Cost-Effectiveness of Breast Cancer Screening in Turkey, a Developing Country: Results from Bahçeşehir Mammography Screening Project

Vahit Özmen[1], Sibel Ö. Gürdal[2], Neslihan Cabioğlu[1], Beyza Özcinar[1], A. Nilüfer Özaydın[3], Arda Kayhan[4], Erkin Arıbal[5], Cennet Sahin[6], Pınar Saip[7], Oğuzhan Alagöz[8]

[1]Department of Surgery, İstanbul Faculty of Medicine, İstanbul University, İstanbul, Turkey
[2]Departments of Surgery, Namık Kemal University School of Medicine, Tekirdağ, Turkey
[3]Department of Public Health, Marmara University School of Medicine, İstanbul, Turkey
[4]Departments of Radiology, University Health Sciences, İstanbul Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey
[5]Department of Radiology, Marmara University School of Medicine, İstanbul, Turkey
[6]Department of Radiology, University Health Sciences, İstanbul Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, Turkey
[7]Department of Medical Oncology, İstanbul University School of Medicine, İstanbul, Turkey
[8]Department of Industrial & Systems Engineering and Population Health Sciences, UW Carbone Cancer Center, University of Wisconsin Hospital and Clinics, Madison, WI, USA

ABSTRACT

Objective: We used the results from the first three screening rounds of Bahcesehir Mammography Screening Project (BMSP), a 10-year (2009-2019) and the first organized population-based screening program implemented in a county of Istanbul, Turkey, to assess the potential cost-effectiveness of a population-based mammography screening program in Turkey.

Materials and Methods: Two screening strategies were compared: BMSP (includes three biennial screens for women between 40-69) and Turkish National Breast Cancer Registry Program (TNBCRP) which includes no organized population-based screening. Costs were estimated using direct data from the BMSP project and the reimbursement rates of Turkish Social Security Administration. The life-years saved by BMSP were estimated using the stage distribution observed with BMSP and TNBCRP.

Results: A total of 67 women (out of 7234 screened women) were diagnosed with breast cancer in BMSP. The stage distribution for AJCC stages O, I, II, III, IV was 19.4%, 50.8%, 20.9%, 7.5%, 1.5% and 4.9%, 26.6%, 44.9%, 20.8%, 2.8% with BMSP and TNBCRP, respectively. The BMSP program is expected to save 279.46 life years over TNBCRP with an additional cost of $677.171, which implies an incremental cost-effectiveness ratio (ICER) of $2.423 per saved life year. Since the ICER is smaller than the Gross Demostic Product (GDP) per capita in Turkey ($10.515 in 2014), BMSP program is highly cost-effective and remains cost-effective in the sensitivity analysis.

Conclusion: Mammography screening may change the stage distribution of breast cancer in Turkey. Furthermore, an organized population-based screening program may be cost-effective in Turkey and in other developing countries. More research is needed to better estimate life-years saved with screening and further validate the findings of our study.

Keywords: Mammography screening, breast cancer screening Turkey, cost-effectiveness of breast cancer screening

Introduction

Mammography screening, which has been shown to reduce breast cancer mortality, has been primarily adopted in developed countries whereas some low-middle income countries (LMIC) such as Turkey are considering to initiate population-based mammography screening as more resources become available (1-3). Mammography screening is becoming potentially more useful in LMIC and/or developing countries including Turkey due to an increase in breast cancer incidence and mortality over time (4-6). For example, while breast cancer incidence in Turkey was 24/100,000 in 1993, it increased to 50/100,000 in 2010 (7, 8).

There was no nationwide organized population-based mammography screening programs in Turkey. However, the Cancer Diagnosis Screening and Education Centers (KETEM) founded by the Turkish Ministry of Health (TMOH) invite women for opportunistic

mammography screening (i.e. mammography is offered to a woman without symptoms of breast cancer who visits a clinic for unrelated reasons) free of charge (8, 9). Furthermore, TMOH published the first population-based mammography screening guidelines in 2004, which recommended biennial screening for women between 50 and 69 years of age. TMOH updated the guidelines in 2013 and changed the starting age for mammography screening to 40. However, breast cancer screening participation rates in Turkey are still very low, estimated to be less than 10% due to high resource needs, insufficient efforts to publicize screening, and lack of breast cancer awareness in target population (10-12). For example, according to the 2010 Turkish Statistical Institute (TUIK) survey on health care resource utilization, only 17% of women over age 35 reported to have ever had a mammography (both diagnostic and screening) in their lifetime (13).

