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# Dynamics of change of prostate cancer epidemiology during cancer screening in Kazakhstan

*Prevalence of prostate cancer (PC) in Kazakhstan is uneven. Regions are divided based on high, medium and low baseline incidence. Since 2013, a population screening for PC was implemented in stages. The marked improvement of epidemiological indicators was due to the increase in early detection. Some regularities associated with the screening for PC were noted when analysing standardized indicators of incidence, mortality and their correlation: the increase in incidence, the mortality to incidence reduction rate is 20.8% higher in the screening period compared to the period of traditional diagnosis due to 40.3% more detection of cases with a simultaneous decrease in detection of advanced cases by 36.5%. The average incidence in regions without screening was 43.3%, in the regions of screening – 72.9%. The mortality in the regions is ambiguous depending on the screening. Taking into account the epidemiological evidence that the mortality decrease or a downward trend were not marked, we consider it necessary to abandon the existing model of screening of prostate cancer in Kazakhstan.*

***Keywords:*** *Prostate cancer, incidence, mortality, screening, early detection.*

Kazakhstan is among countries with low PC morbidity and mortality. Still, the Program of development of cancer care in the Republic of Kazakhstan for 2012-2016, approved by the Government of the Republic of Kazakhstan on March 29, 2012, No. 366 [30] has initiated the staged increasing of PC screening starting from 2013: in 2013, the screening was implemented in East Kazakhstan, West Kazakhstan, Kyzylorda, Pavlodar regions, Astana and Almaty, in 2014 – in Aktobe, Atyrau, Karaganda, Qostanay, North Kazakhstan regions. Due to the optimization of the Republican budget, implementation of PC screening in the remaining regions (Akmola, Almaty, Zhambyl, Mangistau, South-Kazakhstan regions) was suspended. This epidemiological analysis of PC prevalence in Kazakhstan during 2001-2015 was conducted to assess the current situation and the impact of screening.

***Materials and methods.*** The subject of research was the refined data from the «Reports on the incidence of malignant neoplasms» and the «Reports on patients with malignant neoplasms» (form № 7, form № 35, approved by the Order of the Minister of Health of the Republic of Kazakhstan No. 128 of March 6, 2013) for 2001-2016 (continuous sampling); data from «Notices of patients with first-ever diagnosis of cancer or other malignancies» (form № 090/u, approved by the Order of the acting Minister of Health of the Republic of Kazakhstan No. 514 of July 31, 2012); data of the Committee on Statistics of the Ministry of National Economy of the Republic of Kazakhstan on the number and sex and age composition of the population of Kazakhstan for 2001-2016. The materials were analysed on the national level and taking into account the administrative-territorial division into 14 regions and 2 cities of republican significance – Astana and Almaty.

The traditional methods were applied for statistical processing [1-3]. Incidence and mortality were calculated as extensive, intensive, standardized, and age indices per 100,000 population. The statistical indices were calculated using IARC recommended methods [4]. Basis for standardized indices was the world standard population of the World Health Organization [5].

***Results and discussion.*** Fig. 1 shows the main figures of PC prevalence. In 2001, it amounted to 3.6 per 100 000 population (both sexes). In 2001-2004, the incidence was stable, with some growth followed by a decrease after 2005. The incidence was constantly growing since 2009, especially after 2013 when the screening was implemented. The growth in 2001-2016 was 241.7%, with annual average growth of T = +8.9%.

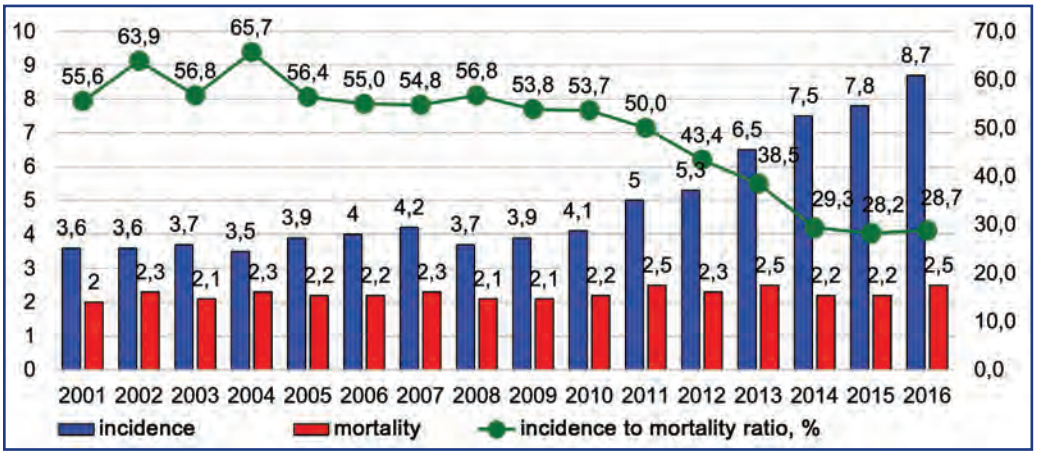



**Figure 1** – Incidence, mortality among the population of the Republic of Kazakhstan from PC, 2001-2016 (intensive indicators per 100,000)

