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# Gender-related trends in key epidemiological indicators of lung cancer in the Republic of Kazakhstan, 2014-2018

Relevance: *Over the past decades, lung cancer (LC) incidence worldwide is adding about 1.5% each year. The risk of LC development increases 4-5 times with age. The mortality-to-incidence ratio (MIR) in LC is the most unfavorable – up to 95.6% of patients die.*

The purpose of this study *was to analyze the epidemiological situation with lung cancer in the Republic of Kazakhstan over the past five years, with the assessment of key epidemiological indicators by gender.*

Results: *In the previous five years (2014-2018), the men to women ratio among LC patients was equal to 4.2:1 and remained stable. A gradual decline in mortality (16‰ in 2014 to 12.9‰ in 2018) correlated with the MIR dynamic pattern (67.5% in 2014 to 60.0% in 2018). The standardized LC incidence in men was declining steadily (46.8‰ in 2014 to 43.0‰ in 2018). A more evident decrease in male mortality from LC (32.0‰ in 2014 to 24.2‰ in 2018) was due to the progress recently achieved in LC diagnostics and treatment in the Republic of Kazakhstan. On the contrary, the LC incidence in women increased by 2.6% a year (7.6‰ in 2014 to 7.8‰ in 2018). The female mortality from LC was declining steadily (4.6‰ in 2014 to 3.5‰ in 2018), with a negative growth rate of minus 31.4%.*

Conclusion: *The analysis of epidemiologic indicators for LC in the Republic of Kazakhstan showed a general downward trend in incidence and mortality regardless of gender. However, we can expect an increase in the female incidence of LC in sync with the global trend. The study period has witnessed the improvement in both the primary diagnostics (due to the renewal of diagnostic equipment in the country) and treatment of LC (through the introduction in the Republic of methods of molecular genetic studies which are the basis for the state-financed personalized drug therapy with targeted agents).*

***Keywords:*** *epidemiology, lung cancer (LC), standardized indicators, intensive indicators, incidence, mortality.*

***Relevance:*** The increase in lung cancer (LC) incidence comparable to an epidemic has started in the 1940s. In recent decades, the LC incidence is adding about 1.5% a year globally. With age, the risk of lung cancer increases 4-5 times [1]. The mortality-to-incidence ratio (MIR) in LC is the most unfavorable – up to 95.6% of patients die [2].

Despite the studies in prevention, diagnosis, and treatment of lung cancer, this disease still ranks first among cancer death causes. LC remains the most "popular" malignancy worldwide, accounting for 20-30% of all cancer deaths in Western and Central Europe, CIS (Russia, Ukraine, Kazakhstan), North America, Western, and South-East Asia, South Africa (white population), Australia and New Zealand. The highest LC mortality among men (more than 60 per 100,000 population) is registered in Eastern and Central Europe. In some regions of the world, standardized LC mortality exceeds 100 per 100 thousand population [3].

This paper presents the results of lung cancer epidemiology analysis in the Republic of Kazakhstan for the previous five years (2014-2018), with the gender-related assessment of LC's key epidemiological indicators.

***Materials and methods:*** Data was retrieved from the registration forms 030-6/u (n 19379 - C34) in the Electronic Register of Cancer Patients (EROB) for 2014-2018. A database was created in Microsoft Excel.

Statistical processing of the material was performed on a personal computer using mathematical data processing software – the IBM SPSS Statistics 19 package (trial version). The statistical indicators were calculated according to the methods proposed by the International Agency for Research on Cancer (IARC) [4]; standardized indicators were calculated based on the World 2001 standard [5]. Epidemiological indicators were calculated based on the data provided by the Agency on Statistics of the Republic of Kazakhstan on the average annual number, age, and sex structure of the population.

Age-standardized *( STAND )* rate was calculated by the formula:

$$STAND = \frac{\sum_{i=1}^{A} a_i w_i}{\sum_{i=1}^{A} w_i}$$

where $w_i$ – the size of age group *i of the* standard population, $i = 1, 2, \ldots A$, $a_i$ – the age-specific indicator of the corresponding age group.

Survival rate was calculated from the date of treatment initiation to the date of death from any cause or to the date of the patient's last visit. The cut-off date was January 1, 2019.

***Results and Discussion:***

*Lung cancer situation in the world*

The GLOBOCAN register provides comprehensive information on the dissemination of cancer pathology in the world. The previous 5th version of GLOBOCAN reported 1.8 million new cases of LC in the world in 2012 (12.9% of all new cancer cases), of them, 58% - in less developed regions; and about 1.59 million deaths from LC (19.4% of all deaths from cancer) [6]. In 2018, LC still led the structure of cancer incidence and mortality, accounting for 2 093 876 new cases in the world (11.6% of all cancers) and 1 761 007 (18.4 %) deaths from LC [7].

The global average LC incidence was 27.4‰, LC mortality – 23.1‰. Despite a positive MIR trend and its decrease from 95.6% in the 1990s to 84.3% in 2018, the proportion of deaths from LC remains high. The incidence per 100 000 population adjusted by age to the World standard varies from 7.0‰ in Uzbekistan and 16.4‰ in Brazil to 81.1‰ in Germany, 85.9‰ in Denmark, and 93.5‰ in Japan. However, despite a high incidence, the MIR in the developed countries is below the world average of 84.3%: Australia – 66.9%, USA – 67.0%, Japan – 69.0%, UK – 72.2%. This may indicate a high level of cancer care service. On the other hand, in the countries with a low burden for LC, like CIS (Uzbekistan, Kazakhstan, Kyrgyzstan, Ukraine, and RF), some West European (Sweden, Poland, Slovakia) and South-East Asian (Korea, China) countries, the objective indicator of the cancer burden for LC not only exceeds the world average but in some countries exceeds 90%, indicating real problems in LC diagnostics and treatment [8].

