Geographic Variability of Gastric Cancer Incidence in Kazakhstan

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Abstract

Objective: The article studies the geographical features of the incidence of gastric cancer (GC) in Kazakhstan.

Methods: The retrospective study was done for the period 2009-2018. Descriptive and analytical methods of oncoepidemiology were used. Crude (CR), age-specific (ASIR), age-standardized (ASR), equalized incidence rates and approximation were calculated. The dynamics of indicators was investigated using component analysis according to methodological recommendations. The method of drawing up a cartogram based on the determination of the standard deviation (ε) from the mean (x) was applied. Results: During the study period, 27,467 new cases of GC were registered. The incidence rate increased from 16.80 (2009) to 15.10 in 2018 and the overall decline was 1.70 per 100,000 population, including due to the age structure – ∑ΔAg=−2.91 and their combined effect – ∑ΔR=−0.31. The component analysis revealed that the increase in the number of patients with GC was mainly due to the growth of the population (Δn=651.8%), changes in its age structure (Δa=+433.9%) and changes associated with the risk of acquiring illness (Δε=−832.1%). The cartograms were allocated according to the following criteria: low – up to 14.8/1000 average – from 14.8 to 19.2/1000 high – above 19.2/1000. The results of the spatial assessment showed the highest levels of GC incidence in following regions: Akmola (22.2/1000), North Kazakhstan (22.3/1000), and Pavlodar (23.2/1000). Conclusion: Thus, as a result of the epidemiological analysis, the role of the influence of demographic factors and the risk of acquiring illness on the formation of the number of patients and the incidence of GC was evaluated, while sex differences and geographical variability were established.

Keywords: Gastric cancer- incidence- component analysis- Kazakhstan

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Introduction

Stomach cancer, despite the global downward trend, remains an important problem in the health system and society. However, it is the most common cancer localization in some countries of the world. According to IARC data, high rates of gastric cancer were found in South Korea 39.6, Mongolia 33.1, and Japan 27.5 (Bray et al., 2018). Mongolia, Bhutan, China, and Kyrgyzstan have high mortality rates (Ferlay et al., 2019).

Gastric cancer is a multifactorial disease (Krejs, 2010; Karimi et al., 2014), the risk factors of which can be divided into genetic (Karimi et al., 2014), environmental (Forman and Burley, 2006) and lifestyle factors (Krejs, 2010). Unmodified risk factors include male gender (Chandanos and Lagergren, 2008), old age, white race (Anderson et al., 2010), and family history (Krejs, 2010; Karimi et al., 2014). Also, there are potentially modifiable factors, such as obesity (Karimi et al., 2014; Forman and Burley, 2006; Yang et al., 2009), smoking (Ladeiras-Lopes et al., 2008; Guggenheim and Shah, 2012; Freedman et al., 2007), H. pylori infection (Fauci et al., 2006; Lee et al., 2016; Ma et al., 2012; Epplin et al., 2008), the impact of which can be minimized by correcting the lifestyle. At

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the same time, there are a number of studies that consider peptic ulcer disease (Forman and Burley, 2006), atrophic gastritis (Karimi et al., 2014), intestinal metaplasia (Guggenheim and Shah, 2012), gastroesophageal reflux disease (GERD) (Karimi et al., 2014), pernicious anemia (Vannella et al., 2012), and surgical interventions, in particular, partial gastrectomy (Krejs, 2010; Karimi et al., 2014). In addition, it is necessary to take into account the low socio-economic status (Uthman et al., 2013), radiation (Karimi et al., 2014) and the peculiarities of the diet, namely the low content of fruits and vegetables and the high content of salted and smoked food in the diet (Guggenheim and Shah, 2012; Lee et al., 2016; Zhang et al., 2013), as risk factors.

GC is one of the prognostically unfavorable forms of malignant neoplasms, since the latent (preclinical) period of this disease is from 10 months to 5 years (Mitelman, 2007) and in 75% of the initially identified patients, the disease is registered in stages III and IV (Poddubny et al., 2002). At the age of <40 years, symptoms such as asthenia, adynamia, weight loss and leukocytosis are poor predictors of prognosis in patients with stomach cancer (Trujillo-Rivera et al., 2021).

