RESEARCH ARTICLE

Malignant Tumours of the Central Nervous System in Kazakhstan - Incidence Trends from 2004-2011

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Abstract

In the article were observed the epidemiological aspects of malignant tumors of the central nervous system (MT CNS) in Kazakhstan in a retrospective study for the years 2004-2011. The material of the study was consolidated accounting data of oncology centers on patients with MT CNS (C70-72) with first time established diagnosis. Calculated were crude, age, standardized (world standard), aligned and predicted incidence of MT CNS among both male and female populations. It was found that over the studied period, there were 4,604 cases of MT CNS. The average annual crude incidence rate of MT CNS in total population was $3.7\pm0.1^{0}/_{0000}$. Trends in aligned incidence rates in the whole country had a tendency to increase (T=+0.9%). Defined levels of morbidity MT CNS in the whole population in different regions of Kazakhstan: low up to $2.87^{0}/_{0000}$, the average from 2.87 to $4.45^{0}/_{0000}$ and high from $4.45^{0}/_{0000}$ and above on the basis of which was given the space-time estimate. Age and sex differences in MT CNS incidence were also clearly established

Keywords: CNS malignancies - incidence - age - gender - trends - cartograms - Kazakhstan

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Introduction

High incidences of tumors of the brain and nervous system have been noted in Brazil, the US and the Hawaiian Islands among the white population, Canada, Italy, Poland, Finland and other European countries. Low incidence was found in Africa and Asia, except for Israel, where the incidence is high among the Jewish population (Yeole, 2008; American Cancer Society, 2009; Davydov et al., 2009; IARC, 2010). In Russia, there are only limited data on incidence of these tumors (Zaridze, 2002; Ishmatov, 2013).

A significant increase in morbidity and mortality from brain tumors was noted in the second half of the last century. This trend is expressed mainly in the age group over 65 years. Increasing incidence in developed countries, especially among the elderly, especially the improvement can be attributed to diagnostic methods (Okada, 2013; van Tongeren et al., 2013; Woehrer, 2013).

The curve of incidence of brain tumors characterized by a small peak at the age of 10, then the incidence is reduced, and after 20 years is progressively increasing, reaching a maximum at the age of 50-60 years. Since of astrocytomas dominate, the age-specific incidence curve of astrocytoma repeats corresponding curve of the tumors of the brain, whereas the age-specific incidence curve oligodendrogliomas, ependymoma, meningioma and embryonic tumors differ from each other and from the curve of astrocytoma, which indicates the difference in the etiology of these tumors. Incidence oligodendrogliomas begins to rise after 10 years and reaches a maximum at 50-60 and then slowly decreases. Incidence of ependymoma is high at the age of 10 years, then its level is reduced, and at 20 years there has been a slight increase with the maximum rates at the age of 50-60 years, followed by a pronounced decline. The highest incidence of embryonic tumors observed in children under 5 years old, then slowly decreases the incidence and reaches very low levels after 20-30 years. The progressive increase in the incidence of meningiomas begins at age 40 and continues until 70-80 years of age. The morbidity of brain tumors is slightly higher in men. Gliomas are also more common in men, while the incidence of meningiomas is higher in women (Plascak et al., 2013).

Thus, numerous studies show that more research is needed in this area. Epidemiological studies on the role of different factors in the development of MT CNS have so far been contradictory. We have earlier looked at trends in incidence of major cancers, as well as geographical distribution of laryngeal cancers (Igissinov et al., 2011; 2013). In the present study, the same approach was adopted for CNS tumours, taking into account age and gender, and variation across the different regions of Kazakhstan, with attention to possible underlying factors.

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Materials and Methods

The data, received from oncological institutes of the republic, on the new cases of malignant tumor of central nervous system (MT CNS) incidence (the brain and central nervous system, C70-72) were used as research materials. Also, the research used the data from the Agency of Statistics of the Republic of Kazakhstan on the entire, male and female populations (www.stat.kz).

