RESEARCH ARTICLE

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Cancer Incidence Relation to Heavy Metals in Soils of Kyzylorda Region of Kazakhstan

Farida Rakhimbekova[1]*, Dilyara R Kaidarova[2], Madina Orazgaliyeva[2], Zhassulan Ryspambetov[3], Anton Buzdin[4], Bakytzhan Anapiyayev[5]

Abstract

Objective: The purpose of this study was to investigate the relationship of soil pollution factors such as heavy metal ions with the incidence of cancer in the Kyzylorda region of Kazakhstan. **Methods:** Concentrations of heavy metal ions in the soils of different sites of Kyzylorda region, Kazakhstan, were sampled and correlated with incidence of cancer in 2021. **Results:** Chromium content in the soil exceeded maximum permissible concentration (MPC) in the samples for all sites except Kazaly and Shieli, and the highest excess of 2.8 MPC was found in Terenozek. Content of copper, lead, and cobalt ions was also increased and varied in the range 1.9-15.4, 1.2-4, and 1.2-2.44 MPC, respectively. In addition, lung cancer incidence was statistically significantly correlated with soil concentration to MPC ratio of copper, cobalt, and lead; colorectal cancer was correlated with soil concentration of chromium. Cases of invasive cancer and mutations were recorded Terenozek and Kyzylorda areas. **Conclusion:** The higher the soil concentration correlate with higher cancer incidence in Kyzylorda region, Kazakhstan.

Keywords: Heavy metals- cancer morbidity- Aral Sea region

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Introduction

Active anthropogenic activities have led to unfavorable environmental shifts and an increase in certain human diseases (Figure 1) [1-4]. One of the global environmentally unfriendly regions of the world is the Aral Sea area. The drying up of the Aral Sea led to the formation of salt marshes and the spread of salt storms. In addition, in the process of active farming, since the 70s of the last century, mineral fertilizers and pesticides containing increased concentrations of heavy metal salts were widely used [1-6].

All these pollutants in the conditions of dry saline soil are spread over long distances and get into the respiratory tract, skin, gastrointestinal tract of people and animals [1-4]. In 2018, a study of sediments in the area of the Northern Aral Sea to a depth of 30 cm from the surface was conducted to investigate the dynamics of accumulation of heavy metal salts by soil, which showed the greatest contamination in the layer deposited in the 1970s, when anthropogenic activity was dramatically intensified [6]. According to some estimates, environmental pollution factors, especially air and water, cumulatively contribute about 8-9% to the development of general morbidity leading to disability and/or death [7]. It is believed that one of the results of the increase in the content of various environmental pollutants is the accumulation of unfavorable genetic mutations, causing malignization and the occurrence of various hereditary diseases and cancers [8].

Causes and mechanisms of cancer development are currently being actively investigated, with pathogenic irreversible changes in the genome generally being named as the main cause of cancer [9-11]. Risk factors for the accumulation of carcinogenic mutations are related to nutrient intake, the characteristics of inhaled air, and the biochemical composition of water and soil [11,12]. Therefore, the development of a number of diseases, including cancer, depends on the content of contaminants in the environment. Malignization depends on the degree of contamination, time of contact with pollutants, the effect of accumulation [13]. For example, limited access to clean water and a healthy diet contributes to the spread of respiratory diseases, which in turn is a risk factor for lung cancer [14].

Molecular effects of some metal ions on cancer development and progression have been studied in depth [15]. Heavy metals, such as cadmium and chromium

*[1]Chemical Processes and Industrial Ecology Department, Mining and Metallurgical Institute named after O.A. Baikonurov, Satbayev University, Almaty, 050013, Kazakhstan. [2]Kazakh National Research Institute of Oncology and Radiology, Kazakhstan. [3]Kyzylorda Regional Cancer Center, Kazakhstan. [4]Department of Genomics and Postgenomic Technologies, Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Russian Federation. [5]Chemical and Biochemical Engineering Department, Geology and Oil-gas Business Institute named after K.Turyssov, Satbayev University, Kazakhstan. *For Correspondence: farida.rakhimbekova@yandex.ru*

