Nazarbayev University

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Master Thesis

Health Economics Analysis of Mammography Screening Program in the Republic of Kazakhstan

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Introduction

Breast cancer (hereinafter - BC) is the most frequent type of cancer among women in the Republic of Kazakhstan, accounting for almost 12% of all cases of cancers in the country [1]. Kazakhstan has the highest rates of breast cancer in the Central Asian region. Local physicians associate it with lack of breastfeeding, use of hormonal drugs, and poor ecological conditions [2]. There were 3,400 new cases of BC in Kazakhstan in 2016 [3], while number of deaths in the same year reached 1,022 [4]. The age-adjusted death rate from BC is 21.50 per 100,000, which ranks Kazakhstan 35th in the world [32]. The prevalence of BC reached 22.7 per 100,000 in 2013, and it has been increasing constantly, affecting younger population aged 25-40. It also takes the first place in mortality rates among all cancers in the 45-50-year age group. Between 1990 and 2010 the annual years of healthy life lost from breast cancer in Kazakhstan has increased by 44.0% [5]. In 1990, BC led to 38,000 years of life lost (hereinafter - YLL) in Kazakhstan. In 2010, the prevalence rate of BC has raised by 17% leading to 44,000 YLL [6].

Early detection of BC is an effective public health measurement taken to decrease both the prevalence and the incidence of BC. There are three methods of detection of BC. The first is self-examination, which is more applicable in resource-limited settings. The second is the clinical examination of women with symptoms and signs. The third is the mammography-screening program (hereinafter - MSP), which is the systematic application of a screening examination in a presumably asymptomatic population. In Kazakhstan, mammography is offered to women aged 50-60 without symptoms of breast cancer and it is free of charge. Its purpose is to identify women with mammary gland abnormalities suggestive of cancer. Until 2008, clinical examination of symptomatic population was the predominant approach.

In Kazakhstan, free, population-based MSP was introduced in 2008 [7]. It is biannual and it targets women aged 50, 52, 54, 56, 58, and 60. In 2011, the whole program underwent a quality improvement in compliance with the European guidelines for quality assurance.

The MSP includes mammography screening with reading of the mammogram by two radiologists. The first reading is conducted in the local hospital where the woman underwent the mammography. Further, the screening is sent to the Kazakh Institute of Oncology and Radiology (hereinafter - KIOR) in Almaty for the second reading. During 2016, the MSP covered 389 352 women and detected 830 new cases of breast cancer, what amounted to 0.2% of the total number of screened women. [8]. According to the international recommendations, the detection rate of BC by mammography needs to be about 0.2% from the coverage rate [11].

Even though mortality rates from BC are decreasing since the introduction of the MSP in 2008, the incidence rates increased between 2006 and 2013. This continuous incidence growth might be explained by improved diagnostic methods and early detection of BC among the asymptomatic population.

According to the KIOR, in the long run, the MSP should reduce the breast cancer mortality rate by 25% [9]. Treatment costs of women diagnosed with BC in Kazakhstan varies significantly depending on the development of the disease in both public and private sector [10].

The MSP has proven to be effective in many developed countries [11]. Moreover, there is evidence a nation-wide MSP can decrease breast cancer mortality by almost 20% in the screened against the unscreened group [12]. In the United States, the MSP helped to decrease breast cancer mortality by 40% since 1990 [12].

Japanese researches has demonstrated that mammography provides the most cost-effective diagnostic approach in comparison with other methods of BC detection [13]. MSP is feasible and effective in countries with proper health infrastructure that can afford long-term organized population-based screening programs [14]. Nevertheless, low-cost screening methods, such as clinical breast examination and self-examination, could be applied in resource-limited settings.

According to the Ministry of Health, decline of BC mortality rates in Kazakhstan is attributed to its early detection by screening [15]. In high-income countries, almost 80% of screened women with BC are diagnosed at stage I, thus, screening leads to higher survival rates compared to women with advanced stages of BC. As a result, BC mortality rates in high-income countries decreased by 30% after 5-7 years of screening. It is projected that further implementation of the nation-wide mammography-screening program in Kazakhstan will obtain additional health benefits in BC outcomes for a low cost.

Objective

The objective of this study is to estimate health and financial outcomes associated with the nation-wide mammography-screening program in Kazakhstan.

Methods

Perspective

A cost-benefit analysis (hereinafter - CBA) was conducted to assess the economics feasibility of the MSP in the Republic of Kazakhstan. The analysis was implemented from the perspective of both screened women and the Ministry of Health (hereinafter - MoH). The MoH was selected as it funds and controls the national screening program. At the same time, the MSP affects women's personal quality of life and its expectancy by early diagnosis and prevention of the development of BC to advanced stages. The introduction of a social health insurance in Kazakhstan necessitates that health services be seen not only as a necessity but also as an economic good that requires health economics assessments.

To conduct an exhaustive health economics analysis we used several measurements of health and financial outcomes of the MSP. These include life years saved, value of a statistical life, quality-adjusted life years, financial outcome and incremental cost-effectiveness ratio.

