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Evaluation of trace element concentration in cancerous and non-cancerous tissues of human stomach

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HIGHLIGHTS

- Trace element concentration was assessed in gastric cancer and normal tissues.
- Concentrations of Fe, Mg, and As were high in cancerous tissues.
- Cr, Cu, Ca, and Ni were higher in non-cancerous tissues of cancerous patients.
- The residence location of patients may play as an environmental factor.
- In general, Cu was significantly higher in cancerous samples ($p < 0.05$).

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ABSTRACT

Gastric cancer has a high mortality rate in west of Iran. Various environmental elements are proposed as cancer risk factors including trace elements. Trace elements can induce initiation or progression of carcinogenesis via oxidative stress and DNA injury. The aim of this study was to measure and compare some trace element concentration (Ca, Cu, Fe, As, Mg, Ni, Cd and Cr) in gastric cancer tissues and normal tissues. For this purpose, 35 patients with gastric cancer and 30 without any cancer were biopsied. Biopsies were taken from cancerous tissue and non-cancerous tissue of gastric cancer patients and gastric tissue of normal patients. The analysis of trace elements was performed using Inductively coupled plasma mass spectrometry (ICP-MS). Data analysis was carried out using SPSS and STATA 12 software. The research found that the concentrations of Fe, Mg, and As were higher in cancerous tissues compared with non-cancerous tissues whereas Cr, Cu, Ca, and Ni concentrations were higher in non-cancerous tissues of cancerous patients. When comparisons were made for cancer and normal samples, copper was the only metal, which was significantly higher in cancerous samples ($p < 0.05$) and Cr mean concentration in normal tissues was significantly higher compared with cancerous tissues ($P = 0.02$). Chi-Square test showed that there was no significant relationship in the demographic information between cancerous and normal patients except for location with $K^2 = 7.604$. Increased Cu and As concentration in gastric patients (both tissues) propose that these elements may have carcinogenic effects, although further study is suggested.

1. Introduction

Despite its decreasing incidence, gastric cancer is globally the third most frequent cause of death from cancer (Rugge et al., 2015). Various factors such as habitual, genetic, nutritional, behavioral,

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and occupational situation have been introduced as cancer risk factors (Ebrahim et al., 2007). Gastric cancer has been related to environmental factors more than genetics as risk factors (Pasha et al., 2010). Importance of identifying these risk factors is evident in both prevention and treatment of cancer (Charalabopoulos et al., 2009).

Poor socioeconomic condition is an environmental risk factor, which have come to close investigation in a region called cancer belt. Regions with higher incidence of gastric cancer have more infertile lands, high mountains, soil ample of heavy metals, and other toxic elements. Epidemiologic studies have shown higher incidence of gastrointestinal cancer in regions with environmental pollution by trace elements and radioactive materials through their industrial and agricultural wastes (Kasper, 2005; Khlifi et al., 2013).

Despite this data, the role of trace elements in the initiation, progression or inhibition on cancer is still debated and numerous studies have been carried out on this subject (Hartwig, 2000; Silvera and Rohan, 2007). Human ingests trace elements via food and water (Reddy et al., 2003). Some trace elements like Cu and Fe take part in physiologic processes of human body through activating or inhibiting enzymes (Kuo et al., 2002; Magalhães et al., 2006). Zn and Cu play important roles in several processes such as RNA replication, DNA repair, and immunity (Al Faris and Ahmad, 2011). However, excess Zn and Cu have shown oxidant properties through generating reactive oxygen species (ROS) and oxidative stress damaging different cell components including DNA (Nanda and Agrawal, 2016). Most of trace elements affect carcinogenicity by inducing ROS production and oxidative stress (Gupte and Mumper, 2009).

ROS and other free radicals are chemical molecules or atoms impairing electrons at their outer orbital layer; therefore, they are highly reactive and bind to different molecules. In cells, ROS molecules bind DNA and different proteins such as enzymes, changing their structures. This structural change can break or disable those molecules or make them hyperactive (Zuo, 2002; Valko et al., 2006). Some other trace elements like Pb, Hg, and Cd can directly inhibit enzymes by binding to SH and SCH_3 ligands in cysteine and methionine amino acids structures. They can also replace ions with the same charge and size at the structure of metal-enzymes, disrupting their normal function (Reddy et al., 2003). These consequences can bring about impaired cell reproduction and genetic mutations, finally ending in carcinogenesis (Valko et al., 2006). Stomach is in direct contact with ingested trace elements because of its anatomic position.

