

Cervical cancer screening: current perspective

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Abstract

Cervical cancer is the second most common cancer among women worldwide. First priority to reduce deaths from cervical cancers is to implement high quality, fully organised screening programmes without delay. Knowledge about cervical cancer and Pap testing influences uptake of cervical cancer screening services. Screening and treatment for precancerous lesions is a more cost-effective intervention compared to management of invasive cervical cancer. Human papillomavirus is the etiologic agent of virtually all cases of cervical cancer worldwide. All women 30 years and older should be routinely screened & screening should continue until the age of 65 years. By reducing the smear interval from 5 to 3 years in the age group < 50 years, the risk reduction for cervical cancer could be improved. About 16% of the world's total cases occur in India. At current incidence rates, the annual burden of new cases in India is projected to increase to 225,000 by 2025. However, the screening coverage in India is low upto 2.6-5 percent. Of all the screening tests available, the three main screening procedures commonly employed are Papanicolaou smears (Pap smears), visual inspection with acetic acid (VIA) and HPV testing. It has also been worked out that 'once in a lifetime' screening would result in reduction of 20-30% of the lifetime risk of cervical cancer. Health education is the most cost-effective approach in reducing the incidence of cervical carcinoma in developing countries like India.

Key words: Cervical cancer, Cervical cancer screening, Pap Screening

Disease Burden

Cervical cancer is the second most common cancer among women worldwide [1]. It is the leading cause of morbidity & mortality in women [2]. About 80% of these cases & deaths occur in developing countries [1].

Role of Screening

Cervical cancer is a preventable disease because invasive cancer is preceded by a long preinvasive stage, (upto 10 years) which may be diagnosed and treated, & the lesion is available for examination by simple methods [3]. Women who are not screened run a higher risk of developing cervical cancer [4]. Early detection of pre-cancerous lesions through cytological screening is the mainstay for global control of the disease. In developed countries, the incidence and mortality have markedly decreased after the introduction of cytologic cervical cancer screening [5]. So our first priority to reduce deaths from cervical cancers is to implement high quality, fully organised screening programmes

without further delay.

Barriers for effective screening

The main barriers are insufficient contact with the physician, anxiety, embarrassment, inappropriate beliefs, misconceptions, being single & psychological unpleasantness associated with the gynecological examination. Women belonging to low socio-economic status & those living in rural locations lack adequate screening facilities. Cervical cancer screening on an opportunistic basis has resulted in low population coverage [6]. Women's knowledge of cervical cancer and Pap smear testing is very limited. About 65% of subjects with invasive cervical cancer had never had a pap smear done until diagnosis [7]. Knowledge about cervical cancer and Pap testing influences uptake of cervical cancer screening services. Screening and treatment for precancerous lesions is a more cost-effective intervention compared to management of invasive cervical cancer. The World Bank estimated that the cost of screening woman every 5 years was USD100 per disability-adjusted life year (DALY) gained compared with USD2600 per DALY for treatment/ palliative care of invasive cervical cancer [8].

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Seminars with experts in preventive care, guidelines & pamphlets & giving patients a follow-up date for their cervical smear results will increase effective screening.

HPV & Cervical Cancer

Human papillomavirus (HPV) is the etiologic agent of virtually all cases of cervical cancer worldwide [1]. When patients with disease are compared for HPV infection with population-based controls, odds ratios of 200 have been observed [9]. HPV 16 and 18 account for nearly 50–70% of cervical cancer cases worldwide [10]. HPV infection is very common amongst sexually active young women with a prevalence ranging between 20% to 46% [11]. The knowledge about HPV is deficit worldwide. For HPV DNA testing to be useful for primary cervical cancer screening, strategies need to be developed that avoid identifying large numbers of women with transient infections (less common beyond 30 years) and focusing on identifying those women with persistent infection. So restricting HPV screening to women 30 years of age and older would be cost-beneficial [12]. One way in which HPV DNA testing could be utilised to screen large numbers of women without access to speculum examinations is through the use of self-collected vaginal samples. The sensitivity of HPV DNA testing of a self-collected vaginal sample for CIN 2, 3 or cancer was 66% (95% CI: 52–78%), which was equivalent to that of the conventional cervical smear [13].

