 specifically affecting the human genital tract (Baseman and Laufer 2005, zur Hausen,1996).The types of HPV are divided into two groups, high-risk types and low-risk types depending on their ability to cause cancer (oncogenicity) (See table 2). The high-risk types are responsible for the development of precancerous lesions and cancer. The low-risk types rarely cause malignancy, they mainly cause genital warts.

Table 2: HPV classification by oncogenicity Source: (Baseman and Laufer, 2005)

Risk classification	HPV types
High-risk	16, 18, 31, 33, 35 39, 45, 51, 52, 56 58, 59, 68, 73, 82
Probable high-risk	26, 53, 66
Low risk	6, 11, 40, 42, 43, 44 54, 61, 70, 72, 81, CP6108
Undetermined risk	34, 57, 83

HPV 16 is the most oncogenic and most prevalent type in cervical malignancies (zur Hausen, 1983). It accounts for about 50% of all cervical cancer cases. Together HPV 16 and 18 account for 70% of all cervical cancer cases. HPV 6 and 11 cause 90% of all genital warts

(Braaten and Laufer, 2008) and also cause low grade cervical lesions (Lacey et al., 2006).

A meta-analysis of 85 studies analyzing the prevalence of HPV types in 10,058 cases of cervical cancer showed that the most prevalent HPV types globally in decreasing order were HPV 16, 18, 33, 45, 31, 58, 52, 35, 59, 56, 51, 39, 6, 68, 73, 66 and 70 (Clifford et al., 2003).

HPV prevalence

Among women, genital HPV is the most common STI with the global prevalence estimated at 10.41% (95% CI 10.2-10.7%). The peak of HPV prevalence and incidence is in young women aged than 20 years with a decrease in women older than 30 years of age (Burchell et al., 2006).

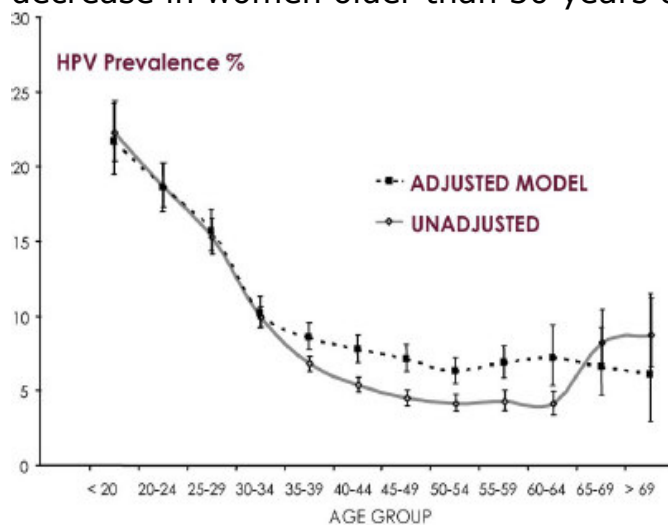


Figure 3: Global age specific HPV prevalence among women with normal cytology. Source: (Burchell et al., 2006) The adjusted model in figure 3 was controlled for confounders like study design and gives the true picture.

In Kenya, 38.8 % of women in the reproductive age are infected with HPV at any one time. HPV 16 and 18 account for about 60.9% of cervical cancer cases (WHO, 2010). A cross sectional study in Kenya showed the prevalence of HPV to be highest (47%) among women aged 17-19 years (Yamada et al., 2008).

HPV transmission

Genital HPV is mainly transmitted sexually. Transmission can occur even without intercourse through direct skin to skin contact of the genital areas. Majority of infections occur in the first years after onset of sexual activity (WHO, 2007). Genital HPV can also be transmitted from mother to child during birth and this results in recurrent warts (recurrent respiratory papillomatosis) in the upper respiratory tract of the child (Lacey et al., 2006).

Natural history of HPV

HPV primarily targets cervical epithelial cells in the cervical transformation zone. A majority of HPV infections are transient and asymptomatic. Studies have shown that on average the infection clears in 12 to 18 months (Hebner et al., 2006). A majority of women turn HPV negative after 30 years of age as the host immune system clears the HPV infection. In these women, no cervical epithelium changes occur (Palefsky et al., 2006).

However, HPV infection persists in about 10-20% of women (Adjorlolo-Johnson, 2005) leading to alteration of the cervical epithelium. HPV persistence is necessary for progression to cervical cancer (Koshiol, 2007).

Cellular changes in the squamous epithelium are referred to as squamous intraepithelial lesions (SILs). SILs are divided into low grade and high grade lesions. HPV associated cervical epithelium changes are also referred to as cervical intraepithelial neoplasia (CIN) when histology is used to diagnose them. Depending on the depth of abnormal epithelium CIN lesions are graded from 1 to 3 (Hebner et al., 2006).

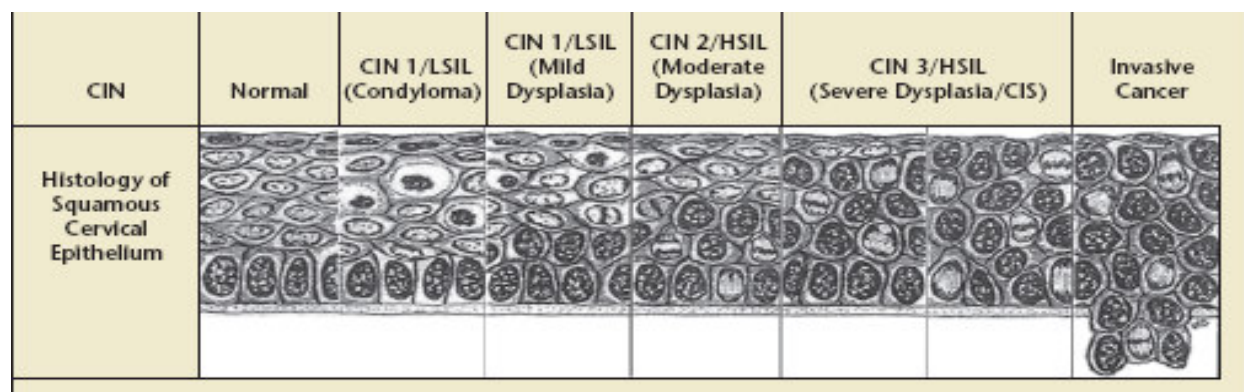


Figure 4: Changes in HPV infected cervical epithelium. Source: (Braaten and Laufer, 2008)

HPV induced CIN can clear spontaneously depending on the grade of the lesion. For example, 60% of CIN-1 lesions compared to only 33% of CIN-3 are likely to resolve. Furthermore, if left untreated CIN-3 progresses to invasive cervical cancer at a rate greater than 12% (Braaten and Laufer, 2008).

On average it takes 7-15 years between HPV infection and the onset of CIN-3 and a further 10-20 years between CIN-3 and the development of cervical cancer (Moscicki et al., 2006, Adjorlolo-Johnson, 2005).

CIN diagnosis occurs mainly in women aged between 25-30 years and a majority of women with normal immunity are usually diagnosed with cervical cancer in their 40s (Braaten and Laufer, 2008).

3.2 Risk factors for HPV infection and cofactors for cervical cancer

The risk factors for HPV infection and cofactors for cervical cancer progression will be discussed in line with the Lalonde model as, life-pattern, biological, environmental and health service factors.

A) Life-pattern Factors

Sexual behaviour

A majority of women acquire HPV infections within a few years of sexual debut. Winer et al (2003) demonstrated that 40% of 603 college students were infected with HPV within 2 years of sexual debut. Earlier age of sexual debut is a risk factor for HPV infection and cervical cancer (Braaten and Laufer, 2008). The likelihood of cervical cancer was 5 fold more in women whose sexual debut was at 18 years of age than those whose debut was 22 years and above (La Vecchia et al., 1986). In Kenya, the median age of sexual debut among women aged 25-40 years is 17.6 years and for men aged 25-54 years is 17.2 years (KDHS, 2003). Earlier age of sexual debut implies a longer period of sexual activity and a higher likelihood of having many sexual partners (Akwara et al., 2003).

The risk of HPV infection and its associated diseases increases proportionately to the number of sexual partners one has. For instance, the risk was significantly elevated 3 fold (RR=3.0, 1.6-5.8) in women who had 2-3 sexual partners and elevated 4 fold (RR=4.2; 1.5-11.5) in women who had more than 4 partners (Ho et al., 1998). In 2002, 37% of men and 18% of women surveyed in Kenya had extramarital sex (KDHS, 2003). This represents a high proportion of people who were at risk of HPV.

Unprotected sex (without condoms) is associated with increased risk of STIs (WHO, 2001). However condoms have been shown to be only partially protective against HPV. This is because HPV is harboured in other genital areas not covered by condoms such as the vulva, scrotum and anus (Manhart and Koutsky, 2002).

Use of alcohol

Increased alcohol consumption is a risk factor for HPV infection. A longitudinal study of college students reported that compared to those who did not consume alcohol, women who consumed alcohol 1-3 times a month had a non significant increased risk of 1.3(0.9-2.1) whereas those who consumed alcohol more than 4 times a month had a twofold significant increase risk of HPV infection ARR=2.0(1.2-3.1) (Ho,1998). Increased alcohol consumption leads to less inhibited behaviour making one more likely to indulge in high risk sexual behaviour. Alcohol use among Kenyan women is low. A rapid situation analysis of alcohol use in

Kenya showed that only 5.9% of the female respondents were currently consuming alcohol (NACADA, 2007).

Smoking

Smoking is an established cofactor for HPV progression to cervical cancer. Carcinogens produced by tobacco are thought to reduce immunity in the cervix thereby facilitating HPV persistence (Munoz et al., 2006). A pooled analysis of 13541 women with cervical cancer and 24017 without cervical cancer showed that compared to women who never had never smoked, current smokers were more susceptible to the squamous cervical cancer (RR= 1.60 (95% CI:1.48-1.73 p<0.001). Past smokers had a slightly increased risk (RR=1.12 (1.01-1.21 p< 0.0001) (ICESC, 2006a). The prevalence of smoking among Kenyan women is 1.6% (KDHS, 2003). Though the prevalence is small, these women are at an increased risk of cervical cancer.