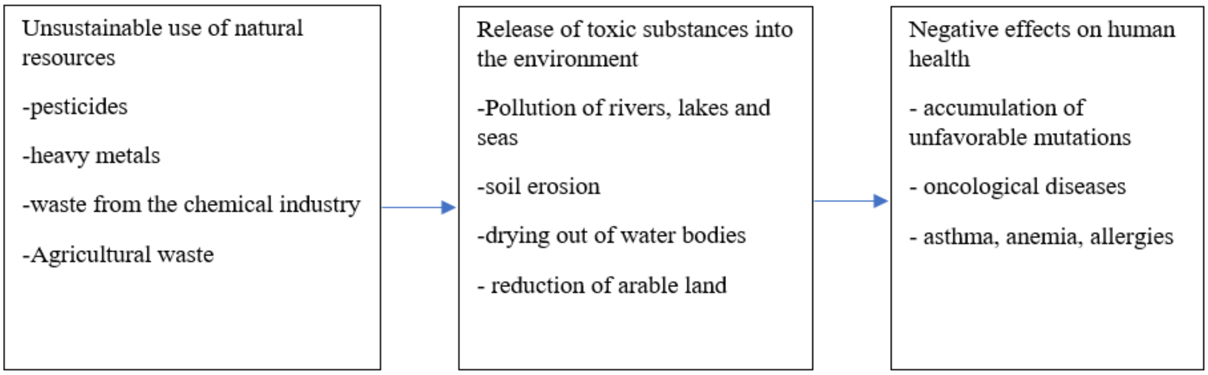

Figure 1. Simplified Scheme of Human Unsustainable Use of Natural Resources Impact on the Environment and Public Healthcare.

are known carcinogens that disrupt DNA repair and tumor suppression on a cellular level [16]. Exceeding concentrations of copper, chromium, cadmium, lead and cobalt damage DNA and lipids formation, further causing oxidative-stress induced cancer and inhibition of DNA synthesis [17-19]. Elevated concentrations of chromium, for example, cause lung and prostate cancer [7].

Furthermore, decoding molecular interactome of human cancer cells allows to describe impact of varying inorganic pollutants on tumorigenesis [20]. Pollutants can disrupt the normal mechanisms of gene expression and gene networks regulation, which sometimes leads to loss of control over the cell cycle and to pathological changes in cell proliferation [21-23]. The purpose of this study was to investigate the relationship of soil pollution factors such as heavy metal ions with the incidence of cancer in the Kyzylorda region of Kazakhstan.

Materials and Methods

This study examined soil samples taken from the disaccotricts of Kyzylorda region along the Syrdarya River to investigate the present concentrations of pollutants, specifically heavy metal ions such as copper, lead, chromium, and cobalt. Soil samples were collected from the locations where cancer patients were living. Those settlements included Kyzylorda, Kamystybas, Baikonur, Aral, Shieli, Zhanakorgan, and Terenozek (Figure 2).

Soil samples were tested in the spring of 2021 in the Testing Laboratory of Republican Research-Production and Information center “KAZECOLOGY”. Soil samples were taken at a depth of 10 cm from the surface.

Copper, lead, cobalt concentrations in soil were determined by ISO standard – atom absorption spectrometric method in aqua regia [24,25]. Hydrochloric acid and nitric acid were used for probe preparation. The method includes aspiration of probe to flame of atom-absorption spectrophotometer Perkin Elmer AAnalyst 400 [26]. Hydrochloric acid and nitric acid were used for probe preparation. For the reaction preparation graduated pipettes, volumetric flask and burettes were used. For calibration curve standard probes dissolved in nitric acid were measured and graphed as standard. For calibration curve standard probes dissolved in nitric acid are measured and graphed as standard. The standard wavelength for detecting copper is 324.7 nm, for lead the standard peaks are 283.3 and 217 nm, for cobalt standard peak is 240.7 nm.