Breast cancer screening recommendations in Turkey are developed typically by adopting the studies conducted in developed countries such as in the US and Europe. However, Turkish female population has unique characteristics that require a study utilizing Turkish data. For example, the distribution of breast density, a significant breast cancer risk factor also affecting the performance of mammography, is significantly different in Turkey than that in the US and Europe (14). Furthermore, almost 50% of all invasive breast cancers in Turkey are diagnosed in women younger than 50 years of age whereas only 25% of all invasive breast cancers are diagnosed in the same age group in the US (8, 15).

Bahçeşehir Mammography Screening Project (BMSP) is exceptional as it provides primary data for potential effects of mammography screening in Turkish population. Briefly, the BMSP is a 10-year-long program (2009-2019) and it is the first organized population-based screening program implemented in Bahçeşehir, a large region of Istanbul, Turkey. The purpose of the this trial is to demonstrate the feasibility of a population-based organized mammographic screening program in an LMIC country, to determine the effectiveness of a screening program for the early detection of breast cancer and to help identify the appropriate starting age of breast cancer screening in Turkish women. The BMSP study has been screening approximately 7500 women between the ages of 40 and 69 biennially. Recently, the study finished the third round of screening with an overall 82% compliance rate. The BMSP study is unique as it screens women in a LMIC country unlike the previous studies primarily conducted in developed countries.

In this study, we report the results from the first three rounds of screening of BMSP and assess the potential cost-effectiveness of a population-based mammography screening program in Turkey. The results of the study may also provide guidance for other LMICs that consider implementing a population-based mammography screening program. To the best of our knowledge, no other studies have used primary-level data from Turkey to estimate the potential cost-effectiveness of mammography screening in Turkey.

Materials and Methods

Overview of the Bahçeşehir Mammography Screening Project
Bahçeşehir Mammography Screening Project started to screen women living in Bahçeşehir County in Istanbul, one of the largest counties of Istanbul, Turkey, in 2009. An approval by Institutional Review Board of Istanbul University was obtained. Each eligible woman was informed and signed the consent form. Between 2009

and 2015, mammograms were obtained by 2-year intervals from women between the ages of 40-69 years (n=7234). Following physical examination, digital 2-view mammograms (Mammography; Lorad, Danbury, USA) were double-read by two independent breast radiologists. The women were recalled with consensus for additional work-up including spot compression/magnification mammograms or breast ultrasound (Ultrasonography; Toshiba, CA, USA) (16). Ultrasound and biopsy were performed in women with suspicious lesions. One physician, three radiology staff members, one nurse and two secretaries worked over the five years' period. One mammography and one ultrasonography device were allocated. Mammographic findings were classified according to the American College of Radiology's (ACR) Breast Imaging Reporting and Data System (BI-RADS) (17). Recall rates were 16.8% and 25.6% for the first and second rounds, respectively and core biopsy was performed in 1.8% of the patients after the second round (18). More information about the BMSP is available elsewhere (16, 18, 19).

Strategies under consideration
We compared the costs and outcomes of two screening strategies: BMSP (which includes three biennial screens for women between 40-69 years of age) and the existing screening policy utilized in Turkey that is referred to as the Turkish National Breast Cancer Registry Program (TNBCRP). While there exists a recommended screening policy in Turkey, the overall participation in screening programs is very low (less than 10%); therefore, we assumed that the total screening costs associated with TNBCRP was 0, which provided a conservative estimate for our cost-effectiveness estimations. The TNBCRP reports the overall incidence of breast cancer and the stage distribution of the diagnosed cancers throughout Turkey including 22 cities representing diverse populations (8).