Use of oral contraceptives

Long term use of oral contraceptives is a cofactor for cervical carcinogenesis. A systematic review of 28 studies reported that the relative risks for cervical cancer were 0.9 (0.7-1.2), 1.3(1.0-1.9), 2.5(1.6-3.9) for HPV positive women taking oral contraceptives for the durations < 5years, 5-9 years and > 10 years respectively (Smith et al., 2003). The risk was significantly elevated for those taking the pills for more than 10 years. The hormonal influence of oral contraceptives increases the expression of HPV genes in the cervix thereby facilitating HPV persistence (Munoz et al., 2006). In Kenya, 7.5% of women use oral contraceptives (WHO, 2010) hence are potentially at risk for cervical cancer if they use the pills for more than 10 years.

Nutrition

Nutrition is classified as a probable cofactor for cervical cancer (Munoz et al., 2006). A systematic review of 33 studies reviewing the role of nutrition in cervical carcinogenesis reported the evidence as "possible" for Vitamins C, E and B12, alpha and beta-carotene, lycopene and "probable" for retinol, folate and homocysteine. The antioxidant properties of these nutrients found in vegetables and fruits are thought to be protective against HPV persistence and cervical neoplasia (Garcia-Closas et al., 2005).

B) Biological Factors

HPV viral characteristics

Infection with high-risk HPV types and infection with multiple HPV types enhance progression to cervical cancer. For instance, HPV-16 has a higher likelihood of persistence in the cervical epithelial cells compared with other HPV types. This facilitates the onset of cervical carcinogenesis (Ho et al., 1998).

Increased parity

Multi-parous women are at an increased risk of cervical cancer (Munoz et al., 2002). This could be due to the enlargement of the transformation zone as a result of hormonal changes in pregnancy and is an indicator of frequent unprotected sex. A pooled analysis of 25 epidemiological studies showed that the risk for cervical cancer was increased almost 2-fold in women with more than 7 term pregnancies compared with those who had 1-2 full term pregnancies (RR=1.76 95%CI: 1.53-2.02) (ICESC, 2006b). The total fertility rate in Kenya is 4.9 children per woman (KDHS, 2003). This represents a moderate risk of cervical cancer.

Co-infection with other STIs

Infection with Herpes simplex-2 (HSV-2) or Chlamydia trachomatis is a cofactor in cervical carcinogenesis. A multi-centre case control study of 1238 cervical cancer cases and 1100 controls showed that the odds of squamous cervical cancer was higher in those co-infected with HPV and Chlamydia trachomatis (OR=1.8; 95% CI=1.2-2.7) compared with those infected with HPV alone (Smith et al., 2004). Another case control study showed that women coinfecting with HPV and HSV-2 were at an elevated risk of squamous cervical cancer (OR= 2.19, 95% CI=1.41-3.40) compared with those infected with HPV alone (Smith et al., 2002). In Kenya, 20% of women are infected with HSV-2 by age 25 (NASCO, 2007). The influence of HIV on cervical cancer will be discussed in detail in the next chapter.

Age

Younger women engage more in high risk sexual behaviour such as multiple partners and unprotected sex therefore are at increased risk of HPV infection. In Kenya, risky sexual behaviour is highest in 15-19 year old women and decreases with age (KDHS, 2003).

In addition, the likelihood of HPV persistence is higher in older women (over 30 years of age) thereby making them susceptible to onset of cervical cancer. A longitudinal study by Ho et al. (1998) reported that for each additional 1 year increase in age, the odds for HPV persistence for more than 6 months is 1.1 (1.1-1.2) $p=0.05$. Increasing age is associated with increased exposure to sexual activity and subsequently a higher likelihood of infection with multiple HPV types of high-risk HPV (Ho et al., 1998).

C) Environmental Factors

Socio-cultural practices

The risk of HPV in women increases proportionately with the number of life time sex partners a male partner has had. For example, Winer et al (2003) reported a fivefold rise in HPV incident infection in women whose male partners had more than one sexual partner (HR=5.2 95% CI 1.3-

21.2). Therefore cultural practices such as polygamy have a bearing on HPV infection. In Kenya, 16% of men are polygamous with polygamy being more prevalent in rural areas (18%) than urban areas (12%) (KDHS, 2003). This can in part explain the high cervical cancer rates in Kenya.

Some cultural practices in Kenya such as 'wife sharing' among the Maasai community and 'wife inheritance' among the Luo community predisposes women to infection with HPV and other STIs. In some cultures, a 'decent woman' is defined as one who is constrained in sexual encounters and a 'macho man' defined as one who has several sexual partners. Many women are expected to be submissive and have no say in negotiating safer sexual practices in their relationships (Akwara et al., 2003).

Furthermore, in a majority of cultures, women tend to have sexual relationships with older men. This enhances HPV transmission as older men tend to have had many life time sexual partners (Burchell et al., 2006). In 2003, only 4% of 15-19 year old Kenyan women had sexual intercourse with men who were 10 or more years older (KDHS, 2003). These women were likely infected with HPV or other STIs.

Education

Women with low education are more likely to have cervical cancer. This could be explained by the fact that they lack knowledge on methods of preventing cervical cancer (Gatune, 2005). In Kenya women (especially rural women) with low or no education are more likely to be married early, be in polygamous marriages and have high parity (KDHS, 2003) therefore putting them at risk for cervical cancer.

Socio-economic factors

Poverty hinders women from seeking good care. For instance many Kenyan women delay seeking diagnosis and treatment due to the travel costs they incur. Furthermore the opportunistic costs of forfeiting work and income even for a day prevents them from going to health facilities (Goldie et al., 2005, Gatune, 2005). Women with a low socio-economic status are more likely to have unprotected sex and multiple sex partners (Akwara et al., 2003) hence exposing them to HPV.

D) Health Service Factors

Poor health infrastructure

Many developing countries lack adequate health infrastructure for screening and diagnostic services (Denny et al., 2006). Therefore precancerous lesions fail to be detected early and advance to invasive cervical cancer. For instance in 2001, only 56% of government health facilities had basic equipment for cervical cancer screening (Chirenje et al., 2001).

Inadequate human resources for health

Lack of adequate staff available to screen and treat women inhibits timely screening, diagnosis and treatment of pre-cancers and early stage cervical cancer (Denny et al, 2006). As discussed in chapter one, Kenya has a critical shortage of health workers. In a study in rural Kenya, women reported that they did not go for pap smears because the health workers sent them away when the clinics were busy (Gatune, 2005)

Conclusion

HPV is the established cause of cervical cancer. It is sexually transmitted hence high risk sexual behaviour is a major risk factor for its transmission. In Kenya, risky sexual behaviour among the youth and socio-cultural practices such as polygamy and wife sharing promote the spread of HPV. The cofactors for cervical cancer in Kenya are smoking, co-infection with STIs, long term use of oral contraceptives, high parity, poor education, poverty among women and inadequate health services. Rural women are especially at risk for cervical cancer.

CHAPTER 4

CERVICAL CANCER AND HIV

HIV-infected women are susceptible to cervical cancer as the process and latency period of cervical cancer is altered by an impaired host immune system (Adjorlolo-Johnson, 2005). With this, the CDC has recognized cervical cancer as an AIDS defining malignancy (CDC, 1992). This chapter discusses the influence of HIV on the presentation of HPV and its associated cervical lesions and the biological and social mechanisms explaining the interactions.

4.1 HPV in HIV-infected women

Distribution: A meta-analysis of 20 studies showed that the most frequent oncogenic HPV types in HIV-infected women are 16, 58, 18, 52, 31 and 33 in decreasing order. Interestingly, among those with high grade cervical lesions, HIV-infected women were less likely than HIV negative women to be infected with HPV-16 (OR=0.6; 95% CI, 0.4-0.7) and more likely to be infected with other HPV types 11, 18, 33, 51, 52, 53, 58 and 61 (Clifford et al., 2006). This finding implies that the HPV types with little oncogenic ability in HIV negative women can cause high grade lesions in HIV-infected women.

Prevalence and Incidence: Studies have shown that the prevalence and incidence of HPV is increased in HIV-infected women. For example, Stickler et al. (2005) demonstrated that, HIV-infected women had a higher HPV prevalence (PR=1.97; 95% CI=1.45-2.66) and higher HPV incidence (HR=1.70, 95%CI=1.35-2.15) than HIV-uninfected women.

Multiple types: Multiple HPV types and high risk HPV types are also more likely to be detected in HIV-infected women compared to HIV-uninfected women (26% vs. 4.5%) and (35% vs. 8.4%) respectively (Yamada et al., 2008).

Persistence: HPV infection has a propensity to persist in HIV-infected women. A follow up study of adolescent girls showed that 59% of HIV-infected women had HPV clearance compared to 75.9% of HIV-uninfected women at end of follow up. Mean time to loss of infection was 689 days for HIV-infected women and 403 days uninfected women ($p < 0.0001$) (Moscicki et al., 2004).

4.2 CIN in HIV-infected women

Risk and Prevalence: CIN is more prevalent in HIV-infected women. A case control study of women attending family planning clinics in Nairobi showed HIV-infected women were at an increased risk of cervical neoplasia (OR=2.78; 95% CI 1.32-5.85) (Maggwa et al., 1993).

Progression: A longitudinal study demonstrated that on average the time difference between high grade cervical neoplasia and the onset of invasive cervical cancer was between 7.6-16.2 years in HIV-uninfected population whereas it ranges from 2.8-3.9 years in HIV-infected women (Frisch et al., 2000).

Recurrence: CIN also recurs more after treatment in HIV-infected women. A follow-up study on CIN patients by Fruchter et al. (1996), showed that HIV-infected women were 4 times more likely than HIV-uninfected women to get recurrent CIN lesions after treatment (RR=4.4 (2.7-7.4) < .01).

4.3 Cervical Cancer in HIV-infected women

HIV-infected women are at an increased risk of cervical cancer. The association between HIV and cervical cancer has been demonstrated more significantly in studies in Europe and the US compared to sub-Saharan African countries (Palefsky et al., 2006, Adjorlolo-Johnson, 2005).

For instance, a large population registry study in the US showed that risk of invasive cervical cancer in HIV-infected women was 5 times more than in HIV-uninfected women (RR=5.4; 95% CI=3.9-7.2) (Frisch et al., 2000). On the other hand, a registry-based study in Kenya of cervical cancer patients between 1989-1998 showed no significant proportional increase in cervical cancer cases despite the 2-3 fold increase in HIV prevalence in that period (Gichangi et al., 2002). The results of this Kenyan study were not convincing as it had several limitations. First, the registry was based in the hospital located in the capital city. Most HIV infections (70%) occur in rural women (NASCOP, 2007) who have poor access to the national hospital hence most HIV-infected women with cervical cancer were not captured in registry. Second, only 5% of the cervical cancer cases in the registry had been tested for HIV and lastly the study period covered the pre-HAART era implying that many women must have been dying of other HIV associated opportunistic diseases before cervical cancer could be diagnosed.

