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Abstract

This paper reports the most cost-effective policy options to support and improve breast cancer control in Costa Rica and Mexico. Total costs and effects of breast cancer interventions were estimated using the health care perspective and WHO-CHOICE methodology. Effects were measured in disability-adjusted life years (DALYs) averted. Costs were assessed in 2009 United States Dollars (US$). To the extent available, analyses were based on locally obtained data. In Costa Rica, the current strategy of treating breast cancer in stages I to IV at a 80% coverage level seems to be the most cost-effective with an incremental cost-effectiveness ratio (ICER) of US$4,739 per DALY averted. At a coverage level of 95%, biennial clinical breast examination (CBE) screening could improve Costa Rica’s population health twofold, and can still be considered very cost-effective (ICER US$5,964/DALY). For Mexico, our results indicate that at 95% coverage a mass-media awareness raising program (MAR) could be the most cost-effective (ICER US$5,021/DALY). If more resources are available in Mexico, biennial mammography screening for women 50–70 yrs (ICER US$12,718/DALY) or screening women 40–70 yrs biennially plus trastuzumab (ICER US$17,115/DALY) are less cost-effective options. We recommend both Costa Rica and Mexico to engage in MAR, CBE or mammography screening programs, depending on their budget. The results of this study should be interpreted with caution however, as the evidence on the intervention effectiveness is uncertain. Also, these programs require several organizational, budgetary and human resources, and the accessibility of breast cancer diagnostic, referral, treatment and palliative care facilities should be improved simultaneously. A gradual implementation of early detection programs should give the respective Ministries of Health the time to negotiate the required budget, train the required human resources and understand possible socioeconomic barriers.

Introduction

Due to population ageing and changing lifestyles in low-and-middle countries (LMICs), breast cancer incidence rates are increasing [1,2]. Given the organizational and financial constraints faced by the health systems in LMICs the majority of breast cancers are diagnosed at late stages [3]. Accordingly, the majority of breast cancer deaths occur in LMICs [4,5]. The World Health Organization (WHO) therefore states that early detection and implementation of cost-effective interventions should be a priority in LMICs [6]. In an attempt to support LMICs with breast cancer control, the Susan G. komen for the Cure foundation provided a grant to investigate the cost-effectiveness of several breast cancer control interventions in 7 LMICs (Brazil, Colombia, Costa Rica, Ghana, India, Mexico and Peru) to a consortium of the WHO, Erasmus University Rotterdam (EUR) and Radboud University Nijmegen Medical Center (RUNMC). Cost-effectiveness analyses may support governments in deciding how to spend scarce resources in health care most efficiently.

In each country, during four phases, the consortium works closely with local authorities and experts in the fields of breast cancer, health economics, epidemiology and public policy. First, a three-day technical workshop is held, where the consortium explains a general cost-effectiveness model based on WHO-CHOICE methodology (described elsewhere [7,8]) which is to be tailored to the country specific situation. In the second phase, lasting approximately six months, local authorities identify and assemble the (local) data required for the cost-effectiveness model. Subsequent in phase three, the cost-effectiveness analyses are carried out. Thereafter, a second workshop is organized. Here the results of the analyses are discussed among representatives of all local institutions involved in breast cancer care and made available for actual policy making by the local health authorities, i.e. the fourth phase. This paper identifies the most cost-effective interventions for breast cancer control in both Costa Rica and Mexico from a health care perspective.

After presenting an overview of the situation regarding breast cancer in both Costa Rica and Mexico, we discuss the methods,
data and interventions considered in this study and discuss the results.

Breast cancer in Costa Rica and Mexico

Cancer incidence and mortality rates are rising across Central America [9,10]. In Costa Rica and Mexico breast cancer ranks among the top-five causes of death for women over 25 years old [11]. Between 1995 and 2003, breast cancer incidence increased by 32.3% to a rate of 40.07 per 100,000 women in Costa Rica [12]. In Mexico, breast cancer incidence increased as well and in both countries breast cancer mortality rates have increased since the 1980s [9,13,14]. In Costa Rica 13.14 breast cancer deaths per 100,000 women in 2006, the highest number among malignant neoplasms, are observed. Mortality rates per 100,000 women range from 29.19 in province ‘Dota’ to 1.23 Guácimo, while in provinces ‘Los Chiles, ‘La Cruz’, and ‘Garabito’ no breast cancer related deaths were registered [12]. In Mexico mortality rates doubled over the last 20 years. The average mortality rate per 100,000 women in Mexico stands at 9.9 with regional differences from 13.2 and 11.8 respectively in the Federal District and the north to 9.7 and 7.0 respectively in the center and the south [15]. This increase caused breast cancer to overtake cervical cancer as the most deadly cancer among females in 2006 [14,15].Where in 1979 1,144 females died from the disease, in 2006 4,497 deaths were registered [15].

Although in Costa Rica and Mexico official recommendations for both breast self-examination (BSE) and mammography screening have existed for over a decade, their coverage levels remain very low and the large majority of breast cancer patients present at the hospital with advanced disease [16–18].

In light of the above, Non-Governmental Organizations (NGOs) and the general public put pressure on governments in Costa Rica and Mexico to improve treatment and early diagnosis through screening [19,20]. Hence, both countries face choices on efficient allocation of scarce resources for breast cancer screening.

Materials and Methods

Methods

General approach. We used the WHO-CHOICE methodology, described in detail elsewhere [7,8], as a basis of our analysis. This approach compares all possible interventions in a specific disease area to a situation where no interventions are implemented. The latter, a counterfactual ‘null scenario’, acts as a reference to compare the costs and effects of existing and new interventions. An intervention in isolation, or a combination of different interventions, is then implemented for 10 years in a modeled population. However, to include effects that occur after these 10 years, this modeled-population is tracked for 100 years. This approach enables us to make comparisons of the costs and health effects across a wide range of competing interventions, identify differences in relative cost-effectiveness and identify the most efficient mix of interventions to improve population health.

Breast Cancer Model. Costs and health effects are calculated using a state transition population model developed and explained in detail by Groot et al. [7]. Its structure is presented in Figure 1 [7]. The model simulates the development of a national population and accounts for births, background mortality and breast cancer epidemiology of a country. It includes a healthy state, a deceased state, and stage I to IV breast cancer states following the classification of the American Joint Committee on Cancer (AJCC) [21]. The effectiveness of each intervention is expressed in changes in disability weights (DWs i.e. health state valuations (HSV)s), case fatality rates (CFs), i.e. improved survival for treatment scenarios), or in more positive stage distributions (in awareness raising and screening interventions). Since the interventions affect mortality (i.e., CFs) and morbidity (DWs), intervention effectiveness is expressed in disability adjusted life years (DALYs) averted. The difference in the total number of healthy years lived by the population between each scenario and the null-scenario gives the population health gains in DALYs averted.Zelle et al. [22] improved the published model [7] by correcting HSVs for relapse, assuming that patients could only relapse to stage IV at a constant rate [23].

Interventions. An important element of the overall project is to select a set of appropriate interventions for breast cancer control in LMICs. Therefore, a study group at WHO-CHOICE defined a mix of 11 common and preferable practices in 2009 [22]. Participating countries can combine and adapt these practices to appropriately inform their specific policy questions. For Costa Rica and Mexico focus was placed on the cost-effectiveness of screening & treatment combinations. The most urgent policy questions in both countries concerned the age groups that should be targeted for screening and whether treating Her2/NEU+ patients with Trastuzumab was cost-effective. Therefore, the basic awareness raising intervention was excluded and different intervention scenarios, including treatment with Trastuzumab, were added. Combining the 11 common practices with or without Trastuzumab led to a total of 19 scenarios. Input from local policy makers led us to model the current situations of breast cancer control in Costa Rica and Mexico at 80% and 70% geographic coverage levels (i.e. reaching 80%/70% of the people who need services) respectively. In line with WHO-CHOICE methodology all other interventions were evaluated at a geographic coverage level of 95% [8]. An overview of the interventions is listed in table 1.

Data

Effectiveness. A key factor is the stage distribution of patients presenting at the hospital, given the breast cancer stage determines the survival and disability of the breast cancer patients and the effectiveness of each intervention [21].