The high mortality rate of GC is attributed to a long period of asymptomatic course and late manifestation (Sitaz et al., 2018; Miки et al., 2009).

For the early detection and treatment of asymptomatic gastric cancer, mass screenings are conducted in countries with high morbidity and mortality rates. A three-year study conducted in Japan, in the early 2000s, determined that endoscopic examination is an effective research method for screening (Tashiro et al., 2006). It is also recommended to maintain an interval between screenings of less than three years (Nam et al., 2012).

Materials and Methods

Cancer registration and patient recruitment

The cancer registry of the population of Kazakhstan covers considering the administrative-territorial division. New cases of GC were extracted from the reporting forms of the Ministry of Health of the Republic of Kazakhstan (form 7 and form 35) from 2009 to 2018 using the International Disease Code 10, code C16.

Population denominators

Population denominators for calculation of incidence rates were provided by the Bureau of National Statistics. At the same time, data on the number of populations of the republic, taking into account the studied regions, are used, all data are presented on the official website (Bureau of National Statistics, 2018).

Statistical analysis

The main method used in the study of incidence was a retrospective study using descriptive and analytical methods of oncoepidemiology. ASRs were calculated for eighteen different age groups (0-4, 5-9, ..., 80-84, and 85+) using the world standard population proposed by WHO (Ahmad et al., 2001) with recommendations from the National Cancer Institute (2013).

The extensive, crude (CR) and age-specific incidence rates (ASIR) are determined according to the generally accepted methodology used in sanitary statistics. The annual averages (M, P), mean error (m), Student criterion, 95% confidence interval (95% CI), and average annual upward/downward rates (T, %) were calculated. We did not justify the main calculation formulas in paper, since they are detailed in the textbooks on statistics (Merkov and Polyakov, 1974; Glanc, 1999; dos Santos Silva, 1999).

Trends were determined using the least squares method, and the average annual growth rates were calculated using the geometric mean.

The dynamics of indicators was investigated using component analysis according to methodological recommendations (Dvoyrin and Aksel, 1987; Chissov et al., 2007).

Viewing and processing of the received materials was carried out using the Microsoft 365 software package (Excel, Word, PowerPoint), in addition, online statistical calculators were used, where Student criterion was calculated when comparing the average values.

The GC incidence rates were calculated per 100,000 population. A retrospective study using descriptive and analytical methods of modern epidemiology were used.

The extensive, crude (CR) and age-specific (ASIR) incidence rates were calculated using the generally accepted methods of medical and biological statistics. Age-standardized incidence rates (ASR, World Standard, WHO, 2001) (Ahmad et al., 2001) were calculated as recommended (http://seer.cancer.gov/stddpopulations/world.who.html). The incidence over time was assessed for 10 years; the trends were determined by the least square method, to calculate the average annual growth/decline rates of the dynamic series.

Incidence rate were used in the preparation of cartograms. The method of mapping is applied, based on the determination of the standard deviation (ơ) from the average (x) (Igissinov, 1974). The annual averages (M, P), mean error (m), Student criterion, 95% confidence interval (95% CI), and average annual upward/downward rates (T%) were calculated (Merkov and Polyakov, 1974; Glanc, 1999; dos Santos Silva, 1999).

The following symbols and abbreviations were used in this article: AN – absolute number; ASIR – age specific incidence rate; ASP (ΔA) – the age structure of the population; ASR – age-standardized rate; END – the expected number of diseases; NGC – the number of GC cases; PN (AΔ) – population number; RAI (ΔA) – risk of acquiring illness; R – the value of the approximation confidence; SI – structural indexes; P – the incidence; 95% CI – prosantimille, designation per 100,000.

Ethics approval

Because this study involved the analysis of publicly available administrative data and did not involve contacting individuals, consideration and approval by an ethics review board was not required.

Results

During the study period, 27,467 new cases of GC were...
registered in the country (17,331 (63.1%) – in men, and 10,136 (36.9%) – in women). The greatest proportion of patients (both sexes) falls on the age of 60-74 years (60-64 years – 15.8%, 65-69 years – 15.1% and 70-74 years – 15.5%), a similar pattern in men and women (Table 1).

Age-related indicators of the incidence of GC had a peak in 75-79 years in both sexes (135.6±4.4/100,000), male (222.9±10.3/100,000) and female (91.2±2.7/100,000) population (Table 1).

