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Chapter

Human Papillomavirus and Cervical Cancer

Kehinde Sharafadeen Okunade

Abstract

Cervical cancer is by far the most common HPV-related disease. About 99.7% of cervical cancer are caused by persistent genital high-risk human papillomavirus (HPV) infection. Worldwide, cervical cancer is one of the most common cancer in women with an estimated 528,000 new cases reported in 2012. Most HPV infections clear spontaneously but persistent infection with the oncogenic or high-risk types may cause cancer of the oropharynx and anogenital regions. The virus usually infects the mucocutaneous epithelium and produces viral particles in matured epithelial cells and then causes a disruption in normal cell-cycle control and the promotion of uncontrolled cell division leading to the accumulation of genetic damage. There are currently two effective prophylactic vaccines against HPV infection in many developed countries and these comprise of HPV types 16 and 18, and HPV types 6, 11, 16 and 18 virus-like particles. HPV testing in the secondary prevention of cervical cancer is clinically valuable in triaging low-grade cytological abnormalities and is also more sensitive than cytology as a primary screening. If these prevention strategies can be implemented in both in developed and developing countries, many thousands of lives could be saved.

Keywords: cervical cancer, high-risk HPV, HPV vaccines, screening, triaging

1. Introduction

Human papillomavirus (HPV) is the commonest viral infection of the reproductive tract and is one of the most common causes of sexually transmitted infection worldwide [1]. Even though it is sexually transmitted, HPV transmission does not require penetrative sexual intercourse. Skin-to-skin genital contact is a well-established mode of transmission. Over 70% of sexually active women and men will be infected at some point in their lives and some may even be infected on more than one occasion [2]. The peak period for acquiring HPV infection is shortly after becoming sexually active. The infection usually clears up spontaneously within a few months after the acquisition with about 90% clearing within 2 years. There are over 200 HPV types recognized based on DNA sequence data showing genomic differences, and many of these are harmless. HPV can infect basal epithelial cells of the mucocutaneous membrane, and it is associated with a variety of clinical conditions that range from innocuous lesions to cancer. Most of the infections are benign, causing lesions such as cutaneous warts on the hands, feet and anogenital regions. Warts are areas of hypertrophied skin filled with keratin and are mainly a cosmetic nuisance; generally, they resolve spontaneously within 1–5 years. Only a

small proportion of infections with certain types of HPV can persist and progress to cancer such as oropharyngeal, cervical, vulvar, vaginal and penile cancer [1].

Cervical cancer is by far the most common HPV-related disease [1]. Nearly all cases of cervical cancer are due to persistent or chronic HPV infection. Cervical cancer is the fourth most common cancer in women worldwide and it accounts for an estimated 528,000 new cases [2]. About 85% of the global burden occurs in the less developed regions, where it accounts for almost 12% of all female malignancies. In 2012, an estimated 266,000 deaths were attributed to cervical cancer, accounting for 7.5% of all female cancer deaths with almost 90% these deaths occurring in the less developed regions [2]. In these developing countries, cervical cancer may constitute up to 25% of all female cancer cases [3] and is only preceded by breast cancer as the most common cause of cancer deaths in women worldwide [4].

