

## Review Article

# Incidence and risk factors associated with cervical cancer in sub-Saharan Africa: A systematic review

Abram Bunya Kamiza\*

Sydney Brenner Institute for Molecular Bioscience, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa

\*Corresponding Author: Abram Bunya Kamiza PhD, Sydney Brenner Institute for Molecular Bioscience, Faculty of Health Sciences, University of Witwatersrand, 9 Jubilee Road, Johannesburg, South Africa; Tel: +270117171000; E-mail: abramkamiza@gmail.com

Received: January 09, 2020; Accepted: January 20, 2020; Published: January 23, 2020;

## Abstract

Cervical cancer is the second most common leading cause of cancer death among women worldwide. Annually,  $\geq 300,000$  women die of cervical cancer and the majority of these deaths occur in developing regions of the world including sub-Saharan Africa. Human papillomavirus (HPV) is necessary but not a sufficient cause of cervical cancer. This review paper evaluated risk factors associated with cervical cancer in sub-Saharan Africa, using recent epidemiological studies. The main risk factors associated with cervical cancer in the sub-Saharan African women were; infection with high-risk HPV subtypes, HIV infection, socio-economic factors, age at first sexual intercourse, multiple sexual partners, and long-term use of oral contraceptives. Multi-parity, early pregnancies, and cigarette smoking are some of the risk factors associated with an increased risk of cervical cancer in sub-Saharan Africa. In addition, candidate gene studies have identified a number of single nucleotide polymorphisms mainly within the immune response genes to be associated with cervical cancer risk. Recently, dysbiosis of the cervical microbiome has been associated with cervical cancer risk in sub-Saharan African women.

**Keywords:** Cervical cancer, Incidence, Sub-Saharan Africa, HPV, Risk Factors

## Introduction

Cervical cancer is the second most common leading cause of cancer death among women worldwide [1]. More than 300,000 cervical cancer deaths are reported annually and the majority of these deaths are from developing regions of the world. Squamous cell carcinoma (SCC) and adenocarcinoma (ADC) are the main histological types of cervical cancer [2,3]. SCC begins in epithelial cells of the ectocervix while ADC develops in the glandular cells that line the endocervix [4]. Approximately 80% and 20% of all cervical cancers are SCC and ADC, respectively [5]. ADC is more aggressive and frequently have distant metastases. Patients with ADC tend to have lower five-year survival rates and require an alternative approach to treatment than those with SCC [6]. This review paper evaluates the incidence and risk factors associated with cervical cancer in sub-Saharan Africa, using recent evidence from epidemiological studies.

### Incidence of cervical cancer

The incidence of cervical cancer has been decreasing steadily for the past three decades in industrialized regions of the world [7]. However, in developing regions of the world especially in sub-Saharan Africa, the incidence of cervical cancer is increasing at an alarming rate [8]. The age-standardized incidence rate (ASIR) of cervical cancer in sub-Saharan Africa was estimated to be 34.9/100,000 women [1]. Moreover, ASIR of cervical cancer varies greatly within sub-Saharan Africa, with ASIRs of 43.4/100,000 women reported in southern Africa, 40.1/100,000 women in eastern Africa, 29.6/100,000 women

in western Africa, and 26.8/100,000 women in middle Africa [1], (Figure 1). According to the global cancer statistics of 2018, Eswatini has the highest incidence of cervical cancer followed by Malawi. The ASIRs of cervical cancer in Eswatini and Malawi are 75.3/100,000 and 72.9/100,000 women, respectively. Moreover, it is estimated that in the absence of any intervention, nearly 16.5 million cervical cancer cases will occur in sub-Saharan Africa in the next five decades [9].

