ABSTRACT
of Assem Yakubbekovna Toguzbayeva's Dissertation on the topic: Medical and Organizational Foundations for the Breast Cancer Burden Reducing and Ways to Improve Screening in Kazakhstan, submitted for the degree of Doctor of Philosophy (PhD) in the specialty 6D110200 – Public Health

Urgency of the Issue

Breast cancer (BC) remains one of the most significant health problems both globally and in Kazakhstan. According to statistics, about 1.7 million new cases of breast cancer are diagnosed annually in the world, which makes it the most common malignant neoplasm among women. The high prevalence of the disease is due to a variety of factors, including hormonal, genetic, and environmental aspects. Despite significant progress in diagnosis and treatment, breast cancer continues to be the leading cause of cancer-related deaths among women, claiming about 500,000 lives annually.

The problem is particularly acute for countries with limited resources, where mortality rates from breast cancer significantly exceed those in high-income countries. This phenomenon is explained by the insufficient availability of modern diagnostic methods, the lack of specialized cancer centers, as well as the late seeking medical advice by patients. Kazakhstan, being a country with a mixed healthcare system, faces serious challenges in the field of early detection and effective treatment of this disease. Despite ongoing government programs, survival rates for breast cancer in Kazakhstan remain lower than in developed countries, due to both limited availability of high-tech diagnostic methods and insufficient public awareness of the importance of regular screening.

Modern approaches to the diagnosis of breast cancer include screening programs based on mammography, clinical examinations, molecular genetic studies, as well as the use of minimally invasive diagnostic methods. However, their successful implementation in Kazakhstan is accompanied by a number of problems, including the low commitment of the population to screening, a shortage of qualified specialists and insufficient technical equipment of medical institutions. The importance of improving the early detection system is due to the need to develop new screening strategies adapted to the country's social and economic structure and the real needs of the female population.

Early detection of breast cancer is a key factor in reducing mortality and improving the prognosis of the disease. According to epidemiological studies, the five-year survival rate in the localized form of breast cancer reaches 99%, while in the metastatic stage it rapidly decreases to 26% [9]. This highlights the necessity to increase the coverage of population with screening programs, especially among women over 40 years of age, who are in the main risk group. In modern cancer research, much attention is paid to the development and implementation of new diagnostic and treatment methods, such as targeted therapy, personalized medicine and chemoprophylaxis, which opens up additional opportunities to reduce the burden of the disease.

This study is aimed at solving one of the key tasks of oncology – reducing the breast cancer burden by improving the organization of screening programs and increasing their effectiveness. It is expected that the results obtained will help optimize

the existing screening system in Kazakhstan, make it more accessible, increase the coverage of target groups and improve the quality of life of patients. The implementation of modern technologies and organizational solutions into screening programs may not only increase early detection of breast cancer, but also significantly decrease mortality rates, which is consistent with global strategic goals in the fight against cancer.

Goal of the study

To develop medical and organizational approaches to reducing the breast cancer burden in Kazakhstan based on the study of epidemiological data and improvement of screening programs to increase their effectiveness and coverage.

Objectives of the study

1. To carry out complex epidemiological analysis of breast cancer morbidity in Kazakhstan taking into account age, regional and stage characteristics. To identify the key determinants of morbidity growth and assess their relative contribution.

2. To assess the impact of implementation of screening programs to early detection of breast cancer in various regions of Kazakhstan. To analyze the coverage of target age groups and increment rate of detectability at early stages depending on the program implementation.

3. To analyze the dynamics and regional specific features of breast cancer mortality in the Republic of Kazakhstan over the specified period, to identify age trends, regional differences and possible causes of persistent mortality.

4. To assess demographic, social and economic losses from breast cancer through the analysis of lost life potential, highlighting age and territorial differences, and to substantiate the possibilities of its use for strategic planning in oncology.

Study methods

To achieve the goal of the study, a set of qualitative and quantitative methods will be used to study in detail the dynamics of breast cancer morbidity and mortality in Kazakhstan, as well as to identify key factors influencing the epidemiological situation.

Quantitative methods:

1. Epidemiological method (retrospective review) will allow analyzing the dynamics and structure of breast cancer morbidity and mortality for the period 2009-2018 using official statistical data from the Ministry of Health and the Bureau of National Statistics of the Republic of Kazakhstan.