2. Basic virology of HPV

HPV is a member of the Papovaviridae family. It is a relatively small, non-enveloped virus of about 55 nm diameter. It has an icosahedral capsid with 72 capsomers and these contain at least two capsid proteins, L1 and L2. Each capsomer is a pentamer of the major capsid protein, L1 [5]. Each virion capsid contains about 12 copies of the minor capsid protein, L2 [6]. The HPV genome consists of a single molecule of double-stranded, circular DNA [7] with all Open Reading Frame (ORF) protein-coding sequences confined to one strand. There are three functional regions in the genome (**Figure 1**) [8]: The first is a "non-coding upstream regulatory region" also referred to as the long control region (LCR), or the upper regulatory region (URR). This region contains the highest degree of variation in the viral genome and contains the p97 core promoter along with enhancer and silencer sequences that control ORFs transcription in the regulation of DNA replication [9]. The second is called the "early region (E)" and it consists of ORFs E1, E2, E4, E5, E6, and E7, which are involved in viral replication and tumorigenesis. The third is referred to as the "late region (L)" and this encodes the L1 and L2 ORFs for the viral capsid. The E6, E7, and L1 ORFs of a new or unknown HPV type should be 90% or less homologous to the corresponding sequences of known HPV types [10].
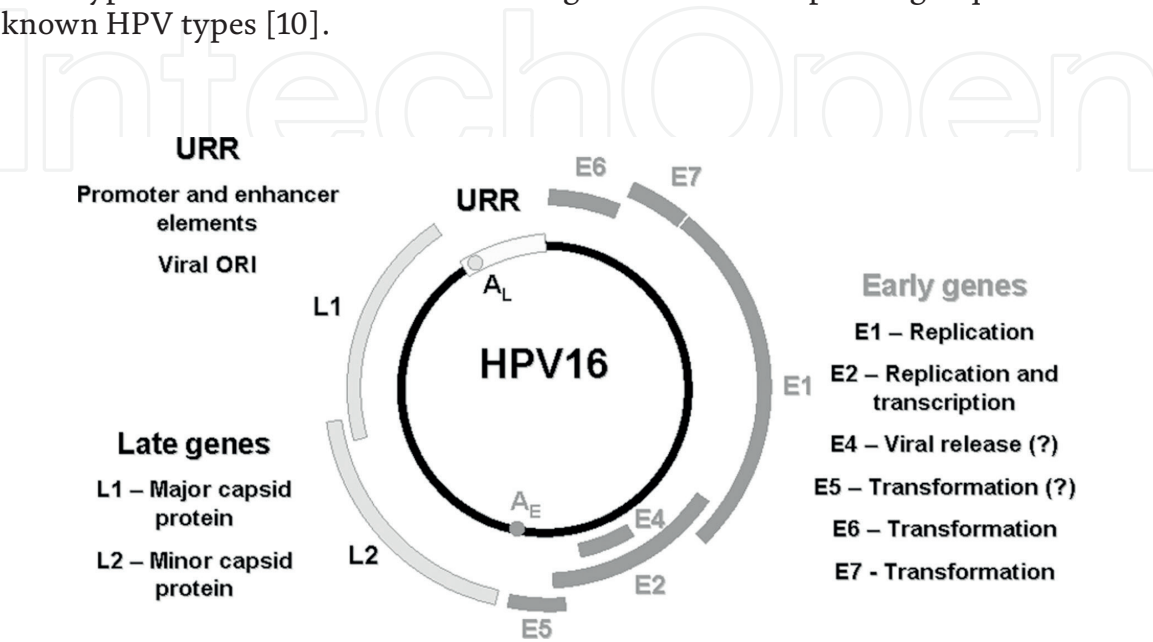

Figure 1.
Genome organization of HPV [9].

3. Epidemiology of genital HPV infection

The worldwide prevalence of high-risk HPV infection is 10.4% [11] and it can be as high as 36.5% in some developing countries [12, 13]. Several epidemiologic studies have clearly shown that the risk of contracting genital high-risk HPV infection and cervical cancer is influenced by sexual activity [14, 15]. An individual is at increased risk of having HPV infection if he or she has had multiple sexual partners at any time or if he or she has a partner who has had multiple sexual partners. Having sexual activity at an early age as well as having a history of other sexually transmitted infections, genital warts, or cervical or penile cancer in an individual or sexual partner may also increase the risk of becoming infected with HPV. In addition to sexual activity, age is an important determinant of the risk of HPV infection [16, 17]. The infection is most common among sexually active young women between the age of 18 and 30 years with a sharp decline in prevalence after the age of 30 years. Although, cervical cancer is more common in older women of 35 years and above, thus suggesting that the infection occurs at a younger age with a slow progression to cancer at an older age. Persistence of HPV infection is commoner with the high-risk or oncogenic types and this plays an important role in the development of invasive cancer of the cervix [1]. Cervical cancer arises at the transformation zone, which is the region between the squamous epithelium of the ectocervix and the columnar epithelium of the endocervix, where continuous metaplastic changes occur. The period of greatest metaplastic activity coincides with the greatest risk of HPV infection and this occurs at puberty and the first pregnancy and subsequently declines slowly after the occurrence of menopause.

