

## RESEARCH ARTICLE

# Risk Factors of Breast Cancer in Kyzylorda Oblast of Kazakhstan: a Case-Control Study

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### Abstract

**Background:** Breast cancer in Kazakhstan and its Kyzylorda oblast is the most prevalent cancer in women and features increasing trends of incidence. The aim of study was to reveal risk factors for breast cancer among women of Kyzylorda oblast of Kazakhstan. **Materials and Methods:** A hospital-based case-control study was conducted at Kyzylorda oblast Oncology Center, including 114 cases of breast cancer and 196 controls. Binary logistic regression analysis was performed. **Results:** Social and behavioral risk factors for breast cancer were evaluated, among which unfavorable living conditions, chronic stress, unilateral breastfeeding, breastfeeding less than 3 months and over 2 years, abortions, and hereditary predisposition were found to be related with increased breast cancer risk. Breastfeeding for 6-24 months was found to be protective. **Conclusions:** The findings may have significant impact on activity planning aimed towards breast cancer reduction among women in Kazakhstan.

**Keywords:** Breast cancer - case - control study - risk factors - Kazakhstan

*Asian Pac J Cancer Prev*, **14** (10), 5961-5964

### Introduction

Worldwide, yearly about 1.38 million of new cases and 458,000 of deaths from breast cancer (BC) are registered. Today it is the most prevalent cancer among women worldwide, both in developed and developing countries (GLOBOCAN, 2008). It is predicted that the incidence in 2050 will reach almost 3.2 million (Hortobagyi et al., 2005; McCormack and Boffetta, 2011; Youlten et al., 2012). The standardized incidence rates range from 19.3 per 100,000 women in Eastern Africa to 89.9 per 100,000 women in Western Europe. High incidence rates (80 per 100,000) are observed in developed regions of the world (excluding Japan), while low rates (less than 40 per 100,000)-in most developing countries. To determine the reasons of these differences, it is required to conduct research aimed to analyse lifestyle and genetic factors, ecological environment of terrain and etc (GLOBOCAN, 2008; Curado, 2011).

In Kazakhstan BC has taken the second place in the structure of total oncopathology after lung cancer since 2007, and in 2011 it took the first place, reaching 11.6 percent. In the structure of female oncopathology BC has the first place for over 20 years, accounting 21.4 percent in 2011 (3525 cases of BC of all 16465 primary cancers in women). It is the third cause of cancer deaths after lung cancer and stomach cancer, accounting for 8.2 percent in 2011 (Nurgaziev et al., 2012).

Kyzylorda oblast (KZO) is characterized by a number of features, among which there are socioeconomic conditions, low level of quality of life in rural areas, lack of good quality drinking water, and poor environmental

situation due to Aral Sea issues (the processes of desertification, soil salinity over large areas, pesticide and herbicide pollution, heavy metal contamination) (Mazhitova, 2007). Baikonur cosmodrome is also located in KZO; it has been functioning for more than 60 years and since 1994 it has been leased to Russian Federation till 2050.

According to the last publications, trends in incidence of major forms of cancer were studied in Aral-Syr Darya ecological area of Kazakhstan and high growth rates of BC were revealed (Igissinov et al., 2011), also the correlation of BC with air pollution was found (Bilyalova et al., 2012). There were no studies on risk factors of BC in Kazakhstan. Therefore it is of essential interest to research possible reasons and risk factors of BC among women of KZO with mainly Kazakh population and characterized by unfavorable ecological situation.

During the study planning process there was suggested a hypothesis about possible influence of low socioeconomic status of rural women on the risk of BC, which includes unfavorable living conditions, poor nutrition, and chronic stress. Thus, the aim of this study was to reveal the risk factors of BC among women of KZO of Kazakhstan.

### Materials and Methods

The role of social factors, lifestyle and reproductive behavior in disease development for women of Karmakshy district of KZO was researched. High prevalence rates with increasing trends observed in the last decade supported the choice of this area.

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Using a specially developed questionnaire in 2011, there were interviewed 310 respondents. As cases, 114 women from Karmakshy district registered on dispensary register (complete observation) were included the group of BC. The control group comprised 196 healthy women, who passed screening testing, and had no diagnosed BC based to clinical and diagnostic examination. The survey was conducted in Kyzylorda oblast oncology center; the questionnaires were filled in anonymously. The groups were similar on ethnical criteria, education level, and marital status. The age of respondents ranged from 30 to 75 years.

