RESEARCH ARTICLE

Epidemiological Evaluation of Laryngeal Cancer Incidence in Kazakhstan for The Years 1999-2009

Nurbek Igissinov[2,3]*, Vera Zatoskikh[3], Malcolm Anthony Moore[4], Saginbek Igissinov[1,5], Rais Toulebaeyev[3], Meruert Mustafina[3], Saule Valieva[6], Gulmira Aldiyarova[3], Zhanar Bukeyeva[3], Anatoly Venglovskiy[2]

Abstract

The purpose was to provide a descriptive epidemiological assessment of the incidence of cancer of the larynx in Kazakhstan and spatial evaluation with gender characteristics. Thgis retrospective study covered all new cases of laryngeal cancer in 11 years (1999-2009). The total number was 4,967 cases, 4,535 (91.3%) in males and 432 (8.7%) in women, with a ratio of 10.5:1. The higher incidence in men compared to women was evident in all age groups, the differences being statistically significant ($p<0.05$). At the same time revealed a unimodal growth with age, peaking at 70 years and older both sexes. In the dynamics, incidence rates of laryngeal cancer demonstrated a tendency to decrease, in women (T=–6.7%) this being more pronounced than in men (T=–3.3%). Levels were determined to produce cartograms of cancer of the larynx for male and female populations, clear geographical variation being evidenced. The data are discussed with reference to possible risk factors.

Keywords: Laryngeal cancer - incidence - gender - age - cartogram

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Introduction

Malignant tumors occur in men and women in all the age groups. Patterns of morbidity and mortality from cancer is different for each gender and age, that, first of all, determined by the physiological characteristics of the organism and exposure to modifiable risk factors (Jemal et al., 2011; Shin et al., 2012; Jung et al., 2012).

The incidence of cancer of the larynx also has statistical differences according to age and sex (Wunsch, 2004; de Souza et al., 2011), geographical features of the place of residence (Dykhno et al., 2002; Saurina et al., 2010), social class and the living standards of the studied group of population (Vassileiou et al., 2012) and a number of other external factors (Wong et al., 1993; Grant, 2012; Romanowicz-Makowska et al., 2012). In Kazakhstan, it has already been shown that there is geographical variation in incidences of breast (Bilyalova et al., 2012), esophageal (Igissinov S et al., 2012; 2013), and cervical cancer (Igissinov N et al., 2012), with changes dover time (Igissinov et al., 2011).

Laryngeal cancer is extremely rare in women (Licitra et al., 2003; Ellis et al., 2012). So according to the International Agency for Research on Cancer in 2008, there were 150,677 cases of cancer of the larynx, of whom 129,651 (86%) cases in men and 21,026 (14%) in women. In this case, the standardized (world standard) incidence of laryngeal cancer /100.000 was among the whole population 2.2, in males 4.1 and in females (Ferlay et al., 2010).

The highest incidence rates (crude rate) have been registered in more developed countries of the world and the lowest in the developing countries.The high incidence among male population (>9 per 100 thousand population) are registered in Spain (Zaragoza), France (Calvados), Belarus, Brazil (Sao Paulo), and in African-Americans in the United States, low (<3) in Asia and Africa. In Russia, the incidence of laryngeal cancer is not high, in women figure does not exceed 1.

The main etiological factor in the development of laryngeal cancer is tobacco (Hashibe et al., 2007; Anantharaman et al , 2011; Ramroth et al., 2011; Sharma et al., 2011). It has been estimated that 87% of laryngeal cancer cases in Central Europe are attributable to tobacco, with 75% and 12% due to current and past smoking, respectively (Hashibe et al., 2007). Both increasing duration and intensity of smoking are important (Ramroth et al., 2011) and involuntary smoking exposure is also a factor (Lee et al., 2008). Smokeless chewing tobacco, however, does not appear to be of significance (Sapkota

*[1]Central Asia Cancer Institute, [2]Research Institute of Traumatology and Orthopedics, [3]Astana Medical University, [4]UICC Asian Regional Office for Cancer Control, Republican Research Center of Neurosurgery, [5]Kazakh National Medical University named after SD Asfendiyarov, [6]Almaty State Institute of Advanced Medical Education *For correspondence: nurbek_igisinov@mail.ru, n.igissinov@gmail.com*

et al., 2007).

