RESEARCH ARTICLE

Analysis of Delays in Breast Cancer Treatment and Late-Stage Diagnosis in Kazakhstan

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Abstract

Objective: Although Kazakhstan has made significant investments to improve health and life expectancy of its population, high cancer rates persist, with breast cancer being the most prevalent type. Factors contributing to delays in treatment and late staging for breast cancer patients were assessed. **Methods:** A retrospective follow-up study with registry data identified 4,248 breast cancer patients in sixteen regions of Kazakhstan in 2014. We used logistic regressions to estimate (i) associations of treatment delays with patient demographics and cancer center regions; and (ii) associations of late-stage (III and IV) cancer diagnosis with patient demographics and cancer center regions, with and without controlling for treatment delays. **Results:** Breast cancer patients treated in regions located further away from Almaty City had higher risks of treatment delays. However, the risks of late-stage cancer diagnosis were greater for patients treated in Almaty City and those with treatment delays. **Conclusion:** The main driver of delayed treatment is cancer center region. Residents of Almaty City, a major urban area of Kazakhstan, may have a better access to a tertiary cancer center, resulting in less treatment delays. Referrals of sicker patients from neighboring regions to Almaty City for cancer treatment is likely to increase risks of late-stage diagnosis. New or upgraded cancer centers may reduce treatment delays, but their case-mix is likely to increase.

Keywords: Breast cancer- delays in treatment- late-stage diagnosis- Kazakhstan

Introduction

Kazakhstan (KZ) is a little-known yet strategically important country situated at the crossroads of Europe and Asia, bordering Russia, China, and other Central Asian countries. More than 100 different ethnic groups live in KZ, including Kazakhs (who are Asian and Muslims), Russians (Caucasian Orthodox Christians), and other Asian and Caucasian minorities. Breast cancer (BC) is the most commonly diagnosed cancer in Kazakhstani women and BC mortality in KZ is the highest in the region (WHO, 1999; WHO, 2014) BC mortality has been rising steadily since the 1980s (WHO, 1999), accounting for 17.3% of all cancer deaths in 2012 (although the mortality rate stabilized around 16% in the early 2000s). (Baizhumanova and Sakamoto, 2010; WHO, 2014). High mortality rates are especially evident in women with late-stage BC diagnoses (Abiltayeva et al., 2016). Between 20% - 50% of patients who were first diagnosed with BC were expected to develop a late-stage disease (Abiltayeva et al., 2016).

Delays in BC diagnosis and treatment likely contribute to advanced BC and negatively affect long-term survival of cancer patients in KZ.

Poor cancer care infrastructure, such as lack of access to oncologists, inadequate BC screening programs and insufficient adherence to treatment among BC patients are drivers of late-stage BC in developing countries (Dickens et al., 2014; Jassem et al., 2014). In neighboring Russia, some patient-related factors, such as practicing breast self-examination, are associated with fewer treatment delays, while perceptions of low BC risk lead to treatment delays (Jassem et al., 2014). Other psychological and behavioral factors are associated with both patient-related and health system-related delays in BC treatment in Eastern European countries (Dickens et al., 2014). In Kazakhstan, important variations in BC incidence and mortality rates have been reported across administrative regions (provinces) and major cities (Astana, the new capital, and Almaty, the former capital of KZ) (Beysebayev et al., 2015a). Astana, Almaty, and

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four central and eastern regions of KZ have the highest BC mortality rates (Beysebayev et al., 2015a). In addition, ethnic differences in BC knowledge, attitudes, and practices that have been reported for Kazakh, Korean, and Russian women (Chukmaitov et al., 2014) may contribute to delays in BC treatment for some ethnic groups, but this is understudied.

Of note, the KZ cancer care system is organized by geographic principles. The KZ Research Institute of Oncology and Radiology (KZ RIOR) is located in Almaty City, and is a 700-bed scientific and clinical referral center for the country (KZRIOR, 2017). KZ RIOR conducts cancer research, trains medical students, residents, and specialists, develops cancer-related health policies, and maintains electronic cancer registry data. KZ RIOR oversees a network of regional cancer centers located in all fourteen regional capitals. A new National Research Oncology Center (NROC) was built in Astana in 2014 to specialize in high-tech cancer care (NROC, 2017). A typical regional cancer center has about 100-150 beds, provides inpatient and outpatient cancer care, and is responsible for collecting cancer statistics for the region. Primary care physicians are responsible for timely clinical screening and referral of suspect cases to oncologists. All cancer care is covered by general taxation. KZ RIOR and a new NROC are directly financed from the republican budget, while regional cancer centers are financed from regional budgets.

