Seroepidemiology of Human Papilloma Virus and HPV Vaccination in Cervical Cancer–Era of New Hope: A brief review of article

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Abstract

Most of the cervical cancer are caused by human papilloma virus (HPV), but risk associated with the various HPV types has not been adequately assessed. We searched literature from Pubmed, Embase and Medline with terms human papilloma virus, HPV, Cervical cancer, CIN and compiled data on seroepidemiological correlation of HPV in carcinoma cervix. There are 200 types of HPV viruses diagnosed by DNA sequencing. They are widely distributed through-out animal kingdom. It associates with various type of cervical lesion ranging from benign to malignant. The most common types observed among invasive cervical cancer cases were HPV 16 and HPV 18. This information is essential for planning prevention by HPV vaccines and for screening programs based on HPV testing.

Keywords: Human Papilloma virus, Cervicalcancer, Low risk, High risk, HPV vaccines

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Introduction

Papilloma virus tumorigenicity has been proven in animals. The epidemiologic suggestion of veneral transmission of an infectious agent involved in cervical cancer and molecular detection of papillomavirus DNAs in various human lesion, confirmed hypothesis of HPV involvement in genital cancer.[1] It associates with various type of disease ranging from benign to malignant. The incidence of HPV infection is increasing in trend. They are widely distributed throughout animal kingdom. There are 200 types of HPV viruses diagnosed by DNA sequencing.[2]

Aim

Seroepidemiology of HPV in cervical cancer and risk association with different types of HPV.

Material and Methods

We searched literature from Pubmed, Embase and Medline with terms human papilloma virus, HPV, Cervical cancer, CIN and thoroughly analyzed and summarized in this review article.

Review of Literature

Cervical cancer burden: Cervical cancer is the most commonly diagnosed cancer in women worldwide. There were 572,624 new cases of cervical cancer worldwide (4th most common cancer in women worldwide, accounting for 7.9% of all cancers in women apart from non-melanoma skin cancers. There were an estimated 265,672 deaths from cervical cancer worldwide (7.5% of the total number of cancer deaths in women, 4th most common cause of cancer-related deaths in women) in 2012.[3]

HPV Virology and Pathogenesis: The association between cervical cancer and HPV virus was first described by German virologist **Harold zurHausen**.[4] It is enveloped double strand DNA virus[5], HPV genome codes only for eight genes. Primary HPV oncoproteins are E6 and E7. These oncoproteins having various cellular target, HPVE6 mainly binds with p53 and inactivates it and increases the chance of cell survival by inhibiting apoptosis. Retinoblastoma (Rb) tumor suppressor gene is main target of E7 oncoprotein. Hence the inactivation of tumor suppressor gene in cells is central to cell transformation by HPV.

Sir Austin Bradford Hill proposed a general criteria[6] to establish causation between disease and environmental factor. Hill criteria are

1. Strength of association - how frequently a virus found in a tumor?
2. Consistency - has the association been observed repeatedly by different people in different place?
3. Specificity of association –is the virus or specific variant of virus uniquely associated with tumor?
4. Temporal relationship association –does virus infection precede tumor development?
5. Biologic gradient –is there a dose response relationship with virus load?
6. Biologic plausibility-is it biological feasible that virus could cause the tumor?
7. Experimental evidence –are there supporting laboratory results?

Seroepidemiolog has shown the association of cervical cancer and HPV fulfilled the Hill's criteria. The International Agency for Research on Cancer (IARC) concluded that four case–control studies in 1995 and sufficient evidence was collected to classify HPV types 16 and 18 as human carcinogens, but the evidence was limited or inadequate for other types.[7] Approximate 30 variants of HPV have been identified, that primarily infect cervix, vagina, vulva, and penis.

Priming step of pathogenesis is initiated by HPV infection of cervical epithelium during sexual intercourse. HPV exposure rate in sexually active women is very much high, but small proportion of them develop cervical cancer. Most of them successfully clear viral infection due to competent immune response.[8,9] The natural history of cervical cancer is a continuous process from CIN 1 to high-grade lesions (CIN 2/3) and finally invasive cancer. It usually associated with conversion of the viral genome to an integrated form from episome form, inactivation or deletion of the E2 region and expression of the E6/E7 product genes. Progression to malignant transformation generally takes place over a period of 10 to 20 years.[10]

