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Cervical Cancer, a Sequela of a Sexually Transmitted Infection: The Human Papillomavirus Infection

Tamunomie K Nyengidiki, Goddy Bassey and
Ikechukwu Durugbo

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Abstract

Cervical cancer has contributed to a large number of gynecologically related oncologic deaths in most developing countries. Almost all cases of cervical cancer are related to the presence of persistent strains of sexually transmitted oncogenic strains of human papillomavirus infection (HPV). Steps taken to decrease infection rate will reduce the long-term sequelae of cervical cancer globally.

Keywords: cervical cancer, sexually transmitted disease, HPV

1. Introduction

Cervical cancer is a malignant lesion of the cervix. The squamous cell carcinoma consists of about 90–95% of the cases while adenocarcinoma makes up about 5–10% [1]. Other histological variants do exist such as adenosquamous, sarcomas, lymphomas, carcinomas, etc. Cervical cancer arises either from the ectocervix or from the endocervix. The site of the growth bears no relationship to the histological type as some squamous carcinoma are found in the endocervical canal [1]. Worldwide, every 2 min, a woman dies of cervical cancer, and it is the leading cause of cancer deaths in women of the developing countries as about 85% of the women dying from cervical cancer reside in the developing countries [2].

Currently, about 200 different strains or genotypes of human papillomavirus infection (HPV) have been isolated. Thirty of these have a predilection for the epithelium of the genital tract of which 15 strains are regarded as oncogenic and are responsible for virtually all cases of cervical cancer worldwide. Oncogenic strains or high-risk genotypes which include serotypes 16,

18, 31, 35 and 45 are responsible for most cases of cervical cancer, although multiple infections with a combination of genotypes have been isolated in 6% of cases. It is estimated that only 20% of women will escape HPV infection in their lifetime and this underscores the importance of this infection [2, 3].

Human papillomavirus, a non-envelop double-stranded DNA virus, measures about 55 nm in diameter and consist of a genome that encodes for early and late proteins. It causes both benign and malignant conditions of the skin, cervix, vagina, vulva and anus. The main routes of transmission are through sexual intercourse and skin-skin contact; it is projected that about half of all sexually active adolescent will acquire the infection; however, the infection is usually self-limiting and harmless depending on the host immunity among other factors. Failure of the host immunity to clear the infection is responsible for persistence of the infection and eventual development of cervical cancer [3–5]. This chapter exploits cervical cancer as sexually transmitted infection sequelae with the human papillomavirus virus, largely the causative agent.

1.1. Epidemiology of cervical cancer

Worldwide, about 500,000 new cases of cervical cancer are diagnosed annually and there are about 300,000 associated deaths per year. Most of the new cases of cervical cancer and the associated cancer deaths occur in the less developed regions of the world [6]. Projections indicate that more than one million new cases of cervical cancer will occur each year by 2050 [7].

Every year, across Africa about 79,000 women are diagnosed with cervical cancer [6]. The epidemiology of cervical cancer is different in North and sub-Saharan Africa, due to differences in cervical screening, cultural differences and human immunodeficiency virus (HIV) prevalence. Organized cervical screening is limited or absent in several African countries [6].

Yearly across Africa, about 62,000 women die from cervical cancer with a similar distribution of mortality rates to incidence rates. High incidence and mortality rates occur in sub-Saharan Africa while lower rates occur in North Africa [6]. In Nigeria, cervical cancer age standard incidence rate at the Ibadan population-based cancer registry was 36.0 per 100,000 and 30.3 per 100,000 at Abuja population-based cancer registry [8].

In Europe and North America, the incidence of cervical cancer is about 60,000 and 14,000, respectively, with a lower annual mortality rate of about 30,000 and 5000, respectively [6, 9]. The low incidence and mortality may reflect the availability of well-established screening program in developed countries [7, 9].

1.2. Burden of HPV infection and regional variation of genotypes

Human papillomavirus virus is a relatively small sexually transmitted virus containing circular double-stranded DNA with affinity to cutaneous and mucosal epithelium resulting in cytopathic changes. It is the most common sexually acquired infection in the world with more than half in young, sexually active adolescents. The persistence of the oncogenic HPV types causes cervical cancer in women. Several studies have been done on the prevalence of HPV genotypes in women with different genotypes implicated in different histological types of cervical cancer.