KZ has made significant investments to improve the health and life expectancy of its population, and reducing the relatively high BC mortality remains a priority for the country. Even as BC mortality has been decreasing in developed countries, developing countries have seen scant improvement in BC mortality, due primarily to delayed BC diagnosis and treatment (Jassem et al., 2014; Abiltayeva et al., 2016). Factors associated with delays in BC treatment have been well-studied in developed countries. However, geographic, patient-, and system-related factors potentially associated with delays in BC treatment and late-stage diagnosis have not been studied in KZ. Identification of such factors is therefore important for development of cancer care policy for early BC detection, treatment, and long-term follow-up of BC patients in KZ. This study is designed to fill this gap in the literature by examining the factors associated with delays in treatment and late-stage diagnosis among Kazakhstani women diagnosed with BC.

Material and Methods

This is a retrospective follow-up study using 2014 registry data from fourteen regions and two major cities in KZ. The KZ RIOR analytical center is the repository for provider and population registries, including the National Electronic Cancer Registry, which contains information on over 140,000 cancer patients (see Web Appendix Figure 1). Baseline and follow-up data for the national registry were retrospectively collected at all cancer centers. The database includes patient identifiers, demographics, tumor types and site(s) as assessed by the International Classification of Disease (ICD-10), cancer stage, number and duration of treatments, delays in treatment, location

of cancer center, and other information. We identified 4,248 BC patients in 2014. We excluded men from the sample. Among the remaining 4,229 patients, nineteen patients were missing information on cancer stage, so we used 4,210 complete cases for the analysis of late-stage diagnosis.

BC outcomes were binary variables that identified patients with delays in treatment and late-stage (III and IV) diagnosis. Delays in treatment were defined as those due to a latent cancer disease, patient-related (i.e., refusal to be screened or treated) and health care-related (i.e., diagnostic and treatment errors) reasons. This information was collected by cancer centers and submitted to the KZ RIOR annually.

We used multivariate logistic regressions to estimate associations of: (1) delays in treatment with patient demographics and cancer center region; and (2) late-stage diagnosis with patient demographics and cancer center region, with and without controlling for delays in treatment. The latter two models were compared in order to understand the role of delays in treatment in mediating the associations of patient demographics and cancer center region with late-stage diagnosis (see Web Appendix Figure 2). Patient demographics included age, ethnicity (Kazakh, Russian and others), urbanicity (urban and rural), and occupation (professional, non-professional, and unemployed). The distinction between professional and non-professional is akin to the American notion of white-collar versus blue-collar jobs.

Odds ratios are notoriously prone to misinterpretation as relative risks, an interpretation that is valid only when the incidence of the outcome is very low (Greenland, 1987). To facilitate correct interpretation of the logit estimates, therefore, we report marginal effects or "risk differences," i.e., the average difference in the predicted probability of the outcome associated with a change in the covariate value, holding other covariates constant at their original values. For continuous covariates, the marginal effects represent partial derivatives. For dummy variables, the marginal effects are evaluated based on a discrete change from 0 to 1. As an example, the marginal risk difference associated with being urban versus rural would be calculated by predicting the probability of the outcome (e.g., delays in treatment) for each individual if s/he were an urban resident (holding all other covariates at their original values), recalculating the same probability if the individual were a rural resident, taking the difference between the two predicted probabilities and averaging across the sample. $P < 0.05$ was used as the cutoff for defining statistical significance. Statistical analysis was performed using STATA version 11 (StataCorp, 2017).

Although our main findings are based on models treating cancer center region as a fixed effect, we also conducted sensitivity analyses estimating multi-level models in which we allowed both the intercept and slope terms to be random. Statistical tests failed to reject the null hypothesis that the slope terms could be treated as fixed and the resulting random-intercept model yielded estimates substantially similar to the fixed-intercept model, so for brevity, we present only the latter.

Results

Table 1 describes the study cohort by whether or not the patient experienced delays in treatment. Delays in BC treatment in KZ were experienced by 10.7% (0.107) of patients and 22.8% (.228) had a late-stage diagnosis. Overall, the sample was diverse in terms of age, ethnicity, occupation and location.

