FEATURES OF ONCOLOGICAL EPIDEMIOLOGY AND PATHOGENESIS OF GASTRIC CANCER (LITERATURE REVIEW)

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Abstract

Gastric cancer is a malignant tumor originating from the epithelium of the gastric mucosa. It is one of the most common cancers. It may develop in any part of the stomach and spread to other organs, particularly the esophagus, lungs, and liver. Because of the gastric cancer over 800 000 people in the world dies per year (as of 2008). The main cause of gastric cancer is the microbe Helicobacter pylori, responsible for more than 60% of cases. Additional risk factors are smoking and fermented foods.

Gastric cancer is characterized by a bad prognosis: 5-year survival in this disease usually does not exceed 20%. It is essential that the timely detection of the disease play a critical role in the formation of the forecast. In particular, in Europe and other industrialized countries, which are characterized by a good standard for the early diagnosis of gastric cancer, it is possible to heal GC in every fourth patient. In Japan, where since the 1960 the GC endoscopic screening is practiced, the figure is closer to 50%, which can rightly be considered as a unique achievement in the health systems of these locations.

Introduction

According to the World Health Organization (WHO), oncological diseases (OD) are one of the major causes of morbidity and mortality in the world. In 2012, there are about 14 million new cases and 8.2 million deaths associated with cancer [2]. There were registered 723 000 deaths from gastric cancer (GC) for the year. In 2013, WHO issued an Action Plan for the fight against non-communicable diseases in the 2013-2030, which is aimed at reducing to 25% of premature deaths from cancer. Some voluntary targets are of particular importance for the prevention of cancer – for example, the goal to reduce tobacco consumption by 30% over the period of 2014-2025 years. It is expected that over
the next 20 years the number of new cases will increase by about 70% [1,2].

About one third of cancer deaths are caused by five major risk factors that are associated with the behavior and diet, such as high body mass index, inadequate intake of fruit and vegetables, physical inactivity, tobacco usage and alcohol consumption. Infections that cause cancer, such as HBV / HCV, Helicobacter pylori and HPV cause 20% of cancer deaths in low- and middle-income countries [2]. More than 60% of new cancer cases are registered in Africa, Asia, Central and South America. There are 70% of all cancer deaths in these regions [1]. According to WHO projections, the number of cases of cancer disease will continue to grow from 14 million to 22 million over the next decade [3]. According to the WHO, the productivity of the health system is determined by the amount of saved (QALY) or lost years of life (DALY) as a result of premature death and disability [4,5]. In the Republic of Kazakhstan (RK) annual loss of life years due to premature mortality account for more than 100 years to 1000, and the highest global burden of disease falls to the OD [6]. In 2012, was approved the National Plan of Action on implementation of the President's Speech to the Kazakhstan people "Socio-economic modernization – main direction of development of Kazakhstan" [7]. There was adopted the Cancer Care Development Program in the Republic of Kazakhstan for 2012-2016, established the National Research Cancer Center in Astana on the basis of the Medical Holding Company and a proposal for the development of the health system, taking into account the implementation of mechanisms for joint responsibility of citizens for their own health [7,8]. Mortality from OD in Kazakhstan takes the second place in the mortality structure (MS) of the population. Cancer kills about 17,000 people every year, of whom 42% are people of working age [10,11,12]. GC on global data occupies the second place in the MS from OD, giving way on this indicator only to lung malignant neoplasms (MN): on GC accounts for about 10-13% of deaths, associated with tumor pathology [9,10,13]. In the Republic of Kazakhstan in 2014 the proportion of patients, who died because of cancer on 10 basic forms, which determined the MS, was 70.7% (71.4% in 2013) from the total number of deaths. General MS from the RK population for three years has remained the same for the top four and including GC, only in the following localizations the location of the ranking has somewhat changed (Table 1).

Table 1.

<table>
<thead>
<tr>
<th>Localization of tumors:</th>
<th>The number of deaths from MN</th>
<th>Rate of increase %</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute number</td>
<td>Per 100 thous. of population %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All the MN,</td>
<td>16855</td>
<td>16962</td>
<td>16241</td>
</tr>
</tbody>
</table>
Thus, in 2014, there was identified the main top 10 of general MS from the MN: 1-lungs’ cancer (LC), 2-gastric cancer, 3-breast cancer, 4-esophageal cancer, 5-pancreatic cancer, 6-rectal cancer, 7-colon cancer, 8-hematological malignancies, 9-cervical cancer and 10-liver cancer [14].

