Recommendations for screening and early detection of common cancers in India

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Cancers of the breast, uterine cervix, and lip or oral cavity are three of the most common malignancies in India. Together, they account for about 34% of more than 1 million individuals diagnosed with cancer in India each year. At each of these cancer sites, tumours are detectable at early stages when they are most likely to be cured with standard treatment protocols. Recognising the key role that effective early detection and screening programmes could have in reducing the cancer burden, the Indian Institute for Cytology and Preventive Oncology, in collaboration with the US National Cancer Institute Center for Global Health, held a workshop to summarise feasible options and relevant evidence for screening and early detection of common cancers in India. The evidence-based recommendations provided in this Review are intended to act as a guide for policy makers, clinicians, and public health practitioners who are developing and implementing strategies in cancer control for the three most common cancers in India.

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Background

Non-communicable diseases were the leading cause of mortality in India in 2012.[1] With an estimated burden of more than 1 million individuals diagnosed with malignant disease in India each year,[2] cancer is a key focus of the National Programme for the Prevention of Cancer, Diabetes, Cardiovascular Disease and Stroke,[3] which has incorporated the earlier National Cancer Control Programme since 2010. Past Reviews in *The Lancet Oncology* have described the growing burden of cancer in India, discussed issues related to the delivery of equitable and affordable cancer care, and highlighted priorities for cancer research in India.[4–6]

Generally, cancers detected at early stages are more likely to be cured with standard treatment protocols than those diagnosed later.[7] The substantial delay in detection and diagnosis of cancers in low-income and middle-income countries is one of the key reasons for the difference in cancer outcomes between high-income countries and low-income and middle-income countries.[7,8] Screening programmes apply the most focused and sometimes resource-intensive, early detection strategies in which patients are tested for cancer before symptoms are apparent or pronounced. Early detection programmes use public health instruments to identify individuals with cancer before their disease develops into advanced stage cancer at which time successful treatment can become difficult or sometimes impossible.

In this Review, we focus on early detection and screening methods of cancers in India. The three most widely recorded malignancies in India are cancers of the breast, uterine cervix, and lip and oral cavity, which together account for about 34% of all cancers in India each year.[2] For each of these three cancer sites, tumours are detectable at early stages. Additionally, cancers of the oral cavity and cervix are amenable to secondary prevention because they can be detected and addressed at precancerous stages.[9]

Recognising the key role that effective early detection and screening programmes can have in reducing the cancer burden in India, the Institute for Cytology and Preventive Oncology (Indian Council of Medical Research) in collaboration with the US National Cancer Institute Center for Global Health, held a workshop in September, 2013, to summarise feasible options and relevant evidence for screening and early detection of common cancers. The invited panel consisted of expert participants including policy makers, researchers, programme implementers, clinicians, and public health professionals. The process to derive recommendations for each cancer had several stages. For each cancer site, experts presented a formal review of the existing evidence for screening strategies for that cancer. The key issues presented were then debated in an open forum. Detailed notes of the sessions were recorded and the final summary of evidence and recommendations were made through summary and revision from all authors. All authors came to a consensus on the final conclusions put forward by the group.

In view of India's tremendous diversity in terms of socioeconomic conditions of the population and health-system capabilities, health-care services for high-income earners can and do provide care that matches the standards of developed countries. However, the guidelines in this Review target public health programmes and thus consider the intrinsic diversity of the country to recommend strategies that may benefit the majority of the population and health-delivery systems, and are sustainable in a wide range of situations. The audience of the report is thus primarily public health practitioners, the medical community, and policy makers.

Early detection of non-communicable diseases is emphasised in the National Programme for the Prevention of Cancer, Diabetes, Cardiovascular Disease and Stroke and the Maternal Health Division of the

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Ministry of Health and Family Welfare is in the process of developing a set of operational guidelines for use in breast and cervical cancer in India. However, these uniform guidelines are not widely available, do not include oral cancer, and have not yet been nationally implemented. Since many states, non-governmental organisations, and clinical institutions have begun screening efforts in various capacities, we put forth a set of evidence-based recommendations to inform and stimulate national strategies for implementation of cancer control for cancers of the breast, cervix, and oral cavity in India.

Cervical cancer

Cervical cancer is one of the most common cancers in women worldwide, with an estimated prevalence of 1 547 161 cases in 2012.[2] In India, cervical cancer is the second most common cancer in women, with almost twice the age-standardised incidence (22·0 *vs* 14·0 per 100 000) and mortality (12·4 *vs* 6·8 per 100 000) compared with worldwide rates in 2012.[2] An overall 5-year relative survival of 46% for all cervical cancers in India is strongly determined by stage at diagnosis, with survival as low as 7·4% for advanced stage disease compared with 73·2% for localised cancer.[7]

Persistent infection with high-risk oncogenic human papillomaviruses (HPV; HPV types 16 and 18 are the most oncogenic, followed by less oncogenic HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73) is the major and primary risk factor for cervical cancer. Other confirmed and suspected risk factors include: immunodeficiency due to HIV infection, organ transplant and other causes; genetic polymorphisms, particularly in the major histocompatibility complex; co-infections with many HPV types and *Chlamydia trachomatis*; lifestyle factors (early sexual activity, many sexual partners, many pregnancies, and smoking); and family history in first degree relatives.[10] Cervical cancer is clearly amenable to screening because its natural history is well understood and it has a reasonably long precancerous state (10–20 years). Widely used methods for screening of precancerous cervical lesions include naked eye visual inspection with acetic acid or Lugol's iodine; visual inspection under a magnifying device with acetic acid; conventional (Papanicolaou [Pap] smear) or liquid-based cytological tests; and HPV DNA testing. These methods have been discussed recently in the context of resource-constrained countries such as India.[11]

Visualisation of the cervix after acetic acid application with the naked eye or under low-level magnification aims to examine the transformation zone for cervical cancer or its precursors as well defined, dense, opaque white areas or growths 1 min after the application of 3–5% acetic acid under a good light source. The transformation zone appears mustard yellow with Lugol's iodine in the presence of cervical precancers or cancers.[12–14] Reported sensitivity of these screening tests varies widely with naked eye visual inspection and acetic acid (41–79%), with Lugol's iodine (56–98%), and under low-level magnification (60–82%). Reported specificity ranges from 14% to 98% with naked eye visual inspection with acetic acid, 75–85% with Lugol's iodine, and 85–88% under low level magnification.[11–14] Studies show that magnification does not improve the performance of visual inspection with acetic acid significantly.