The mortality in 2001 was 2.0 per 100,000 populations with a growth trend and a peak of 2.5% in 2013. The growth in 2001-2016 was 125%, with annual average growth of T =+1.6%. The mortality to incidence ratio was at a maximum level of 65.7% in 2004. It was constantly reducing since 2010 and reached 28.7% in 2016.

The ranking of PC has changed in the period of study. In 2001, PC ranked 14 among other cancers; in 2013, after implementation of screening, it ranked 8; in 2016 it ranked 7. The same growth was in the structure of mortality: it ranked 15, 13, and 11, respectively.

Standardized incidence by regions was studied to assess terrestrial and territorial differences.

Annual average incidence was studied for 2004-2008 and 2009-2013 when the traditional PC diagnostics was mostly used but the National screening program was already implemented (Fig. 2).

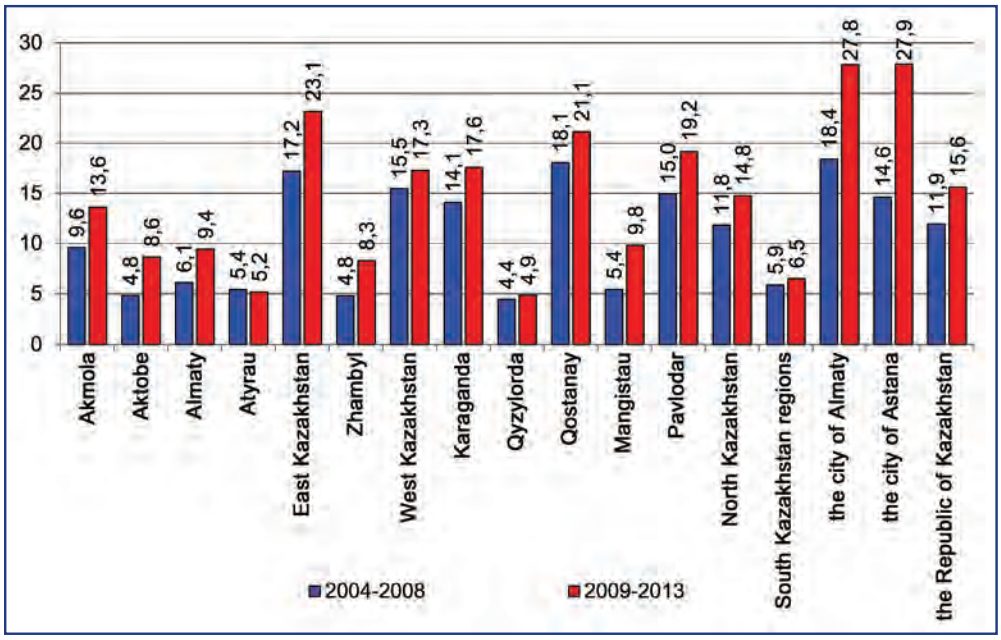



**Figure 2** – Territorial levels of incidence among the population of the Republic of Kazakhstan with malignant neoplasms of the prostate (standardized WHO World indicators per 100,000 male population, 2004-2013)

The annual average standardized PC incidence in Kazakhstan was equal to 11.9 per 100,000 male population in 2004-2008, and 15.6 – in 2009-2013. The incidence varied from 4.4 per 100,000 of male population in Qyzylorda region to 18.4 per 100,000 in Almaty in 2004-2008, and from 4.9 per 100,000 in Qyzylorda region to 27.9 per 100 000 in Astana in 2009-2013. Given the median of mean annual incidence, the country regions were divided into three groups with high, medium and low incidence (Table 1). Assessment of the dynamics of average annual indicators did not influence the low incidence group. West Kazakhstan region and Pavlodar region were removed from the high incidence group. The city of Astana was removed from the medium incidence to high incidence group.