Cervical cancers constitute two-thirds of all genital cancers in developing countries like Nigeria with most of the patients presenting with clinical stage III or IV disease [4, 10]. Therefore, the main burden of cervical cancers is in the developing world where it contributes significantly to maternal death. This is contrary to the developed countries where there is decreasing incidence of cervical cancer. This is due to the establishment of effective cervical cancer screening protocol, education and access to good medical care [10, 11]. In the UK, screening has prevented up to 70% of cervical cancer death since its inception in 1988 [12].

Worldwide, an estimated 291 million women are harboring HPV DNA at any point in time and 23% of these infections are related to HPV 16 while 8.5% are related to HPV 18 [13]. The adjusted global prevalence has been reported to be 10.41% [14]. The oncogenic HPV incidence is highest in young women and the risk of infection remains throughout life [15]. There are regional differences in the prevalence of the oncogenic HPV infection [16].

A study done in Benin, West Africa, showed an overall prevalence of 32.2% [17]. High-risk types were involved in 88% of the infection, most notably HPV 16, 18, 35, 45, 58 and 59. Another study done in Mexico for a prevalence of HPV genotypes in women from a rural region of Puebla revealed the prevalence of 25.4% [18]. The study also revealed two peaks of higher HPV prevalence in those aged 18–24 and 55–64 years. The individual genotypes in the study were 9.6% HPV 6, 4.6% HPV 11, 54.2% HPV 16, 37.3% HPV 18 and 9.6% HPV 31. HPV 16 was the most common type found in all the cervical lesions.

A study on the prevalence of HPV and its genotypes done in Ibadan, Nigeria, showed that the overall prevalence of HPV was 26.3% in women with cervical cancer and 24.8% in the women without cervical lesions [4]. It also revealed that the high-risk HPV was predominant (19.7%) and was mostly due to viral types 16, 31, 35 and 58. The low-risk HPV were found in 6.6% and mixed infections of more than one HPV type occurred in 33.5% of HPV-positive cases. A similar incidence of 21.6% was found in Okene, north-central Nigeria with the high-risk HPV prevalence of 16.6 and 3.5% having mixed infections [19].

In immunocompromised patients, the genotypic distribution also differs as observed in a cross-sectional prospective study conducted out in LUTH, Lagos which determined the prevalence of high-risk HPV among HIV-positive and HIV-negative women in 2012 [20]. The study revealed that the prevalence of HPV among the HIV-positive women was 44.9% with the prevalence of the high-risk types constituting 37.5%. The most common high-risk types seen were types 31, 52, 53 and 35. It also showed that the prevalence of HPV among the HIV-negative women was 11% while the most common high-risk types seen in them were types 18, 16, 52 and 56. Similar study for the prevalence of HPV genotypes enrolled HIV-positive and HIV-negative women presenting for cancer screening program [21]. Among the HIV-positive women, HPV 35 (8.7%) and HPV 56 (7.4%) were the most prevalent high-risk HPV while HPV 52 and HPV 68 (2.8% each) were the most prevalent among HIV-negative women. The study suggested that the oncogenic HPV types 35, 52, 56 and 68 may be more important risk factors for cervical pre-cancers among African women hence polyvalent high-risk HPV vaccines meant for African populations should protect against HPV types other than 16 and 18.

A cross-sectional epidemiological study that assessed HPV prevalence and type distribution in women with invasive cervical cancer in Ghana, Nigeria and South Africa revealed that the most commonly detected HPV types were HPV 16 (51.2%), HPV 18 (17.2%), HPV 35 (8.7%), HPV 45 (7.4%), HPV 33 (4.0%) and HPV 52 (2.2%). The prevalence of single and multiple HPV infections seemed higher among the HIV-positive women. Therefore, HPV 16, 18, 45 and 35 were the most common HPV types in sub-Saharan African women [22]. Another study in Abuja showed HPV types 18 and 16 to be the most predominant in the metropolis [23].

2. HPV genotypes and distribution in cervical cancer

The most common oncogenic HPV genotypes are 16, 18, 45, 31, 33 and 51 [24]. Others are 52, 56, 58, 59 and 68. HPV genotypes 16, 18, 45, 33 and 31 are usually associated with squamous cell carcinoma while types 16, 18, 45, 31 and 51 are usually associated with adenocarcinoma [24]. These oncogenic strains are those linked to cervical cancer.