Table 2 presents the regression-adjusted associations of cancer center region and patient demographics with the probability of experiencing delays in treatment. Most of the regional indicator variables showed significant associations with delays in care, with substantial variation seen in the risk of treatment delays. For example, compared to South Kazakhstan, which is closer to the tertiary cancer care center in Almaty City, Astana City had

a 19.3 percentage point higher risk of delays in treatment (absolute risks of .038 versus .230 respectively, with a marginal risk difference of .193).

Older age was associated with a higher risk (1/10ths of a percentage point for every additional year) and Kazakh (compared with Russian) ethnicity was associated with a lower risk. On average, holding everything else constant, a patient of Kazakh ethnicity would have a risk of delayed treatment around 2.6 percentage points lower than that of a patient of Russian ethnicity (absolute risks of .093 versus .119 respectively, with a marginal risk difference of .026). This 2.6 percentage point difference represents a 22% reduction in the risk of delays in care associated with being Kazakh (0.026/.119).

Table 3 shows the regression-adjusted associations of patient demographics and cancer center region with late-

Table 1. Demographic Characteristics of Female Breast Cancer Patients in Kazakhstan by Delays in Treatment

| Characteristics	Delay	No Delay	All	P-Value
Number of patients (%)	453 (10.7)	3776 (89.3)	4,229 (100.0)	
Median age, years (IQR)	59.0 (49.7, 68.3)	56.7 (49.0, 65.2)	56.9 (49.2, 65.6)	<0.001
Ethnicity, n (%)				<0.001
Kazakh	158 (34.9)	1672 (44.3)	1830 (43.3)	
Russian	215 (47.5)	1442 (38.2)	1657 (39.2)	
Other	662 (17.5)	80 (17.7)	742 (17.6)	
Cancer stages, n (%)				<0.001
I	3 (0.7)	659 (17.5)	662 (15.7)	
II	22 (4.9)	2560 (67.8)	2582 (61.1)	
III	275 (60.7)	449 (11.9)	724 (17.1)	
IV	151 (33.3)	91 (2.4)	242 (5.7)	
Missing	2 (2.4)	17 (0.5)	19 (0.5)	
Geography, n (%)				0.317
Urban	319 (70.4)	2743 (72.6)	3062 (72.4)	
Occupation, n (%)				0.004
Professional	275 (60.7)	2585 (68.5)	2860 (67.6)	
Non-Professional	139 (30.7)	921 (24.4)	1060 (25.1)	
Unemployed	39 (8.6)	270 (7.2)	309 (7.3)	
Location, n (%)				<0.001
Astana city	45 (9.9)	165 (4.4)	210 (5.0)	
Almaty city	12 (2.7)	709 (18.8)	721 (17.1)	
Aktobe region	27 (6.0)	130 (3.4)	157 (3.7)	
Almaty region	23 (5.1)	384 (10.2)	407 (9.6)	
Atyrau region	8 (1.8)	95 (2.5)	103 (2.4)	
East Kazakhstan region	58 (12.8)	396 (10.5)	454 (10.7)	
Zhambyl region	8 (1.8)	135 (3.6)	143 (3.4)	
West Kazakhstan region	18 (4.0)	131 (3.5)	149 (3.5)	
Karaganda region	49 (10.8)	378 (10.0)	427 (10.1)	
Kostanay region	66 (14.6)	223 (5.9)	289 (6.8)	
Kyzylorda region	10 (2.2)	94 (2.5)	104 (2.5)	
Mangystau region	8 (1.8)	65 (1.7)	73 (1.7)	
Pavlodar region	33 (7.3)	226 (6.0)	259 (6.1)	
North Kazakhstan region	36 (8.0)	154 (4.1)	190 (4.5)	
South Kazakhstan region	12 (2.7)	310 (8.2)	322 (7.6)	
Akmola region	40 (8.8)	181 (4.8)	221 (5.2)	
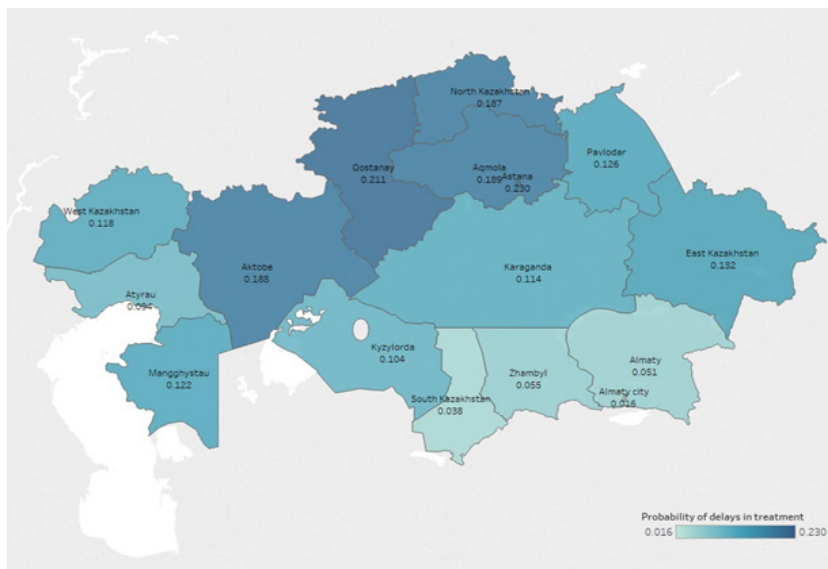
Figure 1. Map of Delays in Treatment by Region, Kazakhstan 2014. Note: Estimates shown are the regression-adjusted probabilities of delays in breast cancer treatment in each region. Models adjust for patient demographics, including occupation.