**Table 1** – Ranking of the regions of Kazakhstan in terms of PC incidence, the world standard, per 100 000 of male population

| Incidence rate | Low level | Medium level | High level |
|---|---|---|---|
| Years | 2004-2012 | | |
| Annual average incidence | Up to 7.9 | 8.0-14.9 | 15.0 and above |
| Regions | Qyzylorda, Aktobe, Zhambyl, Atyrau, Mangistau, South Kazakhstan, Almaty regions | Akmola, North Kazakhstan, Karaganda regions, the city of Astana | Pavlodar, West Kazakhstan, East Kazakhstan, Qostanay regions, the city of Almaty |
| Years | 2013-2015 | | |
| Annual average incidence | Up to 9.9 | 10.0-19.9 | 20.0 and above |
| Regions | Qyzylorda, Atyrau, South Kazakhstan, Zhambyl, Aktobe, Almaty, Mangistau regions | Akmola, North Kazakhstan, West Kazakhstan, Karaganda, Pavlodar regions | Qostanay, East Kazakhstan regions, the city of Almaty, the city of Astana |

The annual average growth rate in the country was 31.1%. Nearly all regions of the country showed a positive growth – from 10.2% in South Kazakhstan, 11.4-11.6% in Qyzylorda and West Kazakhstan regions to 73% and above in Aktobe, Zhambyl, Mangistau regions. The highest growth was found in Astana (T=91,1%). Only Atyrau region had a negative growth of T=-3.7%.

The regions with low basic incidence had the highest growth rates what evidenced the improvement of quality of diagnostics. Thus, the analysis of incidence during two 5-year periods has shown a growth in PC detection in all regions of the country regardless the implementation of screening. It was associated with an increase in the level of oncological care, diagnostics and registration of cancer pathology.

The annual average incidences before screening (2004-2012) and after screening (2013-2015) were compared to assess the impact of screening on the incidence and mortality levels.

The intensive (crude) annual average RC incidence in the RK in 2004-2012 amounted to 8.9‰, at that, all the regions were split into two groups – below the national level (low incidence group, from 2.1‰ in Qyzylorda region to 4.9‰ in Almaty region) and above the national level (the regions with medium and high incidence, from 9.3‰ in the city of Astana to 17.5‰ in Qostanay region).

The same situation with region ranking was found during the comparison of annual average standardized indices in the same period, only the annual average incidence nation-wide was 12.9‰ (Fig. 3). The incidence in low incidence regions varied from 4.4‰ in Qyzylorda region to 7.5‰ in Almaty region, with the exception of Mangistau region that ranked last but one in the intensive ranking and 11th – in standardized ranking.

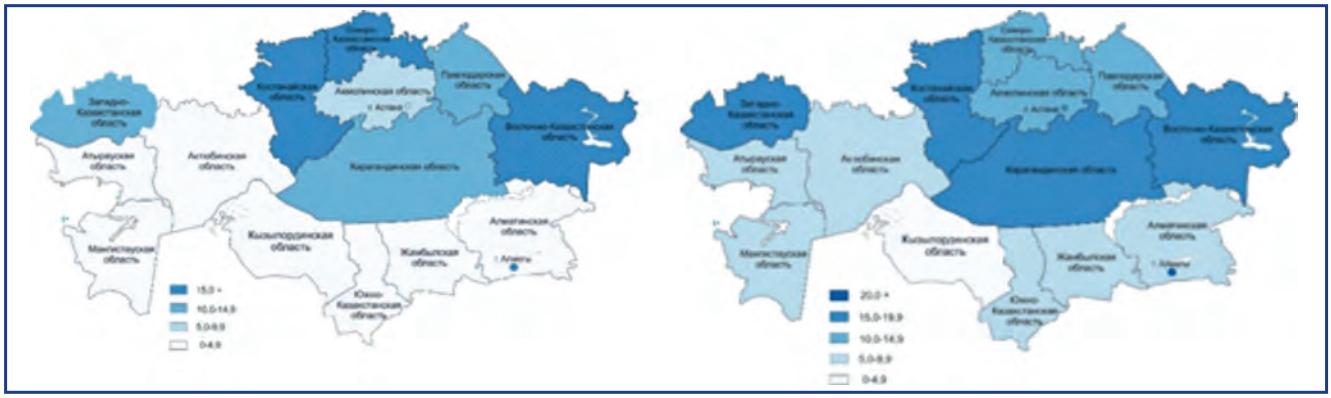


**Figure 3** – Cartograms of the average annual RC incidence among the population of the Republic of Kazakhstan per 100,000 male populations, 2004-2012. Intensive (left) and standardized (right) indices

Figure 4 shows cartograms of incidence in the screening period. The crude annual average incidence in the RK in 2013-2015 was 15.5‰ (T = 74.2%), standardized – 22.3‰ (T = 72.9%). The average incidence rates have become an order of magnitude higher. If the step of the colour intensity corresponding to the incidence rate was equal to 5‰ before screening, it has reached 10‰ during the screening.