However, the GC is an example of the absolute progress of medical oncology. Epidemiological studies have identified the major risk factors for gastric cancer, in particular the Helicobacter pylori infection, and helped to formulate a series of recommendations aimed at the prevention of this disease [2]. Development of the instrumental method for early diagnosis has led to an improvement in the definition of this disease at early, surgically treatable stages. Intestinal mucin MUK2 plays an important role in differentiation of normal and pathologically altered cells of the stomach, and is expressed in the focus of intestinal metaplasia [15]. The information on the molecular pathogenesis of GC allows conducting a directed search for new approaches of the gastric cancer treatment.

Expression of the apoptosis indicates in GC is associated with morphological features of tumors that may have prognostic value in predicting the course of the disease. However, the data obtained by different authors is ambiguous [15].

The first mention of gastric cancer (GC) is found in the Egyptian papyri dating back to XVI century B.C. [16]. Currently, GC takes the second place in the MS, giving way on this indicator only to lungs’ MN: GC accounts for about 10-13% of deaths, associated with tumor pathology [10,17]. The essential selection of proximal (cardiac) and
distal forms of the disease is represented in the classification of gastric cancer. These species of GC differ markedly between each other on the epidemiology, etiology and pathogenesis, at that the cardiac form of gastric cancer shows a significant similarity with esophageal tumors. In addition, it is common that GC divided into the intestinal and diffuse histological types [15]. Intestinal tumors are characterized by the preservation of glandular epithelium and the structures show signs of differentiation; In contrast, diffuse gastric cancers are presented as relatively homogeneous, undifferentiated cell masses. Although the GC histological classification to some extent is arbitrary, especially with the account of the frequent occurrence of mixed GC forms, it certainly reflects the diversity of the molecular pathogenesis of the disease [18, 19].

Materials and Methods

Research methodology was based on general scientific methods: analysis and synthesis, comparison, abstraction, concretization, generalization of research papers provided by relevant specialists in this subject, examination of documents and medical performance results, expert assessment.

The paper was based on the observation method. This method allowed considering all aspects of the studied phenomenon and its processes. Comparison made it possible to evaluate the similarity and difference of the studied objects. Abstracting was helpful in terms of considering the individual parts of the whole subject as independent objects.

Features of Gastric Cancer Epidemiology

Morbidity and mortality

Since the beginning of the systematic registration of neoplastic diseases, GC had occupied a leading place in the structure of cancer incidence and mortality. The tendency to change the situation began to occur in the second half of the twentieth century, at that the changes of the lifestyle played the decisive role in this issue. On the one hand, the development of agriculture, transport, storage technology products (in particular, the emergence of refrigerators) led to a decrease in salt intake. On the other hand, GC turned to be displaced by "diseases of civilization": in particular, emerged in the early twentieth century, the pandemic of smoking had led to the growth of lungs’ cancer, and birth control to an increase in the incidence of breast cancer.

Currently, GC takes fourth place among the oncological pathologies on the occurrence, giving way to the breast tumors, skin and lungs [14, 20]. In 2014, Kazakhstan registered 34352 new cases of MN (33029-2013), of which 45.5% (45,5-2013g.) are found in men, and 55.0% (54,5-2013g.) – in women (Table. 2).