A life years (hereinafter - LYs) saved estimate was calculated, since it shows how many additional LYs the MSP saved among screened women compared to the unscreened cohort.
To estimate economic outcomes of the MSP, cost-utility analysis was applied. It uses quality-adjusted life years (hereinafter - QALYs), which is a gain in life expectancy adjusted for its quality. This supports a patient-centered decision-making to judge the benefits of the mammography screening while taking into consideration its financial and non-financial burden.
Measurement often used in cost-benefit analysis is a value of statistical life (hereinafter - VSL), which represents the marginal rate of substitution between income and mortality risk. The VSL estimate has been selected as it shows the societal impact of the MSP.
Another financial outcome applied in this research is financial savings for treatment of BC. In other words, we assessed how much money the MSP saved due to the difference in stage distribution among screened and unscreened women with BC.
Finally, using such indicators as cost of screening, cost of treatment, and the number of QALYs gained per each group, we were able to calculate the incremental cost-effectiveness ratio (hereinafter - ICER) to estimate the amount of money spent per one QALY.
CBA was chosen for our economic analysis since it allows costs to be justified not only in terms of health effects but also in monetary benefits, thus, allowing us to see the effectiveness of the use of an allocated budget.
Based on the availability of the data, the analysis and calculations consider the MSP in a year 2016.

Comparison Group

According to current literature, the comparison group in our analysis comprises those women, who were not screened, as there is no other traditional method of breast cancer screening.

However, some research compare effectiveness of mammography screening with other diagnostic tools, such as MRI or ultrasound [16].

Discounting

We developed a model where we are follow a screened woman, in theory, 11 years, between the time they are 50 and 60. We use a uniform distribution to calculate constant probabilities of treatment. Furthermore, we have each "screened" woman screened 6 times over the 11-year period. Relevant cost data were provided by the Center of Oncology and Radiology in Astana [35]. To conduct a more accurate representation of financial outcomes, a discount rate of 4.8% per annum was applied for all costs. Such discount rate was used as average inflation in Kazakhstan is equal to 4.8% [40]. All costs were converted to USD, the dollar to tenge exchange rate for the June 30, 2016 was utilized at USD 1= 339 KZ tenge.

5-year survival analysis

A key assumption about mammography is that it detects a higher proportion of breast cancers at earlier stages that would have otherwise developed to advanced stages.

First of all, to make adequate comparison, we assume equal number of women in both screened (n=830) and unscreened groups. Based on 5-year survival rates and distribution of women with different stages of breast cancer we are able to calculate the potential number of lives saved by mammography. Survival rates and distribution of women across cancer stages have been obtained from the Center of Oncology in Astana.

The analysis of a group 5-year survival has been conducted by multiplication of survival rates of woman with BC by the proportion of women with a corresponding stage of breast cancer.

Life Years Saved

Understanding the additional life years given to women by early detection of breast cancer is essential as substantial finances are invested to provide mammography to population. Median survival rates were applied to estimate the difference of life years saved due to screening versus no screening.

To estimate the amount of life years gained in both screened and unscreened groups, the number of median survival rates have been multiplied by the number of women with a corresponding stage of breast cancer.

Quality-Adjusted Life Years

Quality adjusted life years (hereinafter - QALYs) is a health outcome measure based on life years gained adjusted for quality of life, which is scored between 0 for death and 1 for full health. QALYs is an effective measurement, used in health economic analysis, which demonstrates the effectiveness of health services and guides future decision-making.

To estimate the number of QALYs gained by the MSP among women aged 50-60 with breast cancer, it is essential to estimate their life expectancy and adjust it for quality of life and compare it with QALYs without screening.

Estimating life expectancy

According to the WHO, life tables, the additional expected life of women aged 50-54 years in Kazakhstan is around 28 years, and the additional expected life of women aged 55-59 is 23.7 years. Weighted average life expectancy of women aged 50-60 is calculated at 26 years. Such an adjustment is necessary for our analysis as it demonstrates that the MSP can save additional life years, which significantly changes QALYs.

Life Years gained (LY) is a measure where remaining life expectancy is taken into account as it gives more weight to younger population because saving the life of a teenager gains more life years than saving the life of a pensioner. LYs are estimated as the remaining lifespan at the point of each averted death.

In our analysis we have accounted for average time of treatment of breast cancer. Therefore, if a woman diagnosed with breast cancer at the age of 50 undergoes treatment until complete recovery, it is expected that she would live about 26 additional years. Table 1 shows life expectancy of the MSP target group.

Table 1. Life expectancy of the MSP target group according to the WHO life tables.

Age group	Life expectancy	Population [37]	Average life expectancy (weighted for population)
50-54	28	285,592	14,6
55-59	23,7	261,366	11,4
Total			26

Estimating quality of life

Quality of life (hereinafter - QoL) is usually measured by five dimensions: self-care, discomfort and pain, mobility, usual activities, anxiety and depression, which is scored between “0” for death and “1” for full health. Because of illnesses related to aging, the normal quality-of-life coefficient of women aged 50-60 years is assumed to be 76%. [19] Table 2 shows QoL coefficients for different stages of BC. Quality-of-life of women with stage I of BC is assumed to be 90% of the estimates for a normal quality-of-life. Quality-of-life for stage II of breast cancer is 75% of the normal state, while it is less than 60% for women with stage III-IV BC and distant metastasis. [19]

The decrease of quality of life is assumed to take place only during treatment and, in some cases, during reoccurrence of breast cancer. In other words, after successful treatment, which depends on the development of BC, a woman continues to live a normal life.