Recommendations for Screening

When to Start: All women 30 years and older should be routinely screened [1]. Several recent reports indicate that the incidence of cancer of the cervix in younger women is increasing [14]. Cytology may be relatively insensitive at detecting invasive tumours in younger women, so the over-diagnosis, over-treatment and anxiety generated by screening the under-25 age group outweighs the small potential benefits. Among women aged 20 to 24 years to prevent 1 invasive cervical cancer, one would need to do between 12,500 and 40,000 additional screening tests & treat between 300 and 900 women [15]. However if the patient is HIV positive, screening should begin at a younger age, or at the age of onset of sexual activity.

When to Stop: The age-specific incidence of cervical carcinoma in a population that does not undergo screening shows a peak at ages 45 to 50 years and a modest decline at older age. Cruickshank et al., & Van Wijngaarden & Duncan questioned the benefit of

screening women over the age of 50 years [16,17]. Enormous smears (420 000) are required to prevent one death in over 50 years age group [17]. Moreover less numerous cells and atrophic cells make the sensitivity of the Pap-smear test lower. The carcinomas in elderly women hardly pass an in-situ stage. Symonds and Lamont however stated that women aged over 50 years are at high risk of developing carcinoma cervix if they have been inadequately screened, the survival after treatment worsened with increasing age, and the preinvasive phase in older women is very short [18]. In contrast to the former natural course, it now appears that there are two age peaks in the invasive squamous cell carcinoma incidence graph [19]. Current NHSCSP guidelines suggest that screening should begin at the age of 25 & continue until the age of 65 years.

Frequency of Screening [20]

Age	Frequency
25	First Visit
25-49	3 Yearly
50-64	5 Yearly
>65	those who haven't been screened before the age of 50 & those who had recent abnormal tests

By reducing the smear interval from 5 to 3 years in this age group < 50 years, the risk reduction for cervical cancer could be improved from 30% to 41%, however the rise in cost may be 60–66% [20].

Methods of Cancer Screening

Pap Smear

PROS : Best Approach, Simple, Relatively Inexpensive, Reliable, Free of Risk, Highly Effective, Highly Specific, Most Cost-Effective, Highly Valid & gives early Diagnosis at a Preinvasive Stage.

CONS: Inherent Subjectivity, Suboptimal Sensitivity, Limited Reproducibility, Equivocal Results, Varying False Negative and False Positive Rates, Varying Accuracy (30% - 90%), Screening insensitivity for Adeno- & Adenosquamous Carcinomas, Technical Capabilities, Requirement of trained personnel & Financial Resources, Lack of coherence in Cytologic and Histopathologic Terminology, Fear, Embarrassment, Pain, Inconvenience & Non-Optimal Participation Rate.

Self-Sampling Device (SSD)

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PROS: High Acceptance. Can increase screening coverage for hard-to-reach populations.

CONS: Inferior Cytological Quality compared with physician-collected samples & cannot be evaluated by Conventional / Liquid-Based Cytology.

Liquid Based Cytology

PROS: Similar Sensitivity and Specificity as Conventional Cytology, reduction in sample processing time .

CONS: Lower Sensitivity & Less Specificity.

Cervicography

PROS : Used together with a pap smear, it can identify nearly 2.5 times the number of women with dysplasia compared with the use of a pap smear alone, more effective than cytology [21], High Sensitivity & Acceptable specificity & more Sensitive in younger women and in women not using progesterone-only contraception, in whom the transformation zone is ectocervical.

CONS: High false positiverate .

Visual inspection of the cervix with Lugol's iodine

PROS : First method of screening of the cervix introduced in the 1930s by Schiller [22].

CONS: Very Poor Specificity & Inherent Subjectivity.

Visual Inspection with Acetic Acid (DVI / Cervicoscopy/ Acetic Acid Test / Vinegar Test)

PROS : Simple, Rapid, Inexpensive , Reliable, Reasonably Sensitive, detects cancer early, Provides immediate results, has superior sensitivity than Pap Smears, Cost-Effective, has high Negative Predictive Value (NPV) which has important implications for national screening programmes. The likelihood of a VIA-based screening programme for reducing cervical cancer rates is being evaluated.

CONS: Inherent subjectivity & Interobserver variability, low specificities and positive predictive values (PPV), Low Sensitivity for HPV, danger of overdiagnosis& over-treatment.

Hybrid Capture-II (HPV DNA Testing) Signal Amplification

PROS : Reliable, Accurate, Objective, greater sensitivity than cytology-based screening, Superior PPV

in detecting CIN compared to Cytology , useful for detecting precursor lesions, Built-in quality control , Robust & Reproducible, useful in older women in whom regression rates are lower. Eliminates 80–90% of screened women from being considered at risk for cervical cancer [23], has higher sensitivity , processing of results can be automated, more objective and requiring less training of healthcare workers. Rapid HPV DNA tests provide results within a few hours making same-day screening and treatment with cryosurgery possible in selected women . Possibility of HPV testing as a screening method for cervical cancer is being investigated.

