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BREAST CANCER EPIDEMIOLOGY IN KAZAKHSTAN FOR THE PERIOD 2012-2021

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Abstract

Background: Breast cancer (BC) is the most frequent cancer diagnosed in women worldwide, including Kazakhstan. Over the last decade, many factors influenced changes in the epidemiological indicators of BC in in Kazakhstan. This study aimed to explore the epidemiological data of BC from 2012 to 2021 in Kazakhstan.

Materials and methods: Official statistics on BC were studied for the period 2012-2021 ("Report on patients with malignant diseases", statistical data of the Committee on Statistics of the Ministry of National Economy of the Republic of Kazakhstan). Prevalence, incidence and mortality rates, average growth incidence and mortality rates, the proportion of BC cases detected in the early stage (I) were analyzed retrospectively.

Results: The crude incidence rate (CIR) and age-standardized incidence rate (ASIR) of BC were 48.2 and 44.4 per 100,000 female population respectively. The crude mortality rate (CMR) from BC was 13.9 (95% CI 12.7-15.1) in study period, the age-standardized mortality rate (ASMR) from 2017 to 2021 was 11.2 (95% CI 10.1-12.3).

The highest incidence and mortality rates of BC per 100,000 population were in Pavlodar region (39.2±1.8 and 10.7±0.9). The lowest rates of incidence and mortality of BC were amounted in Turkestan region (11.0±1.1 and 3.5±0.06). The mortality incidence coefficient was 0.28 average and varied by region from 0.21 (Karaganda region) to 0.41 (Zhambyl region). From 2017 to 2021 the proportion of patients diagnosed with BC in stage I was 28.8% and in stage II 55.7%.

Conclusion: The epidemiological situation of BC in Kazakhstan showed a tendency for improvement, with a decrease in the mortality rate and a rise in the incidence rate. During the study period, the identification of patients with stage II breast cancer prevailed. Substantial variability of epidemiological data among the regions of Kazakhstan indicates the necessity of a detailed study of risk factors of BC and the effectiveness of mammographic screening in the regions in order to take impactful healthcare measures.

Keywords: *breast neoplasms, breast cancer, incidence, mortality, early diagnosis, Kazakhstan.*

Резюме

ЭПИДЕМИОЛОГИЯ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ В КАЗАХСТАНЕ ЗА ПЕРИОД 2012-2021 ГГ.

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Актуальность: Рак молочной железы (РМЖ) является наиболее частым онкологическим заболеванием, диагностируемым у женщин во всем мире, в том числе и в Казахстане. За последнее десятилетие на изменение эпидемиологических показателей РМЖ в Казахстане повлияло множество факторов.

Целью нашего исследования было изучение основных эпидемиологических показателей РМЖ в Республике Казахстан (РК) за период 2012-2021г.

Материалы и методы. Для проведения эпидемиологического анализа использованы данные официальных статистических отчетов за период 2012-2021г («Отчет о больных злокачественными заболеваниями», данные Комитета по статистике Министерства Национальной экономики РК). Изучены показатели распространенности,

заболеваемости, смертности («грубые» и стандартизированные по возрасту), средний прирост заболеваемости и смертности, а также доля случаев РМЖ, выявленных в ранней стадии (I).

Результаты. «Грубая» (CIR) и стандартизованная заболеваемость (ASIR) РМЖ составили 48,2 и 44,4 на 100 000 женского населения, соответственно. Средний показатель «грубой» смертности (CMR) за период 2012-2021г составил 13,9 (95% ДИ 12,7-15,1), стандартизированный показатель смертности (ASMR) с 2017 по 2021г. - 11,2 (95% ДИ 10,1-12,3) на 100 000 женского населения. Самые высокие показатели заболеваемости и смертности от РМЖ на 100 000 населения были в Павлодарской области (39,2±1,8 и 10,7±0,9). Самые низкие показатели заболеваемости и смертности от РМЖ отмечены в Туркестанской области (11,0±1,1 и 3,5±0,06). Соотношение смертности и заболеваемости (M/I ratio) в среднем составил 0,28 и варьировал по регионам от 0,21 (Карагандинская область) до 0,41 (Жамбылская область). С 2017 по 2021 г. доля больных с диагнозом РМЖ I стадии составила 28,8%, II стадии – 55,7%.

Заключение: эпидемиологическая ситуация по РМЖ в Казахстане демонстрирует тенденцию к улучшению за счет снижения смертности на фоне роста заболеваемости. За изучаемый период превалировало выявление больных со II стадией РМЖ. Существенная вариабельность эпидемиологических данных по регионам Казахстана свидетельствует о необходимости детального изучения факторов риска РМЖ и эффективности маммографического скрининга в регионах для проведения эффективных лечебно-профилактических мероприятий.

Ключевые слова: *рак молочной железы, заболеваемость, смертность, ранняя диагностика, Казахстан.*

Түйіндеме

ҚАЗАҚСТАНДАҒЫ 2012-2021 ЖЫЛҒА АРНАЛҒАН СҮТ БЕЗІ ОБЫРЫНЫҢ ЭПИДЕМИОЛОГИЯСЫ

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Кіріспе. Сүт безі обыры (СБО) бүкіл әлемде, оның ішінде Қазақстан Республикасында (ҚР) әйелдер халық арасында онкологиялық аурулармен сырқаттанушылық құрылымында жетекші ауру болып табылады. Соңғы онжылдықта ҚР сүт безі обырының эпидемиологиялық көрсеткіштерінің өзгеруіне көптеген факторлар әсер етті.

Мақсаты: Біздің зерттеуіміздің мақсаты 2012-2021 жылдар аралығындағы ҚР сүт безі обырының негізгі эпидемиологиялық көрсеткіштерін зерттеу болды.