Onset of disease: Evidence of early onset of cervical cancer in HIV-infected women has been consistent. Studies in the US (Frisch et al., 2000, Moodley, et al, .2006), Cameroon (Adjorlolo-Johnson, 2005) and Kenya (Gichangi et al., 2003) have shown that cervical cancer occurs earlier in HIV positive women. For instance a US study showed HIV-infected women with CC were 6 years younger than HIV-uninfected women (median age 40 vs. 46 p=0.004) (Moodley et al., 2006) and a case control study by in Kenya showed that compared to HIV-uninfected women, HIV-infected women were on average 10 years younger (40±10 vs. 50±12; p<0.001) (Gichangi et al., 2003).

Advanced disease: HIV-infected women with cervical cancer present more with advanced cervical disease. A case control study in Kenya showed that HIV-infected women compared to HIV negative women were more likely to present with poorly differentiated tumours (76.9% vs. 51.5%, AOR ,2.9;p=0.038) (Gichangi et al., 2003).

4.4 Influence of CD4 count on HPV and associated cervical lesions

The level of CD4 count has only shown a significant association with HPV prevalence and cervical neoplasias. It does not influence the occurrence of cervical cancer. For instance, a cross sectional study demonstrated a higher risk of cervical neoplasias with CD4 counts < 200 cells/mm³ compared with CD4 levels > 500 cells/mm³. Also the prevalence of HPV was higher in those with lower CD4 counts (92% vs. 64.7% p<0.01) (Firnhaber et al., 2010).

CIN is also more likely to recur after treatment in those with lower CD4 counts. A cohort study demonstrated that after treatment for CIN, the percentage of women with recurrent lesions was 55.5%, 36.0% and 8.5% for the corresponding CD4 levels of <200, 200-499 and 500 cells/mm³ respectively (Adam et al., 2008).

On the other hand, the incidence of cervical cancer does not increase with lower CD4 counts (Palefsky et al, 2006). In fact a number of studies have shown that a majority of cervical cancer cases occurred in women with CD4 cell counts above 200 cells/mm³ (Adjorlolo-Johnson, 2005). A case control study in Kenya did not show a big difference in CD4 counts among the HIV positive cases (with cervical cancer) and HIV positive controls (532±320 vs. 588±463 p=0.001) (Gichangi et al., 2003).

4.5 Influence of HAART on HPV and associated cervical lesions

Whereas HAART has shown a clear beneficial effect on the incidence of AIDS associated malignancies like Kaposi's sarcoma, its effect on cervical neoplasia and cervical cancer is inconclusive (Appleby, 2000, Magure, 2005, Brachter, 2010).

4.6 Biological mechanisms of HIV influence on HPV and cervical cancer

In describing the epidemiological synergy of coinfection with sexually transmitted diseases, Wasserheit (1992) described the relationship between HPV and HIV as unidirectional meaning that whereas HIV augments the presentation and progression of HPV, its transmission is not facilitated by HPV infection.

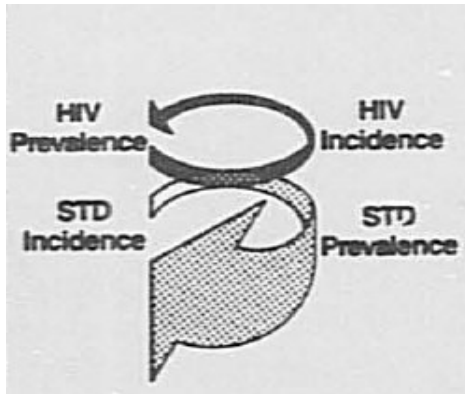


Figure 5: Unidirectional model explaining the relationship between HIV and HPV (Source: Wasserheit, 1992)

The exact mechanisms by which HIV potentiates HPV associated disease are still not fully understood. So far it is thought that HIV alters HPV infection progression through immunologic, genetic factors and interaction of HIV proteins with HPV oncoproteins (Palefsky et al., 2006, Hebner et al., 2008).

a) Immune response

HPV replication and subsequent disease is contained as long as there is minimal HIV immunosuppression. As an individual's immunity decreases as a result of HIV, HPV replication and CIN occurrence and progression increases (Palefsky et al., 2006).

T cells and Langerhans cells are key cells in the host's systemic and local immune response respectively to HPV infection. In HIV-infected women effects of these cells are attenuated. The HPV primary oncoproteins E6 and E7 thrive due to the reduced capacity of cytotoxic T cells in HIV. This could be the reason behind the rapid progression of low grade lesions to high grade cervical lesions. Furthermore the reduced langerhans cells could be the reason behind the aggressive forms of cervical dysplasias seen in HIV-infected women (Adjorlolo-Johnson, 2005, Frisch et al., 2000). Usually the immune response to HPV infected cells is minimal at CD4 cell counts below 200 cells/mm³ (Frisch et al., 2000).

However immune response only has a significant role in protecting against HPV persistence and progression to cervical dysplasias. It has a minimal role in preventing progression of high grade cervical dysplasias to cancer (Palefsky et al., 2006).

b) Genetic instability

The persistence and progression of high grade dysplasias to cervical cancer may be as a result of genetic damage. In these advanced stages, the accumulated genetic changes make the lesions resistant to the beneficial effects of HAART (Palefsky et al., 2006).

The early HPV oncoproteins E6 and E7 through their influence on p53 and RB genes respectively interfere with DNA repair and control of the cell cycle. The integration of HPV DNA into the genome of the host cell is associated with progression of high grade cervical dysplasia to cervical cancer. During integration, the activity of E6 is increased and genetic instability occurs (Palefsky et al., 2006).

c) HIV and HPV protein interactions

Though not conclusive, it is thought that the activity of the HIV-1 tat protein results in the increased expression of E6 and E7 oncoproteins. However this has only been demonstrated by in-vitro studies but not in-vivo studies (Nyangol et al., 2006).

4.7 Social influence of HIV on HPV and cervical Cancer

A majority of people are thought to contract HPV and HIV at the same time or contract HIV some time after HPV infection (Palefsky et al., 2006). HIV and HPV being both STIs share similar risk factors related to sexual behaviour such as multiple sexual partners, early sexual debut and unprotected sex. This can be one of the reasons why HIV-infected women have a high HPV prevalence and are infected with multiple HPV types. Sexual behaviour has been discussed in the previous chapter.

Conclusion

HIV influences the natural history of cervical cancer. Biological and social mechanisms partly explain the interaction of HIV and HPV. Immune response facilitates HPV persistence and progression to cervical dysplasia but does not influence the progression of high grade cervical dysplasias to cervical cancer. Genetic damage of host cells by HPV is responsible for progression of high grade dysplasia to cervical cancer. This explains why cervical cancer is refractory to the effects of HAART and occurs at any CD4 level. However, these mechanisms still don't explain why cervical dysplasias are refractory to HAART. Sexual behaviour such as multiple sex partners, early sexual debut and unprotected sex is common to the transmission of both HPV and HIV. This explains why HIV-infected women have a higher incidence of HPV than HIV-uninfected women and are more likely to be infected with multiple HPV types.

CHAPTER 5 PREVENTION OF CERVICAL CANCER

“At least 1/3 of all cancer cases are preventable. Prevention offers the most cost-effective long term strategy for the control of cancer” (WHO, 2006)

The long latency period between HPV infection and the onset of cervical cancer, makes cervical cancer a highly preventable disease. This chapter reviews primary and secondary prevention strategies suitable for cervical cancer with a focus on low resource settings.

5.1 Primary prevention

Primary prevention of cervical cancer aims at preventing HPV infection and other cofactors associated with increased cervical cancer risk (WHO, 2006). Since a majority of HIV infected women are likely to be co-infected with HPV, primary prevention in this population aims at preventing reinfection with other HPV subtypes and preventing multiple HPV infections. Primary prevention strategies include behaviour modification, male circumcision and HPV vaccination.

5.1.1 Behaviour modification

Behaviour modification involves strategies aimed changing behaviours or life patterns that are associated with increased risk for HPV infection and cofactors for cervical cancer progression. A key strategy to achieve this is via health education.

Reducing risk of HPV infection: To reduce the risk of HPV infection, health education aimed at reducing high risk sexual behaviour should be employed. This should be done with an aim to encourage abstinence, delay sexual debut, reduce number of sexual partners, encourage faithfulness to one sexual partner and use of barrier methods such as condoms (Denny et al., 2006). Some of these strategies can be through curriculum-based sex education in schools; community-based sexual health programs, and advocacy with mass media such as radio, television, newspapers, posters and brochures. Sex education needs to be targeted to youth through schools, youth centres, adolescent health programs and churches (Kirby et al., 2005). Successful interventions can be drawn from the response to the HIV epidemic. For instance, the changes in sexual behaviour such as reduction of sexual partners, condom use and delay in sexual debut played a significant role in reducing the incidence and prevalence of HIV in Uganda in the 1990's and first few years of the 21st century (Kirby, 2008). A community-based sexual education program in Kenya led to reduction in sexual partners, increased condom use but did not delay sexual debut among young adolescents (Erulkar et al., 2004). A review of 83 sex-education programs by Kirby et al (2005) showed that most of the programs greatly increased knowledge of STIs but reduced

sexual risk one average by one third. Therefore sex education cannot be used on its own but as a component of the prevention program.

To note, whereas condoms have been effective in controlling HIV transmission (Davis, 1999) their effect on preventing HPV transmission has been inconclusive. A meta-analysis of 20 published studies concluded that though there was no clear evidence that condom use diminishes the risk of HPV infection there was evidence of reduced risk of genital warts, CIN2/3 and cervical cancer (Manhart, 2002). However, WHO recommends that though condoms offer partial protection against HPV acquisition, their use should still be encouraged as they still diminish the risk of genital warts, cervical disease and other STIs such as HIV, HSV-2 and Chlamydia which are co-factors for cervical cancer (WHO, 2006).

Reducing cofactors for cervical cancer progression: These cofactors include smoking, high parity, poor diet and long term use of oral contraceptives (Munoz, 2006). Women ought to be educated to avoid smoking, to reduce their family sizes and to improve their diets. With respect to use of oral contraceptives, the WHO still recommends their use since the risk associated with cervical cancer is small and its other associated benefits such as family planning are significant in reducing maternal mortality and other health risks associated with high parity (WHO, 2006).

