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Cancer Screening: Should Cancer Screening be Essential Component of Primary Health Care in Developing Countries?

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ABSTRACT

Background: Cancer is a fatal disease and is on the rise across the globe. In India, breast, cervix and the oral cavity are the leading cancer sites, but, unfortunately, in-spite of availability of screening tools, there is no organized cancer screening program in India. The main objective of this study was to review the performance of various cancer screening modalities in a resource poor setting.

Methods: MEDLINE and web of science electronic database was searched from January 1990 to December 2013, using keywords such as "breast cancer, cervical cancer, oral cancer and their corresponding mesh terms were also used in combination with Boolean operators OR, AND." Two authors independently selected studies published in English and conducted in India. A total of 16 studies was found relevant and eligible for the review. The data on sensitivity and specificity of various screening tool was extracted and analyzed.

Results: Most of the reported screening trails in India are on cervical cancer and few on breast and oral cancer screening. The pooled estimates of sensitivity and specificity of cervical cancer screening test such as visual inspection with acetic acid, magnified visual inspection with acetic acid, visual inspection with Lugol's iodine, cytology (Papanicolaou smear) and human papillomavirus deoxyribonucleic acid was found to be 68.76% and 84.02%, 63.27% and 85.43%, 81.86% and 87.03%, 63.25% and 93.17% and 75.04% and 91.66%, respectively. Sensitivity and specificity of clinical breast examination was found to be 94.30% and 94.30%, respectively. Oral cancer screening through visual inspection by trained health care worker was found to have 87.90% sensitivity and 92.05% specificity.

Conclusions: Our study highlights the availability and success of visual screening tools in early detection and mortality reduction of major neoplasia in resource-poor health care settings and recommends implementation of oral and cervical cancer screening as part of assured primary health care package in developing countries.

Keywords: Breast cancer, cervical cancer, oral cancer, primary health care, screening, visual inspection

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INTRODUCTION

Cancers figure among the leading causes of death worldwide. Each year around 14 million new cancer cases and 8.2 million cancer deaths are reported across the globe. GLOBOCAN 2012 figures indicate that the incidence of cancer has increased from 12.7 million in 2008 to 14.1 million in 2012, and this trend is projected

to continue with a number of new cases expected to rise a further 75%.[1] The greatest impact of this rising trend would unquestionably be in low and middle-income countries that are ill-equipped to cope up with the escalation of a number of cases of cancer.

In India, approximately 1-million new cases were detected, and 680,000 deaths occurred due to cancer in 2012. The top three leading sites of cancer for both the sexes combined are breast, cervix and oral cavity. The age-standardized incidence rate of breast, cervical and oral cancer has been reported to be 25.8, 22.0 and 7.2/100,000 population of India respectively. These three cancer sites together amount to 34% incidence and 27.8% cancer related mortality in India.[1,2] In the near future with a growing population and the increasing life expectancy, the numbers of cancer cases are only going to increase. This rising burden of cancer, coupled with spiraling cost of cancer treatment would place enormous strain on healthcare systems of India. Therefore, prevention is central to reducing or reversing the rise in cancer burden, and the good news is that these three sites are easily accessible and can be subjected to cancer screening.

The goal of medical screening programs is to detect disease at a latent or early stage in order to deliver more timely interventions, leading to reduced morbidity and/or mortality. In 1960, Wilson and Junger described the characteristic of an effective screening program [Table 1].[3] Subsequently, Rose and Barker[4] suggested that an effective screening program must answer three important questions: "Does early treatment improve prognosis? How valid and repeatable is the screening test? What are the yields of the screening service? When breast, cervical and oral cancer was examined in the context of these principles, they appeared to be well suited for a screening program. In addition, due to significant morbidity and mortality associated with these cancers, the ability to diagnose early lesion with clinical examination, and the presence of identifiable risk factors associated with substantially higher cancer incidence, screening for oral, breast and cervical cancer screening may prove beneficial.

