Environmental Science and Pollution Research (2021) 28:62530–62540
https://doi.org/10.1007/s11356-021-15224-3

RESEARCH ARTICLE

Association between trace element concentrations in cancerous and non-cancerous tissues with the risk of gastrointestinal cancers in Eastern Iran

Fatemeh Nozadi[1] · Namamali Azadi[2] · Borhan Mansouri[3] · Tahmine Tavakoli[4] · Omid Mehrpour[4,5]

Received: 15 April 2021 / Accepted: 26 June 2021 / Published online: 1 July 2021

Abstract

This study was conducted to investigate the association between trace elements including cadmium (Cd), chromium (Cr), cobalt (Co), copper (Cu), iron (Fe), lead (Pb), nickel (Ni), selenium (Se), zinc (Zn), and arsenic (As) in gastrointestinal cancer tissue and non-cancerous tissue (suspected gastrointestinal cancer) in Eastern Iran. The samples of 63 gastrointestinal cancers (stomach (n = 20), esophageal (n = 19), and colorectal (n = 24) along with 63 controls in South Khorasan Province, Iran, were collected and analyzed using ICP-MS (Agilent 7900). Our results indicated that the concentrations of Co (1.3 ± 0.8, 1.3 ± 0.8 μg kg^{-1}), Cr (8.1 ± 7.3, 11.0 ± 14.8 μg kg^{-1}), Ni (29.0 ± 20.1, 39.5 ± 30.2 μg kg^{-1}), Pb (6.9 ± 4.0, 6.1 ± 4.6 μg kg^{-1}), and Zn (867.6 ± 159.1, 935.6 ± 196.2 μg kg^{-1}) were significantly higher among esophagus and colon cancer cases than controls ($p < 0.05$). Similarly, stomach cancer cases showed higher Co, Cr, Ni, Se, and Zn and lower Cu concentrations than their controls ($p < 0.05$). Moreover, the Spearman correlation between metals revealed a mostly low to moderate correlation between metals. Our finding illustrated that the significant risk differences of Cr, Ni, Pb, Se, and Zn metals on esophagus cancer when considered the single predictor unadjusted for other metals and covariates RD (95% CI) – Cr: −0.274 (−0.463, −0.086), Ni: −0.288 (−0.457, −0.118), Pb: −0.171 (−0.463, −0.086), Se: −0.243 (−0.434, −0.051), and Zn: −0.094 (−0.143, −0.045) respectively. This study suggests that the trace element's exposure may be associated with gastrointestinal cancer risk. Additional studies are needed to elucidate the mechanisms underlying trace element carcinogenesis further.

Keywords Environmental exposure · Lead · Chromium · Nickel · Stomach cancer · Esophageal cancer · Colorectal cancer

Responsible Editor: Lotfi Aleya

✉ Borhan Mansouri
borhanmansouri@yahoo.com

✉ Tahmine Tavakoli
tahminetavakoli95238@yahoo.com

[1] Student Research Committee, Birjand University of Medical Sciences, Birjand, Iran

[2] Biostatistics Department, Faculty of Public Health, Iran University of Medical Sciences, Tehran, Iran

[3] Substance Abuse Prevention Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran

[4] Medical Toxicology and Drug Abuse Research Center (MTDRC), Birjand University of Medical Sciences, Birjand, Iran

[5] Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ, USA

Introduction

Cancer is the main source of mortality in the age group of 40 to 70 years and the subsequent driving reason for death in all age groups, representing a fourth of all passings worldwide (Siegel et al. 2016). As per worldwide reports, the quantity of death because of cancer in 2012 was 14.1 million, and the quantity of deaths from cancer is projected to be 22.2 million by 2030 (Bray et al. 2012). According to a nationwide cancer registry in Iran, cancer is the third leading cause of death, with more than 30,000 people dying of cancer each year. Also, according to 2010 surveys, the highest incidence of cancers in Iran was reported in gastric, esophageal, breast, prostate, and colon cancers, respectively (Kolahdoozan et al. 2010; Saadat et al. 2015). In light of a public cancer registry, cancer is the third driving reason for death in Iran, and over 30,000 individuals die of cancer every year. Likewise, gastric, esophageal, breast, prostate, and colon cancer were the most well-

known cancer types in 2010 (Khlifi et al. 2013). Gastric cancer is the most common cancer in males and third in females (Fauci 2011). Then again, colorectal cancer is the third and fourth most normal cancer in people internationally and has, as of late, been perceived as a significant wellbeing concern around the world. Colorectal cancer accounts for a significant share of cancer mortality and disability (Parkin et al. 2005; Siegel et al. 2013). The incidence of gastrointestinal cancers has been steadily increasing in recent years. Gastrointestinal cancer's risk factors are diet, socioeconomic conditions, toxic substances, and environmental contaminants through food chains.

Heavy metals are among the most serious pollutants in the environment that play an essential role in human diseases. Increased amounts of heavy metals as a result of natural processes (weathering and biodegradation in nature) and human-made (industrial activities, agriculture, vehicles) in the environment and cause various clinical effects in human and animals (Mansouri et al. 2012a, 2012b; Rezaei et al. 2021; Farnia et al. 2021). Heavy metals in two groups of essential metals (including iron (Fe), zinc (Zn), and copper (Cu)) and non-essential metals (such as cadmium (Cd) and lead (Pb)) for biological activities can have human health effects (Norouzi et al. 2012; Mansouri et al. 2012c; Majnoni et al. 2013; Maleki et al. 2015). Metals such as Cd and Pb as potential carcinogens are associated with some diseases, including cardiovascular diseases, kidney, nervous system, hypothyroidism, and thyroid cancer (Solenkova et al. 2014; Rezaei et al. 2019, 2021). Metals like Fe, Cu, and Zn are essential minerals that play an important role in the body's metabolic and physiological activities. Still, their concentrations should not exceed the permissible limit, otherwise damaging the target tissues. When Fe and nickel (Ni) exceed the body's amount, it reacts with peroxides to produce free radicals. The free radicals can cause DNA, lipids, proteins, and tissue carbohydrates damage that eventually lead to oxidative stress (Al Faris and Ahmad 2011; Nanda and Agrawal 2016). Sohrabi et al. (2018) stated that heavy metal concentrations as environmental pollutants play an important role in developing gastrointestinal cancers; they also found that the concentration of metals in patients with gastrointestinal cancer was significantly different from control samples. Ionescu et al. (2006) also found significant Ni concentrations in breast cancer tissue compared to healthy samples.

Some studies have been carried out on heavy metals' effect on gastrointestinal cancer samples (Roy et al. 2004; Pasha et al. 2010; Rinaldi et al. 2015). Still, insufficient attention has been paid to existing research on the amount and impact of heavy metals on Iran's gastrointestinal cancer incidence. Also, given the increasing trend of gastrointestinal cancers in Iran and especially in the eastern part of the country in recent decades, such studies are needed. Therefore, in this study, we conducted a case-control study to assess the association between heavy metals including cadmium, chromium, cobalt, copper, iron, lead, nickel, selenium, zinc (Cd, Cr, Co, Cu, Fe, Pb, Ni, Se, and Zn) and arsenic (As) in cancerous and non-cancerous tissues with the risk of gastrointestinal cancers in Eastern Iran.