In general, grouping of regions according to the levels of low, medium and high incidence remained according to Table 1, but the ranking criteria have changed. Thus, the low incidence group now included the regions with the incidence up to 15‰, and the high incidence group was from 30‰ and above.

Incidence growth rates in intensive indices varied from 18.5% in Atyrau region to 130.1% in Pavlodar region, in standardized indices – from 23% in South Kazakhstan region to 113% in Pavlodar region. The average level of growth in the regions of no screening was 43.3% (in crude and standardized indices), in the regions of screening – 77% (in crude indices) and 72.9% (in standardized indices), what was a significant difference.

Figure 5 shows the rates of growth of annual average incidence during the study period split by regions. Figure 6 shows the cartograms of annual average mortality from PC among male population of Kazakhstan in 2004-2012.

High mortality was found in the regions with high incidence – East Kazakhstan, Qostanay, North Kazakhstan, Pavlodar regions and the city of Almaty. In those regions, the annual average mortality exceeded the republican level of 4.7 per 100,000 of male population (crude) and 7.0‰ (standardized).

Visually, the mortality in 2013-2015 in intensive indices split by regions has not changed. Still, standardized indices of annual average mortality during the screening period show a different situation (Fig. 7). With the nation-wide mortality index of 6.8‰, Mangistau (6.7‰) and Zhambyl (5.7‰) regions have joined the group with a relatively high mortality.

A negative growth in mortality noticed during the periods of study was equal to T= -2.1% in intensive indices and T= -2.9% in standardized indices.

Fig. 8 shows an ambiguous situation in terms of changing the dynamics of mortality by regions. Thus, there was a growth in average annual mortality in Akmola, Atyrau,

Zhambyl, Qyzylorda, Mangistau, and Pavlodar regions, the cities of Astana and Almaty, with quite a significant growth in Zhambyl, Mangistau regions and the city of Astana: from 35% to 46% in standardized indices.

It is too early to assess the impact of screening on the dynamics of changes in mortality rates, still the knowledge of the structure, reasons and tendency of mortality will allow a proper interpretation of efficiency of screening.

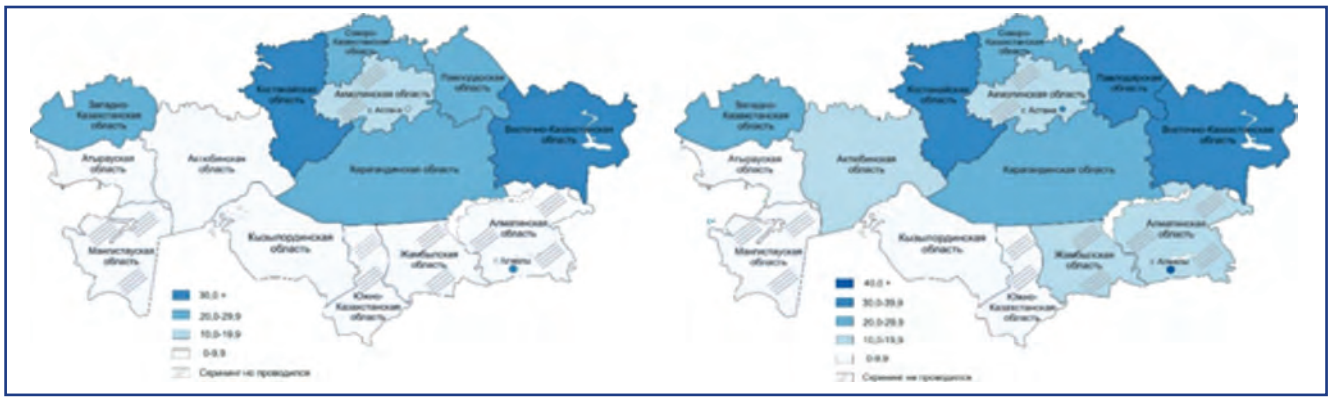


**Figure 4** – Cartograms of average annual RC incidence among the population of the Republic of Kazakhstan per 100,000 male populations, 2013-2015. Intensive (left) and standardized (right) indices