India is a very large and culturally diverse country. Worldwide, cervical cancer is ranked as 5th most common cancer, and oral cancer is ranked 11th, whereas these cancers including breast cancer are top three leading causes of cancer in India. India alone accounts for a quarter of the world cervical cancer burden[5] and is home to a third of the world oral cancer burden.[1,5] Breast cancer that was earlier thought to be a disease of developed countries is now the leading cause of cancer in Indian women as well. In-spite of such disturbingly high figures, there are no organized early detection programs for breast, cervical or oral cancers in India.

Table 1: Wilson-Junger principles of effective screening programs[3]

The condition sought should be an important heath problem
There should be an accepted treatment for patients with recognized disease
Facilities for diagnosis and treatment should be available
There should be recognizable latent or early symptomatic stage
There should be a suitable test or examination
The test should be acceptable to the population
The natural history of the condition should be adequately understood
There should be an agreed policy to whom to treat as patients
The cost of treatment should be economically balanced in relation to possible expenditure on medical care as a whole
Case finding should be continuing process and not a "once and for all" project

As a result, these early detectable and treatable cancers usually present at late stage resulting in increased treatment morbidity and reduced survival rates. This study was, therefore, planned to review research initiatives undertaken in India to access efficacy of various available screening modalities and make suitable recommendations' for control of three leading cancers in India that is, breast, cervical, and oral cancer.

METHODS

Data sources and searches

This paper is based on information gathered from a review of peer-reviewed publications on cervical, breast and oral cancer screening and prevention in India. MEDLINE (http://www.pubmed.com) and web of science electronic database was searched from January 1990 to December 2013, using the using keywords such as "breast cancer, cervical cancer, oral cancer, cancer screening, diagnostic accuracy, visual inspection, and their corresponding mesh terms were also used in combination with Boolean operators OR, AND." We also examined bibliographies of included articles to identify additional references. The search strategy was limited to English language. Only journal article type was included. Figure 1 presents the search strategy and screening process.

Study selection

Inclusion criteria

- Study designs eligible for inclusion in our review were randomized controlled trials, nonrandomized controlled trails, cohort studies and cross-sectional studies conducted to evaluate the performance of the screening tests for detection of cervical, breast and oral cancer
- Studies conducted in India only were included in the review.

Exclusion criteria

Studies not providing data on sensitivity and specificity of the screening test evaluated were excluded from the review.

Data extraction and analysis

The title and abstract of each citation were screened first, and full report was screened second if necessary to select the relevant articles according to selection criteria. Full texts of these selected studies were retrieved, reviewed and extracted for relevant data by authors independently. A total of 16 studies was included in the review, and their findings have been presented.

RESULTS

Cervical cancer

Cervix is amenable to screening by a number of methods; these include visual inspection with acetic acid (VIA), magnified visual inspection with acetic acid (VIAM), visual inspection with Lugol's iodine (VILI), the Papanicolaou (Pap) test and human papillomavirus deoxyribonucleic acid (HPV DNA) testing. A brief overview including strengths and weaknesses of each screening modality is presented in Table 2.[6-12]Salient findings of Indian studies[13-23] on screening test performance are summarized in Table 3.