In order to study the role of trace metals in carcinogenesis, there are various studies conducted on comparing trace metals in both cancerous and non-cancerous tissues. Different results have been gained. For example, Yaman found higher Zn and Cu (Yaman, 2006) while Kobayashi found Se to be higher in cancerous tissue whereas Fe was lower in cancerous tissue (Kobayashi, 1990). Another study showed that the concentration of trace elements like Cu was the same in tumor and normal tissues (Magalhães et al., 2010).

The incidence and prevalence of gastric cancer in the west of Iran is much higher compared with other parts of the country (Kolahdoozan et al., 2010). Moreover, water quality assessment has revealed that the concentration of some of the trace elements like Hg, Pb and As measured is higher than the World Health Organization (WHO) guideline levels (Ebrahimi and Ebrahimzadeh, 2013). Hence, there is a possibility to find a relationship between these two issues. Thus, the aim of this study was to evaluate trace elements concentrations in gastric cancer. We measured some trace elements in cancerous and non-cancerous tissues of gastric cancer patients and in gastric biopsies of non-cancerous patients.

2. Material and method

2.1. Sample collection

The study was carried out in a group of 65 patients (35 gastric cancer patients and 30 non-cancer patients with complaints of gastric disorders). The inclusion criteria for gastric cancer patients group were history, physical exam, and endoscopic study indicating gastric cancer and exclusion criteria for this group were non-cancer pathologic study and for non-cancer group inclusion criteria were history, physical exam, and endoscopic study not indicating cancer and exclusion criteria for this group were cancerous pathologic study results. Informed consent was filled by patients participating in research project. Moreover, the Ethic Committee of the Kurdistan University of Medical Sciences approved this research work. Two endoscopic samples were taken from each cancer patient, one from normal and another one from neoplastic tissue. Samples were preserved in tubes washed completely with nitric acid and then with distilled water and contained 10% formaldehyde solution (PARS Chemie, Art.402, U.S.P). Later, the samples were transferred to laboratory where they were kept in refrigerator until tissue preparation processes. It is noteworthy that in this paper, we refer to non-cancer tissue of cancer patients as non-cancerous tissue and gastric tissue of non-cancer patients as normal tissue.

2.2. Tissue preparation

Exactly 40 mg of each sample was mixed with 500 μL of ultrapure nitric acid 65% (Merck, Germany). The mixture was placed in water bath at 70 °C for 1 h, later the mixture was put in a Teflon vessel and then in microwave digester for 10 min under radiation of 450 W. After cooling, the mixture was made up to 25 mL by adding double distillated water and centrifuged.

2.3. Trace metals analysis

The prepared solution was measured for Ca, Cu, Fe, As, Mg, Ni, Cd, and Cr using Inductively coupled plasma mass spectrometry (ICP-MS) (Djedjibegovic et al., 2012). These metals were chosen due to their possible role in carcinogenesis in recent literature (Klimczak et al., 2015; Li et al., 2015).

The instrument used was ICP-OES with flared end EOP Torch 2.5 mm and a pump rate of 30 RPM (Spectro arcos, Germany). Tables 1 and 2 present further information about the device.

Table 1
ICP-OES ICP-OES, Spectro arcos, Spectro arcos properties.

Parameter:	
RF generator (W)	1400
Plasma, auxiliary and nebulizer gas	Argon
Plasma gas flow rate (l/min)	14.5
Auxiliary gas flow rate (l/min)	0.9
Nebulizer gas flow rate (l/min)	0.85
Sample uptake time (S)	240 total
Delay time of (S)	–
Rinse time of (S)	45
Initial stabilization time (S)	Preflush:45
Time between replicate analysis (S)	–
Measurement replicate	3
Element (λ/nm)	As below
Frequency of RF generator (MHz)	resonance frequency: 27.12 MHz
Type of detector Solid state	CCD
Type of spray chamber Cyclonic	Cross flow

Table 2
Limit of detection, limit of quantification and wave length of ICP-OES, Spectro arcos for each element.