Though the evidence associating a diet lacking fruits and vegetables with cervical cancer is weak, health education promoting the intake of these foods diets should still be encouraged as these foods are protective against other health ailments.

5.1.2 Male circumcision

HPV load in the male anogenital area is highest in the shaft, foreskin, glans and scrotum (Dunne, 2006). Penile HPV in particular has been shown to elevate the risk of cervical HPV 4 fold (Castellsague et al., 2002).

Male circumcision has been shown to reduce transmission of HPV infection. For instance, a pooled analysis of 1913 couples demonstrated a reduced risk of HPV infection in circumcised men (OR=0.37; 95% CI 0.16-0.85) and a diminished cervical cancer risk in monogamous women who had circumcised husbands with multiple life time sexual partners (AOR=0.42; 95% CI 0.23-0.79) (Castellsague et al., 2002). A systematic review addressing HPV in men showed that male circumcision reduced the risk of HPV infection in men by 20-48% (Dunne et al., 2006). The effect of circumcision is only partial as HPV is harboured in other anogenital areas such as the scrotum and anus. Hence, it should be used in conjunction with other preventive strategies.

5.1.3 HPV Vaccination

Vaccines against HPV have great potential as a primary prevention strategy. There are currently two prophylactic HPV vaccines that have been licensed. A bivalent vaccine (Cervarix®) which confers protection against HPV types 16 and 18 and a quadrivalent vaccine (Gardasil®) which protects against HPV types-16/18/6/11. These vaccines also offer cross protection to HPV types 31 and 45 which are genotypically related to HPV-16/ 18.

These vaccines are safe, well tolerated and efficacious in the general population. Gardasil® is over 96% effective in preventing precancerous lesions while Cervarix® is over 75% in preventing HPV 16/18 infection and over 90% effective in preventing incidence of precancerous lesions (WHO, 2007). However the duration of protection is still unclear (Lehtinen et al., 2006). Preliminary evidence shows that Gardasil is protective for five years in the general population (Braaten and Laufer, 2008).

These vaccines are only effective when given to those not exposed to HPV infection. Therefore they need to be administered prior to sexual debut (Braaten and Laufer, 2008). The WHO recommends that the primary target group for routine HPV vaccination should be girls aged 9-13 years and a secondary target group "catch-up population" should be girls aged 14-26 years. The catch up campaign targets girls who missed HPV vaccination and who are not yet exposed to HPV (WHO, 2007).

Currently there is limited data on the safety and efficacy on HPV vaccines in HIV-infected women. Vaccine trials in HIV-infected women are ongoing. To note, unlike in HIV negative women, less oncogenic HPV types have the potential to cause cervical cancer in HIV infected women (Clifford et al.,2006).This will limit the impact of the currently available vaccines as they mainly protect against the oncogenic types 16 and 18 (Palefsky et al., 2006).

HPV vaccines are expensive (US\$ 300 for total course). Therefore they are difficult to implement in most developing countries. Financing mechanisms can be sought from GAVI (Global Alliance for Vaccines and Immunization) which subsidizes costs of vaccines for developing countries (Batson, 2006).

The benefits of HPV vaccines are substantial. For instance, some models predict that under certain assumptions, if 90% of female adolescents are vaccinated before sexual debut, cervical cancer incidence can potentially decrease by 91% (Garnett et al, 2006).In GAVI eligible countries, vaccinating young females has the potential of averting 3 million deaths in 10 years. Specifically, 17 deaths per 1000 vaccinated females can be averted in African countries (Goldie et al., 2008).

Mathematical models have shown that the introduction of the HPV vaccine in a country can be cost effective depending on how factors such as vaccine cost, vaccine coverage and presence of a screening program are organised (Marra, 2009, Garnett et al., 2006). The vaccine has been found to be cost-effective at \$10 per female for the total course in GAVI-eligible countries. This cost covers the cost of vaccine itself and logistics (Goldie et al., 2008). If implemented, the vaccines can be delivered through a country's existing vaccination program, adolescent or youth programs or school based vaccination programs (Kane, 2006, WHO, 2007). In Kenya, both vaccines were licensed for use for the general population in 2009 (WHO, 2010b) but are yet to be used for the mass population.

5.2 Secondary Prevention

Secondary prevention involves screening, detection and treatment of pre-clinical disease in otherwise asymptomatic women before the disease progresses. The available screening, diagnostic and treatment options can be used in HIV-infected and uninfected women (WHO, 2006).

5.2.1 Screening

Screening for cervical cancer aims at detecting precancerous lesions before they progress to invasive cancer. Since cervical cancer is uncommon before 30 years of age, WHO recommends that screening should be done at 30 years and above. For high risk groups like HIV-infected women screening can be done earlier when they are 25 years old and above (WHO, 2006). Before screening is carried out, the screening criteria by Wilson and Jungner must be met (see Annex 6).

The tests available for cervical cancer screening include: cytology (Pap smear and liquid-based cytology), HPV DNA tests, visual inspection with acetic acid (VIA) and visual inspection with lugol's iodine (VILI) (WHO, 2006). So far the only test with proven effectiveness in decreasing cancer rates in large population based screening is the Pap smear. The other tests have only shown good efficacy in research settings and there is no concrete evidence on their effectiveness in a large population (WHO, 2001, WHO, 2006).

a) Cytology screening

Cytology involves sampling cells from the cervical transformation zone by a special brush or spatula. Organized cytology programs have been highly beneficial in decreasing cervical cancer incidence and mortality in a majority of developed countries (WHO, 2002). For instance cervical cancer rates have decreased by about 80% in Canada and Nordic countries and by 75% in the United States of America (WHO, 2006, Cuzick et al., 2008).

Cervical cytology test has the same effectiveness for both HIV sero-negative and sero-positive women (WHO, 2006). There are two types of cytology screening tests; conventional (Pap smear) and the liquid based cytology (WHO, 2006).

Pap smear: In this test, the cells sampled from the cervix are smeared on a glass slide and prepared for examination (WHO, 2006). This test has a high specificity that ranges between 91-96% but its sensitivity is generally low and can range from (44-78%). This leads to many false negative results (Cuzick et al., 2008).

Liquid-based cytology: In this test, the cells sampled from the cervix are placed in a liquid cytology medium rather than smeared onto a glass slide. This method has a higher sensitivity than the Pap smear but its specificity is similar. Its preparation time is also shorter than that of pap smears and is more efficient (WHO, 2006).

In general cytological screening is both labour intensive and expensive. It requires a system that facilitates efficient transport of specimens to the laboratory. Cytology screening is also subjective and in the absence of good quality assurance the accuracy is unreliable (Cuzick et al., 2008). It therefore requires high laboratory quality assurance (WHO, 2006). Furthermore, a cytology based screening program involves a 3 visit strategy and effective follow up system. The first visit involves sampling of the cells, the second involves relaying results to the client and referral for further diagnosis and the third visit involves treating the lesion (Ansink, 2007). These factors make it difficult for low resource settings to widely implement cytology based screening.

b) HPV DNA testing

This test detects high risk HPV DNA in cervical cells. Cells are sampled from the cervix with a special brush or swab, transferred to a bottle with a preservative solution then transported to the laboratory for processing and interpretation (WHO, 2006).

Compared to cytology, the sensitivity of this test is generally higher (62-94%) and its specificity is lower (41-94%). Some programs therefore recommend a combination of cytology and HPV testing. In this case women first screened by the HPV DNA test then those with positive results screened with cytology. This yields a higher sensitivity and specificity. However this combination is expensive hence more applicable to high resource settings. Self sampling using tampons or swabs can be used though samples taken by providers show a higher sensitivity than by clients (Cuzick et al., 2008).

Since most HPV infections in young women are transient, this test is recommended for women aged 30 and above. HPV DNA is more sensitive

(91% vs. 62%) but less specific (4% vs. 75%) in HIV-infected than uninfected women (WHO, 2001).

DNA based screening gives automated and objective test results and quality assurance procedures are less demanding. Furthermore, women can sample themselves and send results to the laboratory which makes it useful in settings with shortages of health workers (Cuzick et al., 2008). The disadvantages of this test include its high costs, need for repeated visits by women, the need for a reliable transport system of the sample to the laboratory and the need for a molecular laboratory. However, a cheaper, faster and more sensitive test, the careHPV test is currently under development by Chinese researchers. Once available, it can be used in low-resource settings (Sankaranarayanan et al., 2009).

c) Screening with visual methods

These methods involve examining the cervix visually with one of the following techniques:

Visual inspection with acetic acid (VIA): This involves applying 3-5% acetic acid onto the cervix then examining it with the naked eye with the aid of a light source. A positive test is defined by well defined aceto-white lesions in the cervical transformation zone (WHO, 2002).

The method has a moderate sensitivity ranging from 67-79% and a low specificity ranging from 49-86%. Compared to cytology it has a higher sensitivity but lower specificity (Cuzick et al., 2008). A cross sectional study in Zimbabwe showed that compared to cytology, VIA had a higher sensitivity (77% vs. 43%) and lower specificity (64% vs. 91%) (WHO, 2001).

VIA is cheap and does not require sophisticated equipment. It is easy to use and can be taught to middle level health staff in 5-10 days. It gives immediate results and treatment can be done on the same day. Hence multiple visits are not necessary and women don't get lost to follow up. Unfortunately, it has a low specificity therefore gives a lot of false positive results leading to over treatment. It is a highly subjective test and lacks standardized quality control procedures. It is also limited in detecting endocervical disease in women aged above 50 years. Its effectiveness is yet to be evaluated in a population-based screening program (Cuzick et al., 2008, WHO, 2006).

Visual inspection with lugol's iodine (VILI): This involves applying Lugol's iodine onto the cervix then examining it with the naked eye with the aid of a light source. A positive test is defined by well defined mustard-yellow areas on cervical transformation zone (WHO, 2002, WHO, 2006). It has a higher sensitivity and specificity than VIA (See table 3). Its strengths and limitations are similar to those of VIA discussed above.

Visual inspection with Acetic acid with Magnification (VIAM): This aims to improve the performance of VIA by magnifying the cervix using a simple 4x magnifying hand held lens. However no significant improvement on sensitivity and specificity has been demonstrated using this method (Shastri et al., 2005).