Although some studies have observed no mortality benefit with visual inspection with acetic acid or Lugol's iodine screening,[15] other evidence suggests these methods might be suitable ways to screen with reasonable accuracy in developing countries.[11,16] A 25% reduction in cervical cancer incidence and a 35% reduction in cervical cancer mortality (incidence hazard ratio [HR] 0·75 [95% CI 0·55–0·95] and mortality HR 0.65 [0·47–0·89] in the intervention *vs* control groups) were observed after one round of screening with visual inspection with acetic acid by trained paramedical workers in the Dindigul district, Tamil Nadu, India (274 430 person-years, 167 cervical cancer cases, and 83 cervical cancer deaths were accrued in the intervention group compared with 178 781 person-years, 158 cases, and 92 deaths in the control group during 2000–06).[17] Preliminary results of a large-scale community-based cluster randomised trial[18] in Mumbai showed significant downstaging of cervical cancer using visual screening with acetic acid with a screening interval of 2 years. Results from the same trial[18] after 12 years (four rounds) of follow-up showed a significant reduction in cervical cancer mortality (rate ratio [RR] 0·69; 95% CI 0·54–0·88; p=0·003).[16] By contrast, visual inspection with Lugol's iodine has not been investigated as extensively as visual inspection with acetic acid. Both methods have limitations such as low sensitivity in women older than 50 years or postmenopausal women, the need for trained personnel, continuous training and supervision, and suboptimum reproducibility in resource-constrained settings.[12]

Conventional Pap smear testing or liquid-based cytological tests are widely accepted and routinely used screening methods in high-income countries, in which a trained health worker obtains cervical samples that are stained in a laboratory and then analysed by a trained cytotechnician or cytopathologist. The sensitivity of cytological tests are low (26–70%), but the specificity can be as high as 96–99%.[11–13] Because cytological interpretation is highly subjective, good quality samples and an experienced cytologist are essential, which can be challenging in a resource-limited setting. If results are inconsistent, repeat procedures and delays between screening results and treatment (three visits are needed) can lead to a loss in follow-up. Liquid-based cytological tests have similar sensitivity and specificity to Pap smears.[19] The liquid-based methods benefit from standardised preparations with minimum artifacts and the ability to use the same samples for further molecular assays of HPV;[20,21] however, they are more expensive than

other screening methods such as visual inspection with acetic acid or Lugol's iodine.

For HPV DNA testing, a health-care provider or the woman herself uses a brush to obtain a cervical sample.[11,12] Several technologies are available to detect either DNA of the most common high-risk HPV types or the mRNA of E6 or E7 protein expressed by these high-risk HPV types. Some HPV detection tests provide HPV genotype information in addition to detecting viral DNA. The sensitivity of HPV testing is higher than for other methods at 66–95%, with specificity between 76% and 95%.[11,12,14,22] HPV DNA testing is objective, has good reproducibility, and needs little training and experience. However, HPV DNA testing is not recommended in women younger than 30 years because of spontaneous regression of HPV infections in this age group.[15,23]

A cluster randomised controlled trial[24] in the Osmanabad district in Maharashtra, India, with a 7-year follow-up reported that one round of HPV testing in women aged 30–59 years was associated with a significant reduction in the number of advanced cervical cancers (53%) and deaths (48%) compared with the standard of care (awareness and opportunistic screening) control group. The same trial detected no significant benefit in terms of early detection or death with Pap smear or visual inspection with acetic acid.[15,24] The need for laboratory set-up, costs for an individual test, and the need for repeat visits are potential disadvantages of HPV DNA testing as a primary community screen in a country such as India.[22] If available at a reasonable cost, development of a simple, rapid, and accurate test for HPV DNA detection, could make HPV DNA testing a viable screening option in women who are older than 30 years. An HPV assay based on next-generation sequencing could provide advantages with respect to cost, to sensitivity, and the ability to run large numbers of assays in a short space of time.[25] One report determined that HPV assays on self-collected specimens approached the sensitivity of HPV assays on specimens collected by health workers, and self-collection can eliminate the need for the woman to attend a clinic for screening.[26] Other novel techniques in development for HPV detection are biomarkers for the proteins p16INK4a, Ki67, HPV-E4 and E6, and methylation of host or viral genes.[14]

A systematic review[27] found that screening every 5 years in women aged 30 years and older (cytological tests or HPV DNA testing *vs* no screening) resulted in a reduced mortality (RR 0·65, 95% CI 0·47–0·90) and downstaging of cervical cancer. Screening women between 30 years and 40 years even once or twice in their lifetime (by visual inspection with 3–5% acetic acid or HPV DNA testing) could reduce cervical cancer risk by 25–76%.[11,17,28] Cervical cancer screening with these methods in one or two clinical visits have been recommended as cost-effective alternatives to the conventional three-visit cytological testing in resource-poor settings.[9] WHO recommends that women younger than 30 years should not undergo screening except for women with HIV.[23]

Recommendations

First, primary screening with HPV DNA testing is the most reproducible and sensitive approach, even in a resource-limited setting such as in India, since a highly sensitive test such as HPV detection needs less frequent screening and could save programme costs. However, issues such as cost per test, protocols for transportation of cervical cell specimens, testing, reporting, treatment, and follow-up care of HPV-positive women still need to be addressed. Effective translation of evidence relies on a range of implementation issues. Development of an affordable, simple, rapid, and accurate test for HPV DNA detection would be ideal, and research funding for such a device should be a priority. Meanwhile, India should follow the stepwise implementation plan advocated by WHO and initiate the screening programme with visual inspection with acetic acid linked to treatment as the core intervention. The HPV detection test could be introduced as an expanded intervention if resources are available to introduce and sustain the technology.

Second, self-collection of vaginal samples for HPV DNA testing for detection of cervical cancer would reduce the need for human resources, and has the advantage of self-empowerment and privacy for these women. The key to successful implementation of self-sampling HPV testing is to promote awareness among women in the community in terms of screening, prevention, early detection, and treatment. This could be achieved, in part, by community health workers. The National Health Mission is a large community-oriented, multifaceted basic health-care delivery programme in India that employs many female community health workers (known as Accredited Social Health Activists). These women can be trained to perform door-to-door counselling and motivate women to undergo cervical cancer screening. With additional remuneration, these workers could obtain self-collected samples from women and transport them to the HPV testing centres.

Third, the number of screening programmes based on visual inspection with acetic acid has been increasing in India. A pilot programme in Tamil Nadu, India, showed the feasibility of an approach to integrate this type of screening into the existing health system. Visual inspection with acetic acid screening is likely to be used in national programmes following WHO guidelines[23] until resources allow the introduction of HPV tests. The expert group recommends the inclusion of quality assurance and evaluation in these programmes, following the latest WHO guidelines on quality assurance of a visual inspection with acetic acid based programmes.[29] The development of strategies for enhancing the implementation of visual inspection with acetic acid screening in India would help to introduce HPV testing as and when a more affordable and point-of-care test is available in the future.