In Costa Rica we obtained the current stage distribution from Ortiz [24], who studied breast cancer survival in Costa Rica between 2000 and 2003. Demographic data and incidence rates were obtained from the Statistical office of the Costa Rican Ministry of Health (MoH). For the prevalence we used the 2004 Global Burden of Disease estimates [25].

For Mexico, we used the current stage distribution from Knauth et al. [17], who studied 1904 patients that were all treated within the Mexican Social Security Institute (IMSS, its abbreviation in Spanish). Demographic data were obtained from the Mexican National Population Council [29]. For Mexico we obtained incidence rates based on GLOBOCAN 2008 adjusted by group of age considering the distribution from the Mexican Histopathology Registry 2006 [30,31]. For the prevalence in Mexico, as in Costa Rica, we used 2004 Global Burden of Disease estimates [25].

The case fatality rates for the treatment scenarios were based on Groot et al. (stage III & IV) and Zelle et al. (stage I & II), who corrected those from Groot et al. for the use of chemotherapy in stage I and II [7,22]. We take these CFs to represent technical efficiency, representing the maximum amount of DALYs that can be averted based on successful implementation of breast cancer diagnosis, treatment and follow-up. Disability weights were derived from the Global Burden of Disease estimates for long term sequelae [23] using quality of life literature [26,27]. For stage I we took the disability estimate of 0.086 [26] and for stage IV we...
combined the terminal estimate of 0.75 [28] with estimates from quality of life literature [26]. Since screening and awareness interventions as defined in international literature, alter the stage distribution, their effects on the stage distribution at presentation were estimated using the same methods applied by Zelle et al. [22]. Zelle et al. [22] use international study results to estimate the health effects of various screening options and account for the sensitivity of the screening

Figure 1. Graphical representation of the model showing the relationships between the different health states through the incidence rates of breast cancer (Ix1–Ix4), the different stage specific case fatality rates (Fx1–4), and the background mortality (M) [7]. Stage specific relapse rates to stage IV were used to correct health state valuations only (Rx1–Rx3).

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Table 1. Definition and classification of individual interventions (coverage) (based on [22]).

| Treatment of individual stages | Down-staging interventions | Palliative care |
|--------------------------------|----------------------------|-----------------|
| Stage I treatment: lumpectomy with axillary dissection and radiotherapy. Eligible patients receive tamoxifen or chemotherapy [7,23,49]. | Basic Awareness Raising (BAR): community nurses training program+opportunistic outreach activities by community nurses to raise breast cancer awareness and educate on breast self-examination techniques (BSE)+enhanced media activities [50]. | Basic Palliative Care (BPC): palliative care volunteers training program+home-based visits by volunteers every fortnight+pain treatment through morphine, laxatives and palliative radiotherapy (8 Gy in 1 fraction) for eligible patients [49–51]. |
| Stage II treatment: lumpectomy with axillary dissection and radiotherapy. Eligible patients receive tamoxifen or Chemotherapy [7,23,49]. | Mass-media awareness raising (MAR): BAR+mass media campaign [50]. | Extended Palliative Care (EPC): BPC apart from community nurses instead of palliative care volunteers, pain treatment strengthened with antidepressants, anti-emetics and zolodronic acid [50–54]. |
| Stage III treatment: modified mastectomy followed by adjuvant chemotherapy and radiotherapy. Eligible patients receive tamoxifen [7,49]. | Biennial clinical breast examination (CBE) screening in asymptomatic women aged 40–69 years: community nurses training program+active outreach screening by community nurses+limited media activities [50,55]. |  |
| Stage IV treatment: adjuvant Chemotherapy and radiotherapy (10 Gy)+end of life hospitalization. Eligible patients receive total mastectomy and/or tamoxifen [49,56]. | Biennial mammography screening in asymptomatic women aged 50–69 years+limited media activities [7]. |  |
| Biennial mammography screening in asymptomatic women aged 40–69 years+limited media activities [7]. |  |  |

*Endocrine therapy consists of 20 mg tamoxifen per day for 5 years.

†Down-staging interventions cause a shift in stage distribution and are only modeled in combination with treatment of all stages (I–IV).

‡BAR was excluded as a standalone intervention in Costa Rica and Mexico.

§Palliative care interventions are only applied to stage IV patients, and substitutes stage IV treatment.

‖The (neo)adjuvant chemotherapy combination regimen consists of 7 cycles of Epirubicin, Fluorouracil and cyclophosphamide (FEC regimen) Given on an outpatient basis.

¶Radiotherapy includes a standard dose of 50 Gy given in 25 fractions of 2 Gy on an outpatient basis.

§§Trastuzumab is given for 8 months.

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| Costa Rica (CR) - Intervention | CF Rates<sup>a</sup> | CF Rates<sup>a</sup> | CF Rates<sup>a</sup> | CF Rates<sup>a</sup> | DW's<sup>b</sup> | DW's<sup>b</sup> | DW's<sup>b</sup> | Stage Dist. | Stage Dist. | Stage Dist. | Stage Dist. |
|-------------------------------|----------------------|----------------------|----------------------|----------------------|----------------|----------------|----------------|-------------|-------------|-------------|-------------|
|                               | stage I              | stage II             | stage III            | stage IV             | stage I            | stage II             | stage III            | stage IV             | % in stage I | % in stage II | % in stage III | % in stage IV |
| Untreated                     | 0.0207               | 0.0654               | 0.1556               | 0.3112               | 0.086               | 0.097               | 0.104               | 0.375               | 14.6%      | 41.6%      | 20.4%      | 23.4%      |
| Stage I treatment             | 0.0056               |                      |                      |                      | 0.086               |                      |                      |                      | 14.6%      |            |            |            |
| Stage II treatment            |                      | 0.0393               |                      | 0.097               |                      |                      |                      |                      | 41.6%      |            |            |            |
| Stage III treatment           |                      |                      | 0.0930               | 0.104               |                      |                      |                      |                      | 20.4%      |            |            |            |
| Stage IV treatment            |                      |                      |                      |                      |                      |                      |                      |                      | 23.4%      |            |            |            |
| Basic Palliative Care (BPC)   |                      |                      |                      |                      |                      |                      |                      |                      |            |            |            |            |
| Extended Palliative Care (EPC)|                      |                      |                      |                      |                      |                      |                      |                      |            |            |            |            |
| Current Country Situation     | 0.0056               | 0.0393               | 0.0930               | 0.2750               | 0.086               | 0.097               | 0.104               | 0.154               | 14.6%      | 41.6%      | 20.4%      | 23.4%      |
| Mass-media Awareness Raising (MAR) |          |                      |                      |                      |                      |                      |                      |                      | 21.1%      | 41.5%      | 24.1%      | 13.3%      |
| Biennial CBE screening (40–69)| 0.0056               | 0.0393               | 0.0930               | 0.2750               | 0.086               | 0.097               | 0.104               | 0.154               | 32.0%      | 34.3%      | 25.8%      | 7.9%       |
| Biennial mammography screening (50–69) |       |                      |                      |                      |                      |                      |                      |                      | 35.0%      | 37.5%      | 21.1%      | 6.5%       |
| Biennial mammography screening (40–69) |       |                      |                      |                      |                      |                      |                      |                      | 40.0%      | 42.8%      | 13.2%      | 4.0%       |
| With Trastuzumab              | 0.0050               | 0.0353               | 0.0835               | 0.2470               | 0.086               | 0.097               | 0.104               | 0.154               |            |            |            |            |