2. Component analysis will provide quantitative assessment of the impact of individual factors, such as changes in the age structure, the size of the female population and the risk of the disease, on the dynamics of morbidity.

3. Age standardization will allow for an objective comparison of morbidity and mortality rates among regions and different age groups, minimizing the impact of the age structure of the population.

Qualitative methods:

1. Analysis of medical documentation and reports of regional cancer detection centers will allow determining regional specific features of organization and effectiveness of breast cancer screening and prophylaxis programs.

2. Expert assessment will allow collecting opinions of experts in the field of oncology and public healthcare about reasons of regional and age differences in the

morbidity and mortality rates as well as determining promising directions for prophylaxis improvement.

The combined use of the specified methods will ensure the reliability and validity of the results obtained, as well as provide an opportunity to develop scientifically sound practical recommendations for reducing the breast cancer morbidity and mortality in Kazakhstan.

Subject of the study

Female population of Kazakhstan as the target group for prophylaxis and early detection of breast cancer.

Topic of the study

Breast cancer in the context of epidemiological characteristics and effectiveness of screening programs in the public healthcare system.

Provisions to be defended

1. Breast cancer morbidity and mortality in Kazakhstan have pronounced age and regional characteristics, which confirms the need to develop targeted prophylactic and organizational measures, including increased screening in regions with the highest risk.

2. The effectiveness of current screening programs varies depending on the region that is conditioned by differences in availability of medical services and coverage of target groups. To increase screening effectiveness, it is necessary to consider regional, age and social characteristics of female population.

3. Social and economic breast cancer burden measured through the lost life potential analysis is most noticeable among the working-age female population. This highlights the importance of early detection of the disease and the need to improve organizational and prophylactic measures.

Practical relevance of the study

The data obtained on the age groups with the highest risk of breast cancer make it possible to develop targeted prophylaxis programs aimed at women in the age categories of 50-69 years, where there is peak morbidity.

The identified regional specific features, such as the highest increase in morbidity in the Karaganda and North Kazakhstan regions, provide grounds for strengthening screening activities in these regions, including increased availability of mammography and training of medical personnel.

Results of morbidity dynamic analysis may apply for optimization of current screening programs, including reduction of intervals between examinations for women from high risk groups and implementation of modern diagnostic methods such as ultrasound investigation and biopsy.

The obtained data about age and regional specific features of breast cancer mortality may be used for the development of special prophylactic and diagnostic activities aimed at reduction of mortality in the most vulnerable age groups and regions.

The assessment of lost life potential allows healthcare authorities to more accurately plan resources and efforts to reduce the social and economic burden of the disease, especially among the working-age female population.

The developed mortality cartograms provide a visual tool for visualizing regional differences in mortality rates, which facilitates decision-making on the priority allocation of resources and optimization of medical programs.

The results of the chapter can be implemented into national cancer control programs, including improvement of screening activities and increasing availability of special medical aid that promotes improvement of general effectiveness of the healthcare system in Kazakhstan.

Scientific novelty

1. For the first time, a comprehensive analysis of the dynamics of breast cancer morbidity in Kazakhstan has been carried out, taking into account age and regional aspects over a long period of follow-up. The study has revealed key factors influencing changes in the morbidity rate, such as the age structure of the population, the size of the female population and the risk of disease.

2. Regional specific features of the disease have been identified, including regions with the highest rates of increase and decrease. These data emphasize the need for a differentiated approach to prophylaxis and screening programs, depending on geographical specific features.

3. Component analysis of factors contributing to the increase in morbidity has been carried out. This made it possible to assess the contribution of demographic changes and risk factors, as well as to identify the age groups showing the greatest increase in morbidity.

4. The effectiveness of screening programs in different regions of the country has been analyzed. The results revealed both positive trends in early detection of the disease and the need to improve programs in a number of regions.

5. For the first time, the detailed analysis of age structure of breast cancer mortality in Kazakhstan has been carried out which made it possible to identify the main age groups with a high mortality rate and establish trends in the average age of persons died during the study period.

6. Regional differences in the mortality levels have been determined, including the identification of the most vulnerable regions such as Almaty, East Kazakhstan and Pavlodar, which underlines the importance of a territorial approach to the prophylaxis and treatment of the disease.