<p>| Table 2 |
|---|---|
| The structure of cancer pathology of the Republic of Kazakhstan in 2013-2014, (%) |
| Localization of tumors | The number of the first established diagnosis of malignancies, taken into account by the oncological organizations |
| | Both genders | Men | Women |</p>
<table>
<thead>
<tr>
<th></th>
<th>Absolute number</th>
<th>%</th>
<th>Rank</th>
<th>Absolute number</th>
<th>%</th>
<th>Rank</th>
<th>Absolute number</th>
<th>%</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>33</td>
<td>34</td>
<td>10</td>
<td>10</td>
<td>15</td>
<td>15</td>
<td>45</td>
<td>45</td>
<td>18</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>47</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>38</td>
<td>41</td>
<td>11</td>
<td>12</td>
<td>1</td>
<td>1 - - - - - -</td>
<td>38</td>
<td>41</td>
<td>21</td>
</tr>
<tr>
<td>Tracheal, bronchus, lungs’ cancer</td>
<td>63</td>
<td>42</td>
<td>7</td>
<td>1</td>
<td>15</td>
<td>15</td>
<td>10</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>36</td>
<td>37</td>
<td>11</td>
<td>10</td>
<td>3</td>
<td>2</td>
<td>15</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>37</td>
<td>36</td>
<td>11</td>
<td>10</td>
<td>2</td>
<td>3</td>
<td>29</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>56</td>
<td>69</td>
<td>4</td>
<td>7</td>
<td>94</td>
<td>56</td>
<td>9</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

In the structure of the cancer pathology the 9 main forms of MN made 63.89% (64.2-2013g.). The location by ranks is the following: 1-breast cancer, 2-skin cancer, 3-lungs’ cancer, 4-gastric cancer, 5-cervical cancer, 6-colon cancer, 7-rectal cancer, 8-hematological malignancies, 9-esophagus and 10-prostate cancer [14].

The MN structure among men by ranks: 1-lungs’ cancer, 2-gastric cancer, 3-skin cancer, 4-prostate cancer, 5-colon cancer, 6-esophageal cancer, 7-rectal cancer, 8-hemoblastoses 9-kidney cancer, 10-bladder cancer [14].

The MN structure among women by ranks: 1-breast cancer, 2-skin cancer, 3-cervical cancer, 4-uterine cancer, 5-gastric cancer, 6-ovarian cancer, 7-colon cancer, 8-rectal cancer, 9-hematological malignancies and 10-tracheal, bronchus, lungs’ cancer [14].
Annually GC affects about 1 million people. Men suffer more than women: standardized rates of GC diseases in the world according to gender show approximately 22 cases and 10 cases per 100,000 person a year, respectively; however, this difference is noted only for intestinal form of GC [19]. The incidence of distal gastric cancer tends to decrease, while the frequency of cardiac GC remains unchanged or even slightly increased [16]. The incidence of gastric cancer, especially intestinal its kind, is characterized by approximately 10 multiple geographic variations. GC is extremely frequent pathologies in East Asia (Japan and Korea), South America and Eastern Europe. In contrast, the population of South Asia, North America, North and East Africa, Australia, New Zealand suffers from gastric cancer in a much lesser extent [18, 19].

**Risk factors**

Gastric cancer is an example of tumors caused by the peculiarities of life style and preventable. The most well-known risk factors of gastric cancer should include the Helicobacter pylori infection, high salt intake, low consumption of fresh fruits and vegetables and smoking.

Helicobacter pylori is a gram-negative bacillus producing urease; frequent Helicobacter pylori persistence in the gastric mucosa was demonstrated recently in 1984, [21]. 10 years later, in 1994, the International Agency for Research on Cancer (IARC; International Agency for Research on Cancer, IARC) included Helicobacter pylori in to the official list of carcinogens [22]. The involvement of the micro-organism in the occurrence of gastric cancer was proved in numerous, well-reproducible epidemiological studies. It is estimated that approximately 60-90% of gastric cancer develop against infection with Helicobacter pylori [23]. In addition, the developed model systems involving the use of experimental animals (Mongolian gerbils or mice) allow study the Helicobacter mechanisms of gastro carcinogenesis in vivo [24, 25]. Infection with Helicobacter pylori usually occurs in childhood. The most common transmitter of infection is the child’s mother [26]. From the outset, it should be noted that the carriage of Helicobacter pylori is quite common, and in any case is not a fatal condition. On the contrary, the degree of increase in the likelihood of developing gastric cancer in lesions of the gastric mucosa by this microorganism is in rather moderate range (2 – 2.5 times), which is incomparably less compared with the importance of other known carcinogens (As an example, smoking increases the likelihood of lung cancer at least an order of magnitude) [25 ].