Материалдар мен әдістер. Эпидемиологиялық талдау жүргізу үшін 2012-2021 жылдардағы ресми статистикалық есептердің деректері («Қатерлі аурулармен ауыратын науқастар туралы есеп», Қазақстан Республикасы Ұлттық экономика министрлігі Статистика комитетінің деректері) пайдаланылды. Таралу, сырқаттанушылық және өлім-жітім (өрескел және стандартталған) көрсеткіштері, олардың орташа өсуі, ерте кезеңде (I сатысы) анықталған сүт безі обыры жағдайларының үлесі зерттелді.

Зерттеу нәтижелері. Сүт безі обырының өрескел (CIR) және стандартталған сырқаттанушылық (ASIR) 100 000 әйел халыққа шаққанда сәйкесінше 48,2 және 44,4 құрады. 2012-2021 жылдар аралығындағы өрескел өлім-жітімнің орташа коэффициенті (CMR) 13,9 (95% CI 12,7-15,1) 100 000 әйел халыққа шаққанда болды. 2017-2021 жылдарда стандартталған өлім-жітім көрсеткіші (ASMR) 11,2 (95% CI 10,1-12,3) байқалды.

СБО сырқаттанушылық пен өлім-жітімнің 100 000 адамға шаққанда ең жоғары көрсеткіші Павлодар облысында (39,2±1,8 және 10,7±0,9) болды, ең төменгі көрсеткіштері Түркістан облысында (11,0±1,1 және 3,5±0,06) байқалды. Өлім-жітім мен сырқаттанушылық коэффициенті (M/I) орта есеппен 0,28 құрады және аймақтар бойынша 0,21-ден (Қарағанды облысы) 0,41-ге (Жамбыл облысы) дейін өзгерді. 2017-2021 жылдар аралығында сүт безі обырының I сатысы диагнозы қойылған науқастардың үлесі 28,8%, II сатысы – 55,7% құрады.

Қорытынды. Қазақстанда СБО эпидемиологиялық жағдайы сырқаттанушылықтың артуы аясында өлім-жітім деңгейінің төмендеуіне байланысты жақсару тенденциясын көрсетеді. Зерттеу кезеңінде сүт безі обырының II сатысы бар науқастарды анықтау басым болды. Қазақстанның аймақтары бойынша эпидемиологиялық деректердің айтарлықтай өзгермелілігі сүт безі қатерлі ісігінің қауіп факторларын егжей-тегжейлі зерттеу қажеттілігін және тиімді емдеу мен алдын алу үшін аймақтарда маммографиялық скринингтің тиімділігін көрсетеді.

Түйінді сөздер: *сүт безі обыры, сырқаттанушылық, өлім-жітім көрсеткіштері, ерте диагностика, Қазақстан*.

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Introduction

The burden on the healthcare system is growing globally year to year due to cancer incidence and mortality. This both reflects the aging and growth of the population as well as the presence of risk factors for cancer associated with socioeconomic development [15]. It is expected there will be 28.4 million cases of cancer in 2040, a 47% rise from 2020, with a more considerable increase in low- or medium-income (from 64% to 95%) versus high-income countries (from 32% to 56%) countries due to demographic changes. However, this may be further exacerbated by increasing risk factors associated with globalization and a growing economy [23].

Breast cancer (BC) is the most frequent cancer diagnosed in women worldwide, with 2.3 million cases annually [23]. The incidence of BC in the world over the past decade has enlarged, that is associated with an absolute and relative increase in incidence [17]. By 2040, the burden of BC is predicted to raise to more than 3 million new cases and 1 million deaths annually due to population growth and aging alone [7].

Incidence rates for female BC lead in Australia, New Zealand, Western Europe, North America, and Northern Europe (>80 per 100,000 female population), and the lowest rates are registered in Central America, East, and Middle Africa, South and Central Asia (<40 per 100,000 female population) [18]. However, mortality rates for female BC are considerably higher (by 17%) in low- or medium-income countries versus high-income countries (15.0 vs 12.8 per 100,000) [23]. Interestingly, it was shown in previous studies that in Asian countries, the peak age of BC incidence is between 40 and 50 years old, while in western countries, it is between 60 and 70 years old [16, 19]. Later on, Fan L et al. demonstrated that the age at BC onset has risen over time in Asia, probably because of an increase in life span, the introduction of BC screening in women over age 50, and more risk factors that the later generations being exposed [12]. It was to notes that the mortality-to-incidence ratio (M/I), generally used as a comparative measure to identify inequities in cancer outcomes is higher in Asia (0.32) than the world's average (0.28) [25]. The reason for this can be linked to varied approaches in BC therapy and discrepancy in clinical protocols utilizing in the countries with different economic conditions.. Most Asian countries are low- and middle-income countries, where access to effective care is limited [28].

In Kazakhstan, as in many countries, BC ranks first in the structure of malignant neoplasms in women. On average, about 4,000 women are diagnosed with BC and 1,400 patients succumb from BC annually in the country [27]. According to *Shatkovskaya O. et al.,* the number of BC cases registered annually has increased by 46.9% from 2014 to 2019 [22]. In 2008 mammographic screening was introduced for women aged 50-60 years old with the biennial frequency of assessment in Kazakhstan [4]. In 2012 international standards were introduced for BC screening (double reading of mammograms, interpretation in accordance with BIRADS system, monitoring of quality indicators, comparison of detected cases of BC with Electronic Registry of Cancer Patients [2]. In 2017 the age groups eligible for this screening was expanded for women aged 40 to 70 years old [3]. The laboratory diagnostics of BC molecular profile (HR and HER2, Ki 67 markers) have been routinely assessed in Kazakhstan since 2012 [22]. The combination therapy of cyclin-dependent kinase inhibitors with endocrine therapy for HR-/HER+ BC was included in Kazakhstan national guidelines for BC therapy in 2019 [22]. All these factors influenced changes in the epidemiological data of BC in the country. Furthermore, the recent pandemic of COVID-19 affected the mortality and morbidity of BC as well because of disruptions to access to cancer-related services for some time.

