

Annex **3A**

**Summary of Salient Features and
Recommendations of Cost-Effectiveness
Studies Relevant to Breast Cancer Screening,
Treatment, and Control in Low- and
Middle-Income Countries**



Table 3A.1 Selected Cost-Effectiveness Studies on Breast Cancer Screening Methods

Study	Country and GDP per capita (US\$) for year of study ^a	Screening methods evaluated	BHGI resource levels ^b in study	Decision modeling framework and perspective, including handling of uncertainty	Effectiveness: how measured and evaluated over time	Cost: what is included and how evaluated over time	ICERs in base case	Are interventions cost effective? ^c
Nguyen and others (2013)	Vietnam, US\$1,070 (2008 \$)	Annual CBE in asymptomatic women, compared with no screening	<ul style="list-style-type: none"> Basic Limited 	<ul style="list-style-type: none"> Markov decision model, assuming annual screening starting at age 40 and with 15 years of consecutive participation, compared with no screening If cancer detected, follow for five years and if survive, assume normal life expectancy <i>Perspective</i> is health care payer (patients, government, third parties) <i>Uncertainty</i> addressed via one-way and probabilistic sensitivity analyses with Monte Carlo methods 	<ul style="list-style-type: none"> Life-years gained per patient from CBE versus no screening <i>Discounted</i> at 3% across remaining lifetime horizon Parameter estimates derived from Vietnam epidemiological data 	<ul style="list-style-type: none"> Direct medical costs associated with screening, follow-up of positive tests, and resulting cancer treatment <i>Discounted</i> at 3% across remaining expected lifetime Data derived from local public sector sources and previous studies of breast cancer treatment costs in Vietnam 	US\$995/LY	<ul style="list-style-type: none"> Very Annual CBE remains very cost effective compared with no screening across most sensitivity analyses and it never fails to be cost effective (with ICER between one and three times GDP per capita) ICER most sensitive to screening participation rate and test specificity
Lee, Jeong, and others (2009)	Korea, Rep. US\$20,870 (2007 \$)	MMG, with focus on identifying optimal age range (starting and stopping age) and screening interval for detecting breast cancer in the preclinical state	<ul style="list-style-type: none"> Limited Enhanced Maximal 	<ul style="list-style-type: none"> Stochastic natural history model of breast cancer progression, focusing on transition from disease-free state to preclinical state, to clinical state, with likelihood of detection in each state a function of screening age range and interval 	<ul style="list-style-type: none"> Breast cancer cases detected in preclinical state per 100,000 screened, as a function of screening age range and interval <i>Discounted</i> at 3% in base case 	<ul style="list-style-type: none"> Direct medical costs associated with MMG screening and follow-up of true-positive and false-positive results, although does not include cost from adverse effects of screening nor cost of treating breast cancer detected via screening 	US\$100,007 per preclinical case detected (in base case scenario where screening is every three years for ages 45–65)	<ul style="list-style-type: none"> Cannot be determined, based on WHO guidelines, which assume that the effectiveness measure in the ICER is a variant of the quality-adjusted life year^c

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Table 3A.1 Selected Cost-Effectiveness Studies on Breast Cancer Screening Methods (continued)

Study	Country and GDP per capita (US\$) for year of study ^a	BHGI resource levels ^b in study	Decision modeling framework and perspective, including handling of uncertainty	Effectiveness: how measured and evaluated over time	Cost: what is included and how evaluated over time	ICERs in base case	Are interventions cost effective? ^c
Wong and others (2007)	Hong Kong SAR, China US\$26,650 (2005 \$)	<ul style="list-style-type: none"> Limited Enhanced Maximal 	<ul style="list-style-type: none"> Perspective is national healthcare system Uncertainty addressed via one-way sensitivity analyses involving mean sojourn time in states, test sensitivity and specificity, other parameters 	<ul style="list-style-type: none"> Data derived from Korea Central Cancer Registry and female population projections from census files 	<ul style="list-style-type: none"> Resulting annual screening costs <i>discounted</i> at 3% across cohort age range (for example, ages 45–65) Cost data locally derived 	<ul style="list-style-type: none"> US\$64,400/LY and US\$61,600/QALY for biennial MMG screening for ages 40–69, compared with no screening Other age ranges and modeling assumptions yielded higher ICERs or represented dominated options 	<ul style="list-style-type: none"> No established criteria for appraising value-for-money when ICER is cost per case detected, although the cost efficiency of alternative screening strategies can be compared, as done here Yes, although MMG is cost effective by World Bank guideposts (with an ICER less than three times GDP per capita), the authors do not embrace that criterion but instead compare ICERs to the frequently cited U.S. threshold value of US\$50,000 per QALY By that criterion, MMG is not cost effective for most model variants