Fourth, if HPV testing is introduced and resources for high-quality cytological tests are available, women who

are HPV positive can be triaged on the basis of this tests before referral to colposcopy.

Fifth, the task group consensus recommendation for the appropriate age and way to screen HPV, is to include visual inspection with acetic acid screening for women aged between 30 and 49 years and HPV testing as it becomes affordable for women aged 30 years and older. On the basis of present WHO guidelines,[23] a woman should be screened for cervical cancer at least once in her lifetime in a resource-poor setting. Once this is achieved, screening women for cervical cancer at more regular intervals (5 years or 10 years) can be considered.

Sixth, screening of eligible women who visit health-care systems for other reasons (opportunistic screening) will increase the level of awareness of cervical cancer in women, and help to integrate cervical cancer screening with other non-communicable disease services.

Oral cancer

Oral cancer includes cancers of the upper-lip and lower-lip mucosa; dorsal, ventral, and border of the anterior two-thirds of the tongue; gingiva; floor of the mouth; hard palate; cheek mucosa; vestibule; and retromolar area. Although the worldwide burden is low (estimated age-standardised incidence in 2012 of 4·0 per 100 000), oral cancer is the third most common cancer in India after cancers of the breast and cervix.[2] In fact, India has the ninth highest incidence of oral cancer in the world (age-standardised incidence 7·2 per 100 000), with age-adjusted incidence in some areas of the country as high as 17·1 per 100 000 men and 7·6 per 100 000 women.[30] National mortality is estimated at 6·7 per 100 000 in men and 3·0 per 100 000 in women.[2] Although 5-year survival is between 54·3% and 60·2% for localised cancers of the mouth, it can be as low as 3·1–3·3% in advanced stages of oral cancer.[7]

Tobacco smoking, smokeless tobacco use, betel quid chewing (paan, betel leaf, areca nut, sweeteners), and alcohol are major risk factors for the development of oral cancer in countries such as India.[31–34] Evidence suggests that cigarette smoking is associated with a 1·9–3·6 times increase in oral cancer risk,[35–37] and that chewing tobacco is associated with an even greater risk (relative risk 4·7–12·8).[37–40] Betel quid chewing with or without tobacco is also an important risk factor of oral cancer and women show increased relative risk for cancer compared with men chewing the same amount.[34] Risks of oral cancer for betel quid chewing with tobacco are 1·5–5·4 times greater than with betel quid chewing without tobacco.[33,34] Alcohol, the next major risk factor, has been found to have a strong synergistic role with tobacco in oral carcinogenesis.[33,38] The population attributable risk of oral cancer for alcohol is about 18%[33] and estimates of the attributable risk of combined exposure to alcohol and tobacco vary from 35% to 80%.[41,42] HPV infection-related risk seems specific to cancers of the oropharynx (base of tongue, lingual tonsil, soft palate, uvula, tonsil, oropharyngeal region, and Waldeyer's ring) as opposed to oral cancer.[33,43]

Despite strong evidence of increased risk with oral (and other) cancers, the number of tobacco and alcohol users in India is growing.[44,45] This group constitutes a high-risk target population for early oral cancer detection.[46] Primary prevention for these high-risk groups in the form of education and counselling towards smoking and alcohol cessation programmes is a key prevention strategy for the future. The discrepancy in the level of awareness of risk factors in different populations of India and the increasing incidence of oral cancer in young adults[47] shows the need for targeted interventions to educate high-risk groups and counsel these individuals towards cessation of tobacco and alcohol programmes. An anti-tobacco community programme in Kolar, Karnataka, India, reported successful tobacco cessation in 26·5% of men and 36·7% of women after education through screening of films, exhibits, and personal contact with photographs displaying the harmful effects of tobacco.[48]

Oral cancers are preceded by potentially malignant disorders that can be readily detected in the oral cavity because of an easy access of the site without privacy requirements (unlike the cervix).[46] Early detection and treatment of these precancerous lesions can substantially reduce the cancer-specific morbidity and mortality.[9] Prospective studies have reported annual incidences of potentially malignant disorders of 1·1–2·1 per 1000 men and 0·2–1·5 per 1000 women.[49–51] In occupational studies of predominantly male workers, incidence was as high as 5·2–30·2 per 1000 individuals dependent on the type and pattern of tobacco use.[51–53] The annual proportion of malignant transformation has been reported as 9·7 per 1000 potentially malignant disorders per year in men and women who use tobacco.[54] Evidence from a population-based cohort study[55] in Kerala, India, showed a particularly high proportion (16% per year) of malignant transformation for nodular leukoplakia. A door-to-door survey in rural India by basic health workers trained by dentists to detect lesions in the oral cavity that might be cancerous showed that the incorporation of an early cancer detection programme in the existing health-care infrastructure was feasible and beneficial.[56] Studies with a 5-year and 10-year follow-up have shown that educational interventions reduce tobacco use and decrease incidence of potentially malignant disorders.[57,58]

Oral visual examination is an established method of screening to detect the presence of potentially malignant disorders or very early stages of oral cancer with systematic visual inspection of the buccal and labial mucosa, gingivae, bucco-alveolar sulci, tongue, palate, and floor of mouth, by trained caregivers under adequate light with disposable instruments. The overall sensitivity (85%, 95% CI 59–95) and specificity (97%, 75–99) of oral visual examinations is moderately high,[59] with evidence from a 15-year follow-up trial[46] showing a 38% (95% CI 8–59) reduction in oral cancer incidence and 81% (69–89)

reduction in mortality in those who complied with all screening rounds in the high-risk population of tobacco and alcohol users. On the basis of these results, oral visual examination screening in high-risk populations was recommended every 3 years for adults aged older than 35 years. This method has been shown to be cost-effective in a resource-limited setting.[60] Although various supportive aids such as dyes, cytological tests, and light-based systems are available as adjuncts to oral visual examination for identification of very early stage oral cancers,[61,62] use of these adjunctive screening aids (summarised in the table) needs further study in high-risk target populations.

Recommendations

First, oral visual examination by well trained auxiliary health workers combined with tobacco and alcohol reduction counselling is recommended as the primary screening strategy in India.