Nevertheless, as far as we know, the epidemiological data of BC exceeded the 10-year period have not been published in English since 2013 in Kazakhstan. Thus, the aim of this study is to analyze the epidemiological data of BC during the period 2012-2021 to build a sustainable infrastructure for cancer prevention measures under the changing approaches to BC screening and therapy, and mitigate the impact of adverse and unexpected factors, such as pandemics, etc.

Materials and Methods

Data from official statistical materials regarding cancer were used: "Report on patients with malignant diseases" (form 7 of the Ministry of Health of the Republic of Kazakhstan dated December 22, 2020, No. ҚР DSM-313/2020). The statistical data of the Committee on Statistics of the Ministry of National Economy of the Republic of Kazakhstan on the size and sex-age composition of the population were used as denominators of the female population of Kazakhstan for epidemiological indicators for the study period [1]. Age-specific rates standardized to the world population were estimated utilizing recommendations of the World Health Organization [8]. Standardized indicators were calculated by a direct method for eleven age groups (> 25, 25-29..., 65-69, and ≤70).

The analysis of epidemiological indicators (prevalence, crude and age-standardized incidence rates, crude and age-standardized mortality rates, average growth incidence

and mortality rates, the proportion of BC cases detected in the early stage (I) was carried out using a retrospective study with standard descriptive and analytical methods for periods from 2012 to 2021 (with an interval of 1 year). Extensive, crude and standardized indicators were calculated by utilizing standard techniques according to the generally accepted methodology used in medical statistics. The annual averages (M), mean error (m), 95% confidence interval (95% CI), and average annual upward/downward rates (T%) of incidence and mortality were calculated.

The main formulas used to calculate epidemiological indicators in this work are described in detail in medical statistical manuals and guidelines [6, 11] and briefly presented below:

$$\text{BC prevalence per 100,000 female population} = \frac{\text{No. of cases of BC present in the female population at a specified time (year)}}{\text{No. of female population at that specified time}} \times 100{,}000$$

$$\text{BC incidence rate per 100,000 female population} = \frac{\text{No. of new cases of BC, diagnosed during a reported year}}{\text{avarage annual female population}} \times 100{,}000$$

$$\text{Annual growth rate of BC incidence} = \frac{\text{No. of new cases of BC, diagnosed during reported year} - \text{No. of new cases of BC, diagnosed during previous year}}{\text{No. of new cases of BC, diagnosed during previous year}} \times 100$$

$$\text{BC mortality rate per 100,000 female population} = \frac{\text{No. of deaths from BC in the reported year (with diadnosed postmortem)}}{\text{avarage annual female population}} \times 100{,}000$$

$$\text{Annual growth rate of BC mortality} = \frac{\text{No. of deaths from BC in the reported year} - \text{No. of deaths from BC in the previous year}}{\text{No. of deaths from BC in the previous year}} \times 100$$

$$\text{Proportion of St I} - \text{II BC, \%} = \frac{\text{No. of new cases of St I} - \text{II BC}}{\text{No. of all cases of BC, diagnosed in the reported year (without diagnosed postmortem)}} \times 100$$

Separation of BC stages I and II was not carried out in statistical forms when identifying new cases of BC and accounting for mortality by age groups until 2017.

Ethical Approval. In this study, publicly available statistical data were used, thus the approval of the ethical committee was not required.

Results. During the study period, 2012-2021 the female population increased steadily in Kazakhstan, from 8.6 million in 2012 to 9.7 million в 2021 (the average growth rate of the female population was 1.33%). At the same time, during the study period, the prevalence of BC increased from 314.4 in 2012 to 444.3 in 2021 per 100,000 of the female population (the average growth rate of the prevalence of BC amounted to 3.92%) (Table 1).

Table 1.

Average growth in the population of female and the prevalence of BC in Kazakhstan, 2012-2021.

Year	Population of female		Prevalence		
	N	T, %	N	N, per 100,000 female population	T, %
2012	8 632 164		27 137	314.4	
2013	8 751 344	1.38	28 277	323.1	2.78
2014	8 876 242	1.43	29 796	335.7	3.89
2015	9 002 614	1.42	31 352	348.3	3.75
2016	9 128 096	1.39	33 053	362.1	3.98
2017	9 249 736	1.33	34 877	377.1	4.13
2018	9 366 039	1.26	36 817	393.1	4.25
2019	9 482 371	1.24	39 648	418.1	6.37
2020	9 597 645	1.22	41 350	430.8	3.04
2021	9 719 153	1.27	43 187	444.3	3.14
Average growth	**120 777**	**1.33**	**1 783**	**14.4**	**3.92**