Trends in the ASIR of GC in the entire population tended to decrease in almost all age groups, except for 80-84 years (T=+1.0%).

Trends of ASIR in the male population increased in 75-79 years (T=+0.2%) and 80-84 years (T=+0.3%). In the female population, the age indicators grown in 65-69 years (T=+0.2%), 80-84 years (T=+1.0%). It should be noted that the value of the accuracy of the approximation of the listed increases is not significant (Table 1).

Trends in age indicators generally affected the overall incidence rates, so the crude rate of GC incidence in the total population of the country lessened from 16.80/100,000 (2009) to 15.10/100,000 in 2018 (p=0.000), the total decline was −1.70/100,000 (Table 2) and depended on changes in the age structure of the population (∑ΔA=+1.51/100,000), the risk of acquiring illness (∑ΔA=−2.91/100,000) and the combined influence of the age structure and the risk of acquiring illness (∑ΔBA=−0.31/100,000). At the same time, the average annual growth rate of the aligned indicator was T=−1.0%, and the approximation confidence value was close to 1 (R2=0.6417).

In the male population of the republic, the crude incidence rates also decreased from 21.65/100,000 (2009) to 19.69/100,000 in 2018, the difference is statistically significant (p=0.006). The overall drop (−1.96/100,000) depended on changes in the age structure of the population (∑ΔA=−2.33/100,000) and the risk of acquiring illness (∑ΔA=−3.78/100,000), and their combined effect was not pronounced (∑ΔBA=−0.51/100,000) (Table 2). The average annual growth rate was T=−0.7% and the approximation value is R2=0.3326 (Table 1).

In the female population of the country, the overall decrease (−1.51/100,000) in crude incidence rates from 12.29/100,000 (2009) to 10.78/100,000 (2018) (p=0.004) depended on changes in the age structure of the population (∑ΔA=+0.92/100,000), the risk of acquiring illness (∑ΔA=−2.20/100,000) and the combined effect of the age structure and the risk of acquiring illness (∑ΔBA=−0.22/100,000) (T=−1.6; R2=0.7849) (Tables 1 and 2).

Further, we will consider the results of a component analysis of the dynamics of the number of patients with GC in the whole population, in men and women (Tables 3 and 4). The results of the study show that the reduction in the number of patients with GC in the republic was associated with the influence of the following factors:

1. Growth of population number ΔN=+651.8% (Male – ΔN=+370.3%; Female – ΔN=−1662.5%).

2. Changes in the age structure of the population ΔA=+433.9% (Male – ΔA=+281.3%; Female – ΔA=−950.0%).

| Age     | Number (Male) | Number (Female) |
|---------|---------------|-----------------|
| 40-44   | 222 (91.2)    | 91 (39.5)       |
| 45-49   | 246 (104.3)   | 110 (46.4)      |
| 50-54   | 262 (119.0)   | 104 (45.2)      |
| 55-59   | 279 (129.8)   | 102 (43.1)      |
| 60-64   | 295 (135.6)   | 118 (50.7)      |
| 65-69   | 310 (147.4)   | 120 (50.1)      |
| 70-74   | 325 (153.8)   | 122 (50.9)      |
| 75-79   | 336 (159.0)   | 125 (52.4)      |
| 80-84   | 377 (178.2)   | 131 (54.0)      |

Table 1. Gastric cancer in Kazakhstan, 2009-2018
### Table 2. Component Analysis of the Gastric Cancer Incidence Growth in Kazakhstan, 2009-2018