Table 3: Screening accuracy of various screening methods. Adapted from (Cuzick et al., 2008)

Screening test	Sensitivity	Specificity
Conventional cytology	44-78%	91-96%
HPV DNA testing	66-100%	61-96%
VIA	67-79%	49-86%
VIAM	62-73%	86-87%
VILI	78-98%	73-93%

5.2.2 Diagnosis

Positive screening results from cytology, HPV testing and VIA need referral for further confirmatory diagnosis. The standard methods of cervical disease diagnosis include colposcopy and histology. A colposcope illuminates and magnifies the cervix so as to facilitate examination of the epithelium. Usually with the help of a colposcope, a tissue sample is removed (biopsy) from the affected area. The sample is then transferred to a laboratory for histological examination and classification. Colposcopic diagnosis has a moderate sensitivity (about 85%) and a moderate specificity (70%). However, examination by colposcopy and biopsy may be difficult to implement in low resource settings because colposcopes are expensive, specialized training is required for colposcopy and biopsy services and a histopathology laboratory is needed to examine biopsy samples. The methods for colposcopic and histological examination for HIV-infected women are similar to HIV-uninfected women (WHO, 2006).

5.2.3 Treatment

Treatment of precancer can be done on an outpatient basis using cryotherapy or loop electrosurgical excision procedure (LEEP) or on an inpatient basis using cold knife conization. It is recommended that outpatient methods be used to treat pre-cancers as much as possible. Inpatient care is only recommended when outpatient care is not possible.

Cryotherapy: This involves removing cervical lesions by freezing them with carbon dioxide or nitrous oxide gas. Cryotherapy has a high cure rate of 85-96% for small cervical lesions. This method is suitable for primary care health centres as it is cheap, simple to perform and can be performed by mid-level health workers. Intensive training is not needed. In addition, the procedure is brief (about 15 minutes) and does not need

anaesthesia or electricity. However, it is largely ineffective for treating large lesions that occupy more than 75% of cervix and usually no specimen available for histological examination. This treatment causes a prolonged watery discharge (WHO, 2006).

LEEP: This method involves removing cervical lesions with a thin heated wire. It has a high cure rate of 91-98%. With this procedure a tissue sample is usually available for histological examination and it causes minimal complications. However, it is unsuitable for primary care settings as it requires expensive equipment, anaesthesia and electricity. Furthermore it requires intensive training and can only be performed by high cadre health workers (WHO, 2006).

Cold knife conization: This involves removing a cone shaped piece of tissue from the cervix. This piece contains inner and outer parts of the cervix. It has a high cure rate of 90-94% and a tissue sample is available for histology. However, it requires hospital admission and the use of a surgical theatre. It can only be performed by medical doctors and it is associated with complications such as bleeding and cervical incompetence (WHO, 2006).

5.2.4 Follow-up after treatment

After treatment women need to be followed up in order to monitor treatment complications or recurrence of the lesions. For pre-cancers, follow up visits are scheduled at 2-6 weeks, 6 months and 12 months after treatment. Since HIV-infected women are prone to recurrence of lesions their follow-up visits need to be scheduled at 2-6 weeks and then every 6 months after treatment (WHO, 2006).

5.2.5 Screening and treatment in low-resource settings

Screening: In low-resource settings, emphasis should be on achieving a wide screening coverage of high risk women with an affordable highly sensitive test. A highly sensitive test will eliminate the need of repeated testing and frequent clinic visits. In developed countries women are screened every 3-5 years (CDC, 2010). This is impractical in low-resource settings due to limited resources (WHO, 2006). Since the latency period of cervical cancer is long, all eligible women in low-resource settings can still be screened once or twice in their lifetime for cervical cancer. Studies have shown that once in a life time screening may yield around 25-30% reduction in the incidence of cervical cancer (WHO, 2001). Screening should occur at the age when the peak incidence of CIN2/3 is expected, between 30-40 years. Preferably screening should be performed at primary care clinics close to the target population (Ansink, 2007).

Strategies that offer screening services in fewer visits such as VIA and HPV testing are deemed most cost effective and they also reduce challenges such as lost to follow-up. For instance a cost-effective analysis

done in 5 developing countries (Kenya, South Africa, Thailand, India, Peru) reported that a once in a lifetime screening of women at 35 years of age with VIA or HPV test decreased the life time risk of cervical cancer by 25-36% and costs less than 500 international dollars per year life saved. Twice in a lifetime screening at ages 35 and 40 decreased the cervical cancer risk by another 40% but cost more (See table 4). In this study, screening with VIA was deemed most cost effective in Kenya. Screening Kenyan women once with a 1 visit VIA strategy costs 91 international dollars per year life saved. Screening a woman twice in a life time with a 1 visit VIA strategy is also very cost effective as it costs 31.74% of Kenya's per capita GDP. A strategy is deemed 'very cost-effective' when it costs less than 100% of the countries per capita GDP (Goldie et al., 2005).

Table 4: "Cost-effectiveness ratios expressed as % of per capita GDP". Source: (Goldie et al., 2005)

Variable	India	Kenya	Peru	South Africa	Thailand
Per capita GDP — international dollars†	2,430	1,005	4,747	9,486	6,373
Screening strategy — %‡					
Once per lifetime					
VIA	0.41	13.33	2.61	D	1.71
HPV DNA test	D	D	3.2	4.92	2.67
Twice per lifetime					
VIA	3.74	31.74	D	D	4.35
HPV DNA test	D	70.15	9.54	11.52	4.86
Three times per lifetime					
VIA	11.03	D	D	D	D
HPV DNA test	24.32	110.35	24.12	25.91	10.32

"D" stands for dominated strategies meaning that they cost more and are less clinically effective or less cost-effective than the next best strategy" Goldie et al, 2005.

Screening and treatment of precancers: The screen-and-treat option is recommended for low-resource settings with inadequate access to services for definitive diagnosis with colposcopy and histology. In this approach, screening and treatment of cervical lesions are done in one visit. The screening tests that can be used in this approach are VIA/VILI and HPV DNA testing. Denny et al (2005) showed that approaches using VIA and HPV tests for screening combined with cryotherapy were effective. For example an algorithm involving screening in primary care settings with VIA/VILI and treatment with cryotherapy was implemented in projects in Kenya and Zambia and proved to be acceptable, cost effective and sustainable (Mwanahamuntu, 2008, PATH, 2004).

Conclusion

Cervical cancer is a highly preventable disease due to its long latency period. Health education, behaviour modification, male circumcision and HPV vaccinations are possible primary preventive strategies but must only be used as a component of the prevention program. HPV vaccines are safe and effective in HIV-uninfected women though limited data is available for their efficacy in HIV-infected women. Screening and treatment of precancers has largely been responsible for the decline in cervical cancer rates in developed countries. For low-resource countries affordable screen-and-treat options using VIA/VILI for screening and cryotherapy for treatment in one clinic visit has been shown to be effective in reducing cancer incidence and are in primary care settings. The available screening and treatment options are equally effective in HIV-infected women. However, HIV-infected women require more frequent screening than HIV-uninfected women as they are more prone to recurrence of pre-cancers after treatment.

CHAPTER 6

BARRIERS TO CERVICAL CANCER PREVENTION IN KENYA

This chapter reviews the barriers to effective cervical cancer prevention for HIV-infected and uninfected women in Kenya.

6.1 Economic barriers

Lack of financial resources

The budget of Kenya's MOH constitutes only 7.3 % of the total government expenditure, 30% of which is allocated to both preventive and curative services (MOH, 2009). This limited budget makes it difficult to implement effective prevention programs. Quality and effective screening and treatment of precancers is under-resourced (Denny et al., 2006,).

High costs of treatment

A screening test requiring multiple visits translates to more travel costs and opportunistic costs. This discourages women from being screened or attending follow up clinic appointments (PATH, 2004 Goldie et al., 2005). The high cost of pap smears has limited the number of women being screened in Kenya (Gatune, 2005).

6.2 Health system barriers

Lack of organized cervical cancer prevention program

Currently there is no organized screening program in Kenya. Services are offered ad hoc for a fee (Huchko, personal communication). As a result, only a minority of women have access to screening services. In 2001, about 64% of the health facilities carrying out screening were family planning clinics. This is not ideal as a majority of women attending family planning clinics are usually under 25 years of age, a group that is low risk for cervical cancer (Chirenje et al., 2001). The absence of a national screening program has serious repercussions as a majority of Kenyan women present with advanced disease. Gichangi et al., (2003) showed that more than 90% of women had advanced cancer at time of presentation. Additionally, only a few health facilities offer targeted and regular cervical cancer screening to HIV-infected women. These are mainly donor supported HIV programs such as PEPFAR (Odek, personal communication). With this, many eligible HIV-infected women lack access to screening services.

Lack of a national cancer registry

Kenya only has a cancer registry that collects data for hospitals in Nairobi including the national referral hospital (NCR, 2006). It is assumed that the patients at the national hospital represent the burden of cancer in the country. However many women in rural areas with cancer have no access

to treatment at the national hospital due to distance and cost. Hence the statistics in the registry represent only a proportion of the actual figure. Furthermore, this data is updated irregularly: the latest data published by the registry was for the years 2000-2002 (Musibi, 2008). This under reporting subsequently leads to poor prioritization and planning of cervical cancer prevention programs.

Inadequate human resources for health

Shortage of health staff hinders effective screening and treatment of cervical cancer. A study in Kenya showed a woman's chance of being screened decreased by 41% (OR 0.59; 95% CI: 0.35-0.98) when they heard that clinics were too busy and health staff were strained (ACCP, 2004). There are only 11 cancer specialists in Kenya, all based in the capital. Of these specialists, only two are gynaecological oncologists (Musibi, 2008). At the time of a cross sectional survey in Kenya in 2001, there were no cytology technicians or pathologists in any of the district hospitals surveyed (Chirenje et al., 2001). Furthermore, cancer training for health workers is inadequate. Duration of cancer training for medical students is short and done in outpatient clinics. Continuous medical education on cancer is carried out mainly in Nairobi (Musibi, 2008). This means that health workers especially in rural areas lack information cervical cancer screening and treatment.

Burden of competing health problems

Kenya like most developing countries is faced with a double burden of diseases. Infectious diseases like HIV, malaria and tuberculosis, and non-communicable diseases like diabetes weigh heavily on the health system and most funds in the MOH have been channelled to fighting these health problems (Musibi, 2008, MOPHS, 2008).

Inadequate health infrastructure

Kenya suffers from lack of adequate screening, diagnostic and treatment facilities. Laboratories are also inadequate in number and poorly equipped (ACCP, 2004). In 2001, only 56% of government health facilities had basic equipment for cervical cancer screening and reagent shortages for performing screening tests like pap smears were frequent. Furthermore, outpatient treatment options such as cryotherapy and LEEP were unavailable in the district and provincial hospitals surveyed. Cone biopsy was the only treatment available for precancerous lesions (Chirenje et al., 2001).