To assess the quality of life of women after remission, the natural decrease of the QoL index needs to be taken into account. Thereby, QoL coefficient of healthy women aged 50-60 is about 76% of a QoL of a healthy women aged 25-30. Whereas for women aged 61-70, QoL coefficient is equal to 74%, and for women aged 71-80 it is 70%. [20]

Table 2. Quality of life coefficients and its reduction due to BC

	Health State				
Age	Healthy	Stage I	Stage II	Stage III	Stage IV
50-54	0.780	0.696	0.644	0.598	0.536
56-60	0.747	0.694	0.636	0.567	0.474

Estimating QALYs

To estimate the number of QALYs, we assumed equal distribution of women across age groups dividing 830 cancer cases by 6 age groups: 50, 52, 54, 56, 58, 60.

To analyze the number of QALYs gained among screened and unscreened women, their life expectancies has been multiplied by the quality of life coefficient, which corresponds to certain stage of BC.

Incremental Cost-Effectiveness Ratio

The Incremental Cost-Effectiveness Ratio (ICER) has been applied as a measure used in benefit-cost and cost-utility analysis of a health care interventions. The ICER is defined by dividing the difference between costs of two interventions by the difference in their health outcomes (QALYs gained).

The ICER represents the average cost associated with one extra unit of the measure of effect (USD per QALY).

The Incremental Cost-Effectiveness Ratio can be estimated as:

$$ICER = \frac{COST\ (screening) - COST\ (no\ screening)}{QALY\ ((screening) - QALY(no\ screening)}$$

Where C1 and E1 are cost and effect in the intervention group (screened) and where C0 and E0 are cost and effect in the control group (non-screened).

Value of a Statistical Life

The value of a statistical life (VSL) is the marginal rate of substitution between income and mortality risk. The VSL indicates how much an individual is willing to pay to reduce the risk of death. The VSL is used in CBA to assess the efficiency of health policies intended to reduce risk. The term "statistical" refers to changes in the risk of death.

The VSL represents the amount of money a person views as equivalent to a change in his own mortality risk, for example, in deciding whether to spend money on protective equipment or safer products.

Value per statistical life year (VSLY) is estimated by dividing VSL by the average (discounted) remaining life expectancy. VSLY is the rate at which an individual substitutes money for gains in life expectancy. To determine the value per statistical case, VSLY is multiplied by the (discounted) expected years of life extension for all people affected by the policy. Therefore, to estimate the total value of life saved by mammography, we multiply the VSLY by the number of QALYs saved.

Cost Savings per Treatment

On average, mammography per one woman in Kazakhstan costs the government 14 USD [33]. . The total cost of the MSP includes the expenses for equipment, technical support, staff education, software, infrastructure and salaries. In total, the annual cost of the program in 2016 was 5,450,928 USD, which resulted from screening of 389,352 women aged 50, 52, 54, 56, 58, and 60.

In Kazakhstan, costs associated with treatment of breast cancer vary depending on tumor development. The average price per consultation for a clinical examination is about 9 USD. One course of chemotherapy costs about 500 USD, while women with advanced stages of BC need at least four such courses. Cost of surgery varies from 700 to 1,500 USD. The most expensive is radiation therapy, which costs about 30,000 USD per woman. Radiation is necessary for patients with advanced stages of BC. In addition, if a woman develops stages III or IV, targeted drugs are included into therapy. Thereby, cost of treatment for a woman with stage I BC is about 5,000 USD, treatment of a patients with stage II BC costs around 30,000 USD, while costs of treatment of women with stage III and IV costs from 36,000 USD to 40,000 USD, respectively [1;10;35].

By identifying breast cancer on earlier stages, screening may lead to timely therapy and large savings. Knowing the cost of treatment and the difference in stage distribution between screened and unscreened groups, we are able to estimate the total cost of treatment per each cohort. In other words, the number of cases has been multiplied by the averaged and discounted cost of treatment of the corresponding stage of BC.

Sensitivity analysis

We conducted 25 different one-way sensitivity analyses. First one is a sensitivity analysis based on the coverage rate observed under the MSP. For this purpose, we used 30%, 50%, 71%, 90% and 100% coverage rates to assess how such diverse screening scenarios can affect our outcomes. Performing second sensitivity analysis, we assessed how different values of a statistical life can change the benefits of mammography. We used such values of VSL as 500,000, 1,000 000, 1,200 000, and 2,000 000 USD. We also conducted sensitivity analysis based on the stage distribution and then assessed the impact of different discount rates on financial outcomes. Therefore, this sensitivity analyses consider scenarios where benefits of screening are much smaller than what was shown in our base case. In addition, we used one-way deterministic sensitivity analyses varying the average cost of treatment from 10,000 to 30,000 USD.

Results

Health outcomes and stage distribution

During 2016, the MSP detected 830 BC cases: 60% diagnosed as stage I; 25% as stage II; 15% as stage III; and 5% as stage IV. The distribution of BC cases among unscreened women showed that around 30% of them developed stage I; 30% stage II; 25% stage III; and 15% stage IV. Table 3 includes survival rates and stage distribution observed among screened and unscreened population.

5-year survival analysis

Table 3 demonstrates proportions of lives saved among screened and unscreened population. We estimated the proportions of lives saved for screened and unscreened population. The table demonstrates that 5-year survival rates for the screened group is about 80%, while it is 65% for the unscreened cohort. Therefore, we can say that 5 years after diagnosis, 80% of women in the screened cohort will survive, whereas only 65% of women will live more than 5 years in the unscreened cohort.