Globally, HPV types 16 and 18 together account for more than 70% of the cervical cancer cases while the next most common oncogenic HPV types are 45, 31 and 33 and together account for about an additional 10% [16, 25]. HPV 18 is more prevalent in adenocarcinoma than the squamous cell carcinoma while HPV 16 in more prevalent in squamous cell carcinoma [16]. The non-oncogenic genotypes are 6, 11, 44, 43, 44, 54 and 55 and are associated with benign genital warts. HPV types 6 is most commonly detected in the benign genital lesions (about 90% of warts) and followed by HPV 11 (10–30% of genital warts) [26].

2.1. HPV and other cancers

Despite its contribution to the development of cervical cancer, HPV is also associated with oropharyngeal, vaginal, vulva and anal cancers [26, 27]. About 12% of cancers of the oropharynx and 3% of cancers of the mouth are attributed to HPV infection [26]. However, the major risk factors for these cancers are tobacco use and alcohol consumption. The effects of these two risk factors are multiplicative [26, 27].

The HPV infection results in about 90% of anal cancers [27]. The other risk factors to the development of anal cancers are HIV infection, cigarette smoking, anal intercourse and multiple sexual partners [27]. The HPV infection and pathologies are both increased in HIV-positive individuals [2]. The mechanism of interaction of HIV and HPV is not known but it may involve immune suppression rather than direct interaction [2].

The vaginal intraepithelial neoplasia, which is a preinvasive disease of the vagina, has been associated with HPV infection [28]. The vagina lacks a transformation zone, whereas in the cervix immature epithelial cells are infected with HPV [28]. It has been theorized that the HPV entry mechanism involves abrasions from coitus and the use of tampons. The HPV may begin its growth in a healing abrasion in a similar fashion as in the transformation zone. The upper third of the vagina is vulnerable to the development of dysplasia and carcinoma *in situ* whether

or not hysterectomy has been performed previously for intraepithelial neoplasia [28]. Each of these entities has a potential for progression to invasive cancer. For this reason, women who have had a hysterectomy with a history of HPV or intraepithelial neoplasia should continue to have periodic cytologic screening of the vaginal apex [28].

The HPV infection is strongly associated in younger women with vulvar cancer. This is preceded with high-grade vulvar intraepithelial neoplasia which is commonly associated with high oncogenic type 16 and to a lesser extent type 18 [25]. Although the incidence of vulvar intraepithelial neoplasia and HPV has increased over the past decade, the incidence of vulvar cancer has remained relatively constant [25].

2.2. HPV and non-oncogenic conditions

The non-oncogenic or low-risk HPV types can cause benign condyloma acuminata (genital warts) [22]. The low-risk HPV types 6 and 11 are found in most of the genital warts [26, 29]. The HPV type 6 is most commonly detected in genital warts (about 90% of warts) followed by HPV type 11 (10–30% of warts) [30, 31]. The low-risk HPV types are rarely associated with dysplasia or cervical cancer [26]. Clinically apparent genital warts affect 1% of the sexually active population (15–49 years) in the USA [26, 29]. In the UK, genital warts were the second most commonly diagnosed sexually transmitted infection (after chlamydia) among young people (16–24 years) in a genitourinary medicine clinic [32].

3. Anatomy of the cervix in relation to HPV infection

Generally, HPV requires epithelial tissue for the completion of its viral cycle and the rich epithelial network of the cervix makes it susceptible to colonization by HPV. The epithelium of the cervix is divided into mature and differentiated cells which constitute the parabasal and basal layers adjacent to the basement membrane and the end-stage fully differentiated cells of the superficial layer [33]. The anatomical placement of the cervix in the vagina exposes it to the seminal fluid which harbor the HPV virus which usually has a predilection to the transformation zone, which has the most actively dividing cells.

3.1. Human papillomavirus, life cycle and invasion

The human papillomavirus measures about 55 nm in diameter and its viral genome is divided into three regions: the upstream regulatory region (URR), the early region (E1–E7) and the late region (L1 and L2) [34]. The genes in the early region dictate the production of copies of viral DNA, development of new messenger RNAs (mRNA) and eventual transformation of the host genome. In addition, E6 and E7 encode for the major transforming proteins which are capable of inducing cell proliferation and immortalization. The genes in the late region are responsible for the development of the viral coat. HPVs are epitheliotropic viruses and are responsible for several mucous and skin lesions. Infection is initiated when the virus gains entry into the basal cells of the epithelium.

