Cancer cervix: Epidemiology and disease burden

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INTRODUCTION
Cervical cancer is the fourth most common cancer affecting women worldwide, after breast, colorectal, and lung cancers, with 569,847 new cases every year. It is also the fourth most common cause of cancer death (311,365 deaths in 2018) in women worldwide. Globally, one in 70 women developed cervical cancer between birth and age 79 years.\(^{[1,2]}\)

Almost 70% of the global burden falls in areas with lower levels of development. India contributed 28% of cervical cancer mortality burden with 87,090 deaths due to cervical cancer, the second most populous country in the world.\(^{[1,2]}\)

It is the second most commonly diagnosed cancer and third leading cause of cancer death among females in less developed countries.\(^{[3]}\) The age standardized incidence rates (ASIRs) and age standardized death rates (ASDRs) per 100,000 in 2013 were higher in developing countries versus developed countries (ASIR, 15.70 vs. 9.58; ASDR, 8.32 vs. 3.96).\(^{[4]}\)

Incidence rates are highest in sub-Saharan Africa, Latin America and the Caribbean, and Melanesia and lowest in Western Asia, Australia/New Zealand, and Northern America.\(^{[3]}\) In 2013, incidence rates per 100,000 were the lowest in Australasia (ASIR, 6.83; ASDR, 2.65), North Africa and Middle East (ASIR, 7.23; ASDR, 3.19) and high-income North America (ASIR, 7.26; ASDR, 2.84), and the highest in Oceania (ASIR, 58.4; ASDR, 26.49), eastern sub-Saharan Africa (ASIR, 31.5; ASDR, 25.57), and western sub-Saharan Africa (ASIR, 30.2; ASDR, 22.3).\(^{[2]}\)

The large geographic variation in cervical cancer rates can be explained by lack of access to effective screening in public health care settings and further to services that facilitate early detection and treatment in less developed regions of the world. Non-existent or inadequate screening and limited access to the standard treatment options that are often unaffordable has led to majority cases being detected in the advanced stages of the disease in these regions.\(^{[5]}\)

TIME TRENDS IN CERVICAL CANCER
In several western countries, where organized cytology based screening programs have long been established, cervical cancer rates have decreased by as much as 65% over the past four decades. In Norway, cervical cancer incidence rates decreased from 18.7 per 100,000 in 1970 to 9.6 per 100,000 in 2011.\(^{[6]}\)

In Finland, cervical cancer incidence rates decreased from 21.1 in 1966 to 7.3 in 2007.\(^{[7]}\) Rates have also decreased in high-risk areas, including China, Taiwan, Korea, in part due to improved screening activities and socioeconomic conditions,\(^{[8-12]}\) although the decreases in proportionate terms were much smaller compared with those in western countries.

National Cancer Registry Programme established under the Indian Council for Medical Research (ICMR) represents the government supported population based cancer registry (PBCR) network across major cities and regions within the country which collects the vital information to project the magnitude, trends and patterns of cancer in the country. Cervix cancer incidence shows wide variations across India with Aizawl PBCR, North East India (24.3) registering the highest Age Adjusted Incidence Rate followed by Barshi, Maharashtra (19.5) and Bengaluru (18.9).\(^{[13]}\)

In an ICMR led study (1990–2003) and an another linear Regression model study (1982–2003) that evaluated trends in cervical cancer for cervix, showed decreasing trend in the age adjusted incidence rate for cervical cancer in all PBCRs except rural PBCR of Barshi in western Maharashtra. The registry of Bangalore and Delhi showed more than 2% mean annual percentage (MAPC%) change, whereas for the rest of...
the registries an MAPC of 1-2% was observed for cervical cancers in the ICMR study.[14,15]

In the recent PBCR report on time trends in cancer incidence rates for 1982–2010, India, all the urban PBCRs at Bangalore (annual percentage change [APC]: –2.0%), Bhopal (–1.3%), Chennai (–3.5%), Delhi (–3.0%), and Mumbai (–1.8%) including the rural PBCR of Barshi (-2.4%) reflected a negative APC for cervical cancer showing statistically significant decrease in incidence rates of cervical cancer.[13,14]

This could be reflective of the socioeconomic development of the regions, with improved access to genital hygiene since none of the registry areas had an organized cervical cancer screening programs in the region.