| Mexico (MX) - Intervention | stage I              | stage II             | stage III            | stage IV             | Stage I              | stage II             | stage III            | stage IV             | % in stage I | % in stage II | % in stage III | % in stage IV |
|---------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|-------------|-------------|-------------|-------------|
| Untreated                 | 0.0207               | 0.0654               | 0.1556               | 0.3112               | 0.086               | 0.097               | 0.104               | 0.375               | 13.8%      | 39.6%      | 33.9%      | 12.7%      |
| Stage I treatment         | 0.0056               |                      |                      |                      | 0.086               |                      |                      |                      |             |            |            |             |
| Stage II treatment        |                      | 0.0393               |                      | 0.097               |                      |                      |                      |                      | 39.6%      |            |            |             |
| Stage III treatment       |                      |                      | 0.0930               | 0.104               |                      |                      |                      |                      | 33.9%      |            |            |             |
| Stage IV treatment        |                      |                      |                      |                      |                      |                      |                      |                      |             |            |            |             |
| Basic Palliative Care (BPC)|                      |                      |                      |                      |                      |                      |                      |                      |            |            |            |             |
| Extended Palliative Care (EPC)|          |                      |                      |                      |                      |                      |                      |                      |            |            |            |             |
| Current Country Situation | 0.0056               | 0.0393               | 0.0930               | 0.2750               | 0.086               | 0.097               | 0.104               | 0.154               | 13.8%      | 39.6%      | 33.9%      | 12.7%      |
| Mass-media Awareness Raising (MAR) |               |                      |                      |                      |                      |                      |                      |                      | 21.1%      | 41.5%      | 24.1%      | 13.3%      |
| Biennial CBE screening (40–69) | 0.0056               | 0.0393               | 0.0930               | 0.2750               | 0.086               | 0.097               | 0.104               | 0.154               | 30.5%      | 32.6%      | 28.3%      | 8.7%       |
| Biennial mammography screening (50–69) |       |                      |                      |                      |                      |                      |                      |                      | 33.9%      | 36.3%      | 22.8%      | 7.0%       |
| Biennial mammography screening (40–69) |       |                      |                      |                      |                      |                      |                      |                      | 39.1%      | 41.8%      | 14.6%      | 4.5%       |
### Table 2: Cont.

| Stage IV | Stage III | Stage II | Stage I |
|----------|-----------|----------|---------|
| Mexico (MX) - Intervention |
| With Trastuzumab |
| % in stage I | % in stage II | % in stage III | % in stage IV |
| 0.0054 | 0.0374 | 0.0865 | 0.2569 |
| aCase Fatality - Estimates for stages III and IV are from Groot et al. [7] and for stages I and II from Zelle et al. [22]. The CFs for the untreated patients are from Groot et al. [7] and were corrected based on Bloom et al. [57]. |
| bDisability Weights - Estimates from Zelle et al. [22]. |
| cCurrent stage distribution CR is based on Ortiz [24]; MX on Knaul et al. [17]; Effects of MAR derived from Devi [50]; Effects of screening interventions were based on stage shifts from baseline Groot et al. [7] to the stage distribution USA in Bland et al. [58]. Stage shifts were adapted by calculating relative differences in detection rates between the USA and CR/MX from Duffy & Gabe [59]. Calculations included age-specific incidence (MoH CR & Unidad Económica MX), prevalence (WHO 2008), sojourn time Duffy & Gabe [59], sensitivity Bobo et al. [60] and attendance rates (75% in the USA vs. 80% in Costa Rica and Mexico). |
| dWe assumed in Mexico implementing MAR could not lead to a higher proportion of stage IV patients and increase stage III with the difference of 0.6%. |

Both health effects (DALYs) and costs (US$) are calculated at a rate of 3% annually, which is recommended by WHO.
Table 3. Average utilization of diagnosis and treatment ingredients and unit costs per patient.

| Procedure and Ingredients | Stage I | Stage I | Stage II | Stage II | Stage III | Stage III | Stage IV | Stage IV | Relapse | Relapse | Palliative Care* | (Extended) | Palliative Care* | (Extended) | Unit cost per patient (US$) | Unit cost per patient (US$) |
|---------------------------|---------|---------|----------|----------|-----------|-----------|----------|----------|---------|---------|----------------|------------|----------------|------------|------------------|-------------------|
| **Initial diagnosis and evaluation during treatment** | Costa Rica | Mexico | Costa Rica | Mexico | Costa Rica | Mexico | Costa Rica | Mexico | Costa Rica | Mexico | Costa Rica | Mexico | Costa Rica | Mexico | Costa Rica | Mexico |
| No. of health center visits | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 23,69 | 25,40 | 45,44 | 42,27 | 63,18 | 80,47 | 17,50 | 10,34 |
| No. of hospital visits | 3 | 2 | 3 | 2 | 3 | 2 | 3 | 2 | 3 | 2 | - | - | - | - | - | - |
| Bilateral Mammography | 1 | 1 | 1 | 1 | 2 | 1 | - | - | - | - | 45,44 | 42,27 | 63,18 | 80,47 | 17,50 | 10,34 |
| Complete blood count | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 6 | 6 | 6 | 71,62 | 91,52 | 71,62 | 91,52 | 17,50 | 10,34 |
| FNA or core needle biopsy | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | - | - | - | - | 71,62 | 91,52 |
| Liver function tests | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 7 | 7 | 7 | 40,31 | 10,34 | - | - | - | - |
| Ultrasonography | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 23,65 | 48,32 | 48,32 | 23,65 | - | - |
| Renal function tests | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 7 | 7 | 7 | 9,81 | 10,34 | 9,81 | 10,34 | 9,81 | 10,34 |
| Bone scan | - | - | - | - | 1 | 1 | 1 | 1 | 1 | 1 | - | - | - | - | 108,01 | 192,57 |
| Chest X-ray | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | - | - | - | - | 16,11 | 14,93 |
| ECG | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | - | - | - | - | 16,11 | 14,93 |
| Her2/neu test | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | - | - | - | - | 10,14 | 27,26 |
| **Non-breast cancer evaluation** | | | | | | | | | | | | | | | | | |
| No. of health center visits | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 23,69 | 25,40 | - | - | - | - |
| Bilateral Mammography | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 45,44 | 42,27 | 45,44 | 42,27 | 45,44 | 42,27 |
| Ultrasonography | 0.28 | 0.28 | 0.28 | 0.28 | 0.28 | 0.28 | 0.28 | 0.28 | 0.28 | 0.28 | 22,62 | 22,59 | 22,62 | 22,59 | 22,62 | 22,59 |
| FNA or core needle biopsy | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 71,62 | 91,52 | 71,62 | 91,52 | 71,62 | 91,52 |
| **Treatment** | | | | | | | | | | | | | | | | |
| No. of hospitalization days | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 6 | 0 | 6 | 0 | 0 | 6 | 0 | 0 | 6 | 0 | 6 | 0 | 239,33 | 805,59 |
| No. of OPD visits radiotherapy | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 0 | 1 | 0 | 63,16 | 80,47 | 63,16 | 80,47 | 63,16 | 80,47 |
| No. of OPD visits chemotherapy % receiving surgical intervention | 6 | 7 | 6 | 7 | 6 | 7 | 6 | 7 | 6 | 7 | - | - | - | - | - | - |
| Lump. | Lump. | Lump. | Lump. | Lump. | Lump. | Lump. | Lump. | Lump. | Lump. | Lump. | 239,33 | 805,59 | - | - | - | - |
| Mast. | Mast. | Mast. | Mast. | Mast. | Mast. | Mast. | Mast. | Mast. | Mast. | Mast. | 243,27 | 857,34 | - | - | - | - |

*Note: Palliative Care (Extended) refers to additional care for patients who have relapsed. Unit costs are calculated based on the number of visits and procedures performed in Costa Rica and Mexico. The table shows the average utilization of diagnosis and treatment ingredients along with the unit costs per patient for both countries.*
Table 3. Cont.