The HPV life cycle is restricted to the cervical epithelium as shown in **Figure 1** [35]. The virus is thought to infect the basal cell layer of the epithelium via micro-abrasions and then uses the host cell machinery to replicate viral DNA and express virally encoded oncogenes [36]. The HPV has several mechanisms for avoiding the immune system. This includes the restriction of its life cycle to the epithelial cells that have short lifespan and therefore has no replication in the blood (no viraemia) and the infection is not spread systematically [35]. As a result, HPV does not need to destroy the host cell, and in the absence of cell death or a danger signal, HPV fails to trigger inflammation and an immune response [35, 36].

In addition, HPV down-regulates the expression of interferon genes. Type 1 interferon is a cytokine that has antiviral and antiproliferative properties. The HPV oncoproteins E6 and E7 can directly inhibit these antiviral pathways in the cell [35]. Then, the new viral particles are assembled in the upper layers of the epithelium. The virus will be released with the cells as they are shed from the epithelial surface. HPV immune evasive mechanisms enable the infection to persist [35].

3.2. HPV transmission

The majority of the anogenital HPV is sexually transmitted. If one partner has HPV, the other partner's chance of being infected with the same HPV type increases by >50 times [37]. Sexual intercourse and/or genital skin-to-skin contact are the primary routes of anogenital HPV transmission [38]. Condom use does not provide complete protection from HPV transmission and self-inoculation is possible [39]. Infection is thought to occur through microscopic tears or abrasions in the epithelium. Transmission by non-sexual routes is thought to be uncommon, but the possible routes include transmission from mother to newborn [40].

Other non-sexual routes of transmission are through finger-to-genital contact and transmission through fomites and environmental surfaces [41]. Vertical transmission together with other non-sexual routes may contribute to anogenital HPV infections in children [42].
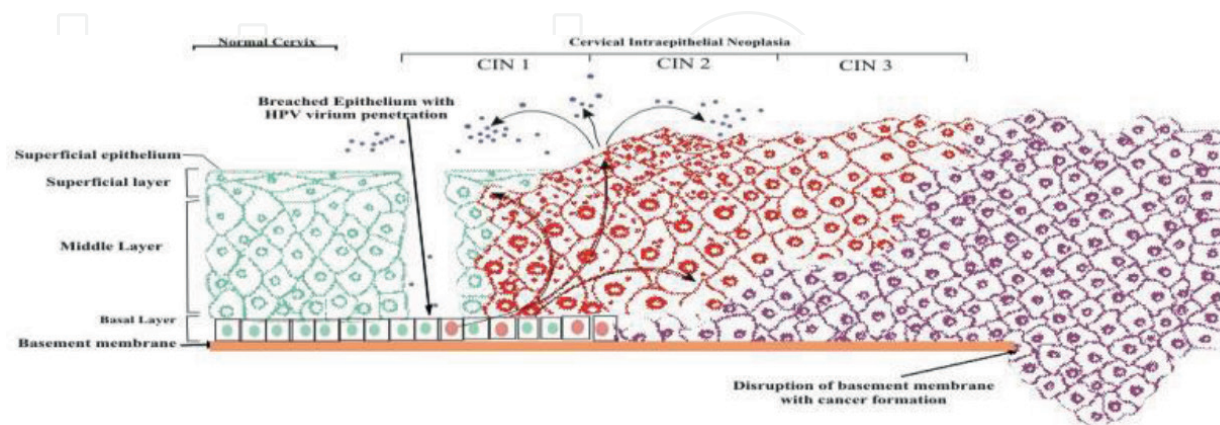

Figure 1. Diagram indicating the life cycle from HPV infection to frank carcinoma (adapted from Nature Rev Cancer, 2007).

In children, prior to any sexual activity, anogenital HPV DNA detection rates range between 3 and 55% and this variation is likely to be caused by different sample collection and HPV detection methods.

4. Risk of HPV infection

Every sexually active woman is at risk of acquiring an oncogenic HPV infection which may cause cervical cancer [43]. The risk of acquiring oncogenic HPV infection is high even after first intercourse and continues throughout a woman's sexually active lifetime [44]. HPV infections are very common with up to 80% of women acquiring HPV infection in their lifetime [26, 44]. While most HPV infections resolve naturally, there is currently no way of predicting which infection will persist [26]. The cumulative risk of acquiring cervical HPV infection in women with only one sexual partner is 46% (3 years after first sexual encounter) [45]. New HPV infections can be acquired at any age [46, 47] and the prevalence of infection is greatest (approximately 20%) in women less than 25 years of age [14]. The incidence of oncogenic HPV infection is around 5% in women 25–55 years of age [48]. Although new infections decrease with age, the risk of persistence of infection increases with age [15].