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Table 3A.1 Selected Cost-Effectiveness Studies on Breast Cancer Screening Methods (continued)

Study	Country and GDP per capita (US\$) for year of study ^a	Screening methods evaluated	BHGI resource levels ^b in study	Decision modeling framework and perspective, including handling of uncertainty	Effectiveness: how measured and evaluated over time	Cost: what is included and how evaluated over time	ICERs in base case	Are interventions cost effective? ^c
Okonkwo and others (2008)	India Int\$2,820 (based on authors' report)	Alternative MMG and CBE screening strategies for asymptomatic women, with each strategy compared with no screening	<ul style="list-style-type: none"> Limited Enhanced Maximal 	<ul style="list-style-type: none"> MISCAN micro-simulation model for natural history of breast cancer and impact of interventions, originally developed for Netherlands and adapted for application in India Perspective is societal Uncertainty is addressed through multiple one-way and multi-way sensitivity analyses, including assumptions about life expectancy, cancer incidence, and time path of clinical stage distribution 	<ul style="list-style-type: none"> Life-years gained per woman under each alternative CBE or MMG screening strategy, compared with no screening Discounted at 3% in base case for CBE and MMG strategies varied by screening age range and interval Data for MISCAN outcome modeling derived from Canadian, Dutch, Swedish, and U.S. sources 	<ul style="list-style-type: none"> Direct medical costs included screening tests and follow-up, cancer diagnosis, primary therapy, adjuvant therapy, palliative care for lethal cancer Discounted at 3% across remaining lifetime Data on resource utilization patterns from Netherlands and unit costs from India 	1. Single CBE age 50 versus no screening: Int \$793/LY 2. CBE every five years ages 40–60 versus no screening: Int \$1,251/LY (versus option 1) 3. Biennial CBE ages 40–60 versus no screening: Int \$1,549/LY (versus option 2) 4. Annual CBE ages 40–60 versus no screening: Int \$3,108/LY (versus option 3) 5. Biennial MMG ages 40–60 versus no screening: Int \$19,257/LY (versus option 4)	1. Very 2. Very

Note: BHGI = Breast Health Global Initiative; CBE = clinical breast examination; DCIS = ductal carcinoma in situ; GDP = gross domestic product; ICER = incremental cost-effectiveness ratio; LY = life-year or when used in the denominator of a ratio X/LY = per life-year gained; MISCAN = Microsimulation Screening Analysis; MMG = mammography; NCI = National Cancer Institute; DALY = quality-adjusted life-year or when used in the denominator of a ratio X/DALY = per quality-adjusted life-year gained; SEER = Surveillance, Epidemiology, and End Results program; WHO = World Health Organization.

a. Conversion to U.S. dollars derived from World Bank World Development Indicators (<http://data.worldbank.org/indicator/NY.GDP.PCAP.CD>).

b. BHGI resource levels are denoted Basic, Limited, Enhanced, and Maximal; see tables 3.1, 3.3, 3.4, and 3.5 in chapter 3 Breast Cancer for detailed specifications pertaining, in turn, to breast cancer early detection; diagnosis; and treatment at stages I, II, III (locally advanced disease), and IV (metastatic).

c. In line with WHO recommendations, health interventions costing less than GDP per capita are designated "very cost effective," those costing between one and three times GDP per capita are "cost effective," and those costing more than three times GDP per capita are "not cost effective" (WHO 2001).

d. GDP per capita denominated in international dollars (reflecting purchasing power parity), <http://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD?page=2>.