| Age group (i) | ASP \( (S_i^g - N_i^g/N_i) \) | Growth \( (S_i^g - S_i^p) \) \( (3)-(2) \) | Incidence \( (P_i^g - P_i^p) \) | Incidence growth \( \Delta_i \) \( (4)-(5) \) | \( \Delta_A \) \( (4)-(7) \) | \( \Delta_A \) \( (4)-(7) \) | \( \Delta_{RA} \) \( (4)-(7) \) |
|---------------|-------------------------------|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 1         | 2009 \( (S_i^g) \) | 2018 \( (S_i^p) \) | 2009 \( (P_i^g) \) | 2018 \( (P_i^p) \) | \( \Delta \) \( (5) \) | \( \Delta \) \( (7) \) | \( \Delta \) \( (7) \) |
| Both sexes  | 5.0217 | 5.0517 | -0.0206 | 0.19 | 0.2 | 0 | -0.004 | 0.003 | 0 |
| <30         | 0.0716 | 0.0837 | 0.0075 | 2.47 | 1.38 | -1.1 | 0.019 | -0.082 | -0.008 |
| 30-34       | 0.0711 | 0.0699 | -0.0012 | 4.23 | 2.52 | -1.7 | -0.005 | -0.121 | 0.002 |
| 35-39       | 0.0669 | 0.0634 | -0.0036 | 8.6 | 6.09 | -2.5 | -0.031 | -0.168 | 0.009 |
| 40-44       | 0.0689 | 0.0589 | -0.0100 | 16.88 | 13.55 | -3.3 | -0.169 | -0.229 | 0.033 |
| 45-49       | 0.0552 | 0.0559 | 0.0008 | 31.99 | 18.42 | -13.6 | 0.025 | -0.749 | -0.010 |
| 50-54       | 0.0432 | 0.0541 | 0.0109 | 53.31 | 39.02 | -14.3 | 0.58 | -0.617 | -0.155 |
| 55-59       | 0.0256 | 0.0399 | 0.0143 | 81.65 | 64.28 | -17.4 | 1.17 | -0.444 | -0.249 |
| 60-64       | 0.0252 | 0.0295 | 0.0043 | 98.26 | 95.71 | -2.6 | 0.423 | -0.064 | -0.011 |
| 65-69       | 0.0227 | 0.0144 | -0.0083 | 140.34 | 125.63 | -14.7 | -1.167 | -0.334 | 0.122 |
| 70-74       | 0.0117 | 0.0159 | 0.0042 | 133.96 | 125.48 | -8.5 | 0.558 | -0.099 | -0.035 |
| 75-79       | 0.0082 | 0.0086 | 0.0004 | 107.06 | 108.57 | 1.5 | 0.042 | 0.012 | 0.001 |
| 80-84       | 0.0034 | 0.0048 | 0.0013 | 59.92 | 54.23 | -5.7 | 0.08 | -0.020 | -0.008 |
| Total       | \( \sum S_{ij}^g = 1 \) | \( \sum S_{ij}^p = 1 \) | \( P_i = 16.80 \) | \( P_{ij} = 15.10 \) | \( \Delta A = -1.51 \) | \( \Delta A = -2.91 \) | \( \Delta A_{RA} = -0.31 \) |
| Male*       | \( \sum S_{ij}^g = 1 \) | \( \sum S_{ij}^p = 1 \) | \( P_i = 21.65 \) | \( P_{ij} = 19.69 \) | \( \Delta A = -2.33 \) | \( \Delta A = -3.78 \) | \( \Delta A_{RA} = -0.51 \) |
| Female*     | \( \sum S_{ij}^g = 1 \) | \( \sum S_{ij}^p = 1 \) | \( P_i = 12.29 \) | \( P_{ij} = 10.78 \) | \( \Delta A = -0.92 \) | \( \Delta A = -2.20 \) | \( \Delta A_{RA} = -0.22 \) |

\( \Delta_i \), the age structure of the population; \( \Delta_i \), risk of acquiring illness; \( \Delta_{RA} \), risk of acquiring illness and age structure of the population; *The calculations were made in the same way as for the entire population.

### Calculation

3. Combined effect of changes in population number and its age structure \( \Delta_{RA} = +58.9\% \) (Male \( \Delta_{RA} = +39.1\% \); Female \( \Delta_{RA} = -125.0\% \)).

4. Change in the risk of acquiring illness \( \Delta_i = +54.4\% \) (Male \( \Delta_i = +454.7\% \); Female \( \Delta_i = +2287.5\% \)).

5. Combined effect of changes in the risk of acquiring illness and population number \( \Delta_{PR} = -12.5\% \) (Male \( \Delta_{PR} = -64.1\% \); Female \( \Delta_{PR} = +300.0\% \)).

6. Combined effect of changes in the risk of acquiring illness and age structure of the population \( \Delta_i = -87.5\% \) (Male \( \Delta_i = -62.5\% \); Female \( \Delta_i = +225.8\% \)).

