Epidemiological Characteristics of Male Reproductive Cancers in the Republic of Kazakhstan: Ten-Year Trends

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Abstract

Background: Epidemiology of male reproductive cancers (MRC) is relatively well studied in developed world nations, but little is known about Central Asian states. We aimed to analyze the changing trends for incidence, mortality and 5-year survival MRC across provinces of the Republic of Kazakhstan.

Methods: This was a retrospective cohort study based on data obtained from the Kazakhstan Cancer Registry, which serves as a nationwide database for all histologically confirmed cancer cases. From this, information on all male patients with prostate (PCa) and testicular cancers (TCa) was retrieved for the period from 2010 to 2019. The statistical analysis of official data on incidence, survival, and mortality rates was performed for both the whole country and its provinces.

Results: There was a substantial instability of PCa incidence rates, attributed to the execution of screening program from 2013 to 2017. Still, there was a lack of variations in TCa incidence rates. However, PCa screening program had no influence on reduction of mortality rates, which remained relatively stable. There is much heterogeneity between country's provinces in incidence and mortality rates. TCa patients were younger than PCa patients and had better 5-year survival.

Conclusion: As compared with many other countries, Kazakhstani men with PCa and TCa have poorer five-year survival, which requires further investigation. Moreover, a careful analysis of diagnostic and treatment strategies utilized at different hospitals across the country would be highly desirable.

Keywords: Prostate cancer; Testicular cancer; Incidence; Mortality; 5-year survival

Introduction

Male reproductive cancers (MRC) constitute a public health problem for both the developed and developing world. The burden of prostate cancer (PCa) is such high that it is the second leading site among non-skin cancers in men worldwide, while testicular cancer (TCa) is the

most common cancer in young men (1). In fact, MRC represent a group of heterogeneous disorders with varying etiology, histopathology and clinical presentation. Moreover, each cancer has a subset of distinct subtypes that differ by age at diagnosis, race, treatment responsiveness, and prognosis. Senile age, African ancestry, and a positive family history were reported to be the major risk factors for PCa, while none of environmental or behavioral risk factors was definitely attributed to it (2). As for TCa, developmental anomalies of gonads and impaired sex differentiation were described as the conclusive causes, whilst environmental and behavioral factors may also play a role, although it was not definitely ascertained yet (3).

Different MRC show non-identical epidemiological trends, explained by a number of reasons. Globally, PCa has downward trends for both incidence and mortality due to widespread introduction of prostate-specific antigen (PSA) screening, started in the early 1980s and increased public awareness of the disease. According to the estimates of Global Cancer Observatory, in 2020 the global cumulative incidence of PCa equaled 3.86% for men aged 0-74 yr and it was the highest in countries of Northern Europe (10.40%). Meanwhile, the cumulative mortality rate in men aged 0-74 yr constituted 0.63% being the highest in countries of Middle Africa (2.55%) (4). As for the TCa, the incidence rates are growing and mortality trends vary significantly between different countries despite relative ease in diagnosis and treatment (5). Such, in 2020 the global cumulative incidence for men from 0 to 74 yr was 0.14% with the highest rates observed in Western Europe (0.74%). In the same year the global cumulative mortality from TCa constituted 0.02% being the highest in Central America (0.07%) (4). Besides, both TCa and PCa present a substantial burden for population of countries with high human development index. For instance, National Cancer Institute projected that the average years of life lost (YLL) in 2018 due to TCa were the highest of all adult cancers and constituted 34.7 years. Still, in the same year the average YLL due to PCa were the lowest of all adult cancers

and equaled 9.9 years (6). As for the years of healthy life lost due to disability (YLD), the global burden of disease estimates for 2015 were 33.1% for PCa and 35.5% for TCa (7).

Although epidemiology of MRC is relatively well studied in developed countries, there is dearth of information about the developing world, to which belong Central Asian states. However, epidemiological evidence witnesses to a large variability in incidence and mortality rates between different countries and even provinces within a country (8). Most likely, this could be explained by different underlying societal and economic factors as well as by implementation of primary and secondary prevention programs. Kazakhstan is a Central Asian state with rapid economic growth, which is transformed into social development (9). Such, since 2011 the country's government started implementing a range of public health programs targeted on improvement of specialized medical care, including oncology practice (10). The impact of these programs on mortality prevention and early detection of MRC has not yet been fully evaluated. We aimed at analyzing the changing trends for incidence, mortality and 5-year survival from MRC across provinces of the Republic of Kazakhstan over a period of 10 years (from 2010 to 2019).

