ORIGINAL ARTICLE: GLOBAL EPIDEMIOLOGIC METHODS

Costs and Health Effects of Breast Cancer Interventions in Epidemiologically Different Regions of Africa, North America, and Asia

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■ **Abstract:** We estimated the costs and health effects of treating stage I, II, III, and IV breast cancer individually, of treating all stages, and of introducing an extensive cancer control program (treating all stages plus early stage diagnosis) in three epidemiologically different world regions—Africa, North America, and Asia. We developed a mathematical simulation model of breast cancer using the stage distribution and case fatality rates in the presence and absence of treatment as predictors of survival. Outcome measures were life-years adjusted for disability (DALYs), costs (in 2000 U.S. dollars) of treatment and follow-up, and cost-effectiveness ratios (CERs; in dollars per DALY averted). Sensitivity analyses were performed to determine the robustness of the results. Treating patients with stage I breast cancer resulted in 23.41, 12.25, and 19.25 DALYs averted per patient in Africa, North America, and Asia, respectively. The corresponding average CERs compared with no intervention were $78, $1960, and $62 per DALY averted. The number of DALYs averted per patient decreased with stage; the value was lowest for stage IV treatment (0.18–0.19), with average CERs of $4986 in Africa, $70,380 in North America, and $3510 per DALY averted in Asia. An extensive breast cancer program resulted in 16.14, 12.91, and 12.58 DALYs averted per patient and average CERs of $75, $915, and $75 per DALY averted. Outcomes were most sensitive to case fatality rates for untreated patients, but varying model assumptions did not change the conclusions. These findings suggest that treating stage I disease and introducing an extensive breast cancer program are the most cost-effective breast cancer interventions. ■

Key Words: breast cancer, cost-effectiveness, costs, developing countries, economic evaluation, modeling

Each year, breast cancer is newly diagnosed in more than 1 million women worldwide and more than 400,000 women die from it (1,2). Breast cancer as a public health problem is growing throughout the world, but especially in developing regions, where the incidence has increased as much as 5% per year (1,3). The mortality: incidence ratio is much higher in developing countries than in developed countries: only half of global breast cancers are diagnosed in the developing world, but they account for three-fourths of total deaths from the disease (1). The increasing burden of breast cancer is also acknowledged in the resolution on cancer prevention and control, as adopted by the 58th World Health Assembly in May 2005 (4). Therein, member states are urged to develop and reinforce comprehensive cancer control programs to reduce cancer mortality and improve quality of life for patients and their families.

Cost-effectiveness analyses (CEAs) can provide useful information for planning and developing a breast cancer control policy. CEAs can be used to guide budget development, justify allocation of scarce resources to national breast cancer control programs, and identify the most efficient ways of delivering diagnostic and treatment services. Nearly all studies of the costs and health effects of breast cancer control interventions have been performed in developed countries (5), so data to guide resource allocation decisions in developing countries are scarce. Moreover, studies to date have focused on individual interventions, and interactions among interventions have been largely ignored. In addition, existing studies have focused on interventions specific to breast cancer control in situations where breast cancer care was already in place. This limitation precludes comparisons with interventions in settings where care systems have not been established or

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with interventions that might be more relevant to other regions of the world.

Our intention was to broadly assess the cost-effectiveness of breast cancer control that covers various interventions in different settings and to enable comparisons with recent CEAs of other health care interventions that follow the same analytic approach (6–9).

METHODS

Study Design

We used a simplified breast cancer model to simulate the impact of six basic interventions on the course of breast cancer in three regions of the world (10). Each intervention was compared with no intervention (i.e., no active case finding or breast cancer treatment). All interventions were introduced starting in the year 2000 for a period of 10 years, after which no breast cancer interventions were available, and the maximum follow-up was 100 years, which is in line with the World Health Organization (WHO) guidelines on CEA (10). Following this standardized approach, we assumed that interventions were performed optimally. The outcomes of our analysis were life-years adjusted for disability (DALYs) and the total costs of breast cancer treatment and follow-up for each of the six interventions.