In contrast to the favorable trends reported above, cervical cancer rates have been increasing among younger generations in several countries, including Finland, the United Kingdom, Denmark, and China.[17] This unfavorable trend is thought to reflect increases in HPV prevalence from changing sexual behaviors.[11,14-18] The exceptionally low overall cervical cancer rates in the Middle East and other parts of the developing world are thought to reflect low prevalence of HPV infections due to societal disapproval of extramarital sexual activity.[19]

**EPIDEMIOLOGY OF HUMAN PAPILOMA VIRUS IN CERVICAL CANCER**

HPV infection is a sexually transmitted disease. Infection with high-risk HPV infection (hrHPV) is now viewed as a necessary preconditon for the development of all cervical cancer and precancerous intraepithelial lesions and is one of the most common sexually transmitted infections worldwide.[20]

Persistent infection with about 15 hrHPV types is the major risk factor for cervical cancer, with HPV-16 and HPV-18 infections accounting for about 70% of the total cases.[21] In a pooled analysis of 11 case–control studies, HPV Types 16, 18, 45, 31, 33, 52, 58, and 35 accounted for 95 percent of the squamous-­cell carcinomas positive for HPV DNA.[12]

Human papillomavirus (HPV) 16 constitutes for approximately more than one half of cervical cancers. Concurrent multiple (type) infections are common and more than one fourth of the HPV infections that occur constitutes multiple HPV types.[22] Progression of HPV infection to cervical cancer occurs through successive steps from HPV transmission, viral persistence, progression of these persistently infected cells to precancer and invasion.[15]

**RISK FACTORS FOR HPV INFECTION AND CARCINOGENESIS**

Several risk factors for contracting HPV infection and its further progress to cervical carcinogenesis has been established. High parity, long-term use of oral contraceptive pills, tobacco consumption, co-infection with other sexually transmitted agents, lifestyle factors such as multiple sexual partners, younger age at first sexual intercourse, immunosuppression, and diet have been identified as the co-factors most likely to influence the risk of acquisition and progression from cervical HPV infection to high grade cervical precancers to invasive cancers.[24,35]

International Agency for Research on Cancer (IARC) pooled analysis suggest that genital HSV-2 infection may act in conjunction with HPV infection to modestly increase the risk of invasive cervical cancer, required the effect been likely to be mediated by the induction of inflammatory responses. A two-fold increased risk for the presence of antibodies to Chlamidia trachomatis (OR_/2.1; 95% CI, 1.1_/4.0) was also demonstrated[26,27] high parity has been associated with cervical carcinogenesis in many case control studies. In the IARC-pooled analysis for the role of parity, the risk increased linearly with an increasing number of full term pregnancies.[28]

High parity is known to increase the risk of cervical cancer since parity and pregnancy associated hormonal changes maintains the transformation zone on the ectocervix for longer durations facilitating the direct exposure to HPV and to other co-factors.[29] Pregnancy induced hormonal changes are also likely to influence the immune response to HPV infection, persistence, and progression.[28,30]

The strongest evidence for a role of OC use in HPV carcinogenesis derives from the large pooled analysis of the IARC studies. The study demonstrated a strong dose–response relationship with increasing years of use.[31] OC induced hormone related mechanisms have been reported to affect the progression from premalignant to malignant cervical lesions most likely due to promoting integration of HPV DNA into the host genome and thereby resulting in deregulation of E6 and E7 expression.[25,32]

Effects of tobacco smoking have been reported in many case control studies. Consistent increased risk of cervical cancer with increasing exposure to tobacco smoking was established in relation to intensity and duration of smoking.[25,33] Nicotine and tobacco specific carcinogens have been detected in the cervical mucus of smokers pointing towards the likely effect of tobacco related carcinogens exerting a direct mitogenic effect causing DNA damage and aiding the development of cervical precancer and cancer.[34,35]

Another prospective study has also shown evidence to the fact that smokers maintain cervical HPV infections for significantly longer durations and take longer time to clear an oncogenic infection than women who never smoked.[36] Exposure to tobacco is hypothesized to compromise effective host local immune response against viral infections, since tobacco smoking has been shown to reduce the number of Langerhans’ cells and other markers of immune function.[37]
Other possible factors include diet, in particular diets poor in fruits and vegetables. An international expert panel and a recent systematic review have provided conclusive evidence that diets high in vegetables and fruits, carotenoids, Vitamin C and Vitamin E were possibly protective and that folate and retinol possibly had no relationship with invasive cervical cancer.

Infection by HIV constitutes a risk factor for infection as well as for neoplastic progression, in particular during the immunsuppression periods. HIV-positive women have consistently been shown to be at increased risk of cervical pre-malignant lesions when compared with their HIV-negative counterparts, association being stronger for women with low CD4/T-lymphocyte count. Women infected with both HIV and HPV were also found to be at a much higher risk of premalignant cervical lesions than women infected with either of the two viruses separately. A meta-analysis investigating the association of genital HPV infection and HIV acquisition showed overall, individuals with genital HPV infection, irrespective of the oncogenic HPV type, had twice the risk of acquiring HIV (OR, 1.96; 95% CI, 1.55–2.49).