| Procedure and Ingredients | Stage I | Stage I | Stage II | Stage II | Stage III | Stage III | Stage IV | Stage IV | Palliative Care (Extended) | Palliative Care (Extended) | Unit cost per patient (US$) | Unit cost per patient (US$) |
|---------------------------|---------|---------|----------|----------|-----------|-----------|----------|----------|---------------------------|---------------------------|--------------------------|---------------------------|
| % receiving anesthesia    | 60%     | 70%     | 90%      | 5%       | 5%        | 5%        | 5%       | 5%       | 61,22<sup>b</sup>          | 76,68<sup>c</sup>          |                         |                          |
| % receiving radiotherapy<sup>h</sup> | 70%     | 86%     | 70%      | 100%     | 100%      | 30%       | 30%      | 0%       | 500,52<sup>b</sup>         | 438,20<sup>c</sup>         |                         |                          |
| % receiving endocrine treatment<sup>i</sup> | 61%     | 50%     | 61%      | 40%      | 61%       | 65%       | 61%      | 40%      | 61% 50%       | 0,04/day<sup>a</sup>       | 0,51<sup>d</sup>           |                         |
| % receiving chemotherapy<sup>j</sup> | 0%      | 80%     | 20%      | 100%     | 60%       | 100%      | 60%      | 90%      | 80% 0%       | 1469,97<sup>a</sup>       | 2327,20<sup>c</sup>         |                         |
| % receiving boost radiotherapy<sup>k</sup> | 41%     | 65%     | 41%      | 65%      | 41%       | 65%       | 41%      | 65%      | 41% 65%       | 71,23<sup>b</sup>          | 106,16<sup>c</sup>          |                         |
| % receiving home based visits | 75%     | 75%     | 75%      | 75%      | 75%       | 75%       | 75%      | 75%      | 75% 75%      | 23,69<sup>a</sup>          | 25,40<sup>c</sup>          |                         |
| % receiving morphine<sup>l</sup> | 84%     | 100%    | 84%      | 100%     | 84%       | 100%      | 84%      | 100%     | 84% 100%     | 0,59/day<sup>a</sup>       | 1,12<sup>c</sup>           |                         |
| % receiving laxative<sup>m</sup> | 50%     | 47%     | 50%      | 47%      | 50%       | 47%       | 50%      | 47%      | 50% 47%      | 0,10/day<sup>a</sup>       | 0,03<sup>c</sup>           |                         |
| % receiving Ondansetron<sup>n</sup> | 36%     | 60%     | 36%      | 60%      | 36%       | 60%       | 36%      | 60%      | 36% 60%      | 2,80/day<sup>a</sup>       | 1,72<sup>c</sup>           |                         |
| % receiving Amitriptyline<sup>o</sup> | 41%     | 100%    | 41%      | 100%     | 41%       | 100%      | 41%      | 100%     | 41% 100%     | 0,04<sup>a</sup>           | 0,37<sup>c</sup>           |                         |
| % receiving Zelodronic Acid<sup>p</sup> | 30%     | 30%     | 30%      | 30%      | 30%       | 30%       | 30%      | 30%      | 30% 30%      | 200,00<sup>a</sup>         | 260,18<sup>c</sup>          |                         |
| % receiving Trastuzumab    | 30%     | 11%     | 30%      | 14%      | 30%       | 21%       | 30%      | 19%      | 30% 7%       | 1800<sup>a</sup>           | 1610<sup>c</sup>           |                         |

<sup>a</sup>Based on estimates by Costa Rican CCSS.
<sup>b</sup>Unit costs WHO-CHOICE database in 2000 US$. Corrected for inflation: 2000–2009 (2.81 in CR & 1.66 in MX). 2009 exchange rates were used (560.45 CRC/US$ & 13.06 MXN/US$).
<sup>c</sup>Based on values of IMSS.
<sup>d</sup>Based on communication with Unidad de Análisis Económico of MoH.
<sup>e</sup>Based on Norum et al. [61].
<sup>f</sup>Based on Knaul et al. [11].
<sup>g</sup>Based on estimates by Costa Rican CCSS.
<sup>h</sup>50 Gy given in 25 fractions of 2 Gy.
<sup>i</sup>Daily dose of 20 mg. Tamoxifen for 5 years.
<sup>j</sup>7 cycles of Epirubicin, Fluouracil and cyclophosphamide (FEC regimen).
<sup>k</sup>1 fraction of 10 Gy.
<sup>l</sup>20 ml/54 s days.
<sup>m</sup>35 mg/54 days.
<sup>n</sup>8 mg/day.
<sup>o</sup>751mg/day.
<sup>p</sup>5 mg/day.

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CHOICE [8]. Working from a health care perspective we did not take into account travel and opportunity costs.

Cost-effectiveness analysis. The average cost-effectiveness ratio (ACER) of each intervention is calculated by dividing the average costs of the intervention by average number of DALYs averted. These ACERs provide information on the set of interventions a region should finance to maximize health gains. The incremental cost-effectiveness ratios (ICERs) are calculated in relation to the last intervention purchased in each country, by dividing the incremental costs by the incremental health effects. These ICERs are used to establish an expansion path which shows the order in which the various interventions should be introduced if cost-effectiveness is the only consideration [39]. Only interventions with the lowest cost for additional effects are considered on this expansion path. WHO-CHOICE defines interventions that have a cost-effectiveness ratio of less than one times the gross
Table 4. Costa Rica - Average costs (US$), effects and cost-effectiveness of breast cancer control scenarios per year.

| #   | Description of intervention                                                                 | Patients per year | Annual patient costs | Annual program costs | Annual training costs | Annual total costs | DALYs averted per year | ACER | ICER |
|-----|--------------------------------------------------------------------------------------------|------------------|----------------------|----------------------|-----------------------|-------------------|------------------------|------|------|
| 1   | Current country specific situation (80%)                                                   | 940              | 4,569,310            | 646,358              | 6,660                 | 5,222,329         | 1,102                  | 4,739| 4,739|
| 2   | Stage I to IV treatment (current)+Trastuzumab (80%)                                       | 940              | 11,078,670           | 646,358              | 6,660                 | 12,361,689        | 1,347                  | 9,180| NA   |
| 3   | Stage I treatment+relapse (95%)                                                           | 163              | 2,862,111            | 854,431              | 7,439                 | 3,723,980         | 404                    | 9,218| NA   |
| 4   | Stage II treatment+relapse (95%)                                                          | 464              | 4,303,195            | 854,431              | 7,439                 | 5,165,065         | 573                    | 9,007| NA   |
| 5   | Stage III treatment+relapse (95%)                                                         | 235              | 3,884,520            | 854,431              | 7,439                 | 4,746,390         | 193                    | 24,587| NA   |
| 6   | Stage IV treatment (95%)                                                                  | 261              | 3,107,345            | 854,431              | 7,439                 | 3,969,215         | 162                    | 24,559| NA   |
| 7   | Basic Palliative Care (BPC) (95%)                                                         | 261              | 2,466,328            | 1,583,922            | 27,897                | 4,078,147         | 163                    | 25,078| NA   |
| 8   | Extended Palliative Care (EPC) (95%)                                                      | 261              | 3,160,703            | 2,022,956            | 27,897                | 5,211,556         | 164                    | 31,852| NA   |
| 9   | Stage I to IV treatment combined (current 95%)                                           | 1,116            | 5,659,297            | 1,421,412            | 7,439                 | 7,088,148         | 1,309                  | 5,417| NA   |
| 10  | Biennial mammography screening (50–70)+treatment of stage I to IV (95%)                   | 1,116            | 12,498,059           | 3,792,653            | 22,317                | 16,313,029        | 2,619                  | 6,228| NA   |
| 11  | Biennial mammography screening (50–70)+treatment of stage I to IV+Trastuzumab (95%)      | 1,116            | 20,438,042           | 3,792,653            | 22,317                | 24,253,012        | 2,886                  | 8,402| NA   |
| 12  | Biennial mammography screening (40–70)+treatment of stage I to IV (95%)                   | 1,116            | 17,546,792           | 3,792,522            | 22,317                | 21,361,632        | 3,015                  | 7,085| 13,426|
| 13  | Biennial mammography screening (40–70)+treatment of stage I to IV+Trastuzumab (95%)      | 1,116            | 25,401,093           | 3,792,522            | 22,317                | 29,215,932        | 3,274                  | 8,924| 30,352|
| 14  | Biennial Clinical Breast Examination (CBE) screening+Mass-media Awareness Raising (MAR)+treatment of stage I to IV (95%) | 1,116 | 6,158,209              | 4,519,154            | 11,159                | 10,688,521        | 1,825                  | 5,857| NA   |
| 15  | Biennial Clinical Breast Examination (CBE) screening (40–70)+treatment of stage I to IV (95%) | 1,116 | 9,255,065              | 3,792,653            | 22,317                | 12,851,779        | 2,381                  | 5,397| 5,964|
| 16  | MAR+BPC+treatment of stage I to III (95%)                                                  | 1,116            | 6,262,398            | 4,733,109            | 39,055                | 11,034,563        | 1,826                  | 6,044| NA   |
| 17  | Biennial CBE Screening+BPC+treatment of stage I to III (95%)                              | 1,116            | 9,422,391            | 3,426,610            | 47,982                | 12,896,984        | 2,382                  | 5,415| NA   |
| 18  | Biennial mammography Screening (40–70)+BPC+treatment stage I to III (95%)                 | 1,116            | 17,578,700           | 4,170,935            | 50,214                | 21,799,850        | 3,016                  | 7,229| NA   |
| 19  | Biennial mammography Screening (50–70)+EPC+treatment stage I to III (95%)                 | 1,116            | 12,620,626           | 4,215,537            | 50,214                | 16,886,376        | 2,621                  | 6,444| NA   |

*aAll costs in this table are in 2009 US$ (1CRC = 0.001784 US$).
*bDALYs, disability-adjusted life-years (age weighted, discounted).
*cACER: Average cost-effectiveness ratio compared to the do nothing-scenario (US$ per DALY averted).
*dICER: Incremental cost effectiveness ratio, ratio of additional cost per additional life-year saved when next intervention is added to a mix on the intervention path (additional US$ per additional DALY saved).