Materials and methods

Study population

The present study is a case-control study. The data collected in this study include the measurement of heavy metals in gastric cancer biopsy specimens in South Khorasan province, eastern Iran. Biopsy specimens of stomach (n = 20), esophageal (n = 19), and colorectal (n = 24) cancers along with controls (n = 63) were collected from patients recruited to Birjand Imam Reza Hospital from January to December 2019.

This study's protocol was approved by the Ethics Committee in Birjand University of Medical Sciences (IR.BUMS.REC.1397.072). The patients for this study were aged between 30 and 70 with confirmed gastric cancer. All cases were newly diagnosed and previously untreated. Clinical characteristics, including basic medical data, were obtained from medical records. Patients in the case group were diagnosed by specialist physicians based on inclusion criteria. Then, the consent form was given to the patients in the research project. If included in the study, the demographic checklist (age, gender, type of cancer, smoking, and anthropometric measurements) of the subjects was completed by the questionnaire. Cases and controls had no distinction between geographic or cultural groups since they were the native aborigines in South Khorasan province. Both cases and controls had no occupational exposure to heavy metals. The inclusion criteria for the gastrointestinal cancer patients group were history, physical exam, and an endoscopic study indicating gastrointestinal cancers. In the control group, inclusion criteria were not indicating gastrointestinal cancer or intestinal diseases. The exclusion criteria were patients' reluctance, history of non-gastrointestinal cancers, malignancies, metabolic or nutritional disorders, vitamin supplementation use, hormones, chelators, and receiving chemotherapy or radiation.

Biopsy samples

The biopsy specimens were then put away in formalin solution with the endorsement of a gastroenterologist and pathologist. Specimens were thought to be cancerous in the control group, yet these tissues were resolved healthy after pathological evaluation. These samples were kept in formalin solution at Imam Reza hospital in Birjand city and selected as a control sample like cancerous tissues.

Determination of heavy metals

We applied the nitric-perchloric acid digestion method to prepare samples for measuring cadmium. Approximately 50 mg of each sample was mixed with 2 mL of ultrapure (HNO_3, 65%, Merck, Germany) and 1 mL of perchloric acid ($HClO_4$, 70%, Merck, Germany), and the samples were left overnight to be slowly digested. Then, the mixture was placed in a water bath (Bain Marie; TW12, Julabo GmbH, Germany) at 100°C for approximately 6 h or until the solutions were clear. After cooling, the mixture was made up to 25 mL by adding double-distilled water (18.2 MΩ-cm at 25 °C, Fistreem, WSC044, UK). The prepared solution was measured for Cd, Cr, Co, Cu, Fe, Pb, Ni, Se, Zn, and As using Inductively Coupled Plasma Mass Spectrometry (ICP-MS; Agilent 7900). The operation parameters for ICP-MS were as follows: Radiofrequency power: 1.5 kW, Plasma gas flow rate: 15 L/min., Carrier gas flow: 1.01 L/min., Make up gas: 0.15 L/min., Sample uptake rate: 1.7, Sample depth: 10 mm, Detector mode: auto, Scan type: peak hopping with three sweeps per reading and three readings per replicate, and scan number: 3.

Statistical analysis

Results were presented as mean ± SD for numerical variables and number (percentage) for categorical variables. A t-test or Chi-squared test was used to evaluate the differences between subjects' characteristics. Since the metal concentrations were highly skewed, to make the analysis more robust against extreme values, the concentrations were standardized using the mean and interquartile range of natural log-transformed concentrations. If the normality assumption was violated, a t-test or Wilcoxon rank-sum test was used to compare the concentrations between cancer and healthy group.

The logistic regression model was used to assess the effect of single and multiple metal exposures of heavy metals on cancer risk using unadjusted and adjusted risk differences (RDs) and respective 95% confidence intervals. The outcome was a binary indicator of participants in the case-control group. RDs were adjusted for age, Body mass index (BMI), smoking status, education concentration, and family history of cancer in first-degree relatives. Risk differences were obtained using single metal exposure (unadjusted), using single metal and covariates (adjusted), and using covariates and multiple metals (adjusted). Furthermore, to deal with the perfect separation issue in the logistic model, a Bayesian model with non-informative prior assumptions proposed by Gelman et al. (2008) was used. Moreover, generalized additive models (GAM) analysis was performed under the logistic regression model to investigate if the effect of the trace elements is present, it is a nonlinear effect or not. As we have mentioned in the Results section, such an effect was not confirmed by GAM analysis. All statistical analyses were performed using R, the open-source language, and computing software.

Results

Characteristic of the study population

Of 126 participants with 63 cases (24 esophagus, 19 colon, 20 stomach) and 63 controls (17 esophagus, 19 colon, 27 stomach), 64 (51%) were men and 62 (49%) were women. The mean age of participants was 59.95 ± 17.41 (18 to 92 years). Moreover, only eight percent of participants had an academic degree, whereas 43% were uneducated, 42% less than five years, and 16% completed high school. Compared to controls, cases were significantly older, less likely to be overweight (57% with BMI < 25), more likely to have a lower level of education (Table 1). Regarding gender, smoking, and family history of cancer among first-degree relatives, cases and controls were comparable. The comparison of participants' characteristics revealed no statistically significant difference in the distribution of gender (Chi-squared test, P = 0.856), BMI (Chi-squared test, P = 0.364), the likelihood to be ever smoker (Chi-squared test, P = 0.611), and the family history of cancer (Chi-squared test, P = 0.676) between the cases and controls (Table 1). However, cases were significantly older than controls (t-test, P = 0.002).

Table 1 Characteristic of the study population

	Controls (n = 63)	Cases (n = 63)	*p*-value
Age (years)			
Mean ± SD	54.46 ± 18.7	65.44 ± 14.15	**0.002**
Sex			0.856
Male	31	33	
Female	32	30	
BMI (kg/m^2)			0.364
<22	3	6	
22.0–24.9	25	30	
25.0–27.9	29	20	
≥28	6	7	
Ever smoker			0.611
No	59	51	
Yes	4	12	
Education (year)			**0.0002**
Never	20	23	
1–5	18	35	
6–11	16	4	
>11	9	1	
Family cancer history			0.676
No	61	59	
Yes	2	4	

Age effects on gastrointestinal cancers

For each cancer type, Table 2 shows the mean age as well as the distribution of education levels for participants in each studied group. The age differences were not statistically significant between cases and controls suffering from the esophagus and stomach cancer. For colon cancer, cases (with a mean age of 64.71 years) were markedly older than controls (with a mean age of 51.65 years) (t-test, P = 0.013). Comparison between education levels showed a significant association between education levels and studied groups for colon cancer (Fisher test, P = 0.0007) and esophagus cancer (Fisher test, P = 0.0006).

A comparison of element concentration levels was made between cases and controls to investigate the effect of age (Table 3). There was no difference between Fe, Se, and Cd concentrations in cancerous and control tissues, but compared to controls, elevated levels of Cr, Co, Ni, Zn, and Pb were observed in cancerous patients. The levels of Cu and As were found to be higher in controls (Table 4).

Mann-Whitney test showed that the concentrations of Cr ($p < 0.001$), Fe (P = 0.021), Co (P = 0.039), Ni (P = 0.0004), Zn (P = 0.034), Se (P = 0.003), and Pb (P = 0.004) were significantly higher among esophagus cancer cases than controls (Table 3). Compared to controls, the concentration concentrations of Cr (P = 0.001), Co (P = 0.015), Ni ($p < 0.001$), Zn (P = 0.002), and Pb (P = 0.003) were markedly high among cases with colon cancer, whereas they had lower concentrations of Cu (P = 0.022) and As (P = 0.007). Similarly, cases with stomach cancer showed higher concentrations of Cr (P = 0.003), Co (P = 0.030), Ni ($p < 0.001$), Zn (P = 0.002), and Se (P = 0.013) and lower concentration concentrations of Cu ($p < 0.001$) when compared to their controls (Table 3).