7. For the first time, a quantitative assessment of the lost life potential caused by breast cancer mortality has been performed, with an emphasis on the working-age groups, which makes it possible to more accurately assess the social and economic burden of the disease.

8. Mortality cartograms have been developed based on crude and standardized markers that visualize the spatial distribution of mortality and identify key regions for prioritizing prophylaxis.

The results obtained contribute to the understanding of regional and age-specific mortality, as well as create a scientific basis for the development of targeted programs to reduce breast cancer mortality in Kazakhstan.

Practical recommendations:

1. To improve prophylaxis. To organize awareness-raising campaigns for women over 40 years of age, with an emphasis on the importance of regular screening and early detection of breast cancer. To strengthen awareness-raising in low-awareness regions, including rural areas.

2. To expand screening. To increase the coverage of women aged 30-44 years

with screening programs, strengthen control over their quality and technical equipment. To create mobile screening centers for remote areas.

3. To improve diagnostics and treatment. To enlarge access to high-tech equipment and modern treatment methods. To create national data base of breast cancer patients in order to improve treatment coordination.

4. Yo develop cancer centers. To increase funding for regional cancer centers in order to equip them, attract specialists, and improve cooperation with central clinics.

5. Rehabilitation. To introduce comprehensive rehabilitation programs for women after treatment, including physical, psychological and social assistance. To create rehabilitation centers in each region.

6. Social support. To develop measures for working-age women, including labor rehabilitation and material assistance. To strengthen interagency cooperation to reduce the lost life potential.

7. Optimization of national programs. To regularly evaluate the effectiveness of existing programs and adjust thereof based on data. To strengthen the training of primary care physicians and the financing of breast cancer research.

Personal Contribution of the Doctoral Candidate

– A comprehensive epidemiological analysis of breast cancer incidence in Kazakhstan was conducted, taking into account age, regional, and stage-specific characteristics. Key determinants of the incidence increase were identified, and their relative contribution was assessed.

– The impact of screening program implementation on the early detection of breast cancer in various regions of Kazakhstan was evaluated. Coverage of target age groups and the growth rates of early-stage detection were analyzed depending on program implementation.

– The dynamics and regional characteristics of breast cancer mortality in the Republic of Kazakhstan over the specified period were analyzed, revealing age-related trends, regional differences, and possible causes of the persisting mortality.

– Demographic and socio-economic losses from breast cancer were assessed through the analysis of lost life potential, highlighting age and territorial differences, and substantiating the possibilities of its use for strategic planning in oncology.

Conclusions

In the period 2004-2023, 80,490 new cases of breast cancer were registered in Kazakhstan. The morbidity showed a steady increase from 39.3±0.7 to 54.4±0.7 cases per 100,000 female population, with an average growth rate of T=+2.0% per year. The highest morbidity rate was recorded in the age groups of 60-64 years (152.7±6.0) and 65-69 years (161.9±9.0 per 100,000). The main contribution to the increase in morbidity was made by an increase in the risk of disease ($\sum\Delta R$=+10.10; 66.8%), age-related population changes ($\sum\Delta A$=+4.32; 28.5%) and their cumulative effect ($\sum\Delta RA$=+0.71; 4.7%).

1. A study of the effectiveness of mammalogical screening in the 40-69 age group in Kazakhstan in 2004-2023 showed an increase in the morbidity from 97.9±2.0 to 125.6±2.6 cases per 100,000 female population (an increase of +27.7 per 100,000;

T=+1.7%). This group accounted for 42.9% of all new breast cancer cases. The largest increase in morbidity due to increased detection at early stages was registered in the Atyrau (+55.04), Kostanay (+41.76) and East Kazakhstan (+43.41) regions. This indicates the effectiveness of screening programs in a number of regions. At the same time, low growth remains in some regions, which indicates the need to strengthen early detection measures and increase screening coverage.

2. The development of prophylactic and diagnostic measures should take into account the identified age and regional characteristics of morbidity. An increase in the number of breast cancer cases among younger women (30–44 years old), especially in groups 30–34 and 40–44 years old (T=+1.1% and T=+1.5%, respectively), may be associated with more aggressive forms of the disease, which requires increased early diagnosis and follow-up in this category. Regional differences in the growth rate and coverage with screening programs underline the necessity to strengthen medical infrastructure, especially in rural and hard-to-reach areas.

