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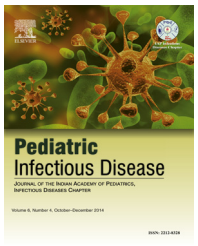

Immunization Update

Human papilloma virus and its relation to cervical cancer prevention strategies

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ABSTRACT

Human papilloma virus is the agent that is responsible for cervical cancer in women, that causes an overwhelming mortality in the developing countries. This is mainly due to the lack of effective screening programs. This DNA virus has over 200 serotypes, of which 18 are classified as oncogenic and 12 of these are high risk HPV prototypes. The time lag between infection and the progression to invasive cancer is almost 20 years. Pap smears are useful to screen women to pick up precancerous lesions. HPV DNA testing is more significant for detecting early changes in the cervix. Several factors increase the risk of developing cervical cancer, including multiparity, co infection with sexually transmitted diseases, smoking, and promiscuity. Vaccination provides a potent modality to improve the immunity to infection by the oncogenic types of HPV and thus reducing metaplastic changes in the cervix which ultimately undergo malignant transformation. This paper looks at the role of screening tests and the available vaccines and their efficacy in reducing the incidence of cervical cancer.

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1. Introduction

The human papilloma virus has been detected as the agent that is responsible for cervical cancer in women. Reports have given the estimated deaths due to this disease to be around 2,66,000 of the total number of 5,28,000 new cases that were reported in 2012.[1] Of these overwhelming numbers, 85% of the mortality occurs in the developing nations that do not have any screening programs nor is there easy accessibility to medical care. According to the WHO position paper 2009, the incidence of cervical cancer ranges for 1–50 per 1,00,000 females, with the highest rates reported in Latin America, Caribbean, sub-Saharan Africa, Melanasia and south central and Southeast Asia.[2] According to the American Cancer Society, almost all cases of CA cervix are related to infections by HPV and approximately 70% of the cases are caused by HPV types 16 and 18.[3] In the US, nearly 5,00,000 precancerous cases of Cervical intraepithelial neoplasia CIN 2 and CIN 3 are diagnosed annually and over half of them are attributed to types 16 and 18, while CIN1 may be related to other HPV types of which about 5% can be attributed to type 6 and 11.[3] These HPV viruses are also implicated in 40% of the cases of vulvar cancer, almost 80–90% of anal cancers and a variable proportion of penile, vaginal, urethral and head and neck cancers.[3] It has been found that the development of cervical

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cancer is closely related to the presence of human papilloma virus types 16 and 18, while types 6 and 11 co-relate with the development of benign lesions.[4] Latest reports have shown that a woman infected with a particular serotype, may be co infected or develop a subsequent infection with several serotypes that may also cause cervical lesions.[5]

2. The organism

The human papillomavirus belongs to the Papovaviridae family, which also includes others like polyomavirus and simian vacuolating virus.[6] It is a small non enveloped virus with an icosahedral capsid with at least 2 capsid proteins, L1 and L2.The HPV genome consists of a single molecule of double stranded circular DNA which is functionally divided into three regions. There are over 200 types of HPV that have been recognized so far, of which eighty five types have been well characterized.[6] The virus is organized into genera and species which is based on the presence of the L1 gene.[7] Most of the virus types that cause genital infection belong to the genus Alphapapillomavirus. Of all the viruses, there are 18 types that are classified as oncogenic and HPV 16 is the prototype of the A9 species, while HPV 18 is the prototype of the A7 species.[7] Of all the virus types, 12 of them have been defined as high risk HPV types and could be responsible for cancer.[5] These include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and additionally 68 and 73 for which the evidence of carcinogenicity is limited.

3. Pathogenesis

Stratifies squamous epithelium is invariably attacked and the virus lodges in the basal cells. The process of differentiation of the keratinocytes is linked to the viral replication.[7] Micro-trauma or microabrasions of the basal layers is adequate for viral attachment, which is aided by the presence of the epithelial receptor α_6-Integrin. This receptor is essential for the attachment of HPV-6, but is not a prerequisite for HPV-11 or HPV-33. The HPV-16 and HPV33 utilize the heparin sulfate present on the cell surface as the receptor for attachment.[6] Once inside, the HPV DNA replicates as the basal cells differentiate and progress to the surface as capsid proteins are synthesized and viral assembly occurs. The basal layer multiplication of the virus is considered to be non productive, and the viral DNA replication occurs once per cell cycle.

The normal host cell differentiation process is allowed to proceed until the appearance of a putative late promoter, which activates the capsid genes L1 and L2. What follows is rapid assembly of viral particles in the nucleus ad release of complete virions, as the cornified layers of the epithelium get shed. At this stage the viral genome is established throughout the entire thickness of the epithelium. Once the excessive viral cell proliferation is found in the basal layers, associated with a large number of mitoses which could be abnormal, it could be the predominant feature of premalignant and malignant disease. The structure and function of the E6 and E7 gene products determines the capability of the HPV virus to remain benign or to become a high risk type. The high risk HPV virus interferes with cell function and is responsible for up regulation of almost 178 genes and down-regulation of 150 genes.

The timeline required from infection with HPV to progress to invasive cancer takes approximately 20 years, though occasionally it may be more rapid.[3] This is the time lag that is essential for the genetic events, as well as the disruption of the host regulatory machinery that paves the way for the DNA damage.

4. Role of cytology for screening

The changes in cervical cytology that occur after infect with HPV virus has been well outlined and documented. This is put to use as an effective screening tool that could help to diagnose cases in the premalignant stages, so that effective treatment can be implemented with excellent patient outcomes. The method introduced by George Papanicolaou in 1949, even before the cause of cervical cancer was detected, continues to be used as the primary method for detection and screening even to this day.[7] This screening tool looks for changes that could occur in the transformation zone of the cervix and is usually linked to HPV infection. Changes that are noted in the Pap smear are classified using either the older CIN system or the later Bethesda system which has been updated several times, in 1991, 1999 and again in 2001. The latest version utilizes the newer cervical screening technologies, adjunctive molecular tests and lessons that have been learnt from legal proceedings, to produce the current version of the Bethesda System.[7] According to this, the squamous cell abnormalities are classified into four varieties: 1. ASC or atypical squamous cell. 2. LSIL or low grade squamous intraepithelial lesions. 3. HSIL or high grade intraepithelial lesions .4. The squamous cell carcinoma stage 4 is that of advanced disease, while the earlier stages, especially stage 1 and 2 are the ideal interventions points in order to reduce the incidence of full blown cancer of the cervix. Current concepts support the use of liquid based cytology technique which has proven to be useful in identifying few more cases of HSIL.[8] The current guidelines recommend the start of PAP smear testing within three years of the onset of sexual activity, in order to identify those who have higher risk of progressing to neoplasia. Women at high risk of attaining this stage include those with a prior history of HSIL lesions, women who are immunosuppressed for any reason like post renal transplant, and those who had been administered diethylstilboestrol before birth and remain at high risk of vaginal adenocarcinoma at any subsequent age.[8] The goal of all screening programs must be to pick up the true precancerous lesions, specifically the CIN 3and to some extent the CIN2 types.[8]

5. HPV DNA testing

The test for HPV DNA is considered to be more significant towards the detection of early changes in the cervix. The HPV DNA test is usually applied to the high risk HPV types, and is considered to be more sensitive for the detection of CIN 2 and CIN 3 types.[9] HPV DNA can be demonstrated in biopsy tissues using probes with radio isotopes or chemical ligands that can

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