CERVICAL CANCER SCREENING IN INDIA: STRATEGIES REVISITED

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ABSTRACT

With the change in the life styles and demographic profiles of developing countries, noncommunicable diseases are emerging to be important health problems that demand appropriate control program before they assume epidemic proportion. One of these is the problem of cancer. In India, cervical cancer is a significant problem in terms of incidence, mortality and morbidity. Cervical cancer is a disease that can be prevented through both primary prevention and early detection using screening techniques. Several screening modalities are now available for early detection of cervical cancer and its precursor lesions. They all differ with regard to their test characteristics, feasibility and economic considerations. This communication reviews different aspects of these screening modalities and provides different options considering mass application.

Keywords: Cervical cancer, human papilloma virus, screening, visual inspection

There has been tremendous change in the demographic profile of India over time, as both vital rates—birth and death rates—have gradually declined. The life expectancy at birth has increased to 65 years. Noncommunicable diseases like cancer have become a major cause of morbidity and mortality in the midst of already existing communicable diseases. According to National Cancer Registry Program of India, cancers of the uterine cervix and of the breast are the leading malignancies seen in Indian women.\(^1\) In view of the well-defined natural history and long detectable preclinical phase, the cancer of uterine cervix gets priority in terms of control program through mass screening.\(^2\) An important reason for higher cervical cancer incidence in developing countries is lack of effective screening programs aimed at detecting precancerous conditions before they progress to invasive cancer.

The different screening modalities have been...
cytology or Pap smear, visual inspection using acetic acid (VIA) or Lugol’s iodine (VILI) and high-risk human papilloma virus (HPV) screening. The sensitivity, specificity and predictive values are the important indicators of any screening tool in considering practical implications. The present communication tries to evaluate the different screening strategies under different resource conditions, with emphasis on developing countries like India. Various articles for the last 10 years, which are published in English, were accessed through the Medline search. The full text articles which were not freely available online were procured from different medical libraries or authors. The articles which were more suited to Indian conditions were considered for the review.

CYTOLOGY SCREENING
The Pap test is a cytological test designed to detect abnormal cervical cells from cervical transformation zone. Collection of Pap smear is relatively easy and painless and can be done by trained paramedical workers. It can detect most of the cancers in the in-situ stage or precursor stage. From the public health point of view, the purpose of Pap smear or any screening modality is to divide population into those who are likely to harbor the disease and those who are not. There are different studies carried out in various parts of world to study the efficacy of cytology screening, but the information available through randomized trials is lacking. Canadian task force evaluated that screening for cervical cancer had significantly contributed to reduced mortality from the disease in Canada.[3,4] A strong relation is observed between initiating of screening and reduction in mortality from cancer of cervix from different approaches.[5,6] Nordic counties have conducted organized cytology screening programs, which have reported rapid reduction in incidence of cervical cancer in Iceland. The nationwide screening programs were introduced in Finland in the early 1960s. In five countries (viz., Denmark, Finland, Iceland, Norway, Sweden and British Columbia), studies demonstrated the efficacy of cytology screening programs. The targeted coverage ranged from 40% in Denmark to 100% in Finland.[7-10] IARC assessed the potential reduction in cumulative incidence rates for cancer of cervix with different frequencies of screening based on experience of the countries with mass screening programs. Assuming 100% screening sensitivity and screening coverage of 80%, screening all women aged 35 to 64 years resulted in 93% reduction in incidence of the disease with annual screening. The incidence remained the same (93 and 91%) for two- and three-yearly screening frequency. Five-yearly screening resulted in 84% reduction, while 10-yearly screening reduced incidence by 64%. Based on these data, developed nations recommended frequent screening to cover up low sensitivity of the pap screening. It however was seen that even infrequent screening could be effective, considering the latest report irrespective of period. Even screening women once in their lives, ideally at an age anywhere from 40 to 45 years, can significantly reduce the mortality from cervical cancer.[10,11]

The multicentric study in India evaluated the accuracy of conventional cytology. The study considered three thresholds to define positivity-atypical squamous cells of uncertain significance (ASCUS), low-grade squamous intra-epithelial lesions (LSIL) and high-grade squamous intra-epithelial lesions (HSIL). The sensitivity was found to vary from 37.8-81.3% for ASCUS, 28.9-76.9% for LSIL and 24.4-72.3% for HSIL, between the centers.[12] Because of large variation in the results, the issues of sampling and quality control were not beyond doubt. The meta-analysis of the Pap test accuracy has also been attempted.[13] It identified 62 studies published by 1992 comparing the Pap test accuracy with histology. It was observed that 82% of the studies had potential for verification bias, and only 37% stated that cytology and histology were independently assessed. The sensitivity ranged from 11 to 99%, and specificity also had this wide variation of 14-97%. The sensitivity of the cytology for detection of high-grade lesions was 57%. Results indicate that specificity in the range of 90-95% corresponds to sensitivity of 20-35%. This analysis definitely points towards the search for a more optimum method of screening.