7. Combined effect of the changes in the risk of acquiring illness, population number and its age structure \( \Delta_{RAP} = -12.5\% \) (Male \( \Delta_{RAP} = -9.4\% \); Female \( \Delta_{RAP} = +29.3\% \)).

The total increase in the absolute number of patients overall (both sexes) equals the sum of components:

\[ n_i - n_p = 365 \times 243 \times 33 \times 466 \times 63 \times 49 \times 7 = 56 \text{ or } +2.1\% \]

in comparison with the primary number of patients \( 56 \times 2685 \times 100 = 2.1\% \).

At the same time, the components of the increasing growth in the percentage at the primary level are equal for the whole population:

\[ 13.6\% + 9.1\% + 1.2\% - 17.4\% - 2.3\% - 1.8\% - 0.3\% = 2.1\% \]

Thus, GC (both sexes) is characterized by an increase in the number of cases because of the changes in the total population size and its structure (23.9% of the total increase of 2.1%). The real increase in the number of cases (risk of acquiring illness) was \( \Delta_i = -17.4\% \).

The dynamics of the incidence of GC had regional characteristics. Thus, the overall increase in the GC incidence was growing only in Kostanay (+0.03\%0000), South Kazakhstan (+0.39\%0000), Mangystau (+1.36\%0000), and Aktobe (+7.76\%0000) regions. In the Aktobe region, the overall increase in the incidence of GC in the entire population was the highest from 13.350/0000 in 2009 to 21.10/0000 in 2018 (p=0.000) (Table 5) and primarily depended on the risk of acquiring illness \( \sum \Delta_i = +4.57/0000 \), secondly on changes in the age structure of the population \( \sum \Delta_i = +2.35/0000 \), and the combined effect of the age structure and the risk of acquiring illness reduced the indicator \( \sum \Delta_{RA} = -0.84/0000 \). At the same time, the average annual growth rate of the...
aligned indicator was $T = +2.8\%$, and the confidence value of the approximation equaled to $R^2 = 0.4435$. Analyzing the role of various components, it was found (Table 5) that the growth of patients in this region is associated with demographic factors ($\Delta_P + \Delta_A + \Delta_P = +42.0\%$) and the complex influence of the risk of acquiring illness ($\Delta_R = +43.2\%$) with the components of the population size, its age structure, and the influence of all the three above-mentioned factors ($\Delta_P + \Delta_A + \Delta_P = +58.1\%$).

Analyzing the average annual growth rate of aligned indicators of GC incidence in the entire population, the most pronounced growing was found in the Mangystau ($T = +5.4\%$; $R^2 = 0.4308$), while the growth in 2018 was statistically significant in comparison with 2009, and the values of the accuracy of the approximation were moderate (Table 5).

Analyzing the results of the influence of various components by region for the entire population (Table 5), it was found that there is a pronounced decrease in the Kostanay region ($\Delta_P = -111.8\%$) due to changes in the population size, and the largest increase is in Atyrau region ($\Delta_P = +511.3\%$). The role of the influence of age structure in the increase in the number of patients was positive in all regions, but most pronounced ones are in the Karaganda ($\Delta_A = +511.4\%$) and Kostanay ($\Delta_A = +1414.3\%$) regions. The combined effect of changes in the population size and its age structure showed a decline only in Akmola ($\Delta_A = -0.02\%$), North Kazakhstan ($\Delta_A = -9.5\%$), and Kostanay ($\Delta_A = -17.1\%$) regions, while in other regions there was an increase – especially in the Zhambyl ($\Delta_A = +22.0\%$) and Atyrau ($\Delta_A = +36.8\%$) regions.

There is a significant decrease in the absolute number of patients with GC due to the risk of acquiring illness in the majority of regions, the most pronounced are in Karaganda ($\Delta_A = -706.6\%$) and Kostanay ($\Delta_A = -946.8\%$) regions. The increase was found only in Mangystau ($\Delta_A = +6.5\%$) and Aktobe ($\Delta_A = +43.2\%$) regions.