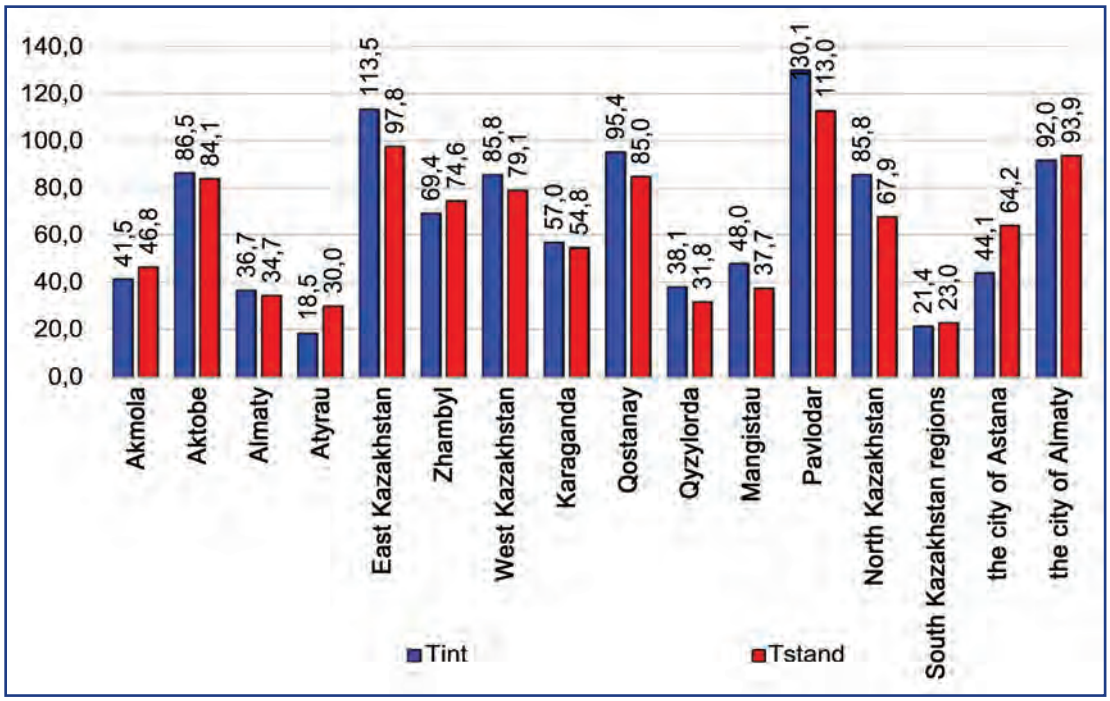



**Figure 5** – Growth rates in average annual incidence of prostate gland malignancies in intensive and standardized indices per 100,000 male population, in 2004-2012 and 2013-2015

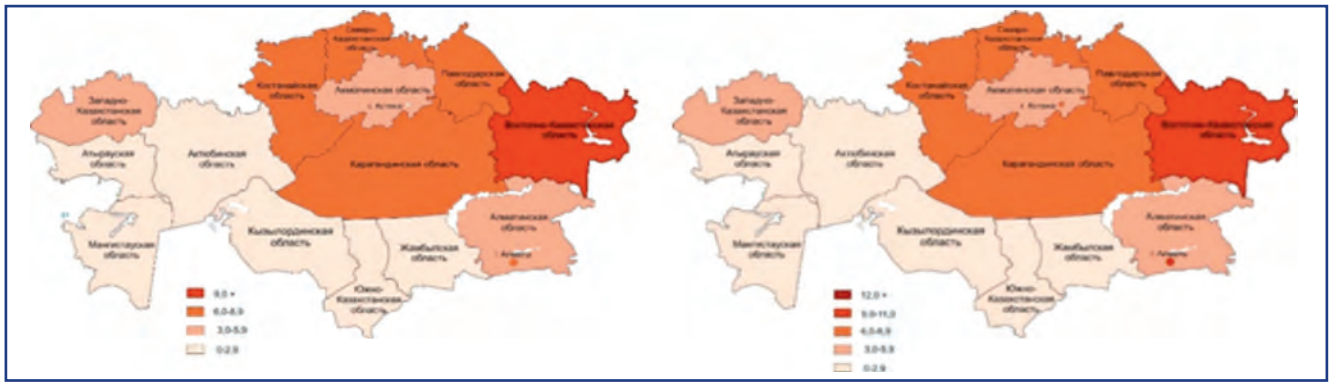


**Figure 6** – Cartograms of average annual RC mortality of the RK population per 100,000 male population, 2004-2012. Intensive (left) and standardized (right) indices