The study was approved by the ethical committee of «National Medical Holding» (Astana, Republic of Kazakhstan) and administrative permission was obtained from JSC «Astana Medical University». The information may be shared for the research purposes only if a requesting organization provides the data security and under takes all the necessary actions in making the identity of respondents confidential, in concordance with the Principles of the World Medical Association (WMA) Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, adopted by the 18th WMA General Assembly in Helsinki, Finland, in June 1964.

According to the law of the Republic of Kazakhstan «About the State Statistics» [http://www.adilet.gov.kz/ru/node/846], the information in the summary report is confidential and may be used for the statistical purposes only. This is a retrospective study for the years 2004-2011. Based on the generally accepted biomedical methods, the extensive, coarse, age-specific, standardized (world standards) and adjusted rates of mortality from MT CNS of the entire population, and, among men and women were calculated. The average annual values (p), mean error (m) and confidence interval of 95% (95%CI) were also determined.

The average compound rate, equal to the ***n***-th root of the product of annual rates, is used to calculate the average annual growth rates and/or increase of dynamic series:

$$T = \sqrt[n]{T_1 \times T_2 \times T_3 \times T_n}$$

Where ***T*** is annual rate of growth/loss and ***n*** is number of rates.

In compiling the cartograms, the standard rates (world standards) of morbidity were used. The cartograms of morbidity were compiled considering the administrative and territorial divisions of the republic (14 regions and 2 cities: Astana and Almaty). The cartogram compiling method, proposed by Igissinov in (1974), is based on the derivation of a standard deviation (σ) from an average of (x). The scale levels are calculated as follows: taking σ as an interval, the maximum and minimum levels of disease have been defined by this formula: $x \pm 1.5\sigma$, with the minimum level of $x-1.5\sigma$ and a maximum equal to $x+1.5\sigma$. Then, we defined the scale levels of the cartogram: *i*) $(x-1.5\sigma)+\sigma$; 2) $(x-1.5\sigma)+2\sigma$; 3) $(x-1.5\sigma)+3\sigma$, etc.; the categorization of indexes was derived from the formula $x \pm 0.5\sigma$, corresponding with the average level $(x-0.5\sigma$ and $x+0.5\sigma)$; the values that are distant from the average incidence by σ, show lower $((x-0.5\sigma)-\sigma)$ and higher $((x-0.5\sigma)+\sigma)$ values. The construction of equal intervals was used for grouping the parametrical series, a formula proposed by Boyarsky: $\gamma=(X_{max}-X_{min})/(1+3.22\ lgn)$

Where X_{max} is a maximum rate; X_{min} is a minimum rate; and n is a number of population, i.e. amount of areas and cities.

Viewing and processing the materials was made on the computer (using software package Microsoft Office: Excel, Word, Access; BIOSTAT, EpiInfo 7). The following abbreviations are used in the article: AN – absolute number.

Results

For the researched period, 4,604 patients with MT CNS diseases were registered in Kazakhstan. Considering the age groups, the incidence of MT CNS was distributed as follows: 'under 30' – 1037 (22.5%), '30-39' – 558 (12.1%), '40-49' – 853 (18.5%), '50-59' – 1135 (24.7%), '60-69' – 702 (15.2%), and '70 and older' – 319 (6.9%) patients. The distribution by gender and age groups is presented in the Table 1.

From the Table 1, we can observe that the average age of patients with MT CNS for the years 2004-2011 was 44.5±0.4, and, in the dynamics, it slightly fluctuated around its average value, but the trend was increasing (T=+0.5%). This was typical for both men and women. The average annual growth rate for women (T=+1.0%) was higher than for men (T=+0.1%). These features are characterized by the tendency of ageing of MT CNS both among the entire population (both genders) and among the researched genders.