Estimating clinical outcomes
We reported the number of women who were diagnosed with breast cancer in the BMSP and classified the stage of breast cancer at the time of diagnosis using the edition of AJCC staging (20). We estimated the stage distribution associated with TNBCRP using a recent study that reports the stage distribution from 13.240 Turkish women, who were diagnosed with breast cancer (8). We used the 5-year survival rates by AJCC stage as reported by the American Cancer Society and calculated by the U.S. National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) database (21). We estimated the stage-specific life expectancies and calculated the expected life-year differences between BMSP and TNBCRP by assuming that survival time follows exponential distribution.

Estimating costs
Total costs associated with BMSP included (a) salaries (b) expenses for recruiting screening group, (c) purchase and maintenance of devices, and (d) diagnosis, treatment, and follow-up & surveillance of detected breast cancer patients. We estimated costs (a)-(c) directly from the BMSP project whereas we used the reimbursement rates of Turkish Social Security Administration (SGK), the organization in charge of reimbursing health expenses in Turkey for (d).

We also considered the additional cost associated with the loss of working months due to cancer treatment as a secondary cost outcome. We estimated the number of work months lost due to being treated by stage to reflect the need for more invasive treatments for advanced breast cancers. We used an annual average cost of minimum salary (869 Turkish Liras on average in 2014) per month to estimate the

Table 1. Stage Distribution according to BMSP with comparison to TNBCRP

Stage (AJCC)	Expected 5-year overall survival by stage (21)	Expected life years at diagnosis	Stage Distribution in BMSP	95% Confidence Intervals	Stage Distribution in TNBCRP (8)	Expected Difference in Stage Distribution (BMSP-TNBCRP)	Work loss (in months)
Stage 0	100%	25.89	19.4%	[10.8%, 30.9%]	4.9%	14.5%	2
Stage 1	100%	25.89	50.8%	[38.2%, 63.2%]	26.6%	24.1%	6
Stage II	93%	18.82	20.9%	[11.9%, 32.6%]	44.9%	-24%	6
Stage III	72%	9.58	7.5%	[2.5%, 16.6%]	20.8%	-13.3%	9
Stage IV	22%	2.93	1.5%	[0.0%, 8.0%]	2.8%	-1.3%	12
Expected life years			22.85		18.68	4.17	
Average work loss (months)			5.54		6.60	-1.06	

AJCC: American Joint Committee on Cancer; BMSP: Bahçeşehir Mammography Screening Project; TNBCRP: Turkish National Breast Cancer Registry Program

total costs associated with loss of work (22). We estimated all the costs using 2014 Turkish Liras (TL) and also converted the costs for summary outcomes into US Dollars using the average exchange ratio of (1 USD=2.2 TL) in 2014 (23).

Cost-effectiveness analysis

We used US dollars as the cost measure and "life years saved" as the effectiveness measure. BMSP has been implemented for five years. Therefore, we calculated the total costs associated with BMSP for five years. Similarly, we estimated the costs under TNBCRP for five years. On the other hand, we used a life-time horizon for the effectiveness outcome, since the full effects of screening on women are observed only until patients die due to breast cancer or non-breast cancer.

We used the society's perspective for our calculations. For this purpose, we obtained all costs related to the diagnosis, treatment, and follow-up & surveillance of cancer cases from SGK's lists of healthcare services and medications. As described earlier, the administrative and operational costs in BMSP were estimated separately using the primary-level data.

Sensitivity analysis

We performed two types of sensitivity analyses. Firstly, we conducted a sensitivity analysis on the stage distribution observed under BMSP. For this purpose, we used the lower and upper bounds for the confidence intervals for the proportion of cancers diagnosed at a particular stage. Namely, we assumed that the proportions of stage 0 and stage I cancers among all cancers under BMSP were equal to the lower bounds for these quantities. We further assumed that the proportion of stage III and stage IV were the same as those observed in TNBCRP and the remaining cancers were observed in stage II and we recalculated the incremental cost-effectiveness ratio (ICER) value. Therefore, this sensitivity analysis considered a scenario where the benefit of screening was smaller than what was observed in our base case. Secondly, we conducted a one-way sensitivity analysis on other inputs and presented them in a tornado diagram (24).