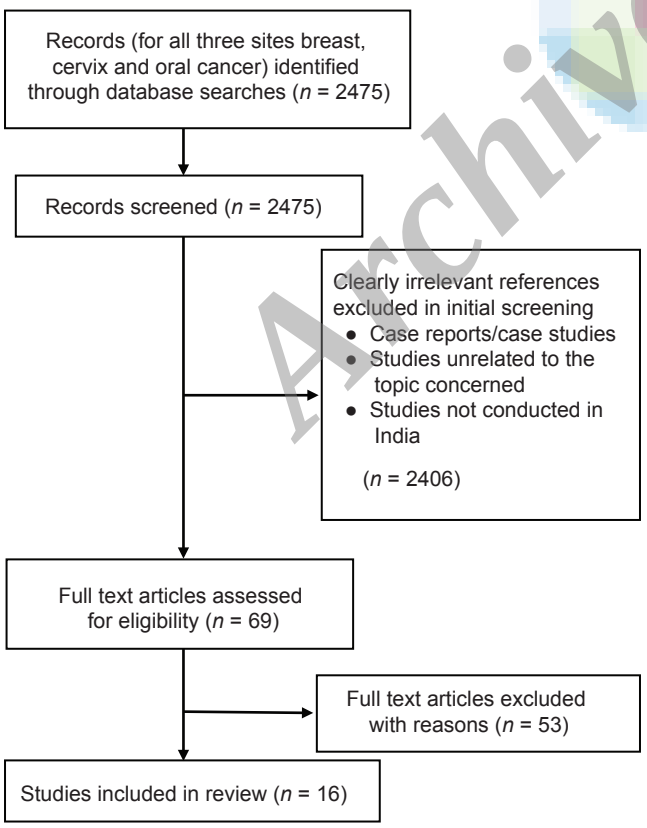

Figure 1: Summary of evidence search and selection

The pooled sensitivity and specificity for VIA was found to be 68.76% and 84.02%, for VIAM the pooled sensitivity and specificity were 63.27% and 85.43% and for VILI the pooled sensitivity and specificity were 81.86% and 87.03%, respectively. The pooled sensitivity and specificity for cytology positivity at low grade squamous intraepithelial neoplasia threshold were 63.25% and 93.17% and for HPV DNA testing of high-risk types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) the pooled sensitivity and specificity were 75.04% and 91.66% respectively.

Breast cancer

A large number of breast cancer screening modalities have been tried across the globe. However, only a few test such mammography, digital mammography, clinical breast examination (CBE) and breast self-examination have shown sufficient accuracy for use in general screening.[25] A brief overview of these accepted breast cancer screening modalities along with their strengths and weaknesses is presented in Table 4.[24-26] There is a dearth of studies conducted in India for evaluation of breast cancer screening modalities. In the few studies conducted in India the sensitivity and specificity of CBE were found to be 94.30% and 94.30%, respectively [Table 3].

Oral cancer

The term "oral cancer" includes all malignancies arising from the lips, oral cavity, oropharynx, nasopharynx, hypopharynx, and other ill-defined sites within the lip, oral cavity, and pharynx.[28] The oldest modality of oral cancer screening is a thorough and methodical examination of the mucosal surfaces of the oral cavity in good lighting, but many studies have also focused on the important role of toluidine blue dye as an adjunct to the detection of oral cancer. A brief description of various oral cancer modalities is provided in Table 5.[29-42] Review of Indian studies has shown that, oral cancer screening through visual inspection by trained health care worker has sensitivity of 87.90%, and specificity of 92.05% and visual inspection using methylene blue has sensitivity and specificity of 91.40% and 66.60% and mouth self-examination (MSE) has sensitivity and specificity of 18.00% and 99.90%, respectively [Table 3].

DISCUSSION

Cervical cancer

In contrast to developed countries cervical cancer is a public health problem in developing countries. It is the one of the leading cause of cancer mortality in India, accounting for 17% of all cancer deaths among women aged 30-69 years.[1] In developed countries, conventional cytology screening programs have

Table 2: Overview of primary screening tools for cervical cancer[6-12]

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 screen Inappropriate for older women (>50 years) because of change in cervix position
VIAM: After application of acetic acid cervix is viewed under low magnification (×2-4)	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 (Pap 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 CIN2+	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 cytotechnicians (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

VIA=Visual inspection with acetic acid, HPV=Human papillomavirus, CIN=Cervical intraepithelial neoplasia, VIAM=Visual inspection with magnification, VILI=Visual inspection with Lugol's iodine, Pap=Papanicolaou, DNA=Deoxyribonucleic acid