A pronounced increase in the combined impact of the risk of acquiring illness and the population size was found in the North Kazakhstan ($\Delta_R = +8.5\%$) and Kostanay ($\Delta_R = +11.4\%$) regions. Changes in the risk of acquiring illness and the age structure led to a sharp decrease in the number of patients in the Kostanay region ($\Delta_R = -455.6\%$), and the maximum rise was noted in Karaganda region ($\Delta_R = +161.8\%$). In Atyrau region, the increase in patients due to the combined influence of the risk of acquiring illness, population size and age structure ($\Delta_R = +14.3\%$) was the highest compared to other regions.

Thus, the component analysis revealed geographical variability in the dynamics of the number of patients and the incidence of GC in Kazakhstan, which were associated with a difference in the influence of demographic factors (changes in population size, its age structure) and the risk of acquiring illness, i.e., a set of reasons that led to an increase, decrease or stabilization of the rates.

Based on the calculated GC indicators, the cartograms were compiled. The levels of CC CR based on the following criteria were determined: low – up to $14.8/10000$; average – from 14.8 to 19.2/10000; high – above 19.2/10000. As a result, the following groups of regions were revealed.

![Cartogram of Gastric Cancer Incidence in Kazakhstan](image-url)
Table 3. Component Analysis of the Gastric Cancer Incidence in Dynamics in Kazakhstan, 2009-2018

| Age group (i) | NCRC (n_i) | PN (N_i) | Crude (P_i) | Standardized (P'_i) | END in 2018 (P_N.10^{-5}) |
|---------------|------------|----------|-------------|-------------------|---------------------------|
| 1990-1991     | 238        | 465562   | 10.7       | 12.4              | 15.1                      |
| 1992-1993     | 253        | 465638   | 11.0       | 13.0              | 15.6                      |
| 1994-1995     | 269        | 465715   | 11.4       | 13.5              | 16.0                      |
| 1996-1997     | 292        | 465791   | 11.8       | 14.2              | 16.5                      |
| 1998-1999     | 305        | 465867   | 12.1       | 14.7              | 17.0                      |
| 2000-2001     | 319        | 465943   | 12.5       | 15.4              | 17.5                      |
| 2002-2003     | 334        | 466019   | 12.9       | 16.1              | 18.0                      |
| 2004-2005     | 349        | 466095   | 13.3       | 16.7              | 18.4                      |
| 2006-2007     | 365        | 466171   | 13.7       | 17.3              | 18.8                      |
| 2008-2009     | 382        | 466247   | 14.1       | 17.9              | 19.2                      |
| 2010-2011     | 401        | 466323   | 14.5       | 18.4              | 19.6                      |
| 2012-2013     | 419        | 466400   | 14.9       | 19.0              | 19.9                      |
| 2014-2015     | 437        | 466476   | 15.3       | 19.5              | 20.2                      |
| 2016-2017     | 455        | 466553   | 15.7       | 20.0              | 20.5                      |

END, the expected number of diseases; *The calculations were made in the same way as for the entire population.

(Figure 1):
1. Regions with the lowest indicators (up to 14.8/100000): Mangistau (10.6/100000), South Kazakhstan (10.7/100000), Almaty (12.2/100000), Atyrau (12.9/100000), Zhambyl (13.8/100000), Almaty city (14.3/100000) and Astana city (14.6/100000).
2. Regions with average indicators (from 14.8 to 19.2/100000): Kyzylorda (14.8/100000), Aktobe (18.4/100000) and West Kazakhstan (18.4/100000).
3. Regions with high indicators (19.2/100000 and above): Karaganda (20.7/100000), East Kazakhstan (21.0/100000), Kostanay (21.8/100000), Akmola (22.2/100000), North Kazakhstan (22.3/100000) and Pavlodar (23.2/100000).

Thus, the incidence cartograms more clearly reflect the spatial distribution of GC in the republic, while the discrepancy between the theoretical and actual distribution incidence by regions and cities is small, the Pearson