4.1. Co-factors that increase the risk of progress to cervical cancer

The persistence of HPV infection with the oncogenic HPV types is necessary but insufficient alone to cause cervical cancer [49]. Approximately 70% of cervical cancers worldwide is associated with HPV types 16 and 18 [25]. The HPV types 16 and 18 persist longer than low-risk HPV types [50]. Several other factors are associated with the development of cervical cancer following oncogenic HPV infection [26, 51]. These factors include environmental factors like smoking, sexual exposure especially for early onset of sex (coitarche) and high parity [46]. The other factors are hormonal, like in long-term use of oral contraceptives and immunosuppressive factors such as HIV, transplant recipients and long-term systemic steroid use [36, 39].

4.2. Pathway of HPV infection to cervical cancer

The progression of HPV infection to cervical cancer is a multi-step process. The initial infection of the cervix with HPV leads to viral entry into target basal epithelial cells. HPV oncogenes (E6 and E7) will be expressed and they modulate the effect of the tumor suppressor proteins p53 and Rb [34]. The HPV genome integrates into the host genome and this results in cytogenetic instability. These genetic changes allow for uncontrolled cell growth (immortalization) [34]. The final stage involves malignant transformation to invasive cervical cancer.

After the cervix is infected with HPV, the infection may cause mild Papanicolaou abnormalities and/or mild cervical intraepithelial neoplasia (CIN), which usually clear spontaneously [49, 52]. Studies have demonstrated that the persistence of high-risk HPV is a key factor in the

progression to precancerous lesions or high-grade dysplasia (CIN 2/3), which has a greater likelihood of progression to invasive cancer [49].

It has also been shown that for every one million women infected with HPV about 100,000 will develop precancerous changes, about 8000 will develop carcinoma *in situ* while about 1600 will develop invasive cervical cancer if precancerous changes and CIS are not detected or treated [38]. Cervical cancer is an outcome of the oncogenic HPV infection. However, over 80% of HPV infection are asymptomatic, transient and resolve spontaneously [49, 52, 53]. This progression of HPV infection from precancerous conditions to cervical cancer is unpredictable and may take up to 20 years to complete [48].

5. Diagnosis

The aim of HPV testing is to determine the presence of high-risk HPV which can persist and result in a premalignant lesion of the cervix and subsequently cervical cancer [52]. The HPV test checks for the genetic material (DNA) of the HPV. The HPV test is done on a sample of cells from cervical smears collected with cytobrush among other methods of collection. The multiplex polymerase chain reaction (PCR) kits are used in determining the specific HPV genotypes while the real-time PCR kits are used in quantifying the HPV genotypes.

HPV genotypes are determined by polymerase chain reaction (PCR) and hybrid capture 2 (HC2). In determining the genotype by PCR, the process by hybridization using type-specific probes is utilized. The sequencing or restriction fragment length of the viral genome is determined in the process. Among various PCR methods, one of the most useful PCR methods for genotyping of HPV is the non-radioactive reverse line blot (RLB). In 37 mucotropic HPV types, the late region (L1) of the HPV genome is amplified using the general primers GP5+/GP6+ [50, 51, 54].

Another method of HPV DNA testing/genotyping is the digene which is a hybrid capture 2 (HC2). Hybrid capture 2 is a commercially available standardized kit that uses RNA probes to detect DNA from the oncogenic HPV types. The DNA of interest is merged with a specific HPV RNA probe cocktail. The combination created is fixed on a microplate coated with antibodies specific for the hybrid created and detected by a chemiluminescent substrate. The ability to detect low-risk or high-risk genotypes are determined by the RNA probe pool used during the process. RNA probe A when used is able to detect low-risk genotypes while RNA probe B identifies oncogenic genotypes. If an HPV test shows that high-risk types of HPV are present, further investigations such as a colposcopy and/or cervical biopsy may be recommended.