### Risk factors for cervical cancer

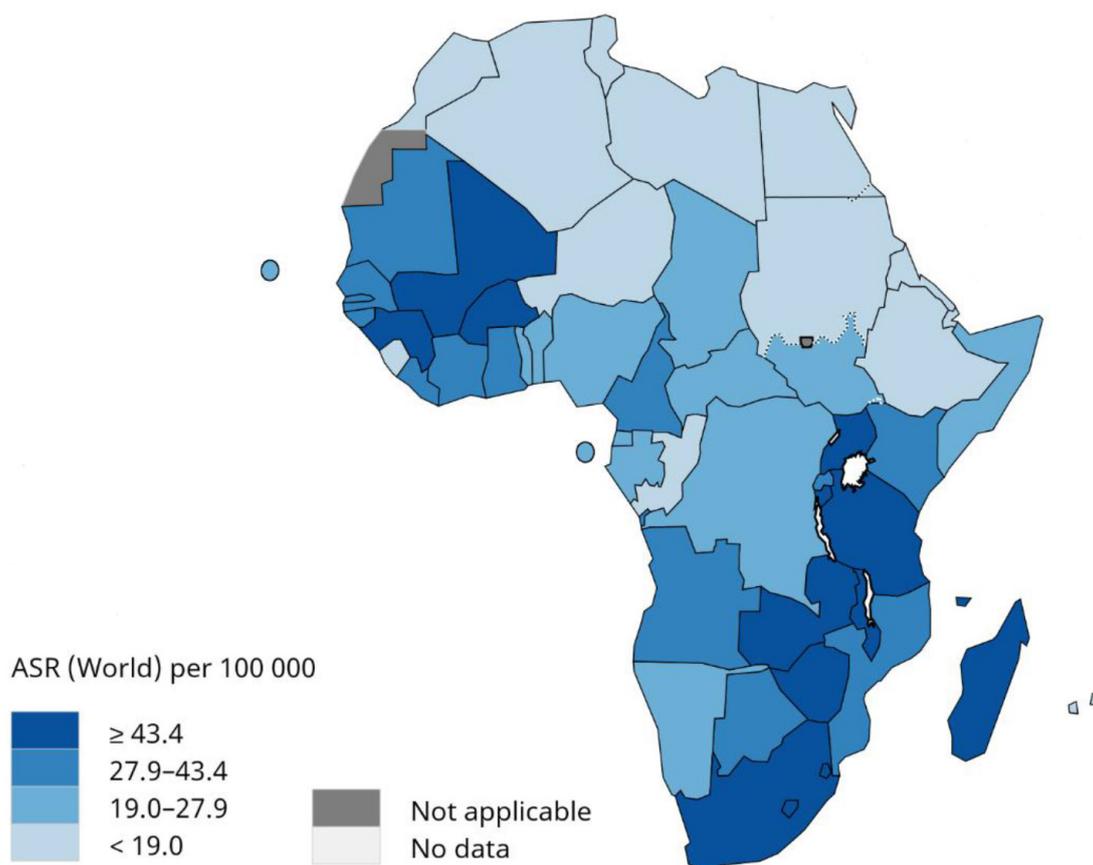
#### 1. Human papillomavirus (HPV) infection

HPV is necessary but not sufficient cause of cervical cancer [10]. Approximately 90% of cervical cancers are attributed to HPV infection [11]. HPV, a small, non-enveloped, double-stranded circular DNA viruses belong to the *Papovaviridae* family [12]. There are  $\geq 150$  HPV subtypes that have been identified and characterized so far. These subtypes are categorized into high and low-risk according to their ability to cause malignant tumours. The high-risk HPV subtypes include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 73, and 82 [13]. Within this category, HPV subtypes 16 and 18 are the most oncogenic and contribute  $\geq 70\%$  of all cervical cancer cases [14].

Over 90% of HPV is cleared by the immune system within two years after infection [15]. However, a small proportion of infections especially those with high-risk HPV subtypes can persist and progress to cervical cancer. HPV encodes eight early viral regulatory protein (E1 to E8) and two late structural proteins (L1 and L2), which are crucial for cervical carcinogenesis [16–18]. The E1 and E2 are required for

viral DNA replication. The E2 suppresses E6 and E7 viral oncoprotein, E4 and E5 help viral assembly, whereas L1 and L2 are involved in capsid formation [19]. HPV usually integrate its DNA into the human genome for replication. However, the integration of HPV into the human DNA disrupts the E2 functionality, thus resulting in a higher expression of E6 and E7 oncoprotein [20]. These oncoproteins invade the host immune

system, deregulate the cell cycle control and apoptosis, thus allowing viral persistence. Dysregulation of the cell cycle and apoptosis lead to cellular transformation and immortalization, which is an important step in cervical tumorigenesis [19]. Specifically, E6 bind to tumour suppressor gene (*TP53*) and prevents apoptosis, whilst E7 oncoprotein promotes cellular proliferation and differentiation [21].