Table 3. Proportion of lives saved

Stage	5-year survival	Distribution Screened	Distribution Unscreened	Cohort 5-year survival		Difference
				Screening	No screening	
Stage I	95%	60%	30%	0.57	0.285	
Stage II	70%	25%	30%	0.175	0.21	
Stage III	50%	10%	25%	0.05	0.125	
Stage IV	22%	5%	15%	0.011	0.033	
Total				0.806	0.653	0.153

Note: Based on 5-year survival rates and stage distribution of BC diseased women in both cohorts we estimated overall difference in survival rates between two groups.

Life Years Saved

Tables 4 and 5 are based on median survival rates and BC stage distribution in both groups. The analysis showed that treatment of screened women saved 6,437 LYs. Whereas treatment without mammography saved 5,271 LYs. Hence, in 2016, the MSP gained 1,166 life years more than the breast clinical examination. Therefore, to increase the number of life years gained due to mammography, its coverage rate should be considered among our most central public health concerns.

Table 4. Median survival rates and LY saved by the MSP in each stage in the screened cohort.

Stage of BC	Median Survival (years)	Number of women	LY saved
Stage I	9	498	4,482
Stage II	7	208	1,456
Stage III	5	83	415
Stage IV	2	42	84
Total			6,437

Table 5. Median survival rates and LY saved by the MSP in each stage in the unscreened cohort.

Stage of BC	Median Survival (years)	Number of women	LY saved
Stage I	9	249	2,241
Stage II	7	249	1,743
Stage III	5	208	1,038
Stage IV	2	125	249
Total			5,271

Quality-Adjusted Life Years

To estimate the number of QALYs gained per woman, her quality of life has been multiplied by her life expectancy. In other words, a woman with stage I BC aged 50 has quality of life 0.75 and 28 years of life expectancy, which yields 21 QALYs. However, the number of women aged 50 with first stage of BC is 83, which means that the number of saved QALYs for this cohort is 1746 (21*83). Tables 6-11 present estimations of QALYs saved in the screened cohort.

The total number of QALYs among unscreened cohort has been estimated by calculating average quality of life in each stage of BC, multiplied by 26, which is the average life expectancy of women at the age 50-60. (Table 13)

Total number of QALYs gained due to screening in 2016 was 14,250 (Table 12). However, without screening, BC treatment led to savings of 13,432 QALYs. Thus, in 2016 screening saved additionally 818 QALYs.

Table 6. QALYs estimates for screened women with BC aged **50**

Stage of BC	Stage I	Stage II	Stage III	Stage IV	Total
QoL	0.75	0.7	0.65	0.59	
QALYs	23	20	18,3	16,6	
Number of cases	83	35	14	7	
QALYs per cohort	1,746	677	256	116	2,795

Table 7. QALYs estimates for screened women with BC aged **52**

Stage of BC	Stage I	Stage II	Stage III	Stage IV	Total
QoL	0.70	0.64	0.60	0.54	
QALYs	19.5	18	16,7	15,0	
Number of cases	83	35	14	7	
QALYs per cohort	1,620	631	234	105	2,590

Table 8. QALYs estimates for screened women with BC aged **54**

Stage of BC	Stage I	Stage II	Stage III	Stage IV	Total
QoL	0.64	0.59	0.54	0.48	
QALYs	18	17	15,2	13,5	
Number of cases	83	35	14	7	
QALYs per cohort	1,493	578	213	95	2,378

Table 9. QALYs estimates for screened women with BC aged **56**

Stage of BC	Stage I	Stage II	Stage III	Stage IV	Total
QoL	0.74	0.66	0.60	0.51	
QALYs	17.5	14.2	14.2	12.2	
Number of cases	83	35	14	7	

QALYs per cohort	1,454	551	199	85	2,289

Table 10. QALYs estimates for screened women with BC aged **58**

Stage of BC	Stage I	Stage II	Stage III	Stage IV	Total
QoL	0.68	0.6	0.54	0.45	
QALYs	16	14.2	12.7	10.7	
Number of cases	83	35	14	7	
QALYs per cohort	1,330	499	178	75	2,081

Table 11. QALYs estimates for screened women with BC aged **60**

Stage of BC	Stage I	Stage II	Stage III	Stage IV	Total
QoL	0.75	0.7	0.65	0.59	
QALYs	23	20	18,3	16,6	
Number of cases	83	35	14	7	
QALYs per cohort	1,746	677	256	116	2,116

Table 12. Total number of QALYs saved by the MSP in the screened cohort with BC

Age	50	52	54	56	58	60	Total
QALYs gained	2,795	2,590	2,378	2,289	2,081	2,116	14,250

Table 13. QALYs for not-screened cohort

Stage of BC	QoL	QALYs/woman	QALYs/cohort
Stage I	0.7	18	4,505
Stage II	0.64	17	4,146
Stage III	0.58	15	3,143
Stage IV	0.51	13	1,637
Total			13,432

Value of a Statistical Life Year

VSL in Kazakhstan was estimated by the next formula:

$$\text{VSL target} = \text{VSL base} * (\text{Income target} / \text{Income base})^{\text{elasticity}}$$

We used VSL and income in Russia as base. Average VSL in Russia is equal to 1.6 million USD. [21] Average monthly income in Kazakhstan in 2016 amounted to 450 USD, while in

Russia it was around 600 USD. [38, 39] Elasticity equal to “1” was used, since changes in income leads to proportionate changes in VSL.