The database was formed in MS Access; the statistical tests were performed using IBM SPSS Statistics 19 and MS Excel programs. The testing of hypotheses for statistical association between risk factor and BC was performed using the Pearson chi-square ( $\chi^2$ ), the expected number of observations was calculated. A quantitative assessment of disease likelihood among risk factor groups was performed using univariate logistic regression analysis, where the odds ratios (OR) and their 95% confidence intervals were calculated.

## Results

Kazakh women accounted for 84.2% of BC patients and 87.8% of controls, women of Slavic origin-8.8% and 8.2%, other ethnic groups-7.0% and 4.0%, respectively ( $p=0.512$ ). Secondary education had 70.2% of cases and 75.5% of controls, higher education-29.8% and 24.5%, respectively ( $p=0.304$ ). Similarly, married women accounted for 78.9% of cases and 76.5% of controls ( $p=0.624$ ). Thus, according to these social characteristics the study groups were not significantly different. In both study groups the first pregnancy and the first delivery occurred most frequently in the age of 21-25 years (50%); the first pregnancy ended with childbirth in 85% of cases, percentage of multiparous women (3 or more births) was 64-65%.

Majority of respondents have practiced a breastfeeding of child (86.0% and 83.6%). Unilateral breastfeeding was more common among BC patients than control (42.1% and 2.0%, respectively,  $p=0.000$ ). By reporting the reasons for unilateral breastfeeding, the 46.4% of cases pointed to shortage and insufficient milk supply in one breast, 39.3%-to their own choice, and 14.3%-to medical indications. The duration of breastfeeding less than 3 months (7.0% vs 1.0%,  $p=0.004$ ), and over 2 years (17.5% vs 5.1%,  $p=0.000$ ) was more frequent among cases than controls, while the breastfeeding for 6-24 months was more common in controls (66.4% vs 43.9%,  $p=0.000$ ).

The history of abortion (54.0% vs 30.5%,  $p=0.000$ ) and miscarriage (40.4% vs 16.8%,  $p=0.000$ ) was higher among cases than controls. Injuries of the breast in the past noted 14.0% of cases and 1.0% of controls ( $p=0.000$ ). Anamnesis of 47.4% of cases included mastitis or mastopathy or benign tumors (compared to 12.2% among controls,  $p=0.000$ ). The absence of breast diseases was more common among controls than cases (87.8% and 52.6%,  $p=0.000$ ). A same pattern was observed with other diseases, where gynecological (58.0% vs 15.3%,  $p=0.000$ )

**Table 1. Risk Factors for Breast Cancer: Univariate Logistic Regression**

Factor	Variables	Odds Ratio	95% Confidence Interval	p
Unilateral breastfeeding	No	1.00		
	Yes	38.40	13.19-55.76	<0.001
Living conditions	Good	1.00		
	Unfavorable	22.17	10.63-46.26	<0.001
Breastfeeding	6-24 months	1.00		
	<3 months	10.40	2.13-50.67	0.004
	3-6 months	1.95	0.86-4.41	0.109
	>2 years	5.20	2.28-11.88	<0.001
Chronic stress	No pregnancies	1.30	0.66-2.57	0.452
	No	1.00		
Stress in family	Yes	3.61	1.75-7.45	<0.001
	No	1.00		
Breast cancer in close relatives	Yes	4.86	2.59-9.12	<0.001
	No	1.00		
Abortion	Yes	3.36	1.36-8.28	0.006
	No	1.00		
	Yes	2.67	1.62-4.40	<0.001

and somatic pathologies (38.6% vs 6.1%,  $p=0.000$ ) were more common in BC group. Breast cancer history among close relatives were reported by 12.2% of cases and 4.0% of controls ( $p=0.006$ ). Regular consumption of fruits and vegetables was more frequent in group of healthy women than among cases (68.4% and 40.4%, respectively,  $p=0.000$ ). Lifestyle of the majority of women in both study groups was not characterized by sufficient physical activity (70% of cases and controls), though there were no obesity. Alcohol use and smoking were not common among women under study. Chronic stress in the past was noted by 91.2% of cases and 73.4% of controls ( $p=0.000$ ). The cases reported more stress within the family (70.2% compared to 36.7% among controls,  $p=0.000$ ), while the controls-at work (35.7% compared to 14.0% among cases,  $p=0.000$ ). Women with breast cancer practiced the self-examination much more rarely compared to control group (31.6% vs 76.5%,  $p=0.000$ ). In group of healthy women living conditions were defined as satisfactory or good more often than in group of cases (95.0% and 45.6%, respectively,  $p=0.000$ ); 54.4% of cases and 5.1% of healthy women noted unfavorable living conditions ( $p=0.000$ ).

