Breast Cancer Screening Policies in Developing Countries: A Cost-effectiveness Analysis for India

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Background India, the largest developing country, has a steadily rising incidence of breast cancer. Estimates and comparisons of the cost-effectiveness of feasible breast cancer screening policies in developing countries and identification of the determinants of cost and efficacy are needed.

Methods A Microsimulation Screening Analysis model of breast cancer was calibrated to available data on breast cancer incidence, stage distribution, and mortality in India. The model was used to estimate the costs of screening for breast cancer in India, its effects on mortality, and its cost-effectiveness (ie, costs of screening per life-year gained or life saved). Screening using clinical breast examination (CBE) or mammography among different age groups and at various frequencies was analyzed. Costs were expressed in international dollars (Int.$), the currency used by the World Health Organization, which has the same purchasing power in India as the US dollar has in the United States. To determine which factors influenced cost-effectiveness, sensitivity analyses were performed.

Results The estimated mortality reduction was the greatest for programs targeting women between age 40 and 60 years. Using a 3% discount rate, a single CBE at age 50 had an estimated cost-effectiveness ratio of Int.$793 per life year gained and a breast cancer mortality reduction of 2%. The cost-effectiveness ratio increased to Int.$1135 per life year gained for every-5-year CBE (age 40–60 years) and to Int.$1341 for biennial CBE (age 40–60 years); the corresponding reductions in breast cancer mortality were 8.2% and 16.3%, respectively. CBE performed annually from ages 40 to 60 was predicted to be nearly as efficacious as biennial mammography screening for reducing breast cancer mortality while incurring only half the net costs. The main factors affecting cost-effectiveness were breast cancer incidence, stage distribution, and cost savings on prevented palliative care.

Conclusion The estimated cost-effectiveness of CBE screening for breast cancer in India compares favorably with that of mammography in developed countries. However, in view of competing priorities and economic conditions, the introduction of screening in India represents a greater challenge than it has been in more developed countries.

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Breast cancer is a major public health problem affecting millions of women in developed countries. Because results of randomized trials showed that mammographic screening substantially reduced breast cancer mortality (1), early detection programs for breast cancer that use mammography as the screening test were initiated in Europe, North America, Australia, Japan, and other developed countries (2). In most developing countries, ie, those classified as low- and middle-income countries by the World Bank (income per capita less than $9075 in 2001) (3), breast cancer incidence is lower than that in high-income countries, and access to state-of-the-art treatment is often limited. Nevertheless, in absolute terms, the number of deaths attributable to breast cancer in developing countries is double the number in high-income countries (4), and breast cancer represents a substantial and growing public health burden for these less-affluent societies. Few evaluations of the effectiveness of breast cancer screening in developing countries have been conducted.

Just a decade ago, infection was the leading cause of morbidity and mortality in India. However, with this nation's recent economic and technological advances, health awareness has improved, and even in the most peripheral regions of the country the focus of attention has shifted from infection to cancer (5). In most of India, breast cancer has become the second most common oncologic disease among women, after cancer of the cervix uteri; there were approximately 79000 new registered cases of breast cancer in 2000 (6–9). In

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New Delhi and Mumbai (cities with approximately 10 million inhabitants each), it is the leading form of cancer (10). With industrialization and urban development, delayed and reduced fertility, increasing longevity, and Westernization of lifestyle, the incidence of breast cancer is rising steadily, particularly in younger birth cohorts (11,12), and it is likely to soon overtake cervical cancer as the most common malignancy among Indian women. As a result of the young age of the population, the low life expectancy (about 62 years), and the age at which incidence peaks (around 45 years) (6), the majority of breast cancers in India occur in premenopausal women. More than 70% of patients are diagnosed with clinically advanced disease (ie, locally advanced breast cancer or higher stage) (5,13).

Due to the large size of the country and its population, health care delivery in India is of variable quality. Health facilities range from peripheral hospitals with only basic medical services to specialized centers in metropolitan areas with specialists and infrastructure to address all aspects of cancer control, including prevention, early detection, diagnosis, and treatment. India also has about 100 large community hospitals associated with government medical colleges, where health care is free and where the majority of the nations's cancer patients are treated (10). However, oncologic services are basic or nonexistent in many of these hospitals, where the majority of breast cancer patients are treated only surgically. Radiotherapy is primarily available in private hospitals and in the 21 regional cancer centers established under India's national cancer control program (14).

The type of treatment that a typical breast cancer patient in India receives depends on where she lives and which institution, if any, she can reach. For example, in Pune, there is only one facility to provide comprehensive breast cancer services for 3.5 million women. Half of Indian women with breast cancer go entirely without treatment (15). For patients presenting with locally advanced breast cancer (stages 3 and 4), treatment at peripheral centers usually consists of a radical mastectomy and surgical oophorectomy, with or without radiotherapy. Inoperable patients might be referred for radiotherapy. In specialized centers, usually found in metropolitan areas, treatment according to the highest international standards, including brachiocephalic trunk or modified radical mastectomy, radiation therapy, and chemotherapy, is available. There are no organized screening programs for any of the common cancers in India, and the regional cancer centers provide only opportunistic screening (14).

The question of which screening program should be instituted in India given its demographic and economic characteristics requires careful consideration. Although mammography is the preferred method of screening in Western countries, clinical breast examination (CBE) is an important means to diagnose symptomatic disease, and it is likely to be of use in the diagnosis of asymptomatic disease in areas where mammography is unavailable. Although CBE cannot detect very small tumors, it has the potential to improve the stage at diagnosis in contexts where the majority of discovered tumors are stage 3 and 4 (16). To address the question of which screening program should be instituted in India, we used a MIcrosimulation SCreening ANalysis (MISCAN) model to estimate effectiveness and cost-effectiveness of CBE and mammography in India for alternative screening policies (ie, with varying eligible age groups and screening intervals). India was selected for this simulation because it is one of the largest developing countries and sufficient data on breast cancer epidemiology to construct a reliable and valid model were available. Due to the high cost of mammography, the consideration that mammography facilities may not be available throughout India, and the fact that the peak incidence of breast cancer is in relatively young, often premenopausal, women, for whom mammography is not the preferred screening tool, we have focused our analyses and interpretations on screening with CBE (17).