Therefore: $VSL_{kz}=VSL_{rs}*(Income_{kz}/Income_{rs})$

$$VSL_{kz}=1,600\ 000*(450/600) = 1,200\ 000\ USD$$

The VSL is usually estimated at the average age, which is 29.3 years for Kazakhstan. [22]. At the same time, the total life expectancy of women aged 50-60 is about 76 years, thus, 46 years after the average age. With a 4.8% social discount rate over 46 years, the average VSLY in Kazakhstan is estimated to be 65,018 USD.

To assess the savings due to the MSP in terms of VSL, we multiply the VSLY estimate by the number of QALYs saved: 65,018 *818 QALYs = 53,184,724 USD.

Thus, with an additional budget of 2,708,953 USD in 2016, mammography saved the value of life estimated for 53,184,724 US dollars.

Table 14. Value of Statistical Life

VSL in Kazakhstan	$ 1,200,000
VSLY in Kazakhstan	$ 65,018
VSL saved by the MSP	$ 53,184,724

Cost Savings for Treatment

Tables 15-20 presents the evaluation of total treatment costs for screened and unscreened cohorts, based on the costs of treatment per stage and the stage distribution of BC cases detected by screening in 2016. To estimate the average cost of treatment per screened and unscreened women we developed a model based on the natural history of breast cancer (tables 16-18). Therefore, since unscreened women do not know about their disease, they are likely to develop advanced BC stages over a 11-year period, from 50 to 60 years of age.

The average cost of treatment of screened women has been also estimated based on cost of treatment per woman and stage distribution (Table 15). All costs have been discounted with 4.8% rate for 11 years (50-60 years).

Table 19 shows that in 2016 the average discounted cost of treatment **per screened woman** with BC was 12,917 USD, while table 20 shows the average discounted cost of treatment **for an unscreened woman** with BC 16,221 USD.

To estimate the total cost of treatment per cohort we multiply these numbers by 830. Therefore, total cost of treatment per screened cohort was 10,721,883 USD, while for unscreened group it was estimated to be around 13,463,857 USD, what means that mammography screening saved 2,708,953 USD.

Table 15. Costs of treatment and stage distribution of screened cohort in the Republic of Kazakhstan.

Stage of BC	Cost of treatment (USD)	Number of women
Stage I	5,000	498
Stage II	30,000	208
Stage III	36,000	83
Stage IV	40,000	42

Note: As screened women are aware of their disease, they undergo timely treatment, thus, preventing BC move to more advanced stages.

Tables 16-18. Costs of treatment and stage distribution of unscreened cohort in the Republic of Kazakhstan.

Table 16. Year 1 to 3 treatment

Stage of BC	Cost of treatment (USD)	Number of women
Stage I	5,000	498
Stage II	30,000	208
Stage III	36,000	83
Stage IV	40,000	42
Average cost	**16,123**	

Table 17. Year 4 to 7 treatment

Stage of BC	Cost of treatment (USD)	Number of women
Stage I	5,000	374
Stage II	30,000	249

Stage III	36,000	125
Stage IV	40,000	83
Average cost	**20,650**	

Table 18. Year 8 to 10 treatment

Stage of BC	Cost of treatment (USD)	Number of women
Stage I	5,000	249
Stage II	30,000	249
Stage III	36,000	208
Stage IV	40,000	125
Average cost	**25,500**	

Note: As unscreened women do not know about the progression of BC, the development of the disease continues over the whole period of time (50-60 years), thus, moving from early to advanced stages making treatment more expensive every year.

Table 19. The discounted average cost of treatment for screened group with BC

Age	50	52	54	56	58	60
Average cost of treatment (USD)	16,123	16,123	16,123	16,123	16,123	16,123
Present value of treatment (USD)*	16,123	14,679	13,365	12,169	11,080	10,088

*4.8% discount rate was applied
Average cost of treatment per screened woman also includes the cost of screening per one woman

Table 20. The discounted average cost of treatment for unscreened group with BC

Age	50	51	52	53	54	55	56	57	58	59	60
Average cost of treatment (USD)	16,123	16,123	16,123	20,650	20,650	20,650	20,650	20,650	25,500	25,500	25,500
Present value of treatment (USD)*	16,123	15,384	14,679	17,940	17,118	16,334	15,586	14,872	17,524	16,772	15,956

*4.8% discount rate was applied
Average cost of treatment per unscreened woman also includes the cost of consultation and clinical examination

Incremental Cost-Effectiveness Ratio

Screened cohort	
Total costs	16.1
Screening costs	5.4
Diagnosis and treatment costs	10.7
QALYs gained	14,250
Unscreened cohort	
Total Costs	13.4
Screening costs	0
Diagnosis and treatment costs	13.4
QALYs gained	13,432
Difference (Screened – Unscreened)	
Total costs (Million USD)	2.7
Screening costs	5.4
Diagnosis and treatment costs	-1.6
QALYs	818
ICER (USD/QALY)	3,311

We already estimated that mammography additionally saved 818 QALYs, but to assess ICER we also need to estimate the difference between costs per screened and unscreened women who had breast cancer.

To assess the cost of the MSP we incorporated the total cost of screening itself and expected cost of treatment of 830 diseased women, which amounted to 16,172,811 USD. Total treatment cost of screened woman equals USD 10,721,883 and screening cost equals USD 5,450,928.