Materials and Methods

Study design and procedures

For this retrospective cohort study, we retrieved data from the Kazakhstan Cancer Registry (KCR), managed by the Kazakh Research Institute of Oncology, Radiology, and serves as a unified database for all histologically confirmed cancer cases in the country. We obtained information on all male patients with PCa (ICD-10-CM Code C61) and TCa (ICD-10-CM Code C62) registered in the country within the period from 2010 to 2019. Overall, there were 5486 cases of PCa and 1293 cases of TCa, which composed the sample for this study. In Kazakhstan, the Ministry of Health obligates all medical doctors operating in the country's primary health care facilities

to report on newly diagnosed cancer patients to the provincial oncological dispensaries. A standardized special form is established for this and provincial oncological dispensaries transfer these data to the electronic database, i.e. KCR. We relied solely on the anonymized data and extracted the information related to patients' date of birth, date of diagnosis, date of death, and cancer stage. The data were analyzed for the country in general as well as for separate provinces. Data on the overall number of male population and the number by age were demographic estimates and were extracted from the statistical compilation issued by the Agency of Statistics of the Republic of Kazakhstan (11).

An approval from the Ethical Committee of Semey Medical University, Semey, Kazakhstan (protocol 2 from 18 Oct 2019) was obtained. Because no identifying patient information was available to the research team, the informed consent was waived. All study methods relied on the relevant ethics guidelines and regulations.

Statistical analysis

Incidence and mortality rates were calculated per 100,000 (0/0000) male population. ICD-10 classification was applied to categorize cancers by stage with subsequent coding as I-II, III and IV. We ranged all country provinces by incidence and mortality rates from minimum to maximum. The overall 5-year survival was calculated as the relation of the number of patients that were alive and followed-up at the end of a calendar year to the total number of patients at the end of a calendar year.

On the next step of our analyses we assessed the upward trend (growing incidence and mortality rates) and the downward trend (declining incidence and mortality rates) for the period from 2010 to 2019 with the help of simple linear regression. The Standard Model equation used was as follows:

$Y=\beta_0+\beta_1*X+\boldsymbol{\varepsilon}$

where Y was a value of dependent variable, X was a value of predictor variable, β_0 was a constant, β_1 was a regression coefficient, and $\boldsymbol{\varepsilon}$ was a random error.

The outcomes of statistical tests were presented as arithmetic means for the study period and non-standardized linear regression coefficients (B) with 95% confidence intervals (CI). For each regression coefficient, the levels of statistical significance were assessed. All statistical analyses were carried out via SPSS software, ver. 20.0 (IBM Corp., Armonk, NY, USA).

Results

Figure 1 depictures the sex-specific incidence rates for selected MRC. During 2010-2019, PCa was the most common MRC with incidence rate ranging from 8.61 per 100,000 male population in 2010 to 17.95 in 2016. Much heterogeneity in incidence rates could be attributed to implementation of PCa screening program started in 2013 and was ended in 2017 (12).
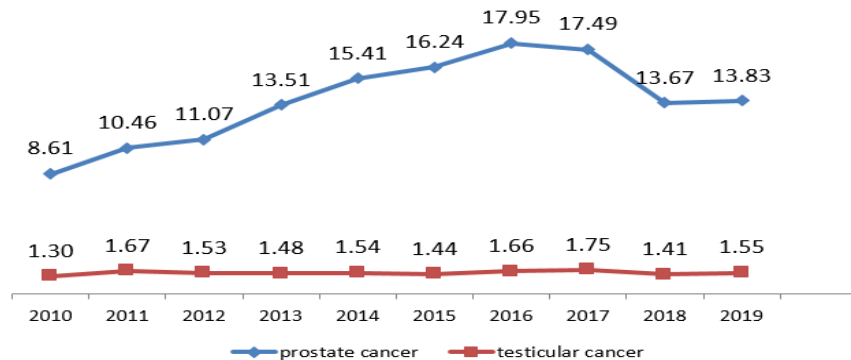