Statistical analysis

All statistical tests were performed in R (25). We used the exact Binomial method for computing confidence intervals and Chi-square test considering continuity correction for comparing stage distributions.

Results

Clinical outcomes and stage distribution observed with BMSP

After the third screening round, a total of 7234 women were screened. Among these, 67 women were diagnosed with breast cancer; therefore, the overall cancer detection rate was 9.3 per 1.000 women (67 out of 7234). We found that 48% of the women diagnosed with breast cancer were women aged 40-49 while 59% of the screened women were in the age group of 40-49 years. The mean age for the women diagnosed with breast cancer was 52. Table 1 includes the breast cancer stage distribution observed in BMSP as well as the stage distribution observed in TNBCRP using the AJCC historical stage definition.

The stage distribution between the BMSP and TNBCRP is statistically significant (p-value<0.0001). The mean life expectancy for the Turkish women in the screened population (40-69) is 25.89 years according to 2010 Turkish life tables (26); therefore, we calculated the rate parameter for survival without breast cancer (β) as 0.0386=1/25.89 using 25.89 years as an input. We found that the total expected life years for 67 patients diagnosed with cancer was 1530.87 years (22.85*67) under the BMSP, and 1251.41 years (18.68*67) under the TNBCRP. Therefore, after three biennial mammography screenings, the BMSP led to a saving of 279.46 life years (1530.87-1251.41) for 67 patients (4.17 saved life years per woman diagnosed with cancer).

Cost outcomes of BMSP

Table 2 shows the costs associated with BMSP and TNBCRP after the third screening round. We provided the details of the computations in the appendix. We assumed that the cost of screening for TNBCRP was 0, which provided a conservative estimate for the cost-effectiveness of BMSP. The costs of diagnosis and treatment are estimated to be higher in TNBCRP than in BMSP due to the additional treatment cost for patients diagnosed at more advanced stages when there is no or limited screening.

Cost-effectiveness analysis

The expected 5-year overall survival rates and expected life years after breast cancer diagnosis by stage, and expected differences among stage distribution of 67 patients were shown in Table 1. Similarly, the cost differences between BMSP and TNBCRP were presented in Table 2.

Table 2. Cost outcomes for BMSP with comparison to TNBCRP

Costs	BMSP	TNBCRP	Expected Difference between BMSP and TNBCRP (in TL)	Expected Difference between BMSP and TNBCRP (in USD)
Cost of screening including false positives	1,875,260 TL	0	1,875,260 TL	852,391 USD
Cost of diagnosis and treatment	1,392,228 TL	1,716,107 TL	-323,879 TL	-147,218 USD
Cost due to work loss	322,214 TL	383,818 TL	-61.604	-28.002 USD
Total Cost	3,579,499 TL	2,087,772 TL	1,491,727 TL	677,171 USD

BMSP: Bahçeşehir Mammography Screening Project; TNBCRP: Turkish National Breast Cancer Registry Program
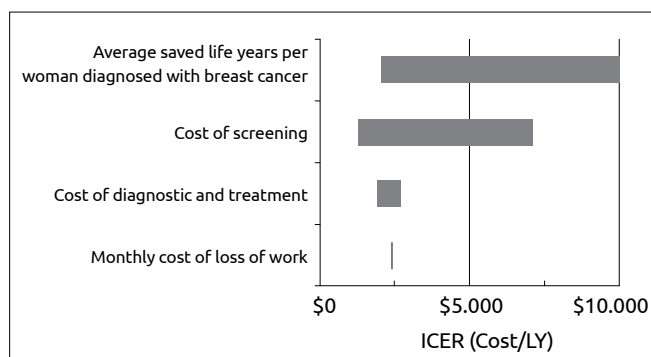

Figure 1. Tornado Diagram. This figure summarizes the results of one-way sensitivity analysis. In this figure, the x-axis represents the ICER per life years (LY) gained by BMSP over TNBCRP and the y-axis lists the parameters that were changed as part of one-way sensitivity analysis that was ordered with respect to their effect on ICER

We estimated that the BMSP program led to an additional 279.46 life years (67*4.17 life years per woman in Table 1) over TNBCRP with an additional cost of $677.171 (Table 2), which implies an incremental cost-effectiveness ratio (ICER) of $2.423 per an additional life year. The World Health Organization recommends that any health care program with an ICER value smaller than the per capita GDP of a nation is highly cost-effective (27). Since the ICER of BMSP program over TNBCRP is smaller than GDP per capita in Turkey ($10.515as of 2014), BMSP program is highly cost-effective (28).