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| #   | Description of intervention (coverage level)                                                                 | Patients per year | Annual patient costs$ | Annual program costs | Annual training costs | Annual total costs | DALYs averted per year$ | ACER$ | ICER$ |
|-----|-------------------------------------------------------------------------------------------------------------|-------------------|-----------------------|----------------------|----------------------|--------------------|-------------------------|-------|-------|
| 1   | Current country specific situation (70%)                                                                     | 12,682            | 105,806,655           | 2,015,857            | 18,055               | 107,840,567        | 18,870                  | 5,715 | NA    |
| 2   | Stage I to IV treatment (current) + Trastuzumab (70%)                                                       | 12,682            | 156,929,320           | 2,015,857            | 18,055               | 158,963,231        | 21,645                  | 7,344 | NA    |
| 3   | Stage I treatment+relapse (95%)                                                                             | 2,375             | 65,738,476            | 2,514,872            | 18,958               | 68,272,306         | 7,993                   | 8,541 | NA    |
| 4   | Stage II treatment+relapse (95%)                                                                           | 6,815             | 103,978,996           | 2,514,872            | 18,958               | 106,512,826        | 10,629                  | 10,021 | NA    |
| 5   | Stage III treatment+relapse (95%)                                                                          | 5,834             | 87,447,510            | 2,514,872            | 18,958               | 89,981,341         | 6,015                   | 14,960 | NA    |
| 6   | Stage IV treatment (95%)                                                                                   | 2,166             | 71,452,527            | 2,514,872            | 18,958               | 73,967,358         | 1,503                   | 49,231 | NA    |
| 7   | Basic Palliative Care (BPC) (95%)                                                                          | 2,186             | 53,723,979            | 15,215,345           | 71,094               | 69,010,419         | 1,513                   | 45,609 | NA    |
| 8   | Extended Palliative Care (EPC) (95%)                                                                       | 2,186             | 101,903,885           | 16,563,415           | 71,094               | 118,538,394        | 1,523                   | 77,813 | NA    |
| 9   | Stage I to IV treatment combined (current 95%)                                                              | 17,211            | 144,702,484           | 3,698,580            | 18,958               | 148,420,023        | 25,609                  | 5,796  | NA    |
| 10  | Biennial mammography screening (50–70)+ treatment of stage I to IV (95%)                                    | 17,211            | 277,083,624           | 33,291,106           | 56,875               | 310,431,605        | 44,192                  | 7,025  | 12,718 |
| 11  | Biennial mammography screening (50–70)+ treatment of stage I to IV+Trastuzumab (95%)                       | 17,211            | 324,996,119           | 33,291,106           | 56,875               | 358,494,310        | 47,616                  | 7,526  | 13,994 |
| 12  | Biennial mammography screening (40–70)+ treatment of stage I to IV (95%)                                    | 17,211            | 389,559,667           | 33,287,097           | 56,875               | 422,903,640        | 50,714                  | 8,339  | NA    |
| 13  | Biennial mammography screening (40–70)+ treatment of stage I to IV+Trastuzumab (95%)                       | 17,211            | 434,231,086           | 33,287,097           | 56,875               | 467,575,157        | 53,998                  | 8,659  | 17,115 |
| 14  | Basic awareness outreach program+Mass-media Awareness Raising (MAR)+treatment of stage I to IV (95%)        | 17,211            | 149,330,033           | 15,890,849           | 28,438               | 165,249,320        | 32,908                  | 5,021  | 5,021  |
| 15  | Biennial Clinical Breast Examination (CBE) screening (40–70)+treatment of stage I to IV (95%)                | 17,211            | 227,545,334           | 32,896,957           | 51,188               | 260,493,479        | 39,769                  | 6,550  | NA    |
| 16  | MAR+BPC+treatment of stage I to III (95%)                                                                   | 17,211            | 184,908,999           | 29,692,145           | 99,332               | 214,700,676        | 32,919                  | 6,522  | NA    |
| 17  | Biennial CBE Screening+BPC+treatment of stage I to III (95%)                                               | 17,211            | 247,889,383           | 31,257,913           | 122,282              | 279,267,378        | 39,778                  | 7,021  | NA    |
| 18  | Biennial mammography Screening (40–70)+BPC+treatment stage I to III (95%)                                  | 17,211            | 400,120,033           | 41,081,697           | 127,970              | 441,301,929        | 50,722                  | 8,701  | NA    |
| 19  | Biennial mammography Screening (50–70)+EPC+treatment stage I to III (95%)                                  | 17,211            | 296,212,416           | 41,169,323           | 127,970              | 337,509,708        | 44,210                  | 7,634  | NA    |

*aAll costs in this table are in 2009 US$ (1MXN = 0.0765697 US$).

*bDALYs, disability-adjusted life-years (age weighted, discounted).

*cACER: Average cost-effectiveness ratio compared to the do nothing-scenario (US$ per DALY averted).

*dICER: Incremental cost effectiveness ratio, ratio of additional cost per additional life-year saved when next intervention is added to a mix on the intervention path (additional US$ per additional DALY saved).

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Table 6. Costa Rica - Results of sensitivity analysis on average cost-effectiveness ratio (ACER).