The Republic of Kazakhstan is among the countries "unfavorable" for LC. For 30 years on, LC is in the top cancer diseases and leads the cancer mortality in Kazakhstan. Compared to other countries (according to GLOBOCAN), the incidence rate in Kazakhstan is below Japan, Denmark, or Germany. This might indicate some gaps in LC diagnostics in Kazakhstan (Figure 1 ).

The recent widespread introduction of computer tomography has increased the share of early detection of LC in low-incidence countries, including Kazakhstan, thus promoting its timely and radical treatment. LC mortality could be reduced by solving two major problems: introducing an early diagnostics and screening algorithm and the organization of efficient precision treatment of LC in all its diversity.

*Lung cancer situation in Kazakhstan*

We made it our mission to analyze the main statistical indicators of LC in Kazakhstan. According to EROB data, in 2018, the LC incidence in the RK amounted to 20.3 per 100 000 population. 2 377 patients (17.6% of all cancer deaths) died of LC [9].

In 2010-2013, LC cancer mortality kept stable at the level of 17.6-17.5‰ and went down to 16.0‰ in 2014 only. We could associate it with the introduction in 2012 of the Republic of Kazakhstan cancer care development program. This program gave access to the patients since 2012 to the first targeted drugs against non-small cell lung cancer (NSCLC), namely the tyrosine kinase inhibitors. The cumulative effect of such free access, sponsored by the state budget, impacted the mortality rate, starting with 2014. The analysis showed a continued smooth decrease in mortality to 14.6‰ in 2015 and 12.9‰ in 2018. At that, the lowest rate of 12.4‰ was registered in 2017 (Figure 2 ).

MIR values correlated with the mortality rate, showing a similar trend. In 2010, MIR was equal to 81.1%, then decreased to 67.5% in 2014 and reached 60.0% in 2018. The maximum decline, according to Kazakhstani oncologists, was registered in 2017 (56.5%). Thus, in this indicator, Kazakhstan has approached and even overtook developed countries [8]. The analysis of several sources on cancer statistics in the Republic of Kazakhstan revealed a difference with GLOBOCAN data. We do not judge the reason. Nevertheless, a positive trend in mortality rate could indicate certain progress in diagnostics and treatment of this nosology in our country (Figure 3).

Besides, we decided to analyze the gender-related dynamics of LC's major statistical indicators in Kazakhstan, taking into account the changes in the structure of NSCLC morbidity in the last two decades. If in the XX century squamous cell carcinoma in smokers prevailed in the structure of NSCLC, then the XXI century was marked by the growth of adenocarcinoma frequency in nonsmokers and women, with a predominance in the Asian population and at a young age. Of course, we have to consider that LC retains its gender specificity in its prevalence and outcomes. In the studied five years (2014-2018), LC incidence analysis in Kazakhstan showed a stable men-to-women ratio of 4.2:1 among patients with LC. This confirms a lack of smoking control effectiveness [9] compared to European countries and the US, which show a clear upward trend in incidence among women and a downward trend among men [10].

To ensure an objective assessment, we analyzed crude and standardized indicators and revealed a downward gender-blind trend in LC incidence in the RK in both crude and standardized rates. The decrease in the intensive indicators was equal to $R^2$ =0.728 vs. $R^2$ =0.34 for standardized indicators (Figure 3).

The mortality rates showed a more pronounced downward trend in standardized compared to intensive (crude) rates: the decline in standardized rates was $R^2$ =0.879 vs. $R^2$ =0.81 in intensive rates (Figure 4).