Sensitivity analysis

For our first sensitivity analysis, we assumed that the proportion of cancers diagnosed in Stages 0 and I was equal to the lower bounds of the confidence intervals, 10.8% for Stage 0 (base-case was 19.4%) and 38.2% for Stage I under BMSP (the base case was 50.85). We assumed that the proportions of cancers diagnosed in Stages III and IV were the same as those observed under TNBCRP, i.e., the proportion of cancers diagnosed in Stage III was 20.8% (base case was 7.5%) and the proportion of cancers diagnosed in Stage IV was 2.8% (the base case was 1.5%), respectively. Finally, the proportion of cancers diagnosed in Stage II was (1-10.8%-38.2%-20.8%-2.8%=27.4%) whereas it was 20.9%. We found that this assumed conservative distribution of stages would save 82.89 life years with an additional expense of $698,931 US dollars; therefore, the ICER was $8.433 US dollars per additional life year, implying that BMSP would still remain cost-effective.

Figure 1 presents the results of our one-way sensitivity analysis on four inputs parameters: average life years saved with BMSP, average cost of

screening including false positives, monthly cost of loss of work, and cost of diagnosis and treatment. We found in Table 1 that the BMSP led to an average saving of 4.17 life years per woman diagnosed with cancer over TNBCRP; therefore, we chose the range of average saved life years per woman between 1 year and 5 years. Similarly,

Table 2 implies that the average cost of screening including false positives was approximately 1,875,260 TL/(7234*3)=86 TL ($39 US Dollars); therefore, we chose the range for cost of screening between $25 and $100. There were many inputs for the average cost of diagnosis and treatment as explained in the appendix; therefore, for this parameter, we used 50% of all input costs as the minimum value and 200% of all inputs costs as the maximum value. Finally, we used the range of ($350, $500) for the monthly cost of loss of work (the base case was $395 US Dollars, i.e., 869 TL). We found that the most critical input parameter affecting the ICER of BMSP was average life-year savings per woman due to the BMSP. As expected, as the cost of diagnosis and treatment, monthly cost of loss of work, and average saved life years per woman due to BMSP increase, the ICER becomes smaller (i.e. BMSP becomes more cost-effective). On the other hand, as the cost of screening increases, the ICER becomes larger (i.e. BMSP becomes less cost-effective). For all the parameter values, we found the BMSP to remain cost-effective.

Discussion and Conclusion

The potential effects and cost-effectiveness of screening programs in LMIC and developing countries such as Turkey are not extensively studied. It is known that breast cancer is typically diagnosed at more advanced stages in countries with little or no screening and a lack of breast cancer awareness compared to countries that have a population-based screening program. In line with this observation, our present study finds that BMSP, first organized population-based screening program implemented in Turkey, led to a shift in the stage distribution of breast cancers such that a smaller number of breast cancers are diagnosed in regional and distant stages with a significant increase in the proportion of DCIS and localized breast cancers. We conducted a simple modeling study to evaluate the potential cost-effectiveness of screening in Turkey and found that a nationwide biennial mammography screening policy between ages 40-69 may be highly cost-effective in Turkey under our base case assumption. We performed an extensive sensitivity analysis and found that for all scenarios, the ICER would stay below the well-accepted cost-effectiveness threshold of GDP per capita.

While our study does not use any data from the other LMIC and developing countries, it demonstrates that breast cancer screening could

be cost-effective for other LMIC countries, as well. Existing modeling studies that evaluated the value and cost-effectiveness of breast cancer screening in LMIC countries typically focused on evaluating clinical breast exam as a screening tool and reported conflicting results (29-32). Despite the controversy, (31) the Middle Resource Scenarios Working Group of the Breast Health Global Health Initiative concluded that "breast cancer early detection programs continue to be important, should include clinical breast examination with or without mammography, and should be coupled with active awareness programs" (33).