BC – Brest cancer

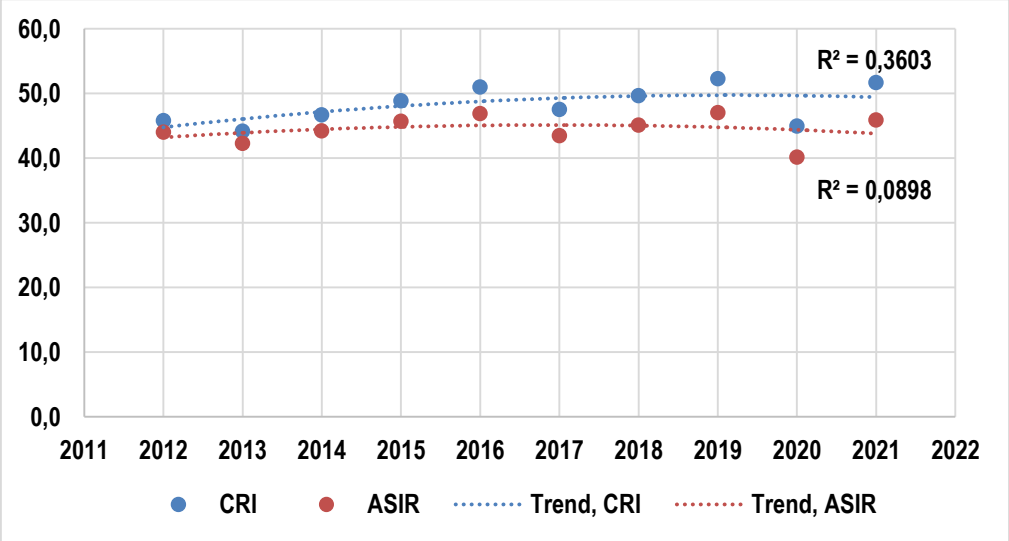
From 2012 to 2021, on average, the crude incidence rate (CIR) and age-standardized incidence rate (ASIR) of BC were 48.2 (95% CI 46.1-50.3) and 44.4 (95% CI 42.9-45.9) per 100,000 female population of Kazakhstan respectively (Table 2). Both CIR and ASIR of BC were the highest in 2019 (52.3 and 12.0 per 100.000 female population) and the lowest in 2020 (44.9 and 11.6) (Fig.1)

Table 2.

Incidence and mortality rate of BC (CR and ASR) in Kazakhstan, 2012-2021.

Rate	Incidence				Mortality			
	per 100,000 female population	95% CI	T,%	R^2	per 100,000 female population	95% CI	T,%	R^2
CR	48.2	46.1-50.3	1.69	0.36	13.9	12.7-15.1	-3,05	0.93
ASR	44.4	42.9-45.9	1.30	0.09	11.2*	10.1-12.3	-3.02	0.70

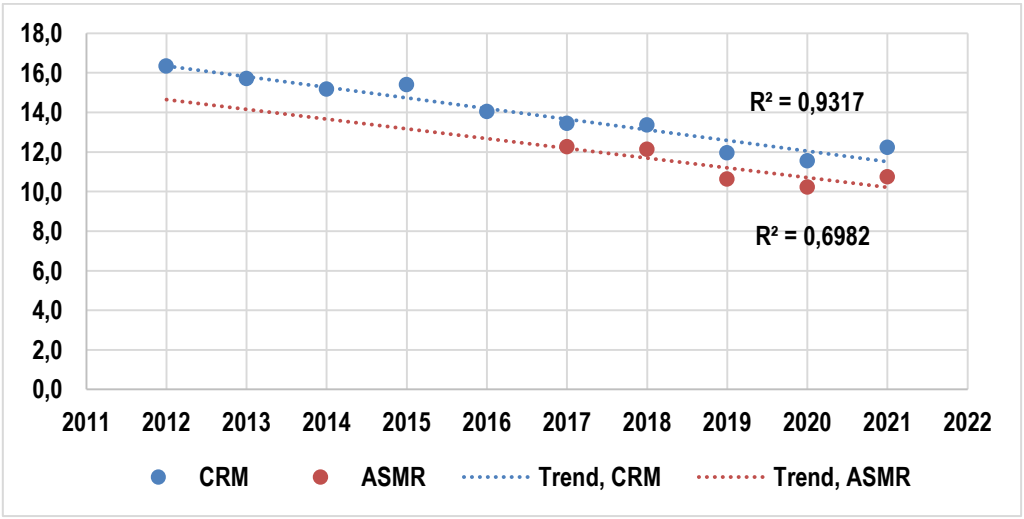
CR – Crude rate; ASR – Age standardized rate; BC – Brest cancer
**2017-2021*



CR – Crude rate; ASR – Age standardized rate; BC – Brest cancer

Figure 1. Dynamics of incidence rate of BC per 100,000 female population in Kazakhstan, CR and ASR in 2012-2021

On average, the crude mortality rate (CMR) from BC was 13.9 (95% CI 12.7-15.1) in the period 2012-2021, the age-standardized mortality rate (ASMR) from 2017 to 2021 was 11.2 (95% CI 10.1-12.3) (Table 1). The highest CMR was registered in 2012 (16.3). Both CMR and ASMR were the lowest in 2020 (11.6 and 10.2) (Fig.2). The annual growth rate of CMR was negative from 2012 to 2021, as well as ASMR in the period of 2017-2021 amounting to -3.05% and -3.02% respectively.



CR – Crude rate; ASR – Age standardized rate; BC – Brest cancer.

Figure 2. Dynamics of mortality rate of BC per 100,000 female population in Kazakhstan, CR in 2012-2021, ASR in 2017-2021.

Table 3 shows CIR and CMR per 100,000 of the general population from BC in 15 regions and 3 cities (Astana, Almaty, and Shymkent) of Kazakhstan from 2012 to 2021. The average incidence rate of BC in Kazakhstan was 24.7±0.5 (95%, CI 23.8-25.6) per 100,000 of the population, with a positive growth rate of 1.6%. The highest incidence rate of BC was in Pavlodar region (39.2±1.8), followed by North Kazakhstan region (37.8±1.2) and Almaty (35.8±1.7). The lowest incidence rates of BC in the study period were in Turkestan region, South Kazakhstan region, and Kzyl-Orda region, and amounted to 11.0±1.1, 12.5±0.5, and 14.2±0.4, respectively (Fig.3a). Turkestan region had the biggest average annual growth incidence rate of BC (15.3%). A negative growth incidence rate was in Zhambyl region (-0.4%).