Table 3: Accuracy of cervical, breast and oral screening tests in detecting cancer and precancerous lesions (Indian studies)

Type of test	Number of subjects studied	Number of studies	Pooled sensitivity %	Range in individual studies (sensitivity)	Pooled specificity %	Range in individual studies (specificity)
Cervical cancer						
Cytology at the ASCUS threshold[13,15-23]	39,632	11	63.25	29.50-91.40	93.17	86.00-99.09
VIA[13-23]	89,461	14	68.76	31.60-100.00	84.02	53.30-91.23
VIAM[13,14,16]	27,902	3	63.27	60.70-64.20	85.43	83.20-86.80
VILI[15,16,19,20,22,23]	64,478	9	81.86	64.50-100.00	87.03	82.90-93.35
HPV testing[15-18,21]	23,244	8	75.04	45.70-97.10	91.66	84.20-94.60
Breast						
Clinical breast examination[27]	115,652	01	51.70	-	94.30	-
Oral cancer						
Visual inspection by healthcare worker[43-45]	81,038	02	87.90	81.50-94.30	92.05	84.80-99.30
MSE[46]	34,766	01	18.00	-	99.90	-
Inspection with methylene blue application[47]	120	01	91.40	-	66.60	-

VIA=Visual inspection with acetic acid, VIAM=Visual inspection with magnification, VILI=Visual inspection with Lugol's iodine, HPV=Human papillomavirus, MSE=Mouth self-examination

shown a marked decline in the incidence of cervical cancer.[48] However, its successful implementation requires a variety of requirements to be fulfilled, such a laboratory infrastructure, microscopes, several resource personnel (smear collectors, cyto-technicians and pathologists), consumables (slides, fixative, Pap

Table 4: Overview of primary screening tools for breast cancer[24-26]

Screening test	Strengths	Limitations
Mammography: Mammography is an X-ray technique that was developed specifically for soft tissue radiography of the breast. It is based on the differential absorption of X-rays between the various tissue components of the breast such as fat, fibroglandular tissue, tumor tissue and calcifications	High specificity	Complex test Many factors affect the accuracy of mammography X-ray machine Film processing Examination technique including positioning and compression Radiologist's performance Radiation exposure Suspected lesions are difficult to localize in the breast
Digital mammography: In digital mammography, the image receptor (screen-film) used in conventional mammography is replaced by a digital receptor and computer generates the image	Easy image processing, display, transmission and storage Lower radiation dose Computer-aided detection	Higher cost than mammography for low-volume operations Same as normal mamography
Clinical breast examination: Involves breast visual inspection and palpation by the physician (a systematic technique described by Pennypacker and Pilgrim)	Requires less infrastructure Cheaper than mammography Immediate results	Variable sensitivity and specificity depending on the expertise of the physician
Breast self-examination: Individual herself carries out breast examination (Mamon and Zapka (1983) outlined eight step technique)	No infrastructure required Empower women by allowing them to take responsibility for their own health	Training women Continuous motivation to maintain regular self-examination

stain containing five dyes and three solutions) and several steps with inbuilt quality assurance procedures, which are not feasible in many low-resource settings. Moreover, cytology must be repeated at frequent 3-5 year intervals to ensure satisfactory sensitivity and optimum detection of cervical cancer precursor lesions and repeat visits are necessary after a positive cytology for diagnosis and treatment, which may lead to drop outs. Several years of cytology screening in low and middle income countries have not led to significant reductions in cervical cancer in these countries, possibly due to the difficulties in offering high-quality cytology, programmatic deficiencies in follow-up and treatment of screen-positive women, and also due to the considerable financial, technical and logistic inputs necessary for effective cytology programs.[22,49] VIA is a widely investigated alternative method for cervical cancer screening. In our review of Indian studies, sensitivity of VIA has been found to be better than cytology, but its specificity is lower [Table 3]. However, the biggest advantage of visual tests is that, it can be implemented through primary health care workers, it does not require a laboratory infrastructure and the results are obtained immediately following testing, thus allowing diagnosis and treatment to be instituted during the same visit. It has been well established that cervical neoplasia are caused by persistent infection with certain oncogenic types of HPV. Testing for HPV DNA in reviewed Indian studies indicate higher sensitivity and comparable specificity when compared to visual inspection and cytology. However, requirement of sophisticated laboratory infrastructure and high cost, make it impracticable to be implementable in resource poor, low-income countries.