Thus World Health Organization (1992) recommended that in low resource settings, the aim should be to screen every woman once in her lifetime at 40 years. Frequency of screening should be increased to ‘once every 10 years’ and then ‘once every 5 years’ for women 35-55 years of age. The frequency could be increased based on resources.[14]

DIFFICULTIES IN ORGANIZING SCREENING PROGRAMS IN DEVELOPING COUNTRIES
Resource constraint has been a major hurdle in organizing screening programs. It has been estimated that in India, even with a major effort to expand cytology services, it will not be possible to screen even one-fourth of the population once in a lifetime in the near future.[15,16] In most developing countries, there has been no success to develop a high quality cytology service. In Mexico, for instance, the low quality of cytology services has been a major barrier. The false negative rate for Pap smear in Mexican cytology centers was as high as 54%. In Colombia, a shortage of cytotecnicians has been a key barrier (PATH 2000).[17,18]

In addition to other resource constraints, deficiencies in record keeping in cytology laboratories and cancer registries make the administrative monitoring and evaluation activities difficult, if not impossible. There is a need to look at alternate practicable options for developing countries.

LIMITED CYTOLOGY SCREENING - OTHER THAN POPULATION BASED
Because of the difficulties encountered in launching population-based programs described above, several attempts were made in developing countries, which were targeted on a smaller group and obviously had a limited impact. These approaches are:

1. Camp approach
2. Hospital-based screening
3. High-risk screening

In the camp approach, one can sensitize the
population for screening but it cannot make any impact on the incidence or mortality as it is a momentary and limited activity.

Several hospital-based screening programs have been conducted in India, especially where a cytopathology department is fully developed and invariably supported by research grants. The screening programs in India are restricted to urban centers and are institution based. Indian Council of Medical Research has taken a lead in launching such programs through its research programs.[19,20] These programs have raised good and authentic scientific information about natural history of the disease and its risk factors. Since these programs are sanctioned for a specific time period, they cannot be absorbed in the system as a continuous activity because of lack of resources.[21,22]

High-risk screening involves screening high-risk individuals who have certain socio-demographic and clinical indicators. In the gynecology outpatient departments, this method is being used for early detection of cancer wherever clinical suspicion exists. The women who had suspicious-looking cervix or bleeding cervix were considered to be in the high-risk category, and they had yielded a substantial yield of high-grade lesions.[23-26]

**INNOVATIVE CYTOLOGICAL SCREENING TECHNOLOGIES**

Several new technologies are being explored in an effort to improve the screening accuracy of Pap smears. While these approaches appear promising, they are expensive and heavily reliant upon technology. These technologies are as follows:

1. In the fluid-based thin-layer processing of cervical samples, the solution is filtered to remove mucous, yeast and bacteria before being applied to a slide-thin layer. This technique attempts to reduce sampling error and thus improve specimen adequacy. A Costa Rican study used this technique, with improved sensitivity and specificity in detecting both ASCUS and high-grade lesions, including invasive cancer.[27]

2. Automated Pap testing attempts to reduce lab-screening errors by computerized analysis to evaluate Pap smear for cancer of cervix. It could be used both for primary as well as secondary screening. The secondary screening involves analysis by the pathologists of potentially abnormal cervical cells highlighted by automated system.

These approaches may be efficient but add considerable cost to the Pap smear based programs.

**FREQUENCY OF SCREENING**

Efforts should be made to direct resources to women who have not been screened rather than repeated screening. It has also been considered that ‘once in a lifetime’ screening approach could form an important strategy for a country like India. As discussed earlier, reduction in cumulative incidence rate of cervical cancer in the age group of 35-64 years with different screening intervals worked out to be in the range of 93-64% for the screening intervals of 1 to 10 years. It has also been worked out in the Indian situation that ‘once in a lifetime’ screening would result in reduction of 20-30% in the life-time risk of cervical cancer.[28-30] This approach could also be one of the options for the limited resource conditions.