3. In the period 2004-2023, a steady decrease in breast cancer mortality was noted in Kazakhstan. The crude marker decreased from 16.6±0.7 to 10.2±0.3 per 100,000 female population ($T_{loss}=-2.8\%$; R²=0.9144), and the standardized marker decreased from 16.1±0.5 to 8.9±0.3 per 100,000 ($T_{loass}=-3.4\%$; R²=0.9304). The average age of died persons increased from 60.0 years in 2004 to 60.6 years in 2023 indicating an increase in life expectancy and the effectiveness of treatment. The highest mortality was registered in the age groups of 70–74 (67.6±4.2), 75–79 (62.7±4.1) and 80–84 years (72.3±6.0 per 100,000), confirming the need for age-based prophylactic and therapy strategies.

4. The analysis of regional differences showed a pronounced variability in mortality from breast cancer between the regions of Kazakhstan. The highest proportion of deaths was recorded in Almaty (14.1%) and East Kazakhstan region (11.5%), the lowest in the Mangystau (1.8%) and Atyrau (2.4%) regions. The most stable and significant decrease in standardized mortality was noted in the Pavlodar ($T_{loss}=-4.7\%$), Kostanay (-4.3%) and Karaganda regions (-3.0%) with high approximation coefficients ($R^2>0.85$). At the same time, there is unstable dynamics and low predictability of trends (R²<0.4) in the Atyrau ($T_{loss}=-1.6\%$) and Zhambyl ($T_{loss}=-2.4\%$) regions requiring additional analysis and correction of local programs.

6. Calculation of lost life potential as a result of breast cancer mortality for 2004-2023 identified significant demographic burden of the disease. The average annual volume of lost life potential was 15,520 person-years, with a clear downward trend — from 20,318 in 2004 to 15,553 in 2023 (-23.5%). The highest losses were registered among working-age women (40-59 years), especially in the 45–49 and 50–54 age groups. By region, the maximum values of the lost life potential (absolute and relative) are observed in Almaty, East Kazakhstan, Karaganda and Pavlodar regions. The introduction of the lost life potential indicator into the cancer care assessment system is recommended as a tool for strategic planning and prioritization of resources.

The principal results of the dissertation study were reported at the following conferences

International conferences and forums:

• X Congress of Oncologists and Radiologists of the CIS and Eurasia, April 24-

26, 2018, Sochi,
- V St. Petersburg International Oncology Forum "White Nights" (St. Petersburg, 2019)
- The 10th APOCP General Assembly and Scientific Conference (Teheran, Iran, 2020)
- Proceedings 46th Annual Meeting of Korean Cancer Association & 6th International Cancer Conference (Seoul, South Korea, 2020)
- Proceedings 47th Annual Meeting of Korean Cancer Association & 7th International Cancer Conference (Seoul, South Korea, 2021)
- The 81st Annual Meeting of Japanese Cancer Association (Japan, 2022)
- 11th General Assembly of the Asia Pacific Organisation for Cancer Prevention (Kolkata, India, 2022)

Republic scientific events:
- Days of Science of the I.K. Akhunbaev Kyrgyz State Medical Academy (Bishkek, Kyrgyzstan, 2022)

Publications on the topic of the dissertation: Twenty publications were published on the topic of the dissertation, including:
- 5 articles in peer-reviewed international journals included in the Scopus database (Q2 percentiles=57% and above).
- 7 articles in journals recommended by the Committee for Control of Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan.
- 10 theses in the materials of international scientific conferences.
- 1 copyright certificate received in 2022.

The published papers highlight key aspects of the dissertation research, including the epidemiological characteristics of breast cancer in Kazakhstan, the dynamics of morbidity and mortality, the effectiveness of screening programs and the impact of risk factors.

Volume and structure of the dissertation: The dissertation thesis is presented on 139 pages of typewritten text, built according to the traditional principle and consists of an introduction, five sections, discussion of the results, opinion, conclusions, practical recommendations, a list of sources used, including 216 sources. The dissertation is illustrated with tables and figures.