ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 9, Issue 3, 2016

Online - 2455-3891
Print - 0974-2441

Review Article

HUMAN PAPILLOMA VIRUS ASSOCIATED CERVICAL CANCER: A REVIEW

KIRTI, PRANAV KUMAR PRABHAKAR*

Department of Paramedical Sciences, Lovely Professional University,Phagwara, Punjab - 144 411, India. Email: pranav.16113@lpu.co.in

Received: 24 January 2016, Revised and Accepted: 25 February 2016

ABSTRACT

Globally, cervical cancer is the second most common cancer, and in India, it is the most common cancer in women. Human papilloma virus (HPV) is the main cause of it. Although there are several methods for preventing cervical cancer, primary prevention by vaccination is the most effective option. HPV vaccine is safe and effective. It is expensive and is not a replacement for periodic cervical screening procedures. In developing countries, the cost-effectiveness of the vaccine and that of effective screening program with broader coverage is questionable. Today, HPV vaccine with regular cervical cancer screening program is the best possible tool to prevent cervical cancer.

Keywords: Papilloma, Cervical, E6, E7, Cancer, Epithelium.

INTRODUCTION

Cervical cancer is the second most prominent type of cancer worldwide. It is a sexually transmitted disease but certain other types of infection causing agents such as some viruses mainly syphilis and gonorrhea, type 2 herpes simplex virus [1]. Cervical cancer develops in four major stages. First, the infection occurs in metaplastic epithelium at the cervical transformation zone, the second step includes 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 [2]. Mostly cervical cancer arises from the cervical transformation zone, but the reasons are not still cleared. Human papilloma virus (HPV) infection is responsible for causing cervical cancer particularly at the transformation zone that is located between different kinds of epithelium, namely anus, cervix, or oropharynx [3]. HPV is the most important risk factor leading to cervical cancer. It is a huge group consisting of 150 related viruses. Various types of HPV are responsible for causing's warts around the female and male genital organs; such types of viruses are called low-risk type of HPV. The other type of viruses that are linked to various cancer including cervix cancer, vaginal cancer in women, and cancer of penile in men, anus, mouth, and throat cancer in both men and women are called high-risk types [4]. On the basis of epidemiologic classification of HPV types (Munoz *et al.*), there are 150 types of HPV out of which high-risk types include 16, 18, 31, 33, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82. Moreover, low risk types include 6, 11, 40, 43, 44, 54, 61, 70, 72, 81, and CP 6108 [5]. The initiation of HPV infection is mostly asymptomatic [6]. HPV transmission occurs before to any clinically detected expression of the virus, basal cells of epithelium are infected by HPV [7]. Virions being shed from keratinocytes get accumulated into the nucleus. Then, there occur proliferation of the epithelial layer, except basal epithelium. The incubation period of virus requires from 3 to 4 months [8].

CERVICAL CANCER

Cervix cells lie in the lower part of the uterus where the cervical cancer starts. Initiations of the cervical cancer proceeds in the cells that lie in the transformation zone such cell are not indigently changed into cancerous cells. First, they slowly grow into precancerous cells that in turn changes to cancerous cells. The features of both cervical cancerous cells and cervical pre-cancerous cells can be best visualised under the microscope. Most of the cervical cancer possess the features of squamous cells while visualisation under a microscope. Such cancerous cells are formed from the cells that lie in the exocervix region. Cervical cancer develop in the transformation zone, its region where both exocervix and endocervix joint together. Usually, cervical cancer develops with precancerous changes but only a few women having precancerous of cervix regionare known to develop cancer. The time period required for cervical precancer together change into cervical cancer is of 7-10 years. Besides adenocarcinomas and squamous cells cancers, various other types of cancers have been known to develop in the cervical regions. These include sarcoma, lymphoma, and melanoma [9].

RISK FACTORS OF CERVICAL CANCER AND HPV

- Early sexual intercourse
- An increased number of vaginal sex partners
- Increased frequency of alcohol consumption
- Membership in a racial or ethnic minority group
- High frequency of vaginal sex
- Smoking habits
- Early age at first pregnancy
- The age at which sexually intercourse was initiated, and the likelihood that each of her sexual partners was an HPV carrier[10-12].

HPV

Over the millions of year, HPV has evolved along with the animal host. The life cycle of each genotype of HPV is closely bound to the differentiation of specific epithelial target. For example, sale of foot, non-genital skin, anogenital skin, anogenital, oropharyngeal mucosa to understand various relationship between HPV and genotype phylogenetic how been created that based on DNA sequence by protein homologies. At leads to understanding of HPV classification [13], 70% of cervical cancer and 50% of cervical intraepithelial neoplasia. Grade 3 [14] are caused by HPV types (16 and 18). Hence, HPV 16 is of higher importance for studying cervical cancers. In contrast of this 90% of genital warts occurs by HPV 6 and HPV 11. As shown in Fig. 1 about 8 genes [15] are codes by HPV, namely, E2, E2, E1, SP1, E2, E2, p97. E6, and E7 being the primary HPV once proteins [16-18]. Each gene contains the number of tumor suppression proteins among them P53 and Prb (retinoblastoma tumors suppression protein) are most important types. Inhibition of P33 by E6 blocks apoptosis and pRB inhibition by gene E7 abrogates cell cycle arrest [19].