Table 3.

Incidence rate (CR) and mortality rate (CR) from BC by Kazakhstan regions, 2012 -2021.

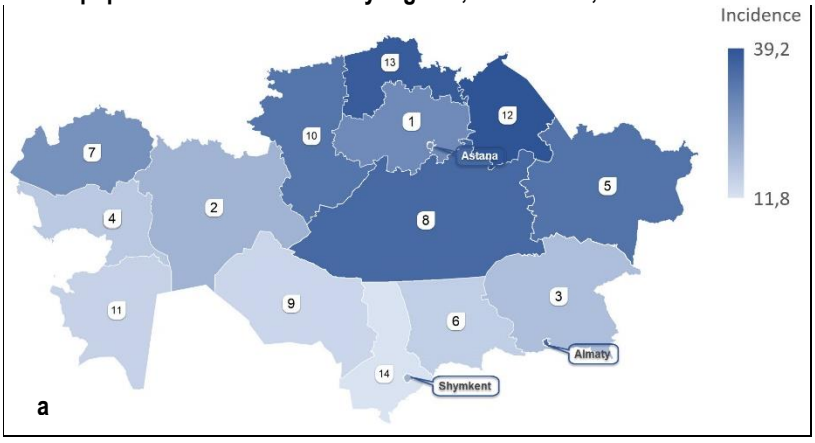
Regions	Incidence (I), per 100 000 population				Mortality (M), per 100 000 population				M/I
	M ± m	95%, CI	T, %	R^2	M ± m	95%, CI	T, %	R^2	
Kazakhstan	**24.7 ± 0.5**	**23.8 - 25.6**	**1.6**	**0.35**	**7.0 ± 0.2**	**6.5 - 7.5**	**-1.1**	**0.74**	**0.28**
Akmola	28.8 ± 1.6	27.1 - 30.4	3.1	0.18	7.4 ± 0.7	6.0 - 7.5	16.7	0.03	0.26
Aktobe	20.9 ± 1.1	18.7 - 23.1	5.2	0.30	5.9 ± 0.3	5.3 - 5.5	6.7	0.07	0.28
Almaty	18.8 ± 1.2	16.4 - 21.2	3.5	0.19	5.6 ±0.4	4.9 - 6.4	-0.6	0.54	0.30
Atyrau	16.8 ± 0.7	15.5 - 18.1	3.6	0.44	5.8 ± 0.7	4.4 - 5.2	24.1	0.58	0.34
East Kazakhstan	33.5 ± 1.1	31.2 - 35.7	4.4	0.60	9.6 ±0.5	8.7 - 10.6	-1.5	0.49	0.29
Zhambyl	15.7 ± 0.4	15.0 - 16.5	-0.4	0.08	6.5 ±0.4	5.6 - 7.3	-0.7	0.68	0.41
West Kazakhstan	27.4 ± 1.2	25.1 - 29.8	1.2	0.02	6.5 ± 0.6	5.4 - 7.6	29.1	0.52	0.24
Karaganda	35.3 ± 1.2	33.0 - 37.6	3.2	0.11	7.6 ±0.4	6.7 - 8.4	-0.2	0.54	0.21
Kyzylorda	14.2 ± 0.4	13.5 - 14.9	0.1	0.03	4.4 ± 0.4	3.6 - 5.2	7.5	0.40	0.31
Kostanay	32.9 ± 1.2	30.4 - 35.3	1.1	0.10	8.1 ±0.4	7.2 - 9.0	-2.7	0.72	0.25
Mangystau	15.0 ± 1.1	12.7 - 17.3	8.2	0.43	3.8 ± 0.2	3.3 - 4.2	2.9	0.11	0.25
Pavlodar	39.2 ± 1.8	35.7 - 42.7	3.8	0.39	10.7 ± 0.9	8.8 - 12.5	15.4	0.42	0.27
North Kazakhstan	37.8 ± 1.2	35.5 - 40.1	1.6	0.45	8.6 ± 0.7	7.3 - 9.9	9.9	0.12	0.23
South Kazakhstan*	12.5 ± 0.5	11.4 - 13.6	9.6	0.99	4.4 ± 0.2	3.9 - 4.9	4.4	0.34	0.35
Turkestan*	11.0 ± 1.1	8.8 - 13.2	15.3	0.84	3.5 ± 0.06	3.4 - 3.6	0.1	0.84	0.32
Shymkent city*	19.9 ± 1.8	16.4 - 23.4	4.1	0.53	5.9 ±1.19	3.5 - 8.3	-10.4	0.65	0.30
Astana city	27.2 ± 0.8	25.6 - 28.8	0.8	0.13	6.8 ± 0.6	5.6 - 7.9	20.9	0.27	0.25
Almaty city	35.8 ± 1.7	32.4 - 39.3	0.8	0.22	10.9 ±0.5	9.9 - 11.8	-2.7	0.81	0.30

**From 2017 South Kazakhstan region was divided by 2 regions (Turkestan region and Shymkent city)*

The mean mortality from BC was 7.0±0.2 (95%, CI 6.5-7.5) per 100,000 of the population from 2012 to 2021, with a negative growth mortality rate (-1.1%). The highest mortality rates from BC were noted in Almaty (10.9±0.5), Pavlodar region (10.7±0.9), and East Kazakhstan region (9.6±0.5). The lowest mortality rates from BC were in Turkestan region (3.5±0.06) and Mangystau region (3.8±0.2) (Fig.3b). The maximum average growth mortality rate was in West Kazakhstan region (29.1%), and the minimum one was in South Kazakhstan region (-10.4%). The M/I was 0.28 average in Kazakhstan and varies by region from 0.21 (Karaganda region) to 0.41 (Zhambyl region) (Fig.3c).