CONTEXT AND CAVEATS

Prior knowledge

The incidence of breast cancer in India is rising, but estimates of costs and effectiveness of different screening strategies in this developing country are needed.

Study design

Life histories of breast cancer patients were modeled as a Markov process using the Dutch MISCAN (MIcrosimulation SCreening ANalysis) model. A lower cumulative incidence and delayed diagnosis based on Indian data was incorporated into the model. Estimates of costs for diagnosis and treatment relied on Dutch data for resource usage and World Health Organization estimates of unit costs for South Asia.

Contribution

Estimated mortality reduction was greatest for screening programs targeting women between the ages of 40 and 60. Clinical breast examination (CBE) performed annually from ages 40 to 60 was predicted to be nearly as efficacious as biennial mammography screening for reducing breast cancer deaths, but only half as costly.

Implications

Although the estimated cost-effectiveness of CBE screening for breast cancer in India compares favorably with that of mammography in developed countries, introduction of screening in India remains a considerable economic challenge.

Limitations

The study relied on a number of assumptions concerning the efficacy of CBE in reducing breast cancer mortality in India that have not been verified in randomized trials.

From the Editors

Methods

MISCAN Model

MISCAN models use a Markov process of states and transitions to simulate and compare individual life histories in a population in the presence and absence of a cancer screening program. To produce reliable predictions of breast cancer incidence and mortality, demographic and epidemiological characteristics of the population are incorporated in the model.

The MISCAN model of the natural history of breast cancer has been described previously (18,19) and is presented schematically in Figure 1. The first state is the absence of breast cancer. Women remain in this state until a transition occurs to a preclinical state that could be detected by screening. Tumor development is modeled as a successive progression through four invasive states (T1A, T1B, T1C, and T2+) defined by tumor size (≤5, 6–10, 11–20, and

≥21 mm, respectively). In each preclinical state, tumors may change from node negative (N−) to node positive (N+). Invasive cancers may be preceded by a screen-detectable ductal carcinoma in situ. In the absence of screening, a preclinical cancer may either present clinically or progress to the next preclinical state. The time a cancer remains in each preclinical state (dwelling time) is exponentially distributed with a state-specific mean, and the next state depends on stage-specific transition probabilities (Table 1). Screening may detect prevalent preclinical cancers depending on state of the tumor and sensitivity of the screening test. As a result of screening a population, a shift is expected to occur from the diagnosis of relatively large clinical cancers toward diagnosis of smaller preclinical cancers, possibly resulting in a breast cancer mortality reduction. The MISCAN breast cancer model has been used to predict mortality trends since the introduction of mammography screening (20,21) and to estimate cost-effectiveness of screening in developed countries (22–24).

Model Parameters

The Dutch MISCAN breast cancer model was used as a template for the development of the Indian counterpart. Key parameters for both models are presented in Table 1. In the Dutch model, the parameters (transition probabilities, mean duration in a given state, and the sensitivity of mammography by stage and age) of the preclinical phase were estimated from data from Dutch screening programs (25–27). Stage-specific survival rates of clinically diagnosed cancers were obtained from the Dutch pilot study of breast cancer screening carried out in the 1980s (28,29) and the effect of age at diagnosis on survival as observed in data from the Swedish Cancer Registry in the same period (30). The effectiveness of mammography in reducing breast cancer mortality was derived from trial results (18). In the model presented here, early detection by screening prevents death from cancer in a fraction of cases that depends on tumor stage and nodal status (Table 1). The stage-specific sensitivities of mammography used in the model for women under age 50 were lower than those for women aged 50 and older (18,29). Stage-dependent sensitivities of CBE in this study were based on data from the Canadian National Breast Screening Study (17). Alternative (lower) estimates of stage-dependent sensitivities of CBE were based on data from 752 000 CBEs delivered to low-income women in the United States between 1995 and 1998 through the National Breast and Cervical Cancer Early Detection Program (31) of the US Centers for Disease Control and Prevention.

Fitting the Model to the Indian Population

The two major changes made to the previous (Dutch) model in adapting it to India were the substitution of a lower cumulative incidence of breast cancer and delayed diagnosis. In the model, delayed diagnosis translates into longer dwelling times in preclinical states, smaller probabilities of clinical diagnosis, and consequently