Sample	As ppb	Ca ppb	Cd ppb	Cr ppb	Cu ppb	Fe ppb	Mg ppb	Ni ppb
LOD	0.3	0.7	0.3	0.3	0.1	0.16	1.3	0.3
LOQ	1	2.2	1	1	0.3	0.5	4	1
WL(nm)	189.042	422.673	228.802	267.716	324.754	259.941	279.553	231.604

2.4. Statistical analysis

The Statistical Package for Social Sciences (IBM SPSS Statistics) software, version 22.0 was used for data analysis and STATA 12 was used for plotting the graphs. Independent sample *t*-test was used for comparing the trace element concentrations in the stomach tissues of cancerous and noncancerous patients and paired sample *t*-test was used for comparing trace element in cancerous and noncancerous tissues of each individual.

3. Results

Demographic information of patients is tabulated in Table 3. Chi-Square test showed that there was no significant relationship in the demographic information between cancerous and normal patients except for location with $K^2 = 7.604$ and P- value = 0.006The trace elements concentration was measured in 35 cancer patients and 30 normal patients. Figs. 1 and 2 present relative concentrations of trace metals in normal and non-cancerous tissues of stomach and relative concentrations of trace metals in normal and cancerous tissues of stomach respectively.

Cu mean concentration in paired cancerous and non-cancerous tissues was 4.09 and 7.86 mg/kg respectively and there was no significant difference between them ($p = 0.208$). But Cu mean concentration in normal tissues was 2.22 mg/kg (Table 4), therefore, Cu mean concentration in cancerous tissues was significantly higher than normal tissues ($p = 0.044$). Cu mean concentration in noncancerous tissues was higher compared with normal tissues, although it was not significant ($p = 0.063$).

Results showed the mean concentrations of Cr was 1.21 and 2.16 mg/kg in cancerous and non-cancerous tissues respectively. There was no significant difference between them ($p = 0.229$). Whilst Cr mean concentration in normal patients was 2.42 mg/kg (Table 4). Mean Cr concentration in normal patient tissues was higher compared with non-cancerous tissues of cancer patients but there was no significant difference ($p = 0.802$). On the other hand, Cr mean concentration in normal tissues was significantly ($p = 0.029$) higher compared with cancerous tissues.

For other trace metals, i.e. Ca, Fe, Mg, As, Ni, and Cd, there was no significant differences between three categories of tissues.

4. Discussion

Gastric cancer is one of the most prevalent cancers with high mortality rate, especially in north and northwestern of Iran (Kolahdoozan et al., 2010). Most of its risk factors are environmental; one of these environmental risk factors is trace elements, which have recently attracted specific attention (Herceg, 2007; Lee and Derakhshan, 2013). Previous *in vitro* and *in vivo* investigations have shown that trace elements can participate in cellular stress mutation and carcinogenicity via oxidative stress and DNA damage mechanisms (Henkler et al., 2010; Wang et al., 2015). Comparison of trace metals concentrations in tissues of gastric cancer and normal gastric tissue was the main aim of the present study.

Yaman et al. evaluated gastric cancer patients in terms of some trace elements in cancerous and non-cancerous tissues of each patient. They found that the average concentration of Cd and Ni were 51/65 and 632/526 ng/g in cancerous/non-cancerous tissues respectively; while the average Cu, Fe, Mg, and Ca concentrations in cancerous/non-cancerous tissues were 1.7/1.1, 30/21, 195/195, and 537/660 mg/kg respectively. Hence, Ni, Cu, and Fe concentrations in cancerous tissues were higher compared with non-cancerous tissues whilst Cd and Ca concentrations in cancerous tissues were lower compared with non-cancerous tissues but Mg concentration was unchanged (Yaman et al., 2007).

In Magalhães study, Fe concentration was higher in cancerous tissues, consistent with Yaman et al. study, but Cr and Ni concentrations were higher in healthy tissues in contrary to Yaman et al. study. Ca and Cu concentrations were unchanged (Magalhães et al., 2010).