**Figure 1.** Age-standardized incidence rate of cervical cancer in sub-Saharan Africa. Adapted from Global cancer statistics 2018, International Agency for Research on Cancer, World Health Organization.

A retrospective study from 38 countries in North America, Latin America, Caribbean, Europe, Africa, Asia, and Oceania revealed that ≥ 85% of cervical cancer tissues were HPV positive [11]. In addition, 70% of cervical cancer cases were reported to be caused by HPV subtype 16 and 18 [22]. Studies have suggested that in addition to high-risk HPV subtypes been associated with cervical cancer, certain low-risk HPV subtypes such as subtype 6 and 11 also play a crucial role in cervical carcinogenesis [23–25]. However, these low-risk HPV subtypes are commonly associated with benign genital warts. Epidemiological studies have confirmed the direct role of several HPV subtypes in the development of cervical cancer [26,27]. Persistent infection with high-risk HPV subtypes has also been implicated in other cancers including that of the anus, penis, vulva, vagina, and oropharynx [10,28]. These findings suggest that HPV is not only associated with cervical cancer but also other cancers.

## 2. Human immunodeficiency virus (HIV) infection

HIV exacerbates the risk of cervical cancer. Population-based studies have reported that HIV-positive women are more likely to develop cervical cancer than HIV-negative women [29,30]. In Senegal, HIV-positive women were 2.55, (95% CI 1.69–3.86) times more likely to progress from HPV infection to cervical cancer than HIV-negative women [31]. A case-control in Eswatini reported that HIV positive women were 5.24 times increased risk of cervical cancer than HIV negative women [32]. The increased risk of cervical cancer among HIV-positive women is particularly important in sub-Saharan Africa, where HIV infection is endemic. In Rwanda, Singh et al. reported a higher prevalence of high-risk HPV subtypes in HIV-positive women than in HIV-negative women [33]. In Zambia, HIV-positive individuals were two-timed more likely to be co-infected with high-risk HPV subtypes than HIV-negative individuals [34]. In Zimbabwe and South Africa, HIV-positive women were more likely to have abnormal cervical cytology than HIV-negative women [35,36]. A number of studies have

indicated that HIV infection suppresses the immune system's ability to clear the HPV infection [37–39], leading to persistent infection, which subsequently leads to cervical abnormalities and cancer. Moreover, HIV infection significantly decreases cervical cancer survival among HIV-positive women in Botswana [40].

### 3. Socio-economic status

Low socioeconomic status (SES) has been associated with an increased risk of cervical cancer in studies from both developing and developed countries [41–43]. A case-control study in the United States reported a 1.8-fold increased risk of cervical cancer among women who reside in poor counties in Ohio compared to those who reside in affluent counties [42]. El-moselhy et al. reported that women with low education level, unskilled, and reside in rural areas in Egypt were more likely to develop cervical cancer than those with high SES [43]. In Tanzania, women with no formal education were 4.30, (95% CI 3.50–5.31) increased the risk of cervical cancer compared to women with high education level [44]. Moreover, women with low SES were 2.3-fold more likely to die from cervical cancer compared to those with high SES [42]. Differences in SES as defined by education, occupation, and annual income play a major role in disparities in the incidence and mortality of cervical cancer. Women with low SES tend to engage in risky sexual behaviour like prostitution [45], which increases the risk of contracting sexually transmitted diseases (STDs) like HPV and HIV, which are important risk factors of cervical cancer. Moreover, women with low SES tend to lack health-seeking behavior [46], hence they are less likely to participate in cancer screening programmes.