Poor quality health services

In many health facilities in Kenya it takes 6-8 weeks to get cytology results after initial screening (Chirenje et al., 2001) and histopathology specimens take months to be reported. Consequently, there are often delays in definitive diagnosis and treatment (Musibi, 2008). Additionally, poor handling of women by health workers is a hindrance to screening.

Women studied in a rural town in Kenya cited insensitive health care givers and scanty counselling by health workers as a reason they shunned being screened (Gatune, 2005).

6.3 Socio-cultural barriers

Lack of knowledge concerning cervical cancer

Poor education is associated with low screening attendance in Kenya (ACCP, 2004). About 30% of Kenyan women are illiterate (UNDP, 2009), a factor that contributes to the high cervical cancer rates in the country. A study in rural Kenya of 160 women showed that only 40% of these women had heard about cervical cancer and even though they had heard about cervical cancer they could not explain its impact or importance (Gatune, 2005). Another study at the national referral hospital in Nairobi revealed that 29% of women with cervical cancer were illiterate and only 51% of women interviewed knew about cervical cancer. Furthermore only 32% were aware of the Pap smear test (Gichangi et al., 2003).

Cultural beliefs and myths

Misconceptions that the screening test was actually a HIV test, the fear of cancer diagnosis, the fear of the screening procedure and the embarrassment associated with pelvic examination have been cited as reasons why Kenyan women have avoided going for cervical cancer screening (PATH, 2004, Gatune, 2005).

Lack of male support

Some Kenyan women reported that they would appreciate it if their male partners supported them in seeking screening services (ACCP, 2004). In many cultures, women tend to be subservient to men and lack authority to make decisions concerning their health (Denny et al., 2006).

Conclusion

Economic and health system factors are the major barriers to cervical cancer prevention in Kenya. Inadequate funds, under-reporting of cervical cancer and competing health problems have led to poor prioritisation of cervical cancer prevention as evidenced by lack of a prevention policy and national screening program. Poor prioritisation subsequently leads to poor investment in adequate health infrastructure and human resources and low awareness of cervical cancer in the community. Poor awareness of the disease leads to lack of male support and promotes misconceptions about cervical cancer thereby further hindering women from seeking available screening services.

CHAPTER 7

DISCUSSION AND CONCLUSION

This chapter discusses the major findings in relation to the objectives of this review.

Determinants of cervical cancer

The principal determinant of cervical cancer is infection with high-risk HPV, a sexually transmitted infection. Most infections occur after sexual debut. In Kenya, the mean age of sexual debut is 17.6 years among females (KDHS, 2003). This therefore explains why the highest HPV prevalence among females in Kenya occurs in 17-19 years olds (Yamada et al., 2008). Globally, HPV prevalence in females is also highest in those aged less than 20 years (Burchell et al., 2006).

The main risk factor for HPV infection is sexual behaviour especially multiple sexual partners and early sexual debut. Unprotected sex is not a sole risk factor as HPV is harboured in the whole anogenital region which cannot be covered fully by condoms. Having multiple sex partners is associated with infection with multiple HPV types, a cofactor for cervical cancer progression. In Kenya, sociocultural practices such as polygamy and wife sharing are common in some communities. These practices promote exposure to multiple sexual partners and subsequent HPV infection. Furthermore, the demographic survey revealed that in 2002, 37% of men and 18% of women had extramarital affairs (KDHS, 2003). This represents a high proportion of Kenyan women who probably got infected by their male partners.

In Kenya, co-infection with other STIs such as HSV-2 and HIV is a major biological cofactor for cervical cancer. For instance, over 840,000 women are HIV-infected and about 20% of women are infected with HSV-2 by age 25 (NASCO, 2007). These STIs are also exposure markers for HPV. Furthermore, poor education and poverty among Kenyan women predisposes them to early sexual debut, polygamous marriages and poor access to health services (KDHS, 2003) hence increasing their chances of HPV infection and cervical cancer. Health service factors in Kenya such as poor health infrastructure, inadequate health workers, poor quality services and lack of a national CC screening program hinder women from seeking cervical cancer preventive services thereby increasing their risk of cancer. Rural women are particularly predisposed to these sexual risk factors and health service cofactors for cervical cancer.

Influence of HIV on cervical cancer

Biological and social factors explain why HIV-infected women are at more risk for cervical cancer. Both HPV and HIV are principally transmitted sexually therefore multiple sexual partners, early sexual debut and unprotected sex put one at risk for both HIV and HPV infection. HIV

induced immunosuppression reduces HPV clearance and promotes HPV persistence in cervical cells, a key factor for cervical cancer progression. Genetic damage of host cells by HPV and not immunosuppression is responsible for progression of cervical dysplasia to cervical cancer. This explains why cervical cancer occurs at any CD4 level and is refractory to HAART.

Prevention of cervical cancer

Prevention of cervical cancer involves preventing initial HPV infection or reinfection with HPV (primary prevention) and preventing progression of precancers to cervical cancer (secondary prevention). For cancer prevention to be effective, both primary and secondary preventive strategies need to be adopted.

The impact of primary prevention through sexual risk reduction such as delaying sexual debut, reducing partners and condom use has been varied in different settings (Kirby et al., 2005). Despite condoms being partially protective against HPV, their use still needs to be promoted to prevent infection with other STIs, which are cofactors for cervical cancer. Although male circumcision has been shown to be partially effective in reducing HPV infection it should still be incorporated as an option into the cervical cancer prevention package. HPV vaccines have been shown to be safe and effective in preventing infection with high risk HPV types. However, duration of protection is unclear hence women still need to be screened. The vaccines are also expensive and can only be cost effective in Kenya if the price is subsidised by GAVI for example.

For secondary prevention, approaches that allow screening and treatment of pre-cancers in one visit have been recommended for low-resource settings. Pilot projects have shown that screening with VIA and treatment with cryotherapy to be most appropriate for primary care clinics in Kenya (PATH, 2004) and also in Zambia (Mwanahamuntu et al., 2008). Though cost effective, VIA is highly subjective and leads to many false positives and subsequent over treatment. Therefore staff need to be supervised frequently. To minimise over treatment, the models mentioned above in Kenya and Zambia added VILI to the screening protocol. Lugol's iodine is applied to the cervix after applying acetic acid distinguishes abnormal lesions better and is affordable.

Primary prevention needs to consider two groups of HIV-infected women. Those who are not yet sexually active hence unlikely to be infected with HPV (such as those who were HIV infected at birth or infected through infected needles and blood transfusion) and HIV-infected women who are sexually active and most likely infected with HPV. Health education needs to focus on sexual risk reduction with an aim of preventing initial HPV infection in the former group and preventing reinfection with other HPV types in the latter. Education also needs to include avoiding cofactors of

cervical cancer like smoking, high parity and poor nutrition. Just like in HIV-uninfected women, male circumcision will also be only partially effective in HIV infected women. The effectiveness of HPV vaccines in HIV-infected women is still under investigation.

The available screening and treatment options are equally effective in HIV infected women. Since they develop neoplasias and cancer earlier than HIV negative women, screening should start earlier at 25 years instead of recommended 30-40 years for HIV negative women (WHO, 2006). Since they are prone to recurrence of pre-cancers after treatment, it is recommended that follow-up screening should be done more frequently (every 6 months). However, a cost-effective analysis has not been done in Kenya to check if screening every 6 months is feasible.

Barriers facing cervical cancer prevention in Kenya

Economic and health system factors are the main barriers facing cervical cancer prevention in Kenya. Kenya lacks adequate financial resources to implement a nationwide organized screening program. Poor reporting and the burden of other competing health problems have also led to poor prioritization of cervical cancer prevention. As a result a comprehensive cervical cancer prevention policy and program is not in place. Kenya also has a shortage of health workers and inadequate health facilities for screening, diagnosis and treatment of pre-cancers. Few health workers and inadequate facilities for screening and diagnosis of cervical cancer are also common to other African countries such as Tanzania, Uganda and Lesotho (Chirenje et al., 2001). Poor prioritisation of cervical cancer by the government has also led to a lack of awareness about the disease by both women and men. The association of cervical cancer with HIV, the fear of cancer and the embarrassment of pelvic examination have made screening unacceptable to many Kenyan communities. With lack of adequate information, myths and fears concerning cervical cancer screening are easily propagated in the community. A prevention program with health education as a key component targeting both women and men would allay these misconceptions.

Strengths and limitations of this review

This was a comprehensive review of the published literature. Cervical cancer prevention strategies suitable for low-resource settings and for both HIV-infected and uninfected women were analysed. Situations in other countries were compared to that in Kenya. However, there was publication bias as published literature was mainly reviewed.

Conclusion

Cervical cancer is a serious yet neglected public health problem in Kenya especially among rural women. Infection with high-risk genital HPV is the necessary but not sufficient cause of cervical cancer. Biological cofactors such as smoking, coinfection with HSV-2 and HIV and infection with

multiple HPV types coupled with health service factors such as inadequate health infrastructure and health workers lead to high risk of CC for women in Kenya. An effective cervical cancer prevention program needs to incorporate both primary and secondary prevention methods. For secondary prevention, managing precancers through the screen-and-treat option using VIA/VILI and cryotherapy is the most cost effective strategy for Kenya. The available screening and treatment methods for pre-cancers are equally safe and effective in HIV-infected women. However, since HIV-infected women are prone to recurrence of cervical lesions after treatment, they require frequent follow-up screening. A cost-effective analysis is needed in Kenya to determine the most effective and feasible screening frequency for HIV-infected women. Economic and health system factors are the major barriers in Kenya hindering prioritisation and implementation of a national cervical cancer prevention program. Poor prioritisation subsequently leads to low awareness of cervical cancer in both men and women.

CHAPTER 8 RECOMMENDATIONS

Based on findings from this review the following recommendations are made for research, policy and program interventions for cervical cancer prevention in Kenya.

8.1 Recommendations for research

1. A cross sectional survey to determine the current incidence and distribution of cervical cancer in Kenya is needed as the available statistics are as at year 2002. This will assist in proper planning of the cervical cancer prevention program.
2. A qualitative study to explore the awareness and perspectives of women and men on HPV and cervical cancer and methods of preventing it. This will give insight on how health education can be done.
3. A study to assess the acceptability of HPV vaccines and cervical cancer screening among women is needed to guide the introduction of prevention strategies in the community.
4. A study to determine the awareness of cervical cancer prevention strategies among health workers will guide the development of the training manual.
5. A cost-effective analysis for introducing HPV vaccines and cervical cancer screening either separately or in combination to assist in developing financing mechanisms. This analysis should include an analysis for both HIV-infected and uninfected women.
6. A situation analysis to assess the current capacity of the health system to handle a cervical cancer prevention program is needed to guide the planning and implementation of the program.