The main objective of any screening program is a reduction in mortality. The efficacy of screening by VIA, in reducing the incidence and mortality from cervical cancer has been investigated through cluster randomized controlled trial, in Dindigul (India), a single round of VIA-based screening led to a 25% reduction in cervical cancer incidence and 35% reduction in mortality over 7 years of follow-up.[50] Similarly in Mumbai, a VIA-based randomized control trial showed a 31% reduction in cervical cancer mortality in the screening group (mortality rate ratio = 0.69; 95% confidence interval: 0.54-0.88; $P = 0.003$) when compared to the control group.[51] Thus, the studies conducted in India provide sufficient evidence to prove that visual screening by VIA for cervical cancer is a simple, affordable, feasible and accurate tool for implementation in all health care setting.

Breast cancer

Breast cancer is the commonest cancer in urban Indian women and the second commonest in the rural women.[52] Over 140,000 new breast cancer patients are diagnosed annually in India.[1] In India, often women do not present for medical care early enough due to various reasons such as illiteracy, lack of awareness, and financial constraints. Hence, it is hardly surprising that the majority of breast

Table 5: Overview of primary screening tools for oral cancer[29-42]

Screening test	Strengths	Limitations
Visual inspection: Involves inspection to detect visible lesions of the oral cavity in a good light. It can be performed by a dentist, physician or a trained heath care worker	Requires less infrastructure Can be done in field Immediate results Neck can also be palpated for any nodes High specificity Simultaneous counseling can be provided to high risk	Training of healthcare worker Maintenance of quality
MSE: Involves inspection of mouth by the patient himself/herself	No infrastructure required	Need to educate the population Literate population required Continuous motivation required
Mythelene/toluidine blue staining: Toluidine blue staining is a simple method, with the dye having an affinity to cancer cells. Commercial kits with protocol are available for large-scale screening of high-risk populations or in clinical patients by topical application or mouth rinsing	Easy and reliable Helpful for patient having panoral field cancerization	False positive and false-negative exits Can be used as an adjunct to clinical judgment and not a substitute for either judgment or biopsy More of a diagnostic test rather than a screening test
Direct fluorescence visualization: Involves visualization of the oral cavity with a hand held device emitting florescent light	Easy	Requirement of specialized equipment Yet to be proven (not many studies reported)
Oral exfoliative cytology: A suspicious area is gently scraped to collect a sample of cells. These cells are placed on a glass slide and stained with dye, so that they can be easily viewed under a microscope	Sample collection is easy Sample can be collected in field setting	Interpretation largely subjective in nature Early cancer cases it is extremely difficult to tell where exactly cancer cells came from There may be only a small number of abnormal cells identifiable in a smear

MSE=Mouth self-examination

cancer patients are diagnosed at a locally advanced stage.[53,54] In addition, lack of an organized breast cancer screening program, paucity of diagnostic aids, and general indifference toward the health of females in the predominantly patriarchal Indian society further compound the problem.[55,56] In this scenario, one of the obvious solutions to the problem seems to be down staging the disease by early detection through screening. However, considering the constraints of huge population and paucity of resources, which is the most practical breast screening test to be introduced remains to be answered. Though, mammography has come to be regarded as being synonymous with breast cancer screening, it may not be ideal in India, as it is expensive, requires skilled manpower and stringent quality control, and is on the whole a complex screening test. In addition, since the median age at diagnosis of breast cancer is approximately 10 years younger in Indians than that in the developed world, and since mammography is less effective in women below the age of 50, this test may not significantly affect mortality in Indian population.[57] Therefore, physical examination (PE) by trained personnel may be a viable option considering human and economic cost and difficulties with optimizing mammographic screening. Some researchers have suggested PE to be as effective as or even better than mammography for breast cancer screening in resource poor settings.[58] CBE trails in India have shown a decent sensitivity and high specificity [Table 3] as well as excellent agreement between expert and the primary health workers as a vast majority of the population would have to depend on primary health workers for their routine health care needs. The trials in India are still not completed hence the question, whether CBE based screening program will lead to a significant reduction in breast cancer mortality is yet to be answered.[27,59]