We adopted a societal perspective (11) and included all costs and effects in our model. Future costs and effects were discounted at a rate of 3% per year (11). The average cost-effectiveness ratio (CER) compared to the do-nothing scenario was calculated for each intervention by dividing the total intervention costs (the costs are zero in the do-nothing scenario) by the total DALYs averted (i.e., the DALYs lost when no intervention is applied minus the DALYs lost when an intervention is applied for 10 years). The interventions were also compared to arrive at the incremental CER, which we defined as the additional costs of a more effective intervention divided by the size of this additional effect in terms of DALYs averted. To calculate the incremental CERs, the interventions were ordered by increasing effectiveness and the ratio of a scenario with its adjacent, less effective scenario was determined.

Study Population and Analyzed Regions

The breast health of adolescent and adult women age 15 years and older was simulated in an open cohort. The costs, effects, and cost-effectiveness of each of the interventions were evaluated for three epidemiologic regions of Africa, North America (including Cuba), and Asia, defined by mortality strata (Appendix A) (10).

Model Assumptions

Interventions In recent years, many developments in diagnosing and treating breast cancer have occurred, and we could analyze a large number of interventions in our model. However, we confined the model to a small set of basic interventions to allow comparability among the regions. We assessed the following six basic interventions:

- Stage I treatment: Lumpectomy with axillary dissection supplemented with external radiotherapy to the breast. Eligible patients also receive endocrine therapy.
- Stage II treatment: Lumpectomy with axillary dissection supplemented with external radiotherapy to the breast. Eligible patients also receive endocrine therapy.
- Stage III treatment: Neoadjuvant chemotherapy followed by mastectomy with axillary dissection supplemented with adjuvant chemotherapy. External radiotherapy to the breast is also administered and eligible patients receive endocrine therapy.
- Stage IV treatment: Systemic chemotherapy, supplemented with endocrine therapy for eligible patients. In this group of patients, these therapies are palliative.
- Treatment all stages: Treatment of all stages as described above.
- Extensive program: Treatment of all stages as described above, plus a breast awareness program and early case finding through biannual mammographic screening in women age 50–70 years.

Model Structure Six mutually exclusive health states were included (Fig. 1): healthy (no breast cancer); American Joint Committee on Cancer (12) stages I, II, III, and

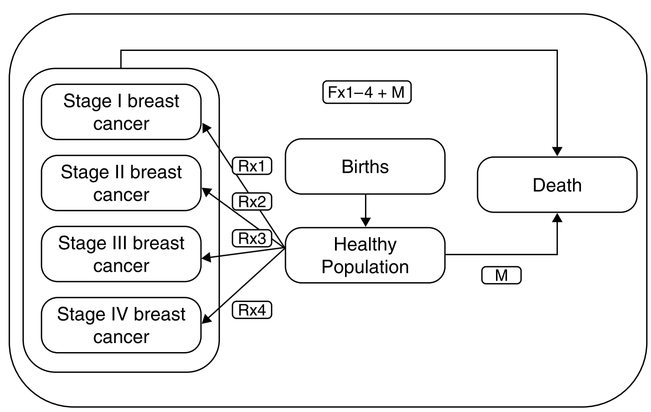

Figure 1. Graphical representation of the model showing the relationships between the six different health states through the incidence rates of breast cancer (Rx1–Rx4) and the different mortality rates for the different breast cancer stages (Fx1–4) and the background mortality (M).

Table 1. Input Data for the Disease Model by Breast Cancer Stage and WHO Region (10)