### 4. Age at first sexual intercourse

Early age at first sexual intercourse is associated with risky sexual behaviour like having unprotected sex and multiple sexual partners, which are important risk factors of HPV and HIV [47]. A number of studies have reported an increased risk of cervical cancer with an early age at first sexual intercourse [48–50]. In Nigeria, women with an early onset of sexual intercourse  $\leq 17$  years were 3.7-fold increased risk of cervical cancer compared to those aged  $\geq 18$  years old [49]. A case-control study in Ethiopia indicated that women who experience sexual intercourse earlier than 15 years were 6.7-times more likely to develop cervical cancer than women who experience sexual intercourse between the ages of 21–25 years [50]. Compared with women with age at first sexual intercourse of  $\geq 18$  years, the odds ratio of developing cervical cancer was 1.90 and 2.60 among women with age at first sexual intercourse between the ages of 16–17 and  $< 15$  years old, respectively [51]. Previous studies have suggested that immature cervix is susceptible to high-risk HPV subtypes, which lead to persistent HPV infection and subsequently increased the risk of cervical cancer among young women [52].

### 5. Multiple sexual partners

Sexual activities are the main risk factors of HPV infection especially among those with multiple sexual partners [32,50]. Kassa et al. reported a 5.86-fold increased risk of cervical cancer among women with multiple sexual partners in Ethiopia [50]. In Eswatini, Jolly et al. reported an odds ratio 3.00, (95% CI 1.02–8.85) of developing cervical

cancer among women with multiple sexual partners after adjusting for age at first sexual intercourse [32]. Moreover, a meta-analysis study suggested that having multiple sexual partners, with or without HPV infection, is an important risk factor of cervical cancer among sexually active women [53].

### 6. Multi-parity and early pregnancy

Multi-parity has been associated with an increased risk of cervical cancer [46,54]. Women who engage in early sexual intercourse may become pregnant at a young age and are more likely to be parous later in life [55]. Early pregnancies have been associated with an increased risk of cervical cancer [49]. The increased risk of cervical cancer among women with early pregnancies may be due to cervical trauma experienced during early childbearing or by high parity births [55]. A pooled analysis of eight case-control studies indicated that women who were parous at a young age were more likely to develop cervical cancer later in life [56]. Louie et al. suggested that the increased risk of cervical cancer among highly parous women may be attributed to sexual and reproductive events occurring at a young age [55].

### 7. Oral contraceptive use

Long-term use of oral contraceptives has been associated with cervical cancer risk [50,57]. In Ethiopia and Kenya, women with long-term use of oral contraceptives were associated with an increased risk of cervical cancer compared to women who do not use oral contraceptives [50,57]. A meta-analysis study of 28 case-control studies concluded that long-term use of oral contraceptive is an important risk factor of cervical cancer [58]. Moreover, an animal model study indicated that mouse treated with longer duration of estrogen developed cervical cancer than mouse treated with short duration of estrogen [59]. Interestingly, the incidence of cervical cancer has been found to decline over time as women stopped using oral contraceptives [60,61]. These findings suggest that long-term use of oral contraceptives is an important risk factor of cervical cancer especially among women of reproductive age.

### 8. Cigarette smoking

While cigarette smoking is commonly associated with lung cancer, it also plays a crucial role in carcinogenesis of many other cancers, including cervical cancer [62]. The International Agency for Research on Cancer classified tobacco as a group one carcinogen. A pooled analysis study revealed an increased risk of cervical cancer in current smokers as compared to non-smokers after adjusting for HPV infection and other environmental factors [63]. Min et al. showed that the risk of cervical cancer increased not only in women who smoke but also in women who are exposed to second-hand smoke [64]. The biological mechanism that underlies the increased risk of cervical cancer among women who smoke is not completely understood. However, studies have suggested that smoking inhibits the clearance of HPV infection by the immune system [65,66]. Surprisingly, the association between cigarette smoking and cervical cancer is stronger in SCC than in ADC [67]. The increased risk of SCC among women who smoke is not fully understood as it has rarely been investigated. However, quitting cigarette smoking has been reported to be associated with a decreased

risk of cervical cancer [68]. Roura et al. reported a 2-fold decreased risk of developing cervical cancer among women who quit cigarette smoking.

