# Human Papillomavirus in the Aetiology of Cervical Cancer: A Literature Review

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**ABSTRACT**

Human papillomavirus a double stranded non-enveloped DNA virus has been well established as a cause of cervical cancer since 1976 following the discovery of the nobel laureate Dr Herald Zur Hansen. This virus infect immature squamous epithelium at the squamocolumnal junction following usually a squamous metaplasia or erosion of the epithelium. This results in viral cytopathic changes which manifest cyologically and histologically as premalignant lesion of the cervix. These premalignant lesions eventully progress to become cancer. Several molecular methods has been used to detect human papillomavirus infection in the cervix. These include Polymerase chain reaction, immunohistochemistry, liquid hybridization, reverse hybridization and human papillomavirus mRNA detection. It is possible to prevent the infection through vaccination against human papillomavirus. Also the unpleasant consequences of persistent human papillomavirus infection of the cervix can be prevented through effective cervical cancer screening programme. Human papillomavirus is not just capable of infecting the cervical epithelium but capable of causing premalignant and eventual malignant transformation. Immunization of females before the debut of sexual intercourse and an effective cervical screening programmes would help in the eradication of cervical cancer.

**Keywords:** Human Papillomavirus, Cervical, Molecular, Aetiology

## INTRODUCTION

Human papillomavirus has been shown to be the most important aetiologic agent in the development of cervical carcinoma.[1, 2, 3]

Guiseppe Ciuffo in 1907, discovered that warts of skin and genitalia were associated with human papillomavirus infection.[4] Peyton Rous and colleague in 1934 demonstrated that HPV and tar together consistently induced squamous cell carcinoma. The sources of tar include cigarette smoking and smoke from coal or burning wood.[4] The famous Dr Harald Zur Hausen a German virologist and Mathias Durst in 1976, established that HPV was the aetiologic agent in cervical carcinoma. In 1983 Dr Harald Zur Hausen was able to isolate the HPV type 16 and in 1984 he isolated the HPV type 18.[5] This led to the development of the vaccine in 2006.[6] Since the discovery of HPV 16 and 18, several other high risk HPV types such as 51, 52, 56, 58, 59, 66, 68 33, 34, 35, 39, 45,70 and 31.[6,7]These HPV type virus with a high tendency of causing cervical cancer are referred to as high risk human papillomavirus.

These viruses infect immature squamous epithelial cells in the basal layer which could be easily found in areas of squamous metaplasia in the squamocolumnar junction or following erosion of the cervix.[2, 7] Ninety percent of those infected are cleared of the infection within two years.[2] When the infection persists it may result in atypical koilocytic changes in the cervical epithelium.[2, 8] At this stage, cervical intraepithelial neoplasia which is a premalignant lesion is said to have developed which could be detected with regular Papanicolaou smear screening. When cervical intraepithelial neoplasia is diagnosed, it could be managed/treated accordingly thus preventing its progression into invasive cervical cancer. Pap smear has been largely responsible for the decline in the incidence of cervical cancer worldwide.[9] Eighty percent of low grade squamous intraepithelial lesion (LSIL) and hundred percent of high grade squamous intraepithelial lesion (HSIL) are associated with high risk HPV infections.[2] About forty percent of those with high risk HPV infection would develop HSIL and of these, ten percent would progress to invasive cervical carcinoma within a period of ten years.[8]

A study by Louie et.al in 2009 stated the cervical cancer screening coverage in sub-Saharan Africa to be 0.4 to 20%.[10,11] Also studies have shown an increase in the proportion of adenocarcinoma of the cervix in many developed countries with organised cervical cancer screening programme.[9] If the cervical cancer screening programme becomes available in developing countries, eradicating cervical cancer would still be difficult since it is mainly cervical squamous cell carcinoma that could be readily prevented by Papanicolaou smear test.[9]

The approval of the 9-valent HPV vaccine by the US food and drug administration in Deceber 2014, has brought a lot of hope to the medical communitee. There is now a possibility of eliminating a significant proportion of cervical cancer worldwide. A study by Zhai and Tumban showed that the 9 –valent HPV vaccine would protect women against HPV types responsible for 90.9% of cervical cancers in Europe, 92% in North America, 86.5% in Australia, and