Model element	North America	Africa and Asia	References
Stage distribution of prevalent cases, 2000 (%)			
Stage I	49.00	9.40	15,16
Stage II	37.40	14.20	15,16
Stage III	8.60	58.00	15,16
Stage IV	5.00	18.40	15,16
Stage distribution of incident cases in absence of an extensive program, 2000–2010 and the whole population thereafter (%)			
Stage I	9.40	9.40	16
Stage II	14.20	14.20	16
Stage III	58.00	58.00	16
Stage IV	18.40	18.40	16
Stage distribution of incident cases in presence of an extensive program, 2000–2010 (%)			
Stage I	49.00	49.00	15
Stage II	37.40	37.40	15
Stage III	8.60	8.60	15
Stage IV	5.00	5.00	15
Case fatality rate of untreated patients, 2000–2100			
Stage I	0.020	0.020	16
Stage II	0.063	0.063	16
Stage III	0.150	0.150	16
Stage IV	0.300	0.300	16
Case fatality rate of treated patients, 2000–2100[a]			
Stage I	0.006	0.006	15
Stage II	0.042	0.042	15
Stage III	0.093	0.093	15
Stage IV	0.275	0.275	15
Quality of life[b]			
Stage I	0.9325	0.9325	17–20
Stage II	0.9301	0.9301	17–20
Stage III	0.9284	0.9284	17–20
Stage IV untreated	0.9097	0.9097	17–20
Stage IV treated	0.9275	0.9275	17–20

[a]Includes the 100% of prevalent cases in North America, 10% in Africa, and 25% in Asia that were treated in 2000 (13).
[b]On a scale from 0 (dead) to 1 (perfect health).

IV breast cancer; and death from breast cancer. Regional age-adjusted population estimates of breast cancer incidence, breast cancer prevalence, percentage of prevalent cases treated, and background mortality rates were based on the WHO Burden of Disease study estimates for 2000 (13).

Following the WHO guidelines (10), the interventions were aimed at initial disease treatment only, but patients could experience a relapse or progression after initial diagnosis; therefore we filtered out the effect of treating patients whose disease progressed. It was assumed that patients could have a progression only to stage IV breast cancer and that cancer progressed at a constant rate (14).

Stage Distribution and Case Fatality Rates The key elements of the model were the stage distribution of both prevalent and incident cases, and the case fatality rate for untreated and treated patients (Table 1). We distinguished between the stage distribution in the developed region (North America) and the two developing regions (Africa and Asia) to reflect the difference in levels of breast cancer care.

Stage distributions for prevalent cases were derived from registry data (Table 1). The stage distribution of prevalent cases in North America was based on the U.S. National Cancer Data Base (NCDB) (15). The stage distribution of prevalent cases in Africa and Asia was based on registry data from Southeast Asia (16).

In the no-intervention scenario, the stage distribution of incident cases and stage-specific case fatality rates were based on registry data from Southeast Asia (16) and applied to all regions. The case fatality rates for treated patients were derived from the NCDB (15). In the extensive breast cancer program scenario, the stage distribution of incident cases and stage-specific case fatality rates were based on data from the NCDB (15) for all regions.

Quality of Life The quality of life of patients with breast cancer (Table 1) was based on the WHO Global Burden of Disease study (17). Using NCDB data on stage distribution (15) and quality of life data from several sources (18–20), we arrived at stage-specific quality of life estimates. The quality of life of the susceptible population was also included (17).

Table 2. Patient-Level Resource Use Patterns for Breast Cancer Interventions

	Resource[a]	No. of outpatient visits	Length of hospitalization (days)
Diagnosis		1	NA
	Bilateral mammography		
	Complete blood count		
	Total bilirubin assay		
	Alkaline phosphatase assay		
	Fine needle aspiration or core needle biopsy		
	Liver function tests		
	ECG in 50%		
	Bone scan in 25%		
	Ultrasonography of the liver in 25%		
Non-breast cancer examination[b]		1	NA
	Bilateral mammography		
	Ultrasonography of the liver in 28%		
	Fine needle aspiration or core needle biopsy in 0.27%		
Stage I treatment		1	2
	Lumpectomy with axillary dissection		
	Radiotherapy[c]		
	Endocrine therapy in 50%[d]		
Stage II treatment		1	2
	Lumpectomy with axillary dissection		
	Radiotherapy[c]		
	Endocrine therapy in 50%[d]		
Stage III treatment		1	2
	(Neo)adjuvant chemotherapy[e]		
	Mastectomy with axillary dissection		
	Radiotherapy[c]		
	Endocrine therapy in 50%[d]		
Stage IV treatment		1	2
	(Neo)adjuvant chemotherapy[e]		
	Endocrine therapy in 50%[d]		
Follow-up year 1–5 (per year)		2	NA
	2 Bilateral mammographies		
	Pelvic examination in 50%		
Follow-up year 6–10 (per year)		1	NA
	Bilateral mammography		
	Pelvic examination in 50%		
Screening		1	NA
	Bilateral mammography		
	Ultrasonography of the liver in 28%[b]		
	Fine needle aspiration or core needle biopsy in 0.27%[b]		