stage diagnosis before controlling for delays in treatment. Patients who were younger, lived in urban areas, were of Kazakh rather than Russian ethnicity, or were unemployed had lower risk of late-stage diagnosis. However, these associations were fully or partially explained by fewer delays in care among these populations; after adjusting for delays in treatment, the estimates for age, urbanicity and unemployment became non-significant and the estimate for ethnicity was reduced in magnitude (Table 4). Even holding delays in treatment constant, however, being Kazakh rather than Russian was still associated with a significant 2.7 percentage point reduction in the likelihood of late-stage diagnosis (absolute risks of .217 versus .244 respectively, with a marginal risk difference of -.027), representing an 11% reduction in risk (.027/.244).

Controlling for delays in treatment also changed the significance and/or signs of some of the regional effects. For example, compared with South Kazakhstan (the reference category), being treated in the Kostanay region was associated with a significantly higher risk of late-stage diagnosis before adjusting for delays in treatment (marginal risk difference of 0.066, p=0.04), but a lower risk (-0.087, p<0.001) after adjusting for treatment delays, suggesting that the risk of late-stage diagnosis was actually lower than would have been expected, given the high rates of delayed treatment among patients in this region. Delayed treatment itself had a very large, positive and statistically significant association with the likelihood of late-stage cancer, increasing this risk by 58.1 percentage points.

Figures 1 and 2 are maps of Kazakhstan, respectively showing regional variation in the probabilities of delays in treatment and late-stage diagnosis, adjusted for patient demographics. (Web Appendix Figure 3 shows a map of regional variation in late-stage diagnosis additionally controlling for delays in treatment; patterns look very
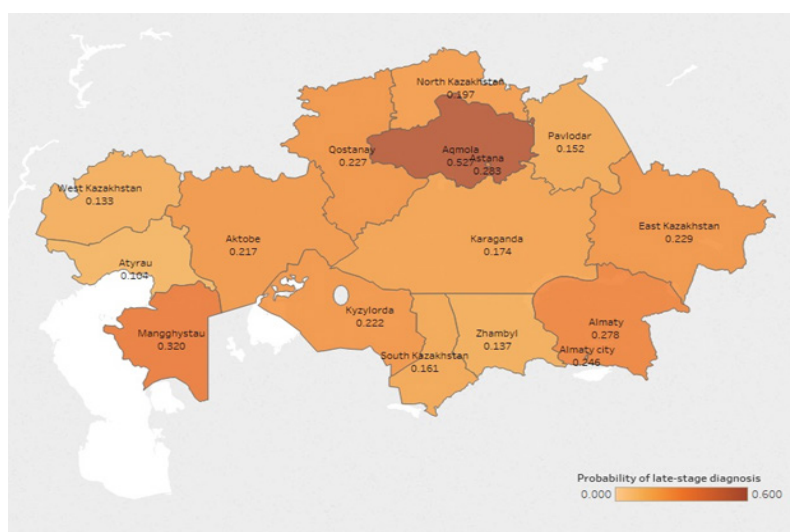

Figure 2. Map of Late-Stage Diagnosis by Region, Kazakhstan 2014. Note: Estimates shown are the regression-adjusted probabilities of late-stage (stages III and IV) breast cancer diagnosis in each region. Models adjust for patient demographics, including occupation.

