Role of Human Papilloma Virus Infection in Cancer of Cervix

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ABSTRACT

Worldwide the Cervical cancer is the second most common type of cancer. This type of cancer that begins in the cervix cells is a sexually transmitted disease. Genital infection having role also in cancer cervix like gonorrhea, herpes simplex virus (type 2) and syphilis.

A virus named human papillomavirus (HPV) causes this type of cancer, and it causes transformation in the cervix. The link between HPV infection of the cervix and the cancer is believed one of the significant scientific findings in the last three decades.

The transformation zone of the cervix is the most common site in which the cancer is related to it for unknown causes. This transformation zone that is located between different type of epithelium mainly in the oropharynx, cervix and anus has a close relationship to the infection by Human papilloma virus (HPV). Although it is expensive, the primary prevention by the vaccine stills the most effective method for cancer cervix. This vaccine is effective and safe.

INTRODUCTION

The cervical cancer was one of the most common causes of cancer death in the United States, the American Cancer Society's estimates about 12,990 new cases of cancer cervix cancer during 2016 and although estimates about 4,120 women will die from cervical cancer there. By the using the Pap test during the last 40 years, the cervical cancer death rate has gone down by more than Fifty percent.

RISK FACTORS OF CERVICAL CANCER

According to the literatures, several factors were mentioned as the causes for cancer cervix. The commonest cause is the infection by HPV, other less common causes and factors that have a relationship to the development of this cancer are:

- Early age at first pregnancy
- Sexual history (Early sexual intercourse-Increased frequency of vaginal intercourse- High number of vaginal sex partners- The risk of HPV carrier for the sexual partners- The age of the first sexually intercourse)
- Special Habits (Smoking habits and alcohol intake)
- Others (long-term oral contraceptive use, immunosuppression and genetic predisposition contribute to the development of cancer cervix).

ROLE OF SCREENING IN CERVICAL CANCER

The role of the screening program is to discover any changes in the cervix early. Most events of cancer cervix are diagnosed in the female less than 50 years old with approximately 20% of the cases diagnosed in the female more than 65 years old. Rarely, cancer cervix can develop in the female less than 20 years old.

A key benefit of HPV initial screening is the prospective and likelihood for the virus testing to elongate screening periods. The complexity of this virus screening is the organization and control of females who are encouraging for the virus testing and

constructiveness for cytology. The threat of prevailing illness in this female population is low, however, in more than six years; it is two times that of the tested group as the entire population of the potential population. The virus is a defined cancer, infectious factor that is STI oriented, and the prevalence has increased has augmented in globe throughout the preceding few years. It is reported that all-inclusive cervical screening strategies have prevented a corresponding stigma and prevalence of cervical cancer [1,2].

In 2012, the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology published Screening Guidelines for the Prevention and Early Detection of Cervical Cancer which considered as the standard by NCCN also **(Table 1)**.

Table 1. Screening guidelines for the prevention and early detection of cervical cancer.

Population	Page numbers	Recommended Screening Method	Management of Screen results	Comments
Aged <21 years	521-522	No screening		HPV testing should not be used for screening or management of ASC-US in this age group
Aged 21-29 years	522-523	Cytology alone every 3 years	HPV-positive ASC-US1 or cytology of LSIL or more severe: Refer to ASCCP guidelines2. Cytology negative or HPV-Negative ASC-US: Rescreen with Cytology in 3 years	HPV testing should not be used for screening in this age group
Aged 30-65 years	523-529	HPV and cytology "co-testing" every 5 years (preferred)	HPV-positive ASC-US or cytology of LSIL or more severe: Refer to ASCCP guidelines 2 HPV positive, cytology negative: Option 1: 12-mo follow-up with contesting Option 2: Test for HPV16/18 genotypes >If HPV16 or HPV16/18 positive: refer to colposcopy. >If HPV16 or HPV16/18 negative: 12 mo follow-up with co-testing. Co-test negative or HPV-negative ASC-US: Rescreen with co-testing in 5 years	Screening by HPV testing alone is not recommended for most clinical settings
		Cytology alone every 3 years (acceptable)	HPV-positive ASC-US or cytology of LSIL or more severe: Refer to ASCCP guidelines 2 Cytology negative or HPV-Negative ASC-US: Rescreen with Cytology in 3 years	
Aged >65 years	529-531	No screening following adequate negative prior screening		Women with a history of CIN2 or a more severe diagnosis should continue routine screening for at least 20 years
After Hysterectomy	531	No screening		Applies to women without a cervix and without a history of CIN2 or a more severe diagnosis in the past 20 years or cervical cancer ever
HPV vaccinated	531-533	Follow age-specific recommendations (same as unvaccinated women)		