[a]Based on clinical practice guidelines (21,22).
[b]Includes resource use of initial evaluation of women without breast cancer who were initially suspected of having breast cancer (23).
[c]Radiotherapy includes a standard dose of 50 Gy given in 25 fractions of 2 Gy on an outpatient basis in all stages of breast cancer (33).
[d]Endocrine therapy consists of 20 mg tamoxifen per day for 5 years (21,22).
[e]The (neo)adjuvant chemotherapy combination regimen consists of four, 21-day cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (830 mg/m^2) supplemented with 4 mg dexamethasone, given on an outpatient basis (21,22).
ECG, electrocardiography; NA, not applicable.

Costs All costs were calculated and are presented in 2000 U.S. dollars. Two types of costs for health services were distinguished: patient-level costs, which were those incurred for individual patients, and program-level costs, which were those incurred at a level above that of the patient (10).

Patient-Level Costs In all regions patient-level patterns of resource use (i.e., initial evaluation, local treatment, and follow-up) were based on clinical practice guidelines (21,22) (Table 2). These costs included evaluation of women without breast cancer; it was assumed that breast cancer was diagnosed in only 6% of all presenting women (23).

Screening in the extensive cancer program included costs of mammographic screening in women age 50–70 years and further diagnostic tests on referral (Table 2). Detailed lists of all tests and procedures, including housing, personnel, and medical devices, were retrieved from a South African database (24) and were validated for western countries by a team of oncologists.

Unit costs were retrieved from the WHO-CHOICE database on prices of traded and nontraded goods (http://www.who.int/choice). Unit costs of health center visits and hospital inpatient days were based on a report by Adam et al. (25). We combined unit costs with resource use patterns to estimate the total costs per patient treated. All unit costs are presented for the regions of Africa, North America, and Asia in Appendix B.

Program-Level Costs We based estimated quantities of resources required to start up and maintain each intervention for 10 years (e.g., personnel, materials and supplies, media, transport, maintenance, utilities, and capital) at national, provincial, and district levels on a series of evaluations made by regional costing teams in the different WHO regions and validated against the literature (26). We obtained unit cost estimates of program-level resources (e.g., the salaries of central administrators, capital costs of vehicles, storage, offices, and furniture) from a review of the literature, which was supplemented by primary data from several countries (the full list of unit cost estimates is available at http://www.who.int/choice). The process and methodology for estimating program costs are described in detail elsewhere (26,27).

Sensitivity Analyses

To address uncertainty and determine the robustness of the model, we conducted both univariate and multivariate sensitivity analyses on key parameters. Specifically we assessed the effects of varying the stage distribution of prevalent cases, the stage distribution of incident cases, and the case fatality rate of treated patients, individually and then collectively.

RESULTS

Intervention Effectiveness

In Africa, the smallest group treated in the 10-year period was women who had stage I breast cancer (Table 3); of these 37,277 cases, 9604 were previously untreated prevalent cases and 27,673 were new cases of breast cancer. Most of the treated women were those with stage III breast cancer (228,914; 58,978 prevalent and 169,936 incident cases). In North America and Asia, the trends were the same, although the absolute numbers of treated patients were higher. The female population in North America was four times smaller than the female population in Asia, but the number of treated breast cancer patients was one-third higher in North America. The population sizes in North America and Africa were similar, but the number of treated patients was four times larger in North America.

Because of these differences between regions, the number of DALYs averted for the total population or per treated patient in the 10-year period also varied considerably (Table 3). For example, in Africa, treatment of stage I patients resulted in a total of 873,000 DALYs averted for the total population and 23.41 DALYs averted per treated patient. Despite the greater number of treated patients with stage II, III, or IV breast cancer, the total number of DALYs averted was considerably less for each of these stages. When all diagnosed cases were treated, 1,490,000 DALYs were averted for the total population (3.77 per treated patient). When an extensive breast cancer program was assumed to exist in Africa, 6,374,000 DALYs were averted for the total population (16.14 per treated patient).