Table 3 Comparison of trace element levels (μg kg^{-1}) between colon cancer cases and their controls using the Mann-Whitney test

	Control (n = 17)	Case (n = 24)	*p*-value
Cr	2.38 ± 0.66	11.05 ± 14.84	**< 0.001**
Fe	478.76 ± 262.77	565.08 ± 384.74	0.543
Co	0.8 ± 0.62	1.34 ± 0.82	**0.015**
Ni	11.94 ± 6.7	39.58 ± 30.28	**< 0.001**
Cu	1036.88 ± 141.8	908.35 ± 145.76	**0.022**
Zn	764.29 ± 117.75	935.67 ± 196.21	**0.002**
As	2.15 ± 2.8	0.43 ± 0.50	**0.007**
Se	101.54 ± 14.56	105.3 ± 16.93	0.634
Cd	0.13 ± 0.09	0.18 ± 0.12	0.073
Pb	1.47 ± 0.42	6.19 ± 4.61	**0.003**

Correlation among trace elements

The correlation between metals with each other is evaluated using spearman's correlation coefficient. The results are presented in Fig. 1. As it can be seen, correlation coefficients between element pairs were mostly positive and low to moderate (less than 0.50). A few exceptions with correlation coefficient over 0.50 and highly significant at 0.001 level were Co-Cd pair (esophagus r = 0.86, colon r = 0.80, stomach r = 0.79), Co-Pb (esophagus r = 0.72, colon r = 0.82, stomach r = 0.66), Cd-Pb (esophagus r = 0.66, colon r = 0.68, stomach r = 0.63), Cr-Ni (esophagus r = 0.70, colon r = 0.64, stomach r = 0.66). Moreover, Cu was negatively correlated with other elements for both colon and stomach cancer types (Fig. 1).

Table 2 Comparison of age and education of participants between three types of cancer

		Colon	Esophagus	Stomach
Age	Case	64.71 ± 12.78 (n = 24)	65.42 ± 12.97 (n = 19)	66.35 ± 17.17 (n = 20)
	Control	51.65 ± 19.41 (n = 17)	65.05 ± 21.02 (n = 19)	55.81 ± 16.99 (n = 27)
t-test, P-value		**0.013**	0.062	0.077
Education	Case			
	Never	8	7	8
	1–5	6	12	7
	6–11	0	0	4
	>11	0	0	1
	Control			
	Never	7	6	7
	1–5	3	3	12
	6–11	5	6	5
	>11	2	4	3
Fisher test, P-value		**0.0007**	**0.0006**	0.749

Table 4 Concentrations of trace element levels (μg kg^{-1}) among cases and controls for three types of cancer

	Cancer type	Controls		Cases		Total		
		Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	P-value
Cr	Esophagus	1.98 ± 0.8	2	8.1 ± 7.31	5.29	5.04 ± 6	2.64	**<0.001**
	Colon	2.38 ± 0.66	2.17	11.05 ± 14.8	3.31	7.24 ± 12.1	2.64	**0.001**
	Stomach	2.33 ± 0.88	2.43	10.83 ± 12.36	4.64	5.94 ± 9.03	2.64	**0.003**
Fe	Esophagus	529.2 ± 256.4	580	686.6 ± 318.1	778	607.9 ± 295.9	654	**0.021**
	Colon	458.8 ± 262.8	570	565.1 ± 284.7	578.5	521 ± 339.9	570	0.543
	Stomach	601.67 ± 345.9	654	549.25 ± 364.5	614	579.4 ± 299.6	654	0.805
Co	Esophagus	0.95 ± 0.65	1.21	1.34 ± 0.88	1.81	1.14 ± 0.79	1.36	**0.039**
	Colon	0.8 ± 0.62	0.6	1.34 ± 0.82	1.78	1.11 ± 0.79	1.28	**0.015**
	Stomach	0.88 ± 0.58	0.84	1.3 ± 0.83	1.77	1.06 ± 0.72	0.96	**0.030**
Ni	Esophagus	11.95 ± 8.04	13	29 ± 20.12	21	20.47 ± 17.41	18	**0.0004**
	Colon	11.94 ± 6.7	9	39.58 ± 30.28	21	28.12 ± 27.12	20	**<0.001**
	Stomach	9.85 ± 6.3	8	34.25 ± 27.06	21	20.23 ± 21.76	18	**<0.001**
Cu	Esophagus	1027.5 ± 73.5	1023.28	983.5 ± 76.65	1005.58	1005.5 ± 77.35	1015.48	0.057
	Colon	1036.9 ± 141.9	995.46	908.35 ± 145.7	974.03	961.65 ± 156.11	984.46	**0.022**
	Stomach	1107.2 ± 113.6	1052.7	877.6 ± 154.4	955.38	1009.5 ± 174.08	1023.18	**<0.001**
Zn	Esophagus	765.9 ± 117.4	811	867.6 ± 159.1	918	816.7 ± 147.2	816.5	**0.034**
	Colon	764.29 ± 117.7	819	935.67 ± 196.2	970	864.6 ± 187.1	857	**0.002**
	Stomach	702.11 ± 169.3	712	882.15 ± 172.4	901	778.7 ± 191.3	814	**0.002**
As	Esophagus	2.34 ± 3.37	0.8	0.95 ± 1.61	0.64	1.65 ± 2.7	0.7	0.328
	Colon	2.15 ± 2.8	1.08	0.43 ± 0.5	0.27	1.14 ± 2.0	0.48	**0.007**
	Stomach	2.3 ± 3.69	1	1.67 ± 2.98	0.56	2.04 ± 3.38	0.72	0.432
Se	Esophagus	97.15 ± 14.8	92.07	115.16 ± 18.22	114.09	106.16 ± 18.75	106.56	**0.003**
	Colon	101.54 ± 14.6	99.16	105.03 ± 16.93	103.03	103.74 ± 15.91	102.09	0.634
	Stomach	95.09 ± 15.09	100.1	111.08 ± 22.24	114.03	101.89 ± 19.92	102.09	**0.013**
Cd	Esophagus	0.12 ± 0.08	0.13	0.16 ± 0.09	0.17	0.14 ± 0.09	0.15	0.207
	Colon	0.13 ± 0.09	0.17	0.13 ± 0.09	0.17	0.18 ± 0.12	0.19	0.073
	Stomach	0.16 ± 0.09	0.19	0.18 ± 0.11	0.22	0.17 ± 0.10	0.20	0.271
Pb	Esophagus	1.99 ± 0.75	1.88	6.91 ± 4.09	9.03	4.45 ± 3.83	2.24	**0.004**
	Colon	1.47 ± 0.42	1.4	6.19 ± 4.61	8.38	4.23 ± 4.23	1.7	**0.003**
	Stomach	1.74 ± 0.71	1.55	6 ± 4.62	8.21	3.55 ± 3.69	1.65	0.087

Relationships between elements and gastrointestinal cancers

The results of Cr, Ni, Zn, Se, and Pb metals showed significant risk differences on esophagus cancer when considered as the single predictor unadjusted for other metals and covariates RD (95% CI) – Cr: −0.274 (−0.463, −0.086), Ni: −0.288 (−0.457, −0.118), Zn: −0.171 (−0.463, −0.086), Se: −0.243 (−0.434, −0.051), and Pb: −0.094 (−0.143, −0.045) (Table 5). The metal significance remained unchanged when adjustment was applied for confounders and other metals. The negative sign of the RD denotes excessive risk of cases when metal concentrations increased. For instance, RD = −0.274 for Cr shows that when the concentrations of Cr increased, on average, the excessive risk of esophagus cancer was 27.4 % and it was significant (CI does not include zero). Similarly, the unadjusted RD of Cr, Ni, Cu, Zn, and As metals were significant for colon and Cr, Ni, Cu, Zn, Se, and Pb metals for stomach cancer. We also assessed the nonlinear relationship of metals using GAM analysis and found no evidence of nonlinear associations.