Comparison of possible risk factors among study groups was evaluated using univariate logistic regression (Table 1). The highest risk of breast cancer was associated with one-sided breastfeeding in anamnesis (OR=38.40) and poor living conditions (OR=22.17). These factors were strongly associated with disease. The following factors were less associated with breast cancer, but still statistically significantly: breastfeeding over 2 years (OR=5.20), chronic exposure to stress factors (OR=3.61), stresses in family (OR=4.86), abortion (OR=2.67), breastfeeding less than 3 months (OR=10.40), and hereditary predisposition (OR=3.36). The optimum interval of breastfeeding associated with smallest risk of breast cancer was 6-24 months.

## Discussion

In Kazakhstan, including Kyzylorda oblast, the breast cancer is the most common cancer pathology among

women and has increasing trends in morbidity. However, there were no studies on the effect of separate factors related to lifestyle, reproductive behavior, and social factors in the country and regions, addressing the issue of breast cancer. Our study has revealed the most important risk factors contributing the development of BC among women in KZO of Kazakhstan-improper maintenance of lactation and poor living conditions.

Over the last three decades, many studies have been conducted to examine the causes of this disease. They report contradictory findings, but it is proven that BC is a multifactorial disease. In developed countries the incidence of BC is higher in the higher social strata of the population (Pukkala and Weiderpass, 1999). According to some researchers, it is associated with an increased tendency to postpone the first childbirth, combined with a low parity and short duration of breastfeeding in developed countries (Kobayashi et al., 2012). There is another trend in Kazakhstan: adverse living conditions of lower social strata of population living in rural areas is a risk factor for development of BC, which is consistent with some recent publications (Nosheen Fatima et al., 2010; Das et al., 2012). Several studies mention the role and significance of such factors like abortion, hereditary predisposition, and chronic stress (Collaborative Group on Hormonal Factors in Breast Cancer, 2004; Santos et al., 2009; Amir et al., 2010; Antonova et al., 2011). Our observation confirms such findings-the abortion (OR=2.67), hereditary predisposition (OR=3.36), and chronic stress (OR=3.61) was more common in cases of breast cancer, but to a lesser extent compared to other identified risk factors.

In the middle of the 20<sup>th</sup> century Kazakh scientists (Nugmanov and Esenkulov, 1977; Abdrahimov, 1996) reported that BC hit Slavic women considerably more often (10.9±1.6 per 100,000 women)-approximately 3 times compared with Kazakh women (3.7±1.3 per 100,000 women). Although over time, the main tendency of lower frequency of BC among Kazakh women remained the same, this difference began to decline and reached 1.5 times difference in 1990s (Abdrahmanova, 2000). As the authors suggest, relatively low incidence of BC among Kazakh women was associated with preservation of their reproductive function. Kazakh women marry at younger age, they usually have more pregnancies and fewer abortions, they often practice breastfeeding, and their lactation period is longer (Statistical Yearbook, 2012). Several studies have found that each subsequent pregnancy followed by childbirth and also the increasing total period of breastfeeding reduce the risk of BC (Collaborative Group on Hormonal Factors in Breast Cancer, 2002).

In our study, 90% of responders were Kazakh women. Including questions related to reproductive behavior into the questionnaire, we wanted to confirm the hypothesis that the reproductive function among Kazakh women is mainly preserved and that women get BC for other reasons. An unexpected finding though was identification of uneven breastfeeding in anamnesis. Women preferred to feed only with the one breast, and problems in the future sooner or later occurred in the other breast. It was also found that unilateral breastfeeding was related with early

supplementation with artificial mixtures. According to a survey, insufficient milk supply in one breast was the most common cause of unilateral breastfeeding among patients with BC. The role of insufficient milk as the cause to stop breastfeeding and the risk of BC was investigated in some studies (Cohen et al., 2009). It was found that such women had a 2.4 times higher risk for developing BC compared to women who did not nurse for other reasons (Byers et al., 1985); in another study, insufficient milk increased the risk 5.5 times (Shema et al., 2007). As for duration of breastfeeding, many studies recommend prolonged breastfeeding as a protective behavior against BC, though the optimal interval is not indicated (Naieni et al., 2007; Shema et al., 2007; Parsa and Parsa, 2009; Liu et al., 2011). We didn't find the studies on the effect of unilateral breastfeeding as a risk of developing BC in other breast.