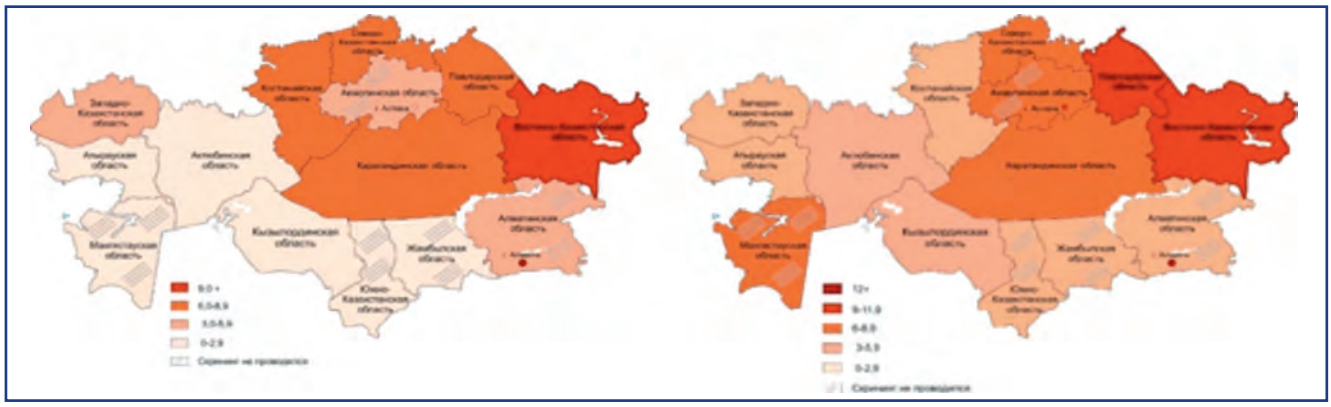


**Figure 7** – Cartograms of average annual RC mortality of the RK population per 100,000 male population, 2013-2015. Intensive (left) and standardized (right) indices

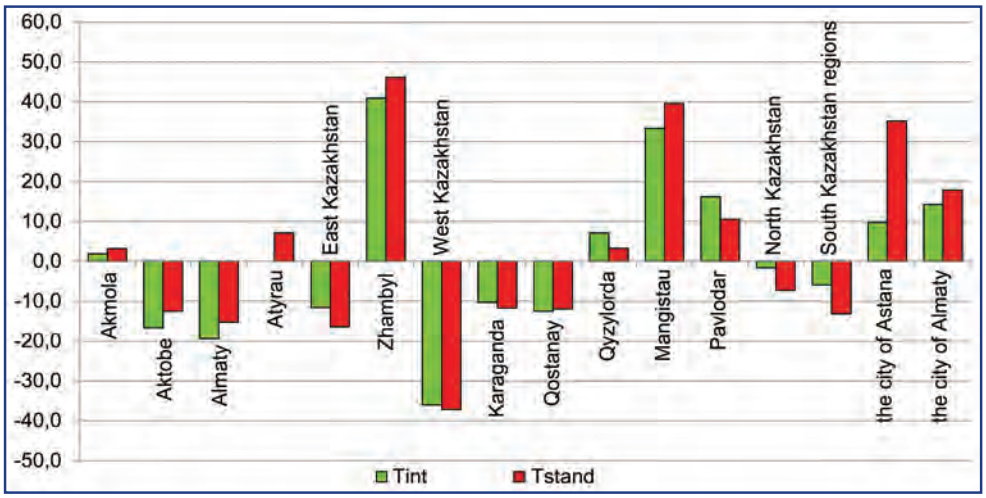
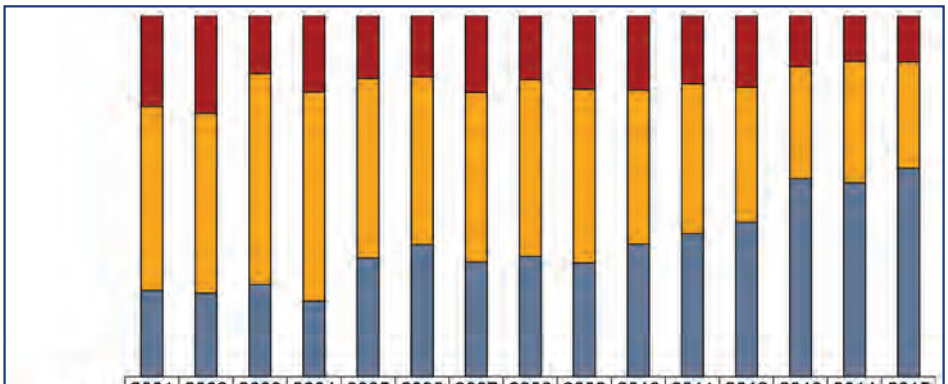



**Figure 8** – Rates of growth of annual average mortality of prostate gland malignancies in intensive and standardized indices per 100,000 of male population, in 2004-2012 and 2013-2015

Early PC detection is an important and main criterion of screening efficiency. Besides the increased incidence, the increased share of early stages of PC is also important. The comparison of early detection by regions of screening has been the other task of the study.