Fig. 1: Incidence rates for prostate and testicular cancers over the period 2010 to 2019 (per 100,000 male population)

Already in the next year following the program's termination, the incidence rate of PCa dropped to 13.67 per 100,000 male population and continued to decline. Meanwhile, the incidence of TCa was characterized by greater stability, ranging between 1.30 and 1.75 per 100,000 male population. The mortality rates from MRC were characterized by greater stability. Such, the mor-

tality from PCa ranged between 4.27 per 100,000 male population in 2018 and 5.17 in 2013. As for TCa, the mortality rates from this disease were substantially lower than those from PCa. The minimum value was observed in 2010 and constituted 0.01 per 100,000 male population, while the maximum value was seen in 2013 and amounted to 0.57 per 100,000 male population (Fig. 2).
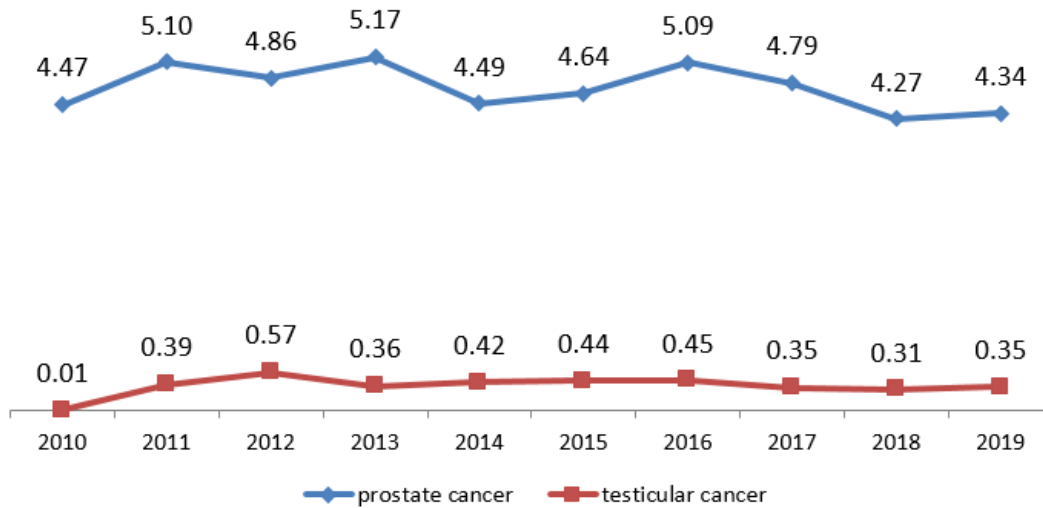

Fig. 2: Mortality rates for prostate and testicular cancers over the period 2010 to 2019 (per 100,000 male population)

Within the period of 10 years (2010-2019), the national incidence rates for PCa constituted 13.83 per 100,000 male population, while those for TCa amounted to 1.53 per 100,000 male population. The highest incidence rates of PCa were observed in northern and northeastern provinces of Kazakhstan: East Kazakhstan region (30.47 per 100,000 male population) followed by Kostanay region (28.93 per 100,000 male population) and North Kazakhstan region (28.91 per 100,000 male population). The same was true for incidence rates of TCa, which reached the highest levels in North-Kazakhstan region (2.17 per 100,000 male population), followed by East Kazakhstan region (2.14 per 100,000 male population) and Pavlodar region (1.89 per 100,000 male

population). Meanwhile, southern and western provinces of Kazakhstan (South Kazakhstan, Atyrau and Mangystau regions) were characterized by the lowest incidence rates of both PCa and TCa (Table 1). Table 3 presents the proportion of early stage cancers at the time of diagnosis across regions of Kazakhstan. The lowest proportions of I-II stage PCa were noted for South-Kazakhstan and Mangystau provinces (0.98 and 1.70, respectively), although this was not statistically significant. The highest proportions of I-II stage PCa were reported for East Kazakhstan (21.47) and North Kazakhstan provinces (17.59). With respect to the national rates, these were equal to 7.26 for PCa and to 1.23 for TCa.