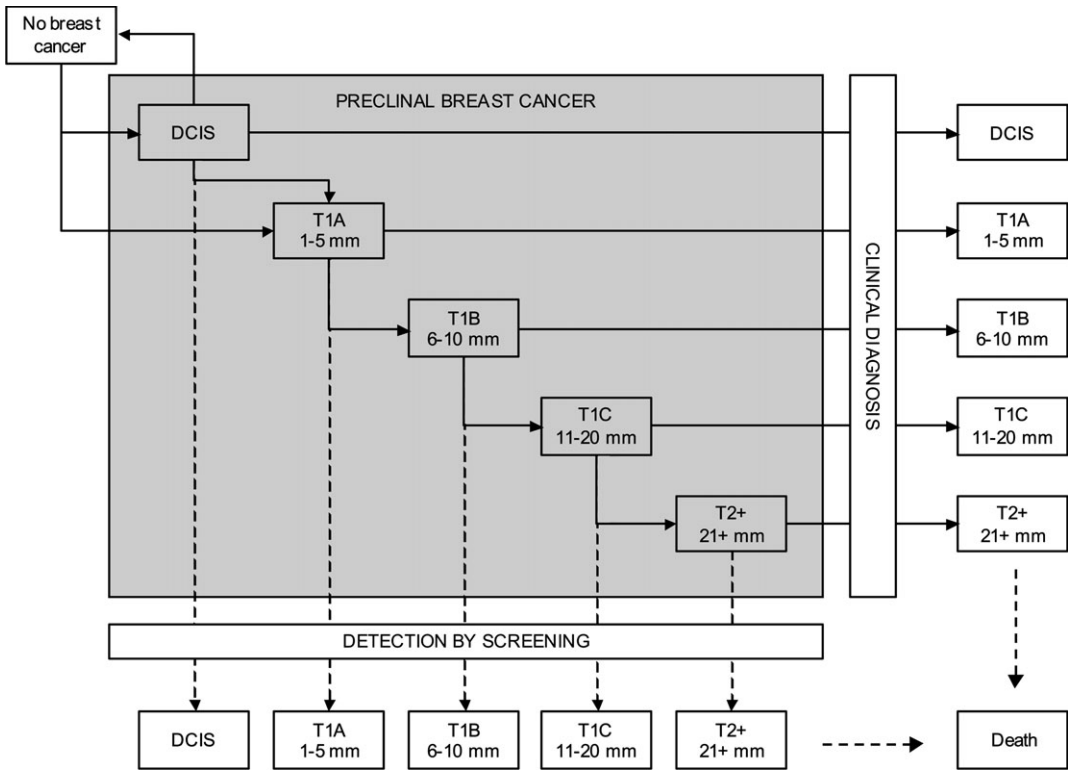

Figure 1. The Microsimulation Screening Analysis natural history of breast cancer. Invasive tumors are characterized by tumor size and nodal status (not shown). Clinically diagnosed tumors are preceded by one or more preclinical states that are detectable by screening. In the absence of screening, from each preclinical state tumors may either be diagnosed clinically or grow into the next state (**solid arrows**). Durations of preclinical states are exponentially distributed. Invasive states may be preceded by ductal carcinoma in situ (DCIS); the model allows for regression from DCIS to the normal state. In each preclinical invasive state, tumors may change from node negative to node positive (transitions not shown). After clinical diagnosis, cancer-specific death follows from stage-specific survival functions. Through screening, tumors may be detected and diagnosed in an earlier state (**dashed arrows**). Early detection may prevent death from breast cancer. This improvement in prognosis is dependent on stage at detection; its size was estimated from results of randomized trials of breast cancer screening.

Table 1. Key parameters in the MISCAN breast cancer model for India and The Netherlands according to stage of breast cancer*

	DCIS		T1A		T1B		T1C		T2+	
	India	Neth.	India	Neth.	India	Neth.	India	Neth.	India	Neth.
Preclinical phase										
Mean duration, y	5.22	5.22	0.10	0.10	0.53	0.50	1.48	1.03	1.55	0.77
Probability of clinical diagnosis	.033	.033	.0003	.016	.0029	.073	.096	.38	1	1
Probability of transition to N+ disease	0	0	.11	.11	.12	.13	.27	.2	.58	.35
Five-year survival†										
N− disease	1.00		0.97		0.96		0.93		0.86	
N+ disease	NA		0.90		0.86		0.76		0.55	
Screening†										
Sensitivity of CBE	0.05		0.01		0.16		0.48		0.65	
Sensitivity of mammography‡	0.40		0.65		0.80		0.90		0.95	
Benefit of screen detection§										
N− disease	1.00		0.92		0.88		0.78		0.60	
N+ disease	NA		0.72		0.60		0.37		0.14	

* Cumulative probability of preclinical cancer in India at ages 30, 50, and 70 is .0019, .0094, and .26, respectively. Cumulative probability of preclinical cancer in The Netherlands at ages 30, 50 and 70 is .0030, .039, and .086. MISCAN = MIcrosimulation SCreening ANalysis; DCIS = ductal carcinoma in situ; T1A, T1B, T1C T2+ = tumor size 1–5, 6–10, 11–20, ≥21 mm, respectively; Neth. = The Netherlands; N+ = node-positive; N− = node-negative; CBE = clinical breast examination; NA = not applicable.

† Parameters are the same in India and The Netherlands.

‡ Sensitivity for ages over 50. At ages 40–45 sensitivity = 60% of specified value; at ages 45–50 sensitivity = 80% of specified value.

§ Fraction of otherwise fatal cases cured when detected early in the given preclinical stage.

larger probabilities of transition to the next (more advanced) preclinical state and to node-positive states (Table 1). The corresponding parameters (probabilities of clinical diagnosis, mean durations, and trasnsition to node-positive disease) were estimated by comparing the stage distribution predicted by the model to the observed clinical stage distribution in India (9,10,32). We assumed, based on weighted averages from the Bangalore, Mumbai, and Madras registries (9,32), that at diagnosis in India, 26% of breast cancer was localized, 49% was regional, 11% was characterized by distant metastasis, and 14% unstaged. Because these registries use a stage classification to define tumors (local, regional, distant, unstaged) that is different from that used by MISCAN (T1A, T1B, T1C, T2+; N−/N+), we assumed that MISCAN's N− category was equivalent to the local category and that MISCAN's N+ category was equivalent to the Indian categories regional and distant.

After changing the preclinical phase parameters (ie, transition probabilities and mean dwelling times in the preclinical phase), we adjusted the parameters of cancer onset, ie, cumulative incidence and dwelling time in the normal state, to reflect the lower age-specific incidence in India. To correctly reproduce age-specific breast cancer incidence as presented in GLOBOCAN 2000 (6), a higher incidence was attributed to younger birth cohorts than to older cohorts. With these adjustments, the model correctly predicted age-specific breast cancer mortality as presented in GLOBOCAN 2000 (Figure 2), and, therefore, we assumed that stage-specific survival rates were similar in India and The Netherlands.

The age distribution of the population in the model was that of India for the year 2000 (33). Death from other causes than breast cancer was determined by the year 2000 life table for India (34).