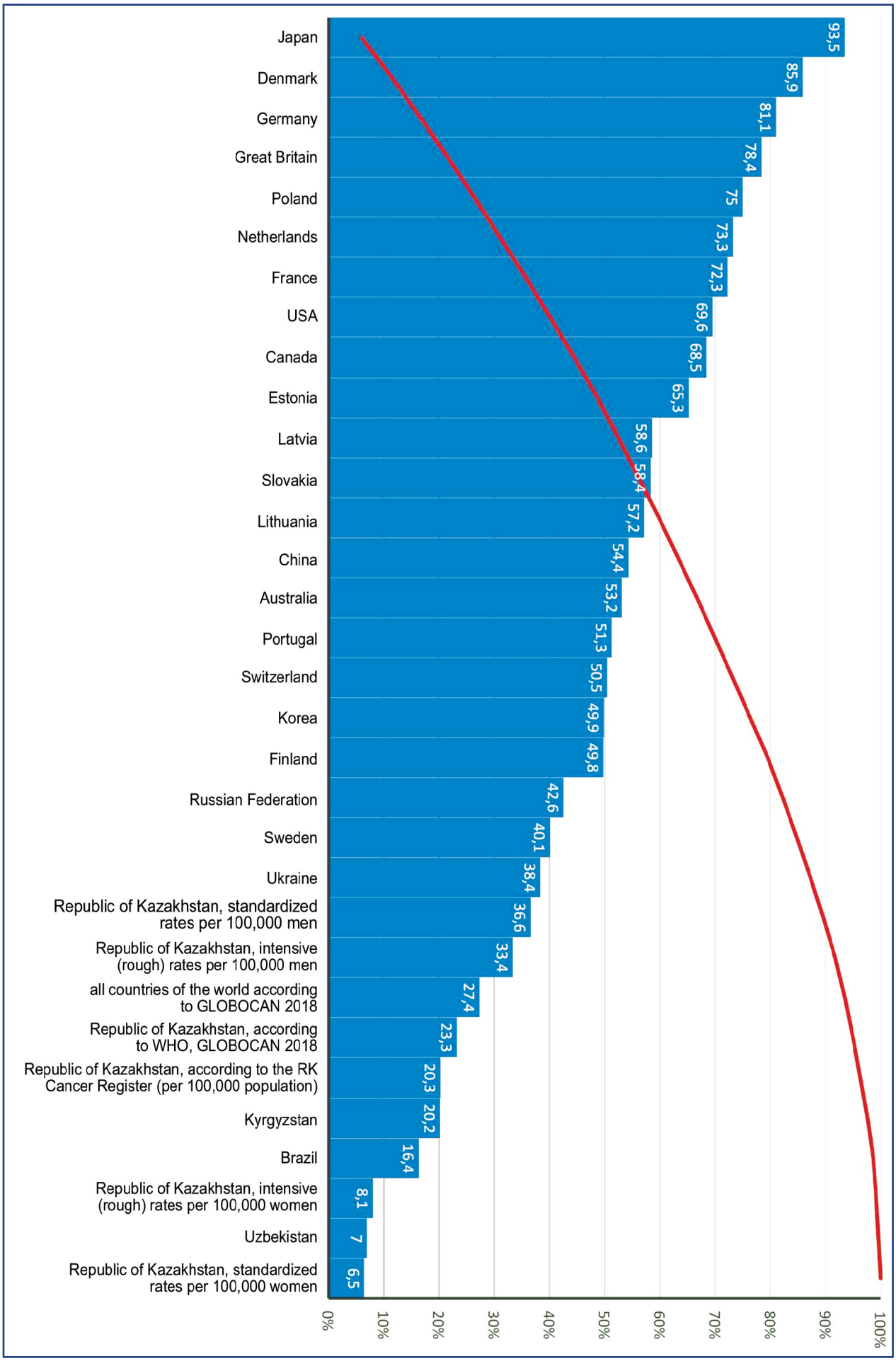


Figure 1 – Global lung cancer incidence per 100,000 population and the Pareto curve

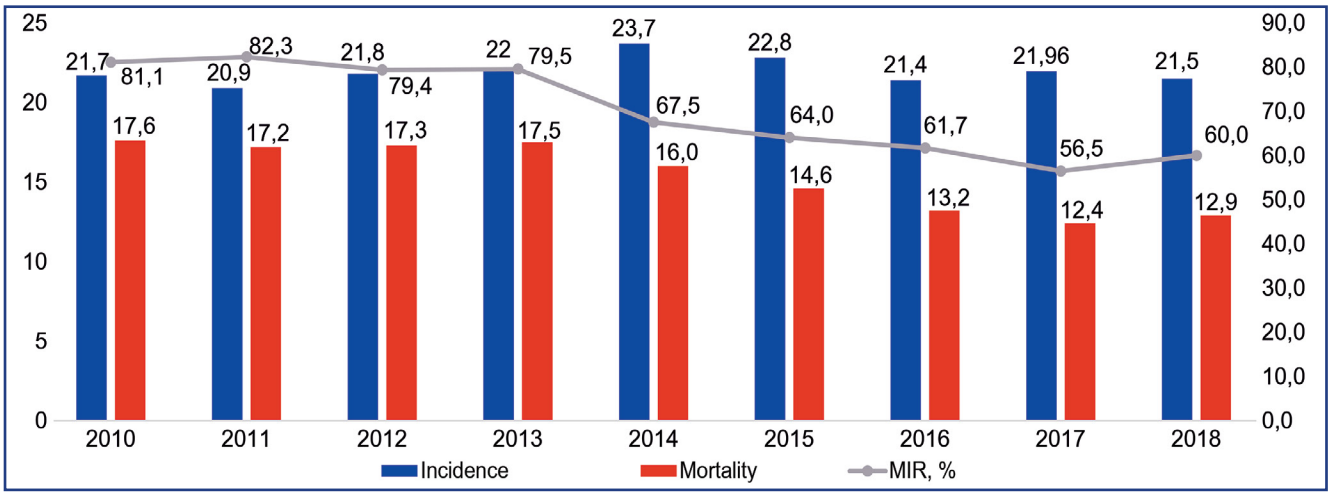


Figure 2 – Trends in key epidemiological indicators of LC in the Republic of Kazakhstan, 2010-2018