Table 1: Incidence rates with 95% CI for male reproductive cancer across regions of Kazakhstan, 2010-2019 (per 100,000 male population)

Region	*Prostate cancer*		*Testicular cancer*	
	Incidence	Regression coefficient with 95% CI	Incidence	Regression coefficient with 95% CI
South Kazakhstan	3.28	0.91 (0.14; 0.31) $P \leq 0.001$	1.27	-0.15 (-8.63; 5.98) $P= 0.687$
Atyrau	3.66	0.70 (0.23; 2.32) $P= 0.023$	1.29	0.18 (-3.71; 5.94) $P= 0.609$
Mangystau	4.05	0.41 (-0.75; 2.55) $P= 0.243$	1.05	0.49 (-1.66; 8.91) $P= 0.153$
Kyzylorda	5.11	0.47 (-0.16; 0.75) $P= 0.170$	1.52	0.09 (-3.22; 4.07) $P= 0.795$
Zhambyl	6.00	0.56 (-0.27; 2.99) $P= 0.090$	1.41	-0.49 (-5.64; 1.05) $P= 0.152$
Almaty	6.82	0.79 (0.78; 3.49) $P= 0.007$	1.31	-0.19 (-5.70; 3.48) $P= 0.593$
Aktobe	6.94	0.86 (0.58; 1.66) $P= 0.001$	1.41	0.10 (-2.74; 3.53) $P= 0.779$
Nur-Sultan city	11.66	-0.03 (-1.13; 1.05) $P= 0.933$	1.50	0.54 (-0.72; 6.12) $P= 0.107$
Akmola	14.16	0.88 (0.43; 1.12) $P= 0.001$	1.57	0.63 (-0.01; 6.80) $P= 0.050$
West Kazakhstan	16.35	-0.00 (-0.49; 0.49) $P= 0.999$	1.87	-0.08 (-3.81; 3.14) $P= 0.831$
Karaganda	21.28	0.53 (-0.06; 0.47) $P= 0.114$	1.59	0.36 (-3.75; 10.40) $P= 0.310$
Pavlodar	24.23	0.55 (-0.04; 0.37) $P= 0.096$	1.89	0.33 (-2.10; 5.22) $P= 0.355$
Almaty city	25.26	0.17 (-0.33; 0.51) $P= 0.631$	1.91	-0.32 (-6.21; 2.55) $P= 0.364$
North Kazakhstan	26.18	0.91 (0.14; 0.31) $P \leq 0.001$	2.17	0.33 (-2.21; 5.53) $P= 0.351$
Kostanay	28.91	0.45 (-0.09; 0.38) $P=0 .195$	1.56	0.08 (-3.99; 4.81) $P= 0.835$
East Kazakhstan	30.47	0.77 (-0.10; 0.52) $P= 0.009$	2.14	0.23 (-1.42; 2.56) $P= 0.529$
Kazakhstan Republic	13.83	0.69 (0.10; 1.26) $P= 0.027$	1.53	0.28 (-11.29; 23.76) $P= 0.435$

The national mortality rates from PCa were 4.73 per 100,000 male population and those for TCa were 0.36 per 100,000 male population. The highest PCa mortality rate was established in East Kazakhstan region (8.65 per 100,000 male population) and the highest TCa mortality rate was reported in Zhambyl region (0.76 per 100,000 male population). The lowest PCa mortality rate was seen in Kyzylorda region (1.42 per 100,000 male population), while the lowest TCa mortality rate was observed in Mangystau region (0.19 per 100,000 male population) (Table 2)

Table 2: Mortality rates with 95% CI for male reproductive cancer across regions of Kazakhstan, 2010-2019 (per 100,000 male population)