Epidemiology of cervical cancer: Cervical cancer usually arises from cervical squamocolumnar junction between the columnar epithelium of the endocervix and the squamous epithelium of the ectocervix. In this transformation zone metaplastic changes is going on continuously. High ermetaplastic activity occurs during puberty and first pregnancy so the chances of HPV infection is higher during this period. High risk factors associated with HPV infection are multiple sexual partner, sexual activity at an early age, genital wart, history of STD, abnormal Pap smear, Age is also an important determinant factor. HPV infection is most common in sexually active young women age 18-30 years of age.[6]

High risk HPV alone is not responsible for development of cervical cancer. Various cofactors along with HPV infection are responsible for development of cervical cancer such as long term use oral contraceptive, smoking, coinfection with herpes simplex virus type 2 may play a role in the initiation of cervical cancer.[11] Cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), and HHV-7 have also been detected in the cervix. Coinfection offers the opportunity for these viruses to interact with HPV.

Both squamous cell carcinoma and adenocarcinoma are caused by HPV infection.[12] About 99.7% of cervical squamous cell cancer are associated with HPV infection worldwide.[13] Genital HPV types have been subdivided into low-risk types and high risk group. Genital warts are mainly associated with low risk HPV and high-risk types which are frequently associated with invasive cervical cancer.[6,14] Nubia Muñoz *et al*[15] collected data from 11 case–control studies from nine countries involving 1918 women with histologically confirmed squamous-cell cervical cancer and 1928 control women to evaluate epidemiologic and phylogenetic classifications of HPV types. (Table 1, 2) A recent meta-analysis reported an overall prevalence of HPV DNA in 89.7% of invasive cervical cancer cases from Eastern Asia. HPV types detected[16]. Various studies[17] have been established the HPV types and cervical lesion, shown in Table 3.

Table 1: Phylogenetic & Epidemiologic classification of HPV Types

Phylogenetic Classification	Epidemiologic Classification	
	High Risk	Low Risk
High Risk	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 82, 26, 53, 66	70
Low Risk	73	6, 11, 40, 42, 43, 44, 54, 61, 72, 81, CP6108

Source of data: [Adapted from reference: N. Munoz et al.[15].

Table 2: Prevalence of the most common HPV types in cervical cancer by region

Sub Saharan Africa		Northern Africa		South Asia		Europe & North America		Central South America	
HPV	%	HPV	%	HPV	%	HPV	%	HPV	%
16	47.7	16	67.6	16	52.5	16	69.7	16	57.0
18	19.1	18	17.0	18	25.7	18	14.6	18	12.6
45	15.0	45	5.6	45	7.9	45	9.0	31	7.4
33	3.2	33	4.0	52	3.4	31	4.5	45	6.8
58	3.2	31	3.4	58	3.0	56	2.2	33	4.3

Source of data: [Adapted from reference: N. Munoz et al.[15].

Table 3: HPV types and cervical lesion association[17]

Cervical Lesion	HPV Type
Condylomaacuminata (Genital Warts)	6, 11, 30, 42, 43, 45, 51, 54, 55, 70
Cervical intraepithelial neoplasia	30, 34, 39, 40, 53, 57, 59, 61, 62, 64, 66, 67, 68, 69
Unspecified	6, 11, 16, 18, 31, 33, 35, 42, 43, 44, 45, 51, 42, 74
Low risk	16, 18, 6, 11, 31, 34, 33, 35, 39, 42, 44, 45, 51, 52, 56, 58, 66
High risk	
Cervical carcinoma	16, 18, 31, 45, 33, 35, 39, 51

Human papilloma virus vaccination

Cervarix, Gardasil, and Gardasil 9 are approved by FDA for prevention of HPV infection in females ages 9 -26 years. These vaccines are very effective in prevention of infection but not very much efficient in established infection.[18] These vaccines provide protection against the two main HPV types (16 and 18) that cause about 70% of cervical cancers worldwide. These vaccine are more effective in Asia, Europe, and North America.[19]

Conclusion

Data from above literature showed the growing evidence of HPV as necessary causative agent in cervical cancer. High risk types 16, 18, 45, 31, 33, 52, 58, and 35 accounted for 95 percent of the squamous-cell carcinomas positive for HPV DNA. So an effective vaccine against the five most common HPV would prevent about 90 percent of the cases of cervical cancer worldwide. Cervical cancer screening and vaccination programed is in rudimentary phase in developing countries. HPV vaccination and regular cervical screening is the most effective way to prevent cervical cancer. These three approved cervical cancer vaccines against prevention of cervical cancer are providing new hope to fight against cervical cancer worldwide.

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