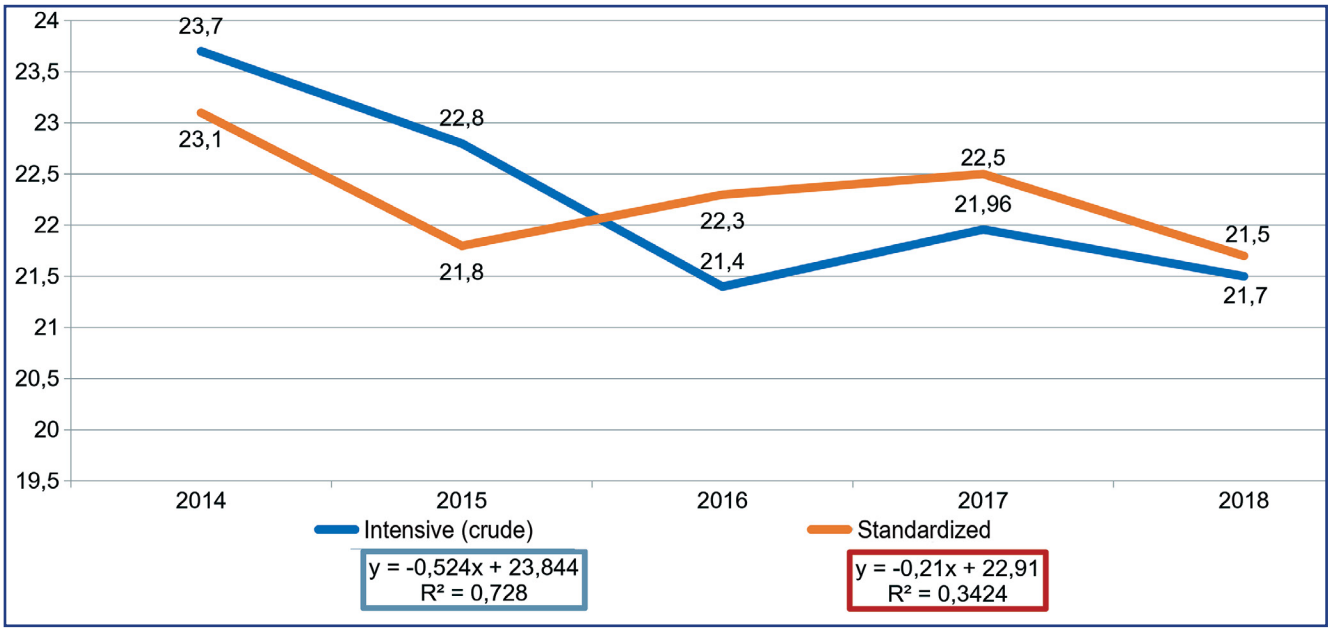


Figure 3 – Intensive (crude) and standardized LC incidence in the Republic of Kazakhstan, 2014-2018, both sexes

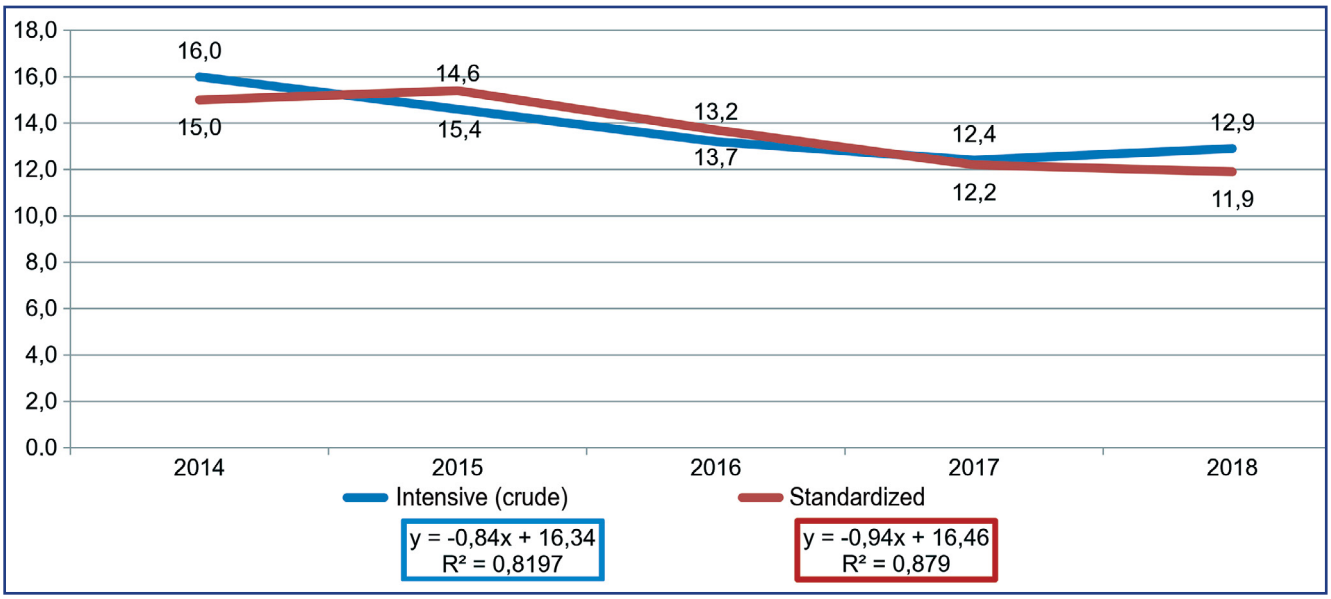


Figure 4 – Intensive (crude) and standardized mortality from LC in the Republic of Kazakhstan, 2014-2018, both sexes

A gender-related analysis revealed a smooth decrease in intensive (crude) LC incidence among the RK male population from 39.8‰ in 2014 to 35.1‰ in 2018. A decrease in male mortality from 27.5‰ in 2014 to 21.6‰ in 2018 could indicate improved diagnostics and treatment quality. MIR, which is the indicator of cancer burden, reduced from 69.1% in 2014 to 62.4% in 2018, evidencing the downward trend in male incidence and mortality from LC. The reduction factor was $R^2$ =0.68 (Figure 5).