Second, oral cancer screening should target high-risk populations (individuals who use tobacco products, alcohol, betel nut, or paan masala) and screening should be focused on adults aged 30–60 years, with a target of screening once every 3 years. Because tobacco users are a high-risk group for non-communicable diseases generally, this offers an opportunity to address multiple non-communicable diseases in the same setting. Effective implementation of this programme will need various initiatives such as increasing oral cancer awareness through various media, context-specific communication strategies, provision of high-quality health services, and opportunistic assessments.

Third, tobacco and alcohol control policies should be implemented at the same time. India was one of the first countries to sign and ratify the WHO Framework Convention on Tobacco Control.[69] The existing tobacco legislation in India, known as the Cigarettes and Other Tobacco Products Act (2003), already incorporates several clauses of WHO's framework. An amended version of the Cigarettes and Other Tobacco Products Act, which would strengthen the legal mandate and be largely compliant with the WHO Framework Convention on Tobacco Control is currently under consideration by the Indian Cabinet. However, the enforcement of the present tobacco policy is moderate to weak since the enactment of the law is by the Central Government in New Delhi, but enforcement is completely the responsibility of individual states, which might or might not give high priority to enforcement of tobacco control. State governments control the sale of alcohol; the present alcohol control policy, which includes a ban on advertisement, is on a voluntary basis and therefore can be easily circumvented by alcohol manufacturing companies.

Fourth, training health workers in the implementation of oral visual examination screening methods can make use of materials (eg, manuals and atlases) developed by the International Agency for Cancer Research and the Regional Cancer Center, Trivandrum, India.[70]

Fifth, facility-based opportunistic screening with selective community outreach clinics to remote communities can be considered. Linking communities together and improving dental access will help cover more patients and create awareness with respect to oral hygiene and oral lesions.

	Procedure	Interpretation of results	Sensitivity and specificity	Comments
Toluidine blue	1% aqueous solution of tolonium chloride, a metachromatic acidophilic nuclear vital dye, stains rapidly dividing cells, such as neoplastic tissue, by contrast with adjacent healthy mucosa, when applied for 30 s; 1% aqueous toluidine blue is applied to the suspected cancerous lesion for 30 s, then rinsed with tap water or a saline rinse and finally rinsed with 1% acetic acid for 30 s to reduce background staining	Subjective and variable; dark/royal blue shows cells positive for malignancy; light blue shows premalignant lesions; no colour shows healthy cells;[63] any staining should be investigated with more sensitive approaches such as directed biopsy or histological tests[64]	Varies on the basis of disease severity and the population screened; sensitivity 38–100% and specificity 9–93%[61,64]	Toluidine blue can be a useful adjunctive in individuals with lesions suspected to be cancerous; toluidine blue can represent underlying molecular changes, but negative results should be interpreted with caution[61,62,64,65]
Brush cytological test	A special brush is used to obtain a transepithelial sample (superficial or intermediate and basal layers) from the mucosal lesion; the material is spread on a clean, sterile glass slide, fixed with cytospray, stained with Papanicolaou stain, and analysed microscopically by a cytopathologist or with a computer-based imaging system	Results are reported as atypical (positive) or negative[62,66]	Sensitivity varies between 71% and 100% and specificity between 24% and 100%[64,66,67]	Although not recommended where a definitive scalpel biopsy is needed,[62,64] can be an effective adjunct screening aid; negative results should be interpreted with caution[65]
Light-based systems	Oral rinse of 1% acetic acid for 1 min followed by inspection with chemiluminescent or fibre optic visible light	Abnormal mucosa reflects light and seems brighter with defined margins, whereas healthy mucosa looks blue in 490–510 nm wavelength light;[61,62] in fluorescence imaging, abnormal tissue looks darker on stimulation with an intense blue light (400–460 nm), whereas healthy mucosa appears pale green in colour[62]	Large variations in sensitivity from 0–100% and specificity from 0–75%[64,68]	Even though these systems show promising results, little consistent evidence exists to support their routine use in screening of oral cancers

Table: **Adjunctive aids for screening oral cancer**

Finally, use of punch biopsy under local anaesthesia in the field by trained clinicians could help to link screening and diagnosis.

Breast cancer

Breast cancer is the leading cancer in women worldwide (annual age-standardised incidence rate in 2012 of 43·1 per 100 000 women) and 25·8 per 100 000 in India,[2] with reported incidence as high as 36·6 per 100 000 women in Bangalore, India.[30] Despite a lower incidence compared with the annual incidence worldwide, mortality for breast cancer in India (12·7 per 100 000) is similar to worldwide mortality (12·9 per 100 000). The 5-year relative survival for breast cancer varies from 76·3% for localised cancers to 14·9% for advanced stage disease.[7] Early detection of breast cancer improves survival and reduces associated medical costs.[71,72]

Factors strongly associated with increased risk of female breast cancer are older age, menopausal status (early menarche and late menopause), pregnancy (nulliparity and older age at first full term birth), and family history of breast cancer, especially in first and second degree relatives. Other important risk factors are lactation (absence or shorter duration of breastfeeding), genetic factors (*BRCA1/2* mutations), and hormonal factors, such as prolonged use of combination hormone replacement therapy after menopause. A high fat diet, obesity, increased alcohol intake, and reduced physical activity have also been associated with risk of breast cancer.[73,74] With the exception of the increased breast cancer risk associated with deleterious mutations of *BRCA1* and *BRCA2*, most of these risk factors convey a low-level increased breast cancer risk (RR ≤2·0), suggesting that the cause of breast cancer is probably multifactorial. Although risk factor modification through exercise and diet might favourably affect breast cancer risk, the magnitude of that risk benefit is likely to be low.

Breast cancer is less amenable to primary prevention through risk factor modification than are other cancers with strong and modifiable risk factors. For example, the incidence and mortality of tobacco-associated cancers are greatly reduced through effective tobacco-control programmes. Modification of breast cancer risk factors (eg, changing reproductive health patterns) is more difficult, and has a much smaller potential quantifiable benefit as measured by shifting incidence or mortality. Thus, the establishment of programmes that promote early detection, accurate diagnosis, and prompt treatment is a top priority for the Indian health system. Primary early detection methods for breast cancer include patient awareness and patient education with regards to screening methods such as breast self-examination, clinical breast examination, and screening mammography. Low awareness of breast cancer and its presentation as painless lumps or thickenings is a common obstacle to early detection in women from low-income and middle-income countries. Women need to be made aware that self-detected breast lumps should be assessed and possibly sampled to detect breast cancer at early stages.[75] Breast self-examination is the systematic assessment of both breasts by women themselves; any abnormality such as lumps or any change in colour or discharge should be noted and followed up. Formal breast self-examination training is not better than basic breast cancer awareness education in improving breast cancer outcomes, and can increase the biopsy frequency of benign lesions. As such, formal breast self-examination training is not recommended as a public health screening approach.[76,77] Nonetheless, women should be encouraged to seek evaluation of breast abnormalities that they find, and diagnostic systems need to be in place to ensure that women with breast abnormalities can undergo prompt and accurate evaluation, since some of these women will be presenting with early stage cancers.[78] Clinical breast examination of both breasts is a thorough, systematic visual and tactile palpation conducted in both sitting and supine positions by a doctor or trained primary health caregivers.[76,77] Although reported sensitivity is low (28–54%), the specificity of clinical breast examination is high (94–99%), and it has been shown to be cost effective.[79] Current evidence regarding the potential benefits of clinical breast examination remains minimal worldwide.[80] The success of clinical breast examinations is still under trial in India, although preliminary evidence suggests downstaging of the disease.[18] Nonetheless, clinical breast examination is a fundamental instrument for breast assessment and should be used as a routine method for breast cancer diagnosis.[81]