In another study conducted by Reddy et al. completely different results were obtained making the conclusion more complicated. Concentrations of Cr, Ni, and As were higher in the cancer tissues while Ca, Fe, and Cu were higher in normal tissues. Moreover, they measured these concentrations in kidney cancer samples and the results showed that the concentrations of As and Cd were higher in the cancer tissues while Ca, Fe, and Ni were higher in normal tissues (Reddy et al., 2003).

The abovementioned studies just compared metals elements in cancerous and non-cancerous tissues of the same patient but we went a step further and compared these tissues with tissues of non-cancerous patients. This research showed that Fe, Mg, and As concentrations were higher in cancerous tissues compared with non-cancerous tissues whereas Cr, Cu, Ca, and Ni concentrations were higher in non-cancerous tissues of cancerous patients.

Fe and Cu are essential components of angiogenesis (Saghiri et al., 2015a, b; Bharathi Devi et al., 2016), therefore, they are utilized by tumors for growth (Raju et al., 2006; Wang et al., 2016). But, the present study found a lower concentration of Fe in cancerous tissues compared with normal tissues. As the tissues were taken endoscopically, they were not locally perfused. Such results have been reported in literature (Puliyel et al., 2015). It has been assumed that Fe might not have a role in carcinogenesis but its lower concentration maybe due to lesser absorption of Fe in cancerous tissue because of the diminished HCl production in cancerous stomach (Von Czarnowski et al., 1997; Reddy et al., 2003). Indeed, Fe is a component of hemoglobin, which may be detected at higher concentration in cancerous tissues because of a better blood supply of tumors. Therefore, further surveys are suggested to demonstrate a role for Fe in carcinogenesis.

Previous studies reported that Ni ion can bind to Ca receptors and vanish intracellular Ca stores; hence, higher Ni can lead to

Table 3
Demographic information between cancerous and non-cancerous patients.

		Sample Category		Total	Chi-Square tests	
		Cancer Tissue	Normal Tissue		Pearson Chi-Square	P-value
Gender	Male	26	16	42	3.102	0.081
	Female	9	14	23		
Location	City	15	23	38	7.604	0.006
	Villages	20	7	27		
Cancer history	No	33	28	61	0.25	0.874
	Yes	2	2	4		
Smoking History	No	19	22	41	2.516	0.115
	Yes	16	8	24		
Addiction	No	33	28	61	0.25	0.874
	Yes	2	2	4		
Alcoholism	NO	34	27	61	1.427	0.236
	Yes	1	3	4		

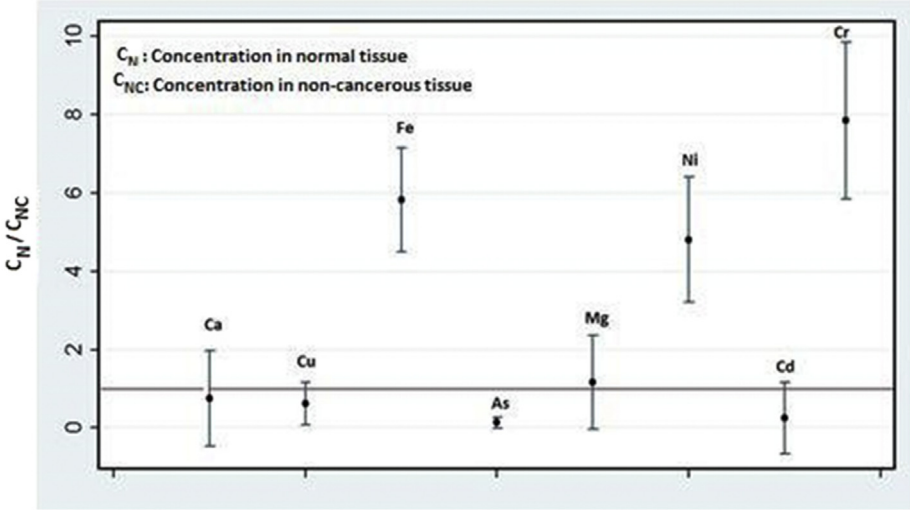

Fig. 1. Relative concentrations of trace elements in normal and non-cancerous tissues of stomach.