In the dynamics, the annual rates of MT CNS morbidity in the whole population grew from 3.34±0.15 in 2004 to 3.90±0.15 $^0/_{0000}$ in 2011 ($p<0.05$). Also, adjusted rates

Table 1. Distribution of MT CNS Morbidity in Kazakhstan by Gender and Age Groups (data for the years 2004-2011)

Age groups (years)	Both genders AN	%	Males AN	%	Females AN	%
<30	1037	22.5	577	23.8	460	21.1
30-39	558	12.1	299	12.3	259	11.9
40-49	853	18.5	451	18.6	402	18.4
50-59	1135	24.7	606	25.0	529	24.3
60-69	702	15.2	352	14.5	350	16.1
≥70	319	6.9	139	5.7	180	8.3
Total	4604	100.0	2424	100.0	2180	100.0
Average age (M±m, 95% CI)	44.5±0.4, 43.7-45.4		43.6±0.5, 42.6-44.6		45.5±0.6, 44.3-46.7	

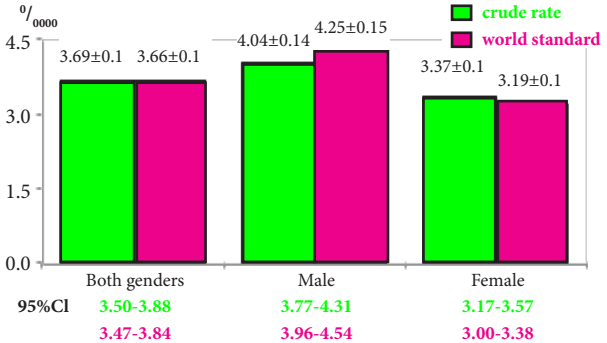


Figure 1. The Average Annual Rates of MT CNS Morbidity in Kazakhstan for the Years 2004-2011

repeated the revealed trends. At the same time, the trends were more expressive in the category for women, with the average annual growth rate T=+1.4%.

When analyzing, the SR of morbidity among men, the figure was higher than the annual rate – 4.25±0.15$^0/_{0000}$ (95%CI=3.96-4.54$^0/_{0000}$), whereas among women, the figure was lower than the annual rate – 3.19±0.1$^0/_{0000}$ (95%CI=3.0-3.38$^0/_{0000}$) (Figure 1). It was observed that the 95%CIs of both, standard and annual rates did not overlap with the males and females figures, so there were statistically significant differences (p<0.05).

Dynamically, the standard rates of incidence in Kazakhstan repeated the same changes as the annual rates. The trends of standard rates are illustrated in Figure 2A.

The age-specific features of MT CNS morbidity in Kazakhstan. The emergence and prevalence of the malignant tumor of central nervous system are directly related to the age composition of the population, since one of the most significant risk factors is the age. Thus, among people under 30, the rate of MT CNS incidence was 1.6±0.08$^0/_{0000}$. At the age of 30-39, the morbidity rate increased 1.9 times compared to the group 'under 30' and reached – 3.1±0.2$^0/_{0000}$. Next, at the age of 40-49, the incidence increased by 1.6 times compared to the group '30-39' reaching – 4.98±0.19$^0/_{0000}$. In the age group '50-59', the incidence rate (9.49±0.39$^0/_{0000}$) was 1.9 times higher than in the previous age group. At the age of 60-69, the maximum incidence rate was registered – 10.26±0.54$^0/_{0000}$, and in the age group '70 and older' the rate was 5.46±0.61$^0/_{0000}$. A unimodal increase of rates reaching a peak in the age group of '70 and older' was also observed among men and women (Figure 3). It was found that the trends of MT CNS morbidity increased in the following age groups: 'under 30' – T=+0.6%, '60-69' (T=+4.9%), and '70 and older' (T=+11.0%), where the growth was highlighted most. Decline was observed in the age groups '30-39' (T=–2.1%), '40-49' (T=–0.2%), and '50-59' (T=–2.0%). Due to the expressive increasing trend in the age groups older than 60, the incidence rate in the whole population had an upward trend (Figure 2B). The trends of age-specific rates of MT CNS incidence among men repeated the above-shown pattern, and the rates of growth were mostly expressive among the patients older than 60.