The average age of the patients with BC was 58.4 (CI 95% 55.6-61.1). The increase in the incidence of BC began with the age group of 40-44 years old. The highest incidence of BC in the female population occurred in the age group of 65-69 years old (CIR 190.1±7.4) followed by the group of 60-64 years old (CIR 162.1±4.1) (Fig.4). In these age groups and in the group of 40-44 years old, the highest average growth incidence rates of BC were noted, 2.87%, 2.62%, and 2.74%, respectively (Table 4).

Figure 3. Incidence (a), mortality (b), and M/I coefficient (c) of BC per 100,000 population in Kazakhstan by regions, crude rates, in 2012-2021



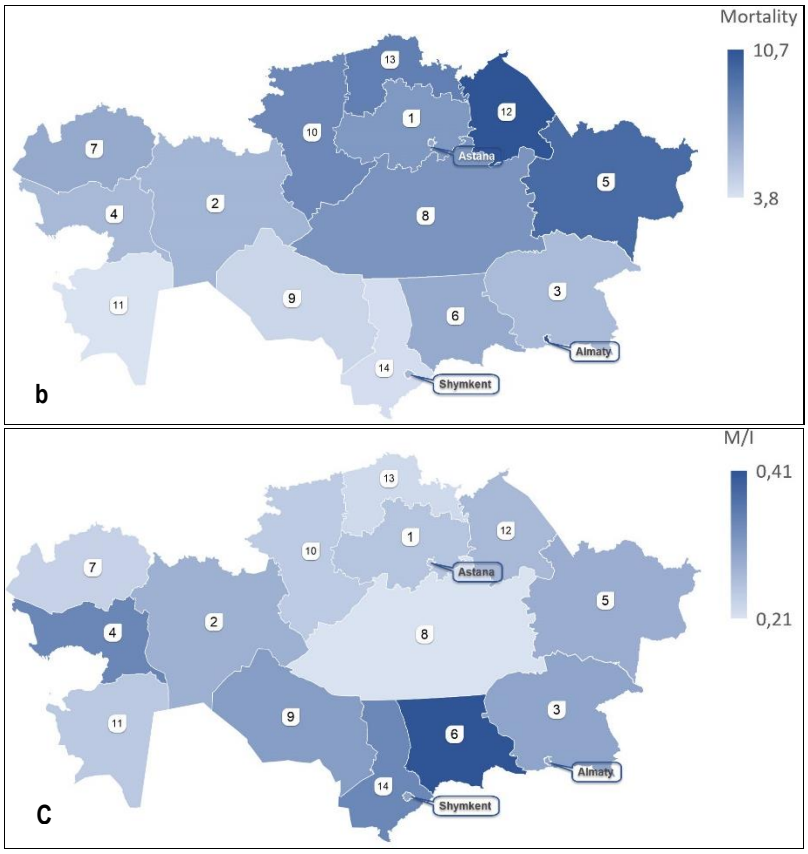
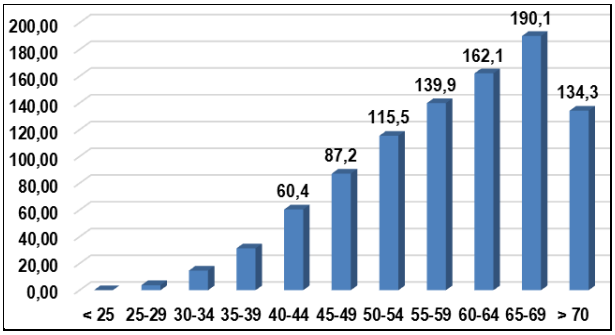


Table 4.

Incidence rate (CR*) of BC per 100,000 female population according to age group in Kazakhstan, in 2012-2021.

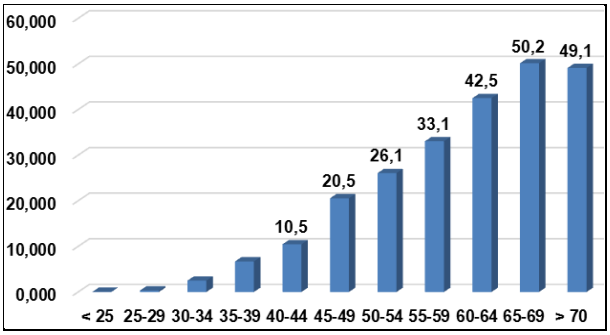
Age groups	M ± m	95%, CI	T, %	R^2	Rank
<25	0.9 ± 0.2	0.6 - 1.4	-	-	11
25-29	3.8 ± 0.4	3.1 - 4.5	0.54	0.36	10
30-34	14.7 ± 0.5	13.6 - 15.8	2.35	0.18	9
35-39	31.4 ± 0.9	29.6 - 33.2	2.17	0.34	8
40-44	60.4 ± 5.9	56.6 - 64.1	2.74	0.42	7
45-49	87.2 ± 1.5	84.3 - 90.1	0.88	0.07	6
50-54	114.5 ± 5.4	104.8 - 126.2	-0.31	0.21	5
55-59	139.9 ± 4.9	130.1 - 149.7	-1.85	0.38	3
60-64	162.1 ± 4.1	153.9 - 170.4	2.87	0.35	2
65-69	190.1 ± 7.4	175.4 - 204.8	2.62	0.19	1
> 70	134.3 ± 3.2	127.9 - 140.6	1.80	0.07	4

**Crude rate*



**Crude rate*

Figure 4. Incidence rate (CR*) of BC per 100,000 female population according to age group in Kazakhstan, in 2012-2021



**Crude rate*

Figure 5. Mortality rate (CR*) from BC per 100,000 female population according to age group in Kazakhstan, in 2012-2021.