Cost-effectiveness Analysis

Screening Policies. The screening policies analyzed were a single test at age 40 or 50 or screening from age 40 to 60 or from age 50 to 70 (inclusive) with intervals of 5 years (5 screens), 2 years (11 screens), or 1 year (21 screens), using either CBE or mammography. Unless specified otherwise, we assumed that screening programs were of 25 years duration, that the attendance rate was 100%, and that there were 100 years of follow-up. All analyses were performed for a population of 1 million women.

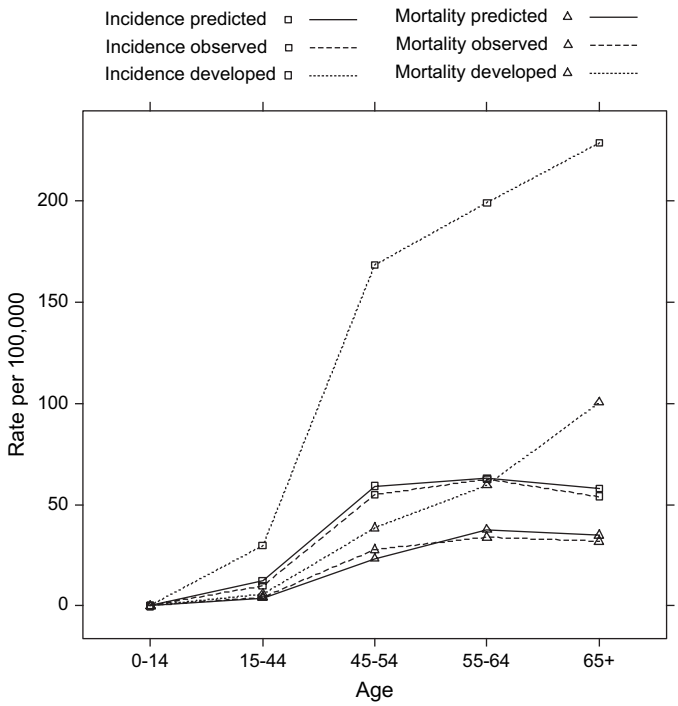

Figure 2. Observed age-specific breast cancer incidence and mortality in India compared with Microsimulation Screening Analysis predictions and to observed age-specific breast cancer incidence and mortality in more developed countries (ie, North America, Europe, Japan, New Zealand, and Australia). Data are from GLOBOCAN 2000 (6).

Screening Effects. The effects of screening were expressed as the number of breast cancer deaths averted, the number of life years gained, and the percent reduction of annual mortality achieved in the steady state, which was reached approximately 15 years after the initiation of the screening program. The percent mortality reduction was calculated over years 20–25, inclusive, of the screening program.

Screening Costs. Cost-effectiveness ratios can be calculated using the MISCAN model by linking the effect estimates described above to the cost of each activity related to screening, diagnostic follow-up, primary and adjuvant systemic treatment, follow-up, and palliative care (27,35). Costs were expressed in 2001 international dollars (Int.$), the currency used by the World Health Organization (WHO) as a means of translating and comparing costs from one country to the other. An international dollar has the same purchasing power as the US dollar has in the United States. A standard template with estimates of use for each relevant item or intervention that was obtained from previous studies in The Netherlands (27) was used in the model for India. Thus, resource use (diagnostics and treatments) was based on practice in The Netherlands, and costs were calculated by multiplying the estimated resource use by the estimated costs per unit for each health care input in India.

Because reliable cost data for India on listed resource items were limited, Dutch unit costs were extrapolated in three ways. In method 1, Dutch unit costs were converted to international dollars using World Bank Purchasing Power Parities for health care (36). In method 2, a conversion factor was calculated based on the percentage of gross domestic product (GDP) dedicated to health care. Dutch unit costs expressed in international dollars (method 1) were multiplied by the ratio of health care expenditures per GDP for India (.051) divided by health care expenditures per GDP for The Netherlands (.089). In method 3, unit costs were calculated based on what has been termed a market basket approach. A conversion factor was calculated that reflects the relative cost of a set (a "market basket") of resources for which both Indian and Dutch unit cost data were available (37). This approach was used as the base case method for estimating unit costs for India. However, in a sensitivity analysis, we explored the implications of using the two other approaches.

Calculation of Cost-effectiveness Ratios. Cost-effectiveness ratios were computed as the predicted costs of gaining an additional health effect from a specified screening policy when compared with a baseline situation of no screening. Ratios were expressed as cost per life year gained and cost per breast cancer death prevented.

Incremental cost-effectiveness ratios (ICERs) that compared two alternative screening programs were calculated by dividing the difference in total net costs and the difference in life years gained between two alternative screening policies. Policies that were estimated to be both more expensive and less effective than a combination of other policies were referred to as dominated, and for those policies no ICERs were calculated. A standard discount rate of 3% was applied to all costs and effects.

Sensitivity Analyses

To explore how epidemiological differences between The Netherlands and India would affect the cost-effectiveness of screening, we changed parameters of life expectancy, cancer incidence, and clinical stage distribution stepwise from Dutch to Indian values and calculated the corresponding cost-effectiveness ratios. We also substituted alternative values for selected input parameters in the base model for India: incidence was replaced by the estimated value in Mumbai, the city with the highest registered breast cancer incidence in India (8); screening attendance was lowered from 100% to a more realistic value of 70%; and Canadian National Breast Screening Study sensitivities for CBE used in the model were replaced with those reported by Bobo et al. (31) for asymptomatic women in the United States, which were 25% lower. In the base model, the net costs of screening include savings on palliative care as a consequence of preventing fatal breast cancer. Given the uncertainty regarding costs of several health care inputs in India, sensitivity analyses were carried out in which the cost estimate used in the base model (method 3) was replaced by the cost estimates derived from the other two methods (method 1 and 2).