Cost of treatment of the unscreened group amounted to 13,463,857 USD (Table 21). Thus, the MSP gained 818 QALYs with an additional budget of 2,708 953 USD. Therefore, ICER of the MSP in 2016 amounted to 3,311 USD per QALY gained, which is less than the national annual GDP per capita in Kazakhstan, which in 2016 was 7,510 USD. According to the WHO policy, the ICER less than the national annual GDP per capita is considered highly cost–effective. [23]

Table 21. ICER of the MSP with 4.8% discount rate (monetary values in USD millions)

Discussion

Mammography screening has proven to be effective in many developed countries. However, the cost-effectiveness of screening programs in developing countries such as Kazakhstan has not been widely studied. To our knowledge, this is the first published health economics analysis of thebreast cancer screening program in Kazakhstan, which began in 2008.
It is known that in countries with established screening programs more cases of breast cancer are diagnosed at earlier stages compared to countries that did not introduce population-based screening.

Mammography has proven to decrease breast cancer mortality, with a population-based sensitivity of up to 80% and specificity 83% (mammograph "Mammonat 3000 NOVA"). One of the indicators of effectiveness of screening is a constant decrease of rates of BC cases at advanced stages (III-IV). In Kazakhstan, mammography led to a shift in the stage distribution of breast cancers in a way that a smaller quantity of cases were diagnosed at stages III and IV. Concurrently, there has been a major increase in the number of breast cancers at Stage I.
We conducted an extensive sensitivity analysis and found that for the majority of scenarios the ICER would stay below the cost-effectiveness threshold.

LYs saved is a relatively simple and transparent measurement of population health. Our analysis shows that mammography saved 1,229 life years. However, the estimate LY saved is often criticized as it ignores changes in health state in comparison with QALYs. Our research shows that in 2016, mammography additionally saved 818 QALYs when compared to no screening scenario. However, the QALY measurement itself cannot be judged upon about the effectiveness of health programs, for this purpose incremental cost-effectiveness ratios are used. Analysis of ICER showed that the MSP in Kazakhstan is very cost effective.

Main objective of this research was not only to assess health outcomes associated with screening, but, also to evaluate the economic aspects and financial justification of using this early detection method in resource-constricted settings. Financial outcomes that we used are ICER, VSL and cost savings for treatment. The study showed that despite the high cost of the program, mammography leads to substantial savings due to prevention of developing advanced stages, thus, cheaper treatment. We used the value of a statistical life to assess the social impact of screening. The VSL estimate showed that the MSP might lead to substantial social savings.

The consequences of late diagnosis of BC are lower survival, higher morbidity, and higher costs of care, resulting in disability and avoidable deaths. Early mammography screening is a vital public health strategy in all settings since it improves outcomes by detecting cancer at the earliest stages.

Because of assumptions and uncertainties in our study we performed an extensive sensitivity analysis, which showed that mammography screening in Kazakhstan is cost effective in the majority of scenarios remaining below the triple GDP per capita threshold. After the program was launched in Kazakhstan, breast cancer mortality rates among screened women has constantly decrease. In the USA mammography led to 23% decline of mortality rates from breast cancer, while in Sweden such rates dropped by 31% [24]. Such decrease in mortality may also be expected in Kazakhstan under higher screening rates.

Strengths

To our knowledge, this is the first published research on the effectiveness of the mammography program in the Republic of Kazakhstan. We used non-monetary and monetary measurements to provide a comprehensive and pervasive picture of the effectiveness of the program to patients, physicians and policy-makers.

The study includes both cost-effectiveness and benefit-cost analysis to assess health outcomes and financial aspects of the screening program using five measurements: LYs, QALYs, ICER, VSL and cost savings for treatment.

Another strong side of this paper is that QALYs were adjusted for both, time of treatment of different BC stages and natural decrease of quality of life over time. Also, detailed data of 5-year survival and stage distribution allowed us to estimate health and financial outcomes more precisely and proved that a nationwide biennial mammography screening policy between ages 50-60 is highly cost-effective.

Limitations

Our analysis has some limitations that should be considered. We have chosen to analyze screening from the perspective of the Ministry of Health, which is why our research does not take into account personal cost of breast cancer, such as salary loss, costs of transportation from rural areas, costs of medicine, etc. In addition, screening itself may cause non-monetary harms like overdiagnosis or false-positive results what may lead to unnecessary treatment and radiation. Estimating such harms would contribute to the comprehensive analysis of breast cancer screening program. Secondly, with such limited data available, we assumed equal distribution of BC cases among age groups. Another assumption that had to be made because of scarce data is that probabilities of each cancerous stage is independent of age. Lastly, we did not conduct standardized survey about the quality of life of women with BC, rather obtained them from the literature review.

Literature Review

Such databases as Medline, PubMed, Cochrane Library, and Up-to-date were utilized using PICO method (Table 22) to find papers with health and financial outcomes relevant to the breast cancer screening program.

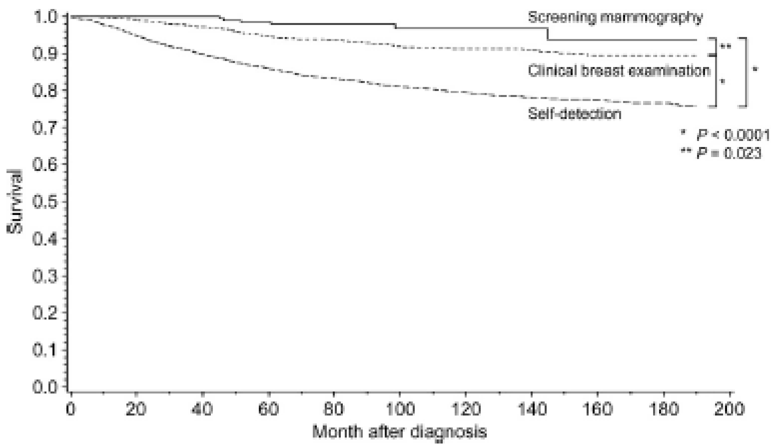
Inclusion and exclusion criteria have been applied. Only Research in English has been chosen for our review. Economic analyses of other diagnostic tools for BC and studies with young population were excluded.