In Kazakhstan as well as in Kyzylorda oblast the breastfeeding is a long-established tradition, however, a decrease in frequency of adequate breastfeeding is being observed. Unfounded early transfer to artificial mixtures and sometimes a total refusal of natural feeding becomes popular. Perhaps this is due to the fact that in recent years, the global industry has created many milk mixtures, close to the composition of human breast milk. A rapid development of technology of artificial feeding together with ubiquitous distribution of early transfer to artificial mixes and the effects of social and psychological factors can be considered as a sort of civilization diseases, having a negative influence, especially for a woman's health.

It is known that many factors that lead to increased morbidity and mortality from BC can be prevented or eliminated without application of expensive medications and medical devices. In 1989, the World Cancer Research Fund announced for the first time a call for breastfeeding as one of the most important protective factors against BC, claiming that this would seem simple and trivial procedure, which however many people approach rather skeptically and do not consider as particularly important aspect in prevention of BC.

Breastfeeding can be considered as a relevant factor for somatic and psychological well-being of woman. The link between skin receptors of nipple and areola with the central endocrine organs (hypophysis) cause an intense stimulation of entire endocrine system. This provides the necessary stimulation of physiological maturation of the female body. Breastfeeding establishes a close emotional and psychological contact between a mother and a child. Neurological reactions are not observed in lactating women. Physiological capabilities of nursing mother can fully provide the child with necessary food ingredients in the optimal composition, exclusively through breast milk. Hypogalactia as the motive and reason for early discontinuation of breastfeeding, in most cases is the result of improper maintenance of lactation. Such hypogalactia is easily reversible and the amount of milk in lactating women increases rapidly corresponding to the child's needs if the methods and techniques of breastfeeding are properly used.

In Kazakhstan, the relevance of correct breastfeeding in formation of women's health and reducing the risk of breast cancer is underestimated. Also, the issue of

optimal feeding duration has not been considered yet. Based on this study, we strongly recommend to pay particular attention to the female population and promote their health through policy change: *i*) to conduct research on issues of breastfeeding in the regions; *ii*) to create a national breastfeeding promotion center; *iii*) to educate the pregnant women about methods and techniques of breastfeeding, informing them about benefits and advantages for both mother and a child, and about the shortcomings of artificial mixtures; *iv*) to train in birthing centers the women in childbirth and postpartum about methods and techniques of breastfeeding; *v*) to train the physicians with certification of training completion; *vi*) to train the nurses by other medical staff; *vii*) the foundation of maternity schools or regular courses for acquaintance of pregnant women with the practice of breastfeeding; *viii*) to orient mothers for a full breastfeeding with both breasts until the child reaches 2 years old; *ix*) to provide timely assistance and support for women facing difficulties of breastfeeding; *x*) to counsel nursing mothers on the issues of prevention of breast diseases.

In conclusion, results of the study show that social, behavioral, and hereditary factors play an important role in development of breast cancer in Kyzylorda oblast of Kazakhstan. Significant factors that increase the risk of breast cancer in women were unilateral breastfeeding (OR=38.40), unfavorable living conditions (OR=22.17), breastfeeding less than 3 months (OR=10.40) and over 2 years (OR=5.20), chronic stress (OR=3.61), abortions (OR=2.67), and hereditary predisposition (OR=3.36). The optimal duration of breastfeeding was 6-24 months-it was related with the lowest risk of breast cancer. In order to provide primary prevention of breast cancer in women the necessity of national breastfeeding strategy policy for comprehensive support and encourage of breastfeeding is highlighted.

## References

Abdrahimov BE (1996). Cancer and medico-social aspects of cancer control in Kazakhstan. *Almaty*, 224.

Abdrahmanova AZh (2000). Clinical and epidemiological aspects of breast cancer in Kazakhstan. Summary of doctoral dissertation. *Almaty*, 47.

Amir E, Freedman OC, Seruga B, Evans DG (2010). Assessing women at high risk of breast cancer: a review of risk assessment models. *J Natl Cancer Inst*, **102**, 680-91.

Antonova L, Aronson K, Mueller CR (2011). Stress and breast cancer: from epidemiology to molecular biology. *Breast Cancer Res*, **13**, 208.

Byers T, Grahan S, Rzepka T, Marshall J (1985). Lactation and breast cancer, evidence for a negative association in premenopausal women. *Am J Epidemiol*, **121**, 664-74.