Region/city	Prostate cancer		Testicular cancer	
	Mortality	Regression coefficient with 95% CI	Mortality	Regression coefficient with 95% CI
Kyzylorda	1.42	0.01 (-4.76; 4.93) $P= 0.968$	0.64	-0.16 (-9.88; 6.66) $P= 0.665$
Atyrau	1.54	0.13 (-1.69; 2.36) $P= 0.713$	0.56	-0.06 (-5.42; 4.72) $P= 0.876$
South Kazakhstan	1.73	0.013 (-6.83; 9.38) $P= 0.725$	0.23	-0.09 (-25.02; 20.05) $P= 0.806$
Mangystau	1.98	-0.01 (-4.47; 4.55) $P= 0.985$	0.19	0.27 (-4.53; 9.21) $P= 0.454$
Aktobe	2.84	-0.27 (-3.00; 1.47) $P= 0.452$	0.26	-0.38 (-9.17; 3.02) $P= 0.279$
Zhambyl	2.91	0.10 (-2.23; 2.90) $P= 0.772$	0.76	-0.30 (-5.87; 2.63) $P= 0.405$
Almaty	3.04	-0.55 (-7.53; 0.81) $P= 0.100$	0.45	-0.40 (-15.15; 4.57) $P= 0.251$
West Kazakhstan	4.19	-0.10 (-2.10; 1.62) $P= 0.774$	0.33	-0.37 (-15.47; 5.28) $P= 0.290$
Nur-Sultan	5.51	0.18 (-1.97; 3.10) $P= 0.623$	0.29	-0.25 (-16.82; 8.77) $P= 0.489$
Kostanay	6.19	-0.73 (-3.84; -0.51) $P= 0.017$	0.47	-0.49 (-8.44; 1.55) $P= 0.150$
Akmola	6.37	0.11 (-1.22; 1.61) $P= 0.764$	0.50	0.02 (-5.31; 5.56) $P= 0.960$
Karaganda	6.54	-0.77 (-3.14; -0.60) $P= 0.009$	0.43	0.06 (-8.14; 9.48) $P= 0.865$
North Kazakhstan	6.89	0.16 (-1.15; 1.72) $P= 0.657$	0.40	0.04 (-7.29; 7.98) $P= 0.919$
Pavlodar	8.31	0.51 (-0.39; 2.60) $P= 0.128$	0.76	-0.63 (-7.10; -0.03) $P= 0.048$
Almaty city	9.08	-0.25 (-1.62; 0.84) $P= 0.488$	0.44	0.09 (-6.94; 8.64) $P= 0.807$
East Kazakhstan	8.65	-0.05 (-1.27; 1.14) $P= 0.900$	0.44	0.33 (-4.49; 11.13) $P= 0.356$
Kazakhstan Republic	4.73	-0.44 (-10.54; 2.61) $P= 0.202$	0.36	0.22 (-12.13; 21.48) $P= 0.539$

Table 3: Proportion of stage I-II cancers at the time of diagnosis with 95% CI across regions of Kazakhstan, 2010-2019 (per 100,000 male population)

Region/city	Prostate cancer		Testicular cancer	
	Proportion	Regression coefficient with 95% CI	Proportion	Regression coefficient with 95% CI
South Kazakhstan	0.98	0.28 (-2.59; 5.53) $P= 0.427$	1.52	-0.44 (-2.79; 0.69) $P= 0.201$
Mangystau	1.70	-0.03 (-3.91; 3.65) $P= 0.939$	0.82	0.32(-2.64; 6.42) $P= 0.364$
Atyrau	2.13	0.64 (0.03; 2.51) $P= 0.046$	0.90	0.32 (-3.49; 8.56) $P= 0.360$
Zhambyl	3.10	0.72 (0.65; 5.09) $P= 0.018$	1.31	-0.36 (-6.42; 2.26) $P= 0.302$
Almaty	3.21	0.90 (1.62; 3.68) $P\leq 0.001$	0.95	-0.18 (-8.23; 5.20) $P= 0.617$
Kyzylorda	3.65	0.41(-0.22; 0.75) $P= 0.242$	1.33	-0.07 (-4.85; 4.10) $P= 0.852$
Aktobe	4.04	0.72 (0.29; 2.29) $P= 0.018$	1.16	-0.02(-3.35; 3.21) $P= 0.961$
Akmola	6.35	0.54 (-0.29; 2.49) $P= 0.106$	1.18	0.78 (1.65; 7.70) $P= 0.007$
Karaganda	6.84	0.74 (0.11; 0.74) $P= 0.015$	1.28	0.19 (-6.07; 9.92) $P= 0.594$
Nur-Sultan	8.20	-0.72 (0.20; 1.19) $P= 0.019$	1.23	0.63(-0.01; 6.76) $P= 0.051$
West Kazakhstan	9.84	-0.15 (-0.78; 0.53) $P= 0.670$	1.74	0.05 (-3.59; 4.06) $P= 0.890$
Almaty city	10.31	0.48 (-0.19; 0.98) $P= 0.158$	1.29	-0.52 (-9.04; 1.27) $P= 0.121$
Kostanay	15.41	0.64 (0.00; 0.37) $P= 0.047$	1.15	0.09 (-5.16; 6.43) $P= 0.807$
Pavlodar	16.45	0.57 (-0.03; 0.41) $P= 0.085$	1.49	0.32(-2.94; 7.18) $P= 0.362$
North Kazakhstan	17.59	0.91 (0.14; 0.31) $P\leq 0.001$	1.77	0.31(-1.59; 3.74) $P= 0.379$
East Kazakhstan	21.47	0.63 (-0.01; 0.56) $P= 0.053$	1.75	0.31 (-1.48; 3.49) $P= 0.378$
Kazakhstan Republic	7.26	0.76 (0.27; 1.53) $P= 0.011$	1.23	0.27(-11.39; 23.48) $P= 0.447$