Discussion

While researchers keep on finding the primary cause, the etiology of a few cancers is as yet indistinct. Numerous studies reported the association of heavy metals like Cd, Cu, Ni, Pb, Zn, and As in the etiology of many cancers, including breast

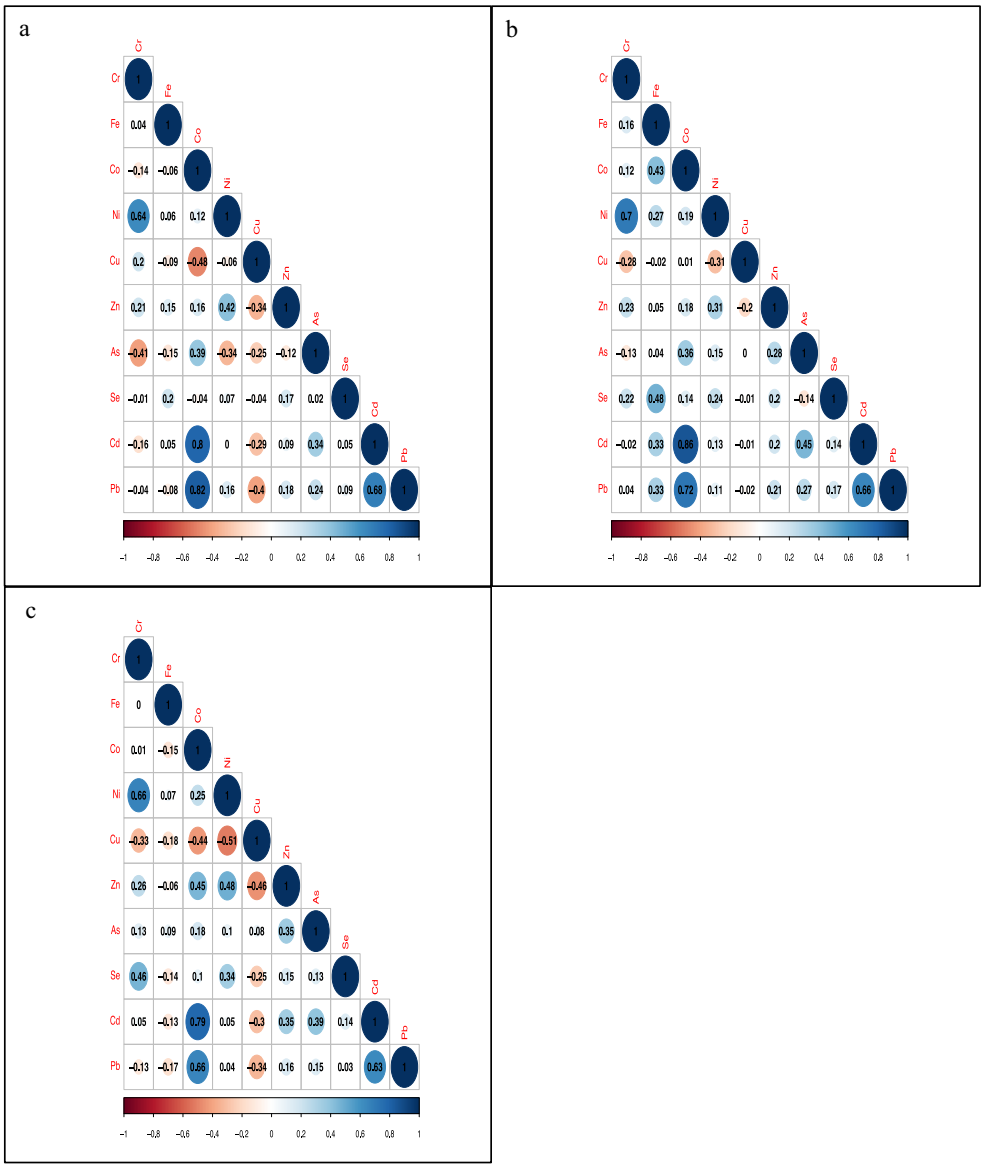

Fig. 1 Correlation plot between trace elements in studied cancer types. The number represents Spearman's correlation coefficients. **a**: colon; **b**: esophagus, **c**: stomach

and prostate cancers (Marouf 2018). The International Agency for Research on Cancer introduced As, Cd, Cr, and Ni as category 1 heavy metals (IARC 1980). These components are found in nature, and exposure to them can inhibit tumor suppressor genes, damage repair processes, and enzymatic activities concerned with metabolism via oxidative damage (Bánfalvi 2011; Kim et al. 2015). We found that the concentrations of Co, Cr, Fe, Ni, Pb, Se, and Zn were significantly higher among esophagus cancer cases than controls. Additionally, the Co, Cr, Ni, Pb, and Zn concentrations were markedly higher among colon cancer cases than controls.

Essential trace elements

In our study, the high concentration of copper (Cu) in cancerous tissues of the stomach and esophagus is consistent with findings from previous studies (Sun et al. 2011; Lin et al. 2020). Also, unlike stomach and esophagus cancers, Cu concentrations in cancerous tissues of colon cancer and the control group were not significantly different ($p > 0.05$). Cu is an essential component of various biochemical functions. Its concentration is increased in cancer tissues to promote cancer development through angiogenesis processes (Wang et al. 2010). High concentrations of Cu were detected in the liver and spleen of patients with the respiratory system, urinary tract, genital tract, breast, esophagus, bronchus, and gastrointestinal cancers (Magalhães et al. 2010; Szewczyk et al. 2013). On the contrary, Reddy et al. (2003) reported lower Cu concentrations in kidney cancer patients than non-cancerous tissues. Zinc (Zn) is a mineral element involved in many homeostatic mechanisms of the body, including specific immunity, inflammation, and oxidative stress (John et al. 2010). Cancer

Table 5 Logistic regression analysis of trace elements among cases and controls for three types of cancer