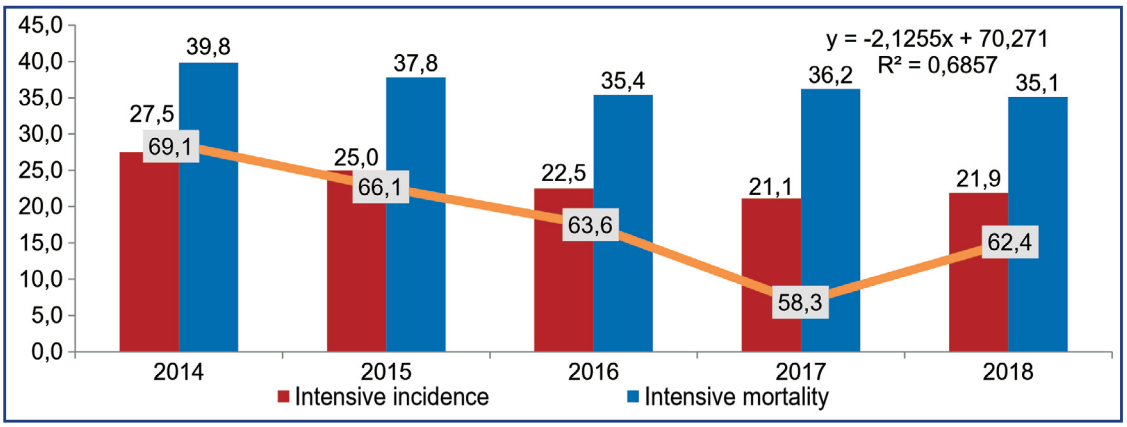


Figure 5 – Five-year dynamics of major intensive epidemiological indicators for LC in men in the Republic of Kazakhstan, 2014-2018

While the dynamics of standardized LC incidence in men was quite stable, with a slight decline in 5 years (from 46.8‰ in 2014 to 43.0‰ in 2018), the mortality graph had a steeper bending (from 32.0‰ in 2014 to 24.2‰ in 2018). This evidenced progress in LC diagnostics and treatment achieved in the RK in recent years. MIR confirms this trend, showing a decrease from 68.4% in 2014 to 56.3% in 2018. The reduction factor for standardized indicators was more expressed than for intensive indicators and amounted to $R^2$=0.96 (Figure 6).

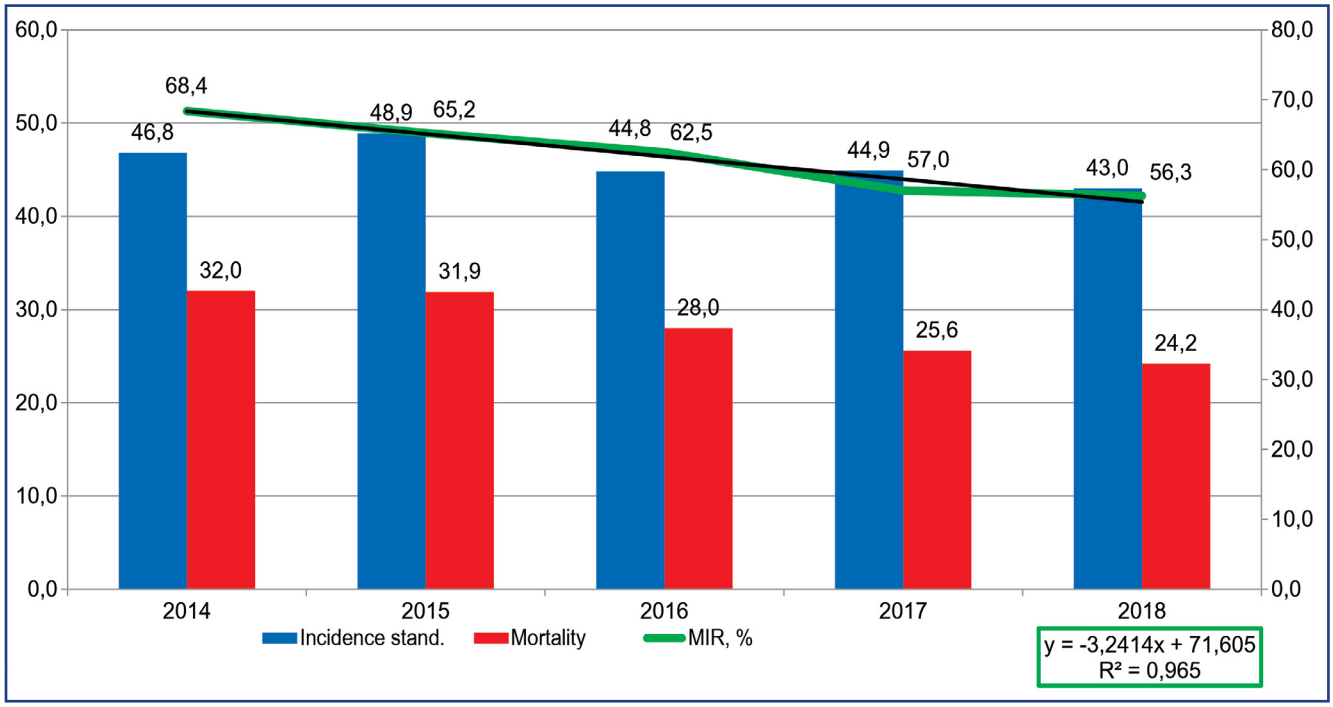


Figure 6 – Five-year dynamics of major standardized epidemiological indicators for LC in men in the Republic of Kazakhstan, 2014-2018