Spatial assessment of the frequency of MT CNS by administrative-territorial division of the Republic is given taking into account the standardized (world standard) incidence in total population, male and female. To produce cartograms of MT CNS disease were determined levels, based on the received scales were composed cartograms. Cartograms for cancer of the central nervous system incidence are shown for regions in Figure 4 (A for males and B for females). Cartograms of MT CNS incidence in the studied population groups more clearly reflect the spatial distribution of the republic. The discrepancy between the theoretical and the actual distribution of the

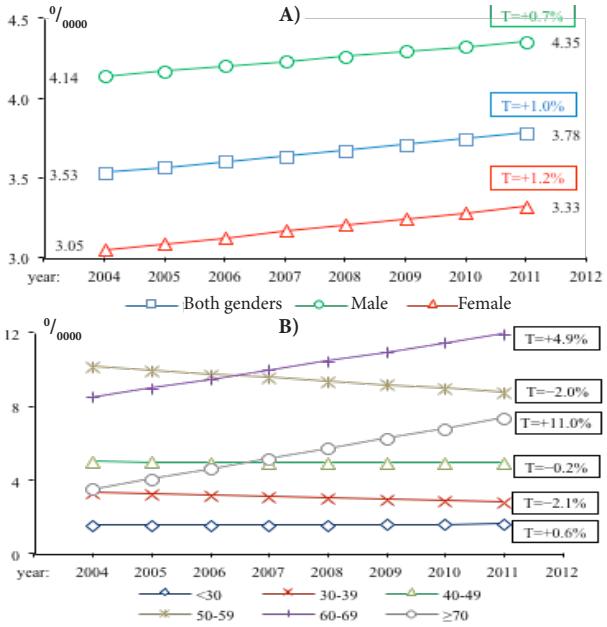


Figure 2. The Trends of Adjusted A) Standardized Rates and B) Age-Specific Rates (in the Entire Population) of MT CNS Incidence of Kazakhstan for the Years 2004-2011

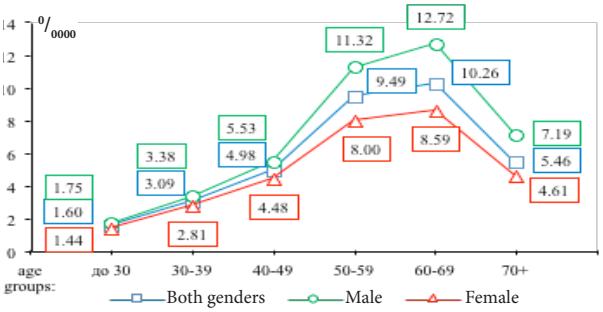
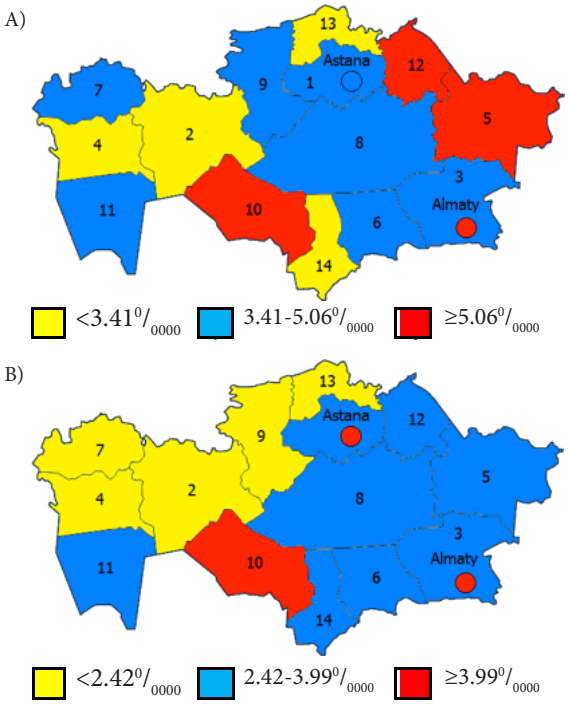