Chromium in soil was determined by atomic emission spectrometry with inductively coupled plasma method. Conical burettes for reference sample preparation and graduated pipettes were used. The probes were prepared in nitric acid and filtrated. Refence probes were used for standard graph, extrapolation of which gave the final

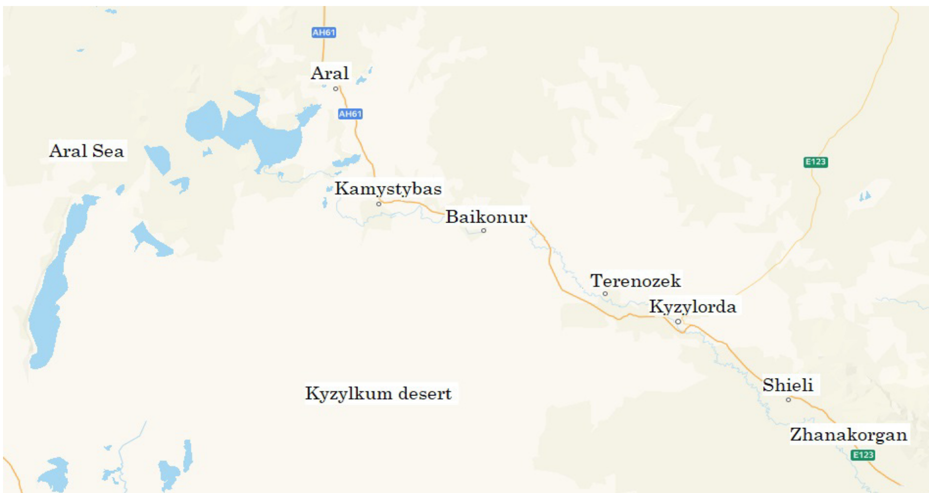

Figure 2. Map of Kyzylorda Region, Showing Settlements, where Soil Samples were Collected.

concentration. The reference peak for chromium is 550 nm [27]. The statistical department of the Regional Oncological Hospital in Kyzylorda provided data on the number of patients with colorectal cancer, lung cancer and melanoma for the period from March 2020 to August 2021, for a total of 214 people.

Oncomarker screening for *KRAS*, *EGFR* and *BRAF* was performed under Local Ethics Commission of Kazakh Institute of Oncology and Radiology (Protocol of LEC meeting № 4 from 12.05.2021). Genotyping of patients with colorectal cancer for *KRAS*, lung adenocarcinoma for *EGFR* and melanoma for *BRAF* were performed in KazIOR by standard methods using Roche Oncology Kit [28]. First, cytologists examined formalin-fixed paraffin embedded (FFPE) blocks of post-operative and biopsy tumor material for areas of the most cancer proliferation. Then, the blocks were cut to obtain sample of tumor on microtome and DNA was extracted from samples [29].

In the pre-PCR step, all samples were tested with Nanodrop to determine DNA concentration and optimal dilution of the PCR reaction. For internal control, the kit includes positive and negative controls to identify questionable samples.

The next step was Real-Time PCR on Cobas z 480 (Roche, US) with the following screening kits cobas *EGFR* Mutation Test v2; cobas *KRAS* Mutation Test; cobas 4800 *BRAF* V600 Mutation Test. Population morbidity rates were taken from annual oncology report handbook and compared with absolute levels of pollutants in 2021.

The values of pollutant levels were correlated with the maximum permissible concentrations (MPC) of these pollutants according to the Republican Research-Production and Information center "KAZECOLOGY" [30,31]. The frequency of MPC was compared with the morbidity in the studied settlements. The population number of the mentioned districts was taken from the official site of statistics of Kazakhstan (Statistics Committee of the Ministry of National Economy of the Republic of Kazakhstan) [32]. Total pollution index (Zc) was calculated, taking into account the MPC of the pollutants under study, adjusted for the toxicity coefficient according to Saet Y.E. [30,31]. Correlation analysis of Zc with morbidity was calculated.

$$Zc = \sum (Kki \times Kti) - (n-1)$$

Where Kкi is the coefficient of the ratio of the concentration of heavy metal ions in the soil to MPC, and Kti is coefficient of toxicity. For lead and chromium coefficient of toxicity is 1.5, and for cobalt and copper 1.0. n - the number of pollutant elements taken into account [30,31].