## 9. Host genetic factors

Approximately 1% of women with chronic HPV infection progress to cervical cancer [69]. Magnuson et al. estimated that 27% of all cervical cancers are attributed to host genetic factors [70]. Studies have identified a number of single nucleotide polymorphisms (SNPs) mainly within the immune response genes to be associated with cervical cancer [71–74]. In Tunisia, a case-control study identified three SNPs (rs1800871, rs1800872, and rs3024490) within *IL10* to be associated with an increased risk of cervical cancer [71]. In South Africa, *CCR2-V64L G>A* was associated with an increased risk of cervical cancer [72]. Zida et al. and Ben et al. identified *TNF- $\alpha$ -308G>A* and *HLA-DRB1\*15* and *DQB1\*06* to be associated with cervical carcinogenesis among HPV-negative women in Tunisia [73,74]. Apart from the immune response genes been heavily associated with cervical cancer, *TP53* has also been implicated in cervical tumorigenesis. A candidate gene study in the black South African population indicated that *TP53* rs1042522 SNP is associated with cervical cancer in HPV-negative women [75]. This finding reveals the direct role of host genetic factors in the aetiology of cervical cancer. However, the association between host genetic factors and cervical cancer has rarely been investigated in sub-Saharan Africa. Hence, more genetic studies with larger sample sizes and probably using genome-wide approaches are needed in sub-Saharan Africa to fully understand the aetiology of cervical cancer.

## 10. Cervical microbiome

Dysbiosis of the cervical microbiome has been associated with cervical cancer risk [76–78]. In Tanzania, Klein et al. reported that *Staphylococcus*, *Pseudomonadales* and *Mycoplasma* species were associated with high-grade squamous intraepithelial lesions in HIV-positive women [76]. Curty et al. found *Gardnerella*, *Aerococcus*, *Schlegelella*, *Moryella*, and *Bifidobacterium* to be associated with cervical lesions [77]. Moreover, a case-control study by Oh et al. reported that *Atopobium vaginae*, *Gardnerella vaginalis*, and *Lactobacillus iners* were associated with an increased risk of cervical cancer [78]. Vagina and ectocervix are normally colonized by *Lactobacillus* species, which inhibit the growth of other bacterial species [79]. Inhibition of these bacteria species is crucial in maintaining the cervical epithelial barrier to HPV entry. However, reduction in the number of *Lactobacillus* species, result in colonization of cervical epithelium by other bacteria species [80]. These bacterial species produce enzymes and metabolites that compromise the cervical epithelium barrier [81], thus facilitating HPV entry into basal keratinocytes. In Kenya, bacterial vaginosis, *trichomonas vaginosis*, and *Candida* species were associated with high-risk HPV infection [82], which is an important risk factor of cervical cancer. Moreover, fungal and some of the bacterial species have been reported to enable HPV persistent, thus leading to cervical cancer [83].

## Prevention and screening

### 1. HPV vaccination

HPV vaccination is becoming the primary prevention of cervical cancer and other HPV-associated cancers. Currently, the Food and Drug Administration approved three HPV vaccines including Gardasil 9, Gardasil, and Cervarix [84]. Gardasil 9 is a nonavalent vaccine produced by Merck [85]. This vaccine target nine HPV subtypes, seven of which are high-risk (16, 18, 31, 33, 45, 52 and 58) and two of which are low-risk (6 and 11). This vaccine target HPV subtypes that cause  $\geq 90\%$  of HPV-associated cancers worldwide [86]. Gardasil (Merck and Kenilworth) is a quadrivalent vaccine, thus targeting two high-risk subtypes (16 and 18) and two low-risk subtypes (6 and 11), and covering  $\geq 80\%$  of HPV-associated cancers [87]. Cervarix is a bivalent HPV vaccine produced by GlaxoSmithKline, targeting two high-risk HPV subtypes 16 and 18, which contribute 70% of cervical cancer worldwide [87].