Table 3A.2 Selected Cost-Effectiveness Studies on Breast Cancer Treatments

Study	Country and GDP per capita (US\$) for year of study ^a	Treatments evaluated	BHGI resource levels ^b addressed in study	Decision modeling framework and perspective, including handling of uncertainty	Effectiveness: how measured and evaluated over time	Cost: what is included and how evaluated over time	ICERs in base case	Are the interventions cost effective? ^c
Fonseca and others (2009)	Brazil, US\$3,960 (2005 \$)	Anastrozole versus tamoxifen for women following surgery for local breast cancer	<ul style="list-style-type: none"> Enhanced and Maximal for each stage of breast cancer Implications for use of tamoxifen-only apply to all resource levels 	<ul style="list-style-type: none"> Markov model of treatment-specific disease progression and outcome <i>Perspective</i> is private health care sector <i>Uncertainty</i> addressed via one-way sensitivity analyses and Monte Carlo simulations 	<ul style="list-style-type: none"> Life-years gained per patient from anastrozole vs. tamoxifen <i>Discounted</i> at 3% across remaining lifetime horizon Data sources include RCT and modified Delphi panel 	<ul style="list-style-type: none"> Direct medical costs associated with each breast cancer state in Markov model, derived via micro-costing techniques <i>Discounted</i> at 3% across lifetime horizon 	US\$11,108/LY	Yes, with ICER = 2.8 GDP per capita; in the Monte Carlo simulations, about 50% of ICERs were below base case ratio
Yang and others (2010)	Korea, Rep. US\$17,531, as computed by authors (2006 \$)	Tamoxifen versus not, for women following surgery for stages I, II, and III breast cancer	<ul style="list-style-type: none"> Basic Limited Enhanced Maximal 	<ul style="list-style-type: none"> Decision tree model of treatment-specific disease progression and outcome <i>Perspective</i> is societal <i>Uncertainty</i> addressed via one-way sensitivity analyses 	<ul style="list-style-type: none"> Life-years gained per patient from tamoxifen versus no tamoxifen <i>Discounting</i> as sensitivity analysis but not evidently in base case result Data derived largely from Korean Breast Cancer Society registry 	<ul style="list-style-type: none"> Direct medical costs associated with breast cancer events, based on insurance charge data; indirect costs reflecting lost productivity based on modeling <i>Discounting</i> as sensitivity analysis, but not in base case; costs are for remaining expected lifetime 	<ol style="list-style-type: none"> ER+ and PR+, stages I and II: US\$739–\$1,939/LY ER+ or PR+, stage I or II: US\$1,712–\$3,107/LY ER– and PR–, stage I or II: No tamoxifen option dominates^d Stage III, any ER-PR status, under age 50: US\$38–\$2,162; for ER– and PR– and ages 50+: US\$19,584/LY 	<ol style="list-style-type: none"> Very Very No Very, in all cases except when patient is ER–, PR–, and ages 50+ In sensitivity analyses involving combinations of ER-PR status, age, and discount rates, tamoxifen was very cost effective throughout, except for ER–, PR–, ages 50+

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Table 3A.2 Selected Cost-Effectiveness Studies on Breast Cancer Treatments (continued)

Study	Country and GDP per capita (US\$) for year of study ^a	Treatments evaluated	BHGI resource levels ^b addressed in study	Decision modeling framework and perspective, including handling of uncertainty	Effectiveness: how measured and evaluated over time	Cost: what is included and how evaluated over time	ICERs in base case	Are the interventions cost effective? ^c
Lee, Jee, and others (2009)	Korea, Rep. US\$18,920 (2006 \$)	Chemotherapy options TAC vs. FAC after surgery for node-positive breast cancer	<ul style="list-style-type: none"> Basic Limited Enhanced Maximal 	<ul style="list-style-type: none"> Markov decision model for treatment-specific disease progression and outcome <i>Perspective</i> is combined view of Korean National Health Insurance Corp. and patients <i>Uncertainty</i> addressed via extreme-range tests for parameters and probabilistic sensitivity analysis 	<ul style="list-style-type: none"> Life-years gained and QALYs gained per patient with TAC vs. FAC, <i>discounted</i> at 5% in base case Data based on RCT, cancer registry, and the literature QALY weights from other studies 	<ul style="list-style-type: none"> Direct medical costs associated with TAC and FAC, derived by applying Korean hospital charges to care patterns associated with TAC and FAC <i>Discounted</i> at 5% in base case; costs are for expected remaining lifetime 	US\$8,492/LY and US\$9,359/QALY	<p>Very</p> <p>In multiple sensitivity analyses, TAC was either very cost effective or cost effective compared with FAC</p>
Liubao and others (2009)	China US\$1,806 (based on authors' use of Chinese government data) US\$3,040 (based on World Bank estimates ^a) (2008 \$)	Chemotherapy options TC vs. AC in operable breast cancer patients, reflecting a mixture of node-positive and hormone receptor-negative cases	<ul style="list-style-type: none"> Basic Limited Enhanced Maximal 	<ul style="list-style-type: none"> Markov decision model for treatment-specific disease progression and outcomes; <i>Perspective</i> is Chinese health care system <i>Uncertainty</i> is addressed via one-way sensitivity analyses, probabilistic sensitivity analysis, and cost-effectiveness acceptability curve analysis 	<ul style="list-style-type: none"> Life-years gained and QALYs gained per patient with TC vs. AC <i>Discounted</i> at 3% in base case Data based on RCT and other published sources QALY weights from other studies 	<ul style="list-style-type: none"> Direct medical costs associated with AC and TC, derived from resource utilization rates based on RCT and other published sources, with unit costs from a single large Chinese hospital <i>Discounted</i> at 3% in base case Costs are for remaining expected lifetime 	US\$3,915/LY and US\$3,559/QALY	<p>Yes</p> <p>Yes</p> <p>In multiple sensitivity analyses, TC is cost effective compared with AC and, in some cases, very cost effective</p>