Maximum permissible concentration exceedance of heavy metals was graphed against cancer incidence per 100000; the graphs were fitted with a linear trend line and the value of the reliability of the approximation (R2 value) was calculated by Excel.

Correlation of the ratio of maximum permissible concentration exceedance of heavy metals with cancer incidence in Kyzylorda region in 2021 was further calculated.

In order to study cumulative disease rates in relation to heavy metal burden, we summed the absolute concentrations of chromium, copper, lead and cobalt and made a linear approximation with sum of all cancer types observed in 2021. The analysis was carried out in MS Excel.

Results

Population of Kyzylorda region

According to Statistics Committee of the Ministry of National Economy of the Republic of Kazakhstan, the population of Kyzylorda was 245054 citizens, the largest city of the Kyzylorda region. Population of Kazaly (77190), Aralsk (79922), Shieli (78564) and Zanakorgan (76004) follows. Population of Terenozek, Zalagash, Baikonur, Karmakshy is halved, compared to Zhanakorgan (around 35000) (Table 1).

Environmental monitoring of Kyzylorda region

The content of heavy metal ions exceeded the maximum permissible concentration (MPC) in many soil samples (Table 2). Soil testing for the heavy metal ions showed exceedance of MPC from minimal to high. Chromium content in the soil exceeded MPC in all samples except Kazaly and Shieli (Table 2). The highest excess was found in Terenozek - 2.8 MPC, and the lowest in Zhanakorgan - 1.11 MPC. Content of copper varied from 1.9 to 15.4 MPC, content of lead - from 1.2 to 4 MPC, content of cobalt - from 1.2 to 2.44 MPC.

Pollutants and cancer incidence in Kyzylorda region

Data on oncological morbidity in the studied districts of Kyzylorda region obtained in the Regional Oncological Hospital are shown in Table 1. The highest incidence of colorectal cancer per 100 000 population was recorded in Kyzylorda: 17.13, in Karmakshy – 12.4, in Baikonur – 10.14 and in Terenozek – 8.36, respectively. The maximum incidence of stomach cancer was recorded in Zhalagash and in Terenozek districts - 8.4 and 7.7, respectively; relatively lower rates were recorded in Kazaly and Shieli districts - 6.5 and 6.1, respectively. Soft tissue sarcomas prevailed in Baikonur city and in Kyzylorda city with 5.1 and 4.1 values, respectively. Breast cancer prevailed in Kyzylorda city and Shieli and Zhanakorgan districts: 7.4, 7.3, and 7.1, respectively. Lung cancer incidence was the highest in Kyzylorda city - 14.7, followed by Terenozek (13.95) and Zhalagash (12 per 100 000 population). Statistics on melanomas was available for three districts: for Shieli (incidence of 2.56), Karmakshy (3.04), and Kyzylorda (2.45 per 100,000 population).

For graphical approximations, positive trends were observed for correlation between soil contamination by lead, cobalt and lung cancer incidence, R^2 =0.55 and 0.49, respectively (Figure 3,4). As shown in Table 3, the most significant correlation coefficient values were obtained between MPC of copper, lead, cobalt and lung cancer incidence rate (r= ~ 0.7). Further, a moderate correlation was noted between the MPC chromium and colorectal cancer (r=0.67). In gastric cancer, there was a moderate