Costs and Cost-Effectiveness

The range in total costs per intervention over the 10-year period was considerable. For example, the total costs for introducing stage I treatment was $68 million in Africa, $3879 million in North America, and $143 million in Asia (Table 3).

The costs of diagnosis were a fixed component in all intervention scenarios because cases must be diagnosed correctly before treatment can be initiated. This category also accounted for the exclusion of women presenting without breast cancer. As a result, costs per treated patient were lowest when all diagnosed cases were treated (Table 3). In all three regions, the diagnostic costs for patients with stage I breast cancer constituted 62–68% of the total costs, whereas the diagnostic costs for all patients made up 17–20% of the total costs.

The costs per treated patient with stage I disease were $1829 in Africa, $24,008 in North America, and $1188 in Asia (Table 3). The costs of treatment represented 16–27% of the total costs in each region.

In the extensive program, different cost items accounted for widely varying proportions of the total costs (Table 3). In Africa, the patient-level costs of screening and associated diagnostic examination of false-positive screens ($180 million) were 38% of the total costs; in North America, these costs ($5299 million) constituted only 26% of the total costs; and in Asia, these costs ($703 million) made up 58% of the total costs.

In each of the six intervention scenarios, the total program costs accounted for 8–24% of the total costs in Africa and Asia, but only 1–4% of the total costs in North America (Table 3).

When we compared the intervention scenarios with the no-intervention scenario, treatment of stage I patients and the extensive breast cancer program were the most cost-effective interventions, with average CERs for stage I treatment and extensive programs, respectively, of $78 and $75 per DALY averted in Africa, $1960 and $915 per

Table 3. Number of Patients Treated, DALYs Averted, Costs, and CERs at an 80% Coverage Level, Over a 10-Year Period (2000–2010) by WHO Region

Region and intervention	No. of patients treated	Total DALYs averted (in thousands)	DALYs averted per patient	Population-level costs (millions of 2000 U.S.$)								Costs per treated patient 2000 U.S.$	CER (2000 U.S.$ per DALY averted)	
				Diagnosis	Non–breast cancer examination	Treatment	Follow-up	Screening	Total per patient	Total per program	Total overall		Average[a]	Incremental[b]
Africa														
Stage I treatment	37,277	873	23.41	11	31	13	2		56	12	68	1829	78	NA
Stage II treatment	55,955	231	4.13	11	31	19	3		63	12	75	1342	324	NA
Stage III treatment	228,914	399	1.74	11	31	93	9		143	12	155	679	389	NA
Stage IV treatment	72,738	14	0.19	11	31	14	2		58	12	70	959	4986	NA
Treatment all stages	394,884	1490	3.77	11	31	138	15		195	42	238	602	159	NA
Extensive program	394,884	6374	16.14	11	20	134	17	180	362	115	477	1208	75	75
North America														
Stage I treatment	161,558	1979	12.25	500	2171	1040	108		3820	59	3879	24,008	1960	NA
Stage II treatment	242,507	542	2.24	500	2171	1562	147		4380	59	4439	18,304	8187	NA
Stage III treatment	992,107	1587	1.60	500	2171	7136	526		10,334	59	10,392	10,475	6549	NA
Stage IV treatment	315,214	56	0.18	500	2171	1074	110		3857	59	3915	12,421	70,380	NA
Treatment all stages	1,711,414	4282	2.50	500	2171	10,812	892		14,375	223	14,598	8530	3409	NA
Extensive program	1,711,414	22,098	12.91	500	1626	10,874	1057	5299	19,356	856	20,213	11,811	915	915
Asia														
Stage I treatment	120,738	2325	19.25	27	64	23	5		120	24	143	1188	62	62
Stage II treatment	181,235	663	3.66	27	64	34	7		133	24	156	863	236	NA
Stage III treatment	741,439	1205	1.63	27	64	178	23		292	24	316	426	262	NA
Stage IV treatment	235,593	42	0.18	27	64	29	4		125	24	149	630	3510	NA
Treatment all stages	1,279,005	4155	3.25	27	64	264	38		393	62	455	356	110	NA
Extensive program	1,279,005	16,086	12.58	27	38	251	42	703	1061	145	1206	943	75	77