Table 22. Search terms

Population	Women aged 45-69
Intervention	Mammogrpahy/Breast cancer screening
Comparator	No screening
Outcome	Cost-effectiveness/cost-utility/cost-benefit

In the study called "Effect of screening mammography on breast cancer survival in comparison to other detection methods: A retrospective cohort study" [28] authors used Kaplan–Meier survival curves for screening mammography, clinical breast examination, and self-detection. Figure 2 demonstrates that women who underwent mammography have 5-year survival rate equal to 98.3%, while clinical examination and self-detection, survival rates amounted to 94.3%, and 84.8%, respectively (Figure 2).

Figure 2.



In the study called “Cost-effectiveness of population-based mammography screening strategies by age range and frequency”, [29] R. Patakya, N. Phillipsb, S. Peacocka observed increase of annual mortality reduction from 9.7% to 17.0% changing target age from 50-60 to 40-74 year old women with ICER of USD 28,921 per QALY relative to no screening.

In “Cost-Effectiveness and Harm-Benefit Analyses of Risk- Based Screening Strategies for Breast Cancer” by E. Vilaprinyo, C. Forne, M. Carles, M. Sala. [30], authors stated that biennial screening of women aged 50-69 is the most cost-effective strategy, with an ICER of USD 28,921 per QALY, while screening of women aged 70-74 provided little benefit, regardless of screening frequency.

Another study that proves mammography screening to be effective is “Cost effectiveness of the NHS breast screening program” [31] by Paul D P Pharoah and B. Sewell.
They followed 364,500 50-year old women for 35 years, comparing them to a similar cohort of women who received screening every 3 years between ages 50 and 70 and further follow up for 15 years. The screened cohort had 1521 less deaths from breast cancer compared to the unscreened women. Also, screening was associated with 2,040 additional QALYs at cost of £42.5 million—and with ICER of £20,800 per QALY gained. This study represents good value, since it has large sample size, long time to follow up and it is implemented on a solid evidence base.
In their book “Radiation Health Risk Sciences” 2009, [36], professors M.Nakashima and S.Yamashita emphasized that due to high levels of radiation in Eastern Kazakhstan (Semipalatinsk nuclear testing), the incidence of breast cancer in in this area is 1.5 fold higher in comparison with the average rate of breast cancer in Kazakhstan, and 2.5 fold higher than BC incidence in South Kazakhstan. [28] Such differences in the incidence of BC have to be taken in account by policy-makers in the process of developing strategy for the MSP in Kazakhstan.

Breast cancer screening programs should always be monitored and constantly evaluated in terms of cost-effectiveness, economic impact, and improved health determinants. There is always an interplay between potential financial burden and potential health benefits. That is why different screening strategies differ in terms of target age, target population, frequency of screenings, and others.

Recommendations

Based on the research findings and international experience, we developed recommendations for the MSP strategy for local and foreign policy makers. Despite the success of mammography screening, mortality rates from breast cancer in Kazakhstan are still very high with annual incidence of BC in Kazakhstan is about 4,000 women [3]. In 2016, 389,352 women were screened, and 830 of them were detected to have breast cancer. Based on above, it can be said that more than 2,500 women were diagnosed with BC using other means of detection. In other words, in 2016 the MSP detected only 20% of new breast cancer cases. Therefore, we may increase this proportion using international guidelines, which recommend biannual screening of women older than 40 years every two years [24]. However, screening in the age group 40-45 is less cost-effective as the incidence of breast cancer in this age group is low. [25]

The research conducted in Canada showed that the most cost effective strategy for mammography is to screen women aged 40-74 biannually [26]. Experience of such countries as Switzerland and Sweden shows that biannual screening of women aged 50-69 can increase coverage rate to almost 75%. [25]

In the systematic review of the cost-effectiveness of different breast-screening programs, authors reviewed 28 articles from 1993 to 2010. [27] Based on the findings, authors concluded that biennial screening for 50-70 aged women is the most recommended and cost-effective strategy.

Thus, taking into account the above-mentioned evidence, and experience of developed countries, we propose including 45-49 and 60-69 aged women into the target group, thus extending the target population to women aged 45-69. Inclusion of wider age range will likely increase the number of women coming for mammography and decrease the proportion of detected malignant cases. Taking into account differences in BC rates in Kazakhstan we propose to pilot the MSP with above-mentioned changes in Eastern Kazakhstan and also include women aged 40-50 in the target group. It would lead to decline in the proportion of detected malignant forms since the onset of breast tumors in most cases takes place among women in their 40s. Additionally, it would lead to large financial savings since more cases would be detected on earlier stages.

Conclusion

Cost effectiveness analyses presented in our paper can contribute to the development of effective breast cancer-screening policies to guide the process of adequate distribution of limited resources and finances. Taking into account distinguishing economic and demographic characteristics, such research can assist governments of developing countries to decide which screening strategy to implement.

It can be said that the mere presence of breast screening-program is not enough. Instead, constant monitoring, evaluation and control of the implementation should be continuously performed. These will help to find a golden standard, a compromise, and a trade-off for fair distribution of scarce resources and limited finances on one hand and increase of early-detected breast cancers on the other hand.