Results

We compared observed and predicted age-specific incidence and mortality for India (Figure 2). Overall incidence in India is lower than that in developed countries (the age-standardized breast cancer incidence rate for India is 19.1 per 100 000 women-years versus 63.2 per 100 000 women-years in more developed countries, ie, North America, Europe, Japan, New Zealand, and Australia. The adjusted model predicted a stage distribution of 31% node-negative and 69% node-positive tumors, and the registries reported a stage distribution of 31% localized versus 69% regional or distant disease (9,32). Thus, the percentage of advanced cancers predicted by the model was supported by data from the registries. In the original Dutch disease model, the predicted stage distribution was 54% node-negative and 46% node-positive tumors.

India also differs from Western countries in the relationship between incidence and age. Whereas in Western countries breast cancer incidence increases with age, in India incidence appears to decrease with age beginning at age 50 (Figure 2). The stable or declining incidence after age 50 has generally been attributed to a cohort effect (11,12), ie, a progressive increase in breast cancer risk from one birth cohort to the next. This effect was incorporated in the model as an increase of cumulative incidence from 3.3% in the older (≥75 years in 2001) to 5.5% in the younger (<45 years in 2001) cohorts.

The costs of biennial screening in a population of 1 million women from age 40 to 60 were estimated (Table 2) as Int.$13.23 million for CBE (3.34 million tests at a cost of Int.$3.96 each) and Int.$44.21 million for mammography (3.34 million procedures at a cost of Int.$13.23 each). However, taking into account all differences in costs of diagnostics and treatment due to screening, the estimated net costs of screening were only Int.$8.39 million for screening with CBE and Int.$38.11 million for mammography because of savings in palliative therapy and diagnostics outside the screening program.

We estimated effects and differential costs (discounted at 3%) of 25 years of screening with various policies compared with no screening (Table 3 and Figure 3). Programs are presented in order of increasing total net costs. One lifetime CBE at age 50

Table 2. Unit, total, and net costs of breast cancer screening, diagnosis, and treatment in India for biennial screening, ages 40–60 (11 screens) with either clinical breast examination or mammography*

	Clinical breast examination					Mammography				
				Change from no screening					Change from no screening	
Cost items	Unit cost,† Int.$	N‡	Total cost, million Int.$	N‡,§	Net costs,§ million Int.$	Unit cost,† Int.$	N‡	Total costs, million Int.$	N‡,§	Net costs,§ million Int.$
Screening tests	3.96	3342199	13.23	3342199	13.23	13.23	3340392	44.21	3340392	44.21
Diagnostics										
Cases detected by screening										
True positives	132.41	2434	0.32	2434	0.32	185.26	3667	0.68	3667	0.68
False positives	121.32	3277	0.40	3277	0.40	129.06	5775	0.75	5775	0.75
Cases diagnosed without screening										
True positives	131.38	21756	2.86	−2301	−0.28	130.68	20710	2.71	−3347	−0.43
False positives	133.76	201512	26.95	−29118	−3.91	133.34	192768	25.70	−37862	−5.16
Primary therapy	999.28	24190	24.17	133	0.76	1009.86	24377	24.62	320	1.21
Adjuvant therapy	85.67	24190	2.07	133	0.04	85.40	24377	2.08	320	0.05
Follow-up	508.90	24190	12.31	133	0.33	537.20	24377	13.10	320	1.10
Palliative therapy for lethal breast cancer	3758.59	11717	44.04	−668	−2.51	3758.59	11244	42.26	−1141	−4.29
All			126.36		8.39			156.10		38.11

* All costs are in 2001 International dollars (Int.$), without discounting and refer to a population of 1 million women with the year 2000 age distribution.

† Costs per screening test or per individual.

‡ Number of screening tests or individuals.

§ Difference from the situation without screening. Net costs of screening are the difference in costs between the situations with and without screening.

was estimated to detect 217 breast cancers, avert 45 breast cancer deaths, and prevent the loss of 625 life years due to breast cancer per 1 million women. The steady-state breast cancer mortality reduction of this program was 2%. The total net costs were estimated as Int.$0.5 million, resulting in a cost-effectiveness ratio of Int.$793 per life year gained. Among the screening policies that we assessed, this policy had the lowest cost-effectiveness ratio.

CBE conducted every 5 years from age 40 to 60 (five screens) was estimated to reduce steady-state mortality by 8% and prevent the loss of 2462 life years at a cost of Int.$2.8 million; the ICER relative to a single CBE at age 50 was Int.$1251 per life year gained. Biennial CBE from age 40 to 60 (base program) was estimated to prevent the loss of 4896 life years at a cost of Int.$1341 per life year gained and with an ICER of $1549 per life year gained compared with every-5-year screening. The steady-state breast cancer mortality reduction for this screening program was estimated to be 16.3%. Annual CBE age from 40 to 60 (21 screens) led to the highest reduction in mortality (23.3%) and the highest number of life years gained (7242) among the programs employing CBE, at an incremental cost of Int.$3108 per life year gained compared with biennial CBE.

The estimated net costs of biennial mammography for women aged 40–60 were Int.$27.6 million, with a cost-effectiveness ratio of Int.$3468 per life year gained. Its effects, a mortality reduction of 25.8% and 7955 life years gained, were nearly equaled by annual CBE at approximately 50% of the cost (ICER Int.$19257 per life year gained).

A single screening at age 40 was dominated by a screening at age 50, and screening from age 50 to 70 was dominated by screening from age 40 to 60. The mammography programs were either dominated by more intensive programs with CBE or calculated to have a very high ICER (Table 3 and Figure 3).