Despite the global upward trend in the female incidence of LC [10], Kazakhstani oncologists did not report such dynamics in the Republic. In 2014-2018, the intensive (crude) indicators of LC incidence in women remained the same (8.8‰ in 2014 vs. 8.7‰ in 2018). Female mortality was slowly decreasing (5.4‰ in 2014 to 4.5‰ in 2018). This could indicate the improved quality of diagnostics and treatment in the Republic of Kazakhstan. Changes in MIR confirmed the positive dynamics of LC epidemiology among Kazakhstani women (61.1% in 2014 to 51.7% in 2018). The approximation factor was $R^2$ =0.73 (Figure 7).

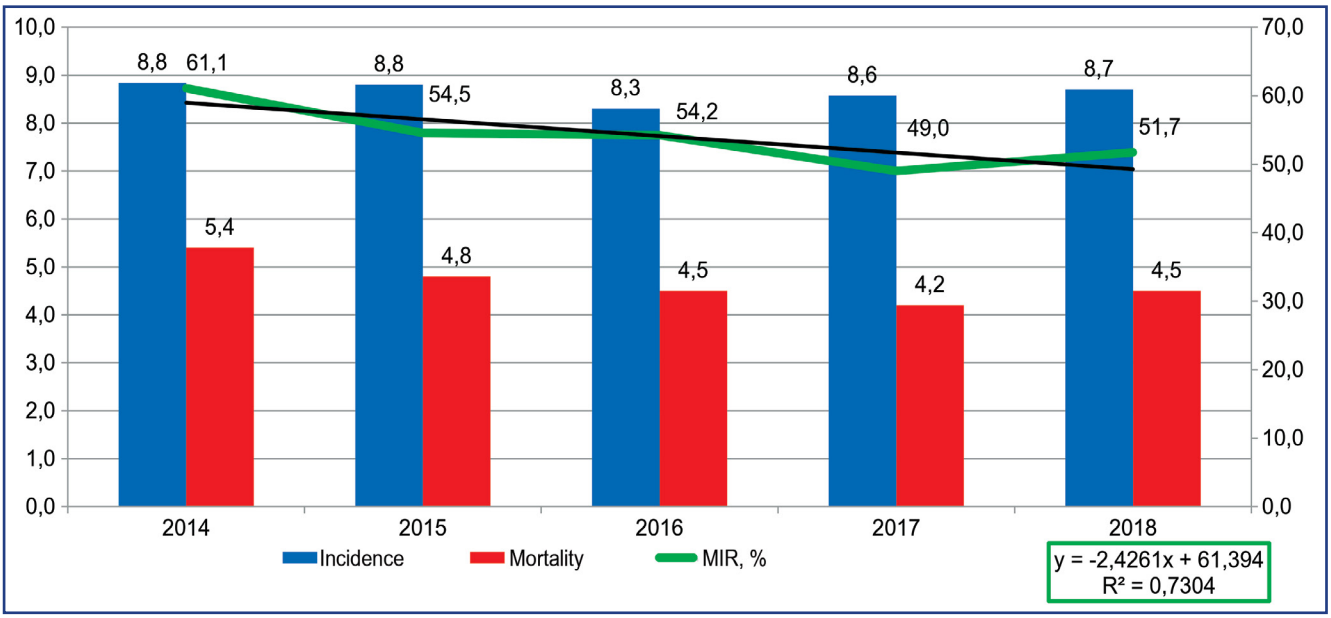


Figure 7 – Five-year dynamics of major intensive epidemiological indicators for LC in women in the Republic of Kazakhstan, 2014-2018

The analysis of standardized indicators showed a somewhat different epidemiological picture of lung cancer among women in the Republic of Kazakhstan. The LC incidence in women has added just 2.6% (7.6‰ in 2014 to 7.8‰ in 2018). In contrast, the mortality was stably reducing (4.6‰ in 201 4 to 3.5‰ in 2018), having lost 31.4%. MIR reflected the general trend in LC female epidemiology in Kazakhstan, reducing from 60.5% in 2014 to 44.9 % in 2018. The reduction factor was $R^2$=0.93 ( Figure 8 ).