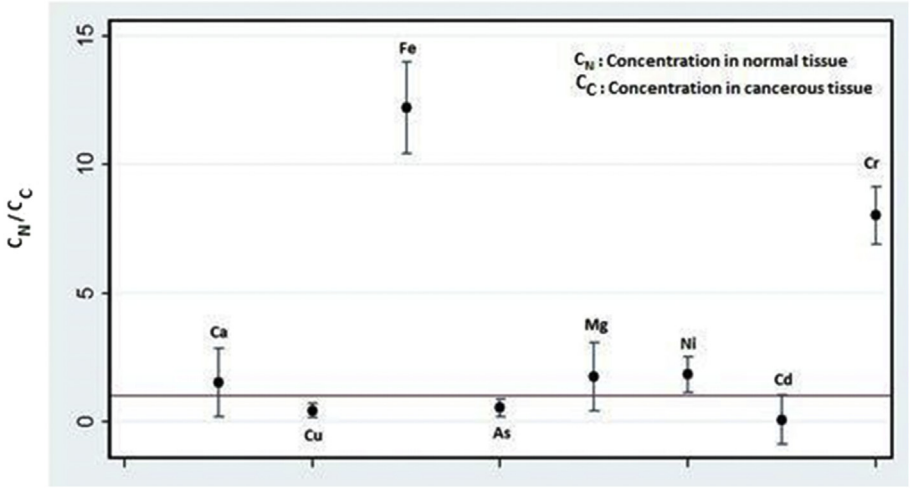

Fig. 2. Relative concentrations of trace elements in normal and cancerous tissues of stomach.

Table 4
Trace elements mean concentrations (mg/kg) in cancerous and non-cancerous tissues of human stomach.

	Cancerous tissue from Cancer patient		Confidence interval 95% for mean		Normal tissue from Cancer patient		Confidence interval 95% for mean		Normal tissues from Normal patient		Confidence interval 95% for mean	
	Mean	S.D	Lower bound	Upper bound	Mean	S.D.	Lower bound	Upper bound	mean	S.D.	Lower bound	Upper bound
Ca	252.3	119.68	2.11.18	293.41	231.03	176.85	170.28	291.78	305.53	163.08	244.63	366.43
Cu	4.09	4.98	2.37	5.80	7.86	17.24	1.9	13.7	2.22	1.72	1.58	2.87
Fe	62.43	49.91	45.29	79.58	46.37	50.03	29.18	63.55	82.82	135.26	32.31	133.32
As	1.76	4.75	0.136	3.40	0.709	1.54	0.177	1.24	0.24	0	0.24	0.24
Mg	28.08	13.44	23.46	32.70	25.33	16.34	19.72	30.95	33.74	25.57	24.19	43.29
Ni	4.67	3.7	3.40	5.94	10.89	17.7	4.8	16.97	7.46	8.36	4.3	10.58
Cd	0.22	0.12	0.18	0.26	0.21	0.06	0.19	0.23	0.2	0	0.20	0.20
Cr	1.21	0.99	0.87	1.55	2.16	4.88	0.49	3.84	2.42	2.75	1.39	3.45

lower Ca concentration but the present study is inconsistent with the suggested mechanism and both Ca and Ni were lower in cancerous tissues, higher in non-cancerous tissues, as some other similar studies reported (Yaman et al., 2007; Celen et al., 2015).

A confounding factor for the theory of increased local metal elements in tissues, which leads to carcinogenesis and cannot be ignored, is higher metabolism of tumors as a result of higher uncontrolled multiplication, which leads to increased vascularity. In this way, metal elements can aggregate more in malignant tissues compared with normal tissues (Raju et al., 2006).

Our results showed that Cu, As, and Cd concentrations were higher in cancer patients than non-cancer patient (control group).