[a]Incremental CER versus less effective alternative. To calculate the incremental CER, the interventions were ordered by increasing effectiveness and the ratio of a scenario with its adjacent, less effective scenario was determined.
[b]Average CER compared to the do-nothing scenario. In the do-nothing scenario costs were zero.
CER, cost-effectiveness ratio; DALY, disability-adjusted life-year; WHO, World Health Organization; NA, not applicable, because the intervention is less cost-effective than others.

DALY averted in North America, and $62 and $75 per DALY averted in Asia (Table 3). The least cost-effective option was stage IV treatment (average CERs of $4986, $70,380, and $3510 per DALY averted in Africa, North America, and Asia, respectively).

Incremental CERs revealed that in Africa and North America, the optimal breast cancer program was the most cost-effective intervention scenario ($75 and $915 per DALY averted, respectively) (Table 3). In Asia, the most cost-effective options were stage I treatment ($62 per DALY averted) and then the optimal breast cancer program ($77 per DALY averted).

The order in which interventions should be introduced according to the cost-effectiveness results (i.e., the "expansion path;" for more details on expansion paths, see Tan-Torres Edejer et al. (10)) is illustrated for Asia in Figure 2. Stage I treatment would be introduced first. With more resources, an optimal breast cancer program would be established.

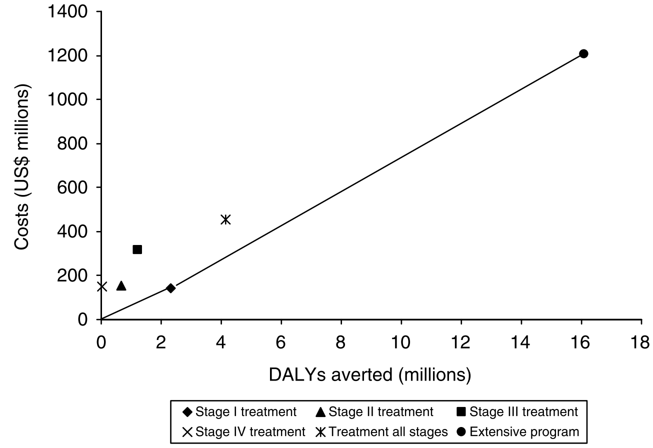

Figure 2. Expansion path for the Asian region.

Sensitivity Analyses

In the first two univariate sensitivity analyses, it was assumed that cancers were diagnosed earlier compared with the base case analysis (i.e., more stage I and II cancers and fewer stage III and IV cancers). This assumption produces a more favorable distribution, with the sole exception of the prevalent cases in North America, where the distribution becomes less favorable. Applying these alternative stage distributions for prevalent and incident breast cancer cases resulted in lower average CERs for stage I treatment and for treatment of all stages in Africa, North America, and Asia because more stage I patients received treatment, which was associated with lower case fatality rates (Table 4 shows results for Asia as an example). For stage III and IV treatment, the average CERs increased because fewer cases were diagnosed at these stages. Because the shift in distribution of incident cases of stage II breast cancer decreased the overall mortality in the no-intervention scenario, the average CERs for stage II treatment and the extensive program also increased.

In a third univariate analysis, the assumption of a 50% reduction in treatment effect on case fatality rates (i.e., higher case fatality rates of treated cases than those used in the base case analysis) increased the average CERs of each of the six interventions in Africa, North America, and Asia (Table 4 shows results for Asia as an example).

Combining all three univariate sensitivity analyses in a multivariate analysis resulted in a further increase in the average CERs for stage II, III, and IV treatment and the extensive program (Table 4). The average CERs for stage I treatment and treatment of all stages were between the CERs calculated in the individual sensitivity analyses.