Table 2. Marginal Effects of Sociodemographic Characteristics and Region on Probability of Delay in Treatment

Characteristics	Marginal Effects	Lower 95% Confidence Limit	Upper 95% Confidence Limit	P-Value
Age	0.001	0	0.002	0.004
Urban	-0.02	-0.042	0.003	0.095
Ethnicity (ref: Russian)				
Other non-Kazakh	-0.01	-0.037	0.017	0.456
Kazakh	-0.026	-0.048	-0.004	0.02
Occupation (ref: Professional)				
Non-Professional	-0.015	-0.04	0.01	0.242
Unemployed	-0.019	-0.054	0.017	0.299
Location (ref: South KZ)				
Astana city	0.193	0.128	0.257	<0.001
Almaty city	-0.021	-0.045	0.002	0.07
Kyzylorda region	0.066	0.002	0.13	0.044
Mangystau region	0.085	0.003	0.166	0.043
Akmola region	0.151	0.09	0.212	<0.001
Almaty region	0.014	-0.016	0.043	0.368
West KZ region	0.08	0.025	0.135	0.005
East KZ region	0.094	0.05	0.138	<0.001
Zhambyl region	0.017	-0.025	0.06	0.423
Karaganda region	0.077	0.039	0.114	<0.001
Kostanay region	0.173	0.122	0.224	<0.001
North KZ region	0.149	0.086	0.213	<0.001
Pavlodar region	0.088	0.042	0.134	<0.001
Atyrau region	0.056	-0.011	0.124	0.102
Aktobe region	0.15	0.083	0.217	<0.001

Covariate references include Russian ethnicity, rural, professional occupation, and South Kazakhstan region; The model includes 4,229 observations; Marginal effects for continuous variables are partial derivatives; Marginal effects for dummy variables are evaluated for the discrete change from 0 to 1. P-value ≤ .05 is the cutoff for defining statistical significance.

Table 3. Marginal Effects of Sociodemographic Characteristics and Region on Probability of Late-Stage (III and IV) Cancer Diagnosis, Not Controlling for Delays in Treatment

Characteristics	Marginal Effects	Lower 95% Confidence Limit	Upper 95% Confidence Limit	P-Value
Age	0.001	0	0.002	0.013
Urban	-0.035	-0.068	-0.002	0.04
Ethnicity (ref: Russian)				
Other non-Kazakh	-0.02	-0.057	0.017	0.298
Kazakh	-0.047	-0.077	-0.017	0.002
Occupation (ref: Professional)				
Non-Professional	-0.02	-0.06	0.02	0.322
Unemployed	-0.054	-0.108	-0.001	0.048
Location (ref: South KZ)				
Astana city	0.122	0.047	0.198	<0.001
Almaty city	0.085	0.032	0.138	0.002
Kyzylorda region	0.061	-0.029	0.152	0.186
Mangystau region	0.159	0.043	0.274	0.007
Akmola region	0.366	0.281	0.452	<0.001
Almaty region	0.117	0.058	0.177	<0.001
West KZ region	-0.028	-0.096	0.04	0.423
East KZ region	0.068	0.002	0.134	0.044
Zhambyl region	-0.024	-0.093	0.045	0.501
Karaganda region	0.014	-0.043	0.07	0.639
Kostanay region	0.066	0.003	0.128	0.04
North KZ region	0.036	-0.04	0.111	0.353
Pavlodar region	-0.009	-0.07	0.052	0.766
Atyrau region	-0.057	-0.136	0.021	0.153
Aktobe region	0.056	-0.024	0.135	0.17

Covariate references include Russian ethnicity, rural, professional occupation, and South Kazakhstan region. The model includes 4,210 observations. Marginal effects for continuous variables are partial derivatives. Marginal effects for dummy variables are evaluated for the discrete change from 0 to 1. P-value ≤ .05 is the cutoff for defining statistical significance.

similar to those shown in Figure 2.) The patterns seen in Figure 1 suggest strongly that delays in care were more prevalent, the further patients live from Almaty City. In Figure 2, the most striking pattern was that Akmola region have higher rates of late-stage diagnosis than any of the other regions.