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Table 3A.2 Selected Cost-Effectiveness Studies on Breast Cancer Treatments (continued)

Study	Country and GDP per capita (US\$) for year of study ^a	Treatments evaluated	BHGI resource levels ^b addressed in study	Decision modeling framework and perspective, including handling of uncertainty	Effectiveness: how measured and evaluated over time	Cost: what is included and how evaluated over time	ICERs in base case	Are the interventions cost effective? ^c
Bai and others (2012)	China US\$5,569 (authors' estimate) US\$5,447 (based on World Bank estimates ^a) (2011 \$)	RT versus no RT, following BCS for early stage breast cancer	<ul style="list-style-type: none"> Limited (if RT can be made available) Enhanced, Maximal for stages I, II, and III 	<ul style="list-style-type: none"> Markov decision model for treatment-specific disease recurrence (local and distant) and survival outcomes <i>Perspective</i> is Chinese society <i>Uncertainty</i> is addressed via one-way sensitivity analyses and probabilistic sensitivity analyses using Monte Carlo techniques 	<ul style="list-style-type: none"> Life-years gained and QALYs gained per patient with RT vs. no RT <i>Discounted</i> at 3% in base case Data derived from published RCTs and meta-analyses QALY weights from other studies 	<ul style="list-style-type: none"> Direct medical costs and selected nonmedical costs (patient time and transportation costs associated with RT care), with resource use derived from local expert panel and published reports <i>Discounted</i> at 3% in base case Costs are for remaining expected lifetime 	<ul style="list-style-type: none"> RT compared with no RT yields a discounted life-years gain of 2.69 years and QALY gain of 1.50, with a net <i>negative</i> incremental cost of US\$628 per patient; hence, RT is the "dominant" choice: it both improves outcomes and reduces cost^e 	<ul style="list-style-type: none"> Very The one-way sensitivity analyses and probabilistic sensitivity analyses generally support the conclusion that RT dominates the no-RT option
Love and others (2002)	Vietnam US\$410 (2001 \$)	O/T in combination vs. "observation" in premenopausal women with operable breast cancer	<ul style="list-style-type: none"> Basic for each stage of breast cancer Limited for each stage of breast cancer 	<ul style="list-style-type: none"> Adapted a previous natural history model of early stage breast cancer^d to carry out what the authors term "preliminary" CEA based on RCT results <i>Perspective</i> of analysis not indicated <i>Uncertainty</i> in the model parameters or structure not addressed 	<ul style="list-style-type: none"> Life-years gained per patient over a 15-year time horizon with O/T vs. observation <i>Discounted</i> at 3% Intervention-specific survival based on clinical trial conducted in Chinese and Vietnamese patients 	<ul style="list-style-type: none"> Direct medical costs associated with O/T, but excluding other cancer-related costs, including for disease recurrence and other downstream events Unit costs from local data <i>Discounted</i> at 3% over 15-year horizon 	US\$351/LY	<ul style="list-style-type: none"> Very Authors note that excluding cost of recurrence from model leans against O/T, since that intervention reduces likelihood of recurrence compared with observation

Note: AC = doxorubicin and cyclophosphamide in combination; BCS = breast-conserving surgery; BHGI = Breast Health Global Initiative; CEA = cost-effectiveness analysis; ER+ = estrogen receptor-positive; ER- = estrogen receptor-negative; FAC = fluorouracil, doxorubicin, and cyclophosphamide in combination; GDP = gross domestic product; ICER = incremental cost-effectiveness ratio; LY = life-year or when used in the denominator of a ratio X/LY = per life-year gained; O/T = oophorectomy and tamoxifen; PR+ = progesterone receptor-positive; PR- = progesterone receptor-negative; QALY = quality-adjusted life-year or when used in the denominator of a ratio X/QALY = per quality-adjusted life-year gained; RCT = randomized controlled trials; RT = radiotherapy; TAC = docetaxel, doxorubicin, and cyclophosphamide in combination; TC = docetaxel and cyclophosphamide in combination.