| # | Intervention scenarios | ACER | Alternative stage distribution* | Case fatality ratesb | Disability weights + 10% | Costs outpatient visits +25% | Costs mammography +200% | Costs mastectomy Mexico | Costs lumpectomy Mexico | Capacity utilization equipment 25%c | Sensitivity of CBE and mammography 25%d | Attendance rates screening program 60% |
|---|------------------------|------|---------------------------------|---------------------|--------------------------|----------------------------|--------------------------|-------------------------|------------------------|-------------------------------|-----------------------------------|-------------------------------------|
| 1 | Current country specific situation 80% | 4,739 | 5,519 | 4,447 | 5,132 | 4,882 | 6,218 | 4,931 | 4,901 | 4,739 | | |
| 2 | Stage I to IV treatment combined (current 80%) + Trastuzumab | 9,180 | 9,838 | 8,226 | 9,796 | 9,325 | 10,402 | 9,337 | 9,313 | 9,180 | | |
| 3 | Stage I treatment | 9,218 | 11,569 | 53,348 | 13,846 | 9,690 | 13,096 | 9,308 | 9,340 | 9,218 | | |
| 4 | Stage II treatment | 9,007 | 16,395 | 5,442 | 9,605 | 9,369 | 12,032 | 9,183 | 9,250 | 9,007 | | |
| 5 | Stage III treatment | 24,587 | 7,630 | 19,586 | 26,352 | 25,608 | 33,092 | 25,133 | 24,709 | 24,587 | | |
| 6 | Stage IV treatment | 24,559 | 29,195 | 25,869 | 26,307 | 25,774 | 33,175 | 24,646 | 24,59 | 24,559 | | |
| 7 | Basic Palliative Care (BPC) | 25,078 | 30,875 | 26,412 | 26,248 | 34,179 | 25,133 | 25,078 | 25,078 | | |
| 8 | Extended Palliative Care (EPC) | 31,852 | 38,068 | 33,542 | 33,245 | 40,897 | 31,895 | 31,852 | 31,852 | | |
| 9 | Stage I to IV treatment combined (current 95%) | 5,417 | 6,254 | 5,082 | 5,866 | 5,592 | 6,895 | 5,609 | 5,579 | 5,417 | | |
| 10 | Biennial mammography screening (50–70 years)+ Stage I to IV treatment | 6,228 | 4,464 | 7,060 | 6,565 | 6,538 | 10,589 | 6,336 | 6,330 | 6,228 | 7,535 | 7,723 |
| 11 | Biennial mammography screening (50–70 years)+ Stage I to IV treatment+ Trastuzumab | 8,402 | 6,251 | 9,013 | 8,807 | 8,684 | 12,365 | 8,501 | 8,495 | 8,402 | 9,856 | 10,058 |
| 12 | Biennial mammography screening (40–70 years)+ Stage I to IV treatment | 7,085 | 5,216 | 8,069 | 7,433 | 7,496 | 13,203 | 7,174 | 7,182 | 7,085 | 7,677 | 8,114 |
| 13 | Biennial mammography screening (40–70 years)+ Stage I to IV treatment+ Trastuzumab | 8,924 | 6,769 | 9,674 | 9,322 | 9,303 | 14,562 | 9,006 | 9,014 | 8,924 | 9,566 | 10,031 |
| 14 | Mass media awareness raising (MAR)+treatment of stage I to IV | 5,857 | 3,965 | 5,947 | 6,247 | 6,017 | 7,232 | 6,010 | 5,987 | 5,857 | | |
| 15 | Biennial clinical breast examination (CBE) screening (40–69)+treatment of stage I to IV | 5,397 | 3,794 | 6,095 | 5,710 | 5,916 | 5,977 | 5,520 | 5,503 | 5,397 | 6,881 | 7,028 |
| 16 | MAR+BPC+Stage I to III treatment | 6,044 | 4,092 | 6,137 | 6,446 | 6,206 | 7,418 | 6,195 | 6,174 | 6,044 | | |
| 17 | Biennial CBE screening (40–69)+BPC+treatment of stage I to III | 5,415 | 3,806 | 6,115 | 5,728 | 5,934 | 5,994 | 5,537 | 5,520 | 5,415 | 6,919 | 7,068 |
Table 6. Cont.

| Case fatality rates\% | Alternative stage distribution\% | ACER | Interventions scenarios | CBE (40–70) | CBE (40–70) I/IV | CBE (40–70) II/IV | CBE (40–70) III/IV | CBE (40–70) IV/IV | CBE (40–70) I/IV | CBE (40–70) II/IV | CBE (40–70) III/IV | CBE (40–70) IV/IV |
|----------------------|---------------------------------|------|--------------------------|-------------|-----------------|-----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| 10%                  | [22]                            | 7.23B | Biennial mammography screening (40–69) A, BPC | 6,792 | 7,304 | 6,256 | 10,803 | 6,551 | 6,444 | 7,318 | 7,229 | 7,195 |
| 15%                  | [22]                            | 7.318 | Biennial mammography screening (40–69) B, CBE | 6,444 | 7,056 | 6,008 | 9,530 | 5,833 | 5,724 | 6,629 | 6,319 | 6,284 |
| 20%                  | [22]                            | 7.405 | Biennial mammography screening (40–69) C, CBE | 6,197 | 6,799 | 5,751 | 9,253 | 5,556 | 5,447 | 6,451 | 6,141 | 6,096 |
| 25%                  | [22]                            | 7.492 | Biennial mammography screening (40–69) D, CBE | 5,950 | 6,552 | 5,504 | 8,956 | 5,259 | 5,150 | 6,154 | 5,844 | 5,800 |
| 30%                  | [22]                            | 7.579 | Biennial mammography screening (40–69) E, CBE | 5,703 | 6,305 | 5,257 | 8,559 | 5,062 | 4,953 | 5,957 | 5,647 | 5,603 |
| 35%                  | [22]                            | 7.666 | Biennial mammography screening (40–69) F, CBE | 5,456 | 6,058 | 4,909 | 8,161 | 4,764 | 4,655 | 5,659 | 5,349 | 5,305 |
| 40%                  | [22]                            | 7.753 | Biennial mammography screening (40–69) G, CBE | 5,209 | 5,811 | 4,661 | 7,763 | 4,466 | 4,357 | 5,360 | 5,050 | 5,006 |
| 45%                  | [22]                            | 7.840 | Biennial mammography screening (40–69) H, CBE | 4,962 | 5,563 | 4,364 | 7,365 | 4,170 | 4,061 | 5,065 | 4,755 | 4,711 |
| 50%                  | [22]                            | 7.927 | Biennial mammography screening (40–69) I, CBE | 4,715 | 5,317 | 4,067 | 6,967 | 3,872 | 3,763 | 4,767 | 4,457 | 4,413 |
| 55%                  | [22]                            | 8.014 | Biennial mammography screening (40–69) J, CBE | 4,468 | 5,069 | 3,819 | 6,569 | 3,574 | 3,465 | 4,470 | 4,159 | 4,115 |
| 60%                  | [22]                            | 8.101 | Biennial mammography screening (40–69) K, CBE | 4,221 | 4,821 | 3,571 | 6,171 | 3,277 | 3,168 | 4,172 | 3,852 | 3,808 |
| 65%                  | [22]                            | 8.188 | Biennial mammography screening (40–69) L, CBE | 3,974 | 4,573 | 3,325 | 5,773 | 2,983 | 2,874 | 3,878 | 3,558 | 3,514 |
| 70%                  | [22]                            | 8.275 | Biennial mammography screening (40–69) M, CBE | 3,727 | 4,326 | 3,077 | 5,376 | 2,690 | 2,581 | 3,586 | 3,266 | 3,222 |
| 75%                  | [22]                            | 8.362 | Biennial mammography screening (40–69) N, CBE | 3,480 | 4,076 | 2,829 | 4,979 | 2,397 | 2,288 | 3,392 | 3,072 | 3,028 |
| 80%                  | [22]                            | 8.449 | Biennial mammography screening (40–69) O, CBE | 3,233 | 3,826 | 2,581 | 4,583 | 2,095 | 1,986 | 3,090 | 2,770 | 2,726 |
| 85%                  | [22]                            | 8.536 | Biennial mammography screening (40–69) P, CBE | 2,986 | 3,576 | 2,333 | 4,186 | 1,803 | 1,694 | 2,893 | 2,573 | 2,529 |
| 90%                  | [22]                            | 8.623 | Biennial mammography screening (40–69) Q, CBE | 2,739 | 3,226 | 2,085 | 3,789 | 1,511 | 1,402 | 2,692 | 2,372 | 2,328 |
| 95%                  | [22]                            | 8.710 | Biennial mammography screening (40–69) R, CBE | 2,492 | 2,976 | 1,837 | 3,392 | 1,220 | 1,111 | 2,490 | 2,170 | 2,126 |
| 100%                 | [22]                            | 8.897 | Biennial mammography screening (40–69) S, CBE | 2,245 | 2,326 | 1,589 | 2,995 | 0,928 | 0,820 | 2,293 | 1,973 | 1,929 |

whereas costs of outpatient visits were increased by 25%, we raised the costs of mammography with 200%. In estimating the impact of various screening interventions we decreased the sensitivity of CBE and mammography by 25% and assumed attendance rates of screening of 60%. When available we also used alternative stage distributions for the current situation and different CFs. The unit costs for surgical procedures Costa Rica were much lower than those of Mexico. To test the impact of this we substituted these costs with the Mexican values.

Results

Tables 4 and 5 show the results for respectively Costa Rica and Mexico. Both costs, effects and cost-effectiveness are presented. In Figures 2 and 3 these results are presented graphically and the expansion paths are shown as black lines.