Epidemiological determinants of cost-effectiveness of biennial screening from age 40 to 60 were analyzed by stepwise replacement of Dutch parameter values for life expectancy, incidence, and stage distribution with Indian values (Table 4). Substitution of the Indian life expectancy (62 years) for that of The Netherlands (80 years) increased the cost-effectiveness ratio of screening with CBE from Int.$444 to Int.$595 per life year gained. Reducing incidence of breast cancer from 186 per 100000 women-years in The Netherlands to 61 per 100000 women-years in India led to a further increase to Int.$3190 per life year gained. Taking into account the unfavorable stage distribution in India lowered the cost per life year gained to Int.$1341. For CBE, the number of life years saved per million women was reduced by 50% when these three parameter values (life expectancy, incidence, and stage distribution) for India were substituted for Dutch parameter values; for mammography, these substitutions reduced the number of life-years saved by 60%.

In the sensitivity analysis, we studied the impact of various factors on the cost-effectiveness of biennial screening with CBE from age 40 to 60 (Table 5). Incorporation into the model of the higher incidence in Mumbai resulted in a somewhat more favorable cost-effectiveness ratio of screening. Changing the attendance from 100% to 70% had a minor effect on cost-effectiveness.

Table 3. Estimated costs and effects of varying screening programs with either clinical breast examination (CBE) or mammography compared with no screening*

	Screening program										
	1	2	3	4	5	6	7	8	9	10	11
Parameter	**One lifetime CBE, age 50**	**One lifetime CBE, age 40**	**5-yr interval CBE, age 50–70**	**One lifetime MMG, age 50**	**5-yr interval CBE, age 40–60**	**One lifetime MMG, age 40**	**Biennial CBE, age 50–70**	**Base program: biennial CBE, age 40–60**	**Annual CBE, age 40–60**	**Biennial MMG, age 50–70**	**Biennial MMG, age 40–60**
Number of screen tests performed	212008	275735	740227	212008	1056544	275735	1620568	2319839	4426854	1619051	2318641
Number of cancers detected by screening	217	97	1004	465	938	128	1683	1689	2330	2649	2561
Number of deaths averted	45	21	172	105	184	28	313	358	528	557	599
Number of life years gained	625	359	1913	1422	2462	476	3464	4896	7242	6180	7955
Steady-state mortality reduction, %†	2.0	0.9	7.8	4.5	8.2	1.2	14.3	16.3	23.3	24.5	25.8
Number of screen tests per death averted	4734	13394	4298	2028	5730	9853	5170	6473	8385	2909	3868
Number of screen tests per life year gained	339	769	387	149	429	579	468	474	611	262	291
Net costs of screening, million Int.$‡	0.5	0.6	2.3	2.3	2.8	3.1	5.5	6.6	13.9	20.4	27.6
Cost-effectiveness											
Cost per death prevented, Int.$	11054	28878	13532	22220	15152	110542	17547	18312	26241	36731	46021
Cost per life year gained, Int.$	793	1657	1218	1634	1135	6496	1588	1341	1913	3308	3468
Incremental cost per life year gained ($) compared with program (×)§		Dominated‖	Dominated	Dominated	1251 (1)	Dominated	Dominated	1549 (5)	3108 (8)	Dominated	19257 (9)

* Screening programs are in order of increasing total net costs. Costs and effects refer to a population of 1 million women a screening period of 25 years and 100 years of follow-up. Costs and effects discounted at 3%; costs in international dollars 2001 (Int.$); CBE = clinical breast examination; MMG = mammography.

† The % reduction of annual mortality achieved in the steady state (reached about 15 years after initiation of screening) calculated over year 20–25.

‡ Net costs refer to the cost difference between the situation with and without screening and include cost of screening, diagnosis, primary therapy, adjuvant therapy, follow-up, and advanced disease (see Table 2).

§ Incremental cost per life year gained represents the marginal cost per life year gained when a more expensive screening program (higher net costs) is compared with a less expensive program (×).

‖ A program is dominated if another program or combination of other programs is more effective at the same or lower costs.

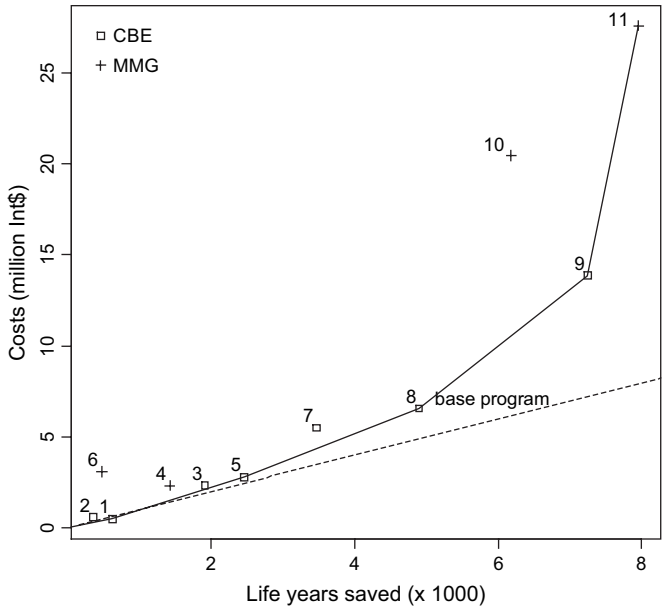

Figure 3. Differential costs and effects of breast cancer screening programs, discounted at 3% per year. The **dashed line** indicates a cost-effectiveness ratio of Int.$1000 per life year saved, and the **solid line** indicates the efficient frontier. The **numbers** refer to the programs in Table 3. The base program is biennial screening with clinical breast examination, ages 40–60. CBE = clinical breast examination; MMG = mammography.

Incorporation into the model of a 25% lower sensitivity of CBE—the stage-specific sensitivities found by Bobo et al. (31) are 20%–25% lower compared with the Canadian National Breast Screening Study sensitivities used in the model—resulted in a 35% higher cost-effectiveness ratio. Not including savings for prevented palliative treatment in the net costs of screening resulted in a 20% higher cost-effectiveness ratio. Finally, unit cost estimates had a major impact on cost-effectiveness. Using Dutch prices resulted in a cost-effectiveness ratio of Int.$7244 per life year gained, more than five times the value in the base model (Int.$1341). After adjustment according to the fraction of GDP spent on health care in both countries, the cost-effectiveness ratio of Int.$4156 was still three times higher than the base model value.