Discussion

In 2014, about one in ten BC patients in KZ experienced delays in treatment, and having a treatment delay was associated with late-stage BC diagnosis. Both delays in BC treatment and late-stage diagnosis were associated with cancer center region, which may have also contributed to the high BC mortality in corresponding regions reported in a prior study (Beysebayev et al., 2015a). Patients treated in Almaty City, where the Kazakh Research Institute of Oncology and Radiology (KZ RIOR) is located, had fewer delays in treatment, but a higher risk of late-stage BC diagnosis, likely due to established referrals of sicker BC patients from neighboring southern regions of KZ. Patients treated in Astana City, where a new National

Research Oncology Center (NROC) was built, had the highest risk of delays in BC treatment, while patients in the adjacent Akmola region had the highest risk of late-stage BC diagnoses in the country. Regional variation in late-stage BC diagnosis was primarily explained by delays in treatment.

KZ RIOR is a tertiary care cancer center where complex cancer patients from the entire country are expected to be referred. Almaty City residents are likely to benefit from direct access to KZ RIOR and its BC prevention and awareness campaigns to detect and treat BC early. However, patients residing in regions located further than nearby southern regions (i.e., Almaty, Zhambyl, and South KZ) are less likely to access KZ RIOR due to cost of travel (e.g., the KZ territory is greater than 1,000 sq. miles). Relative to other regions, Almaty City residents may have higher socioeconomic status. These factors may contribute to lower delays in BC treatment in Almaty City. However, increased risks of late-stage BC diagnosis in Almaty City may be related to referrals of sicker BC patients to KZ RIOR from nearby southern regions. As in the U.S., referrals of patients with comorbid

Table 4. Marginal Effects of Sociodemographic Characteristics and Region on Probability of Late-Stage (III and IV) Cancer Diagnosis, Controlling for Delays in Treatment

Characteristics	Marginal Effects	Lower 95% Confidence Limit	Upper 95% Confidence Limit	P-Value
Delayed treatment	0.581	0.538	0.624	<0.001
Age	0	-0.001	0.001	0.438
Urban	-0.02	-0.047	0.008	0.162
Ethnicity (ref: Russian)				
Other non-Kazakh	-0.012	-0.041	0.018	0.438
Kazakh	-0.027	-0.051	-0.003	0.028
Occupation (ref: Professional)				
Non-Professional	0.002	-0.035	0.038	0.935
Unemployed	-0.038	-0.087	0.01	0.119
Location (ref: South KZ)				
Astana city	-0.041	-0.095	0.012	0.13
Almaty city	0.098	0.05	0.146	<0.001
Kyzylorda region	0.005	-0.067	0.078	0.885
Mangystau region	0.089	-0.01	0.189	0.079
Akmola region	0.247	0.162	0.332	<0.001
Almaty region	0.104	0.051	0.158	<0.001
West KZ region	-0.099	-0.147	-0.052	<0.001
East KZ region	-0.017	-0.071	0.037	0.534
Zhambyl region	-0.038	-0.095	0.019	0.19
Karaganda region	-0.053	-0.098	-0.008	0.02
Kostanay region	-0.087	-0.13	-0.045	<0.001
North KZ region	-0.094	-0.141	-0.046	<0.001
Pavlodar region	-0.085	-0.13	-0.041	<0.001
Atyrau region	-0.105	-0.159	-0.051	<0.001
Aktobe region	-0.075	-0.127	-0.023	0.004

Covariate references include Russian ethnicity, rural, professional occupation, and South Kazakhstan region. The model includes 4,210 observations. Marginal effects for continuous variables are partial derivatives. Marginal effects for dummy variables are evaluated for the discrete change from 0 to 1. P-value ≤ .05 is the cutoff for defining statistical significance.

conditions to tertiary care cancer centers increase the case-mix of these centers (Birkmeyer et al., 2005).