5.1. Treatment and prevention of HPV infection

The prevention of HPV infection is very important if the associated disease conditions are to be reduced. Abstinence and HPV vaccines are the two most important ways of preventing HPV infection. However, there are other ways of reducing the risk of transmission of the

virus. Not having genital intercourse is an important way of avoiding the HPV infection but this is not realistic for most adults hence the need for other methods of prevention. For the sexually active women, the use of barrier methods such as condom during intercourse and dental dams for mouth-to-genital contact can help to reduce the transmission of HPV [50].

To be most effective, these barrier methods should be used with every sex act, from start to finish. The HPV can infect the areas that are not covered by a condom, so condoms may not fully protect against HPV infection. The other methods of reducing the risk of HPV infection are by having a faithful relationship with one partner, limiting the number of sexual partners and being with a partner who has had no or fewer prior sex partners [50]. But even people with only one lifetime sex partner can get infected with human papillomavirus [55, 56].

5.1.1. HPV vaccines

The HPV vaccines generate neutralizing antibodies which prevent the HPV infection. The induction of high and sustained levels of the neutralizing antibodies is a key mechanism of vaccine-induced protection. The neutralizing antibodies bind the HPV's outer shell (capsid) and prevent infection of the host cell [57]. Therefore, the neutralizing antibodies are likely the mediator of the protection [57, 58]. Currently, there are two vaccines administered for the pre-vention of HPV. They are the Cervarix and the Gardasil as illustrated in **Table 1**. The Cervarix contains antigens of virus-like particles of HPV 16 and 18 while the Gardasil contains those of HPV 16, 18, 6 and 11. The Cervarix protects against HPV 16 and 18 while the Gardasil protects against HPV 16, 18, 6 and 11. Therefore, the Gardasil protects against cervical cancer like the Cervarix and also protects against genital warts [59]. The vaccines are most effective if given before the female becomes sexually active. It is recommended that they are administered at the age of 11 or 12 years although a 9-year-old child can receive the vaccines (before the age of sexual debut) [59].

Catch-up vaccines could be given to girls and women between the ages of 13 and 26. This is for those who did not get any or all of the doses when they were younger. The vaccines are safe and effective and given in 3 doses over 6 months [60]. Boys and men can also get the HPV vaccines to prevent the HPV infection and the associated conditions such as genital warts and anal cancers. In addition, the male vaccination is recommended in order to reduce the reservoir

Vaccine	Target population	Serotypes	Disease targets	Dose schedules
Cervarix (Glaxosmithkline)	Girls and women aged 9–26 years	16 and 18	Prevention of cervical cancer caused by the 16 and 18 genotypes	Dose: 0.5 ml IM Schedule: 0, 1 and 6 months
Gardasil (MSD)	Girls and women aged 10–26 years	6, 11, 16 and18 (1° Gardasil) inclusive of HPV types 31, 33, 45, 52 and 58 (Gardasil 9)	Prevention of cervical cancer of listed serotypes and genital warts	Dose: 0.5 ml IM Schedule: 0, 2 and 6 months

Table 1. Vaccines against the human papillomavirus infection in prevention of cervical cancer [59].

load of the HPV in the males and hence reduce its transmission to the female partners. Neither Gardasil nor Cervarix can provide complete protection against the persistent infection with other HPV types, some of which also cause cervical cancer [61]. Therefore, about 30% of cervical cancers and 10% of genital warts will not be prevented by these vaccines. Despite the two vaccines, there are debates and researches on the need for booster doses [62–64]. In December 2014, Food and Drug Administration in the USA approved a nine-valent Gardasil-based vaccine called Gardasil-9. Gardasil-9 protects against infection with the four strains of HPV covered by the first generation of Gardasil as well as other strains responsible for 20% of cervical cancers (HPV types 31, 33, 45, 52 and 58) [65].

5.1.2. Booster vaccines for HPV

Vaccinations raise antibody levels to HPV, then antibody levels wane. The immune correlate of protection for HPV vaccination remains unknown [61]. Additional vaccine dose will boost immune memory in vaccinated women but recall of vaccine-induced immune memory by natural HPV exposure is unproven [62, 63]. The pace of HPV pathogenesis is uncertain, therefore, the requirement for booster vaccination is currently unknown [61].

Author details

Tamunomie K Nyengidiki*, Goddy Bassey and Ikechukwu Durugbo

*Address all correspondence to: tammynyengs@yahoo.com

Gynaecological Oncology Unit, Department of Obstetrics and Gynaecology, University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria

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