Excessive consumption of alcohol, particularly alcoholic beverages increases the risk of cancer in sites like the larynx (Islami et al., 2010; Tavani et al., 2012). In one study approximately 39% of casaes appeared attributable to the interaction between alcohol and tobacco (Hashibe et al., 2007). In another, the population attributable risk of tobacco and alcohol for upper aerodigestive tract cancer hypopharyngeal/laryngeal cancer was 85% (Anantharaman et al , 2011).

The tobacco and alcohol roles are supported by evidence from genetic studies. Sequence variants in DNA repair and cell cycle genes are significant (Hall et al., 2007), an impaired nucleotide excision repair pathway is a risk (Sliwinski et al., 2011), the GSTM1 null genotype contributes to increased laryngeal cancer risk in both Caucasians and East Asians (Xiao et al., 2013) and GSTM1 gene polymorphisms demonstrate associations, particularly in Caucasians (Kumar et al., 2011; Ying et al., 2012). Combination of polymorphisms in COX-2 or EPHX1 with high activity polymorphisms in UGT1A1, UGT1A6, or UGT1A7 showed a risk-modulating effect in head and neck carcinogenesis, especially among heavy smokers and patients with laryngeal cancer (Lacko et al., 2013). N-acetyltransferase 2 slow acetylation may contribute to a risk factor for laryngeal cancer in Asians but not in Caucasians (Ying et al., 2011). The fact that low selenium consumption could be a risk factor (Jaworska et al 2013) is in line with a role for oxidative stress.

Type of food consumed also influences laryngeal cancer development (Bradshaw et al., 2012; Tavani et al., 2012). A possible unfavorable effect of dietary patterns based on meats and animal products has been reported (Bravi et al., 2012), while conversely a prudent diet protected in Uruguay (De Stefani et al., 2013). Fried foods, high-fat and processed meats, and sweets pattern was positively associated with laryngeal cancer in the USA (Bradshaw et al., 2012). In central and Eastern Europe, dairy products and yellow/orange vegetables appear protective while preserved vegetables might entail risk (Sapkota et al., 2008). Similarly, in China, eating sauerkraut and BBQ food were found to be risk factors and regular consumption of fresh vegetables, coarse grains, eggs and milk appeared protective (Wang et al., 2011). In contrast yogurt was found to be beneficial in Japan (Kawakita et al., 2012). Consumption of Greek/Turkish coffee may promote (Vassileiou et al., 2012) but no association with caffeinated coffee drinking was found (Al-Dakkak, 2011). Regular physical exercise may reduce risk (Wang et al., 2011) but recreational physical activity was not fou d to exert any effect in Europe (Nicolotti et al., 2011).

Air pollution with emissions and transport industries, and water and soil with heavy metals above the maximum permissible concentrations and evolution of other exogenous and endogenous risk factors lead to an increase in illness, especially cancer pathology, and in particular cancer of the larynx (Enomoto et al., 2008; Poirier, 2012). Environmental carcinogens and materials causing irritation are well known to be aetiological factors for laryngeal cancer. Several epidemiological studies have found that exposure to asbestos in the workplace increases the risk (Chan et al., 1988; Parnes, 1990). A study in Russia and other countries of Eastern and Central Europe, revealed an increased risk of laryngeal cancer among workers exposed to coal dust, hard metals, chlorinated solvents, as well as formaldehyde (Shangina et al., 2006). Use of coal (Sapkota et al., 2013) and silica dust exposure have also been implicated (Chen and Tsu, 2012). A similar irritation dependent mechanism might be relevant for the finding that gastrectomy for peptic ulcer disease might entail a long-term increase (Lagergren and Lindam, 2012) as does laryngopharyngeal reflux (Tae et al., 2011) but apparently not gastroesophageal reflux (Coca-Pelaz et al., 2013).

Regarding infectious disease associations, HPV infection is a risk factor, especially with high-risk type HPV-16 (Li et al., 2013) and a very high prevalence of oncogenic HPV-16 was found in a series of benign and malignant laryngeal lesions in Belgium (Duray et al., 2011). *Helicobacter pylori* can colonise the larynx and therefore might exert an influence.(Siupsinskiene et al., 2013)

The study of the epidemiological features of laryngeal and geographical variation has a scientific and practical interest because it allows for monitoring for preventive measures and to assess the impact of possible causal factors of risk. This paper focuses on the descriptive epidemiologic assessment of cancer of the larynx in the republic of Kazakhstan with an especial focus on age and sex characteristics.