ROLE OF HUMAN PAPILLOMAVIRUS (HPV) IN CERVICAL CANCER

Worldwide, the Human papillomavirus (HPV) is one of the most common causes of sexually transmitted disease in male and female. HPV is associated with different clinical conditions, including benign and malignant diseases.

Commonly HPV infection is transient and self-limiting, but sometimes, this infection persists and transform to high grade lesions then cancer. Through sexual contact, about 30 HPV types infect the genital tract. These genital HPV types infect mainly the cervix, vagina, vulva, penis and anus.

Based on cancer risk, these genital-type HPVs are divided into high and low-risk types. The Low-risk HPV types include types 6, 11, 42, 43, 44 and usually cause benign ano-genital warts.

High-risk HPV types include types 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and 70 and cause ano-genital cancer. HPV type 16, 18, 31 and 45 contributing for more than 90% of cancer cervix. HPV type 16 is the most often found, accounting for about 50% of the cancer cervix cases in the western countries. Although high risk of HPV types have been related to the development of different male and female genital cancers **(Table 2)**.

Table 2. Human papillomavirus types and clinical manifestations.

Clinical Manisfestation	HPV type[b]
Plantar warts	1, 2, 4, 63
Common warts	2, 1, 7, 4, 26, 27, 29, 41, 57, 65, 77, 3, 10, 28
Flat warts	3, 10, 26, 27, 28, 38, 41, 49, 75, 76
Other cutaneous lesions (e.g. epidermoid cysts, laryngeal carcinoma)	6, 11, 16, 30, 33, 36, 37, 38, 41, 48, 60, 72, 73
Epidermodysplasia verruciformis	2, 3, 10, 5, 8, 9, 12, 14, 15, 17, 19, 20, 21, 22, 23, 24, 25, 36, 37, 38, 47, 50
Recurrent respiratory papillomatosis	6, 11
Focal epithelial hyperplasia de Heck	13, 22
Conjuctival papillomas/carcinomas	6, 11, 16
Genital warts (condyloma acuminatum)	6, 11, 30, 42, 43, 45, 51, 54, 55, 70
Low-risk cervical intrapithelial neoplasia	6, 11, 16, 18, 31, 33, 42, 43, 44, 45, 51, 54, 55, 70
High-risk cervical intrapithelial neoplasia	16, 18, 6, 11, 31, 34, 33, 35, 39, 42, 44, 45, 51, 52, 56, 58, 66
Cervical carcinoma	16, 18, 31, 45, 33, 35, 39, 51, 52, 56, 58, 66, 68, 70
Other genital carcinomas (vagina, vulva, penis and anus)	16, 18, 31, 45, 33, 35, 39, 51, 52, 56, 58, 66, 68, 70

SIGNS AND SYMPTOMS

Many studies have demonstrated that the commonness of HPV comprises a blending of occurrences and constant or recurrent infections over a long period due to lack of clearance. The studies show that over 90% of new HPV contagions regress in half to one and half years and more continual contagion is a precondition for cervical intraepithelial neoplasia (CIN) [1]. The cancerous cells are created in the exo-cervix region, then cancer cervix grows in the transformation area where both endo-cervix and exo-cervix meet.

Under the microscope, the changes of cervical cells, both in pre-cancerous stage and in the cancerous stage can be seen [3]. The symptoms associated with these changing including: vaginal discharge, bleeding (Inter-menstrual, Post-coital, post menopause) and pain (lower abdominal, during intercourse).

PATHO-PHYSIOLOGY OF CANCER CERVIX AND VIRUS

The cancer cervix starts in the lower part of the uterus where cervix cells lie in the transformation zone. The development of cancer cervix occurred in 4 stages, in the 1st stage, the infection occurs in the epithelium in the cervical transformation zone in which they grow slowly in precancerous cells then changes to cancer cell which can visualize under the microscope. The 2nd stage includes the persistence of viral infection gradual progression of the infected epithelium to cervical pre-cancer. And finally, infection invades through the basement layer of the epithelium. In the first stage of sexual activity in young women's infected is common **(Figure 1)**.