Discussion

Our estimate of the cost-effectiveness of breast cancer screening in India compares favorably with estimates of cost-effectiveness of breast cancer screening in Western countries. We estimated that in India it costs Int.$1341 per life year gained to screen women aged 40 to 60 with biennial CBE and Int.$3468 per life year gained with biennial mammography. Estimates of cost-effectiveness for biennial mammography for women aged 50–70 in Europe have ranged from approximately €2650 (Int.$2889) to €9600 (Int.$10464) per life year gained (38). The negative effect of the lower incidence of breast cancer in India on the cost-effectiveness of screening was balanced by the high incidence of advanced breast cancer, which resulted in a larger effect of screening. A contributing factor to a lower cost-effectiveness ratio was the assumed increasing trend in breast cancer incidence in India. It has been estimated that by 2020, 70% of all breast cancer cases worldwide will occur in developing countries (15). However, our estimates of the cost-effectiveness of breast cancer screening compare less favorably to the cost-effectiveness of cervical cancer screening with a single PAP smear at age 45 (39) (Int.$25 per life year gained).

Table 4. Epidemiological factors affecting the cost-effectiveness of biennial screening from age 40 to 60 with clinical breast examination or mammography*

	Clinical breast examination				Mammography			
	Dutch value replaced with Indian value				Dutch value replaced with Indian value			
Parameter	None	Life expectancy	Life expectancy and incidence	Life expectancy, incidence, and stage distribution	None	Changed life expectancy	Changed incidence	Changed stage distribution
Life expectancy, y	79.7	62.3	62.6	62.5	79.7	62.3	62.6	62.5
Incidence 40–60, $\times 10^{25}$ women-years	186	185	61	63	186	185	61	63
Stage distribution, % N+	46	46	46	69	46	46	46	69
Effectiveness								
Number of breast cancer deaths averted	601	543	175	358	1211	1058	354	599
Number of life years gained	9784	7397	2365	4896	19144	14117	4677	7955
Mortality reduction (steady state), %†	9.3	10.5	11.9	15.9	18.9	20.5	22.4	25.5
Total net costs, million Int.$‡	4.3	4.4	7.5	6.6	26.7	23.6	28.4	27.6
Cost-effectiveness								
Cost per death prevented, Int.$	7229	8099	43028	18312	22012	22342	80221	46021
Cost per life year gained, Int.$	444	595	3190	1341	1393	1674	6075	3468

* Effect of stepwise replacement of Dutch parameter values for life expectancy, incidence, and stage distribution by Indian values on costs and effects of biennial clinical breast examination or mammography from age 40 to 60 for a population of 1 million women (for a screening period of 25 years and 100 years of follow-up). Int.$ = 2001 International dollar.

† The % reduction of annual mortality achieved in the steady state (reached about 15 years after initiation of screening) calculated over year 20–25.

‡ Difference between the situation with and without screening and including costs of screening, diagnosis, primary therapy, adjuvant therapy, follow-up, and advanced disease.

Table 5. Sensitivity analysis for the cost-effectiveness of a biennial screening clinical breast examination from age 40 to 60*

Alteration to the model	Life years gained	Total net costs,† million Int.$	Cost-effectiveness, Int.$ per life years gained
None (base model for India)	4896	6.6	1341
Incidence in Mumbai	5371	6.4	1194
Attendance rate 70%	3498	4.6	1320
Clinical breast examination sensitivities from Bobo et al. (31)	3893	7.1	1812
No palliative treatment	4896	7.9	1616
Cost estimation method 1‡	4896	35.5	7244
Cost estimation method 2§	4896	20.3	4156

* Discount rate 3%; costs in international dollars 2001; costs and effects refer to a population of 1 million women, a screening period of 25 years and 100 years of follow-up. Int.$ = international dollars.

† Total net costs (×1 000 000) refer to the cost difference between the situation with and without screening and include cost of screening, diagnosis, primary therapy, adjuvant therapy, follow-up, and advanced disease.

‡ Dutch unit costs were converted to international dollars using World Bank Purchasing Power Parities for health care.

§ A conversion factor was calculated based on % gross domestic product (GDP) dedicated to health care. Dutch unit costs expressed in international dollars (method 1) were multiplied by the ratio of health care expenditures per GDP for India (.051) divided by the ratio of health care expenditures to GDP for The Netherlands (.089).

We found that in India, screening from age 40 to 60 was more cost-effective than screening from age 50 to 70 due to the young age of the population, the low life expectancy (62 years), and the young age at which the peak incidence is reached. Our results indicate that every-5-year, biennial, and annual CBE for women aged 40–60 all lead to considerable reductions in mortality and high numbers of life years gained (Table 3 and Figure 3). Biennial screening with mammography led to higher reductions in mortality in our simulations and saved more life years, but at high incremental costs. The choice of the most appropriate screening policy for India will depend largely on the amount that health authorities are willing or able to pay. Complicating this decision are the many competing priorities for health care resources in India. Although substantial progress has been made in controlling leprosy, blindness, tuberculosis and iodine deficiency disorder, infant and maternal mortality, and HIV/AIDS, important challenges will be posed by infectious diseases, cardiovascular disease, diabetes, trauma-related injuries, mental disorders, and cancer (40).

The screening costs for CBE and mammography were estimated to be only 10% and 28%, respectively, of the total costs of breast cancer diagnosis and treatment; thus, a societal commitment to treating breast cancer will likely entail a commitment to screen for it. In India, combining breast cancer and cervical cancer screening during the same visit and/or adding other health services to cancer screening is worth exploring (41).