Table 4. Influencing Components on the Number of Cases of Gastric Cancer in Kazakhstan

| Components of growth in the number of cases due to: | Both sexes | Male | Female |
|---------------------------------------------------|------------|------|--------|
|                                                   | AN, %, growth | AN, %, growth | AN, %, growth |
| 1. Growth PN. : Δp = N_2 - N_1 - n_2/n_1          | 365        | 651.8 | 13.6   |
| 2. Changes ASP. : Δa = N_1 (P_1 - P_0) - n_2 - Δa  | 243        | 433.9 | 9.1    |
| 3. Combined effect of changes in PN+ASP. : Δp+a = N_2 + N_1 - N_1 - N_1/ N_1 Δa | 33        | 58.9  | 1.2    |
| 4. Change of RAI. : Δp = N_1 P_0 - P_1) × 10^{-5}  | -466       | -832.2 | -17.4 |
| 5. Combined effect of changes of RAI+PN. : Δp+a = N_2 - N_1 - N_1/ N_1 Δa | -63       | -112.5 | -2.3   |
| 6. Combined effect of changes of RAI+ASP. : Δp+a = N_1 - N_1/ N_1 Δa | -49       | -87.5  | -1.8   |
| 7. Combined effect of the changes RAI+PN+ASP. : Δp+a = N_1 - n_2 - n_1 - N_1/ N_1 Δa | -7        | -12.5  | -0.3   |
| Total ∑1-7                                        | 56         | 100   | 2.1    |
Table 5. Component Analysis of Gastric Cancer Incidence by Regions of Kazakhstan, 2009-2018 (both sexes)

| Region            | Total Incidence, 0/0000 | Sex Male | Sex Female | Change Compared % | p-Value |
|-------------------|-------------------------|----------|------------|-------------------|---------|
| Mangistau         | -13.2                   | -2.8     | -13.6      |                   | 0.1500  |
| South Kazakhstan | -10.9                   | -10.0    | -0.9       |                   | 0.546   |
| Kostanay          | -1.03                   | -1.0     | -0.2       |                   | 0.935   |
| North Kazakhstan | -10.2                   | -1.0     | -9.2       |                   | 0.107   |
| Akmola            | -5.4                    | -0.3     | -5.1       |                   | 0.803   |
| Zhambyl           | -3.8                    | -0.4     | -3.4       |                   | 0.914   |
| Total             | -10.7                   | -1.0     | -9.7       |                   | 0.110   |

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Gastric Cancer Incidence in Kazakhstan

Including due to changes of population number and sex structure.

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Table 5. Component Analysis of Gastric Cancer Incidence by Regions of Kazakhstan, 2009-2018 (both sexes)
Discussion

The results of our study show that in Kazakhstan there is a global trend of reducing the incidence of gastric cancer (Rugge et al., 2015; Siegel et al., 2014), which is certainly related to the diagnosis and successful treatment of Helicobacter pylori (Siegel et al., 2014; Fuccio et al., 2006; Lee et al., 2016). The trends of incidence reduction in the female population were characterized as more pronounced ($R^2=0.7849$) than in men ($R^2=0.3326$). It should be noted that the crude incidence rate in men (21.1/100000) was almost 2 times higher than in women (11.5/100000). While the standardized incidence rate in women (10.7/100000) was three times less than in men (31.1/100000). In our previous studies, the same pattern was revealed (Igissinov et al., 2018). Especially pronounced decrease was in men aged 55-59 ($R^2=0.6589$), and in women aged 60-64 ($R^2=0.7287$). Forman and Burley (2006), having studied the incidence rates obtained from population cancer registries around the world, found that the incidence rates in men are about twice as high as in women, and in both sexes they are closely related to age. According to GLOBOCAN 2020 similar difference in morbidity by sex was found in South Korea, China, and Iran. At the same time, there are studies explaining these sexual differences in incidence. Hormonal influences were put forward as an explanation. So, longer years of fertility and the use of hormone replacement therapy reduce the risk of stomach cancer by about 25%, while the use of tamoxifen increases the risk by about 80%, which indicates the protective effect of estrogens in the risk of gastric cancer (Camargo et al., 2012).