Oral cancer

Oral cancer is a fatal disease, accounting for the second highest incidence of malignancy in males and the fifth in females in India.[1] The relatively high prevalence of oral cancer in India is mainly because of extremely popular use of the smokeless tobacco product called gutkha and betel quid chewing (with or without tobacco), which renders its population and especially its youth to a greater risk of developing oral submucous fibrosis, a premalignant disease resulting in increased incidence of oral cancer in younger patients.[60] Unfortunately, large numbers of new cases are detected in advanced stages, resulting in poor survival rates. However, in view of the high incidence, a recognizable precancerous lesions and improved

survival after treatment of early-stage disease oral cancer is a suitable disease for screening.[5] The UK working group on screening for oral cancer and precancer in 1990's had concluded that the most suitable screening for oral cancer and precancer is a thorough and methodical examination in good lighting of the mucosal surfaces of the oral cavity.[31] Trials in India of oral, visual inspection to detect lesions by trained health workers have shown pooled sensitivity of 87.90% and specificity of 92.05% [Table 3]. Results of community-based cluster randomized controlled intervention trial in Trivandrum district, Kerala, South India, conducted to evaluate the efficacy of screening in reducing incidence and mortality from oral cancer have also shown significant reduction in oral cancer mortality among users of tobacco or alcohol, or both.[61] As an alternative MSE was evaluated in a study involving 34,766 subjects in India and was found to have low sensitivity of 18% [Table 3] as well as role of health education in sustained practice of MSE needs to be evaluated. A study of 120 subjects was conducted to establish the usage of methylene blue technique in detecting oral precancerous/cancerous lesions was found to have comparable sensitivity, but lower specificity, and the result establishes methylene blue as an alternative to toluidine blue as a diagnostic agent rather than a method for screening. Hence, in addition to primary preventive efforts to reduce tobacco and alcohol use, oral cancer screening through visual inspection of the oral cavity by a trained health worker can be a worthwhile initiative for control of oral cancer.

CONCLUSIONS

India is at a crossroads and needs to undertake urgent steps to introduce appropriate screening methods to reduce late stage cancer presentations and mortality. However, before implementation of a screening program it should be borne in mind that though screening has potential benefits such as reduced mortality from cancer, reduced incidence of invasive cancer, reassurance for those screened negative and decreased costs of treatment, it also has certain disadvantages such as psychological trauma for false-positive cases, unnecessary treatment of precursor lesions which may never have progressed, false reassurance for false-negatives, and not least, the financial costs of setting up the program.[62,63] The outcomes from the Indian studies provide sufficient evidence for the development of public health policies and implementation of screening for cervical cancer using VIA and oral cancer using a visual examination by trained health worker as part of primary health care delivery system. For breast cancer, though CBE by primary health workers appears to be a simple and feasible strategy for reduction in breast cancer mortality, there is a lack of evidence from Indian studies to support or refute the introduction of CBE screening programs in primary health care package. This however provides a window of opportunity to conduct further studies using a high-quality methodology for recommending effective breast cancer screening tool for developing countries. In conclusion, our study highlights the success and availability of visual screening tools in early detection and mortality reduction of major neoplasia in resource-poor setting and thus, oral and cervical cancer screening can be implemented as an integral part of assured primary health care package in developing countries.

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