Unpublished data from the IARC series of case-control studies showed that associations between various cofactors and cervical carcinogenesis are not modified by specific genotypes.

HPV viral cofactors such as the viral type, the persistence of the infection, the viral load per cellular unit, as well as the integration of the viral DNA into the cellular DNA are other major determinants of progression to cervical precancers and invasive cancers. Most cervical HPV infections though are transient and cleared by cell-mediated immunity within 1–2 years of exposure. The median time to clearance of HPV infections is 6–18 months. There is no defined period for determining persistence of the HPV infection however infections lasting more than about 1–2 years are likely to pose greater risk for progression to premalignant and malignant cervical disease.

The detailed natural history and pathogenesis will be discussed in the chapters ahead.

**BURDEN OF CERVICAL HPV INFECTION AND TYPE DISTRIBUTION**

In a five continents meta-analysis among women with normal cytology findings, HPV infection prevalence (all types) varied widely, from as high as 21% in Africa and 16% in Latin America and the Caribbean to 9% in Asia and 5% in Northern America.

Overall, HPV prevalence in women with normal cervical cytology was estimated to be 10.4% (95% CI 10.2–10.7). The five most common HPV types in HPV-positive women worldwide were HPV16, HPV18, HPV31, HPV58, and HPV52, representing 50% of all HPV infections. HPV16, HPV18, and HPV31, respectively, were the three most common types in studies using MY09/11, GP5+6+, and other PCR primers. HPV16 was observed with a prevalence of 2.5% followed by 0.9% for HPV18.

In all world regions, HPV prevalence was highest in women younger than 35 years of age, declining to a plateau in middle age. In Africa, the Americas, and Europe, a clear second peak of HPV prevalence was observed in women aged 45 years or older. At the ages of peak sexual activity, the prevalence of HPV infections in the female population is estimated around 40%, with an annual infection rate of 10–15%. The prevalence decreases after the age of 30 years to around 5–10%. The infections by HPV 16 are those that present the most prolonged longevities with average persistence values of 16 months in some studies.

World HPV prevalence for most common five top hrHPV types among women with normal cytology findings worldwide were reported to be HPV 16: 55.4 (95% CI; 55.0–55.8), HPV 18: 14.6 (95% CI; 14.3–14.9), HPV 45: 4.8 (95% CI; 4.6–5.0), HPV 33: 4.2 (95% CI; 4.1–4.4), HPV 58: 3.8 (95% CI; 3.7–4.0), and HPV 31: 3.5 (95% CI; 3.4–3.7), respectively.

Based on Indian studies performing HPV detection tests among normal women, about 5.0% of women in the general population are estimated to harbor cervical hrHPV infection at a given time and 82.7% of invasive cervical cancers are attributed to HPVs 16 or 18. The prevalence (%) of HPV 16 and/or HPV 18 among women with low-grade cervical lesions (LSIL/CIN-1) was 28.2% and, with high-grade cervical lesions (HSIL/CIN-2/CIN-3/CIS) was 62.8%.

Epidemiological studies with HPV typing have estimated HPV-16/18 to account for 70% of all cervical cancers worldwide. The HPV-16/18 fraction is reported to be slightly higher in more developed (72–77%) than in less developed (65–72%) regions.

The reported HPV-16/18 fraction in various squamous intraepithelial lesions is about 41–67% in high-grade squamous intraepithelial lesion (HSIL), 16–32% in low-grade squamous intraepithelial lesion (LSIL) and 6–27% in atypical squamous cells of undetermined significance. After HPV-16/18, the six most common HPV types were found to be the same in all world regions, namely 31, 33, 35, 45, 52 and 58 and these account for an additional 20% of cervical cancers worldwide.

HPV16 and HPV18 were consistently the two most common types identified in each decade and showed a stable adjusted relative contribution (RC) from 1940 to 2007. The RC of other HPV types too did not show variation over time.
CONCLUSION

Incidence and mortality due to cervical cancer remains a major public health problem globally despite decreasing trends observed in some developed regions of the world. Capturing variations in the cervical cancer epidemiological patterns and tracking changing trends will provide valuable information for the assessment of progress and challenges in disease control and further guide effective prevention and control measures that will facilitate the elimination of cervical cancer.

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ABBREVIATIONS IN ALPHABETICAL ORDER

hrHPV – High-risk human papillomavirus
ASIRs – Age standardized incidence rates
ASDRs – Age standardized death rates
NCRP – National cancer registry programme
PBCR – Population based cancer registry
IARC – International agency for research on cancer
ASCUS – Atypical squamous cells of undetermined significance
LSIL – Low-grade cervical lesions
HSIL – High-grade cervical lesions
CIN – Cervical intraepithelial neoplasia.

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