Figure 3 depictures the overall 5-year survival of PCa and TCa patients. In general, the survival remained stable over 2010-2019 with mild increase for TCa, observed within the last two years (2018-2019). The survival for TCa patients was two-fold higher than that for PCa patients, possibly reflecting their younger age. TCa survival ranged from 55.6% in 2010 to 62.2% in 2019, while PCa survival ranged between 20.7% in 2016 and 32.5% in 2011.
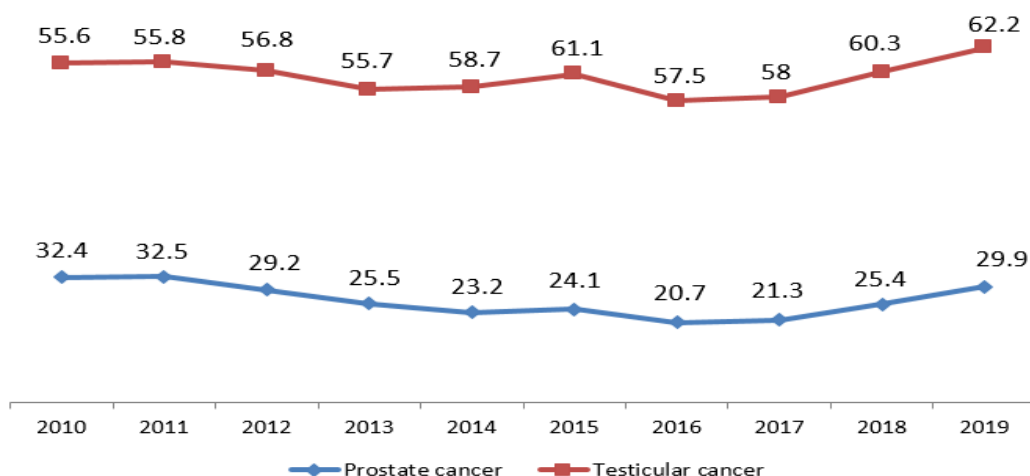
Fig. 3: The overall five-year survival of patients with prostate and testicular cancers in the Kazakhstan Republic in 2010-2019 (%)

Discussion

This study was focused on deciphering the changing trends for incidence, mortality and survival from MRC across provinces of the Republic of Kazakhstan over a period of 10 years. The main findings of this study include substantial instability of PCa incidence rates following application of screening program with lack of variations in TCa incidence rates reflecting absence of targeted control programs. However, execution of PCa screening program had no influence on reduction of mortality rates, which remained relatively stable over the study period. Moreover, there is much heterogeneity between the country's provinces in relation to incidence and mortality from both cancer types with higher rates observed in northern and northeastern provinces. Finally, TCa patients were younger than PCa patients were and had better 5-year survival.