Table 2. Chromium, Copper, Lead, and Cobalt Concentrations in Soil Samples

Sample collection areas	Chromium (Cr), mg/kg	MPC for Cr, mg/kg	Copper (Cu), mg/kg	MPC for Cu, mg/kg	Lead (Pb), mg/kg	MPC for Pb, mg/kg	Cobalt (Co), mg/kg	MPC for Co, mg/kg
Zhanakorgan	6.7	6	24.7	3	18	6	7	5
Shieli	5.4		26.3		18		8.1	
Kyzylorda	13		19.4		21.03		9.83	
Terenozek	17		34.4		20.8		12.2	
Zhalagash	9.9		9.5		13		6.23	
Baikonur	13.5		11.9		10.3		7.93	
Karmakshy	15.2		8.7		7.23		5	
Kazaly	4.9		1.17		1.37		1.53	
Aralsk	8.4		7.2		7.4		3.4	

Table 1. Distribution of Cancer Morbidity by Districts of Kyzylorda Region in 2021

Sample collection areas	Population, people.	Incidence of cancers											
		Colorectal		Gastric		Soft tissue sarcomas		Breast		Lung		Melanoma	
		Absolute	Per 100,000 population	Absolute	Per 100,000	Absolute	Per 100,000	Absolute	Per 100,000	Absolute	Per 100,000	Absolute	Per 100,000
Zhanakorgan	76,004	4	5.26	1	1.32	2	2.63	6	7.89	7	9.21	0	0.00
Shieli	78,564	5	5.10	5	6.36	3	3.82	6	7.64	9	11.46	2	2.56
Kyzylorda	245,054	42	17.13	8	3.26	10	4.10	18	7.35	36	14.70	6	2.45
Terenozek	35,855	3	8.36	3	8.37	1	2.79	1	2.79	5	13.95	0	0.00
Zhalagash	33,320	4	12.00	3	9.00	0	0.00	0	0.00	4	12.00	0	0.00
Baikonur	39,432	4	10.14	2	5.10	2	5.10	1	2.50	2	5.07	0	0.00
Karmakshy	32,945	4	12.14	0	0.00	0	0.00	3	9.10	3	9.10	1	3.04
Kazaly	77,190	4	5.18	5	6.50	2	2.60	4	5.20	6	7.77	0	0.00
Aralsk	79,922	3	4.11	1	1.30	2	2.50	1	1.30	4	5.48	0	0.00

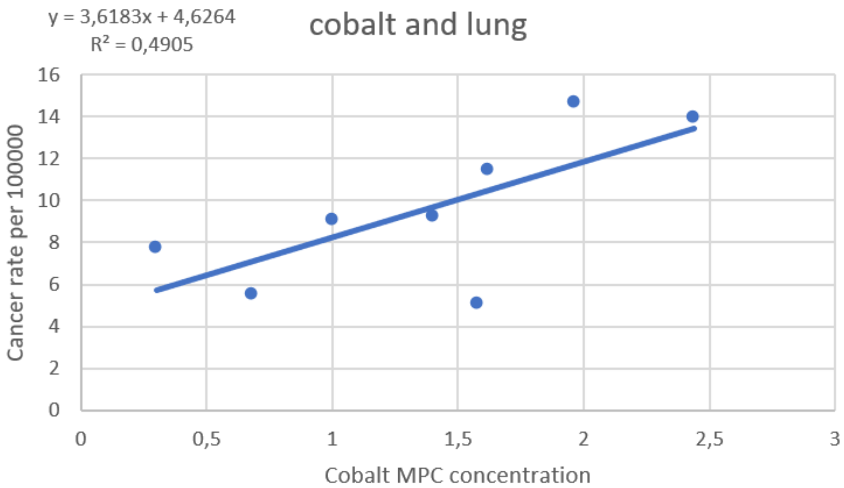

Figure 3. Dependence of MPC Multiplicity (Kki) of Cobalt in Soil on the Incidence of Lung Cancer in Kyzylorda Region.

Table 3. Correlation of the Ratio of the Concentration of Heavy Metal Ions in the Soil to MPC (Kki) with Cancer Incidence in Kyzylorda Region in 2021.

