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# HPV Infection and Cervical Cancer-Key Statistics in India

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**Abstract—***Human Papillomavirus is a member of family papillomavirdiae. Cervical cancer is the third most common cancer among women worldwide. Cervical cancer ranks as the 2nd cause of female cancer in India. It is the 2nd most common female cancer in women aged 15 to 44 years in India. Worldwide, mortality rates of cervical cancer are substantially lower than incidence with a ratio of mortality to incidence to 50.3%. The majority of cases are squamous cell carcinoma followed by adenocarcinomas. Data on HPV role in anogenital cancers other than cervix are limited, but there is an increasing body of evidence strongly linking HPV DNA with cancers of anus, vulva, vagina, and penis. Although these cancers are much less frequent compared to cervical cancer, their association with HPV makes them potentially preventable and subject to similar preventative strategies as those for cervical cancer. HPV cervical infection results in cervical morphological lesions ranging from normalcy (cytologically normal women) to different stages of precancerous lesions (CIN-1, CIN-2, CIN-3/CIS) and invasive cervical cancer.*

**Keywords***: HPV; Pathogenesis and infectious cycle; Immune response; Classification of HPV; Causes of HPV; HPV vaccination.*

## 1. INTRODUCTION

Human papillomaviruses (HPVs) are small dsDNA tumor viruses, which are the etiologic agents of most cervical cancers and are associated with a growing percentage of oropharyngeal cancers. The HPV capsid is non-enveloped, having a T=7 icosahedral symmetry formed *via* the interaction among 72 pentamers of the major capsid protein, L1. The minor capsid protein L2 associates with L1 pentamers, although it is not known if each L1 pentamer contains a single L2 protein. The HPV life cycle strictly adheres to the host cell differentiation program, and as such, native HPV virions are only produced *in vivo* or in organotypic "raft" culture. Research producing synthetic papillomavirus particles—such as virus-like particles (VLPs), papillomavirus-based gene transfer vectors, known as pseudovirions (PsV), and papillomavirus genome-containing *quasi*virions (QV)—has bypassed the need for stratifying and differentiating host tissue in viral assembly and has allowed for the rapid analysis of HPV infectivity pathways, transmission, immunogenicity, and viral structure [1]. India has a population of 432.20 million women aged 15 years and older who are at risk of developing cervical cancer. Current estimates indicate that every year 122844 women are diagnosed with cervical cancer and 67477 die from the disease. Cervical cancer in India ranks as the 2nd most frequent cancer among women and the 2nd most frequent cancer among women between 15 and 44 years of age. Based on India studies performing HPV detection tests in cervical samples, about 5.0% of women in the general population are estimated to harbour cervical HPV-16/18 infection at a given time, and 82.7% of invasive cervical cancers are attributed to HPVs 16 or 18 [2].

Persistent infections caused by Human Papillomavirus (HPV) can result in cervical lesions and cervical cancer [3]. HPV is a nonenveloped virus with a circular double-stranded DNA [4]. This virus group belongs to the Papillomaviridae family, which comprises 29 genera and 189 Papillomaviruses (PV) [5]. To date, more than 120 HPV types have been identified and these can be divided into five genera: *Alphapapillomavirus* (Alpha), *Betapapillomavirus* (Beta), *Gammapapillomavirus* (Gamma), *Mupapillomavirus* (Mu), and *Nupapillomavirus* (Nu) [5, 6]. Among these, 40 HPV types infect the genital tract, 15 of which are considered to be High-Risk (HR) HPV(16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and82); sixspecies are considered Low-Risk(LR)HPV (6, 11, 42, 44, 51, 81, and 83) and three species are considered.

Intermediate Risk (IR) HPV (26, 53, 66) [7]. Treating patients with infectious diseases relies heavily on rapid and proper diagnosis. Molecular detection such as PCR has become increasingly important and efforts have been made to simplify these detection methods.

## 2. PREVALENCE OF CERVICAL CANCER IN INDIA

Cancer of the cervix uteri is the 4th most common cancer among women worldwide, with an estimated 527,624 new cases and 265,653 deaths in 2012. Worldwide, mortality rates

of cervical cancer are substantially lower than incidence with a ratio of mortality to incidence to 50.3% (GLOBOCAN 2012). The majority of cases are squamous cell carcinoma followed by adenocarcinomas. About 122,844 new cervical cancer cases are diagnosed annually in India (estimations for 2012). Cervical cancer ranks as the 2nd cause of female cancer in India. Cervical cancer is the 2nd most common female cancer in women aged 15 to 44 years in India [2].

**Table 1: Incidence of cervical cancer in India**

| Indicator | India | Southern Asia | World |
|---|---|---|---|
| Annual number of new cancer cases | 122,844 | 145,946 | 527,624 |
| Crude incidence rate[a] | 20.2 | 17.1 | 15.1 |
| Age-standardized incidence rate[a] | 22.0 | 19.3 | 14.0 |
| Cumulative risk (%) at 75 years old[b] | 2.4 | 2.1 | 1.4 |

[a] Rates per 100,000 women per year.