HPV TRANSMISSION

There are various modes of HPV transmission anogenital HPV infections can be transmitted through skin to skin contact or through mucosa to mucosa contact [21,22] another ways of HPV transmission

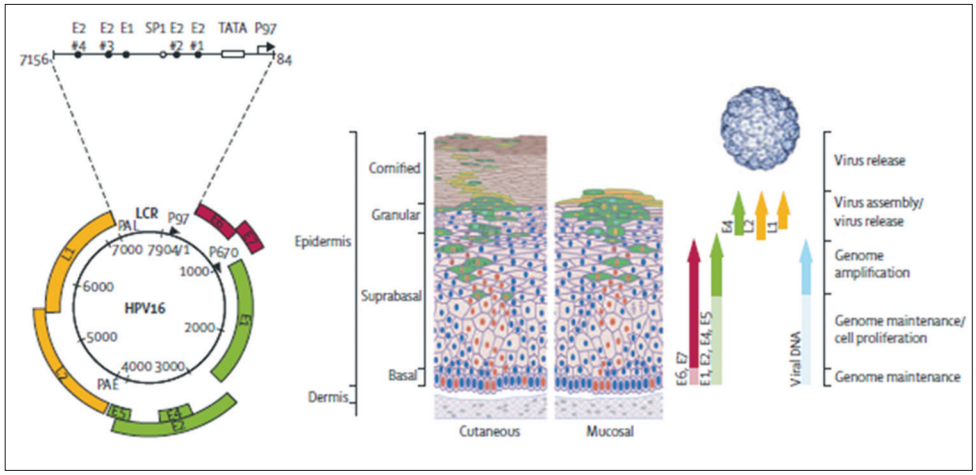

Fig. 1: In epithelium layer, the expression of human papilloma virus Genome [20]

is through sex, vaginal, anal or in oral sex [4]. Various types of HPV cause warts around female and male genital organs particularly in anal area. Such types of HPV are called low-risk types because they are rarely linked to cancer. High-risk types of HPV are strenuously linked to HPV cancers; these include cancer of cervical, vulva, and vagina in women, penile cancer in men, besides cancer of anus, mouth or through in both men and women [4]. Women during the course of their sexual life are infected at least one if not several ties of HPV [23]. Every year millions of women's HPV infections are being diagnosed [24]. As DNA detection is temporary and serology to being accurate, therefore, it is difficult to measure the total exposure of HPV [25]. All types of HPV are transmitted together [26,27]. Thus, resulting in high proportion of coincidental infections in the women's. Besides men are also the victims of several HPV types signaling that sexual act could transmit of several types of HPV [24]. Next stage of HPV infection is its passage into the germinal cells lying in the basal layer of mucosa [4]. HPV infection in males is decreased by male circumcision because of toughness of cretinized epithelium, therefore, reducing HPV transmission [28].

HPV CLEARANCE VERSUS PERSISTENCE

The majority of HPV infection with cytological abnormalities are either cleared or suppressed by cell-mediated immunity following the exposure of 2 years [29]. Thus, HPV prevalence is equal to the incidence multiply by duration. The persistence of HPV types is changed due to their detection and treatment. longer the HPV persistence lesser will be the probability of subsequent clearance or a fixed interval that intern increases the risk of pre-cancer diagnosis further the average persistence of HPV 61 can also be increased [30,31] prevalent HPV infections that are detected during cross-sectional screening persist to be longer. In older women rather than younger women because older women are more lightly to represent the infection that is of longer durations [32] the median time of HPV clearance is roughly about 16-18 months [29] but the infection could also proceed up to 2 years of duration, following the greater risk of temporary infections [33] up to the 10 years of data from cohort studies gives us the evidence that after HPV clearance the same HPV type have the chance to reappear [34].

SIGN AND SYMPTOMS

- Vaginal discharge
- Intermenstrual
- Postcoital bleeding
- Lower abdominal pain
- Bleeding after menopause
- Having (menstrual) periods that are longer or heavier than usual
- Pain during intercourse [4].

HPV TESTING

Primary screening test which is also called as triage test is done in certain cases of mild to moderate abnormalities [35,36] for detection of high-grade lesions HPV sensitivities test are more preferred [37-39] than repeated cytological test preferred than repeated cytological test but several studies have suggested that sensitivity of HPV test is lower than that of standard cytology in case of younger women's [40-44]. Thus, we can predict that different types of HPV sensitivity tests are done in cervical cancer based on the different age groups for, e.g. for women's above the ages (35-40 years). Specific HPV sensitivity tests are preferred and in contrast to this younger women's standard cytological tests are mostly preferred. Thus, we can say that specificities are age dependent [45-47].