a. Conversion to US\$ derived from World Bank World Development Indicators (<http://data.worldbank.org/indicator/NY.GDPPCAPCD>).
b. BHGI resource levels are denoted Basic, Limited, Enhanced, and Maximal; see tables 3.1, 3.3, 3.4, and 3.5 in chapter 3 Breast Cancer for detailed specifications pertaining, in turn, to breast cancer early detection, diagnosis, and treatment at stages I, II, III (locally advanced disease), and IV (metastatic).
c. In line with recommendations by the World Health Organization, health interventions costing less than one times GDP per capita are designated "very cost effective," those costing between one and three times GDP per capita are "cost effective," and those costing more than three times GDP per capita are "not cost effective" (WHO 2001).
d. In the ER-, PR- case, tamoxifen both increases costs and reduces expected life-years, compared with the no-tamoxifen option.
e. The authors elect to summarize these findings in the form of negative ICERs: US\$ -233/LY and US\$ -421/QALY. Although these calculations are consistent with the data here, the calculations are not conventional summary statistics in cost-effectiveness analyses that generate dominant solutions. To see why, note that the larger is the cost saving, the smaller in algebraic value (the more negative) is the ICER, while the larger is the QALY gain, the larger in algebraic value is the ICER (for that serves to produce a smaller negative ratio). Thus, incrementally favorable changes in cost (more cost savings) and in QALYs (better outcomes) move the ICER in opposite directions, potentially leading to ambiguity in the ranking of interventions that share this feature of having a dominant option.
f. See Hillner and Smith (1991).

Table 3A.3 Selected Cost-Effectiveness Studies on Breast Cancer Control Strategies

Study	Country and GDP per capita (US\$) for year of study ^a	Cancer control strategies evaluated	BHGI resource levels ^b addressed in study	Decision modeling framework and perspective, including handling of uncertainty	Effectiveness: how measured and evaluated over time	Cost: what is included and how evaluated over time	Cost-effectiveness ratios in base case	Are the interventions cost effective? ^c
Groot and others (2006)	Africa, Asia ^d US\$765 (a threshold for "low-income" countries) (2001 \$)	Six alternative interventions (regarded here as mutually exclusive): 1. Stage I disease: BCS with radiation; some get endocrine therapy 2. Stage II: same as for stage I 3. Stage III: neoadjuvant chemo; mastectomy; adjuvant chemo; radiation and endocrine therapy, as needed 4. Stage IV: Systemic chemo; some endocrine therapy 5. Treat all stages per 1–4 6. Treat all stages, plus breast awareness program and biennial mammogram screening for women ages 50–70 ("extensive program")	1. Limited, Enhanced 2. Limited, Enhanced 3. Basic, Limited, Enhanced 4. Limited, Enhanced 5. and 6. Basic, Limited, Enhanced	<ul style="list-style-type: none"> Simulation model for individual transitions between and sojourn times in the following states: good health, four invasive breast cancer disease stages, and death—conditional on choice of intervention (1–6) Perspective is societal Uncertainty addressed via one-way and multi-way deterministic sensitivity analyses on key model parameters 	<ul style="list-style-type: none"> DALYs averted per person Discounted at 3% in base case Regional age-adjusted estimates of breast cancer incidence, prevalence, percent cases treated, and background mortality derived from WHO Burden of Disease studies Stage distribution of prevalent and incident cases; case fatality rates conditional on treatment, derived from regional registry data from Southeast Asia and U.S. National Cancer Database DALY estimates based on WHO-CHOICE burden of disease studies 	<p>Direct medical costs of two types:</p> <ul style="list-style-type: none"> Patient level, reflecting resource use patterns for treatment and screening consistent with guidelines and unit input costs from WHO-CHOICE database on prices for traded and nontraded goods; all integrated via a micro-costing ("ingredients approach") methodology Program level, reflecting resources needed to start up and sustain interventions over time, with estimates based on primary data from countries and the literature All costs <i>discounted</i> at 3% over modeled individual's lifetime in the base case 	<p>Africa (ACERs)</p> <ol style="list-style-type: none"> US\$78/DALY US\$324/DALY US\$389/DALY US\$4,986/DALY US\$159/DALY US\$75/DALY <p>Asia (ACERs)</p> <ol style="list-style-type: none"> US\$62/DALY US\$236/DALY US\$262/DALY US\$3,510/DALY US\$110/DALY US\$75/DALY <p>ICER analysis indicates option 6 as optimal choice, with its ICER relative to option 5 (next most efficient) being US\$48/DALY^{e, f}</p> <p>ICER analysis indicates option 6 as optimal choice, with its ICER relative to option 5 (next most efficient) being US\$63/DALY^{e, f}</p> <p>All cost-effectiveness ratios assume 80% coverage of eligible population</p>	Very (option 6)

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Table 3A.3 Selected Cost-Effectiveness Studies on Breast Cancer Control Strategies (continued)