Fig. 9 shows a constant increase of share of stages I-II since 2001, mainly due to a decrease in the share of stage III.



| | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stage IV | 25,1 | 27 | 16 | 21,1 | 17,3 | 16,9 | 21,2 | 17,7 | 20,4 | 20,6 | 18,8 | 19,8 | 14,1 | 12,6 | 12,8 |
| Stage III | 51 | 49,9 | 58,5 | 58 | 49,9 | 46,5 | 47,1 | 49 | 48,1 | 42,7 | 41,6 | 37,5 | 31,1 | 33,7 | 29,5 |
| Stages I-II | 23,9 | 23,1 | 25,5 | 20,9 | 32,8 | 36,6 | 31,7 | 33,3 | 31,5 | 36,7 | 39,6 | 42,7 | 54,8 | 53,7 | 57,7 |

**Figure 9** – Dynamics of distribution of stages of primary cases of PC, %, 2001-2015

It was especially evident from the moment of implementation of screening for PC. Thus, the share of stages I-II in 2012 was 42.7% vs. 54.8% in 2013. The annual average growth rate was Tav= +19.5%. During screening, the rates decreased up to Tav= +13.0% with the same positive trend.

The assessment of dynamics of detection of advanced stages of PC by traditional diagnostics has shown a stable indice value ($R^2$ = 0.0028) at a varied growth from -18% (2005) to +25.4% (2007). The annual average growth amounted to Tav=+0.8%. During the screening, there was a clear reduction of stage IV share (У = -0,65x + 14.467, $R^2$ = 0.6369), approaching the statistical significance. The annual average growth was negative and amounted to Tav= -5.1%. In total, during 2013-2015 the early diagnostics of PC in the regions of screening was higher than in the regions of "traditional diagnostics". The regions of screening had a better share of early detection during screening than during "traditional diagnostics" (Fig. 10).

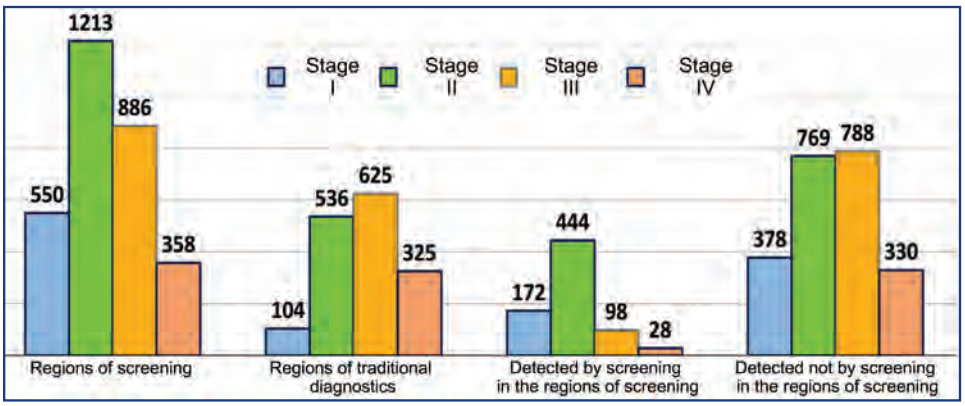



**Figure 10** – Distribution by stages of newly diagnosed cases of PC depending on screening, 2013-2015

The 11 regions of Kazakhstan with screening have detected 1,763 of stage I-II PC cases (58.6%) vs. 1244 (41.4%) cases of stage III-IV PC. 5 regions with no screening had 372 (43.5%) cases of stage I-II PC, and 483 (56.5%) cases of stage III-IV PC, RR 1.35 95% CI (1.24–1.46), OR 1.84 95% CI (1.58–2.15). In total, 6.16 cases have to be screened to prevent detection of 1 case of stage III-IV PC.

During screening, 616 (83%) cases of stage I-II PC and 126 (17.0%) cases of stage III-IV PC were detected. In the same regions, the "traditional methods" have revealed 1147 (50.7%) cases of stage I-II PC vs. 1118 (49.3%) cases of stage III-IV PC, RR 1.64 95% CI (1.56–1.73), OR 4.77 95% CI (3.87–5.87). In total, 3.09 cases have to be screened in target groups to prevent detection of 1 case of stage III- IV PC.

Besides early detection, timely treatment of the detected pathology is required. The mortality to incidence ratio that characterizes the level of development of cancer care in the country has exceeded 60% in 2004. This indice is reducing with the improvement of diagnostics and treatment. It especially went down in 2013-2015 thanks to screening as it resulted in the growing incidence and stabilized mortality.