Approximately 50% of the world's population (30% in Western Europe and North America, and 60-90% in Asia) in one form or another were or are carriers of Helicobacter pylori [27]. This figure tends to a steady decline due to improved hygiene standards and the systematic use of antibiotics. Most carriers of the infection are not suffering from
any significant signs of the disease. They are virtually asymptomatic. Certain proportions of patients have an increase in the acidity of the stomach, antral gastritis and duodenal ulcer lesion. Both the asymptomatic carriage and hyperacid gastritis are not associated with increased risk of gastric cancer. Noticeable carcinogenic effect of Helicobacter pylori is observed only in the event that leads to infection of antral atrophic gastritis, which affects the organs’ body. Acidosis of the stomach can have both the iatrogenic nature and caused by the microorganism. Helicobacter pylori is much better preserved and propagated in the conditions of low acidity, at that induced by this bacillus cytokines – interleukin 1 beta, alpha tumor necrosis factor – have the ability to cause an inflammatory reaction and suppress the production of hydrochloric acid. The development of atrophy that occurs due to inflammation, contributes to the further progression of acidosis due to functional inactivation of the specialized structures of the gastric mucosa. Thus, the emergence of the Helicobacter induced antral gastritis is a typical example of pathophysiological "vicious circle" [28, 29, 30]. The Helicobacter pylori infection is associated only with the distal, but not proximal form of GC. The disease risk is largely modified both by the features of microorganism strain and by the host factors. In particular, the most dangerous are the species of Helicobacter pylori, having in its genome composition of the cytotoxin-associated gene A (cytotoxin associated gene A, CagA). Surprisingly, the product of this gene is able to penetrate the gastric epithelial cells and incorporated into regulatory signaling cascades by affecting the processes of proliferation, morphogenesis, apoptosis. In particular, after penetrating into the cell CagA protein undergoes tyrosine phosphorylation and obtains the ability to activate cell of protein tyrosine phosphatase SHP2. As a result of such interaction, the MAP kinase cascades are triggered, which are associated with the transmission of proliferative signals and the production of certain inflammatory cytokine is provoked [29, 25]. As it was mentioned above, an essential component of carcinogenic Helicobacter pylori infection is a provocation of chronic nonspecific inflammatory. In addition to reducing the acidity, inflammation creates the conditions that trigger the appearance of cancer due to the activation of cell division and the allocation of the tumor stimulating humoral factors [31]. The intensity of the inflammatory response can be modulated by the individual characteristics of the patient’s genetic code – gene polymorphisms. In particular, the literature often quotes the association between certain interleukins genotypes, tumor and cytokine necrosis factor and the risk of gastric cancer [29, 32]. It should be noted that the field of molecular epidemiology is replete with "false positive" observations. For example, in the context of genetic determinants of susceptibility to gastric cancer, the TNF alpha gene polymorphism is mentioned often enough, but a systematic review of publications on this issue casts doubt on the legitimacy of these findings [33]. In addition to
inflammatory action, Helicobacter pylori infection is accompanied by activation of the plurality of growth factors. In particular, the presence of Helicobacter pylori in mucous is associated with the production of epidermal factor of growth (EGF, epidermal growth factor), heparin linking the EGF of such growth factor (HBEGF, heparin-binding epidermal growth factor), endothelial growth factor (VEGF A, vascular endothelial factor A) and etc. [23]. The production of these polypeptides accelerates the cell proliferation and promotes angiogenesis. Recovery from the Helicobacter pylori carrier reduces the risk of gastric cancer. It should be taken into account that the carcinogenic effect of this microorganism is delayed in time. Therefore, if antimicrobial treatment is performed relatively late, on the stage of existence of precancerous lesions of the gastric mucosa, the preventive effect of treatment can be expressed in an incomplete extent or as inexistent [34, 23, 35]. In addition, many experts have expressed concerns about the consequences of the destruction of the ages existing prevailing biocenosis, which includes Homo sapiens and Helicobacter pylori [16].