4. Link between genital HPV infections and cervical cancer

In the past 3–4 decades, the natural history of cervical cancer has been well studied, and persistent infection of the cervix with certain types of HPV has been reported as a necessary causative factor for its occurrence [18]. The link between HPV and cervical squamous cell carcinoma has become well established since the early 1980. The magnitude of the association between HPV and squamous cell carcinoma of the cervix is higher than that for the association between smoking and lung cancer [19]. About 30 HPV types that are transmitted through sexual contact and infect primarily the cervix, vagina, vulva, penis, and anus have been identified. At least one of these HPV types has been implicated in 99.7% of cases of squamous cell carcinoma of the cervix [18]. HPV is a family of closely related viruses with each designated as a type based on their nucleic acid sequencing and then numbered in the order of discovery. More than 200 HPV types are known to exist [1, 20] with 15 types associated with cervical cancer. Genital HPV types can be grouped as high-risk (oncogenic) and low-risk (non-oncogenic) HPV types based on this association with cervical cancer and its precursor lesions. Low-risk or non-oncogenic HPV types include types 6, 11, 42, 43, and 44 while the high-risk or oncogenic HPV types include types 16, 18, 31, 33, 34, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 [18]. Low-risk subtypes are also occasionally found in cervical carcinomas. The virus usually infects the mucocutaneous epithelium and produces viral particles in matured epithelial cells and then causes a disruption in normal cell-cycle control and the promotion of uncontrolled cell division leading to the accumulation of genetic damage [20]. Adenocarcinomas of the cervix are also less commonly related to HPV infection and is age dependent [21]. Almost 90% of adenocarcinoma of the cervix in women younger than 40 years of age are related to HPV infection, whereas it was observed in only 43% of adenocarcinomas in those aged 60 years and older. Most

HPV-induced cervical changes are transient with 90% regressing spontaneously within 12–36 months [22–26]. However, various other factors such as the individual's genetic predisposition, genetic variation within different HPV type, coinfection with more than one type of HPV, frequency of reinfection, hormone levels, and immune response may alter an individual's ability to clear the infection. Therefore, detection of high-risk HPV is necessary but may not be enough for the development of cervical cancer. Whether a woman will develop cervical cancer depends on several factors that act in conjunction with oncogenic HPV types in a process that leads to cervical cancer. These factors or modifiers of HPV activities include:

4.1 Suppressed primary immune response

Immune response to HPV infection is cell mediated and thus conditions that impair cell-mediated responses such as renal transplantation or HIV disease increase the risk of acquisition and progression of HPV [10, 27, 28]. Studies have consistently shown higher prevalence of HPV infection and cervical cancer precursors in HIV infected women [29–31].

4.2 Long-term use of oral contraceptives

This is a significant risk factor for high-grade cervical disease according to some studies [16, 32]. This is because the upstream regulatory region of high-risk HPV contains sequences which are similar to the responsive elements of glucocorticoid that can be induced by steroid hormones such as progesterone which is the active component of oral contraceptives and dexamethasone.

4.3 Cigarette smoking

The suppression of local immune response induced by smoking and the mutagenic activity of tobacco components have been demonstrated in cervical cells and this may contribute to HPV persistence or to malignant changes in the cervix [33–35]. It appears that smoking is the most important risk factor independent of HPV infection for high grade cervical disease [16]. Smoking shows little or no relationship to low grade cervical disease [1].

4.4 Increasing parity

Having an increasing number of full-term pregnancies is a significant independent risk factor for persistent HPV infection and cervical cancer [36, 37]. The possible mechanisms proposed for this are the increased hormone levels and impaired immune response of pregnancies [38]. In multiparous women, the transformation zone remains longer on the ectocervix and this facilitates its direct exposure to the virus and other potential cofactors [39]. However, the most plausible mechanism is the local tissue damage occurring during vaginal childbirth or cellular oxidative stress with the increased likelihood of DNA damage and HPV integration [40, 41].

5. Prevention of HPV-associated cervical cancer

The natural history of cervical cancer offers unique opportunities for prevention of the disease [42]. Conventionally, Pap smear and liquid-based cytology, combined with treatment of cervical pre-cancerous lesions and early-stage cancer, has been successful in preventing up to 80% of invasive cervical cancer cases in

the developed world [43, 44]. Cervical cancer screening involves testing for HPV infection and cervical cancer precursor lesions among women who have no symptoms. When screening detects cervical pre-cancerous lesions, treatment can easily be instituted, and cancer avoided. Screening can also detect early stage cervical cancer at a time when treatment has a high potential for cure. Currently, primary approaches to HPV prevention include both risk reduction and development of vaccines again HPV. The risk of contracting HPV may be decreased with the use of latex condoms and spermicides. However, these are not totally reliable, since HPV infection may be transmitted through contact with other parts of the body, such as the external genitalia, or anus, that are not protected by a condom [1].