Costa Rica

Table 4 shows the annual number of DALYs averted in treating the individual stages I–IV to vary between 193 (stage III) and 573 (stage II), Jointly these interventions in each stage can averet almost 1,400 DALYs per year. Adding palliative care only averts a small number of DALYs. The costs of treating the individual stages range between approximately US$4 million and US$5 million per year. Adding basic and extensive palliative care programs to stage IV treatment adds approximately US$0.1 million and US$1 million to the yearly costs of stage IV treatment. At the 80% coverage level the current country situation in Costa Rica is highly cost-effective with an ICER below the country’s GDP per capita, i.e. US$4,739/DALY. In expanding Costa Rica’s breast cancer services, our analysis shows that treatment of all stages plus a CBE screening program targeting women between 40 and 70 years of age (I–IV) is the next best option. At a total yearly cost of US$13 million, CBE averts 2,381 DALYs per year. This can be considered a very cost-effective intervention as the ICER of this intervention is below one time Costa Rica’s GDP per DALY.

From figure 2 it follows that although the ACER of implementing mammography screening for women between 50–70 years is still below Costa Rica’s GDP per capita per DALY, the ICER (as compared to CBE screening) is not lower than this threshold (i.e. the slope of the expansion path is steeper than US$6,629/DALY). While still considered a cost-effective intervention, mammography screening in age group 50–69 averts 2,619 DALYs per year at a yearly cost of US$16 million. Increasing the age group for mammography screening to women between 40–70 years shows a similar trend, i.e. avering 3,015 DALYs at an annual cost of US$21 million can be considered cost-effective. Adding Trastuzumab to this intervention, while resulting in the highest number of DALYs averted per year, i.e. 3,274 DALYs at a total yearly cost of US$29 million, is not considered cost-effective as its ICER is above the three times GDP per DALY threshold.
### Table 7. Mexico- Results of sensitivity analysis on average cost-effectiveness ratio (ACER).

| #   | Intervention scenarios                                                                 | ACER | Alternative stage distribution | Alternative stage distribution | Alternative stage distribution | Case fatality rates | Disability weights + 10% | Costs outpatient visits +25% | Costs mammography +200% | Capacity utilization equipment -25% | Sensitivity of CBE and mammography -25% | Attendance rates screening program 60% |
|-----|---------------------------------------------------------------------------------------|------|--------------------------------|--------------------------------|--------------------------------|---------------------|-------------------------|----------------------------|----------------------------|--------------------------------|--------------------------------|----------------------------------|
| 1   | Current country specific situation 70%                                                 | 5,715| 6,081                          | 6,576                          | 5,742                          | 7,696               | 7,764                   | 5,865                      | 6,861                     | 5,713                          |                                              |                                   |
| 2   | Stage I to IV treatment (current 70%) combined (current 70%)+ Trastuzumab              | 7,344| 7,405                          | 7,330                          | 7,513                          | 9,031               | 8,768                   | 7,482                      | 8,400                     | 7,342                          |                                              |                                   |
| 3   | Stage I treatment                                                                     | 8,541| 11,835                         | 11,407                         | 9,745                          | 19,263              | 11,997                  | 8,933                      | 11,407                    | 8,534                          |                                              |                                   |
| 4   | Stage II treatment                                                                    | 10,021| 9,613                          | 9,026                          | 16,334                         | 11,433              | 14,721                  | 10,326                     | 12,416                    | 10,014                         |                                              |                                   |
| 5   | Stage III treatment                                                                    | 14,960| 12,661                         | 15,139                         | 9,786                          | 18,509              | 31,038                  | 15,515                     | 19,071                    | 14,950                         |                                              |                                   |
| 6   | Stage IV treatment                                                                    | 49,231| 55,817                         | 169,157                        | 37,773                          | 46,698              | 52,548                  | 51,336                     | 63,668                    | 49,192                         |                                              |                                   |
| 7   | Basic Palliative Care (BPC)                                                           | 45,609| 53,896                         | 193,026                        | 31,995                          | 43,268              | 48,621                  | 47,661                     | 59,946                    | 45,569                         |                                              |                                   |
| 8   | Extended Palliative Care (EPC)                                                        | 77,813| 85,844                         | 229,906                        | 62,358                          | 73,838              | 82,886                  | 90,805                     | 92,056                    | 77,774                         |                                              |                                   |
| 9   | Stage I to IV treatment (current 95%) combined (current 95%)                           | 5,796| 6,168                          | 6,637                          | 5,820                          | 7,804               | 7,874                   | 5,946                      | 6,942                     | 5,793                          |                                              |                                   |
| 10  | Biennial mammography screening (50–70 years)+ Stage I to IV treatment                 | 7,025| 5,703                          | 8,161                          | 4,043                          | 9,059               | 7,649                   | 7,397                      | 11,541                    | 10,041                         | 10,567                          |                                   |
| 11  | Biennial mammography screening (50–70 years)+ Stage I to IV treatment+ Trastuzumab    | 7,526| 6,261                          | 8,495                          | 4,607                          | 9,462               | 8,108                   | 7,526                      | 7,526                     | 7,526                          | 10,051                          | 10,460                          |                                   |
| 12  | Biennial mammography screening (40–70 years)+ Stage I to IV treatment                 | 8,339| 6,992                          | 9,425                          | 5,169                          | 10,572              | 8,945                   | 8,863                      | 15,109                    | 8,338                          | 9,525                          | 10,509                          |                                   |
| 13  | Biennial mammography screening (40–70 years)+ Stage I to IV treatment+ Trastuzumab    | 8,659| 7,377                          | 9,599                          | 5,602                          | 10,859              | 9,226                   | 9,148                      | 14,974                    | 8,658                          | 9,821                          | 10,688                          |                                   |
| 14  | Mass media awareness raising (MAR)+treatment of stage I to IV                          | 5,021| 3,656                          | 6,503                          | 2,293                          | 6,604               | 5,799                   | 5,172                      | 6,186                     | 5,019                          |                                              |                                   |
| 15  | Biennial clinical breast examination (CBE) screening (40–69)+ treatment of stage I to IV | 6,550| 5,149                          | 7,837                          | 3,510                          | 8,579               | 7,246                   | 7,218                      | 7,097                     | 6,549                          | 11,097                          | 11,711                          |                                   |
| 16  | MAR+BPC+Stage I to III treatment                                                      | 6,522| 4,751                          | 8,452                          | 2,981                          | 8,661               | 7,531                   | 6,671                      | 7,613                     | 6,520                          |                                              |                                   |
| 17  | Biennial CBE screening (40–69)+BPC+ treatment of stage I to III                       | 7,021| 5,519                          | 8,402                          | 3,763                          | 9,195               | 7,766                   | 7,690                      | 7,568                     | 7,019                          | 12,194                          | 12,893                          |                                   |
Table 7. Cont.

| Intervention scenarios | Alternative stage distribution | Alternative stage distribution | Alternative stage distribution | Alternative stage distribution | Alternative stage distribution |
|------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| #                      | 18                             | 19                             | 20                             | 21                             | 22                             |
|                       | Biennial mammography screening (40–69) | Biennial mammography screening (40–69) | Biennial mammography screening (40–69) | Biennial mammography screening (40–69) | Biennial mammography screening (40–69) |
|                       | 8.926                          | 7.896                          | 6.200                          | 3.874                          | 2.896                          |
|                       | 9.886                          | 8.874                          | 6.395                          | 4.395                          | 3.874                          |
|                       | 11.032                         | 10.010                         | 8.333                          | 6.324                          | 5.224                          |
|                       | **ACER of US 5,715** per year at a yearly cost of US 165 million.** | **ACER of US 5,715** per year at a yearly cost of US 165 million.** | **ACER of US 5,715** per year at a yearly cost of US 165 million.** | **ACER of US 5,715** per year at a yearly cost of US 165 million.** | **ACER of US 5,715** per year at a yearly cost of US 165 million.** |

The combinations of various interventions are all close to the expansion path meaning they avert DALYs at a slightly less favorable ICER but could nevertheless be meaningful to implement. For example, expanding the current program’s coverage to reach 95% or implementing a Mass-media Awareness Raising program (MAR), could be interesting options if the available budget is not sufficient to implement a screening strategy.

**Mexico**

Table 5 shows that the annual number of DALYs averted in the individual stages I–IV varies between 1,503 (stage IV) and 10,629 (stage II). Jointly these interventions in each stage avert approximately 26,000 DALYs per year. The addition of palliative care does not gain much health.