Study	Country and GDP per capita (US\$) for year of study ^a	Cancer control strategies evaluated	BHGI resource levels ^b addressed in study	Decision modeling framework and perspective, including handling of uncertainty	Effectiveness: how measured and evaluated over time	Cost: what is included and how evaluated over time	Cost-effectiveness ratios in base case	Are the interventions cost effective? ^c
Ginsberg and others (2012)	Sub-Saharan Africa and Southeast Asia Int\$2,000 (authors' selection of representative GDP per capita for subregions in study) ^e (2005 Int\$)	For breast cancer, the same six interventions considered in Groot and others (2006) ^h	Same mapping of interventions to resource levels as for Groot and others (2006)	<ul style="list-style-type: none"> Based on the WHO-Choice framework, an epidemiological-oriented, population-based Markov state transition model was used to estimate the number of years of healthy life experienced over a lifetime for a defined population at risk to cancer, conditional on intervention in comparison with baseline (no intervention) <i>Perspective</i> is societal <i>Uncertainty</i> is addressed via graphical analyses, probabilistic sensitivity analysis, and one-way sensitivity analyses on selected parameters (for example, discount rate, fraction of eligible population covered by intervention) 	<ul style="list-style-type: none"> DALYs averted per person, <i>discounted</i> at 3% and weighted for age in base case Underlying demographics, cancer incidence, and prevalence rates and remission and case-fatality rates drawn from WHO Global Burden of Disease database Parameter estimates on intervention effectiveness derived from systematic reviews, single studies, and expert judgment; disability weights for DALYs from WHO-CHOICE burden of disease studies 	<ul style="list-style-type: none"> Direct medical costs for the six intervention strategies were identified and estimated similarly to Groot and others, at patient level and program level All costs <i>discounted</i> at 3% over modeled individual's lifetime in the base case 	<p>Sub-Saharan Africa: Lowest ICERs among almost equally efficient options.^{i, f} Option 6 "extensive program" with 50% population coverage: Int\$2,248/DALY Option 6 with 80% population coverage: Int\$2,261/DALY Option 6 with 95% population coverage: Int\$2,696/DALY</p> <p>Southeast Asia: Lowest ICERs among almost equally efficient options.^{i, f} Option 6 with 50% population coverage: Int\$4,338/DALY Option 6 with 80% population coverage: Int\$4,401/DALY Option 6 with 95% population coverage: Int\$4,596/DALY</p>	Yes Yes Yes Yes

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Table 3A.3 Selected Cost-Effectiveness Studies on Breast Cancer Control Strategies (continued)

Study	Country and GDP per capita (US\$) for year of study ^a	BHGI resource levels ^b addressed in study	Cancer control strategies evaluated	Decision modeling framework and perspective, including handling of uncertainty	Effectiveness: how measured and evaluated over time	Cost: what is included and how evaluated over time	Cost-effectiveness ratios in base case	Are the interventions cost effective? ^c
Zelle and others (2012)	Ghana US\$649 (2011 \$)	<ul style="list-style-type: none"> Basic Limited Enhanced 	17 mutually exclusive interventions that extend the original six in Groot and others: * Status quo (10% coverage) * Treatment for Stages I, II, III, or IV; or all four stages together * BPC * EPC * BAR + treatment for all four stages * MAR + treatment for all four stages * Biennial CBE screening ages 40–69 + treatment for all four stages * Biennial mammography screening (ages 50–69) + treatment for all four stages * Biennial mammography screening (ages 40–69) + treatment for all four stages * MAR + BPC + treatment for stages I, II, and III	<ul style="list-style-type: none"> Based on WHO-CHOICE framework,^j with a simulation model building directly on Groot and others and consistent with approach taken in Ginsberg and others Groot and others model updated in several specific ways, including treatment of health state valuations for cancer relapse and stage-specific case fatality rates; as in Ginsberg and others, interventions are implemented for 10-year period, while individuals in model are followed across lifetime (and up to 100 years post intervention) Except for status quo option, all interventions assumed to operate at 80% population coverage 	<ul style="list-style-type: none"> DALYs averted per person, <i>discounted</i> at 3% in base case Data on demographics and the stage distribution of breast cancer from Ghana; information on intervention impacts on stage distribution and case fatality rates derived largely from published sources Palliative care impacts supplied by an expert panel Health state valuations for DALYs based on Global Burden of Disease study estimates 	<ul style="list-style-type: none"> Direct medical costs for the 17 interventions were computed following WHO-CHOICE modeling guideposts, including separate analyses for patient-level and program-level costs All costs <i>discounted</i> at 3% Data on resource use and unit prices derived from Ghana sources wherever possible, otherwise from WHO-CHOICE database or the literature 	Among the 17 alternatives, those remaining in the efficient choice set, after removing dominated options, ^f are as follows: a. Biennial CBE screening ages 40–69 + treatment for all four stages, compared with do-nothing option: ICER = US\$1,299/DALY b. Biennial mammography screening (ages 40–69) + treatment for all four stages, compared with alternative a: ICER = US\$12,908/DALY c. Biennial mammography screening (ages 50–69) + EPC + treatment for stages I, II, and III, compared with alternative b: ICER = US\$553,616/DALY	Yes

