CHAPTER

1

Epidemiology of Cervical Cancer

A Public Health Problem, Barriers and Challenges, WHO Elimination Call 2030

INTRODUCTION

Globally, noncommunicable diseases (NCDs) accounted for 71% of total deaths. In India, NCDs were estimated to account for 63% of all deaths, and cancer was one of the leading causes (9%).[1] Cancer registries are recognized as vital components of national cancer control programs.[2]

In India, the systematic collection of data on cancer has been performed since 1982 by the population-based cancer registries (PBCRs) and hospital-based cancer registries (HBCRs) under the National Cancer Registry Programme (NCRP)–National Centre for Disease Informatics and Research (NCDIR) of the Indian Council of Medical Research (ICMR; ICMR-NCDIR-NCRP), Bengaluru.

Cervical cancer is a leading cause of mortality among women. In 2020, an estimated 604,000 women were diagnosed with cervical cancer worldwide and about 342,000 women died from the disease. Cervical cancer is the most commonly diagnosed cancer in 23 countries and is the leading cause of cancer death in 36 countries. The vast majority of these countries are in sub-Saharan Africa, Melanesia, South America, and South-Eastern Asia.[3]

It is the one of the leading causes of cancer mortality, accounting for 17% of all cancer deaths among women aged between 30 and 69 years. It is estimated that cervical cancer will occur in approximately 1 in 53 Indian women during their lifetime compared with 1 in 100 women in more developed regions of the world.[4]

The 5-year relative survival rate for cancer cervix in India has been reported to be approximately 46% (34–60),[5] which much lesser than survival rates reported from other Asian countries such as China, South Korea, Singapore, and Thailand . In addition, cervical cancer survival rates in India also shows a wide variation ranging from 59.6% in Chennai to 34.5% in Bhopal. The 5-year age-standardized relative survival of cervical cancer for different Indian registries and its comparison with other Asian registries are shown in the **Table 1.1**.[5,6]

As per the GLOBOCAN 2018 in India new cases annually reported are 96,922 with 60,078 deaths annually due to cervical cancer, one lady loses her life every 8 minutes with 200 women dying daily due to cervical cancer. As per Globocan 2020, the incidence of new cases of cervical cancer in India is 1,23,907 accounting for 18.3% of all the cancer cases in India. It is second leading cause of deaths due to cancer after Breast Cancer with 77,348 deaths per year.

Table 1.1: Five-year age-standardized (0–74 years) relative survival for cervix uteri cancer in selected Indian populations and selected Asian countries

Population/country	*Years*	*Relative survival, % (range)*
Mumbai*	1990–2001	46.4
Chennai*	1990–2001	59.6
Bhopal*	1990–2001	34.5
Barshi*	1990–2001	35.7
Karunagappally*	1990–2001	57.8
India (overall)*	1990–2001	46 (34–60)
China*	1990–2001	67 (48–79)
Singapore*	1990–2001	66
Turkey*	1990–2001	63
South Korea*	1990–2001	79 (76–79)
Thailand*	1990–2001	61 (54–63)

Source: *Reference (Survcan); [+]Reference (Shankar)

HPV AS MAJOR CAUSE OF CERVICAL CANCER

HPV as the major causative factor for cervical cancer. It is now an established fact that cervical cancer is caused by persistent infection with high-risk HPV strains. Four out of five women in our country is affected with HPV, HPV being a sexually transmitted virus. The prevalence of HR-HPV in women with normal cervical cytology varies among the different regions of the world. Global HPV prevalence was estimated to be approximately 12%, higher prevalence was noted in sub-Saharan Africa 24%.[7,8]

Usually, HPV infection being a local infection is symptomless and does not evoke any systemic inflammatory reactions. Most of the HPV positive cases turn negative within 8–12 months. Persistent high risk (HR) HPV is necessary for development of precursor lesions and cervical cancer. The major steps in cervical carcinogenesis include HPV infection, HPV persistence for a certain period of time, progression to precancer and invasion.[9]