5.1 HPV testing

This is a laboratory test in which cells from the cervix are tested for DNA from certain types of HPV that are known to cause cervical cancer. This may be done alone (primary HPV screening) or in combination with cervical cytology (hybrid HPV screening). These 2 screening strategies are meant to minimize unnecessary follow-up visits and invasive procedures without compromising the detection of disease.

5.1.1 Hybrid screening

This test is usually done using the sample of cells removed during a Pap smear test or Liquid Based Cytology (LBC). It is done if the results of a Pap smear test show certain abnormal cervical cells (reflex testing). When both the HPV test and Pap test are done using cells from the sample removed during a Pap test, it is called a Pap Smear/ HPV co-testing. Large-scale studies to evaluate management options for women with abnormal Pap smear results have been conducted and these studies indicate the potential utility of HPV DNA testing in the management of women with Pap smear results of Atypical Squamous Cells of Undetermined significance (ASCUS) [45–47]. Based on the results of these studies, screening strategy options that include testing for high-risk HPV DNA as an adjunct to cytology have been developed to triage and monitor ASCUS patients. These improvements in cytologic screening through LBC as well as the introduction of HPV DNA testing greatly facilitate the identification of women at risk for cervical cancer. There are three recommended options in the management of women with ASCUS [47] and these include:

5.1.1.1 Repeat cervical cytology

In this approach, ASCUS patients would undergo cytology at 4 to 6-month intervals until two negative results are obtained after which the patient can be returned to routine cytologic screening. If any repeat cytology shows ASCUS or greater, referral to colposcopy is recommended.

5.1.1.2 Immediate colposcopy

If this is used, women with biopsy-confirmed CIN are treated as per standard protocol for management of cervical intraepithelial neoplasia (CIN) using excision or coagulation techniques. If biopsy is negative for CIN, patients will undergo repeat cytology at 12 months. In postmenopausal women who have ASCUS and clinical or cytologic evidence of atrophy, a 6-week course of intravaginal estrogen is recommended if there are no contraindications to estrogen use. A repeat cytology is performed after completion of the estrogen regimen and if this is negative, the test

is repeated in 4 to 6 months. If the repeat test shows ASCUS or greater, the patient is referred to colposcopy. Immunosuppressed women with ASCUS should be referred directly to colposcopy.

5.1.1.3 HPV DNA testing

This the most preferred approach especially if liquid-based cytology (LBC) is used or if specimens are co-collected for HPV DNA testing. If HPV DNA testing is negative for high-risk HPV types, the patient undergoes repeat cytology testing at 12 months. However, direct referral to colposcopy is recommended for women who test positive for any of the high-risk HPV types. If biopsy confirms CIN, patients are treated per standard protocol for management of CIN. If biopsy does not confirm CIN, then cytology should be repeated at 6 and 12 months with referral back to colposcopy if results show ASCUS or greater or repeat HPV DNA testing at 12 months with referral back to colposcopy if high-risk HPV types are detected.

5.1.2 Primary HPV screening

HPV DNA testing alone without a Pap smear test may also be used for screening in women aged 25 years and older [48, 49]. It is as effective as a hybrid screening strategy that uses cytology in women aged 25–29 years and co-testing in those at 30 years or older [49]. However, HPV primary screening requires less screening frequency (every 5 years). This involves direct referral to colposcopy for women who test positive for HPV types 16/18 and cytology for those who test positive for any of the other high-risk HPV types [50]. The International Agency for Research on Cancer (IARC) and the World Health Organization (WHO) have endorsed HPV testing as the primary screening method for cervical cancer. Several developed countries are now changing to HPV primary screening [50–52].