DETECTION METHODS

For the detection of cervical cancer, we use some techniques.

Papanicolaou (PAP) smear

In the case of cervical cancer, there is a spatula named as Ayer's spatula which is used for taking the sample from cervix. We obtained cervical smear from the region of cervix. The tip of the spatula containing the sample from cervix. Then, the sample is rinsed in the phosphate buffered saline. The pH of the buffer is 7.4 [48].

DNA extraction

There is a standard protocol for this 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. Extraction of DNA is done by using of phenol chloroform is amyl alcohol mixture, and they precipitated with the help of isopropanol. Quantity analysis of DNA was detected with spectrophotometrically. For internal control, each sample performed β-actin with the help of polymerase chain reaction (PCR) technique.

PCR for HPV

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 [48] with E1 open reading frame through staining. The sequence of sense primer is use in 5'-TATGGCTATTCTGAAGTGGAA-3' and the antiprimer which is use in 5'-TTGATATACCTGTTCTAAACCA3'. The whole reaction is performed and in a volume of 20 µl that is containing 2 µl ×10 Taq buffer, 2 mM (Sigma, USA), 250 µM dNTP mix, 2.0 units Taq polymerase (Invitrogen, USA) and sterile distilled water. After that 3 microliter template of DNA is added in reaction. For this reaction, plasmid DNA for HPV type 6, 11, 16, and 18 is applied as a positive control. As per the understated protocol. The whole reaction with carried out in DNA thermal cycler.

At 94°C for 10 minutes the denaturation is completed for the first cycle for 38 cycles. The annealing at 46°C and extension at 72°C by the following of 1 minute each of denaturation at 94°C. The last step of cycle is carried out at 72°C for 10 minutes that should be extended after that electrophoresis process applied that amplified the protocol. Amplification is done in 1.5% agarose gel to visualize the amplified product of PCR the gel is stained with ethidium bromide, on a UV trans illumination, a 526-594 base pair band is visualized in HPV-positive sample.

Types of specific PCR for HPV 16 and 18

A pair of oligonuctidiprimer that was specific for consensus is used to subject the positive sample on PCR, spanning the E6 open reading frame of high-risk HPV types 16, 18, 31, and 33 [49]. Forward primer sequence used is 5'- TGTCAAAAACCGTTGTGTCC-3' and that of reversed primer is 5'-GAGCTGTCGCTTAATTGCTC-3'. After abstraction of positive sample they use subjected to type-specific PCR for HPV type 16 and 18 [49]. For HPV 16 type specific primer used to perform PCR. Forward primer sequence used is 5'-ATTAGTGAGTATAGACATTA-3'and that of reverse primer is 5'-GGCTTTTGACAGTTAATACA-3'. For HPV type 18Forward and reverse sequence primer used is 5'-ACTATGGCGCGCTTTGAGGA-3', with the help of 2% agarose gel. The product fragments are 109 base pairs and 334 base pairs, for HPV 16 and 18 are visualized. Forward and reverse sequence of HPV type 18 specific primers, is 5'-ACTATGGCGCGCTTTGAGGA-3' and 5'-GGTTTCTGGCACCGCAGGCA-3', respectively. The generated fragments of 109 bp and 334 bp for HPV 16 and 18, respectively and visualized on 2% agarose gels.

Vaccines

- Gardasil
- Cervarix.

Both vaccines are used in the national NHS cervical cancer vaccination programme. These vaccines protect against HPV both the medicine gives orally [4].

CONCLUSION

Cervical cancer is the most common cancer in women. The HPV is a virus which causes cervical cancer. HPV has more than 100 types from which 70 % causes cancer and 90% causes warts on the skin. There is 16 and 18 types of HPV which are high-risk factor for causing cervical cancer. HPV comes in the nucleus of the cervical cells then change the normal cervical cancer into cancerous cells. The growth of the cells is uncontrollable. Firstly it causes warts which are low risk factor [6,11]. It may change into cancer in months or years. When the women are infected with this virus never show the symptoms. When the pre-cancerous stage occurs or changes into cancer, and then the symptoms is shown. HPV infection begins in the basal layer. Where it shut off the early gene expressions, and formed L1 and L2 protein. When the high risk of HPV occur, and then the DNA of HPV is mixed into host DNA than expressed E6 and E7 protein which extend the life span of cells. Then, it develops into pre-cancer or cancer. No treatment for low-risk infection (warts), because no symptoms are shown during this period. But when it develops into pre-cancer or cancer, then we do any treatment because the symptoms of cervical cancer shown. If the symptoms are not shown then women never recognize that she is infected with cervical cancer. For the prevention of cervical cancer, women should examine PAP smear regularly so that if the women is infected with the virus the early stage can detect and it should be treated.

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