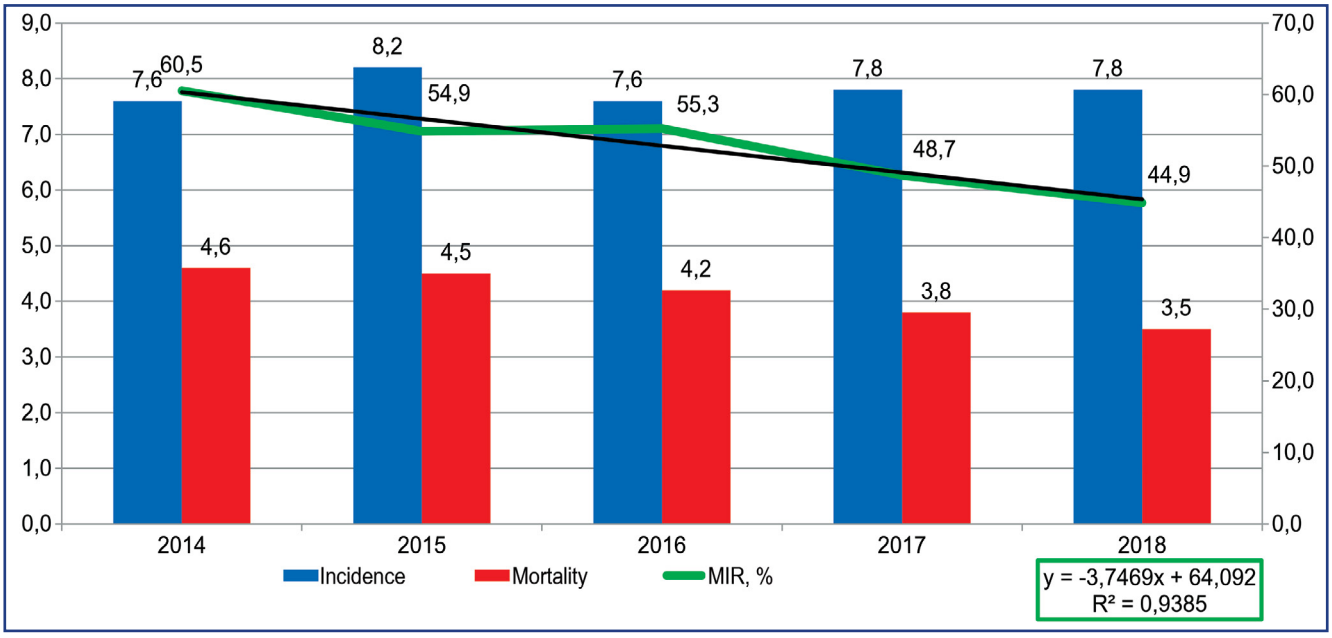


Figure 8 – Five-year dynamics of major standardized epidemiological indicators for LC in women in the Republic of Kazakhstan, 2014-2018

***Conclusions:*** Thus, the analysis of five-year changes in LC's major epidemiological indicators has shown a downward trend in male incidence with a stable female incidence in intensive (crude) rates (Figure 9 ).

It is worth noting that the male mortality of LC was five times higher than the female. That is, the male-to-female mortality ratio was 5:1 vs. the incidence ratio of 4.2:1. This suggests the male gender in the Republic of Kazakhstan as a risk factor and a poor prognosis factor for LC. This fact is evident only when evaluating gender-related survival (Figure 10). The intensive male mortality was stably decreasing over five years from 2014 to 2018, with a negative growth of 20.4%, which cannot be said about women. Female mortality from LC has lost only 16.6% in 5 years. The female-to-male mortality ratio has slightly increased, indicating an increased share of women dying from LC (Figure 10).