[b] Cumulative risk (incidence) is the probability or risk of individuals getting from the disease during ages 0-74 years. For cancer, it is expressed as the % of new born children who would be expected to develop from a particular cancer before the age of 75 if they had the rates of cancer observed in the period in the absence of competing causes.

Data sources:

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 15/01/2014.

Specific methodology for India: Incidence data is available from high quality regional (coverage lower than 10%). Data is included in Cancer incidence in Five Continents (CI5) volume IX and/or X. Incidence rates were estimated as the weighted average of the local rates. For more detailed methods of estimation please refer to http://globocan.iarc.fr/old/method/method.asp?country=356

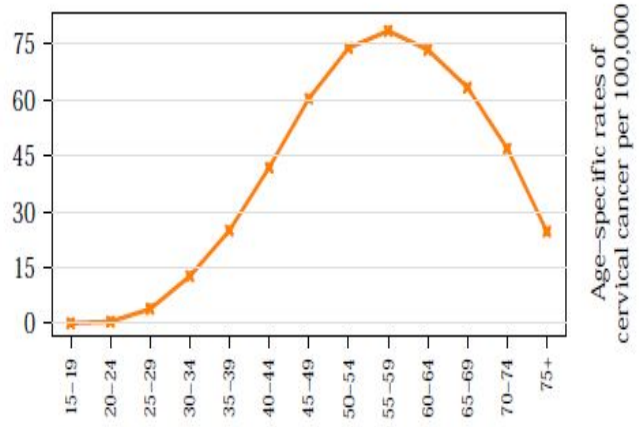



**Fig. 1: Annual number of cases and age-specific incidence rates of cervical cancer in India.**

Human papillomavirus (HPV) infection is now a well-established cause of cervical cancer and there is growing evidence of HPV being a relevant factor in other anogenital cancers (anus, vulva, vagina and penis) and head and neck cancers. HPV types 16 and 18 are responsible for about 70% of all cervical cancer cases worldwide. HPV vaccines that prevent against HPV 16 and 18 infection are now available and have the potential to reduce the incidence of cervical and other anogenital cancers. This report provides key information for India on cervical cancer, other anogenital cancers and head and neck cancers, HPV-related statistics, factors contributing to cervical cancer, cervical cancer screening practices, HPV vaccine introduction, and other relevant immunization indicators. The report is intended to strengthen the guidance for health policy implementation of primary and secondary cervical cancer prevention strategies in the country [2].

**Table 2: Percentatge distribution of microscopically verified cases of cervical cancer by histological type and cancer registry in India**

| Cancer registry | Period | Carcinoma | | | | Number of cases | |
|---|---|---|---|---|---|---|---|
| | | Squamous | Adeno | Other | Unspec. | MV cases | Total cases |
| Chennai | 1998-2002 | 92.6 | 2.8 | 1.2 | 2.6 | 2253 | 2550 |
| Karunagappally | 1998-2002 | 91.3 | 6.3 | 1.3 | 1.3 | 80 | 93 |
| Mumbai | 1998-2002 | 88.0 | 8.9 | 1.2 | 1.6 | 2731 | 3121 |
| Nagpur[a] | 1998-2002 | 93.1 | 4.7 | - | 0.3 | 722 | 741 |
| New Delhi[a] | 1998-2002 | 65.8 | 5.4 | - | 28.6 | 2965 | 3653 |
| Poona[a] | 1998-2002 | - | - | - | - | 1010 | 1138 |
| Trivandrum[a] | 1998-2002 | 87.4 | 6.1 | 2.3 | 2.7 | 261 | 284 |

Standardized rates have been estimated using the direct method and the World population as the references. Accumulated number of cases during the period. MV: Microscopically Verified.

a Data sources:

Curado, M. P., Edwards, B., Shin, H.R., Storm, H., Ferlay, J., Heanue, M. and Boyle, P., eds (2007). Cancer Incidence in Five Continents, Vol. IX. IARC Scientific Publications No. 160, Lyon, IARC.

Mortality from cervical cancer in India is about 67,477 new cervical cancer deaths annually. Cervical cancer ranks as the 2nd cause of female cancer deaths in India. Cervical cancer is the 2nd leading cause of cancer deaths in women aged 15 to 44 years in India.