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89.9% worldwide.[10] The vaccine is composed of viral like proteins which are produced using recombinant technology. This vaccine is capable of stimulating the immune system against the human papillomavirus. Introducing this vaccine into the immunization programmes in every country, would make successful coverage feasible. It is expected that about that 89.9% of invasive cervical cancer could be prevented if this vaccine is incorporated into immunisation programmes of every country and administered to females from 9 years who had never been immunised before and are not sexually active.[2, 8]

## STRUCTURE OF THE VIRUS

The human papillomaviruses (HPV) have a diameter of 55nm and contain an 8kbps DNA genome. It is a non-enveloped viruses which possess icosahedral symmetry, 72 capsomeres and double-stranded DNA genome. The viral genome possess an early region which is involved in oncogenesis and the late region. The open reading frames include E1 to E8 (early region) and the late region which include L1 and L2.

## HOW HUMAN PAPILLOMAVIRUS CAUSE CERVICAL CANCER

The high risk oncogenic HPV is responsible for this malignant transformation in cervical epithelium. The virus infects immature squamous epithelium and integrates the DNA into the DNA of the cell. The HPV produce the E6 and E7 proteins which is responsible for the oncogenic process in the cervical epithelium.[8]

E6 Oncoprotein binds to p53 and stimulates ubiquitin - dependent proteolytic degradation of p53, thus interrupting the death pathway. E6 also up regulates telomerase, preventing replicative senescence. Also E7 binds to hypophosphorylated Rb protein, promoting its proteolytic degradation thus allowing E2F to freely stimulate transcription. E6 and E7 induce centromere duplication and genomic instability.[2,8] These two Oncoproteins promote deoxyribonucleic acid (DNA) synthesis and interrupt p53 mediated apoptosis or cell growth arrest in mutant cells. These effects of these Oncoproteins result in malignant transformation of cells. The integration of HPV virus into host DNA enables the expression of the genes in the HPV genome.[8,9]

HPV infections are sexually transmitted and commonly seen in young women.[2] Within 2 years of acquiring the infection it is usually cleared in most persons. Persistent infection by this oncogenic virus results in malignant transformation of the infected cells.[12] Persistent infection is associated with immunosuppression, multiple sexual partners, low socio-economic status, cigarette smoking and early debut of sexual intercourse.[8]

## CERVICAL SQUAMOUS INTRAEPITHELIAL LESIONS

Morphological changes characteristic of a given infecting virus can often be observed in the infected cell. The effects seen in virally infected cell cultures are well-known and are designated by the term “cytopathic effect” (CPE). These effects can also be exploited for diagnostic purposes.[13,14]

In cervical squamous intraepithelial lesion, there are obvious atypic changes in the epithelium but with no evidence of breach of the basement membrane. They are graded into two low grade squamous cervical intraepithelial lesion(LSIL), and high grade squamous intraepithelial lesion (HSIL).

## HUMAN PAPILLOMAVIRUS (HPV) VACCINATION

The HPV vaccine that has been produced following the isolation of the HPV type 16 and 18 by Prof Harald Zur Hausen is the HPV 16 and 18 vaccine.[5,6]

The vaccines are a recombinant vaccine composed of recombinant proteins which are viral like particles. There are three types of vaccine that has been developed against cervical cancer. These vaccines include include cervarix (bivalent vaccine), Gardasil (quadrivalent vaccine) and Gardasil 9 (9-valent vaccine).