The highest mortality rate in the female population registered in the age group of 65-69 years old (CMR 50.2 ± 2.6) and among patients over age 70 (CMR 49.1 ± 1.1) (Fig.5). In age groups of 35-39 and 40-44 the highest average growth mortality rates were observed, 3.01%, and 2.74%, respectively (Table 5).

Table 5.

Mortality rate (CR*) from BC per 100,000 female population according to age group in Kazakhstan, in 2017-2021.

Age groups	M ± m	95%, CI	T, %	R^2	Rank
<25	0.03 ± 0.04	0.0 - 0.1	-	0.47	11
25-29	0.30 ± 0.03	0.2 - 0.4	-0.06	0.12	10
30-34	2.5 ± 0.2	2.1 - 2.9	0.30	0.10	9
35-39	6.7 ± 0.6	5.5 - 7.9	3.01	0.71	8
40-44	10.5 ± 0.9	8.7 - 12.2	2.74	0.13	7
45-49	20.5 ± 1.3	18.0 - 23.1	-2.16	0.57	6
50-54	26.1 ± 1.2	23.7 - 28.5	-1.39	0.52	5
55-59	33.1 ± 2.2	28.7 - 37.4	-5.79	0.79	4
60-64	42.5 ± 1.4	39.8 - 45.3	-2.32	0.67	3
65-69	50.2 ± 2.6	44.9 - 55.4	-2.46	0.82	1
> 70	49.1 ± 1.1	47.0 - 51.2	-0.74	0.72	2

**Crude rate*

As it is shown in table 6 there was an increase in the proportion of BC patients who had stage I-II the moment of diagnosis since 2012 (from 76.4% to 84.6% in 2021). In the period of 2017-2021 the proportion of patients with BC stage I was 28.8% and with stage II 55.7% (Fig.6). The highest annual growth rate in the detection of BC stage I was in 2018 (44.0%). At the same time in that year, the lowest annual growth rate was in the detection of BC stage III (-18.1%). In 2020, there was a considerable decrease in the annual growth rate of detection of BC stages I-II (-15.4%), followed by increasing to its maximum (16.1%) in 2021. The highest annual growth rate in the detection of BC stage III and IV was registered in 2021, 6.8% and 29.2% respectively.

Table 6.

Staging of new BC cases in Kazakhstan, 2012-2021.

Year	I-II Stage		I Stage*		II Stage*		III Stage		IV Stage	
	N (%)	T, %	N (%)	T, %	N (%)	T, %	N (%)	T, %	N (%)	T, %
2012	2998 (75.9)	-	-		-		698 (17.7)		218 (5.5)	
2013	2943(76.2)	-1.8	-		-		678 (17.6)	-2.9	188 (4.9)	-13.8
2014	3297 (79.6)	12.0	-		-		593 (14.3)	-12.5	192 (4.6)	2.1
2015	3483 (79.2)	5.6	-		-		593 (13.5)	0.0	204 (4.6)	6.3
2016	3817 (82.2)	9.6	-		-		569 (12.2)	-4.0	197 (4.2)	-3.4
2017	3677 (83.7)	-3.7	1001 (22.8)		2676 (60.9)		486 (11.1)	-14.6	162 (3.2)	-17.8
2018	4031 (86.7)	9.6	1441 (31.0)	44.0	2590 (55.7)	-3.2	398 (8.6)	-18.1	167 (3.6)	3.1
2019	4255 (85.9)	5.6	1553 (31.4)	7.8	2702 (54.5)	4.3	411 (8.3)	3.3	206 (4.2)	23.4
2020	3599 (83.6)	-15.4	1261 (29.3)	-18.8	2338 (54.3)	-13.5	428 (9.9)	4.1	212 (4.9)	2.9
2021	4177 (83.2)	16.1	1481 (29.5)	17.4	2696 (53.7)	15.3	457 (9.1)	6.8	274 (5.5)	29.2
Average	**36277 (81.8)**	**4.2**	**6737 (28.8)**	**50.4**	**13002 (55.7)**	**0.7**	**5311 (12.0)**	**-4.2**	**2020 (4.6)**	**3.6**

*BC – Brest cancer; *registration started in 2017*

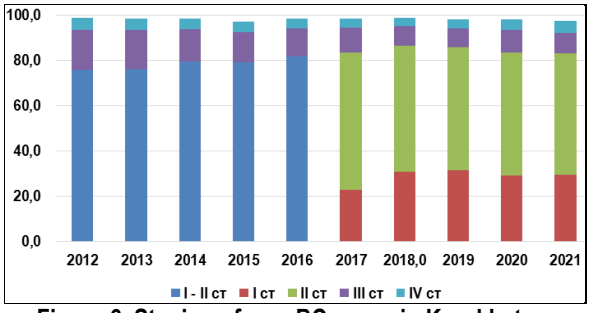


Figure 6. Staging of new BC cases in Kazakhstan, 2012-2021.

Discussion

This study reported the epidemiological characteristics of BC in Kazakhstan in the period 2012-2021. The study demonstrated notable changes in the epidemiological indicators of BC in ten years period, reflecting the effectiveness of BC preventing measures and implementation of new approaches in BC therapy in recent years in the country.