Desired outcome measure in our benefit-cost analysis: number of quality-adjusted life years saved (QALYs), life years saved, cost saving per treatment, and value of a statistical life.

Thus, based on the findings and data provided, referring to the published research articles, and based on their results, it can be concluded that the existing breast-screening program is already quite efficient. Moreover, it has to be taken into account that women in Kazakhstan tend not to visit their family physician right after the first signs of cancer or any disease due to specific population-wide national set of mind.

Considering reviewed studies, it can be deduced that there are no publications in Kazakhstan regarding this important topic. That is why researchers and public health professionals should not underestimate the importance of evaluating screening programs in terms of their cost-effectiveness. This will help to make necessary adjustments and improve further decision-making determined to increase proportion of early-screened breast cancer cases and help women to undergo treatment as early as possible.

In conclusion, it can be said that more research should be conducted on cost-benefit, cost-effectiveness, and cost-utility analyses for screening programs in Kazakhstan. Mammography screening is a complex public health approach that needs additional resources, infrastructure and coordination. Such programs should be implemented only when effectiveness is proved and resources are sufficient to justify the effort and costs of screening.

Finally, when planned efficiently, properly financed and implemented, screening can reduce mortality and the risk of developing late stages of breast cancer by 50%. [34]

Sensitivity analysis

To assess the impact of different variables on health and financial outcomes we conducted 25 one-way sensitivity analyses. Regardless of the discount rate applied, the organized breast cancer screening dominated no screening scenario. Even with the attendance rate equal to 30% the ICER is still lower than the GDP per capita threshold. Higher attendance rates in mammography resulted in lower ICERs.

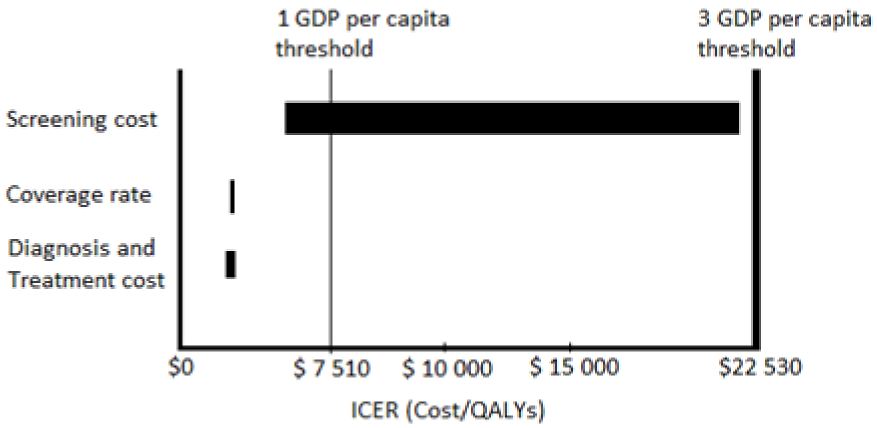
Changing average cost of treatment did not affect the domination of mammography. As the cost of treatment and the number of life years saved rise, the ICER decreases.

The greatest impact on ICERs was observed with the rise of the average cost of screening per woman. Its increase to 50 USD moves ICER to the triple GDP per capita threshold.

Changes in the stage distribution of BC cases from earlier to advanced stages also increases ICER, decreases the number of life years saved, and even may result in dominance of no screening scenario. Despite variations in coverage rates, the MSP dominated over no screening scenario.

If we restrict the VSL in Kazakhstan to 100,000 USD, we see a decrease in the benefits of the MSP. However, such restriction does not lead to financial ineffectiveness of the MSP.

Figure 1. Tornado diagram.



The diagram summarizes the results of one-way sensitivity analysis. The x-axis represents the ICER per QALY gained by the MSP over no screening. The y-axis represents the parameters that were changed and affected the ICERs.

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Abstract

Background: We conducted cost-effectiveness and benefit-cost analysis of the organized breast cancer-screening program in the Republic of Kazakhstan. The program has been introduced in 2008, until then, clinical breast examination and self-referral were the only ways of diagnostic of breast cancer.

Objectives: to evaluate health and financial outcomes of the organized mammography-screening program comparing with clinical breast examination without screening.

Methods: a cohort of 830 women, which has been detected to have breast cancer by mammography, was compared with 830 women, which has been diagnosed with breast cancer by other diagnostic means. Financial and health outcomes have been estimated using such measurements as life years saved, quality-adjusted life years, incremental cost-effectiveness ration, and value of statistical life year. Sensitivity analyses were performed to assess uncertainty.

Results: compared to clinical breast examination, an organized mammography yielded additional 1,229 life years and 818 quality-adjusted life years. Since the incremental cost-effectiveness ratio was equal to 3,311 USD per QALY and less than GDP per capita in Kazakhstan, breast cancer screening can be considered as highly cost-effective. Moreover, mammography led to cost savings associated with treatment. Value of a statistical life estimate demonstrated that social savings by mammography were equal to 53,184 724 USD.

Discussion: The mammography program has proved to be an efficient use of limited resources in Kazakhstan. This health-economic analysis showed that the mammography is cost-effective and financially beneficial alternative to not using screening. Sensitivity analysis showed that the mammography remains cost-effective in a majority of scenarios.

Keywords: breast cancer, mammography screening, cost-effectiveness analysis, benefit-cost analysis.

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