Materials and Methods

As a source served a data of oncology centers about new cases of laryngeal cancer (form 7), and the information of the Agency of statistics of the Republic of Kazakhstan for the years 1999-2009 taking into account the age and sex composition (www.stat.kz).

The main method used in the study of the incidence of a retrospective study using descriptive and analytical methods of oncoepidemiology. The incidence is calculated per 100,000 of the population concerned. Have been calculated extensive, crude, age and aligned incidence rates average values (P), the mean error (m), 95% confidence interval (95% CI), the average annual growth/loss (T, %) (Merkov et al., 1974; Stanton, 1999).

Results and Discussion

Over 11 years (2009-2011) in Kazakhstan were registered 4,967 new cases of cancer of the larynx, of which 4,535 (91.3%) men and 432 (8.7%) women. The ratio of male and female patients was 10.5:1 and the crude incidence rate in men ($5.7/10^5$) was higher ($p<0.05$) than in women (0.5). Highest age-specific incidence in male and female populations were established in the older group of 70 years and over: 41.4 and 2.6.

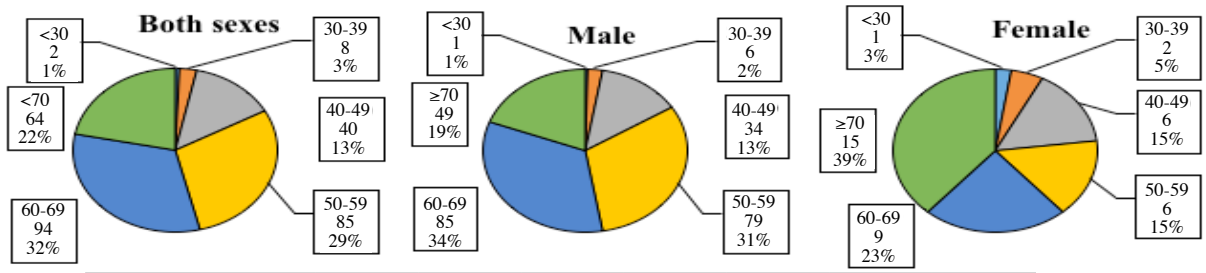
The distribution of patients with laryngeal cancer in the whole country, taking into account age and sex is shown in Figure 1. A high proportion of patients (both sexes) were installed in 60-69 years (36.2%), a similar pattern

was for men (37.4%), while the high proportion of women were in the age group of 70 years and older (30.1%). The average age of patients with laryngeal cancer in the whole country among men was 61.4±0.2 years (95% CI, 61.1-61.8 years), women: 45.5±0.6 years (95% CI, 58.9-61.0 years), difference is statistically significant ($p<0.05$), as their 95% confidence intervals don't not overlap.

The average annual crude incidence rate of the male population of the Republic with laryngeal cancer was 5.7, and the rate of women was 11.4 times lower: 0.5±0.06, the difference being statistically significant ($p<0.05$). In the dynamics crude incidence rate in both men (T=–3.3%) and in women (T=–6.7%) decreased, wherein among women trends were more pronounced.

Analysis of the 95%CI indicates that between age indicators there are statistically significant differences ($p<0.05$), where they do not overlap, i.e., the formation of various indicators affect the causal factors (Table 2).

Next, we made cartogram of cancer of the larynx in all, male and female population according to the administrative-territorial division of the country. The cartogram laryngeal cancer incidence among all population has the same regularities described in this study, and more accurately represents the spatial distribution of laryngeal cancer for individual regions. The discrepancy between the theoretical and actual distribution of laryngeal cancer incidence for individual regions and cities are small; the Pearson criterion (χ^2) was equal to 12.7 (calculations are



Ratio of men to women	<30	30-39	40-49	50-59	60-69	≥70	Total
	1.7÷1	2.9÷1	5.9÷1	14.9÷1	16.1÷1	7.5÷1	10.5÷1

Figure 1. Distribution of Patients with Laryngeal Cancer by Age and Gender in Kazakhstan for The Years 1999-2009