On the other hand, Fe, Mg, and Cr concentrations were higher in control group, although just Cr higher concentration was significant ($p = 0.029$) Cu and Ni were significantly higher in cancer patients. Based on EPA report, there is no evidence for human cancer incidence connected with copper and animal evidences are "inadequate" to make a link between Cu and any cancer in humans (U.S. EPA. 20xx. Integrated Risk Information System (IRIS). Online www.epa.gov/iris. National Center for Environmental Assessment). Cu content of non-cancerous tissue of the patients was higher than cancerous tissue although not significant ($p = 0.208$). This research proposes Cu as a potential risk factor of cancer, but further studies are required to confirm it. Excess Cu can oxidize lipids, proteins, and DNA by binding to cysteine thiol group, catalyzing a Fenton-type reaction and producing reactive hydroxyl radicals and ROS, therefore, it potentially can induce cancer (39) (39) (38). On the other hand, newer studies have utilized Cu as a potential cancer therapy. Cu compounds and complexes have apoptotic effect by producing ROS, DNA, and mitochondrial damage, in breast and colorectal cancer and can act as chemotherapy agents (Koňariková et al.; Pramanik et al., 2016; Sandhaus et al., 2016). It is obvious that Cu can induce oxidative cell stress, but whether it can induce cancer or not, could not be answered by present amount of data. Cu metabolism and protein binding have a tight control mechanism in body, but disequilibrium of Cu balance leads to aforementioned consequences (Malandrinos and Hadjiliadis, 2014; Kurasaki and Saito, 2016). Another possible mechanism for Cu carcinogenicity is alterations of the gastrointestinal permeability to other coexisting carcinogens like *Helicobacter pylori*, a definite and high prevalent gastric carcinogen. In this regards, Gotteland et al. found reduced gastric mucosal barrier capacity after administrations of 10 mg Cu per litter via drinking waters to human subjects (Gotteland et al., 2001). Ceruloplasmin is Cu carrier and index (Kurasaki and Saito, 2016). Its measurement in cancer patients with or without a high concentration of Cu in their tissues, can be helpful in clarifying the role of ceruloplasmin and Cu in carcinogenesis, which was not carried out in the present study. A high Cu content of gastric tissue with a normal level of ceruloplasmin may indicate a local Cu precipitation and a dietary exposure. However, more investigation is required mainly on the soil and water interaction.

There are huge data regarding the carcinogenicity of As in different cancers. Arsenic is a well-defined carcinogen and is a member group 1 carcinogens (Loomis et al., 2014). Higher concentrations of this trace element were frequently reported in the biological samples like blood, hair, and nail in different cancers (He, 2011). . Stomach is the organ, where it is more accessible to dietary rote of As exposure; hence, it is possible to absorb As and get influenced by its presence. Our results showed that As concentration was higher in cancer patients both in cancerous and noncancerous tissues than the normal group, which may indicate an etiologic role for As.

As abovementioned, we also measured metal elements concentration in gastric biopsies of non-cancerous patients. By comparing these data with that of cancerous patients, we found that Fe, Mg, and Cr concentrations were even higher in non-cancerous patients than those observed in cancerous and non-cancerous tissues of cancerous patients. All of discussed issues demonstrate a need for much further evaluation and scrutiny on the role of trace elements in carcinogenesis and their local aggregation as a factor, due to inconsistent available findings. Meta-analysis and review studies even may give better and more reliable information on this subject.

5. Conclusion

Due to gastric cancer morbidity and mortality and its burden on social health, it is crucial and essential to identify its risk factors. Environmental factors are the most important risk factors specially because they are preventable. Trace metals have been proposed as gastric cancer risk factors due to their biochemically carcinogenic effects. The results of this study does not support the idea except for copper. Although copper has been introduced as an antioxidant and anti-cancer agent due to its role in immune system and its accumulation may be as a result of increased local immune response. Indeed, Ni was found to be higher in non-cancerous tissues of gastric cancer patients, which may be concluded to have a role in pre-cancerous changes. The residence location of patients may play as an environmental factor in this regard. Studies with more samples could be helpful because recent studies have had inconsistent results.

5.1. Limitations

Because of using endoscopic sampling, the sample size was small and made its digestion, analysis, and concentration balance a bit harder. It took a much longer time to collect the samples than we thought first because of weak cooperation of the patients.

Financial restricts made no water or soil analysis of the studied cases, which could give a clearer picture of the results.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.chemosphere.2017.06.071.

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