As noted before, there are no cost-effectiveness studies utilizing primary-level screening mammography data from the Turkish female population. There are few studies that report on potential cost-effectiveness of mammography screening in Turkey. While two prospective studies (34,35) found that mammography screening reduced costs compared to the no-screening scenario (i.e. mammography screening is less expensive and leads to better health outcomes than no screening), another recent study (36) found that mammography screening was highly cost-effective (i.e. the ICER of 40-69 biennial screening over no screening is $330 US dollars). Similarly to these studies, we found mammography screening to be cost-effective but with a higher ICER value.

There are several important points as the findings of our study are translated into a nationwide screening program. On one side, it is likely that the positive findings on the benefits of screening with BMSP may not be observed at the same level when a nationwide screening program is implemented. For example, the performance of radiologists in a nationwide program may be worse than that of radiologists working for the BMSP and our findings may have overestimated the benefits of screening. On the other hand, it is also possible that we may have overestimated the cost of screening such as the cost of screening mammography. In summary, there are several similar translational issues that need to be considered carefully before making use of our findings.

Our study has several limitations. Firstly, while this is the first attempt for such a study in Turkey, our study's sample size is still limited. Therefore, we found wider confidence intervals for the breast cancer stage distribution under the BMSP. Secondly, our estimates for costs are very accurate whereas our estimates for life years are based on a simple approach utilizing data from SEER and stage-specific 5-year survival rates due to the unavailability of realistic estimates for stage-specific life expectancies for Turkish women. For example, it is possible that associating the same stage-related survival for the BMSP and the TNBCRP may lead to less favorable outcomes for the TNBCRP (37). Therefore, this assumption may have caused our study to underestimate the benefits of screening. Ideally, one would use an established microsimulation model such as those used as part of NCI's Cancer Intervention Surveillance Network (CISNET) project to estimate the life expectancies for women undergoing screening more accurately (38-40). However, there is no such validated model that uses primary data of Turkish female population; therefore, we leave this for future research. Finally, although our study implicitly accounts for over-diagnosis (i.e. the life-year savings for women diagnosed with cancer are 0 as they may die due to other causes before death due to cancer occurs), we are unable to estimate the rate of over-diagnosis, which is a potential harm of screening.

In summary, we found that mammography screening may significantly shift the stage distribution of breast cancer in Turkey. Furthermore, we found that an organized population-based screening program may be cost-effective in Turkey as well as in other LMIC countries. However, due to the limitations described above, more research is needed to further validate the findings of our study.

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APPENDIX

In this appendix, we provide the details of our calculations for the clinical and cost outcomes.

Estimating Clinical Outcomes

We estimated the rate parameter for the breast cancer specific survival time (i.e., λ_i, where i represents the AJCCC stage) by assuming that post-cancer survival of a woman diagnosed with breast cancer follows the exponential lifetime distribution and using 5-year breast-cancer stage-specific relative survival rate as an input. We assumed that the death from other causes in Turkish female population also follows exponential distribution and estimated the rate parameter of the survival time for women due to non-breast cancer (β) using the life tables for Turkish women. We assumed that the lifetime of a woman diagnosed with breast cancer in a particular stage follows exponential distribution and calculated the rate parameter as ($\lambda_i + \beta$) by assuming independence between the two survival lifetimes. Finally, we used the mean values of these exponential distributions ($1/\lambda_i + \beta$) for each stage as the stage-specific life expectancies and calculated the expected life-year differences between BMSP and TNBCRP.

BMSP Screening Costs

Screening costs for BMSP included (a) the salaries paid to the staff worked for the BMSP project and (b) the expenses for purchasing and maintenance of diagnostic devices used for screening. Appendix Table A1 summarizes the cost components associated with screening in BMSP.

Appendix Table A1. Screening cost components of BMSP. The costs include salaries, equipment and miscellaneous costs spent during 5-years implementation of the program.