Screening mammography is the most thoroughly studied screening approach and is the only method that has been shown through randomised trials to reduce breast cancer mortality. Although mortality is reduced on average by 23% in women aged 50–69 years,[82] the amount of benefit from mammography is under debate compared with the number of women who have false-positive results that need diagnostic work-up, or who undergo treatment for disease that would be unlikely to progress to life-threatening cancer in the patient's natural lifetime.[76,80] Reported sensitivity varies from 64% to 90% and specificity from 82% to 93%.[77] Screen film mammography and full-field digital mammography produce radiographical images. Digital mammography uses computer-aided detection software, but is costly. Generally, increased breast tissue density decreases test sensitivity. For women younger than 40 years, who have fewer breast cancers and also have denser breasts on average compared with women older than 40 years, the yield of cancers diagnosed is very low, which increases the number of false positives reported. Feasibility and affordability of mammography, along with the risk of increased false positives and over-diagnosis are major concerns with mass routine mammography screening in low-income and middle-income countries such as India.[71,76,77] In India, where the peak incidence of breast cancer is in younger women,[30]

breast cancer detection by mammography will probably be lower than in other countries.[76]

Breast ultrasonography is a key diagnostic adjunct to any early detection programme based on mammography or clinical breast examination. Reports from low-income and middle-income countries suggest that the use of screening ultrasonography might be an effective alternative screening facility that can be adopted in low-resource settings, with an overall sensitivity of 53–67% and specificity of 89–99%.[83,84] Ultrasound might be particularly helpful in younger women (aged 40–49 years) with dense breasts, where sensitivity using ultrasound can exceed 75%.[85,86] However, the requirement of trained professionals to perform and interpret ultrasound is a major hurdle. Although ultrasound is not recommended as a clinical screening test, its usefulness in population-based mass screening programmes needs to be properly evaluated in clinical trials, especially with respect to false positives and subsequent numbers of unnecessary biopsies and surgeries.[80,87] New efforts are underway to develop automated, more objective ultrasound techniques and equipment.[88–90] In view of India's expertise in computer software technology and its advanced medical community, India could make a substantial contribution to ultrasound research for breast cancer detection. Other technologies for breast cancer screening that need further investigation include MRI, computer-aided detection of mammography, tomosynthesis, thermography, and tissue sampling.[80,91]

Screening strategies are moving towards a risk-based approach rather than a broad age-based and sex-based recommendation. To use this risk-based approach, India will need to assess risk factors and incorporate this information into breast cancer screening in the near future.[92]

Recommendations

First, early detection of breast cancer is a public health priority in India. However, early detection programmes should be appropriately cautious to avoid the risk of false positives and unnecessary biopsies and surgeries. As mammography is not an affordable approach for population-based screening in a low-resource setting, clinical breast examination combined with diagnostic ultrasound should be considered for breast cancer screening in this setting, especially in women younger than 50 years where the risk–benefit ratio of screening mammography seems to be more problematic. When mammography is available, its primary use is for diagnostic assessment of focal breast findings such as lumps, thickenings, or localised symptoms. Breast ultrasound is even more useful for diagnostic work-up in a resource-limited setting and can improve the specificity of findings from a clinical breast examination. Diagnostic mammography provides a complete picture of the breast; however, its usefulness is reduced in women with dense breasts, whose cancers can be obscured from view. On average, premenopausal women younger than 50 years are more likely to have dense breasts, although tremendous variation exists at all ages. In view of India's large population, mammography might be applicable to many women as a diagnostic method for women older than 40 years with signs or symptoms suggestive of breast cancer, even if the proportion of high-income women is small. When screening mammography is a realistic option with existing resources, women aged 50–65 years should be prioritised, because mortality reduction and relative-risk ratios are the highest in this group. Tissue sampling methods should be carefully considered in any early detection programme to determine how detected lesions will be diagnosed. Fine needle aspiration cytological tests should be considered for community early detection and screening programmes, particularly in young women in India. Fine needle aspiration cytological tests are the most technically simple and low-cost approach to tissue sampling, but also need highly trained cytologists to provide accurate diagnoses.[88] Ultrasound-guided core biopsy can be used in settings where resources are available.

Second, for effective breast cancer prevention, awareness and education (starting at age 30 years) supplemented with clinical breast examination screening and early detection programmes (at age 40–60 years) should be promoted in women at least once in every 3 years. Linking these initiatives with breast health might create a positive influence: education and screening can be included in antenatal and postnatal check-ups to encourage a lifelong habit and create awareness about breast cancer.

Third, to provide patient access to prompt diagnosis and treatment, access to fine needle aspiration cytological tests or core needle biopsy with appropriate follow-up services should be made available. Systems can and should be set up in different ways depending on the unique environment and organisation of the health system in different regions; this has been addressed in detail by groups such as the Breast Health Global Initiative.[75]

Fourth, on the basis of the epidemiological profile of breast and cervical cancers in India, education and clinical breast examination could be integrated in one screening visit along with cervical cancer screening that begins at the age of 30 years.

Fifth, women should be provided with awareness education about breast cancer, partnered with access to diagnostic services and prompt and adequate stage-based treatment.