**ALTERNATE STRATEGIES**

**Visual inspection with acetic acid application (VIA)**

This involves swabbing the cervix with 3-5% acetic acid (vinegar) solution prior to visual examination. VIA is a simple and inexpensive test, which can be provided by trained paramedical personnel (such as midwives, nurses and other health workers) with a short training. Its accuracy at detecting cervical neoplasia has been extensively studied and found to be satisfactory.[31-34]

Differences in study protocols, population characteristics and outcome make it difficult to summarize results (PATH 2000).[17] Many studies are subject to verification bias, as the reference test was not performed on all study subjects, including women with negative screening test results. In general, the sensitivity of VIA in detecting high-grade dysplasia is at least equal to or higher than that of cytology, while VIA’s specificity is somewhat lower. The pooled sensitivity of VIA has been found to be 76.9% (range 56.1-93.7% across studies), while the pooled specificity was 85.5%. This is in sharp contrast to the pooled sensitivity of cytology (58%), with a range of 28.9-76.9% from different studies, and specificity of 95%. Specificity of VIA remains a cause of concern due to likelihood of over-treatment resulting in health risk and increased costs. Since visibility of SCJ is age related, a higher
proportion of VIA-positive women are of lower age compared to women testing positive on cytology or HPV testing. Unlike cytology, where different grades of severity are stated as mild, moderate or severe or as low-grade and high-grade lesion, VIA is recorded only as positive or negative. Thus, concerns have been expressed about reproducibility and quality control of VIA in field conditions. Clearly a significant challenge is to bring about standardization of VIA and to train health workers so as to enable them to recognize often subtle characteristics that differentiate degrees of dysplasias.

Many aspects of VIA make it an attractive approach for use in low-resource settings. It is a low-tech approach with minimum reliance upon infrastructure for performance. Results of the procedure are available immediately for initiating treatment at the same visit.

Thus, although VIA is a useful alternative to cytology in low-resource settings, the test positivity and detection rates of lesions have to be carefully monitored to maintain satisfactory performance. Regular training of health care providers is an important component. As VIA is an entirely provider-dependent screening method, clear standards for identifying precancerous lesions that should be treated are essential.

Visual inspection with magnification (VIAM)

VIAM is the visualization of cervix under low magnification after application of acetic acid. Several devices have been used by different investigators. These are hand-held devices with built-in source to view cervix in community settings - a special lightweight monocular telescope called gynoscope (PATH 2000) and a magnivisualizer (Parashari et al., 2000). The experience showed that approximately 10-12% of women with normal cervix might have some acetowhitening, which may be confused for premalignant or malignant tissue (i.e., false positives). Compared to colposcopy, it has much better specificity because of the use of low magnification in screening magnifying devices (compared to colposcopic magnification). The low magnification tends to miss some of the benign acetowhite tissue (otherwise picked up by colposcope) and thus results in higher specificity.

Blumenthal noted that CIN I (low-grade lesions) are less frequently detected by magnified visual technique compared to cytology, and for high-grade lesions magnifying devices would have a better sensitivity (compared to Pap smear).

The pooled sensitivity of VIAM (64.2%; range 61-71.4%) was found to be better than that of cytology (58%; 28.9-76.9%) but was less compared to that of VIA (76.9%; 56.1-93.9%). It is not yet known whether use of magnification offers a significant advantage over VIA. Investigation by Basu et al. and Sankaranarayanan et al. showed that VIAM was not superior to VIA, but there was some loss of specificity. The pooled specificity, however, was the same for VIA (85.5%) and VIAM (86.8%).

Parashari argued that these devices have one advantage - that of having an in-built light source - which comes handy in rural areas where electricity access is a problem. Magnification did not give any improvement in detection rate of high-grade dysplasia or cancers over the use of VIA in studies from South Africa also.

Visual inspection after application of Lugol’s iodine (VILI)

VILI is the visualization of cervix after application of Lugol’s iodine. On liberal application of Lugol’s iodine over the cervix and vagina, the normal squamous epithelium (that contains glycogen) will be strongly stained almost black or dark brown. On the other hand, columnar epithelium lacks glycogen and does not stain with iodine. Likewise, immature metaplasia, dysplastic epithelium or atrophic epithelium also does not stain. Normally invasive cancer does not contain glycogen and does not stain, but some invasive cancers do contain some glycogen and may stain. Thus VILI is considered positive if SCJ or entire cervix or growth turned yellow (non-uptake areas). In a study conducted in 11 centers in India and Africa, VILI had a greater sensitivity (91%) compared to VIA (75%).

