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

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%. 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 650,000 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. 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]. Subsequently, Rose and Barker 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 and is home to a third of the world oral cancer burden. 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.

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 trials, 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.

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 87.05%, respectively. The pooled sensitivity and specificity for cytology positivity at low-grade squamous intraepithelial neoplasia threshold were 65.25% 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 one of the leading cause of cancer mortality in India, accounting for 17% of all cancer deaths among women aged 30-69 years. [31] In developed countries, conventional cytology screening programs have
Table 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 (×2-4) | Same as VIA                                                                                                                                   | Magnification does not improve the test performance over and above that of naked-eye visualization, Variable (low to moderate) sensitivity and specificity for CIN2+ |
| 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”) | 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) |
| 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+                                                                                                                   | Requires laboratory and specialized technicians, Lag in test results can contribute to loss to follow-up and delay treatment |
| 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 | 39,632 | 11 | 63.25 | 29.50-91.40 | 93.17 | 86.00-99.09 |
| VIA[12-23] | 89,461 | 14 | 68.76 | 31.60-100.00 | 84.02 | 53.30-91.23 |
| VIAM[12,14,16] | 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[45-49] | 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, Pap=Papanicolaou, 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 as 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                                     |
| 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 | Higher cost than mammography for low-volume operations |
| Clinical breast examination: Involves breast visual inspection and palpation by the physician (a systematic technique described by Pennypacker and Pilgrim) | Lower radiation dose                | Same as normal mammography                       |
| Breast self-examination: Individual herself carries out breast examination (Mamon and Zapka (1983) outlined eight step technique) | Computer-aided detection            | Variable sensitivity and specificity depending on the expertise of the physician |
|                                                                                | Requires less infrastructure        | Training women                                   |
|                                                                                | Cheaper than mammography            | Continuous motivation to maintain regular self-examination |
|                                                                                | Immediate results                   |                                                 |
|                                                                                | No infrastructure required          |                                                 |
|                                                                                | Empower women by allowing them to take responsibility for their own health |                                                 |
| 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. [41] 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 cancer is diagnosed in advanced stages. The screening and early detection of breast cancer is therefore of paramount importance in India. |                                    |                                                 |
Cancer patients are diagnosed at a locally advanced stage. 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. 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. 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. 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.

**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. 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. 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

| 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 health care worker | Requires less infrastructure | Training of healthcare worker |
| MSE: Involves inspection of mouth by the patient himself/herself | No infrastructure required | Need to educate the population |
| 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 | False positive and false-negative exits |
| Direct fluorescence visualization: Involves visualization of the oral cavity with a hand held device emitting florescent light | Easy | Requirement of specialized equipment |
| 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 | Interpretation largely subjective in nature |

MSE=Mouth self-examination

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Table 5: Overview of primary screening tools for oral cancer

| 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 health care worker | Requires less infrastructure | Training of healthcare worker |
| MSE: Involves inspection of mouth by the patient himself/herself | No infrastructure required | Need to educate the population |
| 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 | False positive and false-negative exits |
| Direct fluorescence visualization: Involves visualization of the oral cavity with a hand held device emitting florescent light | Easy | Requirement of specialized equipment |
| 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 | Interpretation largely subjective in nature |
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% \([\text{Table 3}]\). 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% \([\text{Table 3}]\) 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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