Table 4. Results of Univariate and Multivariate Sensitivity Analyses for Asia[a]

	Univariate analyses							
	Alternative stage distribution of prevalent cases[b]		Alternative stage distribution of incident cases[b,c]		Alternative case fatality rates[d]		Multivariate analysis[e]	
Intervention	Average	Incremental[f]	Average	Incremental[f]	Average	Incremental[f]	Average	Incremental[f]
Stage I treatment	45	45	48	48	162	NA	107	107
Stage II treatment	224	NA	261	NA	609	NA	618	NA
Stage III treatment	283	NA	390	NA	642	NA	1186	NA
Stage IV treatment	4103	NA	4888	NA	5175	NA	8875	NA
Treatment all stages	79	NA	84	NA	255	NA	178	NA
Extensive program	73	82	127	182	113	113	216	274

[a]Data are presented as cost-effectiveness ratios, calculated as cost (in 2000 U.S.$) per DALY (disability-adjusted life-year) averted.
[b]Stage distribution: stage I, 29%; stage II, 26%; stage III, 33%; and stage IV, 12%.
[c]In the absence of an extensive breast cancer program.
[d]Case fatality rates of treated patients: stage I, 0.013; stage II, 0.053; stage III, 0.122; and stage IV, 0.288.
[e]All adjustments in the three univariate sensitivity analyses were implemented simultaneously.
[f]Incremental cost-effectiveness ratio versus lesser effective alternative.
NA, not applicable, because the intervention is less cost-effective than others.

DISCUSSION

Our analyses showed that treating early stage breast cancer is more cost-effective than treating late-stage disease. In Africa and Asia, treatment of stage I, II, or III disease costs less than $390 per DALY averted, whereas treatment of stage IV disease costs more than $3500 per DALY averted; in North America, the respective values were $6550 and $70,400. For comparison, we can use benchmarks suggested by other researchers to assess whether a health intervention is cost-effective: cost per DALY averted or life-year gained equal to the per capita income (28), twice per capita income (29), or three times per capita income (30) (low-income countries are defined as having per capita incomes of $765 or less per year, and high-income countries are defined as having per capita incomes of more than $9386 per year). According to these benchmarks, all interventions except treatment of stage IV disease were cost effective in all three regions.

The incremental CERs indicated that priorities in national breast cancer control programs would be treatment of stage I disease or implementation of an extensive cancer control program (including breast cancer awareness campaigns and active mammographic screening).

Although the extensive cancer control program reflects the economic attractiveness of diagnosing breast cancer at an earlier stage, many developing countries may not be able to meet the total costs of such a program (including the required infrastructure, logistics, and expertise). Given the limited available resources, priorities are probably best directed at treatment of early stage disease and at developing a less expensive means of early diagnosis. We did not evaluate clinical breast examination or breast self-examination because currently there is no consensus on their value alone or in addition to mammography. Nevertheless, together with other ways of raising awareness, clinical breast examination and breast self-examination could be a cost-effective means by which to diagnose breast cancer earlier in resource-poor settings.

A number of our study limitations have to be addressed. We used data on stage distribution and case fatality rates from a sample of developing countries to reflect the absence of breast cancer control interventions. For the same variables, we used data from U.S. cancer registries to reflect intervention effectiveness. Whether these data are accurate can be assessed only when studies on the effectiveness of breast cancer interventions in developing countries become available.

We did not include stage 0 disease (i.e., ductal carcinoma in situ) in our model because very little information is available on this type of breast cancer in developing regions. Furthermore, the WHO Global Burden of Disease study provides information only on the prevalence and incidence of palpable breast cancer. From the NCDB, it is clear that through screening, the proportion of disease diagnosed at stage 0 increased substantially in the United States (15). Although not all stage 0 breast cancer will result in breast cancer-related death if not treated, and overtreatment (with its associated costs) will likely be introduced, including stage 0 disease in the model will probably reinforce our conclusion that treating earlier stages of breast cancer is the most cost-effective intervention.

We estimated program costs for breast cancer interventions that are not yet in place on this scale in developing countries and therefore cannot be validated. However, an extensive cancer control program was estimated to cost $50 million for 95% geographic coverage in The Netherlands; this value compares well with the costs of breast cancer screening in that country, which were $49 million in 2003 (31).