With an ACER of US$5,715 the current situation with 70% coverage is very cost-effective. The analysis shows it is better to increase the coverage level of the current intervention to 95% instead of adding Trastuzumab. In our analysis, implementing a program of Mass-media awareness raising (MAR) buys health most efficiently. Our results show that MAR averts 32,908 DALYs per year at a yearly cost of US$165 million, which leads to an ACER of US$5,021 per DALY averted. When a higher budget would be available, implementing mammography screening for women aged 50–70 would be the first next step. This intervention averts 44,192 DALYs per year at an estimated yearly cost of US$310 million. Even more resources would allow to subsequently add Trastuzumab and increase the age group to 40–70. These interventions fill out the expansion path and avert 47,616 and 50,714 DALYs per year at an estimated yearly cost of US$358 and US$471 million respectively. It should be noted that a CBE screening program, with an expected health gain of 39,769 DALYs averted at a cost of US$260 million, could be an interesting ‘in-between’ option.

**Sensitivity analysis**

Sensitivity analysis showed our results to be particularly sensitive to different assumptions on stage distribution at presentation and case fatality rates (tables 6 and 7). The Costa Rican CFs we obtained from Ortiz [24] differed strongly from those we deem to reflect technical efficiency [7,22]. Using these CFs causes the ACERs to vary between minus 82.7% for stage I and plus 65.5% for stage II. With regards to the current stage distribution, for Costa Rica we used the distribution from Groot et al. [7]. With this less favorable stage distribution, the current country situation was not part of the expansion path anymore. Rather, the CBE screening program now became the most cost-effective.

For Mexico we ran the model with three different current stage distributions obtained from different studies [7,41,42]. These different stage distributions caused the ACERs to increase between 0–15%. When using the higher CFs from Salomon et al. [35] for the intervention scenarios, the ACERs increased to a larger extent (34.7% for the current country situation).

For both countries, changes in the other parameters also led to different outcomes although their impact was smaller. For example, in Costa Rica the WHO default unit costs for a mastectomy or a lumpectomy were relatively low. Unable to obtain these unit costs from Costa Rica, using the higher Mexican unit costs showed their impact on the ACERs to be marginal.

**Discussion**

Our results indicate that in both Costa Rica and Mexico treating stage IV disease only, or treating stage IV and providing basic or extended palliative care is not cost-effective. In general,
interventions ensuring more patients to present at the hospital in earlier stages seem the most cost-effective. These results are in line with other studies which find mammography screening for women aged 50–70 to be cost-effective in sub-Saharan Africa and South East Asia [7,43]. Although Ginsberg et al. did not study the cost-effectiveness of clinical breast examination or other awareness raising programs, they acknowledge less expensive means of early detection in limited resource settings could be cost-effective in LMICs [43]. When modeling the expected outcomes of such strategies - though based on limited evidence - Zelle et al. find that CBE screening or mass media awareness raising interventions seem indeed cost-effective in Ghana [22].

Although mammography interventions can be considered cost-effective, their total annual costs (budget impact) are high and may therefore not be appropriate for wide scale implementation. If the necessary resources are not available both countries could choose to lower coverage levels or implement interventions with comparable ACERs (buying health just as efficiently) but with lower budget impact. For Costa Rica, our analysis shows the most cost-effective option for expanding the current breast cancer services would be a CBE screening program combined with treatment of all stages. The yearly costs of this program are about US$12 million. In 2009, the per capita health expenditure in Costa Rica was US$660 (10.3% of total GDP) [37]. With a population of approximately 4.5 million, implementing a CBE screening program would add US$2.82 to this amount (0.43% increase). Although this increase may seem feasible, the implementation and effectiveness of this program is highly dependent on the availability of human resources and the capacity of the healthcare system to refer and treat all new-found cases [44–46]. Also, if the implementation of a CBE screening program would be unfeasible, MAR could be an interesting option as it is slightly less cost-effective but has a smaller yearly budget impact (US$10 million). Yet, the very limited evidence on MAR’s effectiveness requires our estimates to be interpreted with caution. Implementing a screening program for which the evidence base is stronger (e.g. mammography for women between 50–70 years of age) could be recommended if the yearly costs of US$16 million are affordable. Mammography screening in age group 40–70 costs much more (about US$21 million) and is therefore less economically attractive.

The Mexican MoH already decided to start increasing the use of the available infrastructure and mammography equipment for the population most at risk (women 50 to 70 years old and women with more than two risk factors). The gradual expansion will give enough time to train the required human resources. From our analysis the yearly costs of a mammography screening program for women 50–70 years of age at 95% coverage eventually would be US$310 million per year, a threefold increase over the current scenario. Next, once a reasonable increase on coverage would be reached the Mexican MoH plans to increase the coverage rate to women between 40–49 years of age [47]. According to our estimates the yearly costs of implementing such a program would be US$12.2 million. With approximately 110 million inhabitants and a per capita health expenditure of US$825 in 2009 (6.43% of total GDP) [37], implementing these programs would add US$2.82 (0.54% increase) and US$3.84 (0.72% increase) respectively to per capita health expenditure.

However, our analysis shows perhaps that strengthening actual MAR or CBE screening programs to be a more attractive first step in improving breast cancer services from an economic perspective. With yearly costs of US$165 and US$260 million if started from zero, the strengthening of existing programs is more affordable and more politically feasible as it would represent modest increases to existing budgets.

One of the principal questions we received from policy makers in both Costa Rica and Mexico concerned the addition of Trastuzumab to the treatment regimens. In Costa Rica we assumed 30% of the breast cancer patients have overexpression of the HER2/neu gene and are eligible for Trastuzumab [48]. As a result of adding Trastuzumab, in Costa Rica between 230–270 extra DALYs/year are averted at an additional cost of approximately US$7 million per year. For Mexico we obtained the actual proportion of patients receiving Trastuzumab in IMSS. Here the health gains comprise between 2,000 and 3,400 extra DALYs/year averted and the additional costs fall between US$45–51 million. It is worth noting that in Mexico Trastuzumab is already provided as part of the treatment for all eligible women in stages I to IV. Our analysis shows the addition of this bio-pharmaceutical to increase the cost of treatment of stages I to IV by more than 48%, generating the need of developing public policies focused on negotiating price reductions that can contribute to the mid- and long-term financial sustainability. The use of tools as the ones presented in this paper can provide technical evidence on the benchmark price that the Mexican health system could use in negotiations considering the threshold of one times the GDP per capita.

The limitations regarding the model are essentially the same as those reported in previous studies [7,22]. First, as evidence on the effectiveness of awareness raising, CBE and mammography screening in Costa Rica and Mexico were absent, we relied on the same model approach as used by Zelle et al. [22]. Second, when calculating unit costs for Mexico we did not account for the mark up of transportation costs (as generally recommended by WHO-CHOICE) and did not include the costs of facilities. Including these costs would have probably resulted in slightly higher unit costs. Third, in adopting a health care perspective we did not take into account travel and opportunity costs. Including these costs would probably have increased costs generally. Fourth, we did not carry out a probabilistic sensitivity analysis. Carrying out such analysis would have shown worse ACERs when parameters are jointly changed in the negative direction (i.e. higher CFs and costs/worse stage distribution). Nonetheless, our deterministic sensitivity analysis shows the direction in which ACERs would change is clear and our general conclusions remain the same although the ranges of several ACERs are overlapping. The limitations fit within the overall goal of WHO-CHOICE which is to provide general indications of cost-effectiveness, i.e. not precise estimates of specific interventions.

In summary, for improving their current breast cancer control programs, our analysis suggests that both Costa Rica and Mexico would benefit from implementing strategies that advance early detection. For these countries, a mass-media awareness raising program and/or a CBE screening program coupled with treatment of all stages and careful monitoring and evaluation could be feasible options. If these strategies are implemented, the provision of breast cancer diagnostic, referral, treatment and, when possible, basic palliative care services is essential and should be facilitated simultaneously.

**Author Contributions**

Conceived and designed the experiments: LMN SGZ. Performed the experiments: LMN SGZ. Analyzed the data: LMN SGZ. Contributed reagents/materials/analysis tools: CGD GRP BRJB ERS. Wrote the paper: LMN SGZ FFHR.
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