**Other risk factors**

High salt intake is an established risk factor for gastric cancer. It is noteworthy that the reception of salt, unlike many other food ingredients is amenable to objective evaluation, for example, by appropriate analysis of daily urine [36]. It is assumed that the salt induces the expression of inflammatory response genes in gastric mucosa. In addition to salt, gastro carcinogenic action is attributed to some other food preservatives. It is believed that pickles consumption became noticeable decline in the second half of the twentieth century, because of the widespread introduction of household refrigerators [19]. The presence of fresh fruit and vegetables in the diet reduces the risk of gastric cancer. This phenomenon is due to the presence of antioxidants in the fresh products of vegetable origin, for example vitamin 'C' (ascorbic acid). It is assumed that green tea has a protective action against the gastric cancer [18, 36]. The animal food consumption, especially grilled meat, may to some extent contribute to the development of gastric cancer. At least partly, this effect is generally attributed to the influence of carcinogenic nitroso compounds N [36]. The risk of gastric cancer is also increased in people, who abuse tobacco [37, 38]. There is information about the association of obesity with gastric cancer, with certain blood groups, alcohol usage, etc. [29]. Traditional ("black") tea and coffee do not have a modulating effect on the risk of gastric cancer [36].

**Molecular Pathogenesis of Gastric Tumors**

Gastric cancer develops due to the combination of activation of oncogenes and inactivation of suppressor genes. Many genetic disorders (amplification and/or overexpression of EGFR (HER1) and HER2 (ERBB2) genes, mutations
in the p53 gene) are relatively nonspecific for GC. They are found in many other human tumors. At the same time, a
number of oncogenes, such as K sam (FGFR2) and CDH1 genes are referred to primarily in the context of gastro
carcinogenesis. The range of molecular anomalies is slightly different between the intestinal and diffuse tumors,
although the majority of known mutations such a difference appears to be somewhat arbitrary.

**Oncogenes violations**

EGFR (HER1) gene encodes the receptor of epidermal growth factor, which is a tyrosine kinase membrane and is
involved into the regulation of many cellular processes. Overexpression of this gene is observed in almost all tumors
of epithelial origin. Gastric Carcinomas express EGFR in almost half of cases [39]. EGFR involvement in the
pathogenesis of gastric cancer suggests the possibility of using the receptor inhibitors for the treatment of malignant
tumors of the stomach.

A close EGFR homolog, HER2 (ERBB2) oncogene, was originally identified in breast tumors. Amplification and
overexpression of this gene is relatively specific event for breast carcinomas and practically does not occur in tumors
of other localizations. Gastric cancer represents one of the few exceptions: the activation of HER2 occurs in about 10-
15% of malignant tumors of the body and is correlated with the aggressive course of the disease [40, 41]. This
observation was the basis for clinical trials of specific humanized HER2 specific antibody – Herceptin drug; it is
assumed that Herceptin can improve the treatment of patients with HER2 positive form of gastric cancer.

Almost all tumors differ in activation of the angiogenesis system. One of the main regulators of angiogenesis is
endothelial growth factor (VEGF), which was already mentioned above. It is found that VEGF overexpression is
associated with a bad prognosis of the disease [42]. Currently, several angiogenesis inhibitors are evaluated in clinical
efficacy to the GC; it is likely that the anti-angiogenic therapy will soon go down in the standards of treatment of this
disease.

The literature, which is devoted to the molecular aspects of gastric, is frequently referred the Ksam oncogene. This
gene encodes the receptor of fibroblast growth factor (FGFR2, fibroblast growth factor), located on the cell surface
and having a tyrosine kinase activity. This receptor is presented in excessive quantities in about one-third of cases of
diffuse gastric cancer. Therapeutic Ksam inhibitors now successfully pass preclinical trials [40]. FGFR2 gene has
recently attracted great attention of researchers due to the quite unexpected discovery: it turned out that a
polymorphism of the gene involved in the formation of predisposition to breast cancer, at that the observed
association is characterized by a unique inter-laboratory reproducibility [43].
In a number of intestinal stomach tumors the point activating mutations in KRAS gene are observed. This gene is a signal transmitter with a surface receptors of protein kinase (EGFR, HER2) to the core. In the case of KRAS activation, the cell acquires independence from the membrane receptor stimulation. Mutations in the KRAS gene are correlated with resistance of colon cancer and lung to treatment by EGFR inhibitors, but such research is not carried out for gastric cancer. Potential interest provides data, which show the involvement of MET gene activation, which is encoding the receptor of hepatocyte growth factor, into gastro carcinogenesis. In the intestinal stomach tumors the increased expression of cyclooxygenase 2 (COX2) is often observed; an inhibitor of this enzyme – celecoxib drug – widely used to treat chronic inflammatory and autoimmune diseases [40, 41].