The results showed a greater average annual growth rate of BC prevalence compared with the average annual growth rate of the female population in Kazakhstan (1.33 vs 3.92) in last decade. This trend is in line with world data and could be explained by the effectiveness of the BC screening program [23]. The BC ASIR in Kazakhstan (44.4) is at the level of BC ASIR in Western (46.6) and Eastern (43.3) Asia regions, but higher than in South Central Asia (26.2) [26]. At the same time, there was a downward trend in mortality during the study period. Meanwhile the CMR was considerably higher in the age groups of 65-69 and ≥70 compared to other age groups, and the ASMR was highest among women over 70 years old. This data was in accordance with data showed by Lima et al. who demonstrated a statistically significant increase in the global mortality rate from BC in the age group over 70 years old [21]. Another study demonstrated that in most countries and regions, the ASIR of BC was the highest among the population over 70 years old and will increase in all age groups until 2035 [20].The study results demonstrated a prominent decrease in the incidence and mortality of BC in 2020 compared with the relatively stable epidemiological situation of BC since 2012. This decrease was probably a consequence of the COVID-19 pandemic, when access to mammographic screening programs was limited and the processes of timely provision of cancer-related services were hindered due to strict quarantine measures. It is assumed, that in some cases the cause of death of BC patients in 2020 could be complications associated

with COVID-19, which led to registering this death as COVID-19 mortality that brought to decrease in BC mortality rate. These findings comply with the observations in other countries made by Breast Screening Working Group [13].

The analysis of the epidemiological indicators of BC in the regions of Kazakhstan showed considerable heterogeneity in incidence and mortality rates, as well as in the M/I in different regions. Thus, in Pavlodar region, with 71% of the urban population [5], the highest incidence and mortality rates and almost the same M/I as the average republican M/I. In Zhambyl region, with 60% of the rural population, the indicators showed a low incidence and mortality, however, the M/I was the highest in the country. In Karaganda region, with 80% of the urban population, there was one of the highest incidence rates in the country (35.3) with a middle mortality rate (7.6) and the lowest M/I (0.21). Among three cities Almaty had the highest incidence and mortality rate, and M/I equal to the average in the country.

In the previous study*, Beysebaev E. et al.* observed relatively the same results in the period of 1999-2013, the highest incidence rate was in Almaty (49.7), Astana (46.8) cities, and Pavlodar region (44.3), the highest mortality rate was registered in Pavlodar region (17.9) and Almaty city (20.1), whereas M/I were comparably equal in all regions of Kazakhstan [9].

The higher level of BC incidence rates in the cities and regions with the majority of urban populations can be aligned with better access to mammography screening in urban areas. As well lower M/I in urban regions can testify that in cities the better oncological services are provided. However, this assumption requires more detailed study of risk factors and their influences.

The identification of truly early stages (0-I), causing favorable clinical outcomes, is still a very important issue to improve survival and longer-term quality of life for patients with BC in Kazakhstan. The study demonstrated that the diagnosis of BC at stages I-II was 81.8% among all new cases, and the detection of BC at stage I increased by 8% to 29.5% since 2017. However, Kaidarova D. et al, demonstrated that the proportion of stage I BC detected as a result of the BC screening program increased more than 2 times, from 21.1% to 45.4% within the period 2008-2019 [2]. This contradiction can be explained by the fact that this study was focused on all primary diagnosed BC cases, but not only those detected by mammographic screening. Thus, the results of this study revealed that BC detection in Kazakhstan most often occurs at stage II, despite the population-based screening program and imaging capabilities being implemented in the country. It might be because not all the eligible women get mammographic screening due to various reasons (low health literacy, busy lifestyle of modern women, temporal/periodical problems with mammography in primary healthcare organizations, etc.). As was pointed out by *Kaidarova D. et al.,* actual screening coverage in Kazakhstan is less than the WHO recommended 70% of the assigned female population. However, early diagnosis of the disease is critical for improving clinical outcomes in patients with BC [14, 24]. Stage II is not always considered as early diagnostic because stage II is a heterogeneous group ranges from T1a (cancer less than 5 mm) to T3 (tumor >50 mm in greatest dimension) [10].

Taking into account the aging and growing population in the country, in line with the global trends, and the increasing prevalence of risk factors in the female population, a further substantial increase in the incidence of BC can be expected in Kazakhstan. Thus, the healthcare strategies need to be tailored according to the burden of BC, like an improvement of health literacy and acceptance of mammographic screening, and availability of medical resources for cancer patients in challenging periods for the healthcare system such as the pandemic.

There are a few limitations in this study. First, official information on the distribution of mortality by the age groups and division between the I and II stages of primarily diagnosed BC was not available until 2017. Second, crude incidence and mortality rates from BC by regions were calculated per 100, 000 of the total population without division by sexes. There was a territorial and administrative division of the South Kazakhstan region (into the Turkestan region and Shymkent city), and it is still difficult to analyze objectively the indicators of this region.

Thus, according to the results of the study for the period of 2012-2021, the epidemiological situation of BC in Kazakhstan showed a tendency for improvement, demonstrating a decrease in the mortality rate (CMR 13.9 per 100,000 female population) when compared to the steadily rising incidence rate (CIR 48.2 per 100,000 female population). The identification of patients with stage II breast cancer prevailed. The proportion of stage I BC, which cause favorable clinical outcomes, was 28.8%, and it is still a crucial issue in improving survival and longer-term quality of life for patients with BC in Kazakhstan. Substantial variability of epidemiological data among the regions of Kazakhstan indicates the necessity of a detailed study of risk factors of BC and the effectiveness of mammographic screening in the regions in order to take impactful healthcare measures.

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Author contribution statement: *All authors were equally involved.*

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