8.2 Recommendations for policy

1. There is need for commitment from political leaders to support policy and allocate more funds for cervical cancer prevention.
2. A clear and comprehensive national cervical cancer prevention policy that is appropriate for local setting needs to be prepared.
3. To aid in advocacy and policy making, there is need to engage key stakeholders from the Ministry of Health (MOPHS and MOMS), Ministry of Gender, NGOs, FBOs, private hospitals, women's groups, community leaders, National AIDS Control Council, National AIDS and STI control program, Kenya Cancer Society and Kenya Obstetrics and Gynaecology Society.
4. The policy should prioritise prevention strategies for HIV-infected women since they are at increased risk for cervical cancer.
5. The policy should prioritise prevention strategies in rural areas as rural women are at an increased risk of cervical cancer.

6. There is need to outline a policy for financing methods and resource allocation for cervical cancer prevention. Funding sources like GAVI for HPV vaccines should be considered.
7. The prevention program should incorporate both primary and secondary prevention methods. Policy for prevention of HPV infection should be within the national policy of STI control. In line with WHO recommendations, HPV vaccines should be administered to the primary target group of 9-13 year old females then rolled out to the secondary group of 14-26 year old females as resources increase. The vaccines should only be administered to HIV uninfected girls as their effectiveness is still unknown in HIV infected girls. Those who are vaccinated will still need to be screened for cervical cancer as duration of protection by vaccines is unclear.
8. An organized screening program needs to be set up with the following features:
 - a) The screening age should be between 30-40 years for HIV uninfected women and from age 25 for HIV-infected women as recommended by the WHO.
 - b) The initial screening coverage target is 80% of eligible women. This target should increase with more resources.
 - c) A one visit screen and treat approach using VIA/VILI for screening and cryotherapy for treatment of pre-cancer lesions should be adopted as recommended by the current evidence.
 - d) Screen positive ineligible for cryotherapy treatment need to be referred to district hospitals for histological examination and treatment with LEEP.
 - e) The screening frequency for HIV uninfected women should be once or twice in a life time as recommended by WHO. This frequency can be increase as more resources become available. The exact screening intervals for HIV-infected women needs to be determined as they require more frequent screening and follow up.
 - f) The role of health workers at all levels of health facilities needs to be outlined. The task of performing VIA and cryotherapy procedures needs to be given to mid-level health workers while LEEP is left to medical doctors.
9. A monitoring and evaluation policy that includes a health management information system needs to be put in place to ensure quality data reporting and analysis.
10. The establishment of a national cancer registry to record cervical cancer incidence and mortality. All government and private hospitals will be required to submit data to the registry.

8.3 Recommendations for program interventions

1. The program will first be piloted in 2 provinces to test the program effectiveness and then rolled out to the other 6 provinces as resources increase. Rural areas will be prioritised.
2. The program will be integrated into the existing reproductive health clinics and HIV clinics.
3. In facilities with pre-existing cytology services, staff need to be retrained on alternative screening services.
4. HPV vaccination will be introduced within the framework of national vaccination program.
5. There will be need to engage local stakeholders (such as the local chiefs, church leaders, traditional birth attendants) who can influence women to go for screening.
6. The MOH needs to implement the strategies for attracting and retaining staff as laid out in the national human resources for health strategic plan. This will ensure availability of adequate health staff to carry out cervical cancer preventive services.
7. A system for recording client data needs to be set up in each of the provinces.
8. A budget must be set in each pilot site to facilitate the running of the program.
9. At the community level, community health workers and peer educators should be used to create awareness in women and men about cervical cancer and mobilize women for screening.
10. In the health centres and sub-district hospitals, mid-level workers should be trained to counsel women, to perform both VIA/VILI and cryotherapy and to refer screen-positive women ineligible for cryotherapy treatment to district hospitals.
11. Initially selected district hospitals should be chosen based on their human resource and infrastructure capacity to be equipped with a colposcope and equipment for LEEP, since it is not economically feasible to have every district. Laboratory staff need training on quality histological examination and doctors need to be trained on use of colposcopy and LEEP. Provincial and the referral hospitals should be set aside for treatment of cervical cancer.
12. To ensure effective screening, certain clinic days should be dedicated for screening and treatment in both primary care clinics and sub-district hospitals. Mobile clinics should also be incorporated on certain days to increase screening coverage.

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Annex 1: MAP OF KENYA (Source; KDHS, 2003)

KENYA



Annex 2: Socio-demographic indicators for Kenya

Indicator	Value
Projected population at end of 2010 ¹	40.9 million
Total surface area ²	582, 646 square kilometres
Total fertility rate 2005-2010 ²	4.9
Crude birth rate 2010(births per 1000 population) ¹	39
Crude death rate 2010(deaths per 1000 population) ¹	11.7
Infant mortality rate (per 1000 live births) ²	77
Under five mortality rate (per 1000 live births) ²	115
Maternal mortality ratio (per 100,000 live births) ²	414
Life expectancy at birth in years (2000-2006) ³	
- Male	53.2
- Female	54.0
Child age dependency ratio 2010 ³	78.5
Old age dependency ratio 2010 ³	4.8
Urban population 2010 ¹	21%
Population living below national poverty line 2006 ³	52%
Gini coefficient 1992-2007 ³	47.7
Literacy rate 1997-2007 ³	
- Male	77.7%
- Female	70.2%
GDP per capita US\$ 2008□	778.765
% of people with access to an improved water source ³	57%

Sources

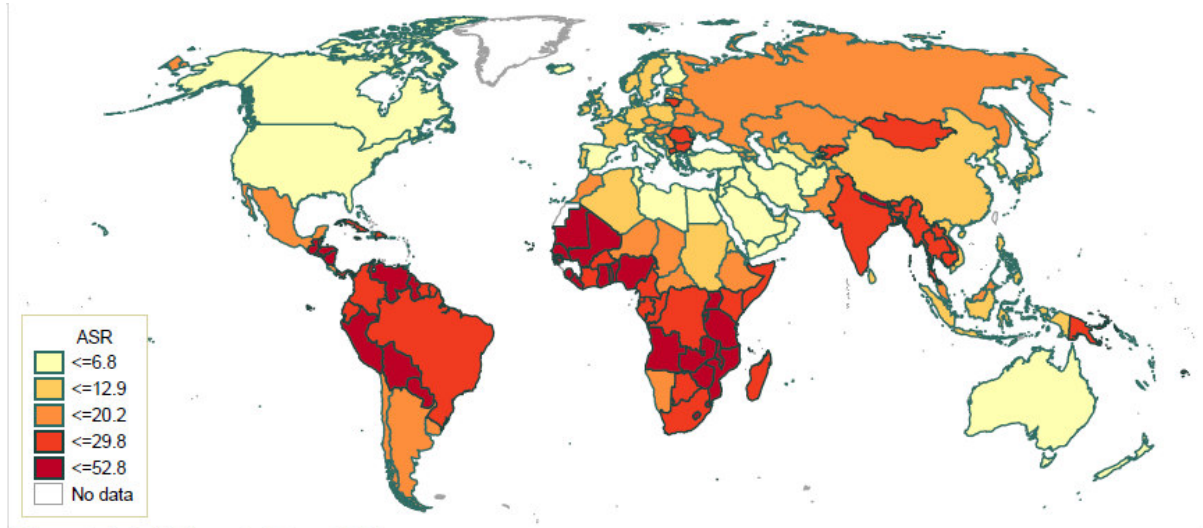
1.....World population prospects

2..... Kenya demographic and health survey (KDHS, 2003)

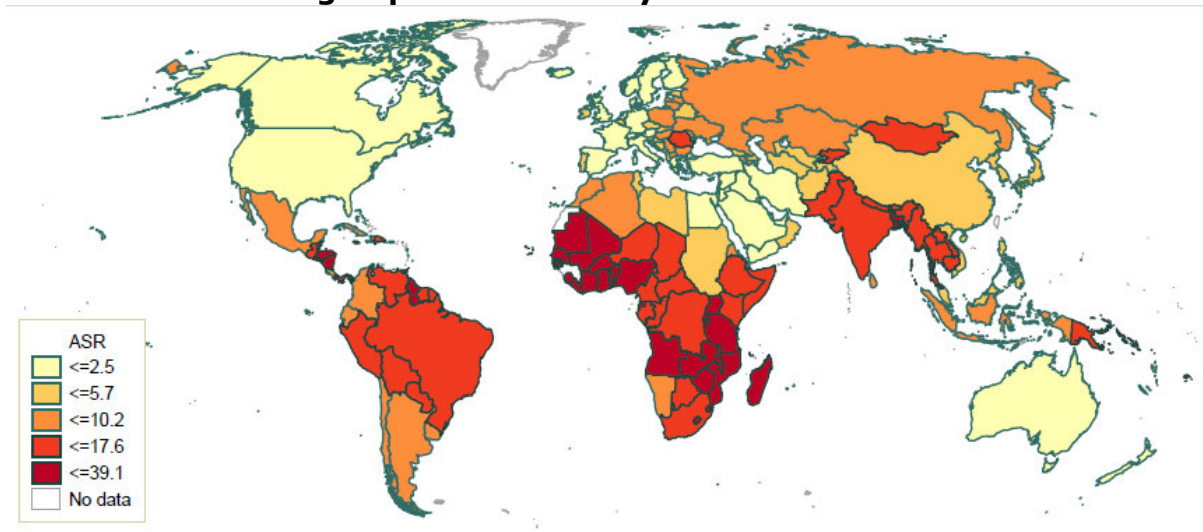
3..... United Nations Development Program (UNDP, 2009)

□..... Kenya National Bureau of Statistics (KNBS, 2008)

Annex 3a: Global age-specific incidence rates of cervical cancer (Source, WHO, 2010)