Risks of delays in BC treatment and late-stage diagnosis in Astana City were among the highest in the country. After adjusting for delays in treatment, Astana City was no longer associated with having high risk of late-stage BC diagnosis. This may suggest that a cancer center in Astana City treated BC patients who lacked adequate access to primary care and cancer prevention services. Elevated risks of late-stage BC diagnosis remained for patients in the adjacent Akmola region even after adjustment for delays in treatment. BC in this region may have been of a different subtype or affected by biological factors that influenced the aggressiveness of cancer and its advanced staging. In addition, population-level factors may have added barriers to accessing primary care and oncology services in Astana City. Astana's population has grown exponentially from about 200,000 residents in 1997, when the capital of KZ moved to Astana, to over 800,000 in 2014. This explosive growth may have disrupted referral patterns of patients from primary care settings to the

Akmola regional cancer center, contributing to delays in BC treatment and late-stage diagnosis. Moreover, not all newcomers have equal access to care. Some new residents live in temporary housing arrangements that are not linked into a local primary care system that may hamper access to mammography and oncologists. A new National Research Oncology Center (NROC) is likely to increase cancer care capacity, focusing on highly specialized services in Astana City. While additional cancer infrastructure is likely to have a positive effect on cancer outcomes in this region, it is also important to establish effective referrals from primary care clinics to oncologists and encourage women to seek timely BC diagnostic and treatment services.

Other unmeasured factors may contribute to regional variation in delays in BC treatment. Regional cancer centers located further away from Almaty City may have experienced budgetary constraints to update their infrastructure for BC diagnosis and treatment (Beysebayev et al., 2015b). Previous studies also suggested that environmental pollution from chemical plants and exposure to radiation from uranium mining may have contributed to increased BC morbidity in the western, northern, and eastern regions of KZ (Bilyalova et al., 2012; Bekmukhambetov et al., 2015; Bersimbaev and Bulgakova, 2015). Higher demand for cancer services in these regions may have contributed to delays in BC treatment.

Patient age, ethnicity, urbanicity, and employment status were also associated with delays in BC treatment and/or late-stage BC diagnosis. As elderly women are the main family caregivers in KZ, potential time constraints and travel costs may have been a deterrent in seeking timely BC care and staying in treatment. Kazakh women were less likely to experience delays in treatment relative to Russian women. In the U.S., racial and ethnic disparities contribute to delays in BC treatment (Sheppard et al., 2015). In our study, the probability of late-stage diagnosis remained significantly higher for Russian women even after adjusting for delays in treatment. Russian women may have suffered from more aggressive forms of BC that regressed to late stages quickly, potentially due to hereditary or other social and behavioral risk factors (Igisinov et al., 2005; Toleutay et al., 2013). In addition, as many Russians moved back to Russia or emigrated to Western countries after the collapse of the Soviet Union in 1991, so the socioeconomic status of Russians who remained in KZ may have declined, negatively affecting BC outcomes. As all national and regional cancer centers are located in major urban settings, urban residence had a protective effect for late-stage BC diagnosis relative to rural residence. However, after adjustment for delays in treatment, urbanicity was no longer associated with cancer outcomes. Finally, unemployed women had a lower risk of late-stage diagnosis relative to professional women, but this association was not significant after adjustment for delays in BC treatment. As the government covers all costs for cancer care, unemployed women were more likely to seek timely BC diagnostic and treatment services in comparison with professional women with demanding careers, who were more likely to delay BC treatment.

Some data limitations exist. We do not have information on women's BC knowledge, attitude, and beliefs that may contribute to delays in treatment and advanced BC diagnosis. Even though BC treatment is covered by the government, other additional treatment (e.g., a second opinion), travel, and time costs may have contributed to delays in treatment. We also do not have information on primary care providers' expertise in identifying early BC symptoms and their proficiency in clinical breast examination. Regional variation in the experience and qualifications of oncologists and primary care providers may have correlated with delays in treatment and late-stage BC diagnoses.

Notwithstanding these limitations, our study identifies a link between cancer center location and delays in BC treatment. This regional association seems likely to have arisen as a result of proximity to highly specialized cancer centers. Such centers may be effective in reducing delays in cancer treatment as more resources are available to both practicing clinicians and patients treated in these centers. However, highly specialized cancer centers can only serve cancer patients in its immediate and neighboring regions. As such, health policy decision makers should consider investing in regional cancer centers to upgrade their infrastructure that may improve cancer outcomes. As delays in BC treatment are a major driver of late-stage diagnosis, BC prevention and awareness campaigns in regions may have positive effects on reducing BC morbidity and mortality in KZ. Finally, access to primary care, preventive services, early BC diagnoses, and cancer treatment should be available to women regardless of their demographic characteristics, occupation, socioeconomic status, and residence. Future research will need to examine the role played by distance to cancer centers in KZ and its association with improved cancer outcomes, conditional on facilities' case-mix and patient complexity.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

For this retrospective study that utilized secondary data, informed consent was not required.