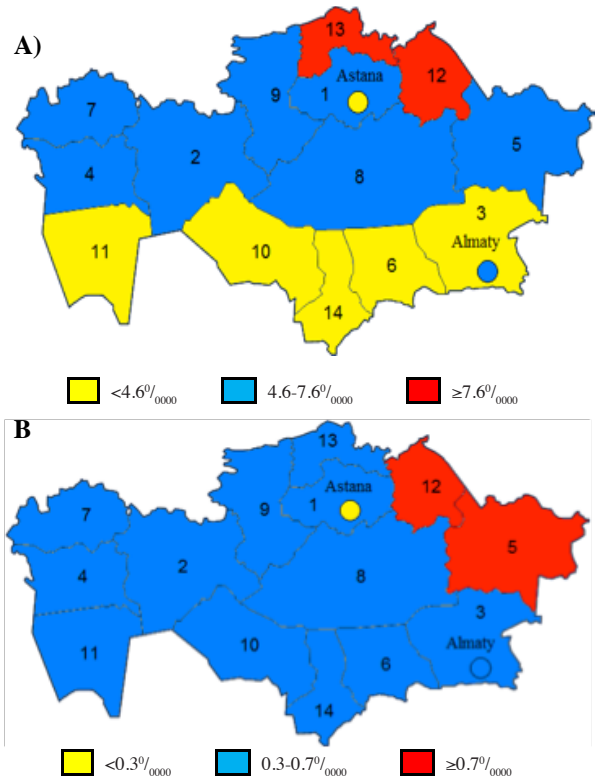
Table 1. Age-Specific Indicators of Laryngeal Cancer Incidence in Kazakhstan for The Years 1999-2009

		Both sexes			Male			Female		
		Incidence, 0/0000		T, %	Incidence, 0/0000		T, %	Incidence, 0/0000		T, %
		P±m	95%CI		P±m	95%CI		P±m	95%CI	
Age groups	<30	0.014±0.01	0.0-0.03	±0.0	0.03±0.01	0.01-0.04	–23.2	0.02±0.01	0.01-0.03	+9.7
	30-39	0.31±0.14	0.03-0.58	+0.7	0.5±0.1	0.3-0.7	–17.2	0.18±0.04	0.1-0.3	+0.5
	40-49	1.6±0.4	0.9-2.3	–7.9	4.4±0.5	3.5-5.3	–8.1	0.7±0.1	0.5-0.9	–8.8
	50-59	6.6±1.4	3.9-9.4	–0.4	21.1±1.5	18.2-24.0	–3.5	1.2±0.2	0.8-1.6	–7.7
	60-69	11.0±1.7	7.6-14.4	–3.5	40.0±2.1	36.0-44.1	–2.8	1.8±0.2	1.3-2.2	–4.3
	≥70	12.1±3.4	5.4-18.8	–0.4	41.4±2.4	36.7-46.1	–2.6	2.6±0.4	1.9-3.4	–10.7
Total		1.3±0.2	1.0-1.7	–1.8	5.7±0.3	5.0-6.3	–3.3	0.5±0.1	0.4-0.6	–6.7

Table 2. Calculation Scheme for Determining Normal and Theoretical Distributions of Laryngeal Cancer Incidence and Pearson Criterion (χ^2)

NN	GR (γ=20.7)	CM (V)	NoD (p)	$V\times p$	$d=V-x$	d^2	$d^2\times p$	$t=(V-x)/\sigma$	F(t)	TF=[($\gamma\times\sum p$)/σ]×F(t)	RTF, p'	$p-p'$	$(p-p')^2/p'$
Male Population													
1.	0.0-2.7	1.3	1	1.3	–4.7	22.5	22.5	+1.57	0.1163	1.641	2	–1	0.25
2.	2.7-5.3	4.0	7	28.0	–2.1	4.3	30.4	+0.69	0.3144	4.436	4	+3	1.48
3.	5.3-8.0	6.7	6	40.0	+0.6	0.3	2.0	–0.19	0.3918	5.528	6	+0	0.04
4.	8.0-10.7	9.3	1	9.3	+3.2	10.5	10.5	–1.07	0.2251	3.176	3	–2	1.49
5.	10.7-13.3	12.0	0	0.0	+5.9	35.0	0.0	+1.96	0.0584	0.824	1	–1	0.82
6.	13.3-16.0	14.7	1	14.7	+8.6	73.6	73.6	+2.84	0.0071	0.100	0	+1	8.08
		$\sum p=n$=16		$\sum V\times p$=93.3			$\sum d^2\times p$=139.1	–	–	–	16		**χ^2=12.2**
Female Population													
1.	0.0-0.3	0.2	1	0.2	–0.4	0.1	0.1	+1.04	0.2323	3.428	3	–2	1.72
2.	0.3-0.6	0.5	10	4.5	–0.1	0.0	0.0	+0.19	0.3918	5.782	6	+4	3.08
3.	0.6-0.9	0.8	4	3.0	+0.2	0.1	0.2	–0.65	0.3230	4.766	5	–1	0.12
4.	0.9-1.2	1.1	0	0.0	+0.5	0.3	0.0	–1.49	0.1315	1.940	2	–2	1.94
5.	1.2-1.5	1.4	0	0.0	+0.8	0.7	0.0	+2.34	0.0258	0.381	0	+0	0.38
6.	1.5-1.8	1.7	1	1.7	+1.1	1.3	1.3	+3.18	0.0034	0.050	0	+1	17.98
		$\sum p=n$=16		$\sum V\times p$=9.3			$\sum d^2\times p$=1.7	–	–	–	16		**χ^2=25.2**