CONS: Less specific, high false negativity, may not be cost-effective if the ratio of the prevalence of HPV infections to the prevalence of CIN is high.

Colposcopy: Examines cervix in greater detail (types of vessels found within acetowhite lesions, quality of the margins, surface configuration, contour & colour of the lesions)

p16INK4a: Indirect marker of persisting HR-HPV infection and malignant degeneration of cervical cells. P16ink4a immunocytochemistry has a significantly better specificity for high-grade CIN than HPV with comparable sensitivity.

E6/E7 viral mRNA : Used to risk-stratify.

Cervical Cancer: Indian Perspective

Disease Burden In India: Cervical cancer is the most common cancer among Indian women [24]. About 16% of the world's total cases occur in india [25]. It is estimated that approximately 100,000 indian women develop cervical cancer each year [26]. At current incidence rates, the annual burden of new cases in India is projected to increase to 225,000 by 2025. 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 [27]. Between 1980 and 2010, little progress was made in reducing cervical cancer mortality in India: 37 women died for every 100 new cases of cervical cancer in 1980 compared with 32 for every 100 new cases in 2010 [80 27]. High mortality rates are largely the result of nearly 70% of cervical cancer cases in India being diagnosed at an advanced stage (stage III or IV) [28].

HPV and Cervical Cancer In India: In india also, HPV is the leading cause and is associated with 90% of

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cases [29]. Approximately 70% of cervical cancers in India are caused by HPV types 16 and 18, which are targeted by the vaccine [30]. HPV vaccine awareness, access, and use are very low in india .

Barriers of Effective Screening In India: The screening coverage in india is low upto 2.6-5 percent [31]. Availability of Pap testing is very limited, and there is hardly any infrastructure for performance of colposcopy or management of cervical precancerous lesions. There is a serious lack of awareness not only in the general population but also in the medical fraternity and policy-makers in India & few large-scale screening programs exist in India.

Role of Cervical Screening In India: From a health policy perspective, the screening system will save the Indian government millions of rupees each year. While it costs about 2,000 rupees to treat a known case of HPV, it can cost as much as 500,000 rupees to treat a woman with an active case of cervical cancer and potentially cost her life. An HPV-based test would probably be best because of its sensitivity. With 38% of cases occurring among women of reproductive age (15–49 years), the adverse social and economic impact of cervical cancer on families and communities is considerable [27].

Screening Procedures In India: of all the screening tests available, the three main cervical cancer screening procedures commonly employed in India are Papanicolaou smears (Pap smears), visual inspection with acetic acid (VIA) and HPV testing. With the limited available resources for cytology the Papanicolaou smear test could not be used as a public health strategy for cervical cancer in India. Although cytology based screening program using Papsmears have been found to be effective in developed countries, alternative screening methods which can be more effective in the settings with low resources is using either VIA or VILI. HPV testing is the most objective and reproducible of all cervical screening tests and is also less demanding in terms of training and quality assurance. The HPV test costs around Rs.1250 per test in private medical centres in India. A simple, affordable, and accurate HPV test (care HPV test, Qiagen) that provides results within 3 hours was evaluated in China. The care HPV test will be a boon to developing countries like India.

Frequency of Screening for India: It has also been worked out in the Indian situation that ‘once in a

lifetime’ screening would result in a reduction of 20-30% of the lifetime risk of cervical cancer [32].

Strategies To Promote Cervical Screening In India:

The strategies include Mobilization efforts led by local health workers, Involvement of community leaders, Use of advertising campaigns through print and other media, Education of women, Recruitment through home visits by known health care workers, Provision of screening appointments and informational cards, Provision of screening & treatment services at locations close to the community by female health care providers & Provision of transportation to referral clinic for diagnostic and treatment services.

Conclusion

There is no doubt that the control of cancer of the cervix is an important issue for the health planners. Screening practices can preferentially be directed to the target population for optimal utilization of resources. Health education is the most cost-effective approach in reducing the incidence of cervical carcinoma in developing countries like India. Our conclusion and recommendations are that heightened public awareness of cervical cancer prevention, focusing on screening will lead to improved survival and a better quality of life.

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