5.2 HPV vaccination

One of the major prevention strategies for cervical cancer is vaccination against HPV infection among adolescents prior to their first sexual exposure [15]. HPV vaccines are composed of virus-like particles (VLPs), which contains the major and minor HPV capsid antigens but lacking viral DNA. The vaccines are produced by expressing the L1 or L1 and L2 ORFs in eukaryotic cells. These proteins then self-assemble into VLPs which are highly immunogenic. There is no cross-protection among the HPV types due to the high level of antigenic specificity of HPV capsid antigens and thus protection against each HPV type requires vaccination with VLPs of that type. Optimal vaccines would contain a cocktail of VLPs of the most common high-risk HPV subtypes. There are currently 2 commonly used vaccines (Bivalent and Quadrivalent) which protect against both HPV 16 and 18, which are known to cause at least 70% of cervical cancers. In addition, the quadrivalent vaccine also protects against HPV types 6 and 11 which cause anogenital warts. Both vaccines are more effective if administered prior to exposure to HPV and thus, it is preferable to administer them before first sexual activity. The WHO recommends vaccination for girls aged 9–13 years as this is the most cost-effective public health measure against cervical cancer [1, 53, 54]. Some countries have started to vaccinate boys as the vaccination prevents genital cancers in males as well as females, and the quadrivalent vaccine also prevents genital warts in males and females. These vaccines may provide some cross-protection against other less common HPV types which cause invasive cervical cancer. At present, vaccination against HPV is not recommended as a replacement for cervical cancer screening and in countries where

the vaccine is introduced, cervical screenings still need to be developed or further strengthened [53]. However, in most developing countries, there is still a generally low level of awareness of the existence and availability of these HPV vaccines [55] compared to the developed countries with well-organized cervical cancer screening and HPV vaccination programs. Recently, a nonavalent vaccine against HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, which has shown a better impact compared to the bivalent and quadrivalent vaccine, has been approved by the US Food and Drug Administration (FDA) and is now commercially available [56].

Other recommended preventive interventions against HPV infections that are appropriate for both boys and girls are education about safe sexual practices including delayed onset of sexual activity; promotion and provision of condoms for those already engaged in sexual activity; male circumcision; and warnings about tobacco smoking.

5.3 Future perspectives

5.3.1 Measurement of HPV oncoprotein levels

Measuring the levels of HPV E6/E7 oncoproteins is now a potential biomarker for high-risk HPV infection and this may have a role in the future screening of women for high-risk HPV especially type 16 which accounts for more than 50% of all cervical cancer cases [57–59]. The E6/E7 oncoproteins are overexpressed after HPV invasion into the host cervical cells in the form of HPV DNA or viral integration into the host's genome and are closely related to the development of cervical cancers [60]. In a recent pilot study, HPV16 E6/E7 oncoprotein test has a satisfactory diagnostic value for cervical cancer screening and demonstrated a better sensitivity than cytological test and a better specificity than HPV DNA testing [61].

5.3.2 Therapeutic HPV vaccines

There are currently no approved therapeutic vaccines against HPV in humans. However, there are many recent studies that have generated promising vaccine candidates tested in clinical trials [62–64]. Despite the success of these vaccine candidates, there still remains the concern that conventional expression methods when fully developed might result in very expensive products [65, 66] that will be inaccessible to the resource-constraint countries who have the highest incidences of cervical cancer.

6. Executive summary/conclusions

Molecular and epidemiologic studies have solidified the association between high-risk strains of genital HPV and squamous cell carcinoma of the cervix. The incidence of cervical cancer and its associated mortality have declined in recent years, largely due to the widespread implementation of screening programs. Screening for cervical cancer remains an important public health and economic concern throughout the world. Large-scale studies to evaluate management options for women with abnormal Pap smear results have been conducted and these studies highlighted the potential utilization of HPV DNA testing in the management of women with ASCUS Pap smear results. From these studies, screening strategies that include testing for high-risk HPV DNA as an adjunct to cytology have been developed for the triage and surveillance of women with ASCUS. Several other studies, such as the ATHENA study [45], have also examined and confirmed the role of HPV

DNA testing as a primary screening for cervical precursor lesions. In addition to the changes in screening strategies, HPV 16 testing through measurement of HPV E6/E7 oncoprotein levels and effective therapeutic HPV vaccines that have the potential to contribute significantly to the control and prevention of cervical cancer are also currently being developed for future use.

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Conflict of interest

The author declared no conflict of interest.

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