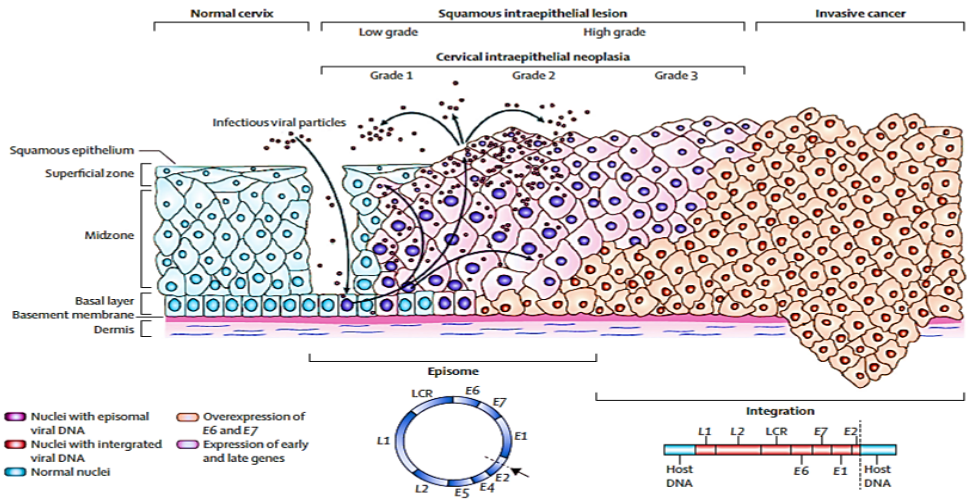

Figure 1. Human papillomavirus lifecycle and organization of its genome.

Kirti and Prabhakar [3] confirmed the above steps in which they explain that cancer cervix is the second most leading cancer type globally. The authors explain that cancer grows in four key phases (The first phase involves the infection in metaplastic epithelium within the cervical region; the second phase comprises of recurrent infection that gradually leads to the transformation of the stained epithelium to the cervical pre-cancer stage. The infection continues to invade and spread through the epithelium cellar layer). During the initial time of sexual intercourse in women infected, the rate of infection is widespread.

According to the authors, the CIN1 is a numb histopathological symptom of the virus infection, CIN2 comprises of a heterogeneous collection of lesions of varied potential, and CIN3 depicts the widespread medically pertinent lesions and has become the substitute endpoint for this type of cancer in vaccination and screening experiments [1].

Approximately 7-10 years is the median time taken for the cervical pre-cancer to transform to cancer cervix. The most common pathologic types of cancer cervix are adenocarcinoma and squamous cell cancer. Less common types include sarcoma, lymphoma and melanoma.

DIAGNOSTIC PROCEDURES

Papanicolaou (PAP) Smear

The aim of this test aims to detect potentially pre-cancerous changes, including cervical intraepithelial neoplasia (CIN) or cervical dysplasia; the squamous intraepithelial lesion system (SIL). It is the most common method for the diagnosis of cancer cervix.

It is carried out by opening the vaginal canal with a speculum (Ayer's spatula) which is used for taking the sample from the outer opening of the cervix at the transformation zone in which the outer squamous cervical cells meet the inner glandular endo-cervical cells and then, the sample is rinsed in the phosphate buffered saline (The pH of the buffer is 7.4) [4]. The collected cells are examined under a microscope for any abnormalities.

DNA Extraction

According to the standard protocol for DNA isolation, the cells are platted out from their natural form of exfoliated cells. After the formation of palleted cells they are re-inserted in tris-EDTA buffer and treated with 10 g/ml proteinase k and with 10% sodium dodecyl sulphate at 65 at for 1 hr. Quantity analysis of DNA was detected with spectrophotometric. For internal control, each sample performed β-actin with the help of polymerase chain reaction (PCR) technique [3].

PCR for HPV

Mainly it is carried to detect type 6, 11, 16, 18, 31 and 33. PCR applied on extracted DNA with the help of primer from consensus sequence, and the HPV genome with E1 open reading frame through staining. For this reaction, plasmid DNA for HPV type 6, 11, 16 and 18 is applied as a positive control [3].