Figure 3. The Average Annual Age-Specific Rates of MT CNS Incidence in Kazakhstan for the Years 2004-2011



Regions: 1. Akmola, 2. Aktobe, 3. Almaty, 4. Atyrau, 5. East Kazakhstan, 6. Zhambyl, 7. West Kazakhstan, 8. Karaganda, 9. Kostanai, 10. Kyzylorda, 11. Mangystau, 12. Pavlodar, 13. North Kazakhstan, 14. South Kazakhstan

Figure 4. The Cartogram of MT CNS Incidence among A) Male and B) Female in Kazakhstan for the Years 2004-2011

incidence of MT CNS in selected areas and small towns, the criterion of Pearson (χ^2) is equal to 22.1, 25.1 and 16.1 in whole, male and female population, which is more than the table value. Therefore, the actual frequency distribution of MT CNS of all, male and female population by regions of Kazakhstan is close to a normal distribution.

Discussion

The present results point to age variation in change in CNS cancer incidences, with clear differences across the vairous areas of the country. In both males and females the slight incresae observed over time was primarily due to cancers in the most aged groups. The north of the country appears at lower risk than the rest of the country, with high rates seen in Kyzylorda and Almaty.

Regarding change in incide, general increases have been noted in India (Yeole, 2009) and China (Ding and Wang, 2011; Wu et al., 2012), and in females in Pakistan (Bhurgri et al., 2011). Increase primarily in the elderly and females has also been observed in France (Baldi et al., 2011), while rise in childhoods rates was reported for Canada (Rosychuk et al., 2012). In contrast the situation appears stable for the Nordic countries (Schmidt et al., 2011) The situation is complicated by the vaious types of CNS tumours whcih have independent risk factors. For example, during the 10 year period from 1995-2004, the rates of meningiomas decreased significantly in Japan, but those of glioblastoma did not (Nomura et al., 2011). One report documented increasing incidence of glioblastoma multiforme and meningioma, and decreasing incidence of schwannoma in Australia (Dobes et al., 2011). Similar histology dependent change has also been described for England (Arora et al., 2010). The mean age vary by sub-site and histology (Bhurgri et al., 2011). It may also be important to take into account actual site, data from the US demonstrating increased incidences of of one type in the frontal lobe, temporal lobe, and cerebellum, despite decreased incidences in other brain regions (Zada et al., 2012).

Regarding geographical variation, in Spain there is evidence of space clustering for medulloblastoma and space-time clustering for all tumors, CNS tumors, astrocytoma, and neuroblastoma. (Ortega-García et al., 2011). In order to understand variation we must look at possible risk factors.

In the etiology of brain tumors important factors are those that are able to overcome the blood-brain barrier. This is primarily ionizing radiation (Yamaguchi, 2013), metals (arsenic, lead) (Wu et al., 2013), solvents (Ruder et al., 2013) and drugs (Garcia-Sevilla et al., 1999). It is proved that ionizing radiation causes brain tumors in humans. Radiation therapy for ringworm in children has led to a significant and statistically significant increased risk of gliomas, meningiomas and nerve sheath tumors (Rivera et al., 2013). The results of epidemiological studies that have investigated the risk of brain tumors in relation to the X-ray examination of skull and teeth, are contradictory. However, shown that the use of X-ray in utero leads to increased risk of brain tumors (Goske et al., 2012). Whether any of these might explain our variation remains unclear.

In some cohort studies that have examined the representatives of the professions which had a contact with sources of ionizing radiation (dentists, doctors, nurses, veterinarians) found increased incidence of brain tumors (Braganza et al., 2012). However, only associate with an increased risk of radiation is not possible, as these specialists have had contact with other possibly carcinogenic factors, such as, for example, arsenic, chemotherapy, etc. Negative results were obtained by observing a cohort of radiologists in China and employees of nuclear facilities of US and UK (Kim et al., 2013). Based on a number of epidemiological studies can be concluded that occupational exposure to ionizing radiation does not increase the risk of brain tumors.