Study of the dynamics of PC mortality to incidence ratio (in intensive and standardized indices) by regions has revealed the following. Some regions showed a stable decrease in PC mortality to incidence ratio – Akmola, East Kazakhstan, Karaganda, Qostanay regions and the city of Almaty. In some regions, the ratio has stabilized with a stable downward trend – in Aktobe, Almaty, West Kazakhstan regions. The situation in Mangistau, Pavlodar regions is of concern. The situation in Atyrau region is very unfavourable since from the implementation of screening this ratio has been consistently growing – from 15.9% in 2013 to 83.8% in 2015 in standardized indices.

To assess the impact of screening on the national standardized rates of incidence and mortality, the period of study was divided into the period of traditional diagnostics (2004-2010), preparation period (2011-2012) and the period of screening (2013-2016). The levels of PC incidence varied from 11.0‰ in 2004 to 26.6 in 2016, the mortality – from 7.2 in 2004 to 6.8‰ in 2016. During the period of traditional diagnostics, standardized indices of incidence have grown by 2.1‰, the annual growth rate of incidence was Tav=+4.0%. in the preparation period, there was a growth in incidence from 15.9‰ to 16.7, T = +5.0%. During the screening period the standardized indice of incidence has grown by 6.5‰; the annual growth rate of incidence was Tav = +9.8% what was nearly 2.5 times higher than during the period of traditional diagnostics, P ≤ 0.05 (Fig. 11).

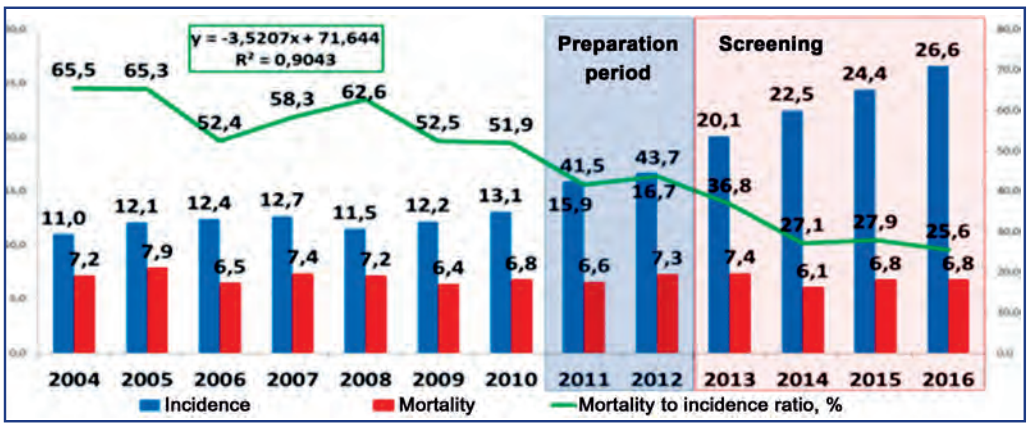



**Figure 11** – Incidence, mortality among the population of the Republic of Kazakhstan from PC, 2004-2016 (standardized indicators per 100,000 populations)

The standardized rates of mortality in the period of traditional diagnostics have decreased by 0.4 per 100,000 populations; the growth rate had direction in different years and varied from +9.7% in 2005 to -17.7% in 2006. The annual growth rate of incidence was negative and equal to Tav = -0.4%.

During the screening period the mortality has reduced by 0.6‰, Tav= -2.0%. That is, the modulus of the average annual growth rate was almost 5 times higher than the same indicator of the period of traditional preparation. It should be noted a mixed trend changes in mortality rates in a given period: in the second year of screening (2014) it went down (T = -17.6%), then it went up (T = +11.5%) and then stabilized. In assessing the mortality rate for 2004-2016, it was established that despite the linear downward tendency of the mortality rate, the coefficient of determination was close to zero (R2 = 0.1557) indicating the unstable nature of the changes. Coefficients of determination in the period of traditional diagnostics ($R^2$ = 0.2609) and the period of screening ($R^2$ = 0.2126) were much below 50% indicating that no correlation between the mortality rate and the organizational measures taken to reduce it.

It is evidently too early to note the impact of screening on the dynamics of changes in mortality rates still the knowledge of the structure, reasons and tendency of mortality will allow a proper interpretation of efficiency of screening. It is premature to make unambiguous conclusions.

Thus, the analysis of the epidemiological situation of PC in Kazakhstan as a whole indicates a positive effect of PC screening. However, the absence of a decrease in mortality or its trend raises concerns about the quality of PC screening. Considering epidemiological evidence, we consider it necessary to abandon the existing model of screening of prostate cancer in Kazakhstan.

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