**Table 3: Cervical cancer mortality in India**

| Indicator | India | Southern Asia | World |
|---|---|---|---|
| Annual number of deaths | 67,477 | 79,958 | 265,653 |
| Crude mortality rate[a] | 11.1 | 9.4 | 7.6 |
| Age-standardized mortality rate[a] | 12.4 | 11.0 | 6.8 |
| Cumulative risk (%) at 75 years old[b] | 1.4 | 1.2 | 0.8 |

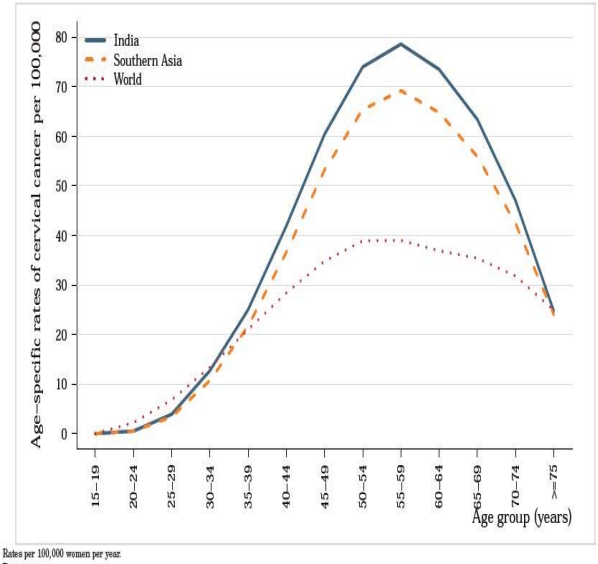
[a] Rates per 100,000 women per year.

[b] Cumulative risk (mortality) is the probability or risk of individuals dying from the disease during ages 0-74 years. For cancer, it is expressed as the % of new born children who would be expected to die from a particular cancer before the age of 75 if they had the rates of cancer observed in the period in the absence of competing causes.

Data sources:

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 15/01/2014.

Specific methodology for India: Mortality data is available from non-vital registration sources (cancer registries, verbal autopsy surveys etc.). Mortality rates were estimated from national incidence estimates by modelling, using country-specific survival. For more detailed methods of estimation please refer to http://globocan.iarc.fr/old/method/method.asp?country=356




Rates per 100,000 women per year.

Data sources:

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 15/01/2014.

**Fig. 2: Age-specific incidence rates of cervical cancer in India compared to Southern Asia in the World.**

## 3. GENOMIC ORGANIZATION OF HPV VIRUS

The HPV virus has a double stranded circular DNA genome of about approx. 8000 base pairs and a well defined physical structure and gene organization. Its genome is divided into three segments, a segment of about 4000bp that encodes mainly protein involved in viral DNA replication and cell transformation. A segment of about 3000bp encodes the structural protein of viral particles and a last segment of about 1000 bp that contains the origin of viral DNA replication and transcriptional regulatory elements [25]. The HPV genome consists of three functional coding regions, E-coding region for early viral function, L- coding region for late viral function and LCR- Long Control Region lies between E & L. The HPV virus has generally three domains: Non coding URR (Upstream Regulatory Region), ORFs- open reading frames and functions of these ORFs are given in Table -2 and Late gene regions (L1 and L2) [26]. The caspid contains 72 pentamers of L1 and 12 molecules of L2 [27]. The L1 region is the most conserved region of the HPV genome [28].

## 4. PATHOGENESIS AND INFECTIOUS CYCLE OF HPV

The life cycle of the HPV genome is completely dependent on the host keratinocyte basal cells, but the assembly of virus particles and viral capsid proteins are limited to terminally differentiated keratinocyte basal cells [29]. The initiation of infection by HPV occurs through micro-abrasions in the epithelial tissue, which triggers the entry of the HPV particles in the basal layer [30]. There are the two types of the dividing keratinocytes in the epidermis- slowly cycling undifferentiated stem cells and transit amplifying cells. These undifferentiated proliferating keratinocytes stem cells are the initial target for the productive HPV infection and then established a latent infection [31]. Some infected cells lose their contact with the basal layer and then integrates with the suprabasal region of the proliferating cells, where they form latently infected proliferating cell population [32, 33]. The successful infection of the HPV virus in keratinocytes involves the initial amplification of papillomavirus DNA copy number [34]. Thisstep is then followed by the stable maintenance phase of the HPV genome per cell. The final step involves the vegetative amplification of viral DNA [35]. The entry of the HPV DNA into the cell assists the expression of the two early proteins of E1 and E2 [36]. E1 and E2 encode proteins responsible for extrachromosomal DNA replication and completion of viral life cycle. The E2 is a DNA binding protein, which makes E1 as the origin of replication and encodes two proteins one stops the transcription of early region while another promotes the transcription of early region [37].

## 5. CONCLUSION

The HPV virus is most common sexually transmitted virus. This review summarizes the epidemiology, natural history and vaccination trial study of HPV virus. In contrast to the clinical application, highly sensitive and reproducible assays, which assess the large spectrum of HPV genotypes, are required. The aim of this review is to obtain maximum information about the HPV status in a population and then monitor the course of infection in detail. Molecular diagnostic methods can prove as better diagnostic and treatment plans for patients.

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