**Suppressor Genes’ Violations**

One of the best-known tumor suppressor genes is p53 gene. It performs a variety of functions. In particular, the p53 gene product is involved in the recognition of DNA chemical damage. In case of violation of the DNA structure p53 gene conveys relevant information to the protection system cells, which are responsible for the repairing (restoration) of DNA. If the repairing of DNA is unable, the cell commits suicide, aimed at preventing the persistent of mutated (potentially malignant) clones. Inactivation of p53 or its target is one of the prerequisite for tumor progression. In gastric carcinoma the p53 gene is exposed the inactivation through micro mutations and because the deletion of the corresponding locus chromosome 17 [41, 30].

Malfunctions of the suppressor gene in stomach tumors often occur due to methylation of their promoter regions. One of the DNA bases – cytosine – may exist in both methylated and unmethylated forms. Methylation of cytosine, which are located in the regulatory regions of the corresponding genes, is associated with the suppression of transcription. Methylation mechanism can be conjugate with the inactivation of DNA mismatch repair genes, such as hMLH1, resulting in a phenotype of microsatellite instability (microsatellite instability, MSI). It is noteworthy that the MSI positive tumors have a relatively good prognosis. Methylation may also inhibit the expression of retinoic acid receptor gene (RARbeta), cell cycle regulators, RUNX family genes [41, 30, 44]. It is possible that the Helicobacter pylori infection plays an important role in the induction of abnormal cytosine methylation [45]. Cases of inheritance of predisposition to gastric cancer are frequently quoted in the medical literature. The most famous victim of family GC is French Emperor Napoleon Bonaparte (Figure 3), who died from this disease and recalled a similar reason of death of closest relatives of his father, grandfather and three sisters [46, 47]. One of the genes associated with the GC hereditary has been already identified. It is the CDH1 gene, which is located on the chromosome 16 and encoding the
E-cadherin [48]. E-cadherin is an adhesion molecule, which is involved in the formation of intercellular contacts. In addition, E-cadherin plays a role in the signaling processes from the membrane to the nucleus. Inactivation of the CDH1 gene can be observed not only in the hereditary, but also in sporadic gastric cancer, and is associated mostly with the diffuse variety of tumors [46]. Inheritance of genetic susceptibility to GC occurs in an autosomal dominant manner. Carriers of this mutation can only be heterozygotes (apparently, homozygous cases of CDH1 mutations are not viable). Thus, only half of the children of affected individuals inherit the mutated gene, while the remaining 50% obtain intact CDH1 allele and remain perfectly healthy. Penetrance of the (probability of phenotypic expression) CDH1 mutation is quite high – it reaches 75-95% [46]. Healthy individuals with genetic disorders of CDH1 are recommended to have regular endoscopic examination of the stomach for early diagnosis of GC, and in exceptional cases – to consider prophylactic gastrectomy [49]. It should be mentioned that CDH1 gene defects account for no more than one third of cases of hereditary gastric cancer [50].

**Conclusion:** Gastric cancer is an example of absolute progress of medical oncology. Epidemiological studies have identified the major risk factors for gastric cancer and allowed to formulate a number of recommendations to reduce its incidence. Development of the instrumental methods of early diagnostic improved detection of this disease in its early, surgically treatable stages.

Currently, the active preclinical and clinical trials of medical drugs are provided, designed for the treatment of gastric cancer. Diagnosis and treatment of GC in the Republic of Kazakhstan has been improved due to the insertion of screening programs in accordance with the Order of the Minister of Health of the Republic of Kazakhstan on 16 March 2011 №145 and the Order of the Minister of Health of the Republic of Kazakhstan on January 8, 2013 №8 «On insertion of screening for early detection of esophageal cancer, gastric cancer, liver cancer and prostate cancer in the pilot regions ". Five institutional reforms and one hundred concrete steps on their implementation in the Plan of the Nation strengthened the stability of the health system on the basis of joint responsibility of the state, employers and citizens. Primary care has become a central part of national public health for the prevention and early disease control. The feature of the availability and quality of the health services in the Republic of Kazakhstan is the corporate governance principles and the insertion of the advanced medical care standards.

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standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants.

Reference


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