*GR: grouping regions, CM: class mark, NoD: the number of districts, TF: theoretical frequency, RTF: refined theoretical frequency, 10th column is determined in a



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 2. Cartogram of Laryngeal Cancer Incidence among the A) Male Population and B) Female Population of Kazakhstan for the Years 1999-2009

shown in Table 2 for the two sexes. Hence, the actual distribution of laryngeal cancer incidence in the regions of the Republic of Kazakhstan is close to the normal distribution.

Cartogram of laryngeal cancer incidence among men has showed following groups of regions (Figure 2A): *i*) Regions with low rates (up to 4.6), South Kazakhstan (2.2), Kyzylorda (2.9), Zhambyl (3.8), Almaty (4.0) regions and Astana city (4.2). *ii*) Regions with the average rates (from 4.6 to 7.6), Aktobe (4.7), Mangystau ($5.1^0/_{0000}$), Atyrau (5.1), Akmola (6.1), Karaganda (6.4), West Kazakhstan (6.8), Kostanai (7.2) East Kazakhstan (7.2) regions and Almaty city (6.1). *iii*) Regions with high rates (from7.6 and above), North Kazakhstan (10.3) and Pavlodar (15.2) regions.

Cartogram of laryngeal cancer incidence among women has showed following groups of regions (Figure 2B): *i*) Regions with low rates (up to 0.3), Astana city (0.2). *ii*) Regions with the average rates (from 0.3 to 0.7), South Kazakhstan (0.3, Aktobe (0.3), Almaty city (0.3), Zhambyl (0.4), Almaty (0.4), Akmola (0.4), Karaganda (0.4), West Kazakhstan (0.4), Kostanai (0.4), Atyrau (0.5), Kyzylorda (0.6), Mangystau (0.60/0000) and North Kazakhstan (0.6) regions. *iii*) Regions with high rates (from 0.7 and above), East Kazakhstan (0.7) and Pavlodar (1.8) regions.

Therefore, the actual distribution of cancer of the larynx, especially in males seems to indicate an increase as one travels north. One possibility is that the ethnic distribution in terms of the relative proportions of Russian and Kazakh regions vary. At the same time it appears that the major cities have relatively low rates. Clearly future work should focus on this ethnicity aspect.

This is particularly with regard to the major laryngeal risk factors, tobacco and alcohol consumption. Tobacco quit ratios are low in the former Soviet Union but desire for control and cessation support does exist (Footman et al., 2013). Smoking prevalence appears to have stabilized and may be declining in younger groups, but remains extremely high among men, especially those in lower socioeconomic groups. Large gaps exist in public understanding of the negative health effects of tobacco use, particularly in Kazakhstan (Roberts et al., 2012).

Regarding dust exposure geographical variation in Kazakhstan might be expected and this possibility deserves exploration. While HPV infection could be a risk factor, the fact that Almaty has a much higher incidence of cervical cancer than Almaty (Igissinov N et al., 2012) would suggest that other factors are in action. The prevalence of *H. pylori* infection has been reported to be almost identical among the two ethnic groups (Russians 79% and Kazakhs 80%) with a negative relation to clean water index (Nurgalieva et al (2002).

In Central Asia worse socio-economic situation, negative health behaviours (smoking and alcohol consumption) and rural residence were all associated with low levels of fruit and vegetable intake (Krull Abe et al., 2013) so that many factors are probably interacting together to determine risk of laryngeal cancer. One area of obvious interest is availability of various detrimental and advantageous factors like alcohol, tobacco and foodstuffs , as highlighted earlier for Almaty (Yim et al., 2003).

In future our results should be used for targeted anti-cancer activities of laryngeal malignancies. Further study of the incidence of laryngeal cancer taking into acoount a variety of exogenous and endogenous causes is a priority of our research.

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