General recommendations for cancer screening in India

Early detection and screening programmes across India need the development of a range of documents and instruments, including guidelines, manuals, and implementation aids such as decision trees and algorithms and investments in human resources. A well-developed system for follow-up and quality assurance is essential. Quality of care and population coverage should be

Search strategy and selection criteria

A literature search was done between Dec 1 and 31, 2013, in PubMed and Google Scholar to identify studies of all relevant randomised controlled clinical trials on oral, breast, and cervical cancer screening conducted in India, and published in English language using the following keywords in titles and abstracts: "cancer screening" OR "oral cancer screening" OR "breast cancer screening" OR "cervical cancer screening" combined with search terms "clinical trials" OR "randomised controlled trials" AND "India". The search was not limited by year of publication. A preliminary review of abstracts was done to determine study relevance. Studies that met the following eligibility criteria were included for further review of the full-text article: studies on randomised controlled trials of cancer screening (oral, breast, and cervical) in India, articles in English, review articles on cancer screening (oral, breast, and cervical) in India. In addition to the electronic search of keywords, we also searched the reference list of all identified relevant studies and review articles on the subject of cancer screening in India.

emphasised, and indicators should measure effect and quality of care in terms of parameters such as sensitivity, specificity, incidence, mortality, downstaging, referral and follow-up services, and human resources. Potential barriers to screening, such as cancer stigma, fatalism, and gender inequities need to be better understood and addressed in qualitative and quantitative studies that inform effective programmes and policies. Finally, health economic analyses of cancer prevention approaches will be key for optimum resource allocation and prioritisation.

Contributors

All authors contributed to the recommendations, critically reviewed manuscript drafts, and approved the final version.

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References

1 WHO. Mortality and burden of disease estimates for WHO member states in 2012. http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html (accessed June 5, 2015).

2 Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0 Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2012. http://globocan.iarc.fr 2013. (accessed Feb 24, 2015).

3 Ministry of Health and Family Welfare. National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke 2010–11. http://www.nhp.gov.in/node/179 (accessed Feb 24, 2015).

4 Mallath MK, Taylor DG, Badwe RA, et al. The growing burden of cancer in India: epidemiology and social context. *Lancet Oncol* 2014; **15:** e205–12.

5 Pramesh CS, Badwe RA, Borthakur BB, et al. Delivery of affordable and equitable cancer care in India. *Lancet Oncol* 2014; **15:** e223–33.

6 Sullivan R, Badwe RA, Rath GK, et al. Cancer research in India: national priorities, global results. *Lancet Oncol* 2014; **15:** e213–22.

7 Sankaranarayanan R, Swaminathan R, Brenner H, et al. Cancer survival in Africa, Asia, and Central America: a population-based study. *Lancet Oncol* 2010; **11:** 165–73.

8 Sankaranarayanan R, Boffetta P. Research on cancer prevention, detection and management in low- and medium-income countries. *Ann Oncol* 2010; **21:** 1935–43.

9 Sankaranarayanan R. Cancer prevention and care in India: an unfinished agenda. *Lancet Oncol* 2014; **15:** 554–55.

10 Schiffman M, Hildesheim A. Cervical cancer. In: Schottenfeld D, Fraumeni JF, eds. Cancer Epidemiology and Prevention. New York: Oxford University Press, 2006.

11 Saxena U, Sauvaget C, Sankaranarayanan R. Evidence-based screening, early diagnosis and treatment strategy of cervical cancer for national policy in low-resource countries: example of India. *Asian Pac J Cancer Prev* 2012; **13:** 1699–703.

12 Arbyn M, Sankaranarayanan R, Muwonge R, et al. Pooled analysis of the accuracy of five cervical cancer screening tests assessed in eleven studies in Africa and India. *Int J Cancer* 2008; **123:** 153–60.

13 Almonte M, Ferreccio C, Winkler JL, et al. Cervical screening by visual inspection, HPV testing, liquid-based and conventional cytology in Amazonian Peru. *Int J Cancer* 2007; **121:** 796–802.

14 Cuzick J, Bergeron C, von Knebel Doeberitz M, et al. New technologies and procedures for cervical cancer screening. *Vaccine* 2012; **30** (suppl 5)**:** F107–16.

15 Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. *N Engl J Med* 2009; **360:** 1385–94.

16 Shastri SS, Mittra I, Mishra GA, et al. Effect of VIA screening by primary health workers: randomized controlled study in Mumbai, India. *J Natl Cancer Inst* 2014; **106:** dju009.

17 Sankaranarayanan R, Esmy PO, Rajkumar R, et al. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. *Lancet* 2007; **370:** 398–406.

18 Mittra I, Mishra GA, Singh S, et al. A cluster randomized, controlled trial of breast and cervix cancer screening in Mumbai, India: methodology and interim results after three rounds of screening. *Int J Cancer* 2010; **126:** 976–84.

19 Arbyn M, Bergeron C, Klinkhamer P, Martin-Hirsch P, Siebers AG, Bulten J. Liquid compared with conventional cervical cytology: a systematic review and meta-analysis. *Obstet Gynecol* 2008; **111:** 167–77.

20 Eide ML, Debaque H. HPV detection methods and genotyping techniques in screening for cervical cancer. *Ann Pathol* 2012; **32:** e15–23, 401–09.

21 Hoda RS, Loukeris K, Abdul-Karim FW. Gynecologic cytology on conventional and liquid-based preparations: a comprehensive review of similarities and differences. *Diagn Cytopathol* 2013; **41:** 257–78.

22 Cuzick J, Clavel C, Petry KU, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. *Int J Cancer* 2006; **119:** 1095–101.

23 WHO. Comprehensive cervical cancer prevention and control—a healthier future for girls and women—WHO guidance note; Geneva: World Health Organization, 2013.

24 Sankaranarayanan R, Nene BM, Dinshaw KA, et al, and the Osmanabad District Cervical Screening Study Group. A cluster randomized controlled trial of visual, cytology and human papillomavirus screening for cancer of the cervix in rural India. *Int J Cancer* 2005; **116:** 617–23.

25 Yi X, Zou J, Xu J, et al. Development and validation of a new HPV genotyping assay based on next-generation sequencing. *Am J Clin Pathol* 2014; **141:** 796–804.

26 Gravitt PE, Belinson JL, Salmeron J, Shah KV. Looking ahead: a case for human papillomavirus testing of self-sampled vaginal specimens as a cervical cancer screening strategy. *Int J Cancer* 2011; **129:** 517–27.

27 Peirson L, Fitzpatrick-Lewis D, Ciliska D, Warren R. Screening for cervical cancer: a systematic review and meta-analysis. *Syst Rev* 2013; **2:** 35.

28 Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD, et al, and the Alliance for Cervical Cancer Prevention Cost Working Group. Cost-effectiveness of cervical-cancer screening in five developing countries. *N Engl J Med* 2005; **353:** 2158–68.

29 WHO. Monitoring national cervical cancer prevention and control programmes: quality control and quality assurance for visual inspection with acetic acid (VIA)-based programmes. Geneva: World Health Organization, 2013.