Bilyalova Z, Igissinov N, Moore MA, 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.

Collaborative Group on Hormonal Factors in Breast Cancer (2002). Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet*, **360**, 187-95.

Collaborative Group on Hormonal Factors in Breast Cancer

(2004). Breast cancer and abortion: collaborative reanalysis of data from 53 epidemiological studies, including 83000 women with breast cancer from 16 countries. *Lancet*, **363**, 1007-16.

Cohen JM, Hutcheon JA, Julien SG, Tremblay ML, Fuhrer R (2009). Insufficient Milk Supply and Breast Cancer Risk: A Systematic Review. *Plos One*, **4**, 1-9.

Curado MP (2011). Breast cancer in the world: Incidence and mortality. *Salud Publica Mex*, **53**, 372-84.

Das S, Sen S, Mukherjee A, Chakraborty D, Mondal PK (2012). Risk Factors of Breast Cancer among Women in Eastern India: A Tertiary Hospital Based Case Control Study. *Asian Pac J Cancer Prev*, **13**, 4979-81.

GLOBOCAN (2008). IARC. Section of Cancer Information. Available from: <http://globocan.iarc.fr>

Hortobagyi GN, de la Garza Salazar J, Pritchard K, et al (2005). The global breast cancer burden: variations in epidemiology and survival. *Clin Breast Cancer*, **6**, 391-401.

Igissinov N, Igissinov S, Moore MA, et al (2011). Trends of prevalent cancer incidences in the Aral-Syr Darya ecological area of Kazakhstan. *Asian Pac J Cancer Prev*, **12**, 2299-303.

Kobayashi S, Sugiura H, Ando Y, et al (2012). Reproductive history and breast cancer risk. *Breast Cancer*, **19**, 302-8.

Liu YT, Gao CM, Ding JH, et al (2011). Physiological, Reproductive Factors and Breast Cancer Risk in Jiangsu Province of China. *Asian Pac J Cancer Prev*, **12**, 787-90.

Mazhitova ZH (2007). Environmentally associated diseases in children (clinic, pathomorphogenesis, diagnosis, treatment and rehabilitation). *Almaty*, 400.

McCormack VA, Boffetta P (2011). Today's lifestyles, tomorrow's cancers: trends in lifestyle risk factors for cancer in low-and middle-income countries. *Ann Oncol*, **22**, 2349-57.

Nugmanov SN, Esenkulov AE (1977). Epidemiology of malignant tumors in Kazakhstan. Collection of scientific papers. *Almaty*, 278.

Naieni KH, Ardalan A, Mahmoodi M, et al (2007). Risk factors of breast cancer in north of Iran: a case-control in Mazandaran Province. *Asian Pac J Cancer Prev*, **8**, 395-8.

Nosheen Fatima, Maseeh uz Zaman, Tehseen Fatima (2010). Increased risk of breast cancer in multiparous and lactating women attending a breast care clinic in pakistan: a paradigm shift? *Asian Pac J Cancer Prev*, **11**, 1219-23.

Nurgaziev KS, Seytkazina GJ, Baipeisov DM, Seysenbaeva GT, Azhmagambetova AE (2012). Indicators of cancer service in RK for 2011 (statistical data). *Almaty*, 108.

Pukkala E, Weiderpass E (1999). Time trends in socioeconom-ic differences in incidence rates of cancer of the breast and female genital organs (Finland, 1971-1995). *Inter J Cancer*, **81**, 56-61.

Parsa P, Parsa B (2009). Effects of reproductive factors on risk of breast cancer: a literature review. *Asian Pac J Cancer Prev*, **10**, 545-50.

Shema L, Ore L, Ben-Shachar M, Haj M, Linn S (2007). The association between breastfeeding and breast cancer occurrence among Israeli Jewish women: a case control study. *J Cancer Res Clin Oncol*, **133**, 539-46.

Santos MC, Horta BL, Amaral JJ, et al (2009). Association between stress and breast cancer in women: a meta-analysis. *Cad Saude Publica*, **3**, 453-63.

Statistical Yearbook (2012). Health of the population of Kazakhstan and activities of health care organizations in 2011. *Astana*, 235-7.

Youlden DR, Cramb SM, Dunn NAM, et al (2012). The descriptive epidemiology of female breast cancer: An international comparison of screening, incidence, survival and mortality. *Cancer Epidemiol*, **36**, 237-48.