	Cancer type	Single metal (unadjusted)		Single metal (adjusted)		Multiple metals (adjusted)	
		RD	95% CI	RD	95% CI	RD	95% CI
Cr	Esophagus	−0.274	**−0.463, −0.086**	−0.160	**−0.256, −0.064**	−0.061	**−0.086, −0.036**
	Colon	−0.102	**−0.167, −0.037**	−0.049	**−0.078, −0.020**	−0.014	**−0.022, −0.006**
	Stomach	−0.113	**−0.158, −0.068**	−0.092	**−0.121, −0.064**	−0.034	**−0.047, −0.021**
Fe	Esophagus	−0.033	−0.095, 0.028	−0.015	−0.046, 0.015	0.003	−0.003, 0.009
	Colon	−0.029	−0.238, 0.180	0.032	−0.107, 0.170	0.003	−0.010, 0.016
	Stomach	0.089	−0.049, 0.229	0.087	−0.038, 0.212	0.025	−0.003, 0.052
Co	Esophagus	−0.13	−0.381, 0.122	−0.105	−0.263, 0.054	−0.004	−0.036, 0.027
	Colon	−0.202	−0.431, 0.027	−0.179	**−0.322, −0.035**	−0.007	−0.023, 0.007
	Stomach	−0.101	−0.274, 0.072	−0.101	−0.239, 0.037	0.027	−0.006, 0.061
Ni	Esophagus	−0.288	**−0.457, −0.118**	−0.162	**−0.245, −0. 080**	−0.066	**−0.1, −0.032**
	Colon	−0.299	**−0.422, −0.176**	−0.153	**−0.213, −0.092**	−0.063	**−0.093, −0.032**
	Stomach	−0.364	**−0.699, −0.028**	−0.294	**−0.540, −0.047**	−0.075	**−0.131, −0.018**
Cu	Esophagus	0.049	-0.021, 0.118	0.027	−0.008, 0.062	0.009	−0.001, 0.019
	Colon	0.074	**0.022, 0.126**	0.029	**0.009, 0.047**	0.005	**0.001, 0.009**
	Stomach	0.434	**0.175, 0.693**	0.275	**0.197, 0.352**	0.130	**0.072, 0.188**
Zn	Esophagus	−0.171	**−0.327, −0.015**	−0.119	**−0.217, −0.021**	−0.032	−0.066, 0.003
	Colon	−0.211	**−0.359, −0.063**	−0.149	**−0.250, −0.047**	−0.027	**−0.050,−0.004**
	Stomach	−0.289	**−0.450, −0.128**	−0.218	**−0.355, −0.080**	−0.040	**−0.073, −0.006**
As	Esophagus	0.077	−0.060, 0.215	0.026	−0.059, 0.112	0.069	**0.022, 0.115**
	Colon	0.237	**0.080, 0.393**	0.080	−0.070, 0.229	0.107	**0.043, 0.171**
	Stomach	0.032	−0.109, 0.174	0.058	−0.051, 0.168	0.002	−0.019, 0.023
Se	Esophagus	−0.243	**−0.434, −0.051**	−0.125	**−0.231, −0.018**	−0.067	**−0.109, −0.025**
	Colon	−0.031	−0.111, 0.049	−0.012	−0.066, 0.043	−0.001	−0.007, 0.004
	Stomach	−0.159	**−0.264, −0.054**	−0.150	**−0.234, −0.065**	−0.050	**−0.088, −0.012**
Cd	Esophagus	−0.124	−0.352, 0.104	−0.085	**−0.219, −0.048**	−0.003	−0.027, 0.022
	Colon	−0.150	−0.381, 0.080	−0.116	−0.265, 0.033	−0.022	−0.049, 0.006
	Stomach	−0.030	−0.263, 0.202	−0.016	−0.212, 0.180	0.051	**0.004, 0.098**
Pb	Esophagus	−0.094	**−0.143, −0.045**	−0.054	**−0.094, −0.013**	−0.063	**−0.094, −0.032**
	Colon	−0.130	−0.186, 0.074	−0.071	**−0.110, −0.031**	−0.053	**−0.075, −0.030**
	Stomach	−0.074	**−0.101, −0.046**	−0.066	**−0.096, −0.037**	−0.034	**−0.051, −0.017**

cells have upregulated zinc importers and frequently increased zinc concentrations, which allow them to survive. Previous in vivo and in vitro studies have shown Zn's role in carcinogenesis (Morton 2016). However, studies that evaluated the role of zinc in malignant diseases have a long history of contradiction. According to this study's results, Zn's mean concentrations in cancerous tissue of patients with gastric, esophageal, and colon cancer tissues were significantly higher than the control group ($p < 0.05$). Klimczak et al. (2016) showed similar results in breast and colon cancers. Oppositely, Yaman et al. (2007) demonstrated higher Zn concentrations in normal tissues than the cancerous gastric tissues (P = 0.005).

Selenium (Se) has various health and disease roles. It can function as a toxin, a carcinogen, and a cancer chemopreventive agent in mammals (Vinceti et al. 2018). Early studies provided evidence that Se has a role in cancer prevention. Decades of studies specifically prove that Se compounds inhibit the development of malignant cells in different laboratory model systems. However, growth-modulating and cytotoxic pathways are complex and far from clear (Wallenberg et al. 2014). However, none of the Se compounds have been scientifically accepted as anticancer drugs, partially because researchers have achieved contradictory findings over the years (Tan et al. 2018). Data on possible associations between selenium and esophageal and gastric cancer are sparse, and even less is known about the subtypes of these cancers. Some studies reported that high Se levels might be inversely associated with gastric cancer (GC) risk and GC mortality (Gong 2016; Charalabopoulos et al. 2009). Our findings indicated that the concentrations of Se were significantly higher among esophagus cancer cases than controls ($p < 0.05$). Similarly, cases

with stomach cancer showed higher Se levels compared to their controls ($p < 0.05$).

Non-essential trace elements

In our study, arsenic concentration was notably elevated in cancerous tissue patients with gastric, esophageal, and colon cancer, consistent with other reports (Yang et al. 2008; Lee et al. 2016; Safarzad et al. 2019). The inorganic form of arsenic (As) is highly toxic and considered group 1 (Straif et al. 2009). The exact association between AS and cancer is still undiscovered. Still, it has been shown that AS can interfere with several biological processes, such as chromosomal damage, DNA methylation, and DNA repair, further producing ROS (Raju et al. 2017). We also showed a high concentration of cadmium (Cd) in cancer tissues. Sayadi et al. (2020) illustrated that the Cd and Cr concentrations in herbs in rural residents living in Eastern Iran were relatively high. Risk assessments revealed that consuming these herbs may affect the health of both children and adults. Cigarette smoking is one of the most important sources of exposure to Cd (Ashraf 2012). Prolonged exposure to Cd leads to cardiovascular disease and cancer. Cd's concentration in cancerous tissue of patients with gastric, esophageal, and colon cancers was significantly higher than the control group in the present study. Kellen et al. (2007) reported a higher concentration of Cd in the blood of patients with bladder cancer than the control group. Strumylaite et al. (2011) evaluated Cd's concentration in breast tissue, urine, and blood of 57 breast cancer and 51 benign tumor patients. The results showed a higher Cd concentration in breast tumors and urine of cancer patients. They supported a possible relationship between Cd and breast cancer.

Meta-analyses and original studies have proposed that there may be excess risks for lung and stomach cancers among industrial workers with lead (Pb) exposed for a long time. However, stomach cancer was associated with organic Pb (Rousseau et al. 2007). In our study, Pb concentration in cancerous tissue of patients with esophageal, gastric, and colon cancers was significantly higher than normal tissues in the control group ($p < 0.05$). Some evidence showed that the level of Pb and Cr contamination of drinking water in Birjand flood plain was higher than international guidelines given by the USEPA and WHO, and that may explain the higher level of both elements in cancerous tissues in our study (Mansouri et al. 2012d; Sinkakarimi et al. 2020). Moreover, the findings of Rezaei et al. (2019) reported that toxic metals such as Pb, Cd, and Cr could increase the risk of developing hypothyroidism and thyroid cancer in patients with thyroid diseases living in Birjand City, east of Iran.