	Monthly cost	Annual cost	Total cost over 5 years
Total		375,052 TL	1,875,260 TL
Salaries		260,926 TL	1,304,630 TL
Physician	4,767 TL	57,209 TL	286,047 TL
Senior radiologist	4,767 TL	57,209 TL	286,047 TL
Assistant radiologist	3,496 TL	41,954 TL	209,768 TL
Radiology technician	3,266 TL	39,191 TL	195,954 TL
Nurse	1,907 TL	22,884 TL	114,419 TL
Administrative secretary	1,633 TL	19,595 TL	97,976 TL
Assistant secretary	1,907 TL	22,884 TL	114,419 TL
Equipment		**108,431 TL**	**542,155 TL**
Mammogram	413,272 TL*	41,327 TL**	206,636 TL
Mammogram maintenance	50,000 TL	50,000 TL	250,000 TL
Ultrasonography	71,039 TL*	7,104 TL**	35,519 TL
Ultrasonography maintenance	10,000 TL	10,000 TL	50,000 TL
Miscellaneous	5,695 TL	5,695 TL	28,475 TL

* Purchasing prices
** Amortization for the equipment was assumed to be 10% per year, i.e. the value of equipment is assumed to reduce by 10% per year.

Cost of Diagnosis and Treatment for BMSP and TNBCRP

The estimation of diagnosis and post-cancer treatment is more complicated. Appendix Table A2 lists the cost items, unit costs, and the resource utilization used for estimating diagnosis and treatment costs. We use these inputs to estimate the costs for diagnosis and treatment for both BMSP and TNBCRP.

Appendix Table A2. Cost items, unit costs, and definitions of resource utilization. These values constitute the primary source data for the calculation of cost components and total costs for TNBCRP and BMSP (see Appendix Table A3).

Cost item	Unit cost (TL)	% of patients	Explanation
Diagnosis*			
MR	65 TL	100%	At diagnosis
Through-cut biopsy	53.68 TL	100%	At diagnosis
Pathology examination (through-cut biopsy specimen)	50 TL	100%	At diagnosis
Preoperative laboratory evaluation	150 TL	100%	At diagnosis

Appendix Table A2. Cost items, unit costs, and definitions of resource utilization. These values constitute the primary source data for the calculation of cost components and total costs for TNBCRP and BMSP (see Appendix Table A3). **(continuation)**

Cost item	Unit cost (TL)	% of patients	Explanation
Pathology examination (incl. receptors)	272 TL	100%	At diagnosis
Bone scan, thorax CT, Abdominopelvic BT, Cranial MR	255 TL	0% at stages 0 & 1 100% at stages 2, 3 & 4	At diagnosis and every year starting from 2nd year at stages 2&3; at diagnosis only at stage 4
PET CT	1,030 TL	0% at stages 0 & 1 100% at stages 2, 3 & 4	At diagnosis and every year starting from 2nd year at stages 2&3; at diagnosis only at stage 4
Treatment**			
Surgery: Lumpectomy or Mastectomy + SLNB	560 TL	100%	
Radiotherapy	935 TL	100%	
Chemotherapy	1,100 TL at stage 1 1,230 TL at stage 2 1,640 TL at stages 3&4	0% at stage 0 63% at stages 1-4	
Trastuzumab	48,750 TL	0% at stage 0 23% at stages 1-4	For one year at stages 1-3, for two years at stage 4
Tamoxifen	120 TL	100% at stage 0 38% at stages 1-4	For five years
Aromatase inhibitor	1,320 TL	100% at stage 0 38% at stages 1-4	For five years
Switch		0% at stage 0 19% at stages 1-4	After two years of tamoxifen
Annual follow-up*			
Physical examination	60 TL in 1st and 2nd years 30 TL then after	100%	Every 3 months in two years, then every 6 months
Radiology	115 TL	100%	Once a year
Biochemistry (SGOT, SGPT, Ca, ALP & blood count)	200 TL	100%	Every 6 months
Gynecology visit	100 TL	100%	Once a year
Psychiatry consultation	360 TL	100%	At diagnosis and once yearly after then.