Early detection of GC requires financial and demographic support, as well as affordable medical services. The Updated Japanese Guidelines (2018) recommend the use of radiographic screening as population-based screening (Hamashima, 2018). The peak incidence of stomach cancer occurs in the 6th decade of human life (Uchendu and Akpo, 2021). The current guideline offers upper endoscopy for men and women aged 50 years or older (Hamashima, 2018), but the endoscopic screening coverage remains low and participation is predominantly in urban areas (Hamashima and Goto, 2017). Endoscopic examination of gastric cancer has a higher sensitivity than the radiographic method (Tsubono and Hisamichi, 2000). Endoscopy of the upper gastrointestinal tract has been recognized as the gold standard for the diagnosis of gastric cancer (Choi and Suh, 2014; Karimi et al., 2014). Both radiographic and endoscopic examinations of patients as a screening method can help to avoid the development of stomach cancer (Matsumoto et al., 2013). The endoscopic screening method reduces mortality from GC by 30% compared to the population where screening is not carried out at all (Hamashima et al., 2013). East Asian countries account for about half of stomach cancer diagnoses worldwide, and with such high incidence rates, aggressive screening programs have allowed for frequent early diagnosis and improved results. However, in Western countries, where the incidence is relatively low, screening is expensive, and stomach cancer is usually diagnosed at a relatively late stage (Johnston and Beckman, 2019). However, under various assumptions about both efficiency and cost, it has been shown that population screening for H. pylori and eradication of infection are cost-effective (Liou et al., 2020). Population-based programs of screening and treatment for H. pylori currently appear to hold the greatest promise for reducing the burden of gastric cancer (Thrift and El-Serag, 2020).

Kazakhstan is one of the regions with high incidence rates (the country maintains its leading position in terms of incidence). In this regard, endoscopic screening for early detection of esophageal and stomach cancer was introduced in Kazakhstan from 2013 to 2018 as part of a pilot project. In 2013, in such regions as: East Kazakhstan, West Kazakhstan, Kyzylorda, Pavlodar regions, the cities of Astana and Almaty. Since 2014, it has been expanded in the following regions: Aktobe, Atyrau, Karaganda, Kostanay and North Kazakhstan regions and by 2016, screening was implemented throughout the republic. Subsequently, taking into account WHO recommendations, gastric cancer was excluded from screening programs.

Higher consumption of fresh fruits and vegetables and limited intake of salt and canned foods, as well as lifestyle changes, including higher levels of physical activity and smoking restriction, can also reduce the risk of contracting this disease (IARC, 2003; Elingarami et al., 2014). Another approach is to prevent the development of GC by eradicating H. pylori. Studies have shown that H. pylori treatment can reduce the incidence of GC (Graham and Shiotani, 2005; Ford et al., 2014; Ma et al., 2012; Fukase et al., 2008).

According to a study conducted as part of the GISTAR regional pilot study, the prevalence of gastric mucosal atrophy among asymptomatic individuals in Kazakhstan was very low, although the incidence of gastric cancer and the prevalence of H. pylori in this area are high. This finding suggests that factors other than atrophy play a role in gastric carcinogenesis (Mezmale et al., 2019). Also, more than half of the study participants were infected with H. pylori, and the prevalence of H. pylori infection was independently associated with old age and regular high salt intake (Mezmale et al., 2021).

According to the results of the component analysis, the reduction in morbidity occurs due to a sharp decrease in the influence of risk factors, especially in men, than in women. Perhaps the male population has become less likely to drink alcohol, smoke cigarettes and eat junk food, further investigations required.

Although the incidence of GC is predicted to continue declining in a growing number of countries in the future, on a global scale the number of newly diagnosed GC cases will remain high, or increase even further, due to changes in population size and increasing risks observed in younger generations.

Cancer remains a problem with noticeable local and international differences in incidence. There is also a need for a targeted cancer screening program among the population, cancer literacy, access to basic cancer
diagnostic tools and treatment facilities to ensure a reduction in morbidity and mortality from it (Uchendu 2020). Thus, the study of GC incidence trends is of both theoretical and practical interest and plays an essential role in monitoring and assessment of screening programs implemented in the country and secondary prevention. Health authorities should consider the obtained results in the arrangement of anti-cancer activities.

**Author Contribution Statement**

RT, ZhT, ZhB, AZh, ZhK, SO, YK – Collection and preparation of data in the whole republic and regions (14 regions and 2 cities), primary processing of the material and their verification.

RT, ZB, GA, YK, LA, DK, KK, ZhT – Statistical processing and analysis of the material, writing the text of the article (material and methods, results).

RT, ZB, GI, KA, KO, SK, ZhA – Writing the text of the article (introduction, discussion).

NI, ML, RT, GI – Concept, design and control of the research, approval of the final version of the article. All authors approved the final version of the manuscript.

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**Conflict of interest**

The authors declare that there is no conflict of interest.

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