Chromium (Cr) is the seventh most common element on Earth. Cr can produce reactive oxygen species in successive oxidation states. As a result, it will be able to damage DNA, causing mutations and eventually cellular changes. Chromium is known to be carcinogenic (Sohrabi et al. 2018). According to the present study results, the mean concentrations of Cr in cancerous tissue of patients with gastric, esophageal, and colon cancers significantly increased compared to healthy tissues ($p < 0.05$). Sohrabi et al. (2018) earned the same result. In their study, the median of Cr in colorectal cancer (CRC) tissues was significantly higher than in healthy tissues. This finding is also in agreement with the meta-analysis results performed by Deng et al. (2019). They showed that male workers exposed to Cr were at risk of prostate cancer, oral cancer, and to a greater extent, stomach cancer. Another meta-analysis performed by Welling et al. (2015) suggested Cr is a stomach carcinogen in humans. Iron (Fe) is an important element in cell proliferation and oxidative activities. While existing research on the carcinogenic function of iron deficiency and over-sufficiency is mixed, there is general support for these possibilities. Both iron deficiency and iron over-sufficiency may raise the risk of gastrointestinal tract cancers such as stomach and CRC cancers (Hossein Davoodi et al. 2016). This increased risk can be explained by biochemical modification and inflammatory status. The difference in the metabolism of iron occurs as an initiator (Verma and Cherayil 2017). In the present study, iron concentrations in cancerous tissues of patients with stomach and esophageal cancers were significantly lower than non-cancerous tissues of healthy controls ($p < 0.05$), which is consistent with the findings in similar studies (Nelson et al. 1994; Pusatcioglu et al. 2014). On the contrary, in a study conducted by Yaman et al. (2007), the iron concentrations in tissue samples of patients with gastric cancer were significantly higher than non-cancerous tissues.

Nickel (Ni) is a heavy metal widely distributed in several forms. Epidemiological studies suggest that occupational exposures to nickel compounds are associated with an elevated prevalence of nasal and lung cancers (Lu et al. 2005). Ni carbonyl inhibits cortisone-induced tryptophan pyrrolase and phenothiazine-induced benzopyrene hydroxylase and protein synthesis and DNA synthesis by interfering with DNA-dependent RNA polymerase (Pavela et al. 2017). Khlifi et al. (2013) showed Ni concentrations in tumor head and neck cancer tissues were significantly higher than the non-cancerous tissues in the control group ($p < 0.05$). Additionally, Pasha et al. (2010) reported a similar result in gastrointestinal cancer. In the present study, the mean concentrations of Ni in the cancerous tissue of patients with gastric, esophageal, and CRC cancers were significantly higher than normal tissues in the control group, which is consistent with the findings in similar studies ($p < 0.05$). On the contrary, Kohzadi et al. (2017) reported that concentrations in non-

cancerous tissue in the control group were significantly higher than cancer tissue in cancer patients ($p < 0.05$).

Age effects on cancers

Cancer development is a long process that takes several years to complete and can be considered an age-related disease because the incidence of most cancers increases with age, rising more rapidly beginning in midlife (White et al. 2014). According to official reports and studies, more than half of cancers occur in individuals older than 70. Several mechanisms include the role of genomic instability, telomere attrition, epigenetic changes, loss of proteostasis, decreased nutrient sensing and altered metabolism, cellular senescence, and stem cell function can share or diverge aging and cancer development (Aunan et al. 2017). The fundamental reasons for the observed changes are still unknown; however, several aging hypotheses are based on an increase in oxidative stress and concomitant accumulation of oxidized and nitrated proteins, oxidized lipids, and DNA damage. According to in vivo studies, essential trace elements are important during the aging process because they modulate both oxidative stress and immune response by their essential functions, such as enzymatic reactions and signaling pathways. Inadequate trace element consumption is common in the elderlies, resulting in a lower amount, especially serum Se and Zn concentrations (Lossow et al. 2020). However, a low-grade chronic inflammation, common in the elderlies, may play a role in the age-related changes in trace element profiles (Wong et al. 2013). There was no significant association in terms of age between cases and controls suffering from the esophagus and stomach cancer in our study. However, for colon cancer, cases (with a mean age of 64.71 years) were markedly older than controls (with a mean age of 51.65 years) ($P = 0.013$) (Table 2)

Correlation among trace elements

The Mann-Whitney test was used to compare the element concentration levels between cases and controls to investigate the effect of age (Table 3). The result showed that the concentrations of Cr, Fe, Co, Ni, Zn, Se, and Pb were significantly higher among esophagus cancer cases than controls. Additionally, the concentrations of Cr, Co, Ni, Zn, and Pb were markedly high among cases with colon cancer compared to controls, whereas they had lower concentrations of Cu and As. Similarly, higher concentrations of Cr, Cu, Ni, Zn, and Se and lower concentration concentrations of Cu were detected in cases with stomach cancer compared to controls. In addition, Spearman's correlation coefficient was used to assess the correlation between metals with each other. The result showed that correlation coefficients between element pairs were mostly positive and low to moderate (less than 0.50).

Conclusion

There is now a considerable amount of epidemiologic evidence concerning trace elements' role in influencing cancer risk. This study aimed to evaluate the association between heavy metals including Cr, Fe, Co, Ni, Cu, Zn, As, Se, Cd, and Pb in cancerous and non-cancerous tissues with the risk of gastrointestinal cancers in Eastern Iran. Based on our result, the concentrations of Cr, Ni, As, Cd, Zn, and Pb in the cancerous tissue of patients with gastric, esophageal, and colorectal cancers were significantly higher than the healthy tissue of non-cancerous patients. Also, we found that the concentration of Fe and Cu in the healthy tissue of non-cancerous individuals was higher than in the cancerous tissues. Although the association between trace element exposure and cancer risk has been examined in some extensive prospective studies, additional studies are needed to elucidate further the mechanisms underlying trace element carcinogenesis.

Acknowledgements The data provided in this study was taken from the first author MSc Dissertation project. The authors would like to gratefully acknowledge all of our colleagues at the Medical Toxicology and Drug Abuse Research Center (MTDRC) of Birjand University of Medical Sciences who provided logistics for chemicals and samples.

Author contribution BM and FN were the overall coordinators. FN, BM, NA, TT, and OM contributed to the design of the study, interpretation of the results, and drafting of the manuscript. FN conducted the data collection. NA did data analysis. All authors have read and approved the final version of the manuscript.

Funding This study was supported by the Birjand University of Medical Sciences (Grant number: 1397/455619).

Data availability The datasets used and/or analyzed during the current research are available from the corresponding author on request.

Declarations

Ethics approval and consent to participate This study was approved by the Research and ethics committee of Birjand University of Medical Sciences (IR.BUMS.REC.1397.072), and relevant descriptions were provided concerning the aims of the research.

Consent for publication Not applicable

Competing interests The authors declare no competing interests.