Metal ion pollutants	Cancer primary localizations				
	Colorectal	Gastric	Soft tissues	Breast	Lung
Chromium	0.67*, p =0,05	-0.12	-0.1	-0.34	0.3
Copper	0.05	0.44	0.18	0.22	0.7*, p =0.036
Lead	0.31	0.32	0.31	0.35	0.76*, p =0.017
Cobalt	0.44	0.34	0.36	0.094	0.7*, p =0.036

correlation with excesses of copper, lead, and cobalt, but no correlation was recorded for chromium. In soft tissue sarcomas, the correlation was 0.31 for lead and 0.36 for cobalt.

The highest total pollution index of heavy metal ions (chromium, copper, lead and cobalt) was observed in Terenozek area, which is 23.8, as well as in the cities of Kyzylorda - 13.9, Shieli - 13.55 and Zhanakorgan - 13.4 (Table 4). A statistically significant correlation for total pollution index (Zc) and cancer morbidity was recorded for lung cancer ($r=0.66$, $p=0.05$). Dependence of sum of cancer cases per 100000 population on total heavy metal concentrations across the Kyzylorda region showed positive correlation with 24% increase in cases and $R2 = 0.33$ (Figure 5).

Pollutants and cancer mutations

Table 5 lists the marker cancer driver mutations found in 214 patients screened for the cancer markers of mutated *KRAS*, *EGFR*, and *BRAF* genes. Out of 214 patients (Table 5), 23 patients had mutation of *KRAS* gene, 13 patients had *EGFR* mutation and 6 patients had *BRAF* mutation. The most abundant mutation among patients with colorectal cancer was codon 12/13 mutation. In

Table 4. Correlation Analysis of the Total Index of Pollution by Heavy Metal Ions with Cancer Incidences

Sample collection areas	Total pollution index (Zc)	Incidence per 100 000 population					
		Colorectal cancer	Gastric cancer	Soft tissue sarcomas	Breast cancer	Lung cancer	Melanoma
Zhanakorgan	13.4	5.26	1.32	2.63	7.89	9.21	0
Shieli	13.55	5.1	6.36	3.82	7.64	11.46	2.56
Kyzylorda	13.91	17.13	3.26	4.1	7.35	14.7	2.45
Terenozek	23.8	8.36	8.37	2.79	2.79	13.95	0
Zhalagash	5.2	12	9	0	0	12	0
Baikonur	8	10.14	5.1	5.1	2.5	5.07	0
Karmakshy	6.5	12.14	0	0	9.1	9.1	3.04
Kazaly	1	5.18	6.5	2.6	5.2	7.77	0
Aralsk	4	4.11	1.3	2.5	1.3	5.48	0
Correlation coefficient		0.13	0.21	0.32	0.18	0.66	0.11
p-value		0.74	0.59	0.4	0.64	0.05	0.78

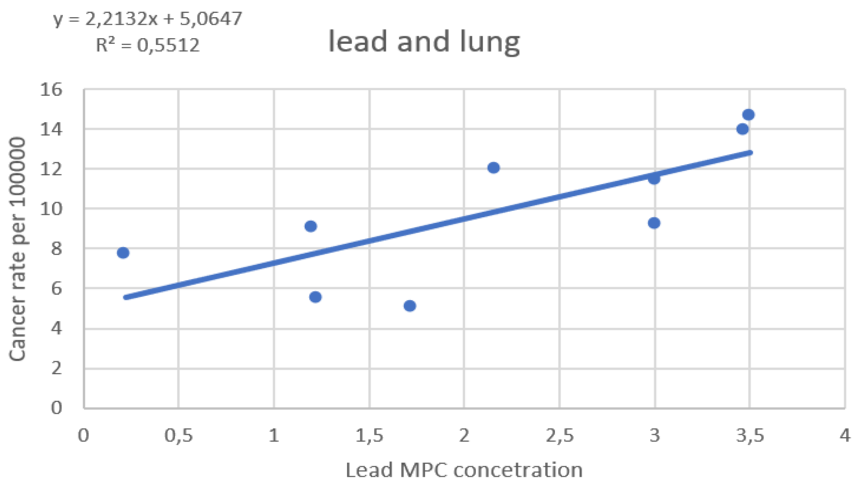

Figure 4. Dependence of the Multiplicity of MPC (Kki) of Lead in Soil on the Incidence of Lung Tumors in Kyzylorda Region.