Carcinogenic effect on the brain and nervous tissue of low-frequency (50-60 Hz) electromagnetic field, which is emitted by power lines and household appliances microwave and radio frequency (0.5-100 MHz), is the subject of many studies (Benson et al., 2013; Kesari et al., 2013). The mechanism of the possible carcinogenic effects of electromagnetic fields is unclear. Analysis of studies devoted to this problem allows us to conclude that exposure to low-frequency electromagnetic field is not the cause of increased risk of brain tumors (Vijayalaxmi and Prihoda, 2012).

Etiological link between mobile phone use and risk of brain tumors was also not confirmed. Electromagnetic field, which generate mobile phones, is in the spectrum of microwave radiation and has a frequency of 450-2200Hz. The study by the "case-control", held at the end of the last century, which included more than 700 patients with intracranial tumors showed no link between mobile phone use and risk of intracranial tumors. Relative risks were below 1 for meningiomas and gliomas, and the risk of acoustic neuroma was slightly elevated and not statistically significant (Berg et al, 2006). While a shift in laterality towards left-sided tumors,for both low and high-grade gliomas, has been proposed as evidence for a link (Barchana et al., 2012), there is no plausible reason why the massively increased use of wireless phones has not affected the relatively stable incidence time trends for brain tumours among children and adolescents in Nordic countries (Aydin et al., 2012) and the US data (Little et al., 2012). A study of the risk of brain tumors among workers of various specialties who could be exposed to low frequency electromagnetic field was also inconclusive (Kleinerman et al., 2005).

The connection between head injury and the subsequent development of brain tumors has been shown in several studies by the method "case-control". For example, a positive correlation between traumatic brain injury and relatively short-term development of malignant neoplasms was noted in Taiwan (Chen et al., 2012). Data from a number of epidemiological studies indicate that brain tumors often develop on the background of epilepsy (Maschio, 2012). However it is possible that the epileptic seizures are early clinical manifestation of tumors of the brain, and not preceded by their development. Were described cases of brain tumors, which preceded the development of multiple sclerosis (Yang et al., 2007).

Steroid hormones overcome blood-brain barrier and affect the function of nerve cells. Many cellular elements comprise brain steroid hormone receptors, estrogen, androgen and progesterone. Therefore hypothesized a possible role of steroid hormones, both endogenous and exogenous, and hence reproductive history in the etiology of brain tumors. Study has shown that brain tumors are more common in infertile women, as well as in women who have given birth to her first child late (after 30 years), and that they are often associated with breast cancer. However, these data are preliminary and require confirmation in well-designed epidemiological studies (Qian et al., 2013).

Based on experimental studies, it was suggested that nitroso compounds, in particular nitrosoureas and nitrosoamines are the most powerful neurocarcinogens. However, epidemiological studies have failed to confirm the role of nitroso compounds in the etiology of brain tumors in humans (Dietrich et al., 2005). Regarding dietary factors, caffeine appears to have no influence (Dubrow et al., 2012) and consumption of processed or red meat, nitrite, or nitrate does not increase adult glioma risk, and that consumption of fruit and vegetables, vitamin C, or vitamin E does not reduce risk (Dubrow et al., 2010).

Study of features of disease in regions with high and low incidences of cancer are of particular epidemiological interest. Rating distribution MT CNS by various territories not only identifies residents of places at greatest risk, but allows you to analyze the processes of emergence and spread of cancer. The role of surveillance in the monitoring program of cancer is essential. Epidemiological studies are a kind of compass, and allows you to answer the question: Where and at what stage are we now? And also helps to put a new question: Which direction to go in the future? The results should be used for targeted anti-cancer activities of the central nervous system malignancies.

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