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Table 3A.3 Selected Cost-Effectiveness Studies on Breast Cancer Control Strategies (continued)

Study	Country and GDP per capita (US\$) for year of study ^a	Cancer control strategies evaluated	BHGI resource levels ^b addressed in study	Decision modeling framework and perspective, including handling of uncertainty	Effectiveness: how measured and evaluated over time	Cost: what is included and how evaluated over time	Cost-effectiveness ratios in base case	Are the interventions cost effective? ^c
		* Biennial CBE screening (ages 40–69) + BPC + treatment for stages I, II, and III		<ul style="list-style-type: none"> • <i>Perspective</i> is societal • <i>Uncertainty</i> is addressed through multiple one-way and multi-way deterministic sensitivity analyses 				
		* Biennial mammography screening (ages 40–69) + BPC + treatment for stages I, II, and III						
		* Biennial mammography screening (ages 50–69) + EPC + treatment for stages I, II, and III						
Salomon and others (2012)	Mexico Int\$10,770 ^a (2005 Int\$)	<ul style="list-style-type: none"> • For breast cancer, approximately the same six interventions considered in Groot and others⁴ • While the stage-specific treatments closely mirrored Groot and others, the screening option in the sixth option (treatment of all stages plus screening) was tailored expressly to current norms in Mexico 	Same mapping of interventions to resource levels as for Groot and others	<ul style="list-style-type: none"> • Based on WHO-CHOICE framework,¹ as described for other studies • Particular focus on bringing Mexico-specific data to bear whenever possible, using administrative registry sources • Population-based estimates of demographics and insurance status • Household surveys that captured health behaviors and local drug cost databases 	<ul style="list-style-type: none"> • DALYs averted per person, <i>discounted</i> at 3% and weighted for age in base case • Data on current demographics, cancer incidence and prevalence rates, and remission and case-fatality rates drawn largely from Mexican sources; consistent with WHO-CHOICE approach, data on effectiveness from meta-analyses and systematic reviews, with DALY weights from Global Burden of Disease study 	<ul style="list-style-type: none"> • Direct medical costs for interventions were computed following WHO-CHOICE modeling guideposts, including separate analyses for patient-level, program-level, and training costs • All costs <i>discounted</i> at 3% • Data on resource use and unit prices derived largely from external sources, including literature reviews, a database on drug prices, and WHO-CHOICE price database 	With the six interventions defined and numbered as in Groot and others, for Mexico: (ACERs) 1. Int\$1,045/DALY 2. Int\$1,680/DALY 3. Int\$4,858/DALY 4. Int\$8,318/DALY 5. Int\$1,600/DALY 6. Int\$13,466/DALY ICER analysis indicates treating all stages (option 5), compared with null option has nondominated ICER of Int \$1,825/DALY	Very (option 5)

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Table 3A.3 Selected Cost-Effectiveness Studies on Breast Cancer Control Strategies (continued)

Country and GDP per capita (US\$) for year of study ^a	Cancer control strategies evaluated	BHGI resource levels ^b addressed in study	Decision modeling framework and perspective, including handling of uncertainty	Effectiveness: how measured and evaluated over time	Cost: what is included and how evaluated over time	Cost-effectiveness ratios in base case	Are the interventions cost effective? ^c
	<ul style="list-style-type: none"> Screening included annual CBE for all patients over age 25, annual mammogram for patients over age 50 (plus high-risk patients over age 40), and biennial mammogram for normal-risk patients ages 40 to 49 years 	<ul style="list-style-type: none"> Perspective is societal Uncertainty is addressed through multiple one-way and multi-way deterministic sensitivity analyses 	<ul style="list-style-type: none"> Outcomes for interventions derived from multi-state population-level model PopMod^d assuming interventions run for 10 years 	Treatment for all stages + screening (option 6), compared with option 5, has nondominated ICER of Int\$21,983 ^f	Yes (option 6)		

Note: ICER = average cost-effectiveness ratio; BAR = basic awareness raising; BCS = breast-conserving surgery; BGHI = Breast Health Global Initiative; BPC = basic palliative care; CBE = clinical breast examination; DALY = disability-adjusted life-year or when used in the denominator of a ratio X/DALY = per disability-adjusted life-year gained; EPC = extended palliative care; GDP = gross domestic product; ICER = incremental cost-effectiveness ratio; MAR = mass media campaign; WHO = World Health Organization WHO-CHOICE = WHO's Choosing Interventions That Are Cost-Effective.