30 Indian Council of Medical Research. Three year report of Population Based Cancer Registries, 2009–2011. Bangalore: National Centre for Disease Informatics and Research/National Cancer Registry Programme, 2013.

31 Gupta PC, Pednekar MS, Parkin DM, Sankaranarayanan R. Tobacco associated mortality in Mumbai (Bombay) India. Results of the Bombay Cohort Study. *Int J Epidemiol* 2005; **34:** 1395–402.

32 Pednekar MS, Gupta PC, Yeole BB, Hébert JR. Association of tobacco habits, including bidi smoking, with overall and site-specific cancer incidence: results from the Mumbai cohort study. *Cancer Causes Control* 2011; **22:** 859–68.

33 Radoï L, Luce D. A review of risk factors for oral cavity cancer: the importance of a standardized case definition. *Community Dent Oral Epidemiol* 2013; **41:** 97–109, e78–91.

34 Guha N, Warnakulasuriya S, Vlaanderen J, Straif K. Betel quid chewing and the risk of oral and oropharyngeal cancers: a meta-analysis with implications for cancer control. *Int J Cancer* 2014; **135:** 1433–43.

35 Muwonge R, Ramadas K, Sankila R, et al. Role of tobacco smoking, chewing and alcohol drinking in the risk of oral cancer in Trivandrum, India: a nested case-control design using incident cancer cases. *Oral Oncol* 2008; **44:** 446–54.

36 Dangi J, Kinnunen TH, Zavras AI. Challenges in global improvement of oral cancer outcomes: findings from rural Northern India. Tobacco induced diseases 2012; **10:** 1–5.

37 Jayalekshmi PA, Gangadharan P, Akiba S, Koriyama C, Nair RR. Oral cavity cancer risk in relation to tobacco chewing and bidi smoking among men in Karunagappally, Kerala, India: Karunagappally cohort study. *Cancer Sci* 2011; **102:** 460–67.

38 Znaor A, Brennan P, Gajalakshmi V, et al. Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. *Int J Cancer* 2003; **105:** 681–86.

39 Madani AH, Dikshit M, Bhaduri D. Risk for oral cancer associated to smoking, smokeless and oral dip products. *Indian J Public Health* 2012; **56:** 57–60.

40 Jayalekshmi PA, Gangadharan P, Akiba S, Nair RR, Tsuji M, Rajan B. Tobacco chewing and female oral cavity cancer risk in Karunagappally cohort, India. *Br J Cancer* 2009; **100:** 848–52.

41 Balaram P, Sridhar H, Rajkumar T, et al. Oral cancer in southern India: the influence of smoking, drinking, paan-chewing and oral hygiene. *Int J Cancer* 2002; **98:** 440–45.

42 Scully C. Oral cancer aetiopathogenesis; past, present and future aspects. *Med Oral Patol Oral Cir Bucal* 2011; **16:** e306–11.

43 Combes JD, Franceschi S. Role of human papillomavirus in non-oropharyngeal head and neck cancers. *Oral Oncol* 2014; **50:** 370–79.

44 Ministry of Health and Family Welfare. Global Tobacco Adults Survey. https://mohfw.nic.in/WriteReadData/l892s/1455618937GATS%20India.pdf (accessed Feb 24, 2015).

45 Arnold F, Parasuraman S, Arokiasamy P, Kothari M. Nutrition in India. National Family Health Survey. In: NFHS 3 I, 2005 06 Mumbai: International Institute for Population Sciences. Calverton: ICF Macro, 2009.

46 Sankaranarayanan R, Ramadas K, Thara S, et al. Long term effect of visual screening on oral cancer incidence and mortality in a randomized trial in Kerala, India. *Oral Oncol* 2013; **49:** 314–21.

47 Gupta PC. Mouth cancer in India: a new epidemic? *J Indian Med Assoc* 1999; **97:** 370–73.

48 Anantha N, Nandakumar A, Vishwanath N, et al. Efficacy of an anti-tobacco community education program in India. *Cancer Causes Control* 1995; **6:** 119–29.

49 Mehta FS, Gupta PC, Pindborg JJ. Chewing and smoking habits in relation to precancer and oral cancer. *J Cancer Res Clin Oncol* 1981; **99:** 35–39.

50 Gupta PC, Mehta FS, Daftary DK, et al. Incidence rates of oral cancer and natural history of oral precancerous lesions in a 10-year follow-up study of Indian villagers. *Community Dent Oral Epidemiol* 1980; **8:** 283–333.

51 Napier SS, Speight PM. Natural history of potentially malignant oral lesions and conditions: an overview of the literature. *J Oral Pathol Med* 2008; **37:** 1–10.

52 Bhargava K, Smith LW, Mani NJ, Silverman S Jr, Malaowalla AM, Bilimoria KF. A follow up study of oral cancer and precancerous lesions in 57,518 industrial workers of Gujarat, India. *Indian J Cancer* 1975; **12:** 124–29.

53 Mehta FS, Shroff BC, Gupta PC, Daftary DK. Oral leukoplakia in relation to tobacco habits. A ten-year follow-up study of Bombay policemen. *Oral Surg Oral Med Oral Pathol* 1972; **34:** 426–33.

54 Critchley JA, Unal B. Health effects associated with smokeless tobacco: a systematic review. *Thorax* 2003; **58:** 435–43.

55 Gupta PC, Bhonsle RB, Murti PR, Daftary DK, Mehta FS, Pindborg JJ. An epidemiologic assessment of cancer risk in oral precancerous lesions in India with special reference to nodular leukoplakia. *Cancer* 1989; **63:** 2247–52.

56 Mehta FS, Gupta PC, Bhonsle RB, Murti PR, Daftary DK, Pindborg JJ. Detection of oral cancer using basic health workers in an area of high oral cancer incidence in India. *Cancer Detect Prev* 1986; **9:** 219–25.

57 Gupta PC, Mehta FS, Pindborg JJ, et al. Intervention study for primary prevention of oral cancer among 36 000 Indian tobacco users. *Lancet* 1986; **1:** 1235–39.

58 Gupta PC, Mehta FS, Pindborg JJ, et al. Primary prevention trial of oral cancer in india: a 10-year follow-up study. *J Oral Pathol Med* 1992; **21:** 433–39.

59 Brocklehurst P, Kujan O, Glenny AM, et al. Screening programmes for the early detection and prevention of oral cancer. *Cochrane Database Syst Rev* 2010; **11:** CD004150.