The higher incidence rates seen in northern and northeastern provinces of Kazakhstan could be explained in two ways. On one hand, these provinces might have better services for early cancer identification resulting in bigger number of patients diagnosed. However, the same provinces face higher mortality rates, which make the hypothesis on the role of health care services rather unlikely. There is an alternative explanation of

this phenomenon, i.e. contribution of environmental factors as northern and northeastern provinces of Kazakhstan are characterized by the cold climates, developed heavy industry and proximity of the Semipalatinsk Nuclear Test Site (SNTS) – the largest Soviet testing ground for nuclear weapons (13). Besides, Northern provinces of Kazakhstan are more prone to Vitamin D deficiency (14), which contributes to epidemiology of both PCa (15) and TCa (16).

PCa screening program based on detection of serum PSA was implemented in Kazakhstan during 2013-2017. The rationale behind its closure was low efficiency despite substantial government funds allocated for the program's implementation. Such, epidemiological and economic evaluation of PCa screening program in Pavlodar Province showed that the average detection rate among the target population group equaled 0.23% within the period of 5 years (10). Globally, PCa screening by means of PSA detection is a matter of debate as it has complex relationship with cancer mortality (17). Obviously, for PSA screening program to be re-initiated in Kazakhstan, it has to be undergone to careful revision and re-planning.

In our study, the five-year survival was higher for patients with TCa as compared to the patients with PCa. This is likely due to younger age of pa-

tients with TCa. The survival rates detected in this study were lower than those reported for the countries with established market economies. Such, according to the large registry-based study, the five-year survival for TCa in the USA and 12 European countries constituted at least 98% for the patients aged younger than 50 years (18), while in Lithuania, which like Kazakhstan belongs to the former Socialist block, the five-year survival was 71.2% (19). As for PCCa, the five-year survival in the USA exceeded 95% (20), in Germany it amounted to 91.2% (21), and in Latvia – another former Socialist economy – the five-year survival was 70.7% (22). Evidently, low overall survival rates seen in Kazakhstan signify that a lot still needs to be done to make the existing cancer services more modern.

This study has certain benefits and drawbacks, which mostly originate from its retrospective design. Since we had to rely exclusively on the data obtained from the KCR, our performance was restrained by the information contained there. Such, the original intention to include penicular cancer in analysis failed, as there was no information on this rare cancer type. Moreover, we could not elucidate the data related to histological subtypes of different tumors and to age-specific mortality since these data are missing. Still, we could obtain the data on all PCa and TCa patients registered in the country within the period of 10 years and the substantial size of the patient sample could potentially overcome the drawbacks listed above.

Conclusion

Over the study period, the incidence of PCa experienced a stable growth following implementation of the targeted screening program with rapid and substantial decline when the screening program was terminated. However, the growing incidence of PCa was not translated into declining mortality, which justifies the decision made by the country's government to stop financing the screening program. Meanwhile, both incidence and mortality rates of patients with TCa were characterized by greater stability attributed to the lack of any targeted interventions. However, the 5-year survival rates of patients with PCa and TCa were gradually improving although not reaching the levels reported for the established market economies. Thus, more studies need to be done to explain the poorer five-year survival of men with PCa and TCa in Kazakhstan. Besides, a careful analysis of diagnostic and treatment strategies utilized at different hospitals across the country would be highly desirable as there is a considerable variation in regional mortality rates and proportions of stage I-II cancers at the time of diagnosis.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Wild CP, Weiderpass E, Stewart BW, editors (2020). World Cancer Report: Cancer Research for Cancer Prevention. Lyon, France: International Agency for Research on Cancer. Available from: https://www.iarc.who.int/featured-news/new-world-cancer-report/

2. WCRF Continuous Update Project (2014). World Cancer Research Fund International systematic literature review: the associations

between food, nutrition and physical activity and the risk of prostate cancer. Available from: https://www.wcrf.org/wp-content/uploads/2021/02/prostate-cancer-slr.pdf

3. Rajpert-DE Meyts E, McGlynn KA, Okamoto K, Jewett MAS, Bokemeyer C (2016). Testicular germ cell tumours. *Lancet,* 387(10029):1762–74.