* These costs are estimated from Turkish Social Security Administration (SGK) reimbursement lists.
** The costs are estimated from the Turkish Ministry of Health's List of Drug prices

We next calculated the costs of screening, diagnosis, treatment, and follow-up & surveillance for each woman at each cancer stage. Appendix Table A3 summarizes these calculations. The costs included in Appendix Table A3 represent the costs for five years per person. Note that screening costs in this table are used only for TNBCRP since for a woman to be diagnosed with cancer, there would have to be a cost associated with mammography. These values are obtained by multiplying the unit costs for resources used in each cancer stage by the amount of resource use presented in Appendix Table A2.

Appendix Table A3. Total cost and costs of screening, diagnosis, treatment and follow-up & surveillance, for each woman diagnosed with cancer.

Cumulative cost for 5 years (TL/person)	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Total cost	6,857.18 TL	21,650.18 TL	28,157.08 TL	28,415.38 TL	34,487.88 TL
Screening*	56.50 TL	56.50 TL	56.50 TL	56.50 TL	56.50 TL
Diagnosis	590.68 TL	590.68 TL	7,015.68 TL	7,015.68 TL	1,875.68 TL
Treatment	2,095.00 TL	16,888.00 TL	16,969.90 TL	17,228.20 TL	28,440.70 TL
Follow-up & surveillance	4,115.00 TL	4,115.00 TL	4,115.00 TL	4,115.00 TL	4,115.00 TL

* only added to the costs for TNBCRP since screening costs are calculated separately for BMSP

In order to estimate the diagnosis and treatment costs, all we need is the number of patients that are diagnosed in each cancer stage. For the BMSP program, during the five years' period, 7234 women were screened. Among these women, 67 of them were diagnosed with breast can-

cer (13, 34, 14, 5, and 1 patients in stages 0, I, II, III and IV, respectively). Patients diagnosed with breast cancer were treated using treatment regimens as shown in Appendix Table A2.

Using the TNBCRP stage distribution, we estimated the number of women who would be diagnosed at different stages of cancer. We found that among 67 women diagnosed with cancer, under TNBCRP, only 4.9% of these 67 cases (n=3.82) is expected to be in stage 0, 17.82 is expected to be in stage 1, etc. (Appendix Table A4).

Once these numbers are estimated, then we multiplied the total cost in each stage with the (expected) number of women diagnosed in that particular stage to find the total expected costs for diagnosis and treatment under a screening program. Appendix Table A4 summarizes these calculations. We then used these values in Table 2 of the main text.

Appendix Table A4. Costs and estimated number of cases in each stage diagnosed by BMSP and TNBCRP. The figures presented in the table represent total costs for five years per strategy (for 67 women diagnosed with cancer).

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Total
BMSP						
Number of cases	13	34	14	5	1	
Total cost of diagnosis and treatment	89,143 TL	736,106 TL	394,199 TL	142,077 TL	34,488 TL	1,392,228 TL
Diagnosis	7,679 TL	20,083 TL	98,220 TL	35,078 TL	1,876 TL	162,936 TL
Treatment	27,235 TL	574,192 TL	237,579 TL	86,141 TL	28,441 TL	953,587 TL
Follow-up & surveillance	53,495 TL	139,910 TL	57,610 TL	20,575 TL	4,115 TL	275,705 TL
TNBCRP						
Estimated number of cases*	3.28	17.82	30.08	13.94	1.88	
Total cost of diagnosis and treatment	22,512 TL	385,850 TL	847,049 TL	395,997 TL	64,699 TL	1,716,107 TL
Screening	185 TL	1,007 TL	1,700 TL	787 TL	106 TL	3,786 TL
Diagnosis	1,939 TL	10,527 TL	211,053 TL	97,771 TL	3,519 TL	324,808 TL
Treatment	6,878 TL	300,978 TL	510,506 TL	240,092 TL	53,355 TL	1,111,808 TL
Follow-up & surveillance	13,510 TL	73,338 TL	123,792 TL	57,347 TL	7,720 TL	275,705 TL