Some limitations in our study suggest a need for caution in interpreting our results. Data on breast cancer in India were scarce, and our estimates of the cost-effectiveness of screening depend on the assumption that, in the absence of screening, a lower incidence and delayed presentation in case of symptoms would be the main differences in the natural history of breast cancer in India compared with more developed countries. We also assumed that detection at an earlier stage leads to improved survival. Support for this assumption may be found in the work of Michaelson et al. (42), which showed that improved survival of breast cancer during 1960–1990 could be explained largely by reduced tumor size at diagnosis. Another limitation of our study is that it is questionable whether the high stage-specific sensitivities of CBE as performed by trained professionals (both nurses and physicians) in the Canadian National Breast Screening Study could be achieved in India. Changing the sensitivities for CBE to those reported by Bobo et al. (31) for asymptomatic women in the US resulted in a considerably higher cost-effectiveness ratio (Int.$1812 per life year gained versus Int.$1341 in the base model). Further grounds for caution in interpreting our results is the fact that the favorable results for CBE compared with mammography depend on the assumption that screening with CBE actually reduces breast cancer mortality. Only screening with mammography has been shown in randomized trials to lead to a reduction in breast cancer mortality. However, reduction of the rate of advanced breast cancer is a fairly consistent predictor of an eventual reduction in mortality (16). Mittra et al. (43) estimated that a 55% reduction in death rate in India could be achieved within 5 years if tumors with a diameter 3 cm or more were detected by CBE, although the evidence for this estimate was limited to indirect results from a few trials.

There is also a considerable uncertainty in our estimates of the costs of screening. Using Dutch costs for diagnosis and treatment instead of those estimated for India using the market basket approach increased the cost-effectiveness ratio sixfold, to Int.$7244 per life year saved. The market basket approach we used combines Dutch data on resource usage with unit cost estimates for South Asia from the Disease Control Priorities project of the WHO (37), but more reliable and detailed estimates of utilization and local costs of diagnostics, treatment, and palliative care for India are needed for better estimates of cost-effectiveness. Finally, we used an attendance rate of 100% to show the maximum attainable health effect of any given screening program. This is an optimistic assumption, but our sensitivity analyses demonstrated that lowering the attendance rate had only a minor effect on the cost-effectiveness ratio (Table 5).

The need for controlled studies of CBE in developing country settings is evident, not least because most of the trial outcomes and experience with breast cancer screening comes from developed countries. A randomized trial of screening for cervical cancer and breast cancer using CBE was initiated in Mumbai in 1998 (44), in which 150 000 women aged 35–64 years were cluster (group)

randomized to a screened arm and a control arm. Compliance in the first round of screening was 76%; 973 women were referred for further clinical follow-up, and in the 573 women (61%) who complied with referral, 45 tumors were detected by screening and 16 interval cancers were diagnosed. In the same period, 55 women in the control arm attended the hospital with symptoms of breast cancer and 20 cases were detected. Although final results from this trial are not yet available, the preliminary report (44) shows that it is possible to implement a screening program under conditions that differ widely from those in Western countries. Furthermore, it has been reported that downstaging of tumors (ie, an increased proportion of tumors detected at stage 1 or 2 as opposed to stage 3 or 4 in patient groups assigned to screening) is already evident (14).

Before any major national screening program is introduced, its efficacy, applicability, and cost-effectiveness must be assessed for the specific locale in which it will be used (45). The Breast Health Global Initiative (16,46) recognizes four levels of resource allocation for early detection and treatment of breast cancer: basic, limited, enhanced, and maximal. For early detection, the basic level includes education, breast self-examination, and CBE. The limited level adds targeted education encouraging CBE for at-risk groups and diagnostic ultrasound and/or diagnostic mammography. Opportunistic or population-based screening with mammography is included in the enhanced and maximal levels. Whichever modality is used in an organized screening program, it is important to monitor the strategy and to perform rigorous evaluations in terms of stage of disease at presentation and deaths from breast cancer (16).

Screening and awareness initiatives may lead to a rapid and increased demand on oncology departments and hospitals. Thus, it is all the more important that before an organized screening program is established, there be consensus on a minimum standard of care for each stage of breast cancer. Care should be specific for the local situation and available to all women. At the basic level of resource allocation, the report of the Breast Health Global Initiative (46) recommends treatment with modified mastectomy for stage 1 or 2 or locally advanced breast cancer; at higher levels of resource allocation, radiation and adjuvant therapy are also recommended. The infrastructure for basic surgery might be available in even modestly equipped hospitals.

Finally, implementation of breast cancer screening programs must be viewed in the context of economic realities. Groot et al. (47) showed that treating early stage breast cancer is more cost-effective than treating late-stage disease in countries with limited resources. They concluded that treatment of stage 1 disease and/or implementation of an extensive cancer control program should be priorities under these conditions. In India, the Gross National Income (GNI) per capita in 2001 was Int.$2820 and health care expenditure was 5% of the GNI. For comparison, The Netherlands had a GNI of Int.$27 190 per capita in 2001, with approximately 10% of GNI spent on health care. In our models, the prices of a CBE and a mammogram are Int.$3.75 and Int.$13.75, respectively, in India and Int.$17.00 and Int.$55.00 in The Netherlands; thus, adjusted for differences in to GNI, the Indian costs are more than twice as high.

In the guidelines proposed by the WHO Commission on Macroeconomics and Health, a cost-effectiveness ratio that is less than the per capita GDP is described as "very cost-effective" (48). We estimated for biennial CBE in India a cost-effectiveness ratio of Int.$1341 per life-year gained, ie, nearly 50% of the GNI per capita. For comparison, the biennial mammography program in The Netherlands has an estimated cost-effectiveness ratio of Int.$2150 per life-year gained, ie, 8% of GNI per capita. According to the WHO criterion, a screening program with biennial CBE would be cost-effective in India; however, intensification to annual screening (ICER Int.$3108) would not meet the WHO criteria for cost-effectiveness. It is clear that the introduction of CBE screening in India represents a far greater economic challenge than the introduction of mammography screening in The Netherlands.

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Notes

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