- Conversion to U.S. dollars derived from World Bank World Development Indicators (<http://data.worldbank.org/indicator/NY.GDP.PCAP.CD>).
- BHGI resource levels are denoted Basic, Limited, Enhanced, and Maximal; see tables 3.1, 3.3, 3.4, and 3.5 in chapter 3 Breast Cancer for detailed specifications pertaining, in turn, to breast cancer early detection, diagnosis, and treatment at stages I, II, III (locally advanced disease), and IV (metastatic).
- In line with recommendations by WHO, health interventions costing less than one times GDP per capita are designated "very cost effective," those costing between one and three times GDP per capita are "cost effective," and those costing more than three times GDP per capita are "not cost effective" (WHO 2001).
- While the study also includes North America as a region, we limit attention to the analyses pertaining to Africa and Asia, given the focus on LMICs.
- Based on further calculations using data reported in table 3 of Groot and others (2006) for Africa, the nondominated interventions are 1, 5, and 6 (in increasing order of effectiveness), with the ICER for adopting 6 rather than 5 (US\$48 per DALY averted) lower than the ICER comparing 5 and 1 (US\$276 per DALY averted). Hence, the extensive program (option 6), which also yields the greatest total DALYs averted, is optimal. If the decision maker deems its total cost (US\$477 million) as affordable. Similar calculations carried out for Asia, based on data reported in table 3 of Groot and others, show that 1, 5, and 6 are the nondominated options, with the ICER for adopting 6 rather than 5 (US\$63 per DALY averted) lower than for option 5 compared with option 1 (US\$170 per DALY averted). Hence, the extensive program is the most cost-effective option, yielding again the greatest number of DALYs averted—although with the largest total program price tag (US\$1.2 billion).
- In general, to identify the optimal intervention or the set of potentially optimal interventions in a cost-effectiveness analysis where the interventions are constructed to be mutually exclusive—the case for the WHO-CHOICE models here—there is a well-defined algorithm: Rank the interventions in order of increasing effectiveness (low to high). Eliminate dominated options (wherein the next most effective option has a lower total cost). For the remaining options, compute the ICER for each successively more effective intervention (starting with the remaining least effective one); if the ICER comparing intervention *j* and *k* is lower than the ICER for *i* and *j*, eliminate *j* from the list and compute the ICER now between *i* and *k* (*j* is inefficient by virtue of "extended dominance"). The interventions that remain will still be in order of increasing effectiveness (with the next most effective option having a lower total cost). For the remaining options, compute the ICER for each successively more effective intervention (starting with the remaining least effective one); if the ICER comparing intervention *j* and *k* is lower than the ICER for *i* and *j*, eliminate *j* from the list and compute the ICER now between *i* and *k* (*j* is inefficient by virtue of "extended dominance"). The interventions that remain will still be in order of increasing effectiveness, with ICERs that are also successively larger as one goes down the (remaining) list of options. If the designated threshold willingness-to-pay for the marginal unit of effectiveness (for example, the dollar value of a DALY averted) is λ , choose the intervention that has the largest ICER that does not exceed λ . It can be shown that this maximizes the total increase in effectiveness (for example, DALYs averted), subject to meeting the decision maker's judgment about the worth of a unit of effectiveness. For example, if the decision maker's aim is to select the optimal "very cost-effective" intervention, the choice would be the intervention that has the greatest DALYs averted with an ICER that does not exceed GDP per capita for the country of application. An implication is that when there are multiple (>2) mutually exclusive options, the most cost effective may not have the lowest ICER. For a thorough discussion, see Johannesson and Weinstein (1993).
- GDP per capita denominated in international dollars (reflecting purchasing power parity), <http://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD?page=2>.
- Although the study also includes cost-effectiveness analyses for cervical and colorectal cancers, we limit attention to the analyses pertaining to breast cancer.
- See Evans and others (2005); Tan-Torres Edejer and others (2003).
- Among this set of nondominated options, all with similar ICERs in Sub-Saharan Africa and Asia and all meeting the criterion of being "cost effective," the choice of intervention would then turn on decisions about resource availability. In particular, the option that generates the greatest number of DALYs averted—namely, the variant of 6 with 95 percent population coverage—also has greatest total cost; the option with 50 percent coverage has lowest total cost but also fewest DALYs averted.
- Although the study also includes cost-effectiveness analyses for nine major clusters of noncommunicable disease, we limit attention to the cluster for breast cancer.
- See Lauer and others (2003).

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