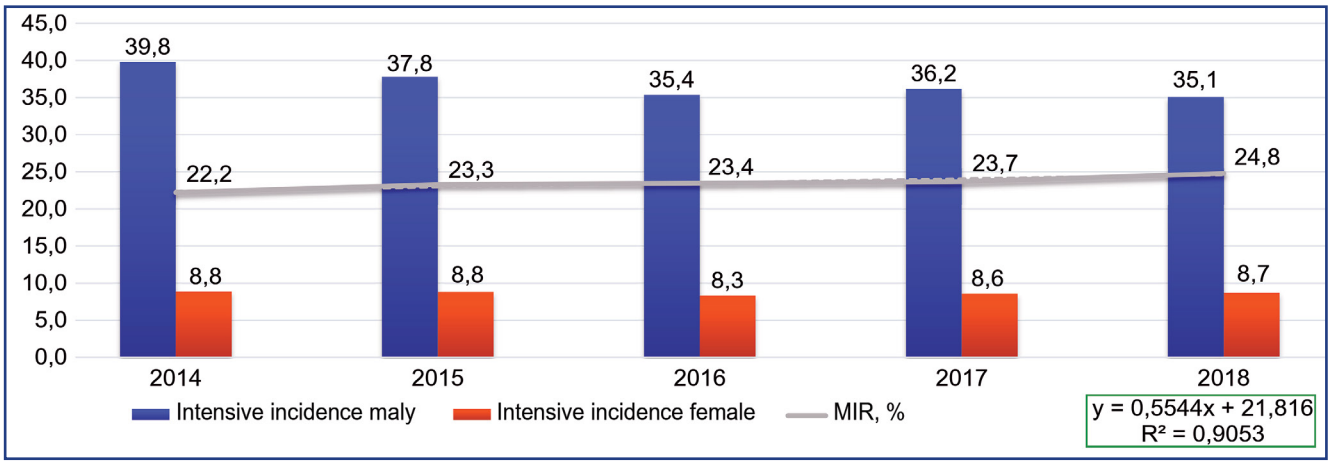


Figure 9 – Gender-related LC incidence in the Republic of Kazakhstan, 2014-2018

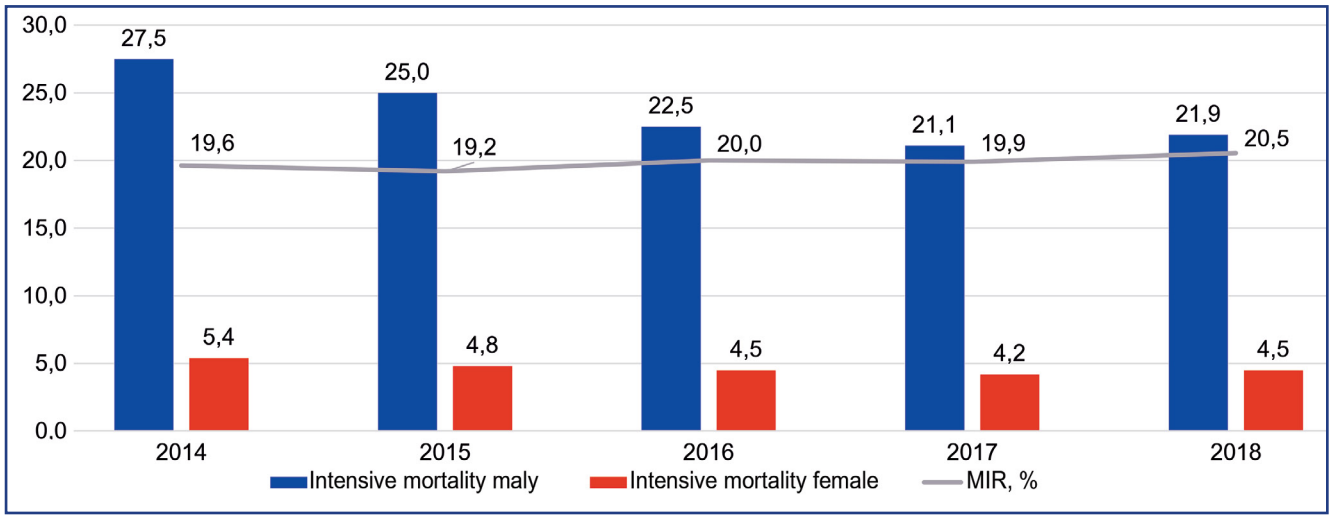


Figure 10 – Gender-related LC mortality in the Republic of Kazakhstan, 2014-2018

We forecasted female/male LC incidence and mortality ratios for the next 20 rounds to confirm or dispute the above statements. The results showed a downward trend of both indicators in men, with a more pronounced dynamics in incidence ($R^2$=0.79) and a smoother decrease in mortality ($R^2$=0.13). In women, the LC incidence is expected to grow significantly ($R^2$=0.69), with a simultaneous downward trend in mortality ($R^2$=0.82) (Figure 11).

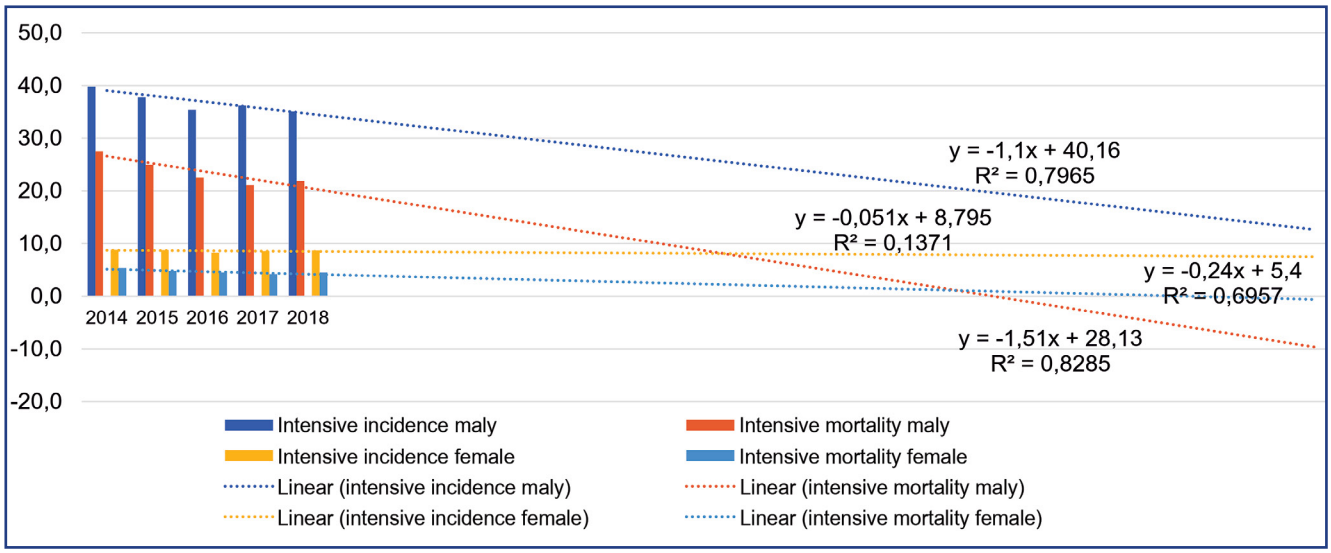


Figure 11 – Gender-related LC incidence and mortality in the Republic of Kazakhstan, both sexes, prognosis

On the one hand, the analysis of LC's epidemiological indicators in the Republic of Kazakhstan showed a general downward trend in both sexes' incidence and mortality. However, we can expect an increase in LC incidence in women, which corresponds to the global trend. Though GLOBOCAN 2018 reports the MIR level in the Republic of Kazakhstan of 89.7%, which is the level of developing countries and therefore reflects some problems in LC diagnostics and treatment, a stable downward trend in mortality from LC in the country is a sign of positive changes in the national cancer service. The primary diagnostics have improved in the study period due to the renewal of the diagnostic equipment in the country and the introduction of methods of molecular genetic studies, which are the basis for a state-sponsored personalized, targeted drug therapy with the use of TKIs, antiangiogenic drugs, and immunotherapy [11].

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