References

Abiltayeva A, Moore MA, Myssayev A, et al (2016) Clinical, histopathological and molecular characteristics of metastatic breast cancer in North-Eastern Kazakhstan: a 10 year retrospective study. *Asian Pac J Cancer Prev*, **17**, 4797-4802.

Baizhumanova A, Sakamoto J (2010). Cancer in Kazakhstan: Present situation on Cancer Ann. *Cancer Res Therap*, **18**, 65-8.

Bekmukhambetov Y, Mamyrbayev A, Jarkenov T, Makenova A, Imangazina Z (2015). Malignant neoplasm prevalence in the Aktobe Region of Kazakhstan. *Asian Pac J Cancer Prev*, **16**, 8149-53.

Beysebayev E, Bilyalova Z, Kozhakeeva L, Baissalbayeva A, Abiltayeva A (2015a). Spatial and temporal epidemiological assessment of breast cancer incidence and mortality in Kazakhstan, 1999-2013. *Asian Pac J Cancer Prev*, **16**, 6795-8.

Beysebayev E, Tulebayev K, Meymanalyev T (2015b). Breast cancer diagnosis by mammography in Kazakhstan-staging results of breast cancer with double reading. *Asian Pac J Cancer Prev*, **16**, 31-4.

Bersimbaev RI, Bulgakova O (2015). The health effects of radon and uranium on the population of Kazakhstan. *Genes Environ*, **37**, 18.

Bilyalova Z, Igissinov N, Moore M, et al (2012). Epidemiological evaluation of breast cancer in ecological areas of Kazakhstan-association with pollution emissions. *Asian Pac J Cancer Prev*, **13**, 2341-4.

Birkmeyer NJ, Goodney PP, Stukel TA, Hillner BE, Birkmeyer JD (2005). Do cancer centers designated by the National Cancer Institute have better surgical outcomes?. *Cancer*, **103**, 435-41.

Chukmaitov A, Wan TT, Menachemi N, Cashin C (2008). Breast cancer knowledge and attitudes toward mammography as predictors of breast cancer preventive behavior in Kazakh, Korean, and Russian women in Kazakhstan. *Int J Public Health*, **53**, 123-30.

Dickens C, Joffe M, Jacobson J, et al (2014). Stage at breast cancer diagnosis and distance from diagnostic hospital in a periurban setting: a South African public hospital case series of over 1,000 women. *Int J Cancer*, **135**, 2173-82.

Greenland S (1987). Interpretation and choice of effect measures in epidemiologic analyses. *Am J Epidemiol*, **125**, 761-8.

Jassem J, Ozmen V, Bacanu F, et al (2014) Delays in diagnosis and treatment of breast cancer: a multinational analysis. *Eur J Public Health*, **24**, 761-7.

Igisinov N, Kokteubaeva N, Kudaibergenova I (2005). Epidemiology of breast cancer in females of reproductive age in Kyrgyzstan. *Asian Pac J Cancer Prev*, **6**, 37-40.

KZRIOR (2017). Kazakh research institute of oncology and radiology. Available at: http://www.onco.kz/ru/ Accessed on July 16, 2017

NROC (2017). National research oncology center. NROC Oncology briefing. Issue 01 June 2014 Available at: http://www.ios-astana.kz/emails/issue01/kz_upmc_newsletter_june2014.pdf Accessed on July 16, 2017.

Sheppard VB, Oppong BA, Hampton R, et al (2015). Disparities in breast cancer surgery delay: the lingering effect of race. *Ann Surg Oncol*, **22**, 2902-11.

StataCorp (2017). Stata statistical software: Release 15. College Station, TX: StataCorp LLC.

Toleutay U, Reznik V, Kalmatayeva Z, Smigelskas K (2013). Risk factors of breast cancer in Kyzylorda oblast of Kazakhstan: a case-control study. *Asian Pac J Cancer Prev*, **14**, 5961-4.

WHO (1999). World health organization. Highlights on health in Kazakhstan. Available at: http://apps.who.int/iris/bitstream/10665/108498/1/E72497.pdf Accessed on July 10, 2017.

WHO (2014). World health organization. Cancer country profiles: Kazakhstan. Available at: http://www.who.int/cancer/country-profiles/kaz_en.pdf?ua=1 Accessed on July 10, 2017.