In another study conducted in Mumbai, sensitivity of VILI (75.4%) was higher, though not statistically significant; compared to VIA (59.7%), VIAM (64.9%), HPV (62%) and cytology (57.4%). The specificities were 98.6% for cytology, 93.5% for HPV, 88.4% for VIA, 86.3% for VIAM and 84.3% for VILI. Among the visual test assessed, VILI seems to be particularly promising, detecting 75% of all cases of HSIL compared to VIA and VIAM, which detected less than two-thirds of cases. The pooled sensitivity of VILI (91.8%; range 76-97.3%) has been shown to be higher compared to those of VIA (76.9%) and VIAM (64.2%).

The other advantage cited for VILI is that the yellow-color changes associated with a positive VILI test result could be recognized with much greater ease by trained health workers compared to the acetowhite lesions associated with VIA. In short, visual modalities are simple, inexpensive and such as to require minimal infrastructure and a short training period for health professionals. A major logistic advantage of the visual tests is the immediate availability of results to carry out treatment. The major disadvantage of VIA and VILI is the low specificity; and to date, there is no universally accepted uniform definition of test results for VIA and VILI.

Considering the variability of results, there is a need for standardization of definitions and treatment approaches. VIA-/VILI-based screening program may be more readily integrated into primary care health services in developing countries.

Model-based simulation of cost-effectiveness indicates that cancer of cervix screenings based on visual technique that eliminates colposcopy (‘see-and-treat’ approach) may be good alternatives to cytology-based screening programs in low resource settings. Another advantage of visual techniques has been very high negative predictive value - more than 99%. A woman negative by VIA/VILI need not further undergo any investigation. These women may however be advised to undergo a VIA or VILI after a minimum interval of 3 years. Only 10-15% women who are test positive with visual techniques require further evaluation, thus
HPV SCREENING

Rational
HPV infections are very common among sexually transmitted infections, but most of these infections are transient. Only 3-10% of women, who cannot clear these infections, become persistent HPV carriers and constitute a high-risk group for progression to cancer of cervix. The high-risk types of HPV are types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68. The risk for any of these types is the same, and the risk related to the presence of multiple-HPV types is no different from that of a single-HPV type. The attributable fraction percentage from many studies ranges from 90-98% compared to a prevalence of 5-20% of control population (Munoz et al., 2003). Since the lifetime risk of HPV infection is 70-80% in many countries, other factors determine the relatively small percentage (less than 5%) of women who develop cancer of cervix. It was further mentioned that few cancer of cervix specimens that appear HPV-DNA negative were largely false negatives. Thus it was claimed that there is a strong rationale for using HPV test in screening programs.

Most of the screening programs make use of hybrid capture II kits.

Test characteristics
The characteristics of HPV screening have been discussed in a review by Cuzick and Womach. Results from various studies highlight that for detection of high-grade lesions, there was a drop in both sensitivity (64%) and specificity (65%). The pooled sensitivity for HPV (hybrid capture II) has been stated to be 66.5% (range 45.7-80.9%) with a specificity of 93.8%.[19,56] HPV testing generally has a negative predictive value of up to 99%, providing a useful reassurance to patients for any further evaluation. In developing countries where screening is infrequent, initial HPV screening at age 35 years may be quite reassuring to the women who test negative.

Generally, this test is not considered very specific, though specificity tends to increase among older women. This indicates potential for over-treatment. This may be due to the fact that many HPV-positive women have not developed any precancerous lesion at the time of examination, though they may be at very high risk of doing so. In the older women (>35 years) where risk of developing persistent HPV infection and precancerous lesions is high, specificity becomes higher. Thus, there is a need for proper health care restructuring at different levels-from periphery to the district level. This massive task needs to be initiated in steps. One of recommendations of the National Workshop of 2001 has been to initiate the program in limited areas of about 54 districts of India where better infrastructure exists.[55]

Women in developing countries should be educated for utilizing the health care system, even after completing the family, especially in rural areas. There are reports that a well-built nationwide educational program for women regarding early warning symptoms resulted in marked reduction in mortality from with the cancer prevention (Monsonego et al., 2004).[51]

Problems encountered
1. In developing countries, available tests are likely to be too expensive and technologically demanding for widespread use.
2. Samples need to be collected from the field and transported in ice and stored at -20°C initially for further processing.
3. The currently available test requires at least 6 h to process in the laboratory and also requires significant lab equipment and supplies. In Barshi, Maharashtra, it could take up to 2 weeks after sample collection to deliver results to women, necessitating a second visit by these women for colposcopic examination.
4. Low specificity necessitates unnecessary investigation.
5. Although treatment is available for the genital warts that caused some types of HPV, no treatment or care is known for latent HPV infection in high-risk types. Likewise, prevention is difficult. Thus, it involves difficulties in counseling the patient regarding treatment or prevention.