Various screening methods which are available **(Table 1.2)**.[10]

RECOMMENDATIONS FOR SCREENING

- ACS recommends "the primary HPV test" as preferred test for cervical cancer screening for ladies 25–65 years of age (a primary HPV test is an HPV test that is done by itself for screening).
- FOGSI GCPR recommends HPV test as Primary Screening test in good resource setting and VIA in limited resource setting for ladies from 30 to 65 years. A single visit approach is encouraged and treatment may be offered based on colposcopy diagnosis (see and treat) or even on the basis of HPV test or VIA results (screen and treat).[11]

Table 1.2: Overview of primary screening tools for cervical cancer

Screening test	*Strengths*	*Limitations*
VIA: Acetic acid is applied to the cervix to identify precancerous and cancerous lesions	Requires less training (5–10 days) than other methods Cheaper than cytology/HPV testing Immediate results Potential for immediate treatment ("screen and treat")	Variable (low to moderate) sensitivity and specificity for CIN2+ Possibility for overtreatment Acetic acid must be prepared directly before screening Inappropriate for older women (>50 years) because of change in cervix position
VIAM: After application of acetic acid cervix is viewed under low magnification (×2–40)	Same as VIA	Magnification does not improve the test performance over and above that of naked-eye visualization
VILI: Lugol's iodine is applied to the cervix to identify precancerous and cancerous lesions. Process is often aided by a magnification tool	Requires less training (5–10 days) than other methods Cheaper than cytology/HPV testing Immediate results Potential for immediate treatment ("screen and treat") Has a 1 month shelf life	Variable (low to moderate) sensitivity and specificity for CIN2+ Possibility for overtreatment
Cytology (Papanicolaou smear) Sample of cells taken from transformational zone of the cervix. Sample is smeared onto a glass slide. Slide is sent to laboratory for reading by a cytologist	High specificity for CIN_{2+}	Relatively low sensitivity Requires laboratory and specialized technicians Lag in test results can contribute to loss to follow-up and delay treatment Long duration of training of cyto-technicians (12–24 months)
HPV DNA test Sample of cells taken from the cervix by a provider or the woman herself. Sample is sent to laboratory for analysis by trained technicians	High specificity and sensitivity for HPV infection Requires minimal training Woman can self-collect sample	Has to be followed by a test for dysplasia Requires laboratory and trained technicians Lag in test results can contribute to loss to follow-up and delay treatment Costlier as compared to other methods

CIN: Cervical intraepithelial neoplasia; VIA: Visual inspection with acetic acid; HPV: Human papillomavirus; VIAM: Visual inspection with magnification; VILI: Visual inspection with Lugot's iodine

- In an Indian study, even a single round of HPV testing was shown to significantly reduce the incidence of cervical cancer.

WHO VALIDATED HPV TESTS

- Cobas 4800 by Roche Diagnostics - RT-PCR Genotyping test which identifies 14 high risk strains–HPV 16, HPV 18 and other 12 high risk strains. This test is approved for primary cancer screening.

- Hybrid capture 2 which estimates 13 high risk HPV by hybridization technique.
- Cervista HPV HR, Hologic Inc, Bedford, MA, USA.
- One RNA assay—APTIMA HPV Assay (formerly Genprobe Inc, San Diego, CA, USA).

EDGE OF HPV TEST OVER PAP TEST AS PRIMARY SCREENING TEST

Clinical detection of human papillomavirus DNA test has become a standard of diagnostic care and treatment for high grade cervical intraepithelial neoplastic (CIN2+) lesion at the outpatient clinics in India. A detection of HPV DNA has been well established to show an increased risk for cervical cancer development owing to its superior sensitivity and its negative precancer disease prediction. Most HPV infections remain asymptomatic, or self-limited that resolve within 12–24 months of primary infection. Therefore, considering a much wider and longer prevalence of HPV among most sexually active women during their active age, a single round of HPV DNA testing is considered as superior primary screening test for cervical cancer.