Our simplified cost-effectiveness model is appropriate to use for broadly assessing the relative economic attractiveness of breast cancer interventions and for comparing interventions among regions. Our analysis shows that there is a broad variation in epidemiology between regions and that there are large differences in cost structure as well. In contrast to North America, where personnel is the major cost component, the costs of personnel are only a small part of the total costs in developing regions (Africa and Asia). Therefore, while the pattern of most cost-effective interventions is the same, there are substantial differences between interventions across regions and likely within a region. A more detailed country-level analysis, using local cost and resource estimates and epidemiologic information, could be useful for testing whether our model assumptions hold and for obtaining more specific information on the impact of interventions on budgets, especially when there is competition for scarce resources with interventions that are more intensive with respect to either personnel time or resource use. We developed the cost-effectiveness model in such a way that these country-specific adaptations can be performed easily.

For reasons of comparability, we were unable to include many of the elements of breast cancer care that are considered standard in developed countries. A few examples are sentinel lymph node biopsy, breast reconstruction after surgery, and variations in surgical treatment of breast cancer within the same stage. Furthermore, we assumed the use of only one type of chemotherapy and one type of hormonal therapy. These issues can be addressed in a more tailor-made country-level analysis using the model's framework.

Finally, we are aware of the current debate surrounding the relative effect of breast cancer screening on reducing mortality rates. This debate focuses on the overtreatment and overdiagnosis that are said to be underappreciated harms of screening (32). In our analysis, we assumed that the introduction of an extensive breast cancer program would cause a shift in stage distribution that would result in reduced mortality rates for all patients, and this assumption probably led to an overestimation of the impact of such a program. Sensitivity analyses showed that varying model assumptions did affect the cost-effectiveness of the interventions, but not our principal study conclusion.

We conclude that both treatment of early stage breast cancer and interventions for down-staging disease at diagnosis are among the most valuable interventions in breast cancer control.

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Appendix A. Epidemiologic Regions as Applied in WHO Generalized CEA (10)

WHO region	Mortality stratum[a]	WHO member states
Africa	E	Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
North America	A	Canada, Cuba, United States of America
Asia	D	Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal

[a]A, have very low rates of adult and child mortality; D, have high adult and child mortality; E, have very high adult and high child mortality.
WHO, World Health Organization; CEA, cost-effectiveness analysis.

Appendix B. Unit Costs and Total Costs per Patient (in 2000 U.S. Dollars) by WHO Region[a]

Resource or intervention	Africa	North America	Asia
Unit costs			
Outpatient visit	0.82	24.05	0.53
Hospitalization	4.65	203.35	3.75
Lumpectomy	34.00	414.72	23.54
Mastectomy	34.56	417.01	24.01
Radiotherapy	323.43	6465.55	173.20
(Neo)adjuvant chemotherapy	75.96	852.72	54.87
Endocrine therapy	0.01	0.04	0.01
Bilateral mammography	3.57	48.36	2.60
Fine needle aspiration biopsy	8.22	51.42	6.47
Chest radiograph	3.05	31.76	2.26
Bone scan	15.96	107.79	13.06
Electrocardiography	1.58	28.47	0.91
Pelvic examination	1.22	20.44	0.70
Ultrasonography of the liver	3.61	66.10	2.12
Complete blood count	2.68	35.10	1.97
Total bilirubin assay	2.23	36.83	1.51
Alkaline phosphatase assay	4.70	46.76	3.59
Total costs per patient			
Diagnosis	30.96	300.23	17.32
Non-breast cancer examination	5.57	91.94	3.85
Stage I treatment	367.54	7311.01	204.77
Stage II treatment	367.54	7311.01	204.77
Stage III treatment	444.06	8166.03	260.11
Stage IV treatment	86.08	1283.47	62.89
Follow-up year 1–5	31.95	547.31	22.75
Follow-up year 6–10	24.26	378.69	17.51
Screening	4.46	62.60	3.15

[a]All unit costs are derived from a South African database (24).
WHO, World Health Organization.