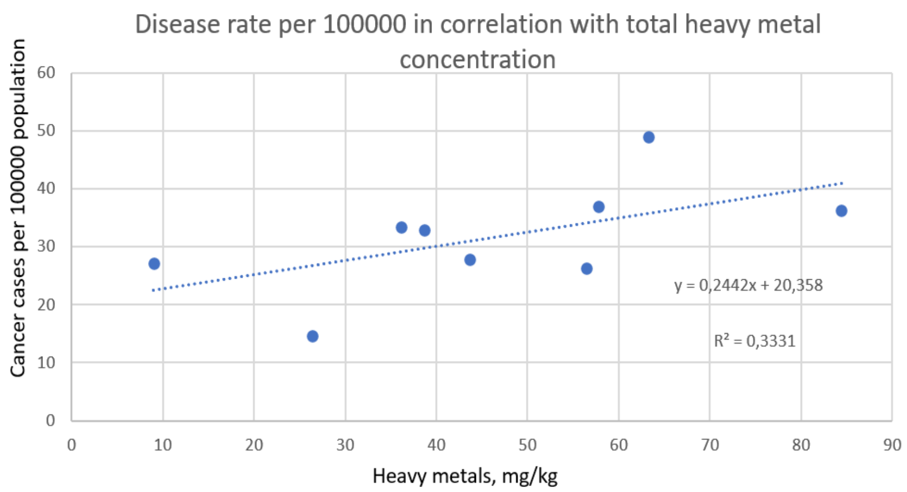

Figure 5. Dependence of Cancer Cases Per 100,000 Population on Total Heavy Metal Concentrations across the Kyzylorda Region

Table 5. Statistics of Marker Cancer Driver Mutations in Colon (*KRAS*), Lung (*EGFR*), and Melanoma (*BRAF*) Cancers.

Characteristic mutation	Number of patients with mutations detected		
	KRAS	*EGFR*	*BRAF*
C12/13	22		
C61	1		
L858R		6	
19th exon deletion		7	
V600E			6

patients with lung cancer, exon 19 deletion was the most abundant mutation. Out of 10 patients with melanomas, 6 had V600E mutation.

Discussion

As described in Table 1, high rates of colorectal cancer incidence were noted in Kyzylorda (17.13 per 100,000 of population), gastric cancer and lung incidence was highest in Terenozek (8.37 and 13.95 per 100,000 of population respectively).

According to our data the highest level of chromium ions in soil at a depth of 10 cm was observed in Terenozek area - 17 mg/kg, Karmakshy area - 15.2 mg/kg (2.5 MPC), the minimum in Kazaly area - 4.9 mg/kg, which is less than MPC (Table 2). Liu et al., 2020 described that in the northernmost point of Lake Aral in the soil at a depth of 30 cm the average level of chromium was 62.2 mg/kg, the interval of samples was from 18.2 to 80.4 mg/kg [6]. In our work, we studied the most recent deposit of soil to illustrate the current ecological status of region, whereas Lui at al., 2020 took single point of study with more depth. In their work on the soil of the Aral Sea zone, Ma et al., 2019 showed that samples of deeper layers (about 30 cm), corresponding to the deposits of the 1970s, had higher concentrations of heavy metal ions, most probably because this period was characterized by the most aggressive agricultural activities [5].

The content of copper in soil samples was maximum in areas of Zhanakorgan and Shieli (24.7 mg/kg and 26.3

mg/kg, respectively); according to Liu et al., 2020 in the northern part of Lake Aral concentration of copper in the soil was 32.3 mg/kg, which is comparable with our results. Lead level according to our data also exceeded MPC in all regions except Kazaly region, reaching the maximum in Kyzylorda city and Terenozek region (21 mg/kg in both regions, exceeding MPC by 3.5 times), which is higher that the levels observed by Liu et al., 2020.