It does not seem to be a cost-effective strategy for the low-resource setting of Barshi. HPV was nearly as expensive as cytology and less effective than cytology.[52]

SELF-COLLECTED SAMPLES

Various approaches to self-collection of samples for HPV testing have been explored in attempts to improve the accessibility of screening. This has important implications, especially where cultural and programs’ barriers may limit acceptance of, and access to, standard gynecologic procedures. While Canadian studies concluded that this approach was acceptable to women and had sufficient sensitivity to warrant further evaluation,[54] a South African study indicated that technique was as sensitive as pap, though less specific.[54]

CONCLUSION

The first step towards increasing policy makers’ awareness and support for effective cervical cancer prevention policy and programs has already been taken in the form of formulation of National Cancer Control Program of the Government of India (NCCP); and for state governments, ‘prevention of cervical cancer through screening’ has been identified as one of the main goals. It is envisaged that the program, as and when feasible, would be implemented through Districts Cancer Control Program (DCCP).

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cervical cancer even before the advent of cytology. Thus, a strengthened primary health care system coupled with women awareness and professional expertise would achieve the necessary objective. Till such time organized screening is initiated, early case detection methodology through educational and awareness programs mentioned would be most appropriate. This model has been tried earlier on research basis in India. Regional centers can play a leadership role in teaching/training/treatment of invasive cancers and evaluation activities. Organized screening has to be done at PHC level or its subcenter, i.e., close to the target population, utilizing the services of paramedical workers under the existing circumstances. VIA/VILI would be the only suitable test immediately available. Though ‘see-and-treatment’ approach in the same sitting and at PHC level would avoid unnecessary referral to CHC and another visit, there is no evidence that it can reduce incidence and mortality from cervical cancer. However, in India the preference of gynecologists is to obtain a colposcopy-directed tissue diagnosis before treatment (National Recommendations 2001).

Treatment of all high-grade lesions (moderate and severe dysplasia HSIL) must be carried out using ablative or excisional procedures. Especially targeting the age group of 35-65 years, the program must cover a high proportion of eligible women (>80%). To begin with, all women should be offered at least one screening test at an age between 40 and 45 years (Prabhakar et al., 1992). DISCUSSION

There is no doubt that the control of cancer of the uterine cervix is an important issue for the health planners. Different screening approaches have been discussed for developing countries like India, which has a large variation in resources-from village to metro cities. Mass scale screening as has been practiced in other countries is just impossible here in the near future. As per the situation discussed, it may not be possible to advocate a uniform policy. There are certain features which the program should contain. This includes quality control, well-defined high-risk group and referral for treatment. The screening strategy could be integrated into the existing infrastructure. Cervical cancer control activities could be included in the existing ‘reproductive and child health program.’ A majority of studies considered subjected a sample of negative cases to standard test. One of the papers suggested that for comparing two screening tests with the reference procedure, which tests positive on old or new procedure can be further evaluated with reference procedure. The sensitivity and specificity pattern is quite different in low-grade lesions (LSIL) as compared to high-grade lesions (HSIL). In a resource-poor setting like India, one may want to concentrate on identification of HSIL. However, it may also be mentioned that one of the ICMR studies had indicated that many of the biopsy-proven high-grade lesions had LSIL in cytology.

Although the discussion has concentrated on secondary prevention approach, the primary prevention approach for control of cervical cancer through managing preventable risk factors could form an important component of control programs. Self-collection of samples for HPV detection may also be encouraged. The costing may be optimized or subsidized. The HPV vaccination could be the ultimate in control of cervical cancer; the issue is in active research. The FDA recently approved HPV vaccines by the two major pharmaceutical companies (Merck and GlaxoSmithKline), which are under field trials. There is a need to plan an appropriate information system involving electronic media with a component of training for statistical work for monitoring and referral. This would facilitate efficient data management. The call-recall method, i.e., regular follow-up of women on schedule, should be developed through the centralized setup.

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