60 Subramanian S, Sankaranarayanan R, Bapat B, et al. Cost-effectiveness of oral cancer screening: results from a cluster randomized controlled trial in India. *Bull World Health Organ* 2009; **87:** 200–06.

61 Mehrotra R, Gupta DK. Exciting new advances in oral cancer diagnosis: avenues to early detection. *Head Neck Oncol* 2011; **3:** 33.

62 Fedele S. Diagnostic aids in the screening of oral cancer. *Head Neck Oncol* 2009; **1:** 5.

63 Epstein JB, Scully C, Spinelli J. Toluidine blue and Lugol's iodine application in the assessment of oral malignant disease and lesions at risk of malignancy. *J Oral Pathol Med* 1992; **21:** 160–63.

64 Patton LL, Epstein JB, Kerr AR. Adjunctive techniques for oral cancer examination and lesion diagnosis: a systematic review of the literature. *J Am Dent Assoc* 2008; **139:** 896–905

65 Messadi DV. Diagnostic aids for detection of oral precancerous conditions. *Int J Oral Sci* 2013; **5:** 59–65.

66 Mehrotra R, Mishra S, Singh M, Singh M. The efficacy of oral brush biopsy with computer-assisted analysis in identifying precancerous and cancerous lesions. *Head Neck Oncol* 2011; **3:** 39.

67 Mehrotra R, Singh MK, Pandya S, Singh M. The use of an oral brush biopsy without computer-assisted analysis in the evaluation of oral lesions: a study of 94 patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008; **106:** 246–53.

68 Mehrotra R, Singh M, Thomas S, et al. A cross-sectional study evaluating chemiluminescence and autofluorescence in the detection of clinically innocuous precancerous and cancerous oral lesions. *J Am Dent Assoc* 2010; **141:** 151–56.

69 WHO. WHO Framework convention on tobacco control. Geneva: World Health Organisation, 2003.

70 International Agency for Research on Cancer. IARC Screening Group. http://screening.iarc.fr/trainingoral.php?lang=1 (accessed June 5, 2015).

71 Sankaranarayanan R, Ramadas K, Thara S, et al. Clinical breast examination: preliminary results from a cluster randomized controlled trial in India. *J Natl Cancer Inst* 2011; **103:** 1476–80.

72 Khokhar A. Breast cancer in India: where do we stand and where do we go? *Asian Pac J Cancer Prev* 2012; **13:** 4861–66.

73 Harris JR, Lippman ME, Morrow M, Osborne CK. Diseases of the breast. 5th edn. Philadelphia: Lippincott Williams and Wilkins, 2014.

74 World Cancer Research Fund and American Institute for Cancer Research. Breast cancer report: food, nutrition, physical activity, and the prevention of breast cancer. http://www.dietandcancerreport.org/expert_report/report_contents/index.php (accessed Feb 24, 2015).

75 Yip CH, Smith RA, Anderson BO, et al, and the Breast Health Global Initiative Early Detection Panel. Guideline implementation for breast healthcare in low- and middle-income countries: early detection resource allocation. *Cancer* 2008; **113** (suppl)**:** 2244–56.

76 Corbex M, Burton R, Sancho-Garnier H. Breast cancer early detection methods for low and middle income countries, a review of the evidence. *Breast* 2012; **21:** 428–34.

77 Elmore JG, Armstrong K, Lehman CD, Fletcher SW. Screening for breast cancer. *JAMA* 2005; **293:** 1245–56.

78 Masood S, Vass L, Ibarra JA Jr, et al, and the Breast Health Global Initiative Pathology Focus Group. Breast pathology guideline implementation in low- and middle-income countries. *Cancer* 2008; **113** (suppl)**:** 2297–304.

79 Okonkwo QL, Draisma G, der Kinderen A, Brown ML, de Koning HJ. Breast cancer screening policies in developing countries: a cost-effectiveness analysis for India. *J Natl Cancer Inst* 2008; **100:** 1290–300.

80 Bethesda M. National Cancer Institute: PDQ breast cancer screening. http://www.cancer.gov/cancertopics/pdq/screening/breast/healthprofessional (accessed Feb 24, 2015).

81 Tsu VD, Jeronimo J, Anderson BO. Why the time is right to tackle breast and cervical cancer in low-resource settings. *Bull World Health Organ* 2013; **91:** 683–90.

82 Lauby-Secretan B, Scoccianti C, Loomis D, et al. Breast-cancer screening—viewpoint of the IARC Working Group. *N Engl J Med* 2015; published online June 3. DOI:10.1056/NEJMsr1504363.

83 Lee T. Comparison of breast cancer screening results in Korean middle-aged women: a hospital-based prospective cohort study. *Osong Public Health Res Perspect* 2013; **4:** 197–202.

84 Mo M, Liu GY, Zheng Y, et al. Performance of breast cancer screening methods and modality among Chinese women: a report from a society-based breast screening program (SBSP) in Shanghai. *Springerplus* 2013; **2:** 276.

85 Kolb TM, Lichy J, Newhouse JH. Occult cancer in women with dense breasts: detection with screening US—diagnostic yield and tumor characteristics. *Radiology* 1998; **207:** 191–99.

86 Buchberger W, DeKoekkoek-Doll P, Springer P, Obrist P, Dünser M. Incidental findings on sonography of the breast: clinical significance and diagnostic workup. *AJR Am J Roentgenol* 1999; **173:** 921–27.

87 Tsunoda-Shimizu H, Nakamura S. Diagnostic assessment of nonpalpable breast cancer--the difference in diagnostic approach for the clinical treatment of breast cancer between the Japanese Guidelines and the National Comprehensive Cancer Network (USA) Guidelines. *Breast Cancer* 2005; **12:** 250–57.

88 Xiao Y, Zhou Q, Chen Z. Automated breast volume scanning versus conventional ultrasound in breast cancer screening. *Acad Radiol* 2015; **22:** 387–99.

89 Brem RF, Lenihan MJ, Lieberman J, Torrente J. Screening breast ultrasound: past, present, and future. *AJR Am J Roentgenol* 2015; **204:** 234–40.

90 Drukteinis JS, Mooney BP, Flowers CI, Gatenby RA. Beyond mammography: new frontiers in breast cancer screening. *Am J Med* 2013; **126:** 472–79.

91 Irwig L, Houssami N, van Vliet C. New technologies in screening for breast cancer: a systematic review of their accuracy. *Br J Cancer* 2004; **90:** 2118–22.

92 El Saghir NS, Charara RN. International screening and early detection of breast cancer: resource-sensitive, age- and risk-specific guidelines. *Breast Cancer Manag* 2014; **3:** 397–407.