According to a study by Mamyrbayev et al., 2016, the R2 for lung cancer and cadmium was 0.4 to 0.7, and in our study (Figure 3,4), R2 was around 0.49 – 0.55 for cobalt and lead [33].

Studying total cancer cases per 100000 with total heavy metal concentrations, showed 24% increase in positive linear correlation with R^2 = 0,33 (Figure 5). Since cancer development and progression is a multifactor process, this finding highlights the link between pollution and cancer.

Cancer is caused by various conditions such as mutations, diet, general health and environmental factors. Thus, the relationship between heavy metals and direct incidences of cancer is complex. The lungs appear to be one of the primary organs responding to environmental risk factors, as some authors have linked environmental pollution to asthma, which has been previously described as a condition that increases possibility of developing lung cancer in the future [13,14]. High correlation of lung cancer with copper, lead, and cobalt pollutant concentrations was found (Table 3).

Total pollution index was especially high in Terenozek (23.8), Kyzylorda (13.9), and Shieli (13.55), which indicates the negative expression of environmental factors in the Aral Sea region. High total pollution index correlated with the incidence of lung cancer r = 0.66; p = 0.05 (Table 4).

In the literature, heavy metals are described as trigger factors for molecular cascades of malignization and accumulation of mutations in cells [8-10]. Out of 214 patients screened for mutations, around 20% (42 patients) had mutations in *KRAS*, *EGFR*, *BRAF* genes. *EGFR*, *KRAS*, *BRAF* proteins are subsequent members of the mitogen-activated protein kinase (MAP) pathway, responsible for cellular growth, proliferation and survival [34]. When mutated, as given in Table 5, overactivation of MAP kinase pathway leads to promotion of cancer growth, tumorigenesis and malignization. Mutations, for example amino acid alteration in codon 12/13 in *KRAS* and deletions in *EGFR* correspond towards more aggressive tumor process, progression and reduced survival.

The burden of disease can be described as environmental factors worsening the chemical and molecular balance of cells and probably enhancing mutation events. The total pollution index contributed more to *EGFR* gene driver mutations in lung cancer.

In this study, pollution factors were identified throughout the whole Kyzylorda region. Soils have unequal absorption and accumulation properties of metal ions. Some of the pollutants are absorbed by accumulating plants and are carried by the wind over long distances. The processes of sedimentation of pollutants in the form of deposits and passive diffusion of pollutants from the zone of higher concentration to a lower one take place.

Heavy metals enter the body with inhaled air, food, water and primarily contact with digestive and respiratory organs and skin. The more a person lives in an environmentally risky region such as those investigated here, the greater the effect of heavy metals on the DNA integrity and cancer.

Author Contribution Statement

All authors contributed to the study concept and drafting of the manuscript. Farida Rakhimbekova analyzed the data, compiled graphical material, worked on data in tables. Bakytzhan Anapiyayev worked on the concept and content of the article. Anton Buzdin corrected the work done by Farida Rakhimbekova and assisted in drafting of manuscript. Dilyara Kaidarova, Madina Orazgalieva, Zhassulan Ryspambetov assisted with data collection and analysis. All authors read and approved the final manuscript.

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Ethics statement

Genotyping of patients with colorectal cancer for *KRAS*, lung adenocarcinoma for *EGFR* and melanoma for *BRAF* were performed in KazIOR. Oncomarker screening was performed under Local Ethics Commission of Kazakh Institute of Oncology and Radiology (Protocol of LEC meeting № 4 from 12.05.2021). Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on a reasonable request.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

ISO: International Organization for Standardization

KRAS gene: Kirsten Rat Sarkoma Viral Oncogene Homologue Gene

EGFR gene: Epidermal Growth Factor Receptor Gene

BRAF gene: Murine Sarcoma Viral Oncogene Homologue B Gene

KazIOR: Kazakh Institute of Oncology and Radiology

MPC: Maximum Permissible Concentrations

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