References

Al Faris NA, Ahmad D (2011) Distribution of trace elements like calcium, copper, iron, and zinc in serum samples of colon cancer: a case-control study. J King Saud Univ-Sci 23:337–734

Ashraf MW (2012) Levels of heavy metals in popular cigarette brands and exposure to these metals via smoking. Sci World J 2012:729430

Aunan JR, Cho WC, Søreide K (2017) The biology of aging and cancer: a brief overview of shared and divergent molecular hallmarks. Aging Dis 8(5):628–642

Bánfalvi G (2011) Heavy metals, trace elements and their cellular effects. In: Banfalvi G (ed) Cellular effects of heavy metals. Springer: Dordrecht, The Netherlands, pp 3–28

Bray F, Jemal A, Grey N, Ferlay J, Forman D (2012) Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. Lancet Oncol 13(8):790–801

Charalabopoulos K, Kotsalos A, Batistatou A, Charalabopoulos A, Peschos D, Vezyraki P, Kalfakakou V, Metsios A, Charalampopoulos A, Macheras A, Agnantis N, Evangelou A (2009) Serum and tissue selenium levels in gastric cancer patients and correlation with CEA. Anticancer Res 29(8):3465–3467

Deng Y, Wang M, Tian T (2019) The effect of hexavalent chromium on the incidence and mortality of human cancers: a meta-analysis based on published epidemiological cohort studies. Front Oncol 9:24

Farnia V, Pirsaheb M, Mansouri B, Azadi NA, Radmehr F (2021) Blood lead concentration among oral/inhaled opium users: systematic review and meta-analysis. Crit Rev Toxicol 51:24–35

Fauci AS (2011) Harrison's Principles of Internal Medicine, 15th edn. McGraw-Hill, New York

Gelman A, Jakulin A, Pittau MG, Su YS (2008) A weakly informative default prior distribution for logistic and other regression models. Ann Appl Stat 2(4):1360–1383

Gong HY (2016) Meta-analysis of the association between selenium and gastric cancer risk. Oncotarget 13:15600–15605

Hossein Davoodi S, Jamshidi-Naeini Y, Esmaeili S, Sohrabvandi S, Mortazavian AM (2016) The dual nature of iron in relation to cancer: a review. Int J Cancer Mang 9(6):5494

Ionescu JG, Novotny J, Stejskal VD, Latsch A, Blaurock-Busch E, Eisenmann-Klein M (2006) Increased levels of transition metals in breast cancer tissue. Neuro Endocrinol Lett 27(1):36–39

IARC (1980) IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 22. Some non-nutritive sweetening agents: Distributed for IARC by WHO, Geneva, Switzerland; 1980.

John E, Laskow TC, Buchser WJ, Pitt BR, Basse PH, Butterfield LH, Kalinski P, Lotze MT (2010) Zinc in innate and adaptive tumor immunity. J Transl Med 8:118

Kellen E, Zeegers MP, Den Hond E, Buntinx F (2007) Blood cadmium may be associated with bladder carcinogenesis: the Belgian case–control study on bladder cancer. Cancer Detect Prev 31(1):77–82

Khlifi R, Olmedo P, Gil F, Hammami B, Chakroun A, Rebai A et al (2013) Arsenic, cadmium, chromium and nickel in cancerous and healthy tissues from patients with head and neck cancer. Sci Total Environ 452:58–67

Kim HS, Kim YJ, Seo YR (2015) An overview of carcinogenic heavy metal: molecular toxicity mechanism and prevention. J Cancer Prev 20(4):232–240

Klimczak M, Dziki A, Kilanowicz A, Sapota A, Duda-Szymańska J, Daragó A (2016) Concentrations of cadmium and selected essential elements in malignant large intestine tissue. Przeglad Gastroenterol 11(1):24

Kohzadi S, Sheikhesmaili F, Rahehagh R, Parhizkar B, Ghaderi E, Loqmani H, Shahmoradi B, Mohammadi E, Maleki A (2017) Evaluation of trace element concentration in cancerous and non-cancerous tissues of human stomach. Chemosphere 184:747–752

Kolahdoozan S, Sadjadi A, Radmard AR, Khademi H (2010) Five common cancers in Iran. Arch Iran Med 13(2):143–146

Lee CP, Lee YH, Lian IB, Su CC (2016) Increased prevalence of esophageal cancer in areas with high levels of nickel in farm soils. J Cancer 7(12):1724–1730. https://doi.org/10.7150/jca.15441

Lin Y, Wu C, Yan W, Guo S, Liu B (2020) Five serum trace elements associated with risk of cardia and noncardia gastric cancer in a matched case-control study. Cancer Manag Res 12:4441–4451. https://doi.org/10.2147/CMAR.S250592

Lossow K, Kopp JF, Schwarz M, Finke H, Winkelbeiner N, Renko K, Meçi X, Ott C, Alker W, Hackler J, Grune T, Schomburg L, Haase H, Schwerdtle T, Kipp AP (2020) Aging affects sex- and organ-specific trace element profiles in mice. Aging 12(13):13762–13790. https://doi.org/10.18632/aging.103572

Lu H, Shi X, Costa M, Huang C (2005) Carcinogenic effect of nickel compounds. Mol Cell Biochem 279(1-2):45–67. https://doi.org/10.1007/s11010-005-8215-2

Magalhães T, Carvalho M, Von Bohlen A, Becker M (2010) Study on trace elements behaviour in cancerous and healthy tissues of colon, breast and stomach: total reflection X-ray fluorescence applications. Spectrochim Acta Part B: Atomic Spectroscopy 65(6):493–498

Majnoni F, Mansouri B, Rezaei MR, Hamidian AH (2013) Contaminations of metals in tissues of common carp, *Cyprinus carpio* and silver carp, *Hypophthalmichthys molitrix* from Zarivar wetland, western Iran. Arch Pol Fish 21:11–18

Maleki A, Azadi NA, Mansouri B et al (2015) Health risk assessment of trace elements in two fish species of Sanandaj Gheshlagh Reservoir, Iran. Toxicol Environ Health Sci 7:43–49

Mansouri B, Pourkhabbaz A, Babaei H, Hoshyari E, Khodaparast SH, Mirzajani A (2012a) Assessment of trace-metal concentration in Western Reef Heron (*Egretta gularis*) and Siberian gull (*Larus heuglini*) from southern Iran. Arch Environ Contam Toxicol 63: 280–287

Mansouri B, Ebrahimpour M, Babaei H (2012b) Bioaccumulation and elimination of nickel in the organs of black fish (*Capoeta fusca)*. Toxicol Ind Health 28:361–368

Mansouri B, Baramaki R, Ebrahimpour M (2012c) Acute toxicity bioassay of mercury and silver on *Capoeta fusca*. Toxicol Ind Health 28(5):393–398

Mansouri B, Salehi J, Etebari B, Kardan Moghaddam H (2012d) Metal concentrations in the groundwater in Birjand Flood Plain, Iran. Bull Environ Contam Toxicol 89:138–142

Marouf B (2018) Association between serum heavy metals level and cancer incidence in darbandikhan and Kalar Area, Kurdistan Region, Iraq. Niger J Clin Pract 21(6):766–771

Morton R (2016) Zinc deficiency: Etiology, screening methods and health implications. Nova Science Publishers, Inc., p 91

Nanda R, Agrawal V (2016) Elucidation of zinc and copper induced oxidative stress, DNA damage and activation of defence system during seed germination in *Cassia angustifolia* Vahl. Environ Exp Bot 125:31e41

Nelson RL, Davis FG, Sutter E, Sobin LH, Kikendall JW, Bowen P (1994) Body iron stores and risk of colonic neoplasia. J Natl Cancer Inst 86(6):455–460

Norouzi M, Mansouri B, Hamidian AH (2012) Metal Concentrations in tissues of two fish species from Qeshm Island, Iran. Bull Environ Contam Toxicol 89:1004–1008

Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55(2):74–108

Pasha Q, Malik SA, Shaheen N, Shah MH (2010) Investigation of trace metals in the blood plasma and scalp hair of gastrointestinal cancer patients in comparison with controls. Clin Chim Acta 411(7-8):531–539

Pavela M, Uitti J, Pukkala E (2017) Cancer incidence among copper smelting and nickel refining workers in Finland. Am J Ind Med 60(1):87–95

Pusatcioglu CK, Nemeth E, Fantuzzi G, Llor X, Freels S, TussingHumphreys L (2014) Systemic and tumor level iron regulation in men with colorectal cancer: a case control study. Nutr Metab 11:21

Raju GN, Sarita P, Murthy K (2017) Comparative trace elemental analysis of cancerous and non-cancerous tissues of rectal cancer patients using PIXE. Nucl Inst Methods Phys Res B 404:146–149

Reddy SB, Charles MJ, Raju GN, Vijayan V, Reddy BS, Kumar MR (2003) Trace elemental analysis of carcinoma kidney and stomach by PIXE method. Nucl Instrum Methods Phys Res Section B Beam Interac Mater Atoms 207(3):345–355

Rezaei M, Javadmoosavi SY, Mansouri B, Azadi NA, Mehrpour O, Nakhaee S (2019) Thyroid dysfunction: how concentration of toxic and essential elements contribute to risk of hypothyroidism, hyperthyroidism, and thyroid cancer. Environ Sci Pollut Res 26:35787–35796

Rezaei M, Błaszczyk M, Tinkov AA, Binkowski LJ, Mansouri B, Skalny A, Azadi NA, Dosa MD, Bjorklund G (2021) Relationship between gestational diabetes and serum trace element levels in pregnant women from Eastern Iran: a multivariate approach. Environ Sci Pollut Res. https://doi.org/10.1007/s11356-021-13927-1

Rinaldi L, Barabino G, Klein JP, Bitounis D, Pourchez J, Forest V (2015) Metals distribution in colorectal biopsies: new insight on the elemental fingerprint of tumour tissue. Dig Liver Dis 47(7):602–607

Rousseau MC, Parent ME, Nadon L, Latreille B, Siemiatycki J (2007) Occupational exposure to lead compounds and risk of cancer among men: a population-based case-control study. Am J Epidemiol 166: 1005–1014

Roy SS, Mukherjee S, Mukhopadhyay S, Das SK (2004) Differential effect of cadmium on cholinephosphotransferase activity in normal and cancerous human mammary epithelial cell lines. Mol Cancer Ther 3(2):199–204

Saadat S, Yousefifard M, Asady H, Moghadas Jafari A, Fayaz M, Hosseini M (2015) The most important causes of death in iranian population; a retrospective cohort study. Emerg (Tehran) 3(1):16–21

Safarzad M, Besharat S, Salimi S, Azarhoush R, Behnampour N, Joshaghani H (2019) Association between selenium, cadmium, and arsenic levels and genetic polymorphisms in DNA repair genes (XRCC5, XRCC6) in gastric cancerous and non-cancerous tissue. J Trace Elem Med Biol 55:89–95

Sayadi MH, Kharkan J, Binkowski LJ, Moshgani M, Blazsczyk M, Mansouri B (2020) Cadmium and chromium levels in water and edible herbs in a risk assessment study of rural residents living in Eastern Iran. Environ Sci Pollut Res 27:9901–9909

Siegel R, Naishadham D, Jemal A (2013) Cancer statistics, 2013. CA Cancer J Clin 63(1):11–30

Siegel RL, Miller KD, Jemal A (2016) Cancer statistics, 2016. CA Cancer J Clin 66(1):7–30

Sinkakarimi M, Rajei G, Mahdijezhad M, Hatamimanesh M (2020) health risk assessment of some heavy metals in groundwater resources of birjand flood plain using Environmental Protection Agency (EPA) model. J Health 11(2):183–193

Sohrabi M, Gholami A, Hosseini Azar M, Yaghoobi M, Mirasgari Shahi M, Shirmardi S, Nikkhah M, Kohi Z, Salehpour D, Khoonsari M, Hemmasi G, Zamani F, Sohrabi M, Ajdarkosh H. Trace element and heavy metal levels in colorectal cancer (2018) Comparison between cancerous and non-cancerous tissues. Biol Trace Elem Res 183(1): 1-8.

Solenkova NV, Newman JD, Berger JS, Thurston G, Hochman JS, Lamas GA (2014) Metal pollutants and cardiovascular disease: mechanisms and consequences of exposure. Am Heart J 168:812–822

Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, Guha N, Freeman C, Galichet L, Cogliano V (2009) A review of human carcinogens - Part C: metals, arsenic, dusts, and fibres, on behalf of the WHO International Agency for Research on Cancer Monograph Working Group. International Agency for Research on Cancer, Lyon, France. Lancet 10:453–454

Strumylaite L, Bogusevicius A, Abdrachmanovas O, Baranauskiene D, Kregždytė R, Pranys D, Poskiene L (2011) Cadmium concentration in biological media of breast cancer patients. Breast Cancer Res Treat 125:511–517

Sun ZG, Song GM, Zhang M, Wang Z (2011) Clinical study on zinc, copper and manganese levels in patients with esophageal squamous cell cancer. Trace Elem Electrol 28:116–120

Szewczyk M, Pasternak K, Andrzejewski A, Dabrowski A, Wallner G (2013) Plasma and cancerous tissue concentrations of Zn, Cu and Mn in patients undergoing surgical treatment for gastrointestinal cancer. J Elem 18(1):135–144

Tan HW, Mo HY, Lau ATY, Xu YM (2018) Selenium species: current status and potentials in cancer prevention and therapy. Int J Mol Sci 20:75

Verma S, Cherayil BJ (2017) Iron and inflammation - the gut reaction. Metallomics 9(2):101–111

Vinceti M, Filippini T, Del Giovane C, Dennert G, Zwahlen M, Brinkman M, Zeegers MPA, Horneber M, D'Amico R, Crespi CM (2018) Selenium for preventing cancer. Cochrane Database Syst Rev 1(1):CD005195

Wallenberg M, Misra S, Björnstedt M (2014) Selenium cytotoxicity in cancer. Basic Clin Pharmacol Toxicol 114:377–386

Wang F, Jiao P, Qi M, Frezza M, Dou QP, Yan B (2010) Turning tumor-promoting copper into an anti-cancer weapon via high-throughput chemistry. Curr Med Chem 17(25):2685–2698

Welling R, Beaumont JJ, Petersen SJ, Alexeeff GV, Steinmaus C (2015) Chromium VI and stomach cancer: a meta-analysis of the current epidemiological evidence. Occup Environ Med 72(2):151–159

White MC, Holman DM, Boehm JE, Peipins LA, Grossman M, Henley SJ (2014) Age and cancer risk: a potentially modifiable relationship. Am J Prev Med 46(3):S7–S15

Wong CP, Magnusson KR, Ho E (2013) Increased inflammatory response in aged mice is associated with age-related zinc deficiency and zinc transporter dysregulation. J Nutr Biochem 24(1):353–359

Yaman M, Kaya G, Simsek M (2007) Comparison of trace element concentrations in cancerous and noncancerous human endometrial and ovary tissues. Int J Gynecol Cancer 17(1):220–228

Yang CY, Chang CC, Ho SC, Chiu HF (2008) Is colon cancer mortality related to arsenic exposure? J Toxicol Environ Health A 71(8):533–538