Annex 3b: Global age-specific mortality rates of cervical cancer

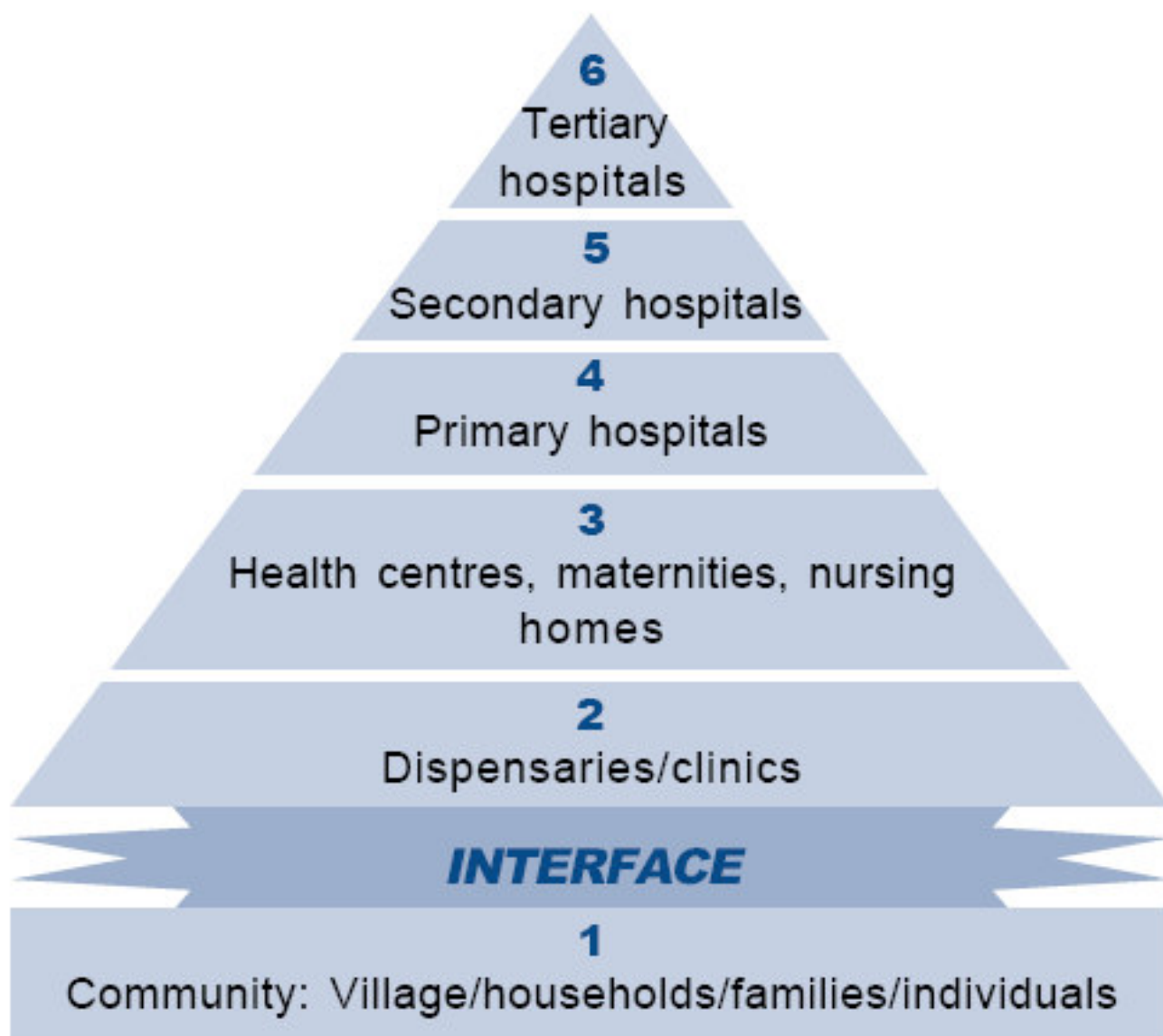


**"ASR –Age standardised rates. Rates per 100,000 women per year"
(Source; WHO, 2010a)**

Annex 4: Roles of Ministry of Medical Services and Ministry of Public Health and Sanitation. (Source; MOH, 2009)

	Ministry of Public Health and Sanitation	Ministry of Medical Services
Health care levels	1-3	4-6
	<ol style="list-style-type: none"> 1. Public Health and Sanitation policy 2. Preventive and Promotive health services 3. Community health services 4. Health education 5. Reproductive health 6. Food quality and hygiene 7. Health inspection and other public health services 8. Quarantine administration 9. Oversight of all sanitation services 10. Preventive health programme including vector control 11. National public health laboratories 12. Government chemist 13. Dispensaries and health centres (i.e. Levels II & III) 14. Kenya Medical Research Institute (KEMRI) 15. Radiation Protection Board 16. Member of KEMSA Board 17. Member of KMTC Board 	<ol style="list-style-type: none"> 1. Medical services policy 2. Curative services 3. HIV/AIDS and other sexually Transmitted Infections (STI) Treatment and Management 4. Maternal Services 5. Rural Medical Services 6. Clinics and hospitals 7. Registration of doctors and paramedics 8. Nurses and midwives 9. National Hospital Insurance Fund 10. Clinical laboratory services 11. Kenya Medical Training College 12. Kenya Medical Supplies Agency 13. Government Chemist 14. Kenya Medical Supplies Agency (KEMSA) 15. Regulatory bodies for pharmacy and medicine 16. Member of KEMRI Board

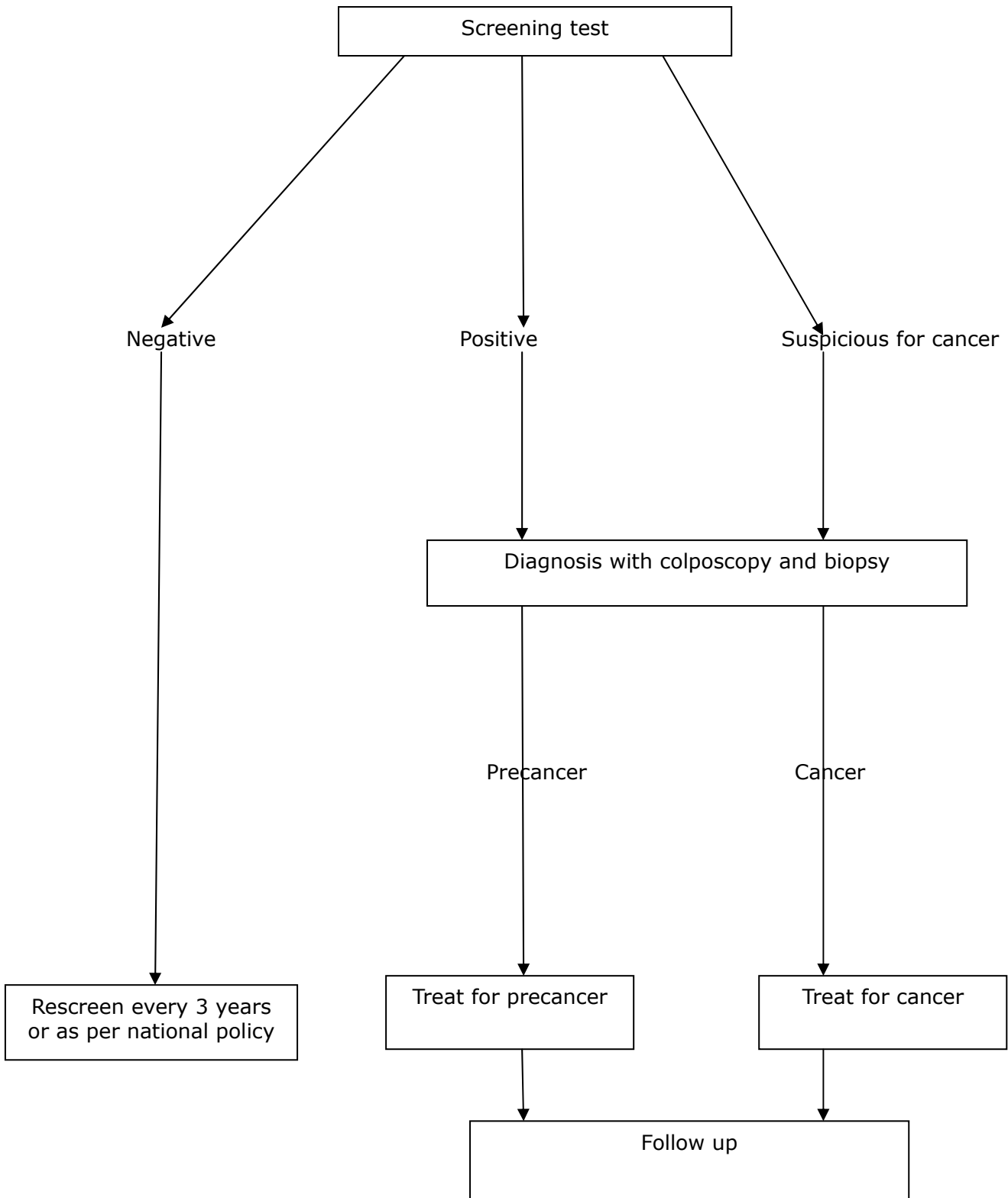
Annex 5: Levels health care in Kenya (Source; MOH, 2005)



Annex 6: Wilson and Jungner Screening Criteria (Source; Andermann et al., 2008)

- The condition sought should be an important health problem.
Cervical cancer is the second leading cause of cancer related morbidity and mortality among women in the world
- There should be an accepted treatment for patients with recognized disease.
Treatment of cervical cancer depends on stage and options include surgery, radiotherapy and chemotherapy
- Facilities for diagnosis and treatment should be available.
In Kenya, diagnostic and treatment services are found in some district hospitals, provincial and national hospital.
- There should be a recognizable latent or early symptomatic stage.
Preclinical disease presents as cervical lesions known as cervical neoplasia. The latent phase is between 10-20 years.
- There should be a suitable test or examination.
Screening tests include use of VIA, HPV DNA and cytology
- The test should be acceptable to the population.
The tests are not fully acceptable as many women don't like the embarrassment associated with pelvic examination
- The natural history of the condition, including development from latent to declared disease should be adequately understood.
The natural history from HPV infection to invasive cervical cancer is well understood
- There should be an agreed policy on whom to treat as patients.
The WHO has guidelines on whom to screen and treat. Kenya is yet to have a comprehensive cervical cancer policy
- The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole. *Cost-effective analysis has shown screening and treatment for precancers is more cost-effective than treatment of cervical cancer*
- Case-finding should be a continuing process and not a "once and for all" project. *An organized screening program ensures continuous screening*

Annex 7: Standard Screening Protocol (Source; WHO, 2006)



Annex 8: Screen and treat protocol with VIA (Source; WHO, 2006)