SIGNIFICANCE OF HPV TEST

- To aid the diagnosis of sexually transmitted HPV infection.
- To screen patients with ASCUS (Atypical squamous cells of undetermined significance) Pap smear and determine the need for colposcopy.
- To aid risk assessment of women with LSIL or HSIL before colposcopy.
- Persistent HPV infection is the primary cause of cervical cancer.
- HPV is proven screening test, if HPV is positive, then this patient will be under surveillance and recalled after one year for repeat HPV test.
- Usually HPV becomes negative in one year, but if HPV persist, it will cause morphological changes in the cervical cells, ideally which should be able to identify in Pap smear.

  Thus, early identification of high-risk case becomes easier with HPV test.

WHO CALL FOR ELIMINATION OF CERVICAL CANCER BY 2030

On 17th November 2021, WHO released a vision document to eliminate cervical cancer as a public health problem by 2030 and set the threshold as 4 per 100,000 women for elimination. In India, many states are reporting 3–4 times higher number of new cervical cancer cases per 100,000 women population. In 2020, India reported >123,000 new cases and >77,000 deaths due to cervical cancer. WHO has further set the 90—70—90 targets by 2030 which specify:

- Vaccination—90% of girls are fully vaccinated with the HPV vaccine by the age of 15 years.
- Screening—70% of women screened using a high-performance test twice in their lifetime by the ages of 35 and 45 years.
- Treatment—90% of women with precancer treated and invasive cancer receive timely treatment.

However, vaccination for cervical cancer is not part of the national immunization program in India, although vaccines are available against most cancerous HPV genotypes. Cervical cancer screening (at least one-time screening in a lifetime) coverage is very low and covers less than 10% of the target population.

It is a long road ahead for us to achieve the target set by WHO, considering our geographical complexity, the infrastructure required, and the prevalent levels of public awareness regarding the disease. We are facing a high disease burden due to the absence of an organized cervical cancer screening program, leading to the detection of cancer at an advanced stage.

One positive development locally has been the publication of the consensus document 'Making a Road Map for India—Implementing Optimal Screening Strategies' towards cervical cancer elimination.

WHAT ARE THE STEPS THAT INDIA NEEDS TO TAKE TO ERADICATE CERVICAL CANCER?

We have to work at multiple levels to implement the robust cervical cancer elimination program.[12]

a. ***Policy change:*** We need major policy changes to include HPV vaccination in the national immunization program, adoption of high-performance tests like a clinically validated HPV DNA test for cervical cancer screening, and enable access to treatment for women with precancerous and cancerous lesions. Political will and insurance coverage for screening could provide a major boost to the programs. Funding support is critical for the sustainable cervical cancer elimination program and support through CSR will provide the much-needed financial support for mass-level programs.
b. ***Infrastructure development:*** We also need a major boost in infrastructure development enabling access to quality care for daycare treatment like colposcopy, Thermalablation, cryo-ablation, etc. for medical intervention at the right time. Molecular testing has received a boost in the country during the pandemic and we can use the existing setup for transitioning to HPV DNA-based screening programs and to establish more molecular diagnostics laboratories. Capacity building is equally important to have trained healthcare staff for sample collection, transport, and testing.
c. ***Public awareness:*** The most critical piece is to overcome the social barriers and encourage women to come forward screening and send their daughters for vaccination. We can use a three-pronged approach—sensitization, advocacy, and acceptance, to increase public awareness and address their myths on cervical cancer. We believe NGOs could play a big role here.
d. ***Role of public private partnership:*** The public-private partnership will be highly useful to build efficiency and momentum in the cervical cancer elimination program and will serve as a sustainable model in the end. It will also address the challenges of geographical complexity, logistical issues, and lack of access to quality care including diagnostics. PPP model could help in building up infrastructure, including setting and running the molecular diagnostics labs for HPV DNA testing and for public awareness initiatives.

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