However, these vaccines cannot prevent pre-existing infections and are administered to pre-adolescent girls between the ages of 9–15 years [84]. Uptake of these vaccines is low in developing countries, especially in sub-Saharan Africa [88]. However, most countries are now implementing HPV vaccination in school-going children. It is estimated that  $\geq 6.7$  million cervical cancer cases could be prevented if HPV vaccination coverage is scaled up to 80–100% globally by the year 2020 [9]. However, it will take several decades in sub-Saharan Africa to see the impact of HPV vaccination.

### 2. Pap smear test

Pap smear is a screening test used to check cervical lesions. It is usually performed in women of reproductive age and who are sexually active [89]. Pap smear can detect early cervical dysplasia in its earliest form. Once cervical abnormalities are detected, the best way is to treat the precancerous lesions before they can fully develop into cancer. Countries that have successfully implemented cervical cancer screening have also significantly reduced both the incidence and mortality of cervical cancer, especially SCC [90,91]. The HPV DNA test has also been recommended to be included in cervical cancer screening package among women of reproductive age [89]. Cervical cytology together with HPV DNA test has higher sensitivity than screening with Pap smear alone [92]. A recent study suggested that rapid scale-up of HPV vaccination and screening from 2020 onwards will rapidly decrease the incidence and mortality of cervical cancer in the next five decades [9]. However, cervical cancer screening coverage is still low in sub-Saharan Africa [93], and there is a need for rapid scale-up to avert the high incidence and mortality of cervical cancer.

### 3. Visual inspection with acetic acid (VIA)

VIA is an alternative cervical cancer screening method viable in sub-Saharan Africa, as it is cheap, easy to use, does not require a physician or pathologist to perform, and tend to have shorter turn-around time than Pap smear [94]. In VIA, about 5% acetic acid (vinegar) is applied to the cervix and then visualized with a lamp. The precancerous lesions on the cervix normally turn white when combined with acetic acid whilst normal cervix do not change colour

[95]. A number of studies in sub-Saharan Africa have indicated that VIA has a higher sensitivity than Pap smear [96–99]. Specifically, VIA has a high sensitivity for SCC which contribute  $\geq 80\%$  of cervical cancers in sub-Saharan Africa [97]. However, previous studies have indicated that VIA tends to have lower specificity than Pap smear [96–98]. Nonetheless, VIA is comparable to Pap smear and the World Health Organization recommended VIA as a primary cervical cancer screening method in developing countries, where pathology laboratories are limited. The low cervical cancer screening rate in sub-Saharan Africa may be attributed to inadequate funding, lack of awareness campaign, lack of health-seeking behaviour, low SES, and long-distance to access healthcare facility [100]. Cervical cancer can also be prevented by having safe sex, monogamous relationship and adopting a healthy lifestyle like quitting cigarette smoking, alcohol consumption and engaging in regular physical activity.

## Summary and conclusion

The incidence of cervical cancer is highest in sub-Saharan Africa. Epidemiological studies have indicated that infection with high-risk HPV subtypes is crucial in the carcinogenesis of cervical cancer. Apart from HPV infection, HIV, SES, age at first sexual intercourse, multiple sexual partners, oral contraceptive use, multi-parity, early pregnancies, cigarette smoking, host genetic factors, and dysbiosis of the cervical microbiome are also important risk factors associated with cervical cancer in sub-Saharan Africa. However, cervical cancer can be prevented by HPV vaccination and early detection through screening. Gardasil and Cervarix are two HPV vaccines that are currently used to prevent cervical cancer and other HPV-associated cancers in sub-Saharan Africa. Scaling up HPV vaccination and decentralization of cervical cancer screening programmes from tertiary-level to primary-level care is crucial in preventing the incidence and mortality of cervical cancer in sub-Saharan Africa. Moreover, future cervical cancer prevention programmes should include other risk factors associated with the disease.

**Funding:** None.

**Conflicts of Interest:** None

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**Citation:**

Abram Bunya Kamiza (2020) Incidence and risk factors associated with cervical cancer in sub-Saharan Africa: A systematic review. *ARCH Women Health Care* Volume 3(1): 1–7.