4. International Agency for Research on Cancer. Prostate cancer statistics: 2020. (2020) https://gco.iarc.fr/today/data/factsheets/cancers/27-Prostate-fact-sheet.pdf (accessed 2 June 2020).

5. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, 68(6):394–424.

6. Cancer trends progress report. National Cancer Institute 2018. (2020) https://progressreport.cancer.gov/end/life_lost#field_most_recent_estimates (accessed 2 June 2020).

7. World Health Organization. Methods and data sources for global burden of disease estimates 2000-2015. (2021) Geneva: WHO. Available online: https://cdn.who.int/media/docs/default-source/gho-documents/global-health-estimates/ghe2019_daly-methods.pdf?sfvrsn=31b25009_7 (accessed 2 June 2021).

8. Ospanov E, Adylkhanov T, Tokanova S, Semenova Y, Dauletyarova M, Bolsynbekova S, Zhumykbaeva N. (2017). Mortality and morbidity from prostate cancer in the Republic of Kazakhstan from 2007 to 2016. *Georgian Med News*, 272:17-22.

9. Yelissinova N, Grjibovski AM, Yelissinova A, et al (2015). Sociodemographic factors associated with infant abandonment in maternity hospitals in Kazakhstan: A case-control study. *Public Health*, 129(7): 1010-1013.

10. Smailova DS, Fabbro E, Ibrayev SE, et al (2020). Epidemiological and Economic Evaluation of a Pilot Prostate Cancer Screening Program. *Prostate Cancer*, 2020;2020:6140623.

11. Demographic Yearbook of Kazakhstan. Statistical compilation. Astana, Ministry of National Economy of the Republic of Kazakhstan, Committee on Statistics 2018.

12. Smailova D, Ospanov E, Gazaliyeva M, et al (2019). Epidemiology of Prostate Cancer in the Republic of Kazakhstan. *Iran J Public Health*, 48(12):2216-2223.

13. Drozdovitch V, Schonfeld S, Akimzhanov K, et al (2011). Behavior and food consumption pattern of the population exposed in 1949-1962 to fallout from Semipalatinsk nuclear test site in Kazakhstan. *Radiat. Environ. Biophys,* 50:91–103.

14. Gromova O, Doschanova A, Lokshin V, et al (2020). Vitamin D deficiency in Kazakhstan: Cross-Sectional study. *J Steroid Biochem Mol Biol*, 1999:105565.

15. Trump DL, Aragon-Ching JB. (2018). Vitamin D in prostate cancer. *Asian J Androl*. 20(3):244-252.

16. Schepisi G, De Padova S, Scarpi E, et al (2017). Vitamin D status among long-term survivors of testicular cancer. *Oncotarget,* 8(22):36780-36786.

17. O'Sullivan J (2017). Controversies in PSA screening. *Evid Based Med*, 22(6):198.

18. Verhoeven RHA, Gondos A, Janssen-Heijnen MLG, et al (2013). EUNICE Survival Working Group. Testicular cancer in Europe and the USA: survival still rising among older patients. *Ann Oncol,* 24(2):508-513.

19. Juška A, Ulys A, Kairevičė L, Smailytė G, Stankevičius E, Jančiauskienė R, Jievaltas M (2011). Survival of patients with testicular cancer in Lithuania during 1999-2002. *Medicina (Kaunas),* 47(1):52-6.

20. Steele CB, Li J, Huang B, Weir HK (2017). Prostate cancer survival in the United States by race and stage (2001-2009): Findings from the CONCORD-2 study. *Cancer*, 15;123 Suppl 24(Suppl 24):5160-5177.

21. Winter A, Sirri E, Jansen L, et al (2017). Association of Population-based Cancer Registries in Germany (GEKID) Cancer Survival Working Group. Comparison of prostate cancer survival in Germany and the USA: can differences be attributed to differences in stage distributions? *BJU Int*, 119(4):550-559.

22. Plonis J, Bokums K, Cauce V, et al (2014). Prostate cancer trends in Latvia during 1990-2012: incidence, prevalence, mortality, and survival rates. *Medicina (Kaunas),* 50(6):313-7.