PREVENTION

Even though many techniques for avoiding cervical cancer, the main prevention technique is through vaccination. Experts explain that the HPV vaccine is effective and safe [3]. HPV infection has been rated as the most widespread sexually transmitted infection (STI) globally, and people acquire it once in their lifetime. The virus is the most risk indicators to the cancer of the cervix [1].

The mainstream of HPV disease with cytological deformities cleared or compressed by cell immunity based on the exposure. Therefore, HPV commonness is equivalent to the commonness proliferate by time. The recurrence of the virus types is transformed because of their exposure and management and longer persistence increase the likelihood of high infection. The unchanging period involving an intern boosts the threat of pre-cancer, finding compared to the mean perseverance of HPV increased and prevalent virus infections detected throughout cross-sectional testing [4].

Primary screening experiments also known as triage test has experimented in various issues of placid to less severe abnormalities for diagnosis of increased lesions HPV responsiveness test preference [3].

The test is better than recurrent cytological experiment, but numerous researches suggested that compassion of virus test at a low rate of paradigm cytology in younger females [3]. Therefore, it is predictable that diverse strain of virus sensitivity experiments is implemented in cervical cancer concerning the diverse women group between 35 and 40 years.

The virus comes with the core of the cervical forms, then modifies usual cancer into cancerous cells and the growth is unconscionable and is low-risk aspect [3]. The pre-cancerous state changes into a cancerous cell in between 6 and 18 months. The moment a female is infected, the virus never manifests the features and the moment the pre-cancerous phase happens or transforms into the cancerous cell and then the signs start to manifest [3].

THERAPEUTIC VACCINES

Human papillomavirus is an ideal target for a therapeutic vaccine. Therapeutic vaccines targeting human papilloma virus E6 and E782–84 along with broadly targeting immunotherapies or peptides 85 are in clinical development. The rationale of these vaccines is to avoid the need for surgical procedures by developing immune responses specific to human papillomavirus.

In June 2006, Food and Drug Administration (FDA) approved the prophylactic quadrivalent HPV vaccine (GARDASIL, Merck and Co., Inc.), for use in women aged 9–26 years old [5].

The quadrivalent vaccine is composed of recombinant L1 protein-based viral like particles from HPV 6, 11, 16 and 18. Phase II and phase III studies have shown efficacy of 100% in preventing cervical dysplastic lesions in women aged 16–26 years, who were not infected by any of the vaccine HPV types. 47 Efficacy in women with simultaneous vaccine type HPV DNA positivity and sero-positivity was about 25%. The most common adverse effects were related to injection site pain (84 vs. 48.6% in treatment and placebo groups respectively). It is expected that the vaccines will achieve a lifetime risk reduction by 20–70% for cancer cervix in females aged 12 years old. The vaccine is typically given in three doses of 0.5 ml at 0, 2 and 6 months.

Subsequently, in October 2009, the prophylactic bivalent HPV vaccine (CERVARIX, GlaxoSmithKline) was approved for use in female aged 10–25 years old [6].

The bivalent vaccine contains recombinant L1 protein from HPV 16 and 18, and phase III study of 18, 644 females followed for 35 months showed efficacy of up to 93% in the prevention of CIN 2 lesions due to HPV 16 and 18. Similar to the quadrivalent vaccine, there was a higher rate of complications at the injection site. The dosage schedule is 0.5 ml at 0, 1–2 and 6 months for a total of three doses. New approaches to vaccine development may help in reducing and controlling HPV acquisition and transmission in the future [6].

CONCLUSION

The virus that is known to cause the disease is said to be harmless, though with persistent infections over a long time it causes pre-cancerous cells that if not cleared leads to cancerous cells. The process of the infection is in four stages with the first phase involving the infection within the cervical region; the second stage involves of persistent introduction to the virus strains and gradually leads to the change of the infected epithelium to cervical pre-cancer phase. The process continues and progresses to the cancerous stage if clearance is not done. The HPV infection has been ranked as the extensive STI globally, and most women get it once in a lifetime though it is not harmful. The virus affects cervical shape and then modifies the usual cells into cancerous cells and they continue to create high with persistent exposure. Early screening, testing, and vaccinations are the primary ways of preventing and controlling HPV and cancer cervix.

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