Cervarix ingredients include insect cell and viral protein, water, aluminium hydroxide, sodium chloride and bacterial protein. It stimulates the production of anti-L1 immunoglobulins against HPV 16 and 18. It is recommended for females at 9 years and given at 0, one and six months.[12,15,16,17]

Gardasil protects against HPV types 6, 11, 16 and 18 infections. This is similar to Gardasil 9 the 9-valent HPV vaccine which protects against HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58. The vaccine ingredient include polysorbate 80, L- histidine, amorphous aluminium hydroxyphosphate sulfate adjuvant, sodium borate, sodium chloride, water and yeast protein. [12]

## DIAGNOSIS OF CERVICAL HUMAN PAPILLOMAVIRUS INFECTION

### Conventional cytology

The commonest method of detecting high risk HPV infection in the cervix is with Papanicolaou (Pap) smear. This method of diagnosing HPV infection was introduced in 1949 and named after George Papanicoloau before the cause of cervical cancer was discovered in 1976. This has helped reduce the incidence of cervical cancer significantly especially in countries with well organised cervical screening programme like the United States of America.[18,19,20] The cytopathic changes caused by high risk HPV infection in the cervical epithelial cells like those in the transformation zone can be detected using this tool.[2,18,19]

### Monolayer cytology

This is a known method of processing specimen for Papanicoloau smear. This method creates a uniform monolayer and prevents drying artefacts, removes contaminating mucus, bacteria, proteins, red blood cells and yeast. The two methods of liquid based cytology are thinprep and surepath system.

### Two computerised systems

AutoPap which have been approved for primary screening and rescreening and PapNet which have been approved for rescreening. In these systems, abnormal cells are displayed on the screen for review and analysis.

**Visual inspection with acetic acid**

This is done for patients with abnormal Pap smear. This involves the application of 3% acetic acid to the cervix and viewing the cervix with a colposcope. A biopsy is obtained from the acetowhite areas and the histology would show dysplasia or carcinoma.

**Immunohistochemical markers for human papillomavirus**

Various immunohistochemistry markers have been used for the detection of HPV infection. The markers include: Immunohistochemistry could be used to detect HPV type16 E7 oncoprotein or HPV type18 E7 oncoproteins and cyclin B1. The immunohistochemistry may involve the use of polyclonal or monoclonal immunoglobulins.[60]

**Reverse line probe hybridization assay**

This is a molecular method of detecting human papillomavirus. In this method extracted DNA is used to perform an SPF-10 Polymerase chain reaction using SPF-10 primers that target the 65 base pair region of the HPV $L_1$ open reading frame. This enable the amplification of at least 54 HPV types. A deoxyribonucleic acid (DNA) enzyme immunoassay (DEIA) is performed on the amplified PCR products, using a probe hybridization with a cocktail of conservative probes that can recognise at least 54 mucosal HPV genotype in a microtiter plate format for HPV DNA detection. The reverse primers contain biotin label at the 5' end, enabling the capture of the reverse strand into the streptavidin-coated microtiter plates. Captured amplimers are then denatured by alkaline treatment and detected by a defined cocktail of digoxigenin – labelled probes, allowing the detection of at least 54 HPV genotypes. The optical densities (OD450) are read on a microtiter plate reader and the samples are categorised as HPV DNA positive or negative. HPV DNA positive samples were subsequently analysed by $LiPA_{25,}$ a reverse hybridization line probe assay technique that detects 25 high-risk and low-risk HPV types. Specimens that are HPV DNA positive but did not hybridize with any of the 25 probes were coded as HPV type X (undetermined type). The SPF-10 amplimers were used to identify HPV genotype by reverse hybridization to the $LiPA_{25}$ genotyping strip. The Positive hybridization on the strips is visualized as a purple band by means of a precipitating colour substrate on the probe site.

**Liquid hybridization**

This is referred to as the Hybrid capture assay which have been widely studied but the Hybrid Capture II is now widely used. This method uses chemilumnescence detection to qualitatively detect the presence of HPV. [22]

## POLYMERASE CHAIN REACTION (PCR) FOR HPV DNA DETECTION

**General primer PCR:** The primer is able to amplify a broad spectrum of HPV subtypes in just one PCR amplification. MY09 and MY11 target a 450bp in the L1 ORF. GP5+/GP6+ primer target a region within that of the MY09 target.

## CONCLUSION

Human papillomavirus infection of the cervix is a big public health challenge. However the unpleasant long term consequences of the infection like cervical cancer could be prevented through public education, effective cervical cancer screening programme and the introduction of effective vaccination against the virus.

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