MAIN EPIDEMIOLOGICAL ASPECTS OF PANCREATIC CANCER IN KAZAKHSTAN

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ABSTRACT

According to GLOBOCAN (2020), pancreatic cancer (PC) is in 12th place among oncopathology in terms of incidence - 4.9 cases per 100,000 population. Most cases of pancreatic cancer are registered in China, the USA, Japan, and Germany. In the structure of mortality among oncological diseases, pancreatic cancer occupies 9th place - 4.5 cases per 100 thousand of the population. According to epidemiological studies, by 2040, a 79.9% increase in mortality from pancreatic cancer is predicted. According to statistics, in the United States, there is an increase in the incidence of cancer in the distal pancreas. In addition, early stages of pancreatic cancer were diagnosed more often and less often - the 4th. One of the trends in the epidemiology of pancreatic cancer is an increase in the incidence of this pathology among young people. Factors contributing to the development of pancreatic cancer in people under 50 years of age are genetic mutations, smoking, and obesity. A retrospective statistical analysis of the epidemiological state of pancreatic cancer in Kazakhstan over 3 years was carried out (standardized WHO World indicators per 100,000 population and intensive indicators of morbidity, mortality, distribution by stage, age, and sex), and regional features of pancreatic cancer were studied.

Keywords: pancreatic cancer, pancreas, epidemiology of pancreatic cancer, morbidity, mortality

INTRODUCTION

The incidence of pancreatic cancer (PC) is at a high level in many countries worldwide. According to the GLOBOCAN 2020 database, the incidence rate of pancreatic malignancies in 2020 was 495,773 (262,865 men and 232,908 women), mortality rate was 466,003 (246,840 men and 219,163 women) [1]. The global average incidence rate was 6.4% (6.7% among men and 6. among women) - it ranks 12th in cancer incidence in the entire population, 12th most common cancer among men and, 11th among women. Pancreatic cancer is the seventh most common cause of death in men and women worldwide [1-4].

Cigarette smoking and diabetes have been associated with increased risk of pancreatic cancer. Current cigarette smoking is associated with a substantially increased risk of pancreatic cancer. Smoking has been shown to increase the risk by at least 5-fold in smokers, and this risk accrues even above average consumption levels ($\geqslant$ 40 pack year). There is growing data suggesting an association between pancreatic cancer and insulin signaling. *In vitro* studies' results indicate insulin and insulin resistance may play a role in etiology of pancreatic cancer through its effects on glucose metabolism [5].

The age-standardized incidence rate is 18.7 per 100,000 standard population; in Asian countries, it varies in a wide range (35.0 and 6.3 per 100,000 population in Japan and Korea, respectively). (Table 1) [1-4]. The rates of morbidity and mortality of PC estimated by WHO, GLOBOCAN 2020 correlate with the data of oncological service Republic of Kazakhstan [2-4]. As can be seen from Table 1, there is no significant difference in morbidity and mortality rate between the genders. An accurate assessment of disease mortality can be achieved by analyzing the morbidity-mortality ratio since this is a way of measuring the level of mortality from a given disease in a particular country. In addition, this ratio helps to understand the level of diagnosis and treatment of pancreatic cancer in the given country. In Israel, the morbidity-mortality ratio is 11.6%, which indicates a low mortality rate from pancreatic cancer with the existing incidence rates, and the effective development of oncological services. In other countries of the world, this ratio exceeds 80%, and in some, it reaches up to 90%, which indicates a fairly high mortality rate from pancreatic cancer and a low level of early diagnosis and treatment options.

Table 1 – Morbidity and mortality rate of pancreatic cancer in selected countries of the world in 2020 (per 100,000 population, world standard World, GLOBOCAN 2020 data) [1-4].

Countries	Incidence rate			Mortality rate			Mortality to incidence ratio (both genders), %
	Men	Women	Both genders	Men	Women	Both genders	
Kazakhstan*	7	5.7	6.3	6.7	5.4	6.1	96.8%
Kazakhstan**	6.2	5.4	6.1	5.8	5.7	5.7	93.4%
Japan	35.3	34.8	35	31.9	31.9	31.9	91.1%
Korea	15.8	15.3	15.6	13.9	13.7	13.8	88.5%

Armenia	16.4	13.3	14.7	15.9	12.9	14.3	97.3%
Israel	14.3	12.7	113.5	14.1	12.4	13.2	11.6%
Singapore	14.3	12.7	13.5	13.6	12.2	12.9	95.6%
Germany	26.2	25.2	25.7	25.4	24	24.7	96.1%
Hungary	26.1	25.6	25.9	24.5	24.1	24.3	93.8%
Finland	25.1	25.7	25.4	24.6	24.8	24.7	97.2%
Italy	21.8	24.9	23.4	21.2	21.5	21.4	91.5%
Czech	23.8	22.2	23	21.5	19.7	20.6	89.6%
France	22.5	21.8	22.2	21.5	20.8	21.1	95.0%
Greece	24.3	20	22.1	22.1	18.2	20.1	91.0%
Austria	22.1	22.6	22.3	21.4	21.7	21.5	96.4%
Slovenia	23	21.3	22.1	20.2	18.9	19.5	88.2%
Estonia	21.8	22.6	22.2	18	22.5	20.4	91.9%
USA	18.2	16	17.1	15.2	13.6	14.4	84.2%
Canada	16.4	15.2	15.8	15.7	13.8	14.8	93.7%
Brazil	6.5	6.1	6.3	6.3	5.8	6.1	96.8%
Argentina	10.7	11.5	11.1	10.2	11.1	10.7	96.4%
Mexico	3.8	3.9	3.9	3.7	3.7	3.7	94.9%
Colombia	5.5	5.1	5.3	5.4	5	5.2	98.1%
Chile	8.7	9.8	9.3	8.4	9.6	9	96.8%

Note: * - according to WHO, GLOBOCAN 2020; ** - according to KazNIIOiR, intensive (rough) rates

As with many cancers, early detection of pancreatic cancer is critical. Unfortunately, pancreatic cancer is most often detected at stage III-IV, and treatment options for advanced pancreatic cancer are limited and most often fail. One of the main issues is the lack of mass screening either in Kazakhstan or in the world medical practice because the question of oncomarkers of this type of cancer in the blood and appropriate diagnostic methods remains controversial. For 2022, Kazakhstan has 5 screening programs for detecting breast cancer, cervical cancer, colorectal cancer, cancer of the esophagus and stomach, and prostate cancer, but there is no developed screening program for detecting pancreatic cancer [6]. Only when clinical symptoms appear, an abdominal ultrasound, CT or MRI of the abdominal segment is performed. A biopsy is rarely done, as this is a complex and dangerous procedure, it is possible only during surgery [7]. Also, the course of pancreatic cancer is often associated with the presence of *KRAS* mutations. Testing for the *KRAS* mutation is not routinely done in pancreatic cancer. According to the protocol for the diagnosis and treatment of pancreatic cancer in Kazakhstan, this analysis is also not provided. According to the protocol of the European Association of Medical Oncologists, more than 90% of pancreatic cancer is caused by a *KRAS* mutation, and in order to personalize treatment, it is necessary to analyze the detection of a *KRAS* mutation [8].

Mutations of codon 12 of the *KRAS* oncogene occur in 90-95% of patients with pancreatic cancer. It has been found that *KRAS* defects are responsible for the activation of the transcription factor NFkB, which leads to the inhibition of apoptosis [9], a decrease in gene control over the coding of proteins that stimulate the formation of metastases, and an increase in radioresistance and drug resistance of pancreatic cancer cells.

The presence of *KRAS* mutations is an important prognostic factor in the survival of patients with pancreatic cancer. Yamada et al. performed a study to evaluate the presence of *KRAS* gene mutations and provide clinical value for pre-surgical diagnosis by determining the percentage of patients who tested positive for *KRAS* mutation. The mutated *KRAS* gene was isolated from plasma proteins in 27 patients out of a total of 35. The median survival rate of this group of patients was 8.2 months, while the survival rate of 8 patients with an undetected mutation of this gene was 12.5 months. Authors reported elimination of *KRAS* gene mutation *KRAS* gene mutations in plasma DNA in 6 of 9 (67%) patients after they received treatment [10].

The American Gastroenterological Association (AGA) has addressed the issue of early diagnosis of pancreatic cancer and described the indications and procedures for screening for pancreatic cancer. Screening for cancer is indicated for individuals who have a high risk of developing this disease due to inheritance. According to AGA experts, this provides an opportunity to diagnose the disease at an early stage and improve the survival of patients at risk [11].

The main risks of developing pancreatic cancer associated with genetic mutations are presented in Table 2. Familial Pancreatic Cancer (FPC) is kindred with two first-degree relatives with pancreatic cancer that do not have a known inherited syndrome putting them at high risk for pancreatic cancer. Hereditary breast and ovarian cancer syndromes are caused by mutations in any genes involved with DNA repair such as BRCA1 and BRCA2 genes. Individuals with BRCA2 mutation represent an increased (fourfold to sixfold) risk population for developing pancreatic cancer in early life.

Table 2 – Risk of pancreatic cancer associated with a germline genetic mutation [11].

Mutation is genes	Inherited cancer syndrome	Pancreatic cancer risk
STK11/LKB1(germline mutation)	Peutz–Jeghers syndrome	RR, 132 (95% CI, 44–261)
PRSS1	Hereditary pancreatitis	SIR, 53 (95% CI, 23–105)
CDKN2A	Familial atypical multiple mole/melanoma syndrome	RR, 13–39
MLH1, MSH2, MSH6	Lynch syndrome	RR, 8.6–11
TP53	Li-Fraumeni syndrome	RR, 7.3 (95% CI, 2–19)
ATM	NA	RR, 3.92 (95% CI, 0.44–14.2)
BRCA1	Hereditary breast and ovarian cancer	RR, 2.26 (95% CI, 1.26–4.06)
BRCA2, PALB2		RR, 3.5–6.2 (95% CI 1.87–6.58)
Familial pancreas cancer in 1 or 2 first-degree relatives	Familial pancreas cancer	RR, 4–9.3

Note: RR-relative risk, SIR- standardized incidence ratio

In this regard, the guidelines for screening for pancreatic cancer have been developed [11].

Screening is especially recommended for those who are at high risk for pancreatic cancer specifically (such as immediate family members, and siblings).

Screening should be considered in patients with genetic syndromes associated with an increased risk of developing pancreatic cancer: Peutz-Jeghers syndrome (hereditary gastrointestinal polyposis), hereditary pancreatitis, CDKN2 gene mutation; if one or more close relatives have pancreatic cancer and Lynch syndrome (hereditary non-polyposis colon cancer), mutations in the BRCA1, BRCA2, PALB2, and ATM genes.

Screening for pancreatic cancer is not recommended for people at average risk of developing the disease (individuals without a family history of pancreatic cancer).

Screening in high-risk patients should begin at age 50 or 10 years before the age of disease onset in a family member. For carriers of mutations in the CKDN2A and PRSS1 genes, screening should be initiated at the age of 40, in the presence of Peutz-Jeghers syndrome - at the age of 35.

A combination of MRI and EUS should be used as the primary screening method.

The screening interval is considered to be 12 months if there are no concerns.

MATERIALS AND METHODS

This retrospective statistical analysis of existing data was carried out in order to evaluate the spread of pancreatic cancer in Kazakhstan from 2018 to 2020. A retrospective statistical analysis of the spread of pancreatic cancer in Kazakhstan for 2018-2020 was carried out (standardized WHO World indicators per 100,000 population and intensive rates of incidence, mortality, distribution by stage, age, gender); territorial incidence rates of malignant neoplasms of the colon and rectum, the structure of the incidence of pancreatic cancer for 2020 (number of newly diagnosed cases of malignant neoplasms of the colon, detection of malignant neoplasms of the colon, percentage of coverage, the proportion of stages I-II, percentage of the number of detected cases) was analyzed.

RESULTS

Analysis of intensive and standardized pancreatic can-

cer incidence rates does not show a significant increase in the incidence of new diseases and remains stable. For 2018-2020, the number of cases with a first-ever diagnosed malignant neoplasm is 6.1, and there is a 1.4% increase in this rate since 2017.

Standardized rates, on the contrary, highlight the increase in the incidence of pancreatic cancer. Pancreatic cancer in the structure of the incidence of oncopathology rose to 8th place in 2020, although in 2018 it was in 12th place and in 2019 in 13th place. The increase in the incidence rate also indicates the ongoing influence of adverse etiological factors. When considering the incidence of malignant neoplasms (MN) of the pancreas, there was a difference in the morbidity rate by gender, the incidence rate in men rose to the 8th ranking place, and in women to the 10th. There is an increase in the overall incidence rate when comparing the standardized rates of the last three years from 5.3 to 5.4 per 100,000 of the population (growth rate - 1.9%), but it is interesting that in men this rate, on the contrary, decreased from 7 to 6.6 per 100,000 population. For women, the rate increased significantly from 4.1 to 4.6 per 100,000 population.

Since 2017, pancreatic cancer has been ranked 4th leading cause of death from cancer in the population of both genders, accounting for 5.6% (2017 - 5.4%). The death rate from this localization of cancer in 2018, as in the previous one, was 4.4 per 100,000 population. Exceeding the average republican level, mortality from pancreatic cancer in 9 regions and cities: Pavlodar (7.6 per 100,000 population), North Kazakhstan (7.2 per 100,000 population), Akmola (6.1 per 100,000 population), East Kazakhstan (6.1 per 100,000 population), Kostanay (5.5 per 100,000 population), Karaganda (5.1 per 100,000 population), West Kazakhstan (4.8 per 100,000 population), Almaty (6.3 per 100,000 population), Nur-Sultan (4.9 per 100,000 population). A low mortality rate was noted in Mangistau (2.1 per 100,000 population), Turkestan (2.1 per 100,000 population), Almaty (2.5 per 100,000 population), Aktobe (2.5 per 100,000 population) and Kyzylorda (3.1 per 100,000 population) regions. The death rate from this localization of cancer in 2019 was 4.2 per 100,000 population (2018 - 4.4 per 100,000 population). Exceeding the average republican level, mortality rates from pancreatic cancer in 8 regions: North Kazakhstan (8.7 per 100,000 population) - the maximum rate, Pavlodar (8 per 100,000 population), East

Kazakhstan (7.8 per 100,000 population), Akmola (6.5 per 100,000 population), Kostanay (5.5 per 100,000 population), Karaganda (5.1 per 100,000 population), West Kazakhstan (4.7 per 100,000 population) regions and the city of Nur-Sul-

tan (5.5 per 100,000 population). A low mortality rate was recorded in Turkestan (1.8 per 100,000 population), Almaty (2.3 per 100,000 population), Kyzylorda (2.6 per 100,000 popula-

100,000 population (2.6 per 100,000 population) regions and Shymkent city - 3.2 per 100,000 population (2.8 per 100,000 population) (Figure 1).
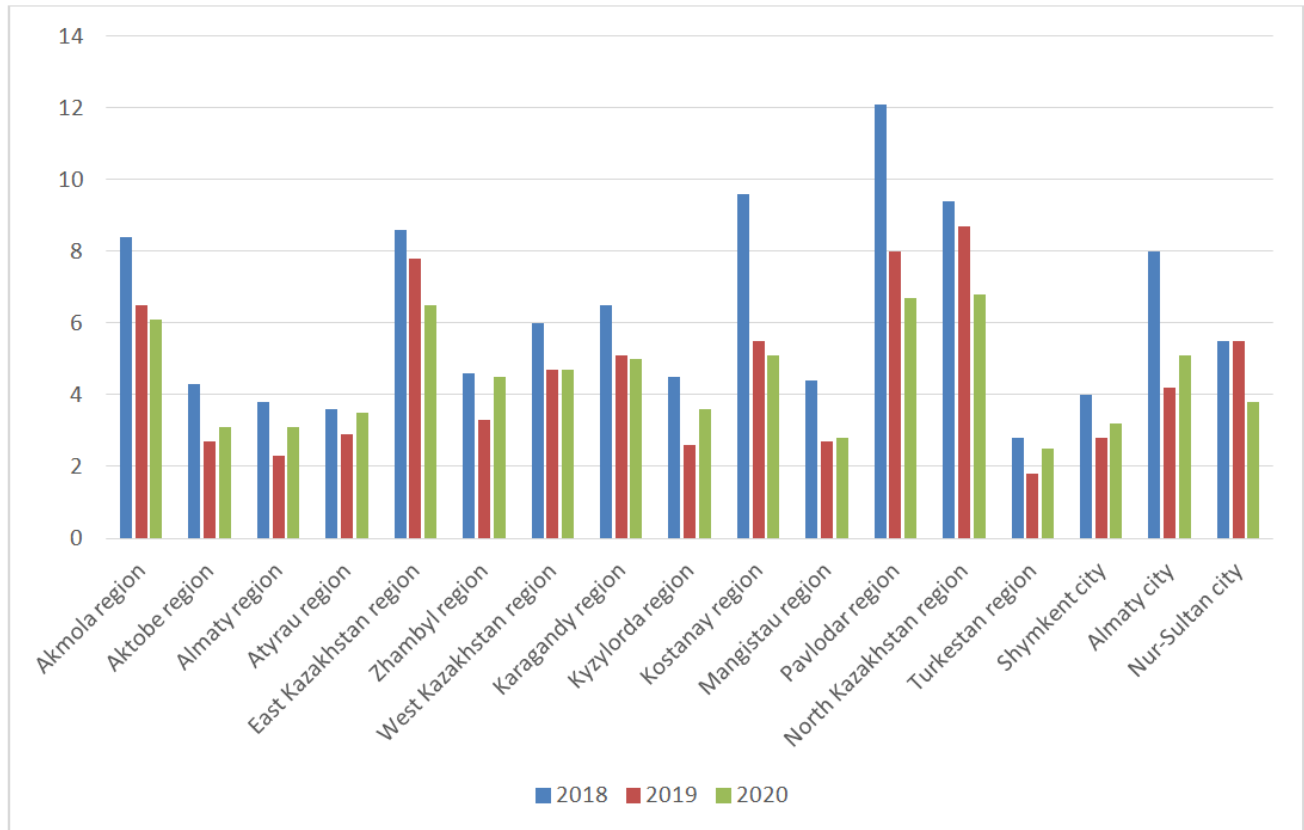
Figure 1 – The number of deaths caused by pancreatic cancer (per 100,000 population) by region of the Republic of Kazakhstan for 2018-2020

tion), Aktobe (2.7 per 100,000 population), Mangystau (2.7 per 100,000 population), Atyrau (2.9 per 100,000 population) regions and Shymkent city (2.8 per 100,000 population). In 2020, the mortality rate was 5.7% (2019 - 5.6%). The mortality rate from this localization of cancer in the analyzed year was 4.3 per 100,000 population (4.2 per 100,000 population). Exceeding the average republican level, mortality rate from pancreatic cancer in 8 regions: North Kazakhstan - 6.8 per 100,000 population (2019 - 8.7 per 100,000 population) - the maximum level, Pavlodar region - 6.7 per 100,000 population (8 per 100 thousand population), East Kazakhstan - 6.5 per 100,000 population (7.8 per 100 thousand population), Akmola - 6.1 per 100,000 population (6.5 per 100,000 population), Kostanay region - 5.1 per 100,000 population (5.5 per 100,000 population), Karaganda region - 5 per 100,000 population (5.1 per 100,000 population), West Kazakhstan region - 4 .7 per 100,000 population (4.7 per 100,000 population), and Almaty city - 5.1 per 100 thousand population (4.2 per 100,000 population). A low mortality rate was recorded in Turkestan - 2.5 per 100,000 population (1.8 per 100,000 population), Mangistau - 2.8 per 100,000 population (2.7 per 100,000 population), Aktobe - 3 .1 per 100,000 population (2.7 per 100,000 population), Almaty - 3.1 per 100,000 population (2.3 per 100,000 population), Atyrau - 3.5 per 100,000 population (2.9 per 100,000 population), Kyzylorda - 3.6 per

The post-mortem cases of pancreatic cancer in 2020, 2019, and 2018 were 4.7%, 4.8%, and 5.7%, respectively.

Due to preventive examinations, the detection rate of pancreatic cancer increased by 8.6% compared to 2018, but despite this, early diagnosis worsened from 26.4 to 20.2%.

The lowest detection rate of stage I among MNs in pancreatic cancer is 4.4% for 2020. In a number of regions, the frequency of diagnosing pancreatic cancer at stages I-II is quite low (26.2%). Above average - in Akmola, Atyrau (51.1% - the second year the best result), East Kazakhstan, West Kazakhstan, Kyzyl-Orda, Kostanay, Mangystau, Pavlodar, North Kazakhstan, Turkestan regions, and Almaty. For the three years, the lowest level of detection is in the city of Shymkent (10.3%).

Most of the advanced forms (stage IV) was detected in pancreatic cancer - 34.1% (2019 - 35.6%, 2018 - 37.1%). In Karaganda - 53.3% - the worst result in the country for the three years (2019 - 53.1%), East Kazakhstan - 48.1% (40.4%), Akmola - 47.4% (32.9%) , Turkestan - 39% (44.7%), Aktobe - 38.9% (34.1%), West Kazakhstan - 37% (28.2%), North Kazakhstan - 35.5% (19.1%) %) regions and Nur-Sultan city - 42.9% (45.1%). The lowest level of neglect is 6.7% (2.9%) in the Atyrau region.

Discussion

An analysis of the prevalence of pancreatic cancer, both by region and in the country as a whole, showed a slight in-

crease in the incidence of this pathology. However, it should be noted that despite the introduction of preventive examinations, early diagnosis and detection of early stages of pancreatic cancer remains at a low level. Mortality from pancreatic cancer invariably ranks 4th and has the highest level of detection at stage IV, which indicates the neglect of the oncological process. Also, the rapid growth of the tumor and its resistance to treatment is affected by the presence of the *KRAS* mutation, which occurs, according to various sources, in 78 to 95% of cases of pancreatic cancer.

Conclusion

Therefore, the development of early diagnosis, as well as the improvement of the treatment of pancreatic cancer, is an important measure that will reduce mortality and improve the quality of life of patients.

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ОСНОВНЫЕ ЭПИДЕМИОЛОГИЧЕСКИЕ АСПЕКТЫ РАКА ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ В КАЗАХСТАНЕ

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АННОТАЦИЯ

По данным GLOBOCAN (2020), рак поджелудочной железы (РПЖ) находится на 12-м месте среди онкологических патологии по уровню заболеваемости — 4,9 случая на 100 тысяч населения. Больше всего случаев РПЖ регистрируется в Китае, США, Японии и Германии. В структуре смертности среди онкологических заболеваний РПЖ занимает 9-е место — 4,5 случая на 100 тысяч населения. По данным эпидемиологических исследований, к 2040 году прогнозируется увеличение смертности от РПЖ на 79,9 %. Согласно статистике, в США отмечается увеличение частоты выявления рака дистального отдела ПЖ. Также чаще стали диагностировать ранние стадии РПЖ и реже — 4-ю. Одной из тенденций в эпидемиологии РПЖ является рост заболеваемости данной патологией среди молодых. Факторы, способствующие развитию РПЖ у людей до 50 лет, — генетические мутации, курение, ожирение. Проведен ретроспективный статистический анализ эпидемиологического состояния рака поджелудочной железы в Казахстане за 3 года (стандартизованные показатели WHO World на 100 000 населения и интенсивные показатели заболеваемости, смертности, распределение по стадиям, возрасту, полу), а также изучены регионарные особенности рака поджелудочной железы.

Ключевые слова: рак поджелудочной железы, поджелудочная железа, эпидемиология рака поджелудочной железы, заболеваемость, смертность

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ҚАЗАҚСТАНДАҒЫ ҰЙЫҚ БЕЗІ РАГЫНЫҢ НЕГІЗГІ ЭПИДЕМИОЛОГИЯЛЫҚ АСПЕКТІЛЕРІ

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ТҮЙІН

GLOBOCAN (2020) деректері бойынша ұйқы безінің қатерлі ісігі (ПК) онкологиялық патологиялар арасында сырқаттану деңгейі бойынша 12 орында – 100 000 халыққа 4,9 жағдай. Қуық асты безінің қатерлі ісігімен ауыратындардың көпшілігі Қытайда, АҚШ-та, Жапонияда және Германияда тіркелген. Онкологиялық аурулардың арасында өлім құрылымында қуық асты безі обыры 9-шы орында – 100 мың халыққа шаққанда 4,5 жағдай. Эпидемиологиялық зерттеулерге сәйкес 2040 жылға қарай қуық асты безінің қатерлі ісігінен болатын өлім-жітім 79,9%-ға артады деп болжануда. Статистикаға сәйкес, Америка Құрама Штаттарында ұйқы безінің дистальды бөлігінің қатерлі ісігінің жиілігі байқалады. Сондай-ақ, қуық асты безінің қатерлі ісігінің ерте кезеңдері жиі және сирек диагноз қойылды - 4-ші. Қуық асты безі обырының эпидемиологиясының тенденцияларының бірі жастар арасында осы патологиямен сырқаттанушылықтың артуы болып табылады. 50 жасқа дейінгі адамдарда қуық асты безінің қатерлі ісігінің дамуына ықпал ететін факторлар генетикалық мутациялар, темекі шегу және семіздік болып табылады.Қазақстандағы ұйқы безі обырының 3 жылдағы эпидемиологиялық жағдайына ретроспективті статистикалық талдау жасалды (100 000 халыққа ДДҰ стандартталған дүниежүзілік көрсеткіштері және аурушаңдық, өлім-жітім, сатысы, жасы, жынысы бойынша таралуы), ұйқы безі обырының аймақтық ерекшеліктері. зерттелді.

Түйін сөздер: ұйқы безінің қатерлі ісігі, ұйқы безі, ұйқы